The design and application of surveillance systems in improving health outcomes and identifying risk factors for healthcare associated infections

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Abstract

The risks of patients acquiring an infection as a result of healthcare are considerable, with between 6.4% and 9.1% of patients in hospital found to have an healthcare associated infection (HCAI). These infections account for a considerable burden of disease; they are associated with significant morbidity and mortality, and incur costs to the patient, healthcare organisations and society. There is considerable evidence for measures that are effective in preventing HCAI, however there are challenges in ensuring that healthcare workers are aware of the risks and adhere to recommended practice. Surveillance systems that systematically capture, analyse and feedback data on rates of HCAI have been found to be a key component of effective infection control strategies, especially when they incorporate benchmarking. The large datasets captured by national surveillance systems also provide a unique opportunity to explore the epidemiology of HCAI, factors that contribute to their occurrence and their impact on public health.

This thesis concerns the design and application of surveillance systems for infections associated with healthcare. It reflects the programme of research originating from my involvement with the development and delivery of national HCAI surveillance systems in England from the mid-1990s. This research has addressed my underpinning hypothesis that: '*there are real differences in rates of HCAI which reflect variation in clinical practice and indicate where improvement may prevent these infections*'. The thesis includes eight primary publications focused on two key types of HCAI, surgical site infections (SSI) and bloodstream infections (BSI). The publications related to SSI describe my work on: the risks of SSI in terms of mortality and increased length of hospital stay; significant independent risk factors for SSI following hip prosthesis; the relationship between duration of operations and risk of SSI; inter-country comparisons of rates; an innovative approach to performance

monitoring based on funnel plots; and the impact of post-discharge surveillance on benchmarking. They are based on the analysis of data contributed to the national SSI surveillance system. A further two publications related to BSI explored trends in causative pathogens and sources of methicillin resistant *Staphylococcus aureus*. The thesis describes the main methods and findings of these studies, their contribution to contemporary knowledge and subsequent contributions to the field, illustrating my contribution to each of the works and my professional development as a researcher.

This body of work has identified important trends in pathogens causing BSI, in particular the emergence of *Escherichia coli* as a major cause of these infections, and provided evidence for possible contributory factors. It has also identified factors contributing to the reduction in methicillin resistant *Staphylococcus aureus* as a cause of BSI. It has added to the body of knowledge on outcomes of SSI, demonstrating that SSI doubles the length of hospital stay and the more severe infections significantly increases the risk of mortality in some types of surgery. It has informed the design and delivery of SSI surveillance systems in England and Europe through identifying the impact of key risk factors, such as the duration of operation and type of hip replacement procedure, and exploring the impact of variation in application of surveillance methods, in particular post-discharge surveillance, on rates of SSI. It has enhanced the value of surveillance as a performance monitoring through the application of innovative approaches to adjusting and comparing rates, such as the use of funnel plots for the detection of outliers. In conclusion, these analyses of data on HCAI have informed the development of national surveillance systems, improved understanding of variation in rates, and identified factors that may influence them. Further work is required to enhance and develop surveillance systems in order that they can continue to support the evaluation of effective infection prevention strategies in a rapidly changing healthcare environment.

Acknowledgements

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The design and application of surveillance systems in improving health outcomes and identifying risk factors for healthcare associated infections

Table of Contents

List of Tables

List of Figures

Abbreviations

ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ASA	American Society of Anaesthesiologists
BSI	Bloodstream infection
CDC	Centers for Disease Prevention & Control
CDSC	Centre for Disease Surveillance & Control
CI	Cumulative incidence
CMW	Community midwife
CSD	Caesarean section delivery
ECDC	European Center for Disease Prevention & Control
HCAI	Healthcare associated infections
HELICS	Hospitals In Europe Link For Infection Control Through Surveillance
HICPAC	Healthcare Infection Control Practices Advisory Committee
HPA	Health Protection Agency
ID	Incidence density
MESS	MRSA electronic Surveillance System
MRSA	Meticillin resistant *Staphylococcus aureus*
NAO	National Audit Office
NCCWCH	National Collaborating Centre for Women's and Children Health
NHSN	National Healthcare Safety Network
NICE	National Institute for Health and Care Excellence
NINSS	Nosocomial Infection National Surveillance System
NNIS	National Nosocomial Infection Surveillance system
PDS	Post discharge surveillance
PHLS	Public Health Laboratory Service
PQ	Patient questionnaire
PREZIES	Dutch SSI Surveillance System
RCS	Royal College of Surgeons
SENIC	Study of the Efficacy of Nosocomial Infection Control
SIR	Standardised Infection Ratio
SSI	Surgical site infection
SSISS	Surgical site infection Surveillance Service

CHAPTER 1

Introduction

1.1 Origins and development of the research programme

The theme of this thesis is the design and application of surveillance systems for infections associated with healthcare. The origin of this programme of research is my involvement with the development and delivery of national healthcare associated infections (HCAI) surveillance systems in England from the mid-1990s through to 2013. These were established with the primary aim of defining the risks of HCAI and supporting hospitals to use the data derived from surveillance as a tool in driving improvements in practice that could secure their prevention (Cooke *et al* 2000; Appendix 1.2). Integral to assuring the quality and efficacy of these surveillance systems has been an on-going commitment to explore how the data can be used most effectively to inform practice. The hypothesis underpinning my research is that: '*there are real differences in rates of HCAI which reflect variation in clinical practice and indicate where improvement may prevent these infections*'. I have therefore directed my research towards informing and improving the design and delivery of HCAI surveillance systems, enhancing understanding of health outcomes, exploring implications for public health, and identifying risk factors that affect the acquisition of HCAI.

1.2 Theoretical principles underpinning the research programme

When the concept of infection related to healthcare interventions was first developed, the term nosocomial, derived from the Greek "nosus" meaning "disease" and "komeion" meaning "to take care of" was adopted. Although, ironically, this term would encompass infection related to any form of healthcare, it was perceived to be synonymous with hospital-acquired infections (Emori *et al* 1991; Horan *et al* 2008). As the delivery of healthcare in non-hospital settings became more

widespread, the term healthcare associated infection has become more widely accepted. Such HCAI occur as a result of the particular risks associated with healthcare that increase patients' vulnerability to infection (Wilson 2006; Loveday *et al* 2014). They include:

- illnesses or conditions that impair the ability of the immune system to counter infection;
- procedures undertaken to treat or manage illness or to deliver healthcare that bypass normal defence mechanisms against infection e.g. skin or ciliated mucosa of the respiratory tract
- the hospital environment which can facilitate the selection of pathogens with virulence factors
- microorganisms that are able to spread readily between patients.

The risks of patients acquiring an infection as a result of healthcare are considerable. Recent prevalence surveys undertaken in the UK in 1995, 2006 and 2010 indicate that between 6.4% and 9.1% of patients in hospital have an HCAI, with urinary tract infection, pneumonia, surgical site infection and bloodstream infection being amongst the most common (Emmersen *et al* 1996; Smythe *et al* 2008; Health Protection Agency (HPA) 2012). These infections account for a considerable burden of disease; they are associated with significant morbidity and mortality, and incur costs to the patient, healthcare organisations and society in terms of both treatment costs and time away from productive activity (Plowman *et al 2001;* Fabbro-Perray *et al* 2007; Perenevich *et al* 2007; Fukuda *et al* 2011). My research has been focused on two key types of HCAI: bacteraemia or bloodstream infections (BSI) and surgical site infection (SSI) and the analysis of data captured on these infections by national surveillance systems in England.

1.2.1 Bloodstream and surgical site infections

The presence of bacteria in the blood is termed 'bacteraemia' or bloodstream infection (BSI). In recent prevalence surveys, BSI account for 7% of HCAI (Smythe *et al* 2008, HPA 2012).

Microorganisms in the blood may represent a *secondary*, systemic infection from another focus of infection such as a pneumonia or urinary tract infection, or may be introduced directly into the bloodstream via an invasive device such as an intravenous catheter when they are commonly called *primary* BSI (Warren *et al* 2001). Whilst relatively uncommon, bloodstream infections are associated with a high level of mortality (Rojo *et al* 1999; Plowman *et al* 2001).

Surgical site infections (refer to infections affecting the tissues involved in an operative procedure (Mangram *et al* 1999). Prevalence surveys indicate that they are the third most common HCAI, accounting for 14.5% to 15.7% of all HCAI (Smythe *et al* 2008; HPA 2012). The risk of a patient developing an SSI depends on a combination of factors (National Collaborating Centre for Women's and Children's Health (NCCWCH) 2008) including the:

- number of micro-organisms introduced into the operative site,
- number that remain when the wound is closed,
- ability of micro-organisms to multiply and invade tissues, and the efficacy of the host's immune defences against them).

1.2.2 Principles of surveillance

The term surveillance was defined by Alexander Langmuir, the Director of the Epidemiology Intelligence Service at the Centers for Disease Control (CDC) in Atlanta USA, as "the systematic collection, consolidation, analysis and dissemination of data on specific diseases" in public health practice (Langmuir 1963). Until Langmuir developed the concept of using surveillance to study the spread of disease the term had been applied to the practice of monitoring people, for example those who had been exposed to a communicable disease in order to expedite quarantine. The use of data on the occurrence of disease to study their epidemiology emerged from the efforts to control malaria in war zones during World War II. The CDC was formed in the USA from the military organisations established during the war and charged with eradicating malaria from the 14 southern

state of the USA where the disease was endemic. It rapidly expanded its role to all areas of communicable disease control. The surveillance systems established for poliomyelitis in the early 1950s demonstrated the value of systematically capturing data on cases of disease and then using it to evaluate the impact of the early vaccination programmes (Langmuir 1980). The Division of Communicable Diseases at the World Health Organisation (WHO) subsequently recognised surveillance as a means of studying the epidemiology of a disease, using it not only as a tool for research, but as fundamental to the planning and evaluation of control measures. The success of the WHO global smallpox eradication programme was driven by the use of weekly reports of cases detected in hospitals and health centres to focus immediate vaccination efforts (Raska 1964). This direct link between data from surveillance and the control of disease led to the definition of surveillance being expanded to encompass the *'study of a disease as a dynamic process involving the ecology of the infectious agent, the host, the reservoirs, and the complex mechanisms concerned in the spread of infection and the extent to which this spread occurs'* (Raska 1964). If information from surveillance is to be effective in understanding and responding to the distribution or spread of disease a systematic approach to collection of data is essential. This requirement highlights the importance of the functional capacity and capability of surveillance systems to support data collection, analysis, and dissemination linked to public health programmes (Thacker and Berkelman 1988).

1.2.3. Strategies to prevent healthcare associated infections

Although the risks of infection associated with healthcare have been recognised for almost as long as hospitals have existed (Selwyn 1991), modern organised structures to support efforts to prevent and control HCAI only began to develop in the UK in the 1940s with the appointment of control of infection officers. The problems caused by the pandemic of staphylococcal infections that severely affected hospitals in the late 1960s drove the development of a specialist infection control service and by 2008 the requirement to have a comprehensive infection control service became enshrined

in law in the form of the HCAI Code of Practice (Nahmias and Eickhoff 1961; Jenner and Wilson 2000; Department of Health 2009). There is an extensive body of evidence that describe strategies to prevent HCAI which focus on practices used in the general care of patients in order to prevent the movement of pathogens between patients, minimise the risk of pathogens being introduced into invasive devices or during invasive procedure; and organisation-wide strategies to minimise the emergence of antimicrobial resistant pathogens and spread between patients (Loveday *et al* 2014; Mangram *et al* 1999; O'Grady *et al* 2011; Gould *et al* 2010; Ashiru-Oredope *et al* 2012). However, many researchers have highlighted the difficulties of ensuring that healthcare workers are aware of the risk of HCAI to patients in their care and that they adhere to recommended practice (Pittet *et al* 2000; Jenner *et al* 2006; Pronovost *et al* 2006) In addition, whilst patients should expect to be provided with reliable information about risks of infection associated with their healthcare, in reality this is rarely possible in the absence of robust surveillance systems (NCCWCH 2008).

1.2.3.1 *Role of surveillance in preventing HCAI*: Evidence for the potential impact of surveillance of HCAI as a mechanism to increase the awareness of clinical staff, improve adherence to best practice and reduce rates of HCAI was first published by Cruse and Foord (1973; 1980) who analysed the impact of 10 years of surveillance on the epidemiology of surgical site infection, demonstrated key factors that influenced the rate of SSI and significant reductions associated with systematic monitoring and feedback of rates to surgeons. Other studies have indicated that surveillance and feedback of data to clinicians is essential for infection control strategies to be effective (Haley 1985; Pronovost *et al* 2006). In a review of studies reporting reductions in rates of HCAI, all the successful quality improvement strategies included surveillance and feedback (Harbarth *et al* 2003). Enabling comparison with other similar organisations can enhance the impact of surveillance though identifying outliers and motivating implementation of reduction strategies. The potent effect of benchmarking of rates of HCAI in national surveillance systems has been demonstrated by significant reductions in rates of SSI reported in hospitals that participate in national surveillance schemes and

report rates of SSI to surgeons. Gastmeier *et al* identified a reduction in relative risk of wound infections following hip prosthesis surgery of 0.54 (between the first and third year of participation in the German national nosocomial infections surveillance system (KISS) (Gastmeier *et al* 2005). Geubbels *et al* also identified a reduction in relative risk of surgical site infection (SSI) associated with participation in the Dutch national surveillance system (PREZIES) between 1996 and 2000 (Geubbels *et al* 2004; 2006a). Significant reductions in rates of SSI have also been observed in hospitals participating in the national surveillance and benchmarking system in French (ISO-RAISIN) with rates declining from 2.04% to 1.26% ($p<0.001$) between 1999 and 2006. Other studies have reported similar reductions in association with surveillance used for benchmarking of hospitals to drive improvements in performance (Rioux *et al* 2007; Taylor *et al* 1994; National Audit Office (NAO) 2004; Barwolff *et al* 2006). However, whilst external benchmarks can be a powerful driver for change they require considerable effort and co-ordination to develop and must use principles that assure, as far as possible, the validity of comparisons, including: standardised case definitions and case finding methods; analysis that accounts for variation in case mix; precision of estimated rates and period of post-operative follow-up; and assurance about the quality of data through validation systems (Cooke *et al* 2000, Wilson *et al* 2002; Gaynes *et al* 2001a; 2000; Ingraham 2010). Despite key advances in preventing HCAI over recent decades, microbial pathogens are able to rapidly evolve and adapt to changing circumstances and surveillance systems must therefore be able to detect changing epidemiology in order to direct appropriate preventative strategies. Using surveillance to support effective benchmarking and explore changing epidemiology of HCAI are key components of this thesis.

1.2.4 Surveillance methodology

The methodology used to capture surveillance data has important implications for the approach to analysis and interpretation, and in supporting comparisons within and between institutions (Gaynes *et al* 2001;2000; Jarvis 2003; Platt 2005). Surveillance of BSI is based on data captured at a

population level. This approach comprises collecting data on the number of reports of a particular disease within a given population. This type of data can be used to describe and compare patterns of disease and exposure to risk factors within different populations and over time (HPA 2008a). In my research on this data I have explored secular trends and sources of these infections in order to improve understanding of their epidemiology and generate research questions about causes or contributory factors. However, in the absence of data on the presence of risk factors in individuals this type of population level surveillance cannot be used to determine associations between risk factors (Hennekens and Buring 1987). In contrast, data for the surveillance of SSI is captured at a patient level. This enables the data to be analysed to identify risk factors and outcomes of infection as well as exploring variation in rates of infection, the impact of case-finding methods and strategies for reliably comparing rates between centres. These are the key concepts which underpin my research studies on SSI that are described in this thesis.

1.3 Structure and content of the submission for PhD by publication

The thesis comprises eight primary publications that demonstrate a coherent theme of research related to the design and application of surveillance systems as a mechanism for improving healthcare outcomes and identifying causal factors for healthcare associated infection. It also includes eight secondary publications that underpin and further enhance the main thesis. The thesis is structured as follows:

Chapter 2*:* provides the context for my research by describing the background and key methodological concepts that underpin surveillance of HCAI in England and how these have informed my research. It includes a discussion of the development of systems for HCAI surveillance in the USA and UK, the metrics used for calculating rates of HCAI, case definitions and case-finding methodology, risk factors for SSI and BSI and analysis and reporting of HCAI surveillance data.

Chapter 3: describes my work on the use of risk factor data, captured through surveillance, to measure the impact and contributory factors for HCAI. It includes the following three published works:

- Coello *et al* 2005 (Appendix 3.1): This study used data captured by the SSI surveillance system to determine the impact of surgical site infection (SSI) on the costs of healthcare and risk of death adjusted for underlying illness, age and other operation related risk factors.
- Ridgway *et al* 2005 (Appendix 3.2): This analysis used multivariate analysis to define rates and identify significant independent risk factors for SSI following hip prosthesis surgery.
- Leong *et al* 2007 (Appendix 3.3): This study explored the impact of a key risk factor for SSI, the duration of operation and validated our methods for identifying prolonged operations associated with an increased risk of SSI.

Chapter 4: builds on these findings by exploring the methodological challenges in comparing rates of HCAI. It includes the following three published works:

- Wilson *et al* 2007 (Appendix 4.1): This work reflected a collaboration with European colleagues to explore the implications of variation in application of case definitions, case mix and duration of follow-up on inter-country comparisons rates of SSI.
- Wilson *et al* 2008 (Appendix 4.2): This publication describes the use of funnel plots to provide a novel methodology for benchmarking SSI surveillance data and identifying hospitals with outlying rates of infection.
- Wilson *et al* 2013 (Appendix 4.3): This pragmatic study was the first to demonstrate significant inter-hospital variation in the application of post-discharge surveillance methods and to define the impact on SSI benchmarking systems.

***Chapter 5*:** focuses on the analysis of trends emerging from national BSI surveillance data and includes the following two published works:

- Wilson *et al* 2010 (Appendix 5.1): Presents an analysis of trends in common pathogens causing bloodstream infection captured by the national laboratory surveillance system which used a Poisson regression model to adjust for variation in case ascertainment.
- Wilson *et al* 2011 (Appendix 5.2): In this publication the Poisson regression methods developed in the previous study were applied to the analysis of trends in sources bloodstream infections caused by meticillin resistant *Staphylococcus aureus* (MRSA).

The final two chapters (Chapter 6 and 7) provide an insight into my personal development as a competent and confident researcher and how I can further develop my area of research

1.4 The published works

These are organised into six appendices each corresponding to the relevant chapter of the thesis:

1.4.1 Primary published works

1. Coello, R.; Charlett, A.; **Wilson, J.;** Ward, V.; Pearson, A,; Boriello, P. (2005) Adverse impact of surgical site infections in English hospitals. *J. Hosp. Infect.* **60**: 93-103 (Appendix 3.1)
2. Ridgeway, S.; **Wilson, J.;** Charlett, A.; Kafatos, G.; Pearson, A.; Coello, R. (2005) Infection of the surgical site after arthroplasty of the hip. *J. Bone Joint Surg*. **87(6):** 844-50 (Appendix 3.2)
3. Leong, G.; **Wilson, J.;** Charlett, A. (2006) Duration of operation as a risk factor for surgical site infection: comparison of English and US data. *J Hosp Infect* **63**: 255-62. (Appendix 3.3)
4. **Wilson, J.;** Suetens, C.; Ramboer, I.; Fabry. J. (2007) Hospitals in Europe Link for Infection Control through Surveillance (HELICS). Inter-country comparison of rates of surgical site infection – opportunities and limitations. *J. Hosp. Infect.* **65(S2)**: 165-70 (Appendix 4.1)

5. **Wilson, J.;** Charlett, A,; Leong, G. *et al* (2008) Rates of surgical site infection after hip replacement as a hospital performance indicator: analysis of data from the English mandatory surveillance system. *Infect. Control Hosp. Epid.* **19(3)**: 219-26 (Appendix 4.2**)**
6. **Wilson, J.;** Wloch, C.; Saei, A. *et al* (2013) Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. *J. Hosp. Infect.* **84**: 44-51 (Appendix 4.3)
7. **Wilson, J.;** Elgohari, S.; Livermore, D. *et al* (2010) Trends among pathogens reported as causing bacteraemia in England: 2004 – 2008. *Clinical Microbiology & Infection***. 17(3):** 451-8 (Appendix 5.1)
8. **Wilson, J.;** Guy, R.; Elgohari, S. *et al* (2011) Trends in sources of meticillin resistant *Staphylococcus aureus* bacteraemia: data from the National mandatory surveillance of MRSA bacteraemia in England, 2006 to 2009. *J Hosp Infect*. **79**: 211-217 (Appendix 5.2)

1.4.2 Secondary published work

1. Cooke, E.M.; Coello, R.; Sedgwick, J.; Ward, V.; **Wilson, J.;** *et al* (2000) A national surveillance scheme for hospital-associated infections in England. *J. Hosp. Infect*. **46**: 1-3 **(Appendix 1.1)**
2. Glen, A.; Ward, V.; **Wilson, J**. et al (1997) Hospital-acquired infection: surveillance polices and practice. Public Health Laboratory Service. (Appendix 2.1)
3. **Wilson, J.** (2013) Surgical site infection: the principles and practice of surveillance. Part 1: Key concepts in the methodology of SSI surveillance. *J Infect Prevent.* **14**: 6-12 (Appendix 2.2)
4. **Wilson, J.** (2013) Surgical site infection: the principles and practice of surveillance. Part 2: analysing and interpreting. *J Infect Prevent.* **17**: 1-5 (Appendix 2.3)
5. McDougall, C.; **Wilson, J.;** Elgohari, S. (2007) A review of compliance with the national protocols for surveillance of surgical site infection. Does deviance impact on the quality of data and detection of SSI? *Amer. J. Infect. Control.* **35**: 271 (Appendix 2.4)

6. **Wilson, J.;** Ward, V.; Coello, R. *et al* (2002) A user evaluation of the National Nosocomial Infection Surveillance System: surgical site infection module. *J. Hosp. Infect.* **52**:114-121 (Appendix 2.5)
7. Wilson, A.P.R.; Gibbons, C.; Reeves, B.C.; Hodgson, B.; Liu, M.; Plummer, D.; Krukowski, Z.H.; Bruce, J.; **Wilson, J.;** Pearson, A. (2005). Surgical wound infection as a performance indicator: agreement of common definitions of wound infection in 4773 patients. *BMJ* **329**: 720-25 (Appendix 3.2)
8. **Wilson, J.;** Saei, A.; Elgohari, S. (2009) The application of small area estimate models to measure the effect of length of post-operative stay on observed changes in rates of surgical site infection over time. Poster presentation. Society of Healthcare Epidemiologists of America. April 2009. ***(Appendix 4.5)***

1.5 Demonstrating the requirements of a PhD by publication

The overview presented in this submission represents a coherent programme of research, linked to my work in analysing data captured in national surveillance systems for HCAI. This research has been informed by my clinical background in nursing which has both influenced my research interests and underpinned my interpretation and analysis of surveillance data.

It demonstrates how my work has influenced the delivery of surveillance and its application to identifying differences in rates of HCAI and improving health outcomes. It has also enhanced understanding of risk factors that affect the acquisition of HCAI. Based on the criteria required of a PhD by submission of published work the following are addressed throughout this thesis:

Conceptual and methodological development of the work: I appraise these aspects in the context of the main methods and findings of the work.

Autobiographical context: My involvement in the conceptual development of the overall programme of research and specific role in the design, methodology and execution is explained in relation to each published work.

Accounts for originality: The rationale and contribution of the published works to knowledge of HCAI and surveillance systems are explained in the context of the evidence-base at the time the work was conducted.

Subsequent contributions to the subject: the originality of the work is reappraised in relation to contributions to the subject area since the completion of the research.

Professional development as a research practitioner: Reflections on my development as a researcher and how undertaking the work has contributed to the development of my knowledge and skills in undertaking research.

1.6 Summary of chapter

I have outlined the origin of the programme of research that forms the basis for my thesis; the theoretical principles that have informed it; how I have structured the thesis; and how I have demonstrated the requirements of a PhD by publication. The following chapter will describe the emergence of surveillance systems for HCAI in the 1960s, the key methodological concepts that have subsequently underpinned them and how these principles have informed both the development of national surveillance systems in England and my role within this research.

CHAPTER 2

The development of national surveillance systems in England

2.1 Introduction - the evolution of healthcare associated infection surveillance

In the 1960s formal structures to support infection control in hospitals began to emerge with the appointment of specialist staff such as infection control nurses, working with microbiologists or hospital epidemiologists. In the USA, the Centers for Disease Control (CDC) recommended that hospitals conduct surveillance of hospital-acquired infections in order to obtain epidemiological data on which to base effective control measures (Langmuir 1963; Haley *et al* 1980a). Subsequently, organised programmes of infection control activity began to develop which, in the USA commonly included surveillance of infection acquired in hospital. The intention of this surveillance was to identify all nosocomial infections through the review of laboratory data and identification of patients with fever, in isolation or on antibiotics with data mostly captured by infection control nurses (ICNs) (Haley & Shachtman 1980; Abrutyn and Talbot 1987). Whilst these systems were comprehensive, they were also highly resource intensive and generated a large amount of data that was not always useful to drive prevention initiatives (Glenister *et al* 1992; Haley 1985a, 1985b).

2.1.1 ***The Study of the Efficacy of Nosocomial Infection Control (SENIC):*** Rising costs led to the benefits of these resource-intensive surveillance programmes being questioned (Haley *et al* 1980a, 1981, 1985a) and in 1980 CDC initiated a large, multicentre study to determine both the magnitude of the problem of HCAI in hospitals and the extent to which the surveillance and control programme approach was effective in reducing the risk of infection. The study drew on a sampling frame of more than 6000 hospitals with infection

control programmes of varying levels of intensity as defined by a prior country-wide survey (Haley *et al* 1980b). In a stratified random sample of 338 of 6000 hospitals, hospital-acquired infections were identified from the case records of a random sample of 500 patients before and after infection control programmes were established (Haley *et al* 1980b). In order to explore the independent effect of varying intensity of surveillance and control programmes on overall rates of HCAI and rates of specific types of HCAI, a multivariable logistic regression model was used. Such models correlate the dependant or outcome variable (i.e. infection) with more than one explanatory (predictor) variable at the same time, enabling the effects of each predictor to be measured whilst accounting for the effect of all the other predictors. This was important in order to distinguish the specific effect of individual variables since many were likely to be related e.g. length of hospital stay and severity of illness. Logistic regression was used because the model was estimating a dichotomous outcome (infection yes or no) and using logit of proportion as the outcome variable, ensuring that meaningless estimated proportions below zero or above one were not generated (Bland 2000 p.321). Examples of this type of modelling are contained in some of the publications included in this thesis (Coello *et al* 2005; Ridgeway *et al* 2005). Using the logistic regression model to control for variation in characteristics of the hospitals and their patients, the SENIC study demonstrated that organised surveillance was an essential component of an effective infection control programme. Hospitals with both surveillance and organised control activities reduced infection rates by 32%, whilst in hospitals with no infection control programme the rate of HCAI increased by 6%. Although surveillance was found to be an essential component of the programme for all HCAI types, the effect was most apparent in relation to surgical infections, pneumonia and urinary tract infection where high intensity surveillance was associated with significant reductions in rates between to two data capture periods of 1970 and 1975/6 (Haley *et al* 1985a). This study was therefore critical in defining the essential role that surveillance played in effective infection

control programmes and it inspired the formation of the national HCAI surveillance systems in England, which have underpinned much of the research included in this thesis (section 2.1.5).

2.1.2 ***The National Nosocomial Infection Surveillance system (NNIS)****:* This system had been established by CDC in the 1970s to provide a mechanism for collecting and analysing data on the frequency of nosocomial infections in US hospitals (Horan *et al* 1986). The early NNIS approach reflected the CDC advice for 'comprehensive surveillance' and involved 51 selected hospitals collecting data on all hospital-acquired infections and the rate for the whole hospital being calculated using the number of patient admissions as a denominator. However, SENIC demonstrated that surveillance programmes were more effective if they provided meaningful feedback on rates of specific infections to relevant clinicians. Indeed, as the SENIC study concluded *'infection control problems and the need for prevention efforts were not apparent to physicians, nurses or administrators until they were given quantitative measures of the problem derived from surveillance data'* (Haley *et al* 1985a). Thus the concept of targeted surveillance emerged in the late 1980s, with specific surveillance activity determined by local priorities and recommended to be objective rather than process driven (Haley 1985; Haley 1995). NNIS was developed accordingly and supported surveillance under three 'components' - adult and pediatric intensive care units, high risk nursery and surgical patients and expanded participation to 300 hospitals (Emori *et al* 1991, National Nosocomial Infection Surveillance (NNIS) System 2004). The standardized protocols developed for capturing this surveillance data began to be adopted by other countries as they also established national HCAI surveillance systems, including the systems that emerged in England in the late 1990s. The NNIS surveillance principles underpin the surgical site infection (SSI) data described in this thesis and are explained in subsequent sections of this chapter.

2.1.3 ***Development of surveillance systems in the United Kingdom:*** In the UK, the collection and collation of infection reports from microbiology laboratories at a national level was established in England in the 1940s. Initially, these reports were only collected from the laboratories that were part of the Public Health Laboratory Service (PHLS) network, but in the 1950s the system was extended to NHS laboratories. For the first 50 years the system relied on manual, paper-based reporting to the PHLS. In 1975, a central computer database called LabBase was established and laboratory reports on micro-organisms causing clinically significant infections were entered manually at the Centre for Disease Surveillance & Control (CDSC), which was established at the Central PHLS in 1977 (Grant and Eke 1993). Originally these included pathogens from stools and urine; then in 1989 this was extended to include all positive blood cultures (Reacher *et al* 2000). In 1991 an electronic reporting system was introduced which was subsequently updated to a unified software system for England and Wales called 'CoSurv'. This system enabled a data captured locally in a laboratory to be entered into a computer and transmitted as a structured dataset to CDSC by a modem link (Grant and Eke 1993). Further developments in the 1990s enabled laboratories to extract data directly from their laboratory information systems to be translated into the CoSurv data format required by CDSC.

2.1.4 *Reporting systems for laboratory infections:* The data from hospital laboratory systems was used by CDSC to generate both weekly and serial reports which were published in the Communicable Disease Report (CDR). The numbers included in these laboratory reports increased by a factor of three between 1975 and 1993 as participation in the surveillance system increased (Grant and Eke 1993). In the mid-1990s regional epidemiology units were developed to support analysis and reporting of the laboratory data. Until the mid-2000s the majority of data was submitted manually, but a project to standardise the direct electronic transfer of data from laboratory systems resulted in over

90% moving over to electronic data transfer by 2009. Although the surveillance only captures a basic dataset on episodes linked to a single pathogen and does not distinguish isolates associated with healthcare from those associated with community-acquired infection, it does provide invaluable data with which to identify trends in pathogens causing infection. This is particular the case with blood cultures, since the laboratory data alone is usually indicative of a systemic infection. In Chapter 5, I describe an analysis of trends in pathogens causing bacteraemia that draws on this laboratory data and demonstrates its value in determining changes in epidemiology at a population level (Wilson *et al* 2011; Appendix 5.1).

2.1.5 ***Systems for surveillance of healthcare associated infections in England***: In the UK, infection control services became widely established in hospitals after their inception in the late 1960's and by 1986 almost 90% of health authorities had appointed an infection control nurse (Howard 1988). However, unlike in the USA most infection control programmes in the UK did not include comprehensive surveillance activity but focused on monitoring for pathogens associated with a risk of transmission e.g. antimicrobial resistant organisms, staphylococcus or streptococcus 'alert organisms'. In a survey of 30 infection control nurses by Glenister *et al* in the early 1990s, 87% (26/30) of infection control teams conducted this type of 'alert organisms' surveillance and only 17% (5/30) produced data on rates of infection and where this was the case, only for surgical site infection (Glenister *et al* 1992). One factor that may have contributed to this difference in focus was the involvement of physicians with a strong interest and expertise in epidemiology in the USA, whereas in the UK the medical microbiologist (a role which did not exist in the USA) was more likely to be part of the infection control team with more expertise and interest in microbiology and control measures than in the capture and interpretation of data. However, the publication of SENIC initiated a change in approach to surveillance of hospital infection in the UK and the

importance of surveillance as a component of infection control programmes in the UK began to feature in policy documents making recommendations about hospital infection control (Department of Health 1995). In addition, when the NHS and Community Care Act was published in 1990, it signalled the emergence of an 'internal market' in the NHS associated with competition to provide services. This, together with an imperative to assure quality, drove the need for data to assess quality and measure outcomes, including those associated with HCAI (Soderlund *et al* 1997; Department of Health 2003; Commission for Healthcare Improvement 2003).

2.1.6 ***Audit of infection control activity project****:* After the results of the SENIC study were published, the Department of Health sought to advance HCAI surveillance in UK hospitals. it therefore funded a study conducted by the PHLS to explore the feasibility of undertaking surveillance in hospitals in the UK for which I was part of the research team. The study involved 19 district general hospitals in England and Wales and found a rate of HCAI 2.7 per 100 patients episodes (excluding surgical site infections) increasing to over seven for patients with an invasive device (Glynn *et al* 1997; Appendix 2.1). This study identified significant variation between specialities and hospitals in risks of infection that were not explained by case-mix. One of the key recommendations we formulated from this study was the need to address the apparent variation in rates of infection by establishing systems for HCAI surveillance based on standard protocols and data capture systems. This recommendation subsequently informed the development of national systems for surveillance of HCAI, the National Nosocomial Infection Surveillance System (NINSS), established in England in the late 1990s (Cooke *el al* 2000; Appendix 1.1).

2.1.7 ***The Nosocomial Infection National Surveillance System (NINSS) in England****:* The PHLS formed this first national surveillance system in 1996 with funding from the

Department of Health. It aimed to both facilitate surveillance of HCAI and enable comparison of rates between institutions in order to inform and support HCAI prevention strategies (Cooke *et al* 2000; Appendix 1.1). Surveillance was subsequently established for three HCAI:

- surgical site infection,
- catheter-associated urinary tract infection,
- hospital-acquired bloodstream infection.

The aim was to establish a voluntary national reporting system that enables hospitals to compare their data against aggregated annonymised data from other participating hospitals. However, whilst external benchmarks can be a powerful driver for change they are acknowledged to require considerable effort and co-ordination to develop (Gaynes *et al* 2001a; Centers for Disease Control 1991). As part of the multidisciplinary team that established these surveillance systems I was involved in establishing the key principles on which they were based to assure, as far as possible, the validity of comparisons. These included standardised case definitions, active case finding methods and analysis that accounts for variation in case mix. In addition, we aimed to use methods that could reliably distinguish outlying rates of infection (Cooke *et al* 2000; Appendix 1.1). The methods chosen were adapted from those used by the CDC NNIS system and used similar datasets, but focused on specific types of infection rather than specialist services. We also devised new methods for defining infections, capturing and reporting data. There was also a focus on publishing benchmarking data, which was not a major feature of other national surveillance systems that were emerging at that time (Smyth and Emmerson 2000; Emori *et al* 1991; Gastemeier *et al* 2008; Haustein *et al* 2011). The bloodstream infection surveillance initiated by NINNS was subsequently replaced in 2001 by a system focused on bacteraemia caused by one particular pathogen, methicillin resistant *Staphylococcus aureus* (MRSA). This

organism was causing concern at this time because it was resistant to the first line antimicrobial agent used to treat staphylococcal infections. Evidence from the routine laboratory surveillance data indicated that resistant strains had become widespread in the UK and that the incidence of invasive infections had increased rapidly in the last decade, with attendant implications for effective treatment of these serious and life-threatening infections (Duckworth *et al* 2002; Shorr 2007). The MRSA surveillance system was originally based on aggregate quarterly reports of cases, but became a patient level, web-based reporting system called the MRSA bacteraemia Electronic Surveillance System (MESS) in October 2005.

2.1.8 The research included in my thesis concerns the analysis, interpretation and application of data from three of these national surveillance systems: the NINSS surgical site infection surveillance system (SSISS), bacteraemia data captured by the routine laboratory reporting system (LabBase) and the MRSA bacteraemia surveillance system. The methodology underpinning these surveillance systems, including the metrics generally used, the definition of cases of infection, methods of case finding and the relevance of risk factor data in surveillance systems will be outlined in section 2.2 to provide the background and context for the research presented in this thesis.

2.2 Methodologies applied to the surveillance of healthcare associated infections

2.2.1 Metrics for calculating rates

2.2.1.1 Surgical site infection: The conventional method of measuring SSI is the cumulative incidence, which is usually expressed as the number of SSIs per 100 operations. This is more accurately described as the *risk* of SSI but is commonly referred to as a *rate* of SSI (NNIS 2004).

This metric is calculated as follows:

$$\frac{\textit{No. SSI in a defined group of procedures}}{\textit{No. operations performed}} \; X\ 100$$

In order to accurately measure risk, cases in the numerator must be drawn from the population included in the denominator. Most national SSI surveillance systems use methods based on those developed in the 1990s for the National Nosocomial Infection Surveillance (NNIS) System in the USA and which were built on the findings of SENIC (Emori *et al* 1991). Surveillance is structured to calculate this metric by following up each patient who has a relevant operation prospectively to determine if they develop an SSI. Since the intrinsic risk of SSI is not the same for all types of operation (being strongly influenced by the presence of microbial flora at the site of the operation) the NNIS system distinguished categories of clinically similar procedures that are likely to have a similar intrinsic risk of SSI (NNIS 2004). This is an important principle in order to report meaningful rates of SSI to surgeons and clinical teams and to ensure that variations in rates of SSI are not explained by differences in the intrinsic risk of infection associated with the combination of procedures included in the surveillance.

For the NINSS SSI surveillance system we expressed the denominator for the surveillance by grouping surgical procedures into 12 categories based on a defined set of Office of Population Census & Statistics (OPCS) procedure codes which are the standard method of coding operations in the UK. We mapped these codes to the categories defined by the NNIS system in the USA in order to enable comparison with data from other surveillance systems. Such comparisons are illustrated in Leong *et al* 2005 (Appendix 3.3) where we explore the duration of operation as a predictor of SSI (see chapter 3; section 3.4) and in my work on inter-country comparison of rates of SSI described in Wilson *et al* 2007 (Appendix 4.1) in

Chapter 4; section 4.4. In selecting NINNS categories we considered the likely cost-benefit of conducting the surveillance and therefore aimed to identify procedures where the underlying risk of SSI was either reasonably high (e.g bowel surgery) or associated with significant morbidity (e.g. orthopaedic surgery) and the costs of surveillance would be more likely to be offset by its impact on prevention of SSI. In addition, we excluded more minor procedures with a length of post-operative stay of less than three days since it can take several days from the time of operation for symptoms of SSI to become apparent and methods based primarily on hospital-based case-finding would therefore not detect SSI in patients with short hospital stays (see section 2.2.3).

2.2.1.2 *Bloodstream infection:* Unlike SSI, any patient who receives healthcare is at risk of developing a healthcare associated bloodstream infection (BSI) and the infection may also occur outside healthcare settings, arising either from community-acquired infections or healthcare delivered in the community (Rojo *et al* 1999). Primary BSI are infections associated with an invasive device such as a vascular catheter, and are always considered as healthcare associated, although not all patients with such devices are hospital inpatients (Warren *et al* 2001). The metrics used to measure risk of BSI therefore depend on the available data, purpose of the measurement, the population at risk and whether the focus for surveillance is primary, secondary or all BSI. The denominator used to measure the risk of BSI may therefore reflect the whole population (if both hospital and community acquired infections are included) or only the population in hospital during the period under study (if focused on hospital-acquired, primary BSI). Metrics are represented as follows:

Risk (cumulative incidence) of bacteraemia/BSI:

$$\frac{\textit{No. cases bacteraemia/BSI (in specified time period)}}{\textit{No. people at risk (in population from which cases are derived)}}$$

Whilst a BSI is more readily identified than most other HCAI because it is primarily a diagnosis based on a laboratory result, defining BSI that are associated with healthcare and capturing corresponding denominator data is much more problematic because healthcare may not be delivered in a hospital setting. In Chapter 5 (section 5.2), my publication on trends in pathogens causing bacteraemia presents an analysis of data captured by the routine laboratory reporting system (LabBase) (Wilson *et al* 2011; Appendix 5.1).

Other forms of BSI surveillance are focused on bacteraemia acquired in a hospital setting where the risk of acquiring bacteraemia is dependant on the number of days spent in hospital. In surveillance of hospital-acquired BSI, the denominator must reflect the patient population at risk and account for length of hospital stay. This approach was used by the NNISS hospital-acquired bacteraemia surveillance and subsequently by the MRSA Electronic Surveillance System (MESS) on which my analyses of trends in sources of MRSA bacteraemia presented in Chapter 5 (section 5.3) are based (Wilson *et al* 2011; Appendix 5.2). An example of this type of metric is shown below:

Rate (incidence density) of hospital-acquired bacteraemia/BSI:

$$\frac{\textit{No. new bacteraemia/BSI acquired in hospital}}{\textit{No. patient-days in population (sum of all hospital days for all patients during the surveillance period)}} \times 1000$$

Unlike these English BSI surveillance systems (LabBASE, NINSS and MESS), the US NNIS system was focused only on the surveillance of primary BSI in intensive care units and did not capture population level data. In this situation, a more appropriate denominator is the number of days of exposure to the devices that are associated with primary BSI and since most are associated with central vascular device, the total number of days with one or more

of these devices for the period under surveillance would be the main denominator (Emori *et al* 1991).

2.2.2 Definitions of infection

2.2.2.1 Surgical site infection: The ability to consistently identify SSI in operative wounds is recognised as an essential requirement of establishing a benchmarking system, however since skin is normally colonised by a range of micro-organisms that could cause infection, wound cultures do not provide a reliable indicator of infection. A number of approaches to defining SSI based on evidence of clinical signs and symptoms of infection have been used for surveillance, ranging from simply the presence of pus in the wound (Cruise and Foord 1973) which may miss a high proportion of infections, to more complex scoring criteria such as ASEPSIS which, whilst detecting more cases, are difficult to apply in routine data capture systems (Wilson *et al*, 1986). However, most SSI surveillance systems use definitions based on those described by CDC which distinguish infections affecting different levels of the operative site, superficial incisional, deep incisional and organ/space (Horan *et al* 1992; Horan *et al* 2008). This definition requires the presence of signs and symptoms that align to a specific set of criteria and occur within 30 days of the operation (or one year if non-human material is left permanently in the operative site (Horan *et al* 1992; Horan and Emori 1997). A key challenge associated with case definitions is ensuring the criteria are sufficiently objective to maximise inter-rater reliability. Objective criteria are more difficult to apply to superficial SSI where symptoms can be non-specific and open to variation in interpretation by clinicians and microbiological cultures from the wound may reflect colonisation rather than infection. In developing the NINNS methodology we chose address this subjectivity by amending the CDC definition to require specific evidence of at least two clinical signs such as inflammation and localised pain, rather than only a clinician's diagnosis for superficial incisional SSI (Health Protection Agency (HPA) 2004). This had implications for making

comparisons with data captured by other SSI surveillance systems and this subject was explored in my work on the analysis of surveillance data collected by a network of European hospitals (Hospitals in Europe Linked in Infection Control though Surveillance) and which is described in Chapter 4 of this thesis (Wilson *et al* 2007; Appendix 4.1).

2.2.2.2 *Case definitions for bloodstream infection:* When HCAI surveillance systems emerged in the USA in the 1980s, cases based on microorganisms recovered from blood were described as bacteraemias and until 1986, the NNIS system was focused on hospital-wide HCAI surveillance which included surveillance for all cases of bacteremia (Haley *et al* 1985b). Subsequently, the methodology was changed to focus on specific groups of patients at high risk of HCAI, including intensive care units and high-risk nurseries. As a result, more precise definitions for HCAI were developed that focused on bacteraemia associated with central vascular devices that were a major risk of HCAI in these settings and termed primary or catheter-related bloodstream infection (CR-BSI) (Garner *et al* 1988; Emori *et al* 1991). The NNIS system thus excluded BSI from which another source of infection caused by the same organisms had been identified and focused only cases occurring in patients with a central vascular catheter. Other surveillance systems in Europe continued to include all BSI in the surveillance, creating more specific criteria to define those where an intravascular catheter was the source (Hospitals in Europe Link in Infection Control though Surveillance (HELICS) 2004b).

In the UK, BSI surveillance had been established as part of the PHLS laboratory surveillance system, but this was 'microorganism' rather than infection focused and therefore referred to as 'bacteraemia surveillance'. Whilst laboratories would be required to report 'clinically significant' isolates from blood, this was not based on defined criteria (HPA 2008b). Thus whilst the laboratory–based surveillance had the advantage of capturing data on a broad

range of pathogens recovered from blood, in the absence of precise case definitions was less useful for comparisons between individual centres. These issues are demonstrated in my publication on the trends in pathogens causing BSI described in Chapter 5, section 5.2 (Wilson *et al* 2011; Appendix 5.1). The NINNS system in England in part addressed this issue by establishing a surveillance module for hospital-acquired bacteraemia that aimed to monitor trends in hospital-acquired infections (Coello *et al* 2003). This surveillance was based on the application of specific criteria to define both that the infection was acquired in hospital, and whether it was specifically associated with an intravascular device (e.g. same organisms isolated from blood and IV line or symptoms resolve once line is removed). When this was replaced by MESS, surveillance data was collected on all cases of bacteraemia due to MRSA, regardless of whether they were hospital or community acquired and whether they were accompanied by clinical signs of infection. This surveillance used crude criteria for defining whether the MRSA bacteremia was hospital acquired, based on the point during admission the blood was taken and used this distinction to report cases of hospital and community-acquired infection. This method has limitations because many patients admitted to hospital with signs of infection have acquired their bacteremia as a result of a previous intervention or on-going hospital care and should therefore for be classified as hospital rather than community acquired cases. These issues are illustrated in Wilson *et al* 2011 (Appendix 5.2) on the analysis of trends in sources of MRSA bacteraemia presented in Chapter 5, section 5.3.

2.2.3 Case finding methodology for Surgical site infection

The methodology for the surveillance of SSI was developed with advice from a multidisciplinary group of experts in surveillance, infection control and surgery. It centred on the recruitment of patients undergoing an operation in one or more of the defined categories of surgery and active, prospective surveillance during the post-operative inpatient

stay for SSI that met the case definitions. Whilst the NNIS system in the USA required participating hospitals to collect data for minimum one-month periods, we made the decision to extend this to three-month surveillance periods for the NINSS protocols in order that rates could be estimated from a larger dataset at each participating hospital. This reflected a pragmatic balance between improving precision to support valid comparison, the need to enable rapid feedback of results to maximise their impact and the resources available to NHS hospitals to undertake surveillance on a continuous basis (Cooke *et al* 2000; Appendix 1.1).

2.2.3.1 The protocols developed by many national surveillance systems, including NNIS, focus mostly on case definitions of infection and not the methods applied to detect them (Coello *et al* 2001; Gastmeier *et al* 2008). However, the efficacy of methods to detect SSIs have a significant impact on the sensitivity of case finding. Prospective methods will find more cases of infection than retrospective methods that rely on access to accurate documentation (Perl 1997). Similarly, active surveillance where trained, designated staff are responsible for systematic review of patients to identify cases of infection are more sensitive than passive methods where infections are reported by staff who do not have designated responsibility for the surveillance programme (Perl 1997). However, even active methods of surveillance have been demonstrated to have different sensitivities of case finding depending on the data sources queried (Glenister *et al* 1993). Since the primary aim of NINSS was to support valid comparisons of rates, assuring sensitive methods of case finding and minimising the risk of selection and measurement bias were key priorities. The methods chosen for the NINSS SSI surveillance were informed by the work of Glenister *et al* (1993) who found that the most sensitive method of detecting HCAI was using a systematic combination of follow-up of laboratory results, liaison with ward staff and review of case notes. This method was found to detect 76% of HCAI compared to the 36% identified when

surveillance was based on the telephone follow-up of laboratory reports (Glenister *et al* 1993). The implications of variation in case finding methodology on the comparison of rates of SSI are explored in my publications on inter-country comparisons (Wilson *et al* 2007; Appendix 4.1) and using rates of SSI as a performance indicator (Wilson *et al* 2008; Appendix 4.2) in Chapters 4 (sections 4.2 and 4.3).

2.2.3.2 *Post-discharge surveillance:* Infection introduced at the operative site during a surgical procedure can take several days to become apparent and signs of infection may not develop until after the patient has been discharged from hospital. Initially, NINSS surveillance methods were based on inpatient surveillance and although hospitals were able to report SSI detected after discharge, this data capture was voluntary, not based on any defined methods and SSI identified post discharge were not included in the main analysis of rates of SSI. This approach was driven by the requirement for the surveillance to support valid comparisons between hospitals, and whilst specific methods could be proscribed to support consistent case finding among inpatients this was acknowledged to be much more difficult, and resource intensive, once the patient had left the hospital (Manian *et al* 1997, Petherick *et al* 2006). Benchmarking was therefore based only on the proportion of SSI that were detected during the inpatient stay (Cooke *et al* 2000; Appendix 1.1). However, we observed that developments in the delivery of healthcare in the 2000's were associated with a marked decline in length of post-operative stay in hospital for some categories of surgical procedure, notably elective orthopaedic surgery. For example, in prosthetic joint replacement the length of stay had changed from nine days to five days and in large bowel surgery from 12 to eight days (Wilson 2013 a and b; Appendix 2.2 and 2.3). Thus, since this surveillance system was based only on SSI detected during the inpatient stay it would miss a large proportion of cases if the length of stay in hospital declined. Whilst some national surveillance systems included SSI detected by post-discharge surveillance there was limited

evidence for the reliability of the methods (Taylor *et al* 2003; Petherick *et al* 2006; McNeish *et al* 2007). A key consideration in defining methods of PDS for SSISS was the resources it required (Mitt *et al* 2005). We already had evidence that at least 17% of hospitals participating in SISS were not resourcing active inpatient surveillance for SSI, and adding a resource-intensive method of PDS would exacerbate this problem (McDougall *et al* 2007; Appendix 2.4). Therefore, in July 2008, we introduced a defined methodology for post-discharge surveillance that included both voluntary and compulsory elements (see Table 2.1). Only SSI detected on readmission to hospital were included with the inpatient detected SSI for benchmarking as these methods were considered to be feasible for all hospitals to implement and least likely to introduce a major case ascertainment effect. Supplementary rates based on all SSI detected were reported separately (HPA 2009). My work on validating these post-discharge surveillance methods and exploring their efficacy as a surveillance method for SSI following caesarean section delivery was published in Wilson *et al* 2013 (Appendix 4.3) and presented in Chapter 4 (section 4.4).

2.2.4 **Case finding methods for blood stream infection**

Laboratory based surveillance is the cornerstone of BSI surveillance since, by definition, a positive culture of blood is fundamental to the characterisation of the infection. The prospective follow-up of positive blood cultures enables data to be collected on clinical signs and symptoms and sources of infection and to more specifically define the BSI as catheter related. Case-finding systems that only include cases with a positive blood culture miss cases of 'clinical sepsis', where the patient has the signs and symptoms of systemic infection but in the absence of positive blood cultures (Horan *et al* 2008). Systems such as the MESS and NINSS captured data on cases of both primary and secondary BSI.

Table 2.1: Methods of PDS incorporated into SSISS in 2008

1. **Follow-up of patients during the inpatient stay (required)**
From the day after surgery until the patient is discharged from hospital designated staff trained to undertake the surveillance should actively and systematically monitor each patient for signs of infection using the following methods: a) Liaise with ward staff and review medical and nursing records, temperature and treatment charts **at least three times a week** to identify signs and symptoms that may indicate an SSI. b) Regularly review microbiology reports to find any positive surgical site cultures from patients in the study population and check why the cultures were taken and if there are clinical signs of infection.
These infections will be included with the SSI detected during the admission when calculating rates of SSI.
2. **Detecting SSI in patient readmitted to hospital (required)**
Systems must be in place to identify patients included in the surveillance that are subsequently readmitted with SSI. These must meet the criteria for SSI and be reported as 'SSI detected on readmission'. These are likely to include the more severe deep and organ/space SSI.
These infections will be included with the SSI detected during the admission when calculating rates of SSI.
3. **SSI detected by other post discharge follow up (optional)**
SSI may be detected and confirmed as meeting the definition of SSI by the following methods: a) Patients should be encouraged to contact a key person at the hospital if they have concerns about their wound and arrangements made to return to the hospital for the wound to be reviewed and SSI that meet the definitions of SSI reported. Provision of a 'drop in' post operative clinic for patients with problem with their wounds could be considered to enhance the surveillance. b) Staff trained in applying the definitions identify SSI in patients included in the surveillance who return to an outpatient clinic appointment. These SSI are more likely to be detected if active surveillance systems are established, for example designated staff are responsible for actively monitoring patients attending outpatient departments to detect SSI and collect the relevant data. c) Community-based healthcare staff trained in applying the definitions report SSI identified when the patients visits/is visited for treatment.
These surveillance methods will provide more complete data on SSI that occur post-discharge and can be confirmed as meeting the definition of SSI. However, since consistent follow-up and reporting using these methods is unlikely across all participating hospitals, the SSI identified will not be included with those detected in inpatients/readmissions when reporting comparative rates of SSI.
4. **SSI reported by Patient Wound Surveillance Questionnaire (optional)**
To obtain more complete data on SSI that develop post-discharge, patients should be asked to report problems with the healing of their wound 30 days after the operation using one of the following methods: a) On discharge patients should be given a copy of the Wound Surveillance Questionnaire and the details of designated staff to contact if they are readmitted, or an SSI is suspected. The 30th post-op date and patient details must be written on the questionnaire and a pre paid addressed envelope should be provided to encourage return. Patients who do not return the questionnaire should be followed-up by letter or telephone. **If the responses in the questionnaire are indicative of an SSI the patient should be contacted and the symptoms confirmed.** b) Designated staff telephone patients on or soon after their 30th post-operative day and ask them the set of questions on the Wound Surveillance Questionnaire. Patients will need to be informed on discharge that they will be contacted one month following their operation to find out if their wound has healed satisfactorily. *If the patient indicates that a healthcare professional e.g. GP, practice/district nurse, have examined the wound they should be contacted and a diagnosis of SSI confirmed. If an SSI reported by the patient has also been identified and confirmed by another method only the confirmed SSI should be reported to avoid counting SSIs more than once.*
Rates based on patient reported SSI will be analysed separately as it is not possible to determine the type of SSI or confirm that they meet the definition of SSI

2.2.4.1 The NINSS bacteraemia surveillance involved a relatively sensitive method of case finding using a laboratory blood culture result as a trigger, but incorporating active surveillance methods to identify infections that meet the case definition (Coello *et al* 2003; Glenister *et al* 1993). However, the passive surveillance methods used by the voluntary PHLS laboratory system to detect cases of bacteraemia illustrates the problem of incomplete case ascertainment that such systems are vulnerable to. For example, the introduction of mandatory surveillance of MRSA bacteraemia, which employed active surveillance methods, identified 40% more cases that the corresponding voluntary system (Pearson 2009). Therefore, in passive surveillance systems, changes in trends of cases may are more complex to interpret since they may reflect changes in case ascertainment rather than true changes in number events. This is discussed in relation to the trend analyses of bacteraemia that forms part of this thesis and are presented in Wilson *et al* 2011 (Appendix 5.1) in Chapter 5; sections 5.2 and 5.3.

2.2.5 Risk factors for SSI

The risk of a patient developing an infection of the tissues involved in an operative procedure depends on a combination of factors but in particular the number of micro-organisms present in or introduced into the operative site during the procedure and the efficacy of the host's immune defences in eliminating any left at the site after the wound is closed (National Collaborating Centre for Women's and Children's Health (NCCWCH) 2008; Mangram *et al* 1999). Variation in these factors among patients undergoing surgery may have a significant effect on the risk of SSI. Methods of adjusting rates of infection for intrinsic variation in the population at risk have therefore been developed to account for this variation and support valid companions between centres or within centres over time (Gaynes *et al* 2001; Emori *et al* 1991). Pathogens that cause SSI may be derived from the patient's own microbial flora on the skin and in the body or from the skin or mucous membranes of operating personnel, or

from the operating room environment (including air), and the instruments and tools used during the procedure (Barrie *et al* 1992, Hoffman *et al* 2002, Mangram *et al* 2009). Occasionally, micro-organisms from a distant infection in the body can establish a SSI by attaching to prosthesis or other implant left in the operative site (David and Vrahas, 2000). Procedures that involve parts of the body with a dense normal flora such as the bowel are associated with the highest risk of SSI as these organisms can remain in exposed tissues where they are able to cause infection. Other tissues, such as bone are sterile and therefore microorganisms are much less likely to contaminate the operative site. A classification system to distinguish risk of SSI associated with the microbial burden encountered in different tissues, together with pre and intra-operative events (such as trauma and presence of infection) was developed by the National Research Council (NRC 1964) in the USA in order to conduct research studies on the use of ultraviolet light to prevent surgical infection. The wound classification system became the standard approach to adjusting for intrinsic risk of SSI in the American NNIS system and other in the early studies on SSI surveillance (Cruse and Foord 1973). However, the wound classification does not take account of patient related factors that might decrease the efficacy of the general immune response (e.g. age, diabetes, immune suppression, malnutrition) and local immune response (e.g. damage to tissue, fluid collection, foreign bodies) (Mangram *et al* 1999; NCCWCH 2008).

2.2.5.1 The NNIS Risk Index: In the SENIC study, logistic regression techniques were used to identify significant independent risk factors for SSI and a combination of four factors likely to reflect intrinsic risk of SSI (wound classification, underlying diagnosis, duration of operation, abdominal surgery) were found to predict the risk of SSI twice as well as the simple wound classification (Haley et al 1985b). Whilst this was an important development, the collection of complex data from patient records was resource intensive and difficult to implement for a routine surveillance system. A subsequent development of this analysis refined the number

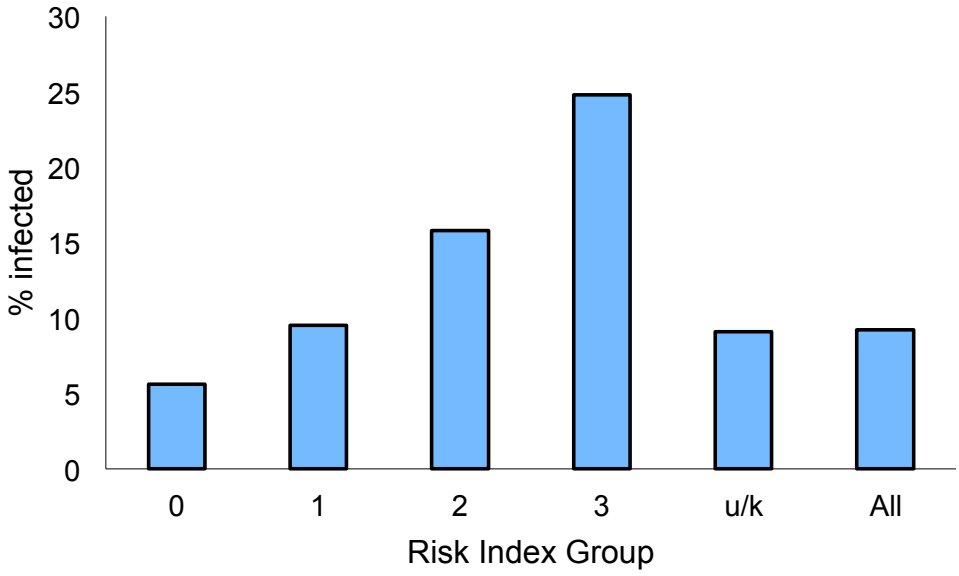
of factors included in this risk index, combining three variables that were routinely collected into a risk index score. This scoring system was found to be a significantly better predictor of SSI risk than the traditional wound classification system and to perform well across a broad range of operative procedures (Culver *et al* 1991). The score ranges from 0 to 3 and is derived from the number of risk factors present among the following:

1) The NRC wound classification of contaminated or dirty denoting microbial contamination in the wound associated with the specific site of surgery (e.g. bowel) or conditions in the surgical site (e.g. pre-existing infection).
2) The pre-operative American Society of Anesthesiologists' classification of physical status is a system used to assess the fitness of patients prior to surgery. A score of three or more denotes patients with a severe systemic disease and is used in the risk index as an indicator of underlying comorbidities that are likely to increase susceptibility to infection.
3) An operation lasting over T hours (time at the 75^{th} percentile of duration of operation for a given type of surgery rounded up to the nearest hour) and is intended to reflect complex surgery through defining unusually long procedures.

This Risk Index became the standard approach to risk adjustment of rates for intrinsic risk of SSI and was adopted by the majority of national surveillance systems. By capturing patient level data on both denominator and numerator the index can be used to determine rates of SSI for specific risk groups, and the effect that variation in distribution of risk groups has on observed differences in rates between centres. Whilst the risk index represents a relatively simple approach to adjustment, it does appear to discriminate differences in risk of SSI (Figure 2.1) and, whilst not explaining all variation in risk, it is a better indicator of risk than wound classification (Culver *et al* 1991, Freidman *et al* 2007).

Figure 2.1: Example of rates of SSI distributed by NNIS Risk Group in large bowel surgery.

Source: Surgical Site Infection Surveillance Service, Health Protection Agency



In the publications on rates of SSI following hip prosthesis and the duration of operation as a predictor of SSI presented in Chapter 3 (section 3.3 and 3.4) I explore the influence of both the components of the NNIS risk index and some of these other risk factors (Ridgeway *et al* 2005; Appendix 3.2, Leong *et al* 2005; Appendix 3.3).

2.2.6 Risk factors for bloodstream infection

As discussed in section 1.2.1 many BSI are a secondary infection related to a focus in another tissue or organ, the risk factors that contribute to their occurrence therefore depend on the risk factors for the source infection. Rojo *et al* used a multivariate model to identify significant independent predictors of hospital-acquired BSI. These were found to include intravascular catheterisation, invasive procedures, malignancy, indwelling devices, stay in ICU or surgical department and length of hospital stay (Rojo *et al* 1999).

2.2.6.1 In the case of MRSA, the epidemiology of BSI in the UK has been strongly influenced by the spread of two epidemic clones (EMRSA15 and EMRSA16) in the 1990s which were carried on the skin of affected patients and able to access devices or other breaches in normal defence mechanisms to cause many different types of infection including primary and secondary BSI (Johnson *et al* 2001; 2005). Prevalence of MRSA carriage and other factors such as underlying illness or invasive procedure are important determinants of the risk of MRSA BSI (O'Grady *et al* 2011). My paper presented in chapter 5 (section 5.3) on trends in sources of MRSA bacteraemia explores these factors in data captured by the MRSA electronic surveillance system (Wilson *et al* 2011; Appendix 5.2).

2.2.6.2 Primary BSI are attributed to an intravascular device which provides a direct route of access into the bloodstream. Any micro-organism can enter the device either along the external surface of the catheter or via the lumen in intravenous fluids or contamination of the internal surfaces of the device (O'Grady *et al* 2011). However, some micro-organisms, notably the common skin commensal *Staphylococcus epidemidis*, are able to form biofilms on the surface of catheters which give them a propensity to a cause BSI (Raad *et al* 1998). The risk of BSI varies according to the type of device, with the greatest risk associated with devices placed into central arteries or veins (Raad *et al* 1998, Rojo *et al* 1999). Since these infections are dependant on the presence of the device, each day that it is in place increases the risk of infection (O'Grady *et al* 2011). The primary approach to risk adjustment in the surveillance of healthcare associated BSI is therefore accounting for the duration of central intravenous devices (see section 3.8.6).

2.3 Data analysis and reporting HCAI surveillance data

The timely analysis and reporting of rates to those able to take action in response to the surveillance data is an essential component of effective surveillance systems (Gaynes *et al*

2001a). However, there are significant differences in approach to data analysis and reporting of data from SSI and BSI data capture systems, driven both by the differences in the structure of the data captured that limits the analyses available, but also by the primary aim of the surveillance systems.

2.3.1 Analysis and reporting of SSI data

Since a key aim of the SSI surveillance system was to provide data that could be used to target infection prevention activity though identifying hospitals with outlying rates of SSI, robust methods of comparing or benchmarking rates of SSI with other participating hospitals were required. However, this presented a number of statistical and practical problems. At the inception of the surveillance scheme, the cumulative incidence was chosen as the measure of SSI risk because it was widely accepted and if expressed as '% operations with SSI' would be readily understood by non-experts. However, difficulties with this metric arise because symptoms of SSI do not necessarily develop immediately after the procedure and the case definitions allow for infections linked to the operation to occur up to 30 days after the procedure (one year if an implant remains at the operative site). Thus, unless patients are actively monitored for SSI for the entire period at which they are at risk of developing SSI, the number of cases detected will depend on the period of active follow-up post-operation. When SSISS was established, the methodology was focused on in-patient surveillance with the option to report SSI detected post-discharge although most hospitals did not establish active systems for post-discharge follow-up. Therefore, for comparison of rates over time or between hospitals the numerator was based only on those SSI detected in inpatients since post-discharge case finding was recognised to be less reliable and not conducted by all hospitals (HPA 2004). It was acknowledged that the inpatient cumulative incidence would not capture the total risk of SSI but since procedures selected for inclusion had several days of postoperative stay the inpatient surveillance would detect a reasonable proportion of SSI.

However, as described in section 2.3.3.2, once the length of post-operative days began to decline in the 2000s we began to explore other approaches to capturing data on SSI after discharge and adjusting rates for length of post-operative stay. My work on developing novel approaches to adjusting for length of follow-up using the incidence density of SSI are presented in Chapter 4, section 4.3 (Wilson *et al* 2008; Appendix 4.2). In the subsequent development of the surveillance methods to include both voluntary and compulsory elements of PDS, we were particularly concerned to minimise the effect of case ascertainment on inter-hospital comparisons. In the study on the efficacy of these PDS methods in detecting SSI following caesarean section I explored their reliability in identifying cases of SSI and the implications of rates based on PDS for the validity of benchmarking hospitals (Wilson *et al* 2013; Appendix 4.3).

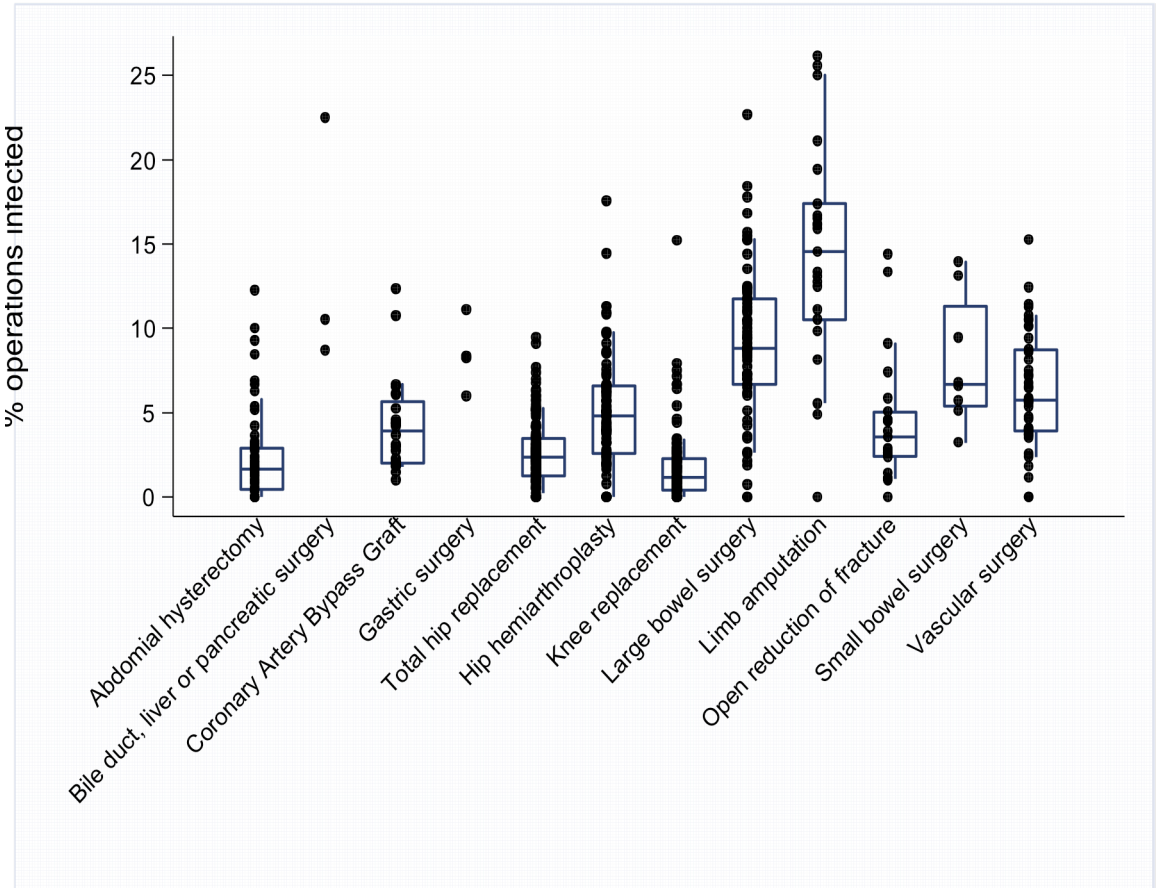
2.3.1.1 Adjusting SSI rates for case-mix: Standardisation is used as a relatively simple approach to comparing a study dataset with a reference or standard dataset whilst accounting for differences in population structure. In SSI surveillance data indirect standardisation is the preferred method since some risk groups have few events. It generates a standardised infection ratio (SIR) by calculating the expected number of SSI in each risk group using the infection rates of the corresponding reference groups, and dividing the number of SSI observed in the surveillance by the number expected. A SIR that is greater than one indicates a higher rate of SSI than the reference rate and if less than one, a lower rate. This approach was used by NNIS in combination with a Fisher's exact test for small samples sizes to test whether the SIR for an individual hospital differs significantly from one which would suggest the infection rate is unusually high or low infection rate (Gaynes *et al* 2001b). Other surveillance systems have recommended more sophisticated methods of adjustment by including additional risk factors in the SIR using a multiple regression model to improve its ability to discriminate risk of SSI (Rioux *et al* 2006; Geubbels *et al* 2006b;

Friedman *et al* 2007). In the English national surveillance system, we considered standardisation as a mechanism for identifying hospitals with outlying rates of SSI but faced the practical problem of incomplete data on risk factors. Many hospitals found it difficult to capture data on the ASA score in particular, as it was not always clearly documented by the anaesthetist. The ASA score was an important risk factor as it was a proxy of underlying comorbidities (Culver *et al* 1991). Thus with this data item missing on approximately a third of records overall and with wide inter-hospital variation in the proportion of records with a missing ASA score, it was not possible to generate a robust SIR. Excluding records with missing ASA scores would have increased the imprecision of the estimated rate, especially where a high proportion of records for a hospital had missing risk factor data. In practice, a separate analysis I undertook on vascular surgery data from 41 hospitals suggested that where rates were adjusted for risk factors, the crude and adjusted rate were very similar in the majority of cases (Wilson 2002). This same finding was also reported by Brant *et al* in an analysis of data from the German SSI surveillance system (Brandt *et al* 2004; Brummer *et al* 2008). This is not surprising as in a health service that is free at the point-of-access such as the NHS, the operations performed and patient case-mix is likely to be broadly similar in most hospitals (Wilson 2002). Therefore the approach we took in SSISS was to stratify the rates of SSI by risk index group, enabling the distribution of risk factors to be considered as a possible factor in explaining high rates of SSI but without calculating an SIR.

2.3.1.2 Identifying outlying rates of SSI: Rather than a simple 'league table' of performance by rate of SSI, we used box and whisker plots as a means of identifying outlying rates of SSI (Wilson *et al* 2008). These placed each hospital rate of SSI in a distribution of all rates within a specific category of surgical procedures and illustrated the rate of infection at the 10^{th}, 25^{th}, 50^{th} and 75^{th} percentiles using the box and whisker (Figure 2.2). Whilst this approach had the advantage of being relatively simple and easily understood, it was based on crude,

unadjusted rates that meant that high rates could have been explained by case mix. A second problem when comparing rates of SSI between hospitals is that many of those contributing data performed fewer than 100 operations in a given category, even in the required three-month surveillance period. This meant that the precision of the rate estimated from the sample of procedures would vary with the number of procedures included, and that the confidence intervals within which the true rate could lie would be wide where the number of procedures was small.

Figure 2.2: Example of a box and whisker plot used to identify hospitals with outlying rates of SSI in each category of surgical procedure. *Source: Health Protection Agency, 2006*



In order to avoid identifying hospitals with highly imprecise rates of SSI as outliers we only included their rate if based on more than 50 operations and used rates above the 90th

percentile as the marker for an unusually high rate that required investigation. Hospitals that fell into this part of the distribution were advised of their high rate and recommended to investigate possible underlying factors. The subsequent work I undertook to develop a method of identifying outliers that also took account of the precision of the estimate is described in Chapter 4 of this thesis (Wilson *et al* 2008; Appendix 4.2).

2.3.2 Analysis of data on bloodstream infections

The approach to calculating and comparing rates of bloodstream infection is dependant of the population included in surveillance and the criteria used to define cases of infection. In the PHLS/HPA laboratory-based surveillance of bacteraemia rates are commonly reported by 100 000 population, since the infections reported by this routine surveillance system do not discriminate those acquired as a result of healthcare and cases are not linked to specific hospitals (Anon 2001). Other surveillance systems that distinguish cases of BSI acquired in hospital use a denominator that reflects this population, for example the number of patients admitted or the total *number* of 'patient-days' during a defined time period, to respectively calculate a cumulative incidence or incidence density (Horan *et al* 1986; Seutens *et al* 2007). The NINNS hospital-acquired bacteraemia surveillance in the UK, derived the denominator for patients at risk of bacteraemia from data supplied by each hospital on admissions and discharges for patients during the relevant surveillance period (Coello *et al* 2003). In the subsequent MESS system, a less resource intensive approach was taken with the denominator estimated for a hospital population by using routinely collected data on 'occupied bed-days' (KH03). These were aggregated to provide the denominator for the relevant surveillance reporting period, although delay in reporting meant that for practical purposes the denominator was estimated from historic periods, with rates expressed as the number of cases by 10 000 bed days. This KH03 data is part of the central return of data that all NHS hospitals are required to report and reflects the number of beds that have been

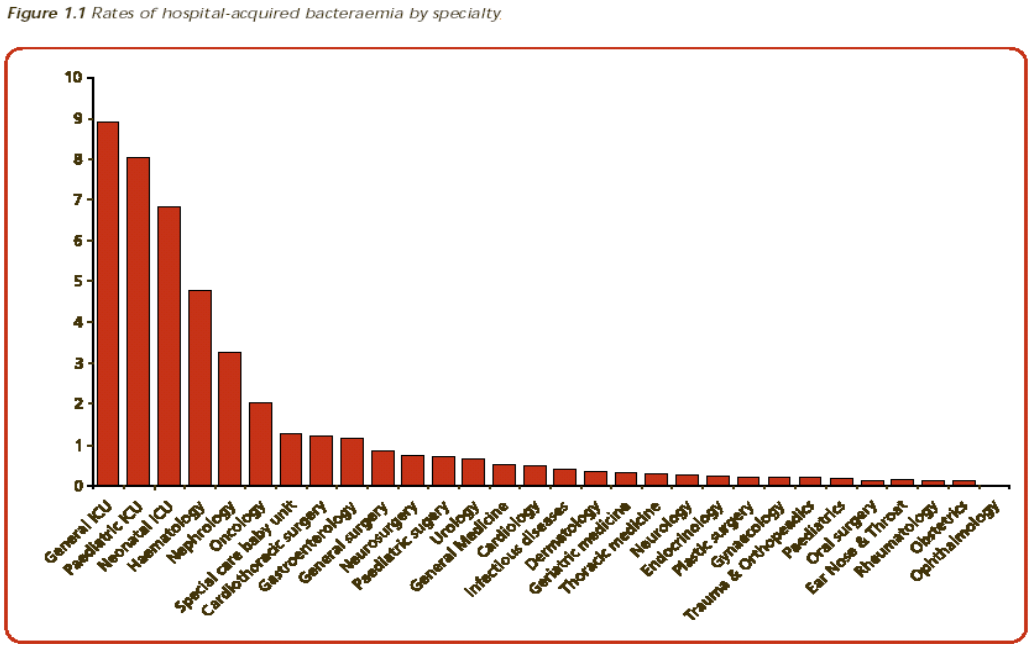
occupied overnight by a patient during each quarterly period (HPA 2008b). This measure is more accurate than the number of beds available in the hospital as it reflects the number of days that beds that are occupied by a patient and hence exposed to a risk of BSI. The metric used in the MESS system to calculate the rate of MRSA bacteraemia is as follows:

$$\frac{\textit{No. bacteraemia in a defined hospital population}}{\textit{No. hospital bed-days}} \quad \textit{X 1000}$$

2.3.2.1 Risk adjustment of BSI rates: An aggregate denominator such as KH03 cannot be used to stratify the risk of infection by different patient groups as they may have very different intrinsic risk of BSI. This requires more detailed data on the number of patient days in a specific speciality of care e.g. medicine or surgery (Figure 2.3). This figure illustrates that the risk of BSI is greatest in intensive care units and many national surveillance systems have therefore focussed efforts on these settings (NNIS 2004; Seutens 2007). From 1990, NNIS defined two intensive care settings for surveillance: intensive care units and high-risk nurseries (neonatal intensive care unit) (Emori *et al* 1991; Emori and Gaynes 1993). In both settings, the surveillance of BSIs was based only on primary BSIs where a central venous catheter (CVC) has been attributed as the source of infection.

2.3.2.2 These catheter-related BSI (CR-BSI) represent a significant burden of HCAI and associated morbidity and mortality in ICUs and considered amenable to prevention through improved infection control practice (Jarvis 1996; Pronovost *et al* 2006; Loveday *et al* 2014; O'Grady *et al* 2011). Since only patients with a CVC could acquire a CR-BSI and the risk of infection increases for each day the catheter is in place, this should be reflected in the denominator used to calculate the risk of infection (Coello *et al* 2003, Suetens *et al* 2007).

Figure 2.3: Rate of hospital-acquired bacteraemia by speciality



Source: Public Health Laboratory Service 2003.

By capturing data on the total number of days with the device for all patients in the period under surveillance, device-days can be incorporated into the denominator and used to adjust rates for the length of exposure to a CVC, generally presented as a rate of:

$$\text{BSI/1000 device-days} = \frac{\textit{No. CR-BSI}}{\textit{No. CVC-days}} \textit{ X 1000}$$

However, in practice capturing data on device-days is laborious and whilst device-days could be captured for intensive care units in the NINSS bacteraemia surveillance, currently there are no national surveillance systems in England that report rate of BSI by device-days.

2.4 Development and evaluation of the national SSI surveillance systems

The methodology and data capture systems for 12 categories of surgical procedure were tested in a pilot study conducted over an 8-week period in 1997 in 35 hospitals. Amendments were subsequently made to facilitate reporting of SSI detected after discharge. Although these SSI were not included in the calculation of comparative rates of SSI because post-discharge surveillance was considered too resource intensive to mandate as part of the surveillance methodology, they did provide hospitals with local data on post-discharge infections and ultimately provided the mechanism to support more fundamental changes to the reporting system in 2008 when post-discharge surveillance was incorporated into the methodology (see Chapter 4, section 4.4). A survey of users of the SSI surveillance system that I conducted three years later demonstrated the importance of comparative rates to user of the service, with 87% of the 113 hospitals that responded to the survey indicating that standard surveillance methods and comparisons with national data as key reasons for their participation (Wilson *et al* 2002**;** Appendix 2.5). The survey also provided evidence that the surveillance contributed to increasing awareness of infection control issues with 57% of hospitals reporting taking action in response to the results of surveillance. In addition, it also gave an indication of the lack of skills within infection control teams in terms of interpreting and using surveillance data, with the majority (87%) of respondents indicating that they would like more training. This was perhaps a reflection of the historic lack of emphasis on surveillance within infection control programmes in the UK (Glenister *et al* 1993).

2.5 Conclusions to chapter

The methodologies that I have outlined in this chapter underpin my research related to surveillance of HCAI and further evidenced in the following chapters. My research begins with analyses of SSI surveillance, which because it captured a full dataset on both the numerator and denominator, can be used to compare risk factors and outcomes in those

patients that develop SSI and those that do not. In Chapter 3, I present three publications that focus on the analysis of this SSI data; the first examines the effect of SSI on length of post-operative stay and mortality (Coello *et al* 2005; Appendix 3.1), the second explores the risk factors that predicted the risk of SSI in hip replacement surgery (Ridgeway *et al* 2005; Appendix 3.2) and the third evaluated the relationship between risk of SSI and duration of operation (Leong et al 2006; Appendix 3.3). This research has been influential in both defining the importance of SSI as an infection and in developing the methods of capturing and analysing surveillance data to ensure that rates could be appropriately risk-adjusted. This experience led to my subsequent research, presented In Chapter 4, which explored the methodology required to support robust comparison of rates of SSI both between countries (Wilson *et al* 2007; Appendix 4.1) and between hospitals in England (Wilson *et al* 2008; Appendix 4.2). The introduction of standard methods of post-discharge surveillance to the SSISS methodology in 2008, led me to evaluate the impact of post-discharge surveillance on rates of SSI and their implication for benchmarking (Wilson *et al* 2013; Appendix 4.3). Finally, I applied my knowledge of both surveillance and HCAI to the analysis and interpretation of data on bloodstream infections. The two publications in Chapter 5 illustrate how I identified emerging trends in pathogens causing bloodstream infection at a population level and explored potential causal factors for MRSA infections (Wilson *et al* 2011; Appendix 5.1, Wilson *et al* 2011; Appendix 5.2).

CHAPTER 3

Investigation of the impact of surgical site infection and the influence of risk factors on rates

3.1 Introduction

As demonstrated in the overview of healthcare associated infection (HCAI) surveillance in Chapter 2, the approach adopted by the Nosocomial Infection National Surveillance System (NINSS) for the surveillance of surgical site infection (SSI) was based on capturing a core set of data for all patients who undergo a relevant operation and then following them prospectively to identify those that develop SSI. These methods provide the opportunity to use cohort study designs to explore the relationship between risk factors (exposures) in the population of patients undergoing the operation and the occurrence of disease, in this case SSI. Similarly, the large national datasets with demographic data captured on all patients makes it possible to undertake novel analyses of both the risk of SSI and the adverse consequences associated with it. These analyses are important in order to target and support preventative strategies, but also to ensure that the methods used for surveillance provide comparable data and take account of risk factors that might explain variation between hospitals (Gaynes *et al* 2001b).

This chapter presents three papers on different aspects of risks and risk factors associated with SSI that were published between 2005 and 2007. Section 3.2 describes the investigation of the costs of healthcare and mortality associated with SSI (Coello *et al* 2005; Appendix 3.1). This work built on an earlier Public Health Laboratory Service study, which had defined the overall costs of healthcare associated infection (Plowman *et al* 1999), and was the first time that such a detailed evaluation of the specific impact of SSI had been published. Section 3.3 explored risk factors for SSI following hip

prosthesis surgery (Ridgeway *et al* 2005; Appendix 3.2). This work was important to inform both prevention strategies and the risk adjustment methodology for data captured by surveillance. Section 3.4 continues with this theme of risk factor analysis by using a novel approach to explore the relationship between the duration of operation and the risk of SSI (Leong *et al* 2007; Appendix 3.3).

3.2 Published Work 1: The adverse impact of surgical site infections

Coello, R., Charlett, A., Wilson, J., Ward, V., Pearson, A., Boriello, P. (2005) Adverse impact of surgical site infections in English hospitals. *Journal Hospital Infection.* **60**: 93-103). (Appendix 3.1)

3.2.1 Background

HCAI are considered to be associated with considerable financial costs to healthcare services in particular and society in general, and risks to the patient in terms of disability, morbidity and mortality (Perencevich *et al* 2007). SENIC provided the initial data on the potential for prevention of HCAI (Haley *et al* 1985a) and a subsequent review by Harbarth *et al* (2003) suggested that up to 70% of HCAI could be preventable, although the potential for reduction was dependent on the type of infection and the baseline rate. However, infection prevention activities also consume resources especially if they include broad-based surveillance programmes that require considerable effort to capture, analyse and report data (Reilly *et al* 2001, Jarvis 1996, Glenister *et al* 1993) or require long-term education and monitoring systems (Halton *et al* 2010). Valid estimates of the costs of HCAI are critical to understanding the cost-benefit of infection control activity and encouraging investment in effective infection prevention strategies (Perencevich *et al* 2007; Graves and McGowan 2008). Although mortality due to HCAI is not directly associated with hospital costs, placing a value on human life is also an important aspect of properly costing the adverse outcome and evaluating the benefit of prevention strategies, regardless of who incurs the cost or receives the benefit (Graves *et al* 2007). If mortality is not considered then the full economic effect of an infection or intervention will be underestimated. This paper describes the analysis of data captured for the Surgical Site Infection Surveillance System (SSISS) in England between 1997 and 2001 that aimed to measure the adverse effects of SSI in terms of both its effect on mortality and additional costs associated with treatment.

3.2.2. Conceptual and methodological development

The main cost associated with an HCAI is additional stay in hospital (Graves *et al* 2010). Although up to 85% of these costs are fixed because they reflect buildings, equipment, administrative systems and salaried staff that cannot be eliminated in the short–term, in economic terms the additional bed-days associated with HCAI reflect 'opportunity costs' because they could be used to treat more patients (Graves *et al* 2010; Perencevich *et al* 2007). Thus, key to defining the costs of HCAI, and hence the cost-benefit of potential prevention strategies, is the number of additional bed days directly attributable to an HCAI and the economic value of those bed-days (Graves *et al* 2010).

3.2.2.1 ***Approaches to measuring costs and morbidity****:* Measuring morbidity or costs associated with HCAI is associated has a number of methodological problems and must take account of other factors that influence hospital stay such as the underlying illness and other comorbidities. There are two main approaches to estimating extra length of hospital stay and costs or mortality/morbidity due to HCAI. Firstly, physician assessment – where a doctor reviews cases to distinguish resources used in the treatment of the primary diagnosis from those used to treat HCAI (Haley *et al* 1980c; Fukuda *et al* 2011). Secondly, matched comparisons of cohorts or cases, where patients who acquire an HCAI are matched to patients with similar attributes but who do not develop an HCAI to determine differences in outcome or resource use. The second approach is much simpler and less resource intensive, but suffers from several potential biases which are difficult to address. In particular, patients who stay in hospital for longer tend to have underlying comorbidities that can explain both increased morbidity and prolonged stay but at the same time also increase the risk of HCAI. Matching therefore needs to include these variables if confounding is to be avoided (Graves 2007). However, attempting to eliminate this bias by increasing the number of variables used to match the cases and controls is likely to result in more cases being eliminated and they no longer become representative of patients with HCAI. A better approach is to control for such endogenous variable confounding in the analysis than in the study design using statistical regression analysis with

a cohort of patients to avoid selection bias completely and reduce the risk of bias from comorbidities (Graves *et al* 2007, Graves *et al* 2010). In our analysis of costs of SSI we had access to data on a cohort of patients from hospitals contributing data to the SSI surveillance system, some of who developed SSI, including basic operation and patient risk factors for all procedures. Our approach was therefore to measure costs associated with SSI by determining the difference in length of stay in hospital after the procedure, and control for the confounding effects of severity of illness on length of stay and SSI though by using a logistic regression analysis (see section 2.1.1). Since the surveillance system did not directly capture data on costs we derived the mean costs of a hospital-day from the study on the socio-economic burden of hospital-acquired infection (Plowman *et al* 1999). This study had captured data on 4000 patients admitted to selected specialties of a district general hospital, identified those that developed infection and recorded the daily resource use for both infected and uninfected patients. Linear regression modeling was then used to estimate how much resource use could be explained by hospital acquired infections by controlling for age, sex, admission specialty, diagnosis, number of comorbidities and admission type (Plowman *et al* 2001). This data was contemporary and based on costs at an NHS hospital in England and therefore could be reasonably applied to our cost estimations for SSI.

3.2.3 Summary of main methods and findings

By 2004, the national SSI surveillance system had been in operation for 5 years and had accumulated a large dataset. Data on more than 67 000 operations and 2832 SSI from nine categories of surgery submitted by 140 hospitals participating in the SSI surveillance were included the analysis of the impact of SSI. We excluded categories where the number of procedures were small and hospitals with data on less than 11 procedures. The first part of the analysis presented in this paper described the rate of SSI in each of the categories of surgery. This was an important milestone since it represented the first time data on the risk of SSI associated with a range of surgery conducted in England had been published. It demonstrated the wide variation in risk of SSI between categories as

would be expected due to differences in intrinsic risk associated with different types of procedure, largely influenced by variation in microbial contamination encountered at the operative site (National Collaborating Centre for Women's and Children Health (NCCWCH) 2008; Mangram *et al* 1999). We also demonstrated a significant linear trend in incidence of SSI with increasing risk index group in all categories apart from knee prosthesis, again for the first time in an English surveillance dataset. This endorsed the value of the risk index as a predictor of risk of SSI, an important step in the context of scepticism among surgeons as to the validly of such risk adjustment especially since one of the parameters – ASA score – was a subjective measurement and may have been prone to variation in how it was applied (Aronson *et al* 2003).

3.2.3.1 ***Estimating the length of hospital stay****:* Key variables captured by the surveillance were the date and reason for the surveillance being discontinued (discharge, transfer or death). For categories of surgery without implants (non-human material left permanently in the operative site) the surveillance could be undertaken for a maximum of 30 days, but this period could be extended to 120 days where the surgery involved an implant (Horan *et al* 1992; 1997). The length of hospital stay from the date of operation to the date of discharge or death was used to determine attributable cost associated with SSI and estimates of mortality were based on patients who died during the in-patient follow-up period. The analysis showed that the crude LOS was longer for patients with SSI in all categories (ranging from 9 to 51 days). However, it was necessary to adjust these values for bias associated with missing follow-up data and the potential confounding effect of severity of illness on LOS.

a) *Missing follow-up data*: Since surveillance was only required during the inpatient stay the majority of patients would be discharged before the end of the surveillance period. However, if patients remained in hospital beyond 30 days then follow-up would be discontinued and therefore data on length of stay and outcome would be missing. The proportion of records affected by this missing

data varied between categories, from 30.4% in limb amputation to 0.3% in abdominal hysterectomy, reflecting differences in the care requirements and demographics of patients undergoing these procedures. In order to include these patients in the analysis our approach was to use a censored normal regression model, which adjusted for the bias that might occur due to this missing data (Schnedler *et al* 2005). The length of stay (LOS) was estimated for all SSI and also for superficial and deep/organ-space infections. The dependent variable included in the regression was the natural log of number of days of post-operative stay, with the SSI and type of SSI (superficial, deep or organ/space) as explanatory variables. The model then estimated the mean LOS for patients with and without SSI. We used the geometric mean rather than the arithmetic mean because this indicates the central tendency of the distribution and therefore it provides a more robust estimate of the mean where there is a wide range in values as was the case for LOS (Bland 2000 p.113).

b) Adjusting length of stay for confounding variables: In order to adjust for the confounding between LOS and underlying comorbidities the following indicators of case-mix captured in the surveillance dataset were used as additional explanatory variables in the model. These were:

- Age
- Sex
- Pre-operative stay in hospital (which is indicative of more severe underlying illness)
- Risk Index factors (ASA score, wound classification, duration of operation)
- Elective/emergency surgery
- Multiple procedures through the same incision (indicative of multiple underlying problems and complexity of surgery)
- Implant present
- Operations due to trauma.

This adjustment reduced the LOS attributable to SSI from between three days after abdominal

hysterectomy to 21 days following limb amputation. However, apart from two categories (abdominal hysterectomy and large bowel surgery) the adjusted LOS was still double that of patients with SSI (see Table 1). The primary analysis included all SSI types but since it could be expected that patients with superficial SSI would not require significant additional hospital treatment we also explored the effect of the more severe (deep and organ/space) infections on LOS. This demonstrated that they had longer adjusted LOS than superficial SSI for all categories except limb amputation, although since the severe SSI accounted for only one third of all SSI, the confidence intervals were fairly wide. For hip and knee prosthesis and abdominal hysterectomy the LOS associated with deep and organ/space SSI was between 2.4 and 2.6 times longer than patients who did not develop SSI.

3.2.3.2 ***Estimating costs****:* We used the costs determined by Plowman *et al* to estimate the costs for this analysis (Plowman *et al* 2001). This study provided estimates of the average cost to a hospital of an SSI and the average adjusted LOS attributable to SSI. For the purposes of our analysis we divided the Plowman estimates of the number of extra days of LOS attributable to SSI by the mean hospital costs to generate a value for a bed-day of £224.50. We then revised this figure for inflation during the intervening years based on the Annual Health and Social Care Inflation values, to £290.60 per extra bed-day spent in hospital due to SSI. This estimated daily cost was then applied to the additional days LOS for SSI for each category of surgery and type of SSI generated in the regression model described in 3.2.3.1. We found that for all SSI these costs ranged from £959 for abdominal hysterectomy to £6103 for limb amputation; for deep and organ/space alone the costs ranged from £1947 for abdominal hysterectomy to £6422 for coronary artery bypass graft (Table 3.1).

Table 3.1: Post-operative mean* length of stay (LOS) for patients with and without surgical site infection (SSI), and adjusted[†] extra LOS and cost[‡] of hospitalisation for patient with SSI by surgical procedure.

Surgical procedure	Mean LOS for patients without SSI (days)	Extra LOS (95% CI) for patients with SSI (days)	Extra cost attributable to each SSI (£)
Limb amputation	13.2	21.0 (13.2-31.1)	6103
Small bowel surgery	11.5	13.2 (6.5-22.4)	3836
Vascular surgery	7.9	12.2 (9.8-15.0)	3545
Large bowel surgery	11.3	9.4 (8.1-10.8)	2732
Coronary artery bypass graft	7.4	13.4 (12.4-14.6)	3894
Hip prosthesis	11.1	11.5 (10.3-12.8)	3342
Knee prosthesis	10.3	10.9 (9.0-13.0)	3168
Open reduction of long bone fracture	9.6	9.9 (6.1-14.6)	2877
Abdominal hysterectomy	5.1	3.3 (2.7-4.0)	959

*Geometric mean. [†]Adjusted by age, sex, pre-operative length of hospital stay, American Society of Anesthesiology score, wound class, duration of operation, elective/emergency surgery, multiple procedures through the same incision, implants and operation due to trauma. [‡]A cost of £290.60 per bed-day derived from Plowman *et al.*[16]

3.2.3.3 ***Estimating mortality****:* The estimated risk of death was based on whether the patient was alive when follow-up was discontinued. A multivariable logistic regression analysis was then used to estimate the odds ratio of death for patients with or without SSI, adjusted for the same explanatory variables used in the LOS analysis to control for confounding between comorbidities and SSI that might affect mortality. A logistic regression model is appropriate for use with dichotomous outcome variable (mortality) with SSI and the other risk factors as predictor variables. The magnitude of the effect of SSI as a predictor of death (adjusted for the other factors) was expressed as an odds ratio with associated confidence intervals. This approach would only provide a minimum estimate of mortality as the surveillance did not capture data on mortality after discharge or the end of follow-up. For all types of SSI, this analysis found that the crude mortality was higher for patients with SSI in all categories but after controlling for the other factors that may have influenced mortality, there was only a statistically significant association between SSI and mortality in hip prosthesis with an odds ratio of 1.8 (95%CI 1.3-2.7). However, for the deep and organ/space SSI, the association between mortality and SSI was statistically significant in three categories, with the odds of death varying from 6.8 (95%CI 3.0-15.4) in vascular surgery to 1.8 in large bowel surgery (95%CI 1.1-3.2) and 2.5 in hip prosthesis (95%CI 1.3-4.5). In some categories the small number of these more severe SSI meant that although the OR was high the confidence intervals were wide and therefore the

estimates of increased odds of death associated with the SSIs may reflect chance variation rather than a true effect.

3.2.4 Conclusions

The variables used for risk adjustment in this analysis were captured routinely as part of the surveillance dataset. This magnitude of data would be difficult and expensive to collect as part of a research study hence it provided an important opportunity to explore the impact of SSI across a range of types of surgery that would not be possible in a single centre study. However, whilst this dataset had the advantage of including a sufficiently large number of records to support measuring the independent effect of predictors, unlike research-based datasets it did not include comprehensive data on potential risk factors. Thus, whilst we were able to adjust estimates of effect of SSI on length of stay and mortality using key variables that reflect underlying illness (ASA score, preoperative LOS, gender), susceptibility to SSI (risk index factors, age, operation data) and risk of mortality (ASA score, age, gender), this adjustment may not have included other important confounders. In particular the ASA score, whilst an apparently good predictor of risk of SSI, provides a relatively crude measure on a 5-point scale of underlying illness and has been associated with poor inter-rater reliability (Mak *et al* 2002; Aronson *et al* 2003;). If ASA score only partly measured the severity of underlying illness and its effect on LOS and mortality, then the adjustment could inflate the estimates of effect.

3.2.4.1 A particular problem with the SSI surveillance data captured for the English surveillance system was the lack of data on SSI that occurred after discharge from hospital. Thus whilst we were able to include variables captured in the dataset in the regression model to adjust for confounding between LOS, mortality and SSI we were not able to include the effect of SSI that occurred after discharge. Indeed our estimates may have been biased by the increased detection of SSI in those patients with extended LOS. Since follow-up was not continued after discharge we were also not

able to consider the costs and mortality associated with subsequent admissions, treatments or operations or the costs of treatment in primary care or of death after discharge (Plowman *et al* 2001). However, one advantage of conducting this study on data captured in the late 1990s to early 2000s was that the length of post-operative stay in England at this time was relatively long thus minimizing, although probably not eliminating, this bias (Wilson 2013). Other studies based on a matched cases design, have measured the longer-term costs related to readmission and long-term treatment and suggest that inpatient costs may significantly underestimate true costs (Whitehouse *et al* 2002; Kirkland *et al* 1999). Whitehouse *et al* (2002) estimated that an SSI after orthopaedic surgery increased the costs by four times as a result of repeat hospitalisation and operations. Kirkland et al (1999) found that an SSI following general and orthopaedic surgery increased the length of hospital stay by 6.5 days, had a significant impact on the risk of death, ICU admission and readmission and their associated costs. Thus our analysis probably represented a significant underestimate of the costs and mortality associated with SSI.

3.2.4.3 ***My contribution to this research***

This paper represented the first major analysis of data captured by the national SSI surveillance system in which I played a major part in the design of the underpinning dataset and data capture systems, and in validating and quality assuring data. I used this expert knowledge to inform the development of the methods for this analysis and subsequently for the interpretation of the results, particularly in the context of limitations of the data and comparison of rates with other surveillance systems.

3.2.5 Contribution of this study to contemporary knowledge

This study represented the first analysis and publication of data on the incidence of SSI nine categories of surgery in the UK based on a large set of procedures from 140 hospitals. It provided indispensable data on the impact of SSI for hospitals to use in both explaining the importance of

measures to prevent SSI and in justifying their costs and the resources required to conduct surveillance. It has subsequently been cited by more than 200 other authors and the risk adjusted estimates of adverse effects of SSI have been used by other studies to calculate the costs of SSI or estimate the efficacy of prevention measures (Brandt *et al* 2006; NCCWCH 2008; Pinkney *et al* 2011; Boltz *et al* 2011; Myles *et al* 2011; Andersson *et al* 2012). The estimates were also used in the National Institute for Health and Care Excellence (NICE) guideline on the prevention of SSI as the data informing all the economic analyses of cost effectiveness (NCCWCH 2008).

3.2.5.1 The SSI surveillance system that we established in England and on which these analyses were based, was one of the largest outside the USA since the National Nosocomial Infection Surveillance (NNIS) system in the USA was limited to around 300 hospitals at this time. Although our surveillance system was based on that used by NNIS, the differences in case definitions and the defined case-finding methodology may have contributed to the higher rates of SSI that we found in the English dataset compared to the NNIS data (NNIS 2002). We found the English rates to be similar to those reported by the Dutch national surveillance system. However, a subsequent analysis that I undertook a few years later (see section 4.2) illustrated the problems of making inter-country comparisons because of the impact of differences in protocol and healthcare delivery systems, in particular the interpretation of case definition and intensity of post-discharge surveillance (Geubbels *et al* 2000; Wilson *et al* 2007, Appendix 4.1). The evaluation of the risk index was also important in terms of confirming its ability, previously only validated with US data, to predict the risk of SSI across most surgical categories in the English data and provide a statically significant measure of increasing trend. This supported the continued use of the risk index as the method of stratification for risk of SSI in the NINNS surveillance system.

3.2.5.2 The analysis of LOS and associated costs that we published in this study was ground-breaking because at that time the few studies that had investigated the costs and mortality

associated with SSI were small scale and used a matched design with the attendant biases described previously (section 3.2.2.1) (Boyce *et al* 1990; Coello *et al* 1993; Hollenbeak *et al* 2002; Kirkland *et al* 1999; 2000; Reilly *et al* 2001). Two studies, conducted in the USA by Hollenbeak and colleagues on cardiac and liver transplant surgery, applied linear regression methods to determine attributable costs of SSI, although these were also small scale and focused on hospital resource utilisation (Hollenbeak *et al* 2000; 2001). An analysis of mortality data captured by the French national SSI surveillance system (INCISCO) did not specifically explore the association between SSI and death in different types of surgery, but found a case fatality rate associated with SSI of 4.5% and estimated that 38% of the cases were directly attributable to the SSI (Astagneau *et al 2001)*. Plowman *et al* (2001) was a landmark study because it captured data in the entire hospital, prospectively and used logistic regression analysis to adjust for confounding between comorbidities and outcome. Whilst Plowman *et al* identified that overall an SSI nearly doubled the length of hospital stay and was associated with a cost of £1594, the numbers of these HCAI included in the analysis was too small (38) to derive procedure-based estimates (Plowman *et al* 2001). Thus the estimates we made in this analysis identified for the first time the effect of SSI on length of hospital stay and mortality using a methodology that adjusted for confounding factors. In addition, the large national dataset based on four years of data from 140 hospitals enabled us to calculate the adjusted risk associated with SSI for nine categories. The accuracy of the estimates has been supported by a recent review which confirmed our findings that an SSI doubles the length of post-operative stay (Broax *et al* 2009).

3.2.5.3 The costs of HCAI were a topical issue at this time, and featured in the second National Audit Office report on progress in relation to the prevention of HCAI that was published in July 2004 (National Audit Office (NAO) 2004). Whilst participation in the NINIS SSI surveillance had increased steadily in the four years since its inception, it was recognised to be resource intensive as, unlike other types of surveillance, it required active case finding though ward visits and assessment of clinical symptoms rather than review of laboratory data (Wilson *et al* 2002; **Appendix 2.5**). Thus this

study provided clear evidence based on a robust methodology of the costs and adverse effects of SSI that could be used by hospitals and other healthcare providers to evaluate and justify the cost benefits of strategies to reduce the risk of SSI.

3.2.6 Subsequent research contributions to the field

Since the publication of Coello *et al* 2005 there have been further studies reporting adverse effects associated with SSI. Studies on mortality have tended to focus on the effect of HCAI as a whole rather than SSI specifically (Fabbro-Peray *et al* 2007, Roberts *et al* 2010). One study by Pollard *et al* (2006) in a matched case control study identified that patients who acquired a deep SSI after proximal femoral fracture repair had significantly longer LOS and were 4.5 times less likely to survive to discharge (p=0.002) and were three times less likely to return their original place of residence (p=0.05). This emphasised that our analysis underestimated the effect of SSI on both LOS and mortality since we were unable to measure their effect after discharge from hospital.

3.2.6.1 Unlike our analysis, most studies which have evaluated the costs of SSI have employed a matched case control design. Monge Jodra *et al* (2006) reported that the median excess length of post-operative stay associated with SSI following hip replacement was 32 days (double that of matched patients without SSI; p<0.001). Although they did not attribute costs to this additional hospital stay, the excess attributable to SSI was the same magnitude as we had identified. Weber *et al* used a nested, matched, case control design on data captured at a European University hospital to determine the additional costs attributable to 168 cases of SSI in general vascular and trauma surgery (Weber *et al* 2008). Again, this study confirmed the findings in our study that SSI more than doubled the length of post-operative hospital stay (29 vs 12 days; p<0.001). Weber *et al* conducted a more sophisticated cost analysis than in our study by using data derived from the hospital internal cost and activity accounting database. This enabled them to include costs associated with all treatments, unit time of attending personnel and hospital overheads unlike the approach of applying

estimated costs that our study had employed. Their estimates suggested that SSIs increased costs by 61% (121% for organ/space SSI) although did not account for any additional costs incurred after discharge. This approach of measuring costs as a percentage increase has the advantage of facilitating comparisons between countries and institutions, regardless of variation in currency or base costs (Weber *et al* 2008). Another approach described by de Lissovoy *et al* used discharge diagnosis codes to determine increased length of hospital stay attributed to SSI, adjusted this using a 'propensity to develop SSI score' and estimated that SSI increased the mean length of stay by 9.7 days (de Lissovoy *et al* 2009). The increase in mean cost of treatment associated with SSI of $20,842 was higher than in Coello *et al*, but this may reflect the approach to billing of costs in the US healthcare system.

3.2.6.2 As discussed previously (section 2.2.3.2), length of stay in hospital has declined during the last decade and this is likely to transfer some of the costs of SSI to primary care settings (Plowman *et al* 2001). Only a few studies have explored costs incurred post-discharge (Graves *et al* 2008, Tanner *et al* 2009). Tanner *et al* reported a cost of £10 523 associated with the treatment of SSI after colorectal surgery, 15% of which were met by primary care (Tanner *et al* 2009). Graves *et al* (2008) used a model to estimate the distribution of economic costs between in-hospital and post discharge. They suggested that 67% of costs occurred in the hospital phase if 'losses to production' after the patient had been discharged were excluded from the total costs but 31% if these were included. These 'losses to production' reflect the amount of time that patients would be unable to work (or contribute to society in other ways) because of impairment of their health due to the infection (Plowman *et al* 2001). Others have studied the impact of advances in medical technology and have evaluated the effect of minimally invasive techniques. Whilst the minimally invasive approach was not found to significantly reduce the risk of SSI in lumbar fusion it was associated with significant cost reductions ($756 vs $1140; p = 0.03) (McGirt *et al* 2011). In colorectal surgery, a laprascopic approach was found to significantly reduce the rate of SSI (9% minimally invasive vs 16% open

surgery; p = 0.001) after accounting for the greater age and ASA score of patients undergoing open surgery, but this study did not evaluate costs (Kiran *et al* 2010). Dobson *et al* (2011) identified reduced costs associated with laprascopic colon surgery due to fewer dressing changes, reduction in use of wound VAC systems and contact with healthcare professionals. This is an important area of development given the widespread emergence of this technology across many types of surgery and the associated reductions in the costs associated with surgery and days spent in hospital. However, at the time of our analysis, minimally invasive surgery was confined to a few procedures in English hospitals and average length of stays for elective surgery were at least seven days (Health Protection Agency (HPA) 2006).

3.2.6.3 Olsen *et al* (2010) studied the attributable costs of incisional SSI and endometritis following caesarean section delivery in 1605 women using multivariate generalized least squares regression models and using two sources of data to estimate costs, either administrative or medical record data. This approach provided a more detailed approach to defining costs than was available for our study. The estimated attributable hospitals costs ranged from $2852 to $3956 depending on the infection type (incisional infection or endometritis) and were similar for both the data sources used for estimation, with the majority of excess costs associated with length of stay and pharmacy costs. However, Graves *et al* (2007) have also argued that estimated costs that include fixed hospital overheads are not useful for influencing the debate on the cost-benefit of investing in infection prevention as fixed expenditure will not be affected by a reduction in rates of HCAI. Economic analyses should therefore be based on length of stay and the variable costs associated with treatment of the infection. Since our costs were derived from Plowman *et al* (1999) and applied to multicentre surveillance data we were not able to make this adjustment.

3.2.6.4 Another aspect of costs that we were unable to address was the financial benefit to the hospital of preventing SSI as a result of increased 'opportunity costs' associated with bed-days not

occupied by patients with SSI. Jenks *et al* (2014) accounted for this by using the hospital patient level costing system to estimate the attributable postoperative length of stay, cost and impact on hospital profitability of SSI in patients undergoing major surgical procedures. Patients who developed SSI had a three to four fold increase in length of stay and were three times more likely to be readmitted to hospitals. However, although SSI were responsible for the loss of 4694 bed days and an aggregate additional cost of almost £2.5 million over a two year period, the predicted financial benefit of eliminating all SSI was only £700 000, and for some categories there was a financial disadvantage. This effect was explained the hospital continuing to receive income for hospital bed days due to SSI thereby obscuring the actual opportunity cost of the infection, plus that it anyway made a loss on most categories of surgery. The findings of Jenks *et al* illustrate the challenge of justifying expenditure on infection prevention, particularly surveillance programmes which, although demonstrable effective, are expensive to establish and maintain and current charging systems in the NHS do not truly reflect the cost of treating patients with SSI.

3.2.6.5 In the next section, I present a study which explored significant independent risk factors for SSI in one important category of surgery, hip prosthesis, in which SSI are relatively uncommon but, as we demonstrated in Coello *et al* 2005, have a major impact on both LOS and mortality.

3.3 Published Work 2: Surgical site infection following hip prosthesis

Ridgeway, S., Wilson, J., Charlett, A., Kafatos, G., Pearson, A., Coello, R. (2005) Infection of the surgical site after arthroplasty of the hip. *Journal of Bone & Joint Surgery*. **87(6)**: 844-50. (Appendix 3.2)

3.3.1 Background

When the Nosocomial Infection National Surveillance System (NINSS) was established in England in 1997, it offered hospitals the opportunity to conduct surveillance in one or more of twelve categories of surgical procedure. As discussed in Chapter 2 (section 2.2.1.1) these categories comprised groups of clinically similar procedure where the intrinsic risk of infection could be expected to be similar. In the first three years of the NINSS surveillance system, data was collected on more than 48 000 operations by 113 hospitals. By far the most common procedure that hospitals included in their surveillance was hip prosthesis, which accounted for 34% of the surveillance data (Public Health Laboratory Service (PHLS) 2000). These procedures involve the replacement of the ball and socket joint comprising the head of the femur and pelvis and are most commonly performed as treatment for severe pain and disability caused by osteoarthritis. Whilst the incidence of deep infections following hip replacement is expected to be low (Royal College of Surgeons (RCS) 2000) the impact of such infections is recognised to be considerable, resulting in prolonged treatment with antimicrobial agents, re-operation to replace the joint and in some cases permanent disability or death (RCS 2000). Whilst multicentre research on the risk of SSI related to hip prosthesis surgery had been conducted in the UK 1980s to establish the effect of ultraclean air systems and antibiotic prophylaxis (Lidwell *et al* 1984; 1987), subsequent studies were largely confined to single centres and therefore limited numbers of procedures collected over prolonged periods (Taylor *et al* 1994; Berbari *et al* 1998). Since the risk of infection in joint surgery is relatively low, such studies were vulnerable to methodological problems associated with small datasets (Berbari *et al* 1998). By the 2000s more than 40 000 primary hip replacements were being performed annually in the UK (National Audit

Office (NAO) 2003), with a further 40 000 or more hip prosthesis operations conducted to treat fractures to the neck of femur, the majority of which occur in women over 75 years of age in association with osteoporosis (Balasegaram *et al* 2001). Since disease of the hip is age-related, the demand for hip replacements was growing in line with increasing life-expectancy (RCS 2000). Two reports by the National Audit Office in 2000 and 2003 highlighted the need for more efficient and effective provision of hip replacement services to meet increasing demand and ensure optimal management. They also identified a widespread lack of complete and accurate data on the risk of infection associated with the procedure, with only about half of orthopaedic consultants collecting outcome data (NAO 2000). This context was an important driver for hospitals to participate in the hip prosthesis category in the English SSI surveillance system and by 2001 data on over 20,000 operations had been included in the surveillance. Since data submitted to NINSS was captured by participating hospitals using a standard methodology comprising active, prospective surveillance for cases of SSI meeting pre-defined case definitions, we could combine the data to measure the rate of SSI with greater precision than could be obtained from a single centre. My next publication reflects a collaboration between myself and an orthopaedic surgeon based on an analysis of data on hip prosthesis submitted to NINSS which defined the incidence of SSI following different types of hip prosthesis procedure and explored key risk factors associated with these infections.

3.3.2 Conceptual and methodological development

Most surveillance systems have historically captured data on risk factors for SSI using the NNIS Risk Index (Culver *et al* 1991). This had been modified from the approach taken by Haley *et al* in the SENIC study who used stepwise logistic regression to develop a simple model that could be used to predict the probability of developing an SSI from a range of pre or intra-operative risk factors (Haley *et al* 1985b). The intention of these risk indices was to provide a practical approach to risk adjustment for SSI surveillance. Simplicity was a key consideration because of the resources required to collect data and the difficulty of enabling complex statistical modelling as part of a routine

surveillance system. The adoption of the simple risk index by national surveillance systems such as SSISS enabled basic risk factor data to be captured on all operations included in the surveillance and analysed to adjust rates for these factors (Gaynes *et al* 2000; 2001b).

3.3.2.1 NINSS had adopted the NNIS Risk Index although the dataset also included some other potential risk factors for SSI. However, crude analysis of hip prosthesis in the NINSS dataset also suggested important differences in the risk of SSI associated with total hip replacements (THR) and partial replacements (hip hemiarthroplasty; HH). The latter are generally undertaken to treat fractured neck of femur and most commonly performed in elderly patients. The crude rate of SSI following the HH was twice that of THR and this difference could not be explained by the NNIS Risk Index and the risk of SSI was higher in procedures where a previous hip replacement procedure was being revised (Mahomed *et al* 2003). This analysis therefore set out to explore the specific risk factors for SSI in patients undergoing hip prosthesis operations in the NINSS dataset with two main aims:

1. To provide precise estimates of the risk of SSI in different types of hip prosthesis procedures (THR; HH)
2. To determine significant risk factors for SSI and determine if these explained the difference in risk of SSI between THR and HH

3.3.2.2 ***Measuring the risk of SSI****:* When the surveillance dataset was initially designed in 1996 it included four-digit Office of Population Censuses and Surveys (OPCS) Surgical Operation Codes. These codes distinguished total and partial hip replacement procedures, with the fourth digit within the main procedure classification indicating when a revision procedure had been performed. This coding structure enabled difference in risk of SSI in sub-groups of hip prosthesis procedures to be distinguished. The surveillance system captured data on three levels of SSI: superficial, deep and organ/space (section 2.2.2.1). Most studies of SSI related to hip prosthesis had focused on deep

wound infections which were indicative of significant morbidity and failure of the joint (Katz *et al* 2001; Coello *et al* 2005; Lidwell *et al* 1984; 1987). We considered it important to include the superficial SSI because they represented a significant burden of disease and SSI rates were conventionally based on all three levels of SSI (Emori *et al* 1991; Horan *et al* 1992). Another argument for combining superficial and deep SSI in the analysis is that superficial infections are also a marker of the efficacy of infection prevention practice. Although, the case definitions used to capture data for the surveillance system did not enable the risk of developing deep SSI subsequent to a superficial SSI to be determined because only the most severe level of SSI would be reported, there was evidence for this association from a case control study (Berbari *et al* 1998). It is possible that risk factors for superficial SSI might differ from those for deep SSI, however although we considered conducting a separate analysis on risk factors for deep SSI only, there were insufficient of these infections to enable a robust analysis of this subset of data.

3.3.2.3 ***Risk factors for SSI****:* The surveillance dataset included a basic set of demographic and operation data captured on all patients undergoing the operation (see Table 3.2). Whilst not a comprehensive set of risk factors, it did include important epidemiological variables such as age and sex, markers of underlying illness previously demonstrated to be associated with increased risk of SSI (ASA score) and intrinsic factors likely to influence the risk of SSI (trauma, duration of operation, wound class). Most previous studies of rates of SSI associated with hip prosthesis had combined all types of hip replacement procedure and adjusted rates only by the NNIS Risk Index score (Delgardo-Rodriguez *et al* 1997; CDC 2004). In this dataset we were able to define the risk of SSI associated with different types of hip replacement procedures using the OPCS codes. A key aim of this analysis was therefore to determine if this difference in risk could be explained by intrinsic risk factors in the patients undergoing HH, in particular their age and exposure to traumatic injury.

Table 3.2: SSISS surveillance dataset for orthopaedic procedures (1997 to 2004)

Data Item	Risk factor
Sex	Gender
Date of birth	Age
Date of hospital admission	Pre-operative length of stay
Data of operation	Pre/post operative lengths of stay
Type of surgery	Elective/emergency operation
Operation due to trauma	Traumatic injury
Implant (permanent, non-human foreign body)	Implant
Use of cement (derived from OPCS code)	Cemented prosthesis
Multiple procedures through the same incision	Increased tissue exposure
Height & weight	BMI
ASA score	Severity of underlying illness
Wound class (clean, contaminated, dirty)	Wound classification
Duration of operation	Complexity of procedure
Peri-operative prophylaxis (at time of operation)	Antimicrobial prophylaxis
Date surveillance discontinued (discharged/died)	Post-operative length of stay

Linear regression methods were employed to determine significant independent predictors of the risk of SSI, which as described in 2.1.1 enabled the dependant variable (SSI) to be correlated with more than one predictor (risk factor) variable at the same time (Bland 2000 p. 321). This approach enabled the strength of relationship between SSI and the available potential risk factors for SSI, expressed as odds ratios, to be measured whilst accounting for the confounding effect of other of inter-related factors, such as age and ASA score. Logistic regression was used as it enabled values between zero and one to be obtained for the estimated proportions and a mixed set of predictor variables to be included in the model, either continuous (e.g. age), discrete (e.g. pre-operative stay)

or dichotomous (e.g. gender). In practice, the model was simplified by converting potential continuous variables such as age and duration of surgery to discrete groups and other scores such as ASA and wound class to dichotomous variables (Bewick 2005). By including the type of hip prosthesis procedure (THR and HH) as a predictor variable in the model it was possible to identify factors that significantly affected the risk of SSI independently of the type of procedure, thereby answering the question as to whether the higher rate of SSI in HH procedures was due to the procedure or explained by specific underlying risk factors.

3.3.3 Summary of main methods and findings

The data included in this analysis was a set of 24 808 hip replacement procedures and 761 SSI from 102 hospitals that had participated in the national SSI surveillance between 1997 and 2001. We included only those SSI identified during the inpatient stay, as defined methods of post-discharge surveillance were not in place at this time and inpatient SSI could be more consistently and reliably identified. Using the 4-digit OPCS codes, hip replacement procedures were assigned to one of four categories: total hip replacement (THR), revision of THR, hip hemiarthroplasty (HH) and revision of HH.

3.3.3.1 ***Rates of SSI and patient characteristics****:* Rates and associated normal approximation confidence intervals were calculated for each category. This analysis confirmed that the crude rate of SSI was significantly greater in HH than primary THR, but since the median length of hospital stay for patients undergoing HH was five days longer than THR (14 vs 9 days) these rates were affected by case-ascertainment bias. This was an important factor to take into account when explaining differences in risk of SSI between the procedures in the multivariate regression models (see section 3.3.3.4). The mean time to detection of SSI varied by type of SSI from eight days for superficial incisional SSI to 11 days for deep incisional and joint/bone SSI and, as established in Coello *et al* 2005, the mean length of stay doubled for patients with a SSI; this effect was apparent across all

types of hip prosthesis procedure. There was also a striking difference in median age at the time of HH (83 years; inter-quartile range 11) and THR (70 years; inter-quartile range 15). HH were more likely to be performed in women (80% compared to 60% in THR) and 85% of HH were performed as a result of trauma compared to only 4% of THR. As might be expected because of the significantly greater age and traumatic injury associated with HH procedures, these patients also had a higher median ASA score than patients undergoing THR. These variations in key characteristics between different types of hip prosthesis procedure highlighted the importance of multivariate regression analysis to determine the factors that were independently associated with SSI and whether the variation in risk could be explained by the type of procedure or underlying intrinsic risk factors. For example, it was possible that the significant effect of age on risk of SSI could be entirely explained by higher ASA score in older age groups.

3.3.3.2 ***Risk factors for SSI****:* The initial univariate analysis of potential risk factors within each category of hip replacement used Chi^2 test and odds ratios to estimate the strength of association and a p value of 0.05 or less to identify significant results. Table 3.3 summarises the significant risk factors for SSI identified for each category of replacement procedure as a result of this analysis.

3.3.3.3 ***The logistic regression model***: Whilst associations in a univariate analysis are of interest in exploring characteristics that increase the risk of SSI, they do not take account of confounding between predictors (Bewick 2005). In order to take account of such confounding the following predictor variables were included in the logistic regression model

- Operation due to trauma
- ASA score
- Wound class
- Prophylactic antibiotic therapy
- Gender

- Age group
- Use of cement
- Pre-operative stay
- Duration of surgery
- Type of hip prosthesis procedure

Table 3.3: Summary of significant risk factors in univariate analysis of risk of SSI following hip prosthesis

Primary THR	**Revision THR**	**Primary HH**	**Revision HH**
n = 16291	*n = 2550*	*n = 5769*	*n = 198*
Risk Index 2 or 3	Risk Index 2 or 3	Age >80	
Female	Male	ASA score>=3	ASA score>=3
Trauma	Trauma	Operation <60min	
Age >75	Pre-op stay>3		
BMI>30	ASA score>=3		
Pre-op stay>3	Wound class not clean		
ASA score>=3			
Operation >120min			

A backward stepwise method was used to construct the model in which all predictor variables are included at the outset and then eliminated in sequence based on the selection of the term with the highest p value. We assessed the goodness of fit of these models using likelihood ratio tests, which provide measures of model deviance by comparing it with a model with theoretically perfect fit and one with no predictors (Bewick 2005). Tests for interactions between significant independent predictors (a variable that has a different effect on the outcome depending on the values of another independent variable) were examined but none identified. Although body mass index (BMI) had

been included in the univariate analysis, it was excluded from the logistic regression model, as it would have restricted the application of the model to the 33% of patients for whom BMI data was available. This multivariable analysis identified four independent risk factors associated with the risk of SSI:

- ASA score greater than or equal to 3
- Age group of patient
- Duration of procedure greater than T time (120mins)
- Procedure performed after trauma

This analysis demonstrated that these four factors were associated with the risk of SSI regardless of the type of hip procedure performed. The combination of higher median age, procedures following trauma and high ASA scores in patients undergoing HH were the key factors in explaining the increased risk of SSI (since the majority of HH were of short duration). This was an important finding given that despite the increased risk of SSI in patients requiring HH due to these underlying risk factors, such patients were often not afforded the same standards of care as those undergoing primary THR, with HH procedures often performed by junior doctors in emergency operating theatres (NAO 2000; 03). The model also tested the effect of including the hospital where the procedure was performed and found that the hospital was a significant independent predictor of risk of SSI, suggesting that there is considerable variation in rates of SSI between hospitals that cannot be explained by the other predictors such as case-mix. Whilst it could be argued that some of this variation was explained by risk factors not included in the dataset, these would need to have a strong effect on the risk of SSI and vary widely in distribution between hospitals in order to explain the observed inter-hospital variation.

3.3.3.4 ***Poisson regression model*****:** Finally, since the length of postoperative stay affected the chance of an SSI being detected and the crude data indicated significant variation in length of post-operative

stay between procedures, we repeated the multivariate analysis as a Poisson regression and used length of postoperative stay as an explanatory variable in order to allow for variation in the time of follow-up. A Poisson distribution assumes that events (SSI) occur independently and with a constant probability within a fixed time and measures the association between SSI and a set of predictor (explanatory) variables. This method would only provide a partial adjustment as the time to detection of SSI does not occur in a linear fashion but appears to peak at six to 10 days post operation (HELICS 2001; 2005). The Poisson analysis found that age was no longer a predictor of SSI, suggesting that at least some of the increased risk of SSI associated with older age groups may be related to their increased length of post operative and stay and therefore chance of SSI being detected.

3.3.4 Conclusions

The use of logistic regression to build an epidemiological model of the relationship between risk factors and SSI has important advantages over testing significant relationships using stratification, in particular it can be used to explore many risk factors at the same time and remove the effect of confounding (Grave *et al* 2010). Our approach was to include all the potential predictors in the model and then using the backwards stepwise method to exclude the least important predictor, one at a time. Whilst the Log Likelihood Ratios for both the logistic regression and Poisson models indicated they significantly improved prediction of SSI, regression models still need to be interpreted with caution as they can generate false positive associations and be distorted by outlier values (Dobson and Barnet 2002). Since the same set of data were used to both estimate and then 'fit' the model, one method that we could have used to improve our analysis was to split the data using one half to develop and the other to validate the model. This was an approach used by Haley *et al* in first designing the NNIS Risk Index (Haley *et al* 1985b).

3.3.4.1 In common with the analyses in Coello *et al* (**Appendix 3.1**) described in section 3.2, this

analysis relied on the risk factors included in the surveillance dataset and these may not have reflected a comprehensive set of risk factors for SSI following hip prosthesis. In addition, records where a high proportion of data was missing (e.g. 25% of records did not have data on ASA score and only a third included BMI data) could not be included in the model. This reduced the records available for analysis and resulted in some important risk factors, such as body mass index (a significant risk factor in the univariate analysis) being excluded from the model. One advantage of conducting this study on data captured in the late 1990s to early 2000s was that the length of post-operative stay in England was relatively long at this time thus minimizing the bias associated with length of follow-up. Interestingly, the median length of stay in the dataset used for this analysis was 14 days for HH and nine days for THR; by 2011 this had reduced to five days for the latter (Health Protection Agency (HPA) 2011). We attempted to adjust for the effect of LOS on risk of SSI using a Poisson regression analysis, and indeed this approach clearly modified the variables included in the risk factor model for hip prosthesis. An enhancement of this method would be to apply a more sophisticated approach to adjusting for time to SSI by segmenting the period of follow-up in order to account for the time to SSI being non-linear and basing the analysis on more complete post-discharge surveillance (PDS) data.

3.3.4.2 Another important disadvantage of using surveillance data for epidemiological analyses is that it may be prone to local variation in application of data collection methods. The SSI surveillance system was based on a standard methodology and surveillance personnel were trained in data collection methods in order to minimise these problems and assure the reliability of the data. Since the data used in this study was captured early in the life of the scheme and prior to mandation of orthopaedic SSI surveillance, the majority of hospitals were participating voluntarily and therefore more likely to be motivated to capture data accurately. Once the surveillance became subject to performance management in 2004 the incentive for hospitals to establish robust data capture systems changed (Tanner *et al* 2013a). Nonetheless, differences in case finding and reporting may

have explained some of the significant hospital-effect that we observed in the risk of SSI following hip prosthesis.

3.3.4.3 ***My contribution to this research***

In this paper I applied the knowledge I had gained from conducting an analysis of risk factors for vascular surgery. I designed the backwards, stepwise regression model using an approach to handling the combination of categorical and continuous variables that I had previously developed as predictors in the vascular dataset (Wilson 2002). In addition to designing the methods and approach to data analysis, I interpreted the results in conjunction with the statistician and developed the conclusions in collaboration with the orthopedic surgeon. This collaborative relationship with a clinician was important in order to set the findings in the appropriate clinical context and prepare a manuscript that would be appropriate for an audience of orthopaedic surgeons.

3.3.5 Contribution of this study to contemporary knowledge

This work was innovative because the large dataset enabled the application of statistical methods that could account for the individual effect of related variables and therefore identify significant independent risk factors for SSI. These analyses influenced the development the national SSI surveillance system methods which subsequently used incidence density to adjust rates for length of post-operative stay and account for the effect of variation of length of stay on the estimated rate of SSI (HPA 2005). In addition, we created a separate category for HH in order to more accurately reflect the different risk factors in these patients without using a complex regression analysis to report rates on a hip prosthesis category (HPA 2004b). At the time of this publication most surveillance systems used the NNIS risk Index as the basis for data capture on risk factors for SSI and there had been little research on the specific risk factors for SSI following hip prosthesis. There were a few examples of the use of this type of methodology in the identification of risk factors for SSI. These had been conducted on considerably smaller populations in case control studies (Minnema *et*

al 2004; Barberi *et al* 1998), a retrospective cohort study (Mahomed *et al* 2003) and small prospective muticenter study (Moro *et al* 1996) and the corresponding power to detect significant risk factors was limited by the small numbers of procedures included. This analysis was therefore important as it was based on a large number of procedures and able to use logistic regression methods to determine independent risk factors for SSI. The significance of the analysis in defining key risks factors for SSI following hip prosthesis is demonstrated by the more than 170 citations of the work since it was published.

3.3.5.1 Whilst since 2011 NHSN has elected to retain the single category for hip prosthesis and the logistic regression model to adjust for the risk associated with the type of procedure and other factors, our approach was different. Our analysis six years previously had demonstrated that the significant difference in risk of SSI between HH and THR could not be adequately adjusted for by the standard Risk Index because both trauma and age were key predictors. However, rather than applying a complex regression model to adjust SSI rates, we chose to retain a separate HH category. There were a number of disadvantages that mitigated against applying the regression model. In particular, the Poisson analysis indicated that length of post-operative stay confounded the effect of age and that this effect would be markedly increased as the length of stay following elective THRs declined over subsequent years (HPA 2009). In addition, since approximately 25% of records had missing data on ASA score and duration of operation, adjustment using standardised infection ratio (SIR) would only be based on 75% of records, with the precision of the estimated rate reduced accordingly. Reporting two separate categories avoided the rates of SSI at each hospital being biased by ratio of total to partial procedures and retained the more direct inter-hospital comparison of rates of the specific procedures. We therefore chose to continue using the standard Risk Index stratification rather than standardisation as the method of demonstrating the effect of risk factors on rates. The impact of procedure type and other risk factors for SSI following hip prosthesis identified in this analysis also informed the analyses of data contributed to the European SSI surveillance

networks, which is presented in Chapter 4, section 4.2 (Wilson *et al* 2007; Appendix 4.1).

3.3.5.2 Whilst the mean length of post-operative stay at the time of the study was much longer than is the case now, SSI after implant surgery are recognised to sometimes take up to one year to become apparent (Horan *et al* 1992; 2008). Since at the time this it was performed the surveillance system did not include a standardised approach to post-discharge surveillance, we were only able to include SSI detected during the inpatient stay in this analysis. Whilst this should be perceived as an important limitation in terms of defining the absolute risk of SSI following these procedures, we were able to accurately define risk factors of early SSI in a large multi-centre dataset which is preferable to previous approaches based on small numbers of cases in single centres. This surveillance data, however, did not enable us to establish whether the risk factors we identified for early SSI would also predict the risk of SSI developing post-discharge as the aetiology of these infection may differ.

3.3.6 Subsequent research contributions to the field

Subsequent studies of data contributed to national surveillance systems have reported similar incidence of SSI to those we reported in Ridgeway *et al* (2.23% after THR and 4.97% after HH). This is despite SSI detected by PDS being incorporated in the results emanating from other surveillance systems. An analysis of data captured by the PREZIES system in the Netherlands, reported an incidence of SSI following THR of 2.2% and HH of 5.3% (Geubbels *et al* 2005). These rates included SSI captured post-discharge via a registration card completed by the surgeon and supplemented by chart review by the infection control practitioner, although these methods are not compulsory (Mannien *et al* 2006). The similarity in rates may suggest that the true rates in England would have been higher than in the Netherlands were post-discharge surveillance (PDS) incorporated. Certainly, once a standard methodology for PDS was incorporated into the SSISS in England in 2008, the detection of deep and organ/space SSI increased by 50% (HPA 2009). However, in Scotland

where surveillance of SSI after hip prosthesis included active PDS, rates of SSI were 2.67% with PDS and 1.75% without PDS and therefore not much higher than that found in England (Reilly *et al* 2006). In Finland, patients are followed up to identify SSI on readmission and at follow-up visits 2 months and 1 year after surgery, and the rates of SSI detected in in-patients and including PDS 2.1 and 3.9% respectively (Huotari *et al* 2006). However, whilst overall 56% were detected by PDS the proportion detected varied markedly between hospitals suggesting considerable variation in sensitivity of case finding that would affect the precision of the estimated rates (Huotari *et al* 2006).

3.3.6.1 A more comprehensive method of measuring the risk of SSI following hip prosthesis is reflected in the Norwegian SSI surveillance system which requires all hospitals to capture three months of data on hip arthroplasty for the SSI surveillance system (NOIS) and follow-up patients with a questionnaire at 30 and 365 days post-operation (Dale *et al* 2011). Post-discharge data is captured on 90% of patients. This more long-term method of follow-up identified higher rates of SSI of 3% after THR and 7.3% after HH, although these were based on analysis of a much smaller number of procedures (approximately 7000) which would have increased the possibility of chance error. Most SSI (72%) in this analysis were identified by PDS but only nine of 270 SSI (3%) were detected between day 30 and 395. The median time to SSI for these procedures was 16 and 15 days respectively indicating that most additional SSI would have been detected in the first five or six days after discharge. This suggests that since the median length of hospital stay in our analysis was nine days for THR and 14 days for HH that most SSI would have been detected even without PDS. It also raises the question as to whether continuing surveillance after day 30 adds sufficient further cases of SSI to make it cost-beneficial (Hall *et al* 2013).

3.3.6.2 Analysis of risk factors for SSI following hip arthroplasty was also explored by Dale et al using both the NOIS data set and a large dataset of 07% (182) of THR and 1.5% (128) of HH revised due to infection in data submitted to the Norwegian Arthroplasty Registry (Dale *et al* 2011). The risk factors

for infection that they identified were comparable to the ones identified by our study suggesting that risk factors between early and late onset SSIs are similar. This study confirmed our findings that after adjustment there was no significant difference in the risk of SSI between THR and HH, although the risk of revision was higher for SSI after HH than THR, and that age and ASA score were significant predictors of both SSI and revision due to infection for THR. The predictors for revision due to infection were slightly different compared to our analysis, with male gender and emergency surgery appearing as significant predictors in addition to age and ASA score (Dale *et al* 2011). Other analyses of national joint registry data, for example in Denmark, have also identified co-morbidities that have increased the relative risk of revision due to infection. These included patients with long duration of surgery, in addition to other more specific factors such as operation due to non-traumatic avascular femoral head necrosis (Pedersen *et al* 2010). In contrast, the National Joint Registry established in England in the early 2000s has focused analyses on the factors related to the operative procedure that contributed to the risk of revision in general rather than exploring the risk factors for revision due to infection in particular (Jameson *et al* 2013). This means that our analysis remains the most comprehensive assessment of the overall risk of SSI following hip prosthesis in England. Other studies have focused only on deep SSI. A systematic review of risk factors for deep SSI following primary THR identified an incidence of 1.1% up to 5 years post-surgery (Urkuart *et al* 2010). Severity of underlying illness and duration of operation were identified as independent predictors of deep SSI. The authors also identified the need for high quality, prospective studies to identify modifiable risk factors for deep SSI after THR.

3.3.6.2 Studies using logistic regression models to improve risk adjustment based on analysis of specific risk factors for SSI following hip arthroplasty have also been conducted (Brandt *et al* 2004; Geubbels *et al* 2006b; Mu *et al* 2011). Geubbels *et al* (2006b) included age, duration of preoperative hospital stay, PDS and two or more discharge diagnoses as this improved the area under the ROC (C index) compared to the NNIS risk index value of 0.56 to 0.64 (p $p<0.001$). Subsequently, the NNIS

system in the USA (now renamed as the National Healthcare Safety Network) has defined category specific risk adjustment models for SSI surveillance. Their model for hip prosthesis was based on 131,826 procedures, and included the factors identified in our analysis: age, duration of surgery, trauma and ASA score, but in addition found the type of procedure, anaesthesia type, hospital size and medical school affiliation to be additional independent predictors (Mu *et al* 2011). The latter two factors may be specific to the US healthcare environment which has a large number of small private hospitals treating patient with a different case-mix to the large public hospitals with affiliated medical schools. It is interesting that, unlike our analysis, the predictors included in the model did not completely explain the variation in risk between THR and HH. This may have been explained by the larger dataset and inclusion of some post-discharge surveillance data. The model increased the c-index from 0.61 to 0.66 compared to the NNIS Risk Index model ($p<0.0008$). Although the differences achieved by these more sophisticated models were statistically significant, in terms of practical relevance considerable extra effort would be required to capture more detailed surveillance data on each procedure in order to achieve a small improvement in risk predicted by the model. The authors suggest that such effort is necessary where rates are to be used for benchmarking or public disclosure and should be focused on deep and organ-space SSI since the predictive power of the models is improved for these infections (Mu *et al* 2011). However, there are disadvantages to this approach in particular the complexity of the analysis makes the calculation of the rates less transparent and more confusing (Brandt *et al* 2004). In addition, procedures could only be included in the rate if complete risk factor data is available and by focusing only on severe infections the number of SSI and therefore the precision of the estimated rate would be markedly reduced. This suggests that there is not a simple answer to handling risk adjustment in HCAI surveillance systems, particularly where benchmarking is a key aim.

3.3.6.3 In my next publication, I explore the effect of a particular risk factor, the duration of operation, on SSI and compare its validity as a predictor of risk with the US NNIS data.

3.4 Published Work 3: Duration of operation as a predictor of surgical site infection

Leong,G.; Wilson, J.; Charlett, A. (2006) Duration of operation as a risk factor for surgical site infection: comparison of English and US data. *Journal Hospital Infection.* **63**: 255-62. (Appendix 3.3)

3.4.1 Background

In section 2.2.5.1 I cited the work of Haley *et al* (1985b) as being instrumental in identifying the duration of operation as a significant risk factor for SSI. In this initial analysis of SENIC data, four factors from a set of 10 most commonly used indicators of SSI risk could be used to predict the majority of the risk. Of these four factors (abdominal surgery, operation lasting more than 2 hours, contaminated or dirty wound classification and three or more underlying diagnoses) the duration of operation was the second best predictor of SSI after 'abdominal surgery'. These four factors can be considered to reflect a spectrum between purely intrinsic patient susceptibility at one end and risk of bacterial contamination of the wound at the other (Haley *et al* 1985b). In the case of duration of operation the position on this spectrum is complex. Longer operations increase the risk of microbial contamination of the wound since the wound is exposed to the environment for longer. However, longer procedures are also likely to reflect intrinsic risks associated with complexity of the underlying condition and impairment in healing associated with the requirement to handle more tissue. Others argue that duration of operation reflects extrinsic factors such as the skill of the surgeon or quality of care in the operating department and argue that complexity of the procedure is an extrinsic rather than intrinsic risk factor (Campos *et al* 2001; Greubbels *et al* 2006). In terms of risk adjustment to support benchmarking of rates of SSI, the aim is to account for intrinsic risk factors on the basis that these are associated with the patient and cannot be changed. On the other hand, adjustment for extrinsic risk factors should be avoided, as these are more likely to reflect variation in infection prevention practice which surveillance is aimed at discriminating (Brandt *et al* 2004).

3.4.1.1 Extended duration of operation is therefore a complex measure of intrinsic risk that probably measures a combination of complexity of the individual case, some aspect of surgical technique and prolonged exposure of tissues to micro-organisms. Whilst an imperfect indicator of intrinsic risk alone, it has been consistently shown to increase the risk of SSI and has therefore been incorporated into the standard adjustment of SSI rates for intrinsic risk factors (Haley *et al* 1985b, Cruse and Foord 1973, Moro *et al* 1996). The simple risk adjustment model developed by Haley *et al* was subsequently modified and the standard two-hour cut point between short and long operations replaced with a more sophisticated, specific cut point or T time for each category of procedure (Culver *et al* 1991). These specific cut points were calculated by identifying the time at the 75th percentile from the distribution of operation times, and then rounding this to the nearest whole number of hours (Culver et al 1991; Gaynes *et al* 2001b). Some further minor modifications were made to the US T times over the subsequent 10 years when the data indicated a change in distribution of operation times associated with changes in surgical technique or case-mix (CDC 1999; CDC 2004).

3.4.2 Conceptual and methodological development

When the NINNS SSI surveillance was established, the duration of operation was included in the denominator dataset and was an essential component of the risk stratification of SSI rates. We had adopted the category-specific cut points for T times developed by Culver *et al* on the basis that these had been validated as associated with risk of SSI (Culver *et al* 1991). Other national surveillance systems adopted cut-points derived from the distribution of operation times in their own data, arguing that these may be a better predictor of SSI in a local setting (Gulacsi *et al* 2000; Campos *et al* 2001; Brandt *et al* 2004). Either method could provide a relatively crude distinction between procedures defined as at increased risk of SSI, and in the case of NNIS T times they were based on duration of operations conducted in the USA in the late 1980s. Thus there were two key questions

that needed to be answered to support the use of duration of operation in the English SSI surveillance system:

- Would a similar T time based on the current distribution of operation times in England be comparable to the US NNIS T times, given differences in surgical technique and improvements in the intervening decade?
- How reliable was the T time in distinguishing operations of increased risk of SSI across a range of categories included in the English SSI surveillance system?

3.4.2.1 In order to answer these questions the NNIS system T times were compared with T times derived from data on duration of operation captured in the English SSI surveillance, and the association between these T times and risk of SSI then evaluated. The English T times were calculated using the same method as Culver *et al* (1991) by taking the time in minutes at the 75th percentile from the distribution of operation times within the category and rounding this time to the nearest whole hour, rounding up where the 75th percentile time was at the half hour. A Chi^2 test was used to compare rates of SSI above and below the T time for both US and English times but then a novel method applied to determine the relationship between T time and risk of SSI that involved plotting the p value for the difference between rate of SSI for procedures above and below a range of cut points in duration of operation set at 15 minute intervals. This enabled the values along the distribution of cut points where the risk of SSI was significantly different to be identified and therefore the T times that were associated with a risk of SSI, including the most appropriate T time to use in the SSI risk Index.

3.4.3 Summary of main methods and findings

Five years of data captured between 1997 to 2002 from 13 categories of surgical procedures was included in the analysis. The English category of coronary artery bypass graft (CABG) was separated into two sub-categories, chest and donor incision and chest only incision, as this allowed it to be

mapped to the data to NNIS in which CABG were reported in these discrete categories with different T times. Data from HH was combined with THR to map to the NNIS hip prosthesis category. However, we were interested in the effect of T time on the risk of SSI for groups of procedures within both the hip prosthesis category and vascular procedures. The latter category comprised procedures on the aorta, carotid and femoral arteries which were likely to be associated with different complexity and therefore duration. After excluding 3% of records with missing operation times or where a missing OPCS code prevented allocation to a specific category, data on 102 847 operations were included in the analysis.

3.4.3.1 ***Comparison between English and US T times****:* The duration of operation at 75th percentile in English dataset differed from the US 75th percentile time in all categories, and the confidence intervals indicated that these differences were significant in all categories apart from large bowel surgery. However, once these times were converted to T times by rounding to the nearest hour, in most categories (apart from vascular and CABG) the T times were the same. This demonstrated that whilst at first sight the significant differences in the 75th percentile times might seem important, the advantage of the T time is that by rounding a specific time in minutes to the whole hour, a more stable cut point is generated against which to define procedures of unusually long duration. In the two categories where the English and US T times differed significantly the differences were likely to be explained by the combination of procedures included in the category. This illustrated a wider problem of ensuring categories include 'clinically similar' procedures and was particularly marked in the vascular category where both the risk of SSI and duration of operation varied widely between different types of procedure. Our analysis showed that the duration at the 75th percentile for vascular procedures varied from 150 mins for carotid procedures to 230 minutes for procedures on the aorta, whilst the risk of SSI was highest in femoral procedures (11.3%) and lowest in carotid procedures (0.2%). Differences in the mix of vascular operations included in the surveillance

between the two countries may therefore have had an important effect on both the rate of SSI and the T time.

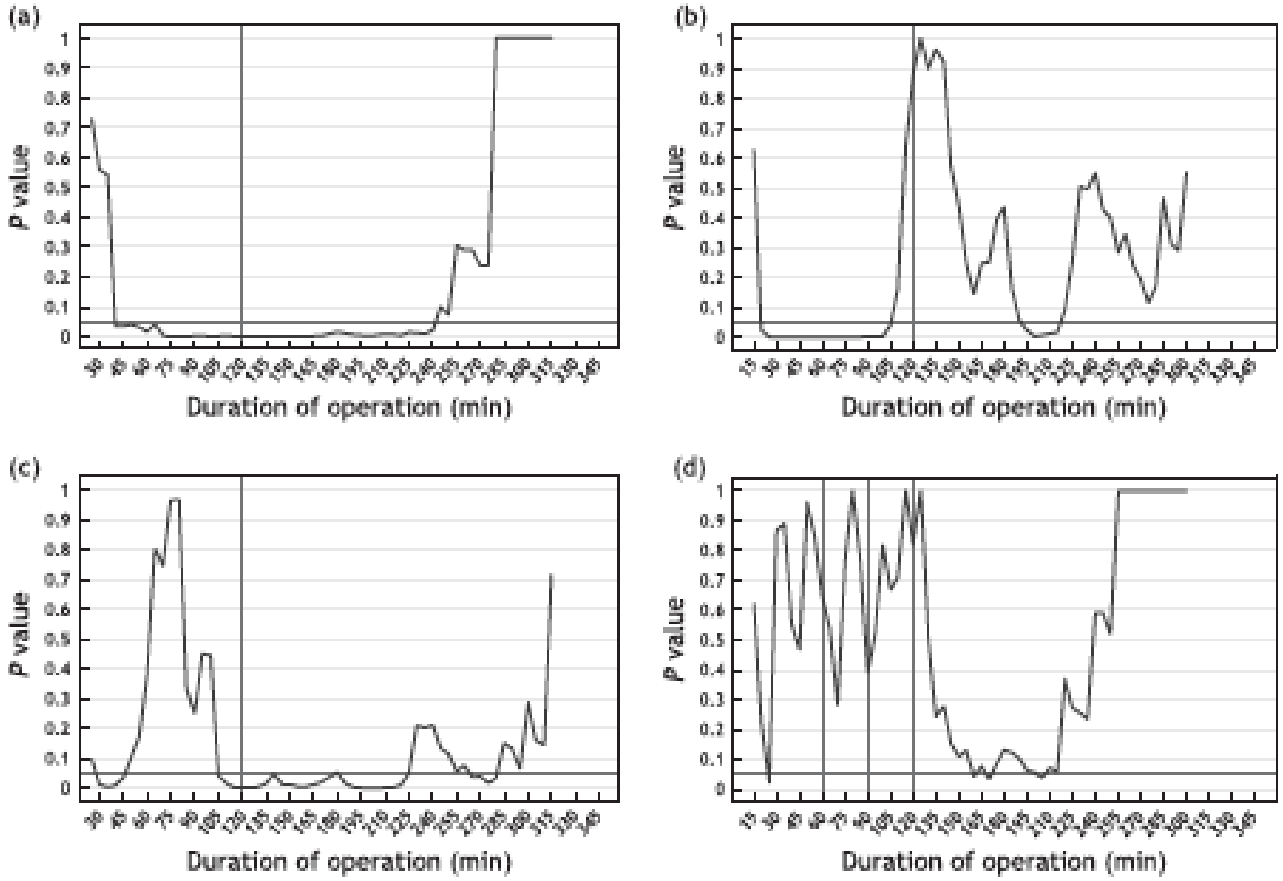
3.4.3.2 The less specific cut point time provided by the T time also acknowledges the imprecision in documentation of this data. Whilst the strict definition of duration is time of incision to time of completion of wound closure, in reality it is more likely to reflect the length of time the patient is in the operating room. In addition, the distribution of documented durations included in this study also showed a marked digit preference, with operations times more likely to be rounded up or down to the nearest five or 10 minute, or 1 hour interval, demonstrating significant imprecision in the recording of operation duration. Whilst digit preference is a recognised phenomenon is has not been previously described in relation to duration of operation (Preece 1981). Again this supports the use of the T time rather than a more specific 75th percentile time since marked digit preference could introduce significant bias into allocation of procedures above or below the cut point if based on a specific time. Since the T times were based on durations above the time at the whole hour, any bias introduced by digit preference would tend to underestimate the association between extended durations and risk of SSI. Overall, this analysis therefore enabled us to conclude that the US T times developed in 1991 were still applicable to current duration of operations for categories included in the English SSI surveillance system and that T times remained a more appropriate indicator of risk associated with duration of operation than specific 75th percentile times.

3.4.3.3 The proportion of procedures which the cut-point ascribed as of long duration was also an important factor to be taken into account and mitigated against applying the standard rule of rounding to the nearest whole hour in all categories. This was clearly illustrated in the sub-category of HH. In the US data these procedures were included in the hip prosthesis category, however the analysis of English data indicated a considerably shorter mean duration of operation with a 75th percentile time of 80 mins versus 130 mins for the hip prosthesis category as a whole. If the 2hr T

time were applied to the HH category then only 4% of the operations would have durations longer than the T time. If the time were to be rounded to the nearest hour, the T time of 1 hour would result in nearly half the procedures being denoted as of extended duration. This would clearly make it an imprecise and impractical indictor of procedures at increased risk of SSI in this category. An important outcome of this analysis was therefore the creation of a specific T time for HH of 1.5hr, which we found distinguished a more appropriate proportion of 15% of procedures as being of extended duration.

3.4.3.4 ***Relationship between T time and risk of SSI****:* The analysis found evidence that the incidence of SSI was higher in operations with duration of operations longer that the T time. This effect was observed in all categories except for hip prosthesis, and for the latter category the incidence was higher for the relevant T time when the procedures were segregated into THR and HH. These differences were statistically significant except for bile duct and cholecystectomy (where less than 200 operations were available and this reduced the power to detect significant differences), and limb amputation, and open reduction of long bone, which may have reflected more heterogenous procedures of widely varying durations. Plotting the p value (set at 0.05) of the association between SSI and duration of operation at 15 minute intervals demonstrated that the relationship between T time and risk of SSI varied according to category and that the cut point used to define the T time could cover a wide range of operation durations whilst still indicating significant differences in risk of SSI above and below the time (see Figure 3.1). For example, in abdominal hysterectomy a T time of between 45 and 240 mins was associated with a significant increase risk of SSI, as illustrated by the line plotted below the 0.05 p value. This analysis also supported our decision to separate HH. When these procedures were included, the T time of 2 hours was not significantly associated with risk of SSI since the shorter duration of HH meant that the increased risk was evidence at durations of between 30 and 100 minutes. By removing these procedures the T time became significant at the 2hr cut point, although no specific cut point was associated with SSI in the HH category (Figure 3.1).

Figure 3.1: Association between p value and cut point for duration of operation for a) abdominal hysterectomy procedures, b) hip prosthesis (total and hip hemiarthroplasty), c) total hip prosthesis d) hip hemiarthroplasty. P value = 0.05 indicated by horizontal line; English and US T times indicated by vertical lines.



3.4.4 Conclusions

Our analysis of the association between SSI and duration of operation provided robust evidence for the association between SSI and prolonged duration of operation and support for the continued use of the T times we had defined at the inception of the surveillance. As in both Coello *et al* (Appendix 3.1) and Ridgeway *et al* (Appendix 3.2), our analyses were limited by the availability of data within the surveillance dataset. In the case of operation duration, whilst the time was missing in less than 3% of records, the marked digit preference illustrated the imprecision with which apparently simple data items may be recorded. Whilst we have demonstrated that this would have resulted in the association between SSI and T time being underestimated rather than overestimated, it does indicate the wider potential for misclassification of data in surveillance datasets. In addition, although our analysis demonstrated a reasonably consistent significant relationship between SSI and operations of prolonged duration, we are not able to distinguish whether this is an extrinsic factor, such as operator technique, or an intrinsic factor associated with the complexity of the procedure. Such an analysis would require more detailed data capture than is possible with a routine surveillance system.

3.4.4.1 ***My contribution to this research***

I developed the concept for the analysis, and subsequently the interpretation of the results and implications of the analysis for the national surveillance system. I worked with the statistician who advised on the methods of identifying valid T times. I also informed the analysis and conclusions though applying my expert knowledge of benchmarking SSI rates, International surveillance systems and approaches to risk adjustment. In this analysis I was supervising a junior scientist who conducted the statistical analysis for the study.

3.4.5 Contribution of this study to contemporary knowledge

This analysis was important since duration of operation was one of three factors used for primary risk adjustment of the SSI surveillance data. The underpinning methodology determining its application as a risk factor was based on US data and this may not have been applicable to surgery performed in the UK. At the time of this research, there had been no specific study on the association between duration of operation of risk of SSI since the Risk Index was defined by Culver *et al* in 1991. In addition, Culver *et al* had validated the impact of the risk index as a whole on the risk of SSI and so our study was unique in evaluating the specific relationship between T time and increased risk of SSI across a range of surgical categories. Other studies have investigated risk factors for SSI but have identified duration of operation as one of a number of significant independent predictors of SSI rather than specifically exploring its relationship with SSI (Moro *et al* 1996; Gulacsi *et al* 2000; Campos *et al* 2001; Anderson *et al* 2008). Whilst duration of operation is consistently associated with increased risk of SSI, controversy still exists as to whether the duration of operation represents a patient related risk factor or better reflects surgical technique (Mu *et al* 2011). Our study has subsequently been cited by over 60 other studies as evidence for the relationship between T time and risk of SSI.

3.4.5.1 The second key contribution that this study made to the evidence base was further confirmation of the significant difference between THR and HH first described in my preceding study of risk factors for SSI following hip prosthesis (Ridgway *et al* 2005 Appendix 3.2). The T time analysis demonstrated that the duration of operation for HH was shorter than for THR and that if the two types of procedure are combined into a single category the standard T time of 2hrs is not a reliable method of distinguishing procedure at increased risk of SSI. This provided further evidence that HH should be separated into a specific category in order more accurately risk adjust and report rates of SSI.

3.4.6 Subsequent research contributions to the field

Our study found that whilst the time at the 75th percentile for duration of operation might vary from those defined by NNIS, it does not significantly affect the ability of the T time to predict SSI. This same finding was also reported by Prospero *et al* (2007) who compared the predictive ability of T times using ROC analysis. Other studies have included duration of operation as a key component of increasingly sophisticated risk adjustment models (Mu *et al* 2011; Cohen *et al* 2013; Walraven and Musselman 2013). However, others have recommended that it is excluded from risk adjustment models as they have considered duration of operation as an indicator of hospital quality rather than intrinsic risk related to the patient (Geubbels et al 2006; Campbell *et al* 2008; Gastemeier et al 2011).

3.4.6.1 Our analysis was able to demonstrate a clear link between risk of SSI and durations of operation but it could not explain the reason for this association. A recent study by Campbell *et al* (2008) has provided some insights into some of the possible clinical explanations for the observed variation in operation duration and impact on the rate of SSI. The premise of Campbell *et al* was that duration of operation was a measure of the quality of the surgical process, acting as a proxy of care such as the characteristics of the operative case, surgeon skill or other factors such as intraoperative teaching. This study used data from 117 hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). This system captures data on risk factors and outcomes up to 30 days post surgery for a defined set of operations. The predicted probability of SSI is calculated for each patient based on their pre-surgical risk factors and these probabilities summed for each centre to give an expected number of SSIs. Campbell *et al* (2008) benchmarked rates based on the ratio of observed (O) to expected (E) SSIs (derived from the above risk adjustment) and those that were 'high outliers' were defined as hospitals with O/E > 1 and those that were low outliers, an O/E <1 (in both cases based on a

reasonable sample size i.e. with 95% confidence limits around the rates excluding one). A range of 'process measures' of operating theatre practice that were considered to be associated with the risk of SSI were identified though survey of all participating centres. Site visits to centres identified as low and high outliers were also made to assess aspects of practice. Operation durations for all procedures were significantly longer (25%) at high outlier hospitals. This was unlikely to be explained by procedure complexity since a comparison of a subset of low complexity procedures (e.g. laparoscopic cholecystectomy, thyroidectomy) found that these were also 30-44% longer at identified high outlier hospitals. High outlier hospitals did have a greater involvement in the training of young doctors and this may have explained the relationship with operation duration since operations assisted by a junior doctor are known to take longer (Papandria *et al* 2012) and the longer the site is exposed the greater the risk of SSI (Hedrick *et al* 2007; Barrie *et al* 1994). This may not have been the only influence, since the study also identified that the time in the operating room before and after the incision was made and closed was also extended in high outliers, which the authors attributed to less efficient 'teamwork'. Low outliers were therefore more likely to have few or no trainees and a very small turnover of staff. These factors are likely to have a positive impact on the coordination of care and efficiency with which the procedure was completed. This study therefore provides important evidence to suggest that the duration of operation is an important extrinsic risk factor for SSI and brings into question whether it should continue to be incorporated into the risk index, which is intended to adjust for intrinsic rather than extrinsic factors.

3.4.6.2 Procter *et al* demonstrated an independent association between increased duration of operation and infection events (SSI, sepsis and post-operative pneumonia) in an analysis of ASC-NSQIP data on a range of general surgical procedures. The logistic regression model found that the adjusted rate of infection complications in general surgery increased

significantly for each 30 mins of operation duration (OR 1.92; p<0.001) and that increased duration of operation also significantly increased length of post-operative stay by 6% for every half hour of duration (Procter *et al* 2010). This study identified a number of factors associated with prolonger operation duration that could explain the increased risk of SSI such as hypoxemia, glove perforation, increased deposition or airborne particles and suboptimal exposure to antimicrobial prophylaxis agents. Some of these could be considered intrinsic factors but others, such as sub-optimal exposure to antimicrobial prophylaxis, are extrinsic risk factors.

3.4.6.3 Gastmeier *et al* (2011) attempted to explore the impact of both hospital and patient factors in determining the duration of operation in data contributed to the national surveillance system between 2004 and 2008 and using type and size of hospital and volume of surgery as 'hospital' factors in the logistic regression modelling. Although the predictive power of the models was low, they found that the duration of operation was partially determined by hospitals with high volume of operations associated with shorter durations and university size greater than the median and status associated with longer operation times. All these studies confirm out findings that duration of operation is an important risk factor for SSI but that it reflects both an intrinsic and extrinsic risk factor. Future work should consider excluding it as a risk factor for adjustment of rates.

3.5 Summary of chapter

The three studies included in this chapter illustrate both the advantage and disadvantage of using surveillance data for epidemiological analyses. The important advantage is that they are able to draw on large datasets, in Coello *et al* over 70 000 records, Ridgeway *et al* over 24 000 and in Leong *et al* over 100 000 records. This enables far greater precision of

estimates of effect and sufficient data across most categories to conduct more complex analyses such as logistic regression. The use of data from many hospitals has the disadvantage of introducing centre-based variation that is not captured in a routine surveillance dataset, for example case-mix may differ and other factors such as surgeon skill and involvement of trainees may also vary between hospitals. However, these disadvantages are outweighed by the difficulty of capturing sufficient data at a single hospital to enable these types of analysis. Coello *et al* 2005 was the first example of my contribution to providing new knowledge about risks of SSI and it finding are widely cited as evidence for the impact of SSI on morbidity and mortality. My analysis of risk factors for SSI in a major category of surgical procedures applying similar logistic regression methods reflects an important and novel analysis of risk factors for SSI captured as part of a national surveillance system. Both this analysis and my investigation of the impact of one particular risk factor, the duration of operation, influenced the subsequent development of the SSI surveillance system in England and Europe. In Chapter 4, I present how I applied this evidence to that analysis of inter-hospital variation in England and inter-country variation in the European SSI surveillance system.

CHAPTER 4

Methodological challenges in comparing rates of surgical site infection

4.1 Introduction

The work presented in this chapter explores some of the important methodological issues that arise when comparing rates of SSI. Chapter 2 (section 2.2.1) described how the findings of Study of the Efficacy of Nosocomial Infection Control (SENIC) provided strong evidence for the premise that providing clinicians with information about the risk of infection in their patients affects the way that they deliver care and as a result reduces subsequent infection rates. This aligns with the models of power described by French and Raven in which information power is one of the six bases of power, but has an important influence on expert power because it supports their legitimacy (French and Raven 1959). Comparing rates with external benchmarks has been proposed as a means of enhancing the power of information to influence practice (Sherertz *et al* 1992; Gaynes *et al* 2001a) and has been associated with significant reductions in rates of SSI (Guebbels *et al* 2004; Gastmeier *et al* 2005; Guebbels *et al* 2006; Barzwolf *et al* 2006; Rioux *et al* 2007). In order to make valid comparisons a number of questions to be considered, in particular the effect of the methodology on the length of follow-up and completeness of case finding, the precision of estimated rates, and the effect of variation in intrinsic risk factors for infection. Methods of analysis are therefore a key factor in assuring validity of benchmarking systems (Haley 1995; Cooke *et al* 2000; Gaynes *et al* 2001; Wilson *et al* 2002). The first study presented in this chapter explores the implications of these factors on inter-country comparisons in data submitted to a collaborative European network of national surveillance systems (Wilson *et al* 2007; Appendix 4.1). The second study demonstrates the development of a method of benchmarking rates of SSI rates that could be used to take into account the precision of estimated rates and provided a visual, and readily understandable method

of indicating high and low performers (Wilson *et al* 2008; Appendix 4.2). The third study, explores the impact of post-discharge surveillance on rates of SSI following caesarean section and the implications of variation in intensity case finding on the reliability of inter-hospital comparisons (Wilson *et al* 2013; Appendix 4.3).

4.2 Published work 4: Inter-country comparison of rates of surgical site infection

Wilson, J., Suetens, C., Ramboer, I., Fabry, J. (2007) Hospitals in Europe Link for Infection Control through Surveillance (HELICS). Inter-country comparison of rates of surgical site infection – opportunities and limitations. *Journal of Hospital Infection.* **65(S2)**: 165-70. (Appendix 4.1)

4.2.1 Background

The demand for information about rates of HCAI has been driven in Europe by a recognition of the significance of healthcare associated infection to public health, in particular the concern about the associated morbidity, with an estimated 10% of hospital patients acquiring an infection and major costs associated with prolonged hospital stay and treatment (Plowman *et al* 2001; Fabro-Perray *et al* 2007; Smythe *et al* 2006). In addition, there were concerns about the control of communicable disease across country borders, including the risk from the emergence of highly resistant pathogens that commonly emanate from healthcare (Hospitals In Europe Link For Infection Control Through Surveillance (HELICS) 2005). At the time that the national SSI surveillance system was being established in England, initiatives to develop systems for HCAI surveillance based on the CDC programme were being developed in several European countries. Collaborations between the European Union (EU) countries targeted at evaluating practice for the prevention of HCAI had begun to develop in the 1990s, and were reinforced by the Treaty of the European Union ('Maastricht Treaty') in 1992, which gave new authority for the EU Commission to develop actions and regulation directed at guaranteeing the peoples' health rather than just contributing to that goal. The subsequent Amsterdam Treaty in 1997 required member states to work together to protect human health through *'the definition and implementation of all Community policies and activities'* directing Community action *'towards improving public health, preventing human illness and diseases'* and promote *'research into their causes, their transmission and their prevention, as well as health information and education.*' These regulations underpinned a series of initiatives focused on harmonisation of public policies, methods of surveillance and prevention of HCAI. These included

hospital based infection studies and projects such as ESCIM antimicrobial surveillance study group, EURO-Nosocomial Infection Study and European point prevalence study on infection (EPIC), as well as the first Hospitals in Europe Link for Infection Control through Surveillance (HELICS) project (Moro *et al* 1996, Vincent *et al* 2000, Cornaglia *et al* 2004; Fabry *et al* 2007).

4.2.1.1 ***The HELICS project*:** The purpose of this project was to create a framework for developing standard surveillance systems for HCAI, consensus on minimum requirements and recommendations for integrating surveillance activity into the routine of healthcare (Moro *et al* 1996; Mertens *et al* 1996; HELICS 2005; Fabry *et al* 2007). The work was undertaken by a group of experts in HCAI and surveillance including representatives from national surveillance centres, related societies and study groups. In 1998 one of the European Parliament decisions (2119/98/EC) concerned the formation of a network for the epidemiological surveillance and control of communicable diseases in the European Community. This included developing a framework for close co-operation and effective co-ordination between Member States to support appropriate actions for the protection of Community's populations, and integration of existing surveillance structures supported by Member States and creation of new structures for diseases not yet covered by existing surveillance networks. The European Commission subsequently commissioned the HELICS project to continue their previous work on developing standards for HCAI surveillance by establishing '*national/regional surveillance networks using common surveillance standards and data quality evaluation systems for all participating networks.'* (HELICS 2002). This resulted in consensus protocols for the surveillance of SSI and ICU-infections, based on systems developed previously by CDC (2.2.2), with an agreed set of mandatory data items and some optional data items (see table 4.1). Rather than establishing a new layer of surveillance, the HELICS protocol aimed to harmonise surveillance currently conducted by European networks, which whilst broadly based on CDC surveillance methodology had some country-specific variations in dataset. In line with the aim of the EU Commission to integrate the existing surveillance structures in Member States, the project aimed to assist the national networks

in adopting the harmonised HELICS master protocols and to assist those countries without a surveillance network to develop their own surveillance organisation within the HELICS partnership (HELICS 2005).

4.2.1.2 In addition to developing a standard approach to surveillance, HELICS also needed to develop indicators for HCAI at a European level and solve the technical problems of producing epidemiological data for HCAI from heterogeneous data captured across different countries in the EU. Whilst participation in HELICS required countries to agree a common protocol comprising a dataset and case-definitions for SSI, the methods of surveillance were not defined. In practice, variation in approach to surveillance, both in terms of interpretation of case definitions and methods of surveillance were likely to impact on both the sensitivity and intensity of case finding (Moro *et al* 2005). Reliance on the standard NNIS Risk Index for case-mix adjustment may not sufficiently adjust for variation on intrinsic risk factors when comparing rates of SSI in a European context and many countries had concerns about being 'labelled' as a poor performer.

4.2.1.3 The draft protocol for SSI surveillance was piloted between 2000 and 2003 and the final standard protocol was published in 2003 (HELICS 2004). I had worked closely with the HELICS data analysis group in Brussels in designing the analysis of the pilot dataset on over 170 000 operations in 10 countries. The indicators for SSI that we developed as part of this analysis, we then applied to the first set of data collected prospectively in 2004 (HELICS 2005), which formed the basis for the paper presented here. This publication explores the approach to the analysis, the potential impact of variation in surveillance methods on interpretation of the results and the limitations of inter-country comparison.

4.2.2 Conceptual and methodological development

As discussed in Chapter 2 (section 2.3.5) the primary method of minimising inherent variation in risk of SSI associated with different types of operative procedure is grouping of operations into defined categories. This enables rates to be calculated for procedures that are both likely to have similar risks of SSI and are relevant to specific groups of specialist surgeons (Health Protection Agency (HPA) 2004; Wilson 2013a; Wilson 2013b). The second strategy for accounting for difference in risk of SSI focused on variation in intrinsic risks between patients undergoing a procedure within a specific operative category. The intrinsic susceptibility to infection of patients undergoing surgery may vary depending on the extent of exposure of the tissues to micro-organisms of varying virulence and the competence of their immune system to combat them (Mangram *et al* 1999, NCCWCH 2008). The system of categorisation of surgical procedures by a Risk Index, developed by the National Nosocomial Infection Surveillance (NNIS) system in the USA in the mid-1980s had been adopted by most national surveillance systems in Europe (Haley *et al* 1985a; Culver *et al* 1991; Geubbels *et al* 2000; Gastmeier *et al* 2003). The factors included in the NNIS Risk Index had therefore been designated as core (mandatory) variables for the HELICS surveillance dataset (see Table 4.1). To explore the potential impact of inter-country differences in case-mix we looked at in the distribution of the NNIS risk index and the types of hip procedure defined by International Classification of Diseases (ICD) CM codes for total and partial hip replacements. This analysis built on the previous work I had undertaken in exploring intrinsic risk factors for SSI following hip prosthesis which had shown that the Risk Index did not sufficiently adjust for major differences in risk of SSI associated with different hip prosthesis procedures (see section 3.2: Ridgeway *et al* 2005; Appendix 3.2).

4.2.2.1 ***Case finding methods****:* As discussed in Chapter 2, the HCAI surveillance systems in England were predicated on methods that were designed to minimise the risk of selection and measurement bias, in order to support the primary aim of the surveillance of permitting inter and intra-hospital comparisons. In the case of the SSI surveillance data, these principles were guided by a defined

method of identifying patients eligible for surveillance (the denominator) and the application of standard, and as far as possible objective, criteria to determine cases of infection (the numerator) with prescribed methods of case finding based on previous research evidence (Glenister *et al* 1990). The HELICS protocol, in common with other national surveillance systems, focused on the definition of terms rather than the methods used to capture the data (Centers for Disease Control (CDC) 1991, Horan *et al* 1992; Emori *et al* 1991). Methods for recruiting eligible patients and identifying those that meet the case definitions for SSI are therefore less standardised in hospitals participating in HELICS. For example, a survey of HELICS partner countries in the early 2000s identified that in six countries the decision on whether an SSI met the case definition was made jointly by the physician and infection control practitioner, whilst in three other countries this decision was made only by the physician (HELICS 2002). Evidence suggests that the clinical criteria used to define SSI can be difficult to judge and there is poor agreement between different healthcare professionals asked to identify SSI especially when they assess the wound at different time points after the operation (Mitchell *et al* 1999, Whitby *et al* 2002). In a study comparing the English case definitions with CDC definitions we had found differences in the detection of SSI and difficulties in applying CDC definitions consistently (Wilson *et al* 2005; Appendix 4.4). Thus variation in the methodology used to identify SSI may affect both the number and type of SSI detected. Measuring the impact of this variation in methodology is difficult when analysing data captured by routine surveillance systems. In this analysis we used distribution in type of SSI (superficial, deep and organ/space) as a proxy indicator of consistency in application of the case definitions and reporting of SSI.

4.2.2.2 ***Adjusting for length of post-operative stay****:* An important difference in surveillance methodology in HELICS participants was the approach to post-discharge surveillance (PDS), which was not a defined requirement of the HELICS protocol. Whilst active and prospective surveillance methods were used in all countries, some continued surveillance after discharge for more than 50% of patients whilst others only followed patients until discharge from hospital (HELICS 2002;

Gastmeier *et al* 2003; Moro *et al* 2005; Mannien *et al* 2006). The duration of post-operative stay in hospital has a significant effect on rates of SSI because the infection may not become apparent until up to 30 days after surgery (up to one year in the case of surgery involving an implant) when most patients will have left hospital. Whilst there is little robust data on the time to SSI, a previous PHLS study which followed over 6000 patients for 28 days following surgery indicated that although 90% of SSI had developed by day 20, only 15% had become apparent by day five (Noel *et al* 1997). Other studies found that up to 70% of SSI were detected post-discharge, depending on the type of surgery and median length of postoperative stay (Stockley *et al* 2001; Reilly *et al* 2006). Even if post-discharge case finding systems exist, the infections are more difficult to detect once the patient has left hospital and the efficacy of detection methods varies (Petherick *et al* 2006). Thus rates for a particular category and country will depend on the average length of post-operative stay in hospital and the intensity and effectiveness of post-discharge surveillance. The cumulative incidence (CI) would therefore only provide an effective comparator if all patients are followed up for the entire period in which SSI could be detected, or at least a similar period in all countries, otherwise it will be biased by length of postoperative stay. Differences in healthcare systems drive considerable variation in length of post-operative stay and even where PDS was conducted there were differences in approach between countries and categories that may have affected intensity of case finding. Another key factor to be considered is the precision of estimated rates of SSI surveillance since networks differed in the number of participating hospitals, categories chosen and duration of surveillance (HELICS 2002, 2005; Mannien *et al* 2008; Reilly *et al* 2006). Methods selected to compare rates of SSI between countries therefore needed to take account of these factors.

4.2.3 Summary of main methods and findings

By 2003, 16 countries in Europe had established national networks for the surveillance of SSI and the majority were either participating or preparing to participate in HELICS. Following the analysis of the pilot data, 2004 was the first year of 'routine' data contributed to HELICS and comprised data on

111,361 operations captured by 14 networks in 11 countries. This dataset was therefore used for analysis of inter-country comparisons in this publication. Data completeness was high with data available for 93% of mandatory variables shown in table 4.1, but lower for the 'required' (86%) and 'optional' (46%) variables. The mandatory fields most likely to have data missing were ASA score (93.9%) and date of SSI (91.6%). However, some 'required' fields also suffered from incomplete data. In particular, date of discharge was not captured by the surveillance systems in some countries (Germany, Poland) and in Finland was missing in 27% of records. These records were therefore excluded from the calculation of ID.

Table 4.1: HELICS SSI Surveillance: Standard dataset

Source: HELICS 2004

Variable	**Data**	**Field rule***
Operative procedure ID	Unique no.	M
Age	Years	R
Gender	M, F, Unknown	R
Data of admission		O
Date of operation		M
Date of last follow-up	In hospital	R
Discharge status	Alive or dead	R
Date of last follow-up	Post-discharge	O
Primary operation code	NNIS procedure code	M
Primary operation code	ICD-9 CM code	O
Endoscopic procedure	Yes/No, 9=unknown	R
Wound class	1-4, 9=unknown	M
Duration of operation	Minutes, 999=unknown	M
Urgent/elective	Urgent = not planned 24hrs in advance, 9=unknown	R
ASA score	1-5, 9=unknown	M
Perioperative antibiotics	Within 2 hrs of primary incision, 9=unknown	O

*M = mandatory (record rejected if missing); R = Required (used for routine analysis but record not rejected if missing); O = optional

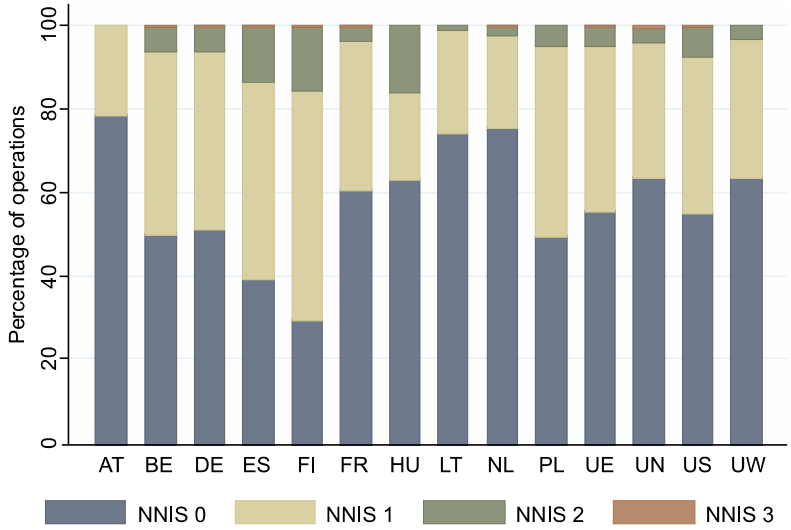
Missing or inaccurate data in other elements of the risk index meant that the risk group could only be calculated for 93% of records, but in order to include all data in the analysis we created a group of 'unknown risk index'. Since hip prosthesis was the only category included by all 14 countries and accounted for 44% of the records we selected this category to explore variation in case mix between countries. The next largest category was caesarean section included by eight countries and accounting for 18% of records.

4.2.3.1 ***Variation in risk factors for infection****:* Some basic aspects of case-mix such as gender and age were found to be similar across all countries, however there were marked differences in distribution for the standard Risk Index within specific categories of procedure. In hip prosthesis, 80% of patients who underwent the procedure had none of the three risk factors (Austria, Lithuania and Netherlands) compared to only 30% of patients in Finland (Figure 4.1). Such variation in distribution across risk index groups may be due to a number of factors: differences in healthcare system that result in patients with different levels of severity of illness accessing treatment, differences in interpretation of definitions of risk index criteria or imprecise distribution based on small numbers of procedures contributed by some countries.

4.2.3.2 Another key factor likely to affect both Risk Index distribution and rate of SSI was heterogeneity of procedures included within a category, reflecting differences between healthcare systems and organisation of national surveillance systems. ICD9-CM codes captured by 10 counties for the hip prosthesis category were used to explore the potential effect of these factors. Using methods previously applied to English SSI surveillance data (section 3.2; Ridgeway *et al* 2005; Appendix 3.2), we identified a higher rate of SSI in patients undergoing partial hip replacement rather than total hip replacement (1.6% versus 4% respectively). Clearly, if similar differences were evident in the European data then the mix of these procedures would influence the rate of SSI and affect the validity of inter-country comparisons. The analysis of HELICS data demonstrated

heterogeneity in the distribution of these two types of procedure with surveillance data from some countries (Germany, Scotland, Hungary) only including total hip replacement procedures, whilst in others more than 20% of procedures were partial hip replacements.

Figure 4.1: Distribution of risk index in hip prosthesis operations contributed to HELICS (2004)



Key: AT Austria, BE Belgium, DE Germany, ES Spain, FI Finland, FR France, HU Hungary, LT Lithuania, NL Netherlands, UE England, UN Northern Ireland, US Scotland, UW Wales.

4.2.3.3 ***Type of SSI****:* The inter-country comparisons also highlighted significant differences in distribution of type of SSI. In hip prosthesis, there were nine countries with data on less than 50 SSI in this category and observed differences may therefore reflect chance variation. Among the other five countries, Finland and Germany reported less than 30% of SSI as superficial whilst England and Scotland reported over 70% and Netherlands 50%, with no distinction between deep and organ/space. Whilst it is possible that these differences reflected true variation in the occurrence of superficial and deep SSI, a more likely explanation is that the differences reflect variation in application or interpretation of the definitions of SSI. Firstly, whilst countries participating in HELICS captured data according to the standard protocol, there were local differences in application of definitions (e.g. in England and the Netherlands a clinicians diagnosis did not meet the definitions if

clinical signs were absent) and in England and Finland extended criteria were applied to wound culture (Wilson *et al* 2004 (Appendix 4.4); HPA 2004; Huotari *et al* 2007). In particular, the HELICS criteria for superficial SSI are relatively subjective and prone to variation in interpretation (Wilson *et al* 2004). The second potential source of variation is post-discharge surveillance methods, which varied in terms of extend and intensity between countries and may have influenced the proportion of more severe SSI detected. In Finland and the Netherlands in particular, PDS was an integral component of the surveillance protocol whereas in England PDS data was not included and in Germany was encouraged but not formalised in the surveillance protocol (Coello *et al* 2001; Huotari *et al* 2007).

4.2.3.4 ***Post-discharge surveillance****:* The analysis found that the follow-up of patients to detect SSI that develop after discharge from hospital was a major source of bias. There were two factors that inter-played in this relationship, firstly the length of post-operative stay in hospital which varied between categories of procedure but also between countries. For example the median length of hospital stay after hip prosthesis for all data combined was nine days but ranged from one to 22 days (excluding outliers). However, the median also varied between countries from six to 12 days and this reflected a decline in length of hospital stay compared to the 2000-03 report where the median was 10 days and range six to 13 days. In some countries, such as Finland, the short length of stay was influenced by a system of accelerated discharge to rehabilitation units (HELICS 2005). If all patients were likely to be followed up equally throughout the surveillance period (1 year for procedures with an implant, 30 days for those without) the length of post-operative hospital stay would not be a source of bias. However, there were significant differences in approach to PDS. Some countries, such as the Netherlands recommended specific methods of surveillance after discharge for hospital participating in the national PREZIES surveillance system. In a study by Mannien *et al*, active PDS was performed for 49% of patients with passive surveillance for the remainder and as expected a greater proportion of SSI detected by the active methods (Mannien *et*

al 2006). In Scotland, a study by Reilly *et al* indicated that PDS was conducted for 59% of procedures included in the surveillance, mostly by active methods and that the rate of SSI was significantly increased where active PDS was performed (Reilly *et al* 2006). This variation in PDS methods meant that for hip prosthesis, whilst overall only 20% of SSI were detected by PDS, in some countries such as England and Spain, there were no SSI reported by PDS whilst in other countries 50% or more of SSI were detected by PDS. Inter-country comparison of cumulative incidence rates would clearly not be valid if based on both inpatient and post-discharge SSI, yet if based only on inpatient SSI would be biased by the duration of follow-up i.e the length of post-operative stay.

4.2.3.5 ***Incidence density rates***: The solution to this problem was to use a metric that we had applied for comparing rates of SSI in the English surveillance system, the incidence density (ID). This approach had been developed as a mechanism for accounting for variation in length of post-operative stay and to adjust for the impact of reductions in length of stay following orthopaedic surgery on trends in rates of SSI (HPA 2005). The ID uses the number of days of post-operative follow-up as the denominator rather than the number of procedures (HPA 2005) and accounts for some of the observation bias associated with different periods of follow-up adjustment. Since the numerator and denominator must be from the same population the ID must be based only on those SSI detected during the hospital stay. Whilst this has the disadvantage of underestimating the risk of SSI (as infections detected post-discharge will be excluded) and is not as readily understood as a CI, it better meets the requirement of a valid comparator especially in the context of wide variation in length of stay. Therefore, in this analysis of the HELICS data the ID and CI metrics for SSI were compared to explore the impact of each on inter-country comparisons.

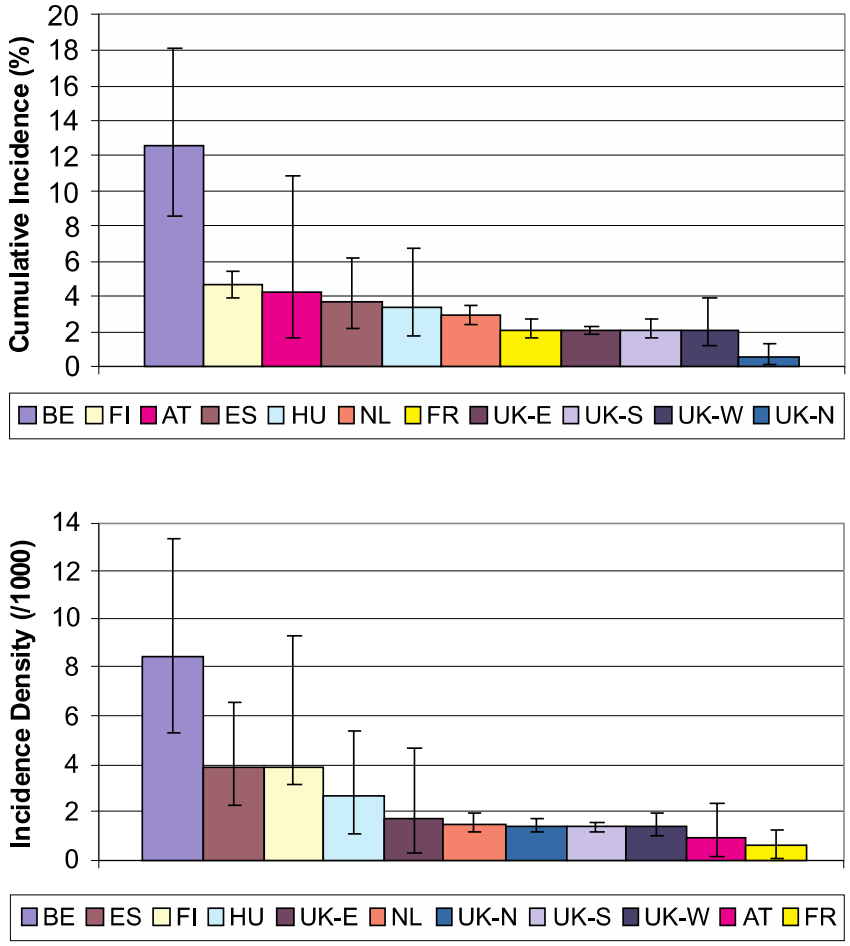
The ID is calculated as follows:

Incidence density (ID) of SSI (per 1000 days of inpatient follow-up):

$$\frac{\text{No. SSI}}{\text{No. days inpatient follow-up}} \times 1000$$

However, this metric only partially adjusts for follow-up period as the risk of SSI cannot be assumed to occur at a constant rate for each day after the procedure. Indeed, there was evidence that the detection of SSI was greatest at between day six and 10 after the operation (HELICS 2005). Another limitation of this approach is that the rate does not include SSI detected after discharge from hospital and as a result would underestimate the true rate. The incidence density could also only be calculated for countries where the date of discharge from hospital was captured, the datasets from Germany, Poland and Lithuania were therefore excluded from this analysis. The value of this metric could be demonstrated by comparing the rank position of countries based on cumulative incidence and incidence density. The relative position defined by these two metrics was different for nine out of 11 counties for whom the incidence density could be calculated for hip prosthesis (Figure 4.2). The confidence limits on this figure also illustrated an additional problem associated with inter-country comparisons, that of precision of estimates. The rate for Belgium, whilst ranked one for both metrics was based on 191 operations and had correspondingly wide confidence limits around the rate. Most differences in rates between countries were shown not to be statistically significant by the overlapping confidence intervals.

Figure 4.2: Comparison between SSI cumulative incidence (top) and incidence density (bottom) for hip prosthesis by country



Key: AT Austria, BE Belgium, DE Germany, ES Spain, FI Finland, FR France, HU Hungary, NL Netherlands, UE England, UN Northern Ireland, US Scotland, UW Wales.

Bars = 95% confidence intervals

4.2.4 Conclusions

This analysis of this first year of SSI surveillance data submitted to HELICS highlighted key methodological issues that are not necessarily addressed in a standardised protocol that tends to focus more on the data items and less on the specific methods of case-finding. The latter are difficult to regulate as they are often dictated by the systems of organising healthcare or the political imperatives of national policy such as the discharge to rehabilitation centres in Finland and

introduction of mandatory orthopaedic surveillance in England (Department of Health 2003; Gastmeier *et al* 2007). Whilst these analyses were able to point to variation that was indicative of differences in underlying surveillance methodology, we could only speculate about the likely contributory factors because the precise causes of the observed variation and the specific effect of differences in methodology could not be determined from these datasets. Another limitation was the paucity of data available for case-mix adjustment. The analysis conducted on different types of hip prosthesis for which data was available from 14 countries, pointed to the potential effect of differences in case mix on rates of SSI, and it is likely that similar factors come in to play in other categories of procedure but these have yet to be determined. Such case-mix differences are likely to be greater when making inter rather than intra-country comparisons because of variation in healthcare systems and patterns of ill-health. Finally, although the completeness of the datasets was good for mandatory and required variables, other missing data, in particular the date of discharge from hospital, limited the ability to adjust for variation in duration of follow-up when calculating rates as incidence densities. Nonetheless, whilst not all of the differences highlighted in this analysis could be explained, understanding their impact was important to ensure that the heterogeneity of apparently similar data is recognised and inappropriate conclusions are not drawn when making inter-country comparisons.

4.2.4.1 ***My contribution to this research***

This paper represented the first major analysis of SSI data contributed to this European collaborative. I was a pivotal member of the analysis team who developed the approach to analysis of the pilot data, I informed the approach of using incidence density and developed the methods for comparing rates of SSI in hip prosthesis. My expert knowledge of SSI and surveillance systems was also instrumental to the interpretation of the results. The principles that we developed for the analysis of the pilot data we then applied to this first prospectively captured dataset. I subsequently wrote this publication as a summary of the detailed analysis and in order to explore and define the

implications for the comparison of rates between the HELICS countries.

4.2.5 Contribution of this study to contemporary knowledge

My work on making inter-country comparisons of rates of SSI represented an important collaboration between the leaders of 14 country networks for SSI surveillance, as well as the data managers for HELICS at the Epidemiology Unit at the Scientific Institute of Public Health in Brussels. At the time of this study there were few examples of such inter-country comparisons in the literature (Mertens *et al* 1994; Coello *et al* 2001; Moro *et al* 2005; Mannien *et al* 2007) and this work has subsequently been cited by at least 60 other publications. Data contributed to the HELICS SSI database by 14 countries provided a unique opportunity to explore inter-country variation in rates of SSI as it is unusual to have access to raw, analogous data from several countries. It was important to describe the key limitations of inter-country comparison to avoid inappropriate conclusions being drawn about relative differences in rates of SSI. This work was also an important landmark for the HELICS network as it represented the first peer-reviewed publication of SSI data. The approach that we developed for this analysis has formed the basis of subsequent annual statistical reports for HELICS (ECDC 2012a, 2012b, 2013). Whilst the HELICS protocol was designed to report the cumulative incidence of SSI, our analysis demonstrated variation in surveillance methods between national systems that required a more sophisticated approach to the calculation of SSI rates. Whilst it represented a unique, large and largely comparable set of data on the risk of SSI across a broad range of operative procedures, the analysis did highlight key aspects of the data that suggested inter-country comparisons should be made with caution. Whilst it is often assumed that standard case definitions will identify the same infections in different centres or countries, they are often not easy to apply consistently and some criteria, in particular clinicians diagnosis and the culture of microorganisms from wound fluid or tissue, are prone to local variation in interpretation (Wilson e*t al*; Appendix 4.4). Ironically, acknowledging the limitations of the inter-country comparisons did help to sustain and increase participation in the surveillance since it enabled countries to explain

possible reasons for apparent differences in their rates of infection compared to other countries that could be used to avoid drawing unreasonable inferences about variation in performance.

4.2.6 Subsequent research contributions to the field

One of the key potential sources of variability that we identified in our attempts to compare rates between countries was the evidence of differences in the application of the case definitions to detect SSI. A study published by Lepelletier *et al* in 2012 demonstrated the complexity of consistently identifying SSI. They asked 140 healthcare professionals from seven specialties to identify SSI from 40 case-vignettes, found consensus in only 52.5% and that reading the SSI definition only improved agreement in specialties where the consensus had been poor initially. Indeed, the relatively low proportion of superficial SSI reported in the French national surveillance system (Figure 2: Wilson *et al* 2007) may have been influenced by the role of surgeons in diagnosing the SSI in this country, albeit according to CDC definitions (Rioux *et al* 2006). Similar variation was found when applied to infectious disease physicians and surgeon across 10 European countries (Birgand *et al* 2013). Talbot *et al* (2013) suggest that HCAI definitions are not intended for clinical diagnosis because the latter depend on subjective judgment to guide treatment whilst the former should, depend on objective criteria in order to achieve high inter-rater reliability. Inter-rater reliability is strongly dependent on the systems established to capture data and audit quality and these are likely to vary widely between countries with different national surveillance systems (Lawson *et al* 2012). Indeed, Gastmeier has called for a standard validation protocol that could be used to conduct validation studies for European surveillance systems to support more robust inter-country comparisons and this remains a goal for the ECDC SSI surveillance network (Gastmeier *et al* 2007; ECDC 2013).

4.2.6.1 Post-discharge surveillance (PDS) was another key influence on rates of SSI that we identified. In a comparison between SSI surveillance systems in Germany and the Netherlands major

differences in intensity of post-discharge surveillance were identified so that in the Dutch system 34% of SSIs were identified after discharge compared to only 21% in the German system (Mannien *et al* 2007). An additional problem with PDS methodology is the bias associated with some methods in the detection of more severe deep and organ/space SSI. Patients with these infections are more likely to be readmitted to hospital for further treatment than superficial SSI and therefore more readily detected by active surveillance for readmissions. This effect was clearly illustrated after the SSISS in England introduced requirements to report patients readmitted with SSI in 2008. In orthopaedic surgery this resulted in the proportion of SSI reported that were deep and organ/space SSI increasing from 30 to over 50% of all SSI (HPA 2010). Some authors do not take account of the effect of length of stay on case-finding. For example, Herrazo *et al* (2013) identified a 7% yearly reduction in rates of superficial SSI in their Madrid hospital, but no variation in rate of deep SSI. Since they did not collect data on length of postoperative stay this study was unable to adjust for the potential effect of declining lengths of stay and the impact that might have on detection of superficial infections over this time period. In the analysis of HELICS data we did not attempt to adjust rates by risk factors because missing data would have markedly reduced the precision of the estimated rates. Adjustment for variation in length of post-operative stay is clearly preferable when comparing rates in the absence of robust PDS, and other have attempted other methods than the incidence density that we used in our analysis. Astagnaeu *et al* (2009) included postoperative follow-up as a confounding variable in the logistic regression analysis that demonstrated reducing incidence of SSI reported by the French ISO-RAISEN surveillance network. Mannien *et al* adjusted rates by the method used to detect SSI post-discharge in order to produce more robust estimates for reductions in rates of SSI following hip prosthesis observed by the Dutch PREZIES surveillance system between 1996 and 2006 (Mannien *et al* 2008). Other surveillance systems have chosen to manage the problem of intensity of case finding post discharge and the bias in type of SSI detected by excluding superficial SSI detected PDS and only including SSI detected in inpatients or on readmission in the calculation of comparative rates (National Quality Forum 2008, HPA 2008).

However, this method also has also been demonstrated to have drawbacks since patients readmitted with SSI to other hospitals will underestimate the rate of SSI and, where used for public reporting, will undermine the accuracy of relative rankings (Yokoe *et al* 2013).

4.2.6.2 The demand for public reporting of rates of HCAI has grown inexorably over the last decade, although is greater in some countries than others (Haustein *et al* 2011). There are undoubtedly important differences between hospitals that are driven by variation in the quality of care and infection prevention practice, and public reporting of rates may have an important part to play in driving improvements (Kiernan 2013). However, differences in case-mix and surveillance methodology have a marked effect on detection of cases of SSI and more work is required to understand how these contribute to both inter-centre and inter-country differences in rates and to develop mechanisms that can be used to account for them when making comparisons. The next publication (Wilson *et al* 2008; Appendix 4.2) continues with this theme of making valid comparisons of rates and is focused on the development of a method for identifying hospitals with unusually high or low rates of SSI. This reflects the key aim of the English surveillance system to enable comparison of rates with robust external benchmarks, thereby enhancing the power of the data to influence clinical practice and improve healthcare outcomes (Gaynes *et al* 2001a; Cooke *et al* 2002).

4.3 Publication 5: Rates of SSI after hip replacement as a performance indicator

Wilson, J., Charlett, A., Leong, G. *et al* (2008) Rates of surgical site infection after hip replacement as a hospital performance indicator: analysis of data from the English mandatory surveillance system. *Infection Control Hospital Epidemiology* **19(3)**: 219-26. (Appendix 4.2)

4.3.1 Background

The demand for measures of performance in relation to healthcare began to emerge in the United Kingdom in the early 1990s with the introduction of the 'internal market' and separation of the roles of purchase and supplier of healthcare (Propper *et al* 2003). This was underpinned by the publication of the *Patient's Charter* in 1991, which introduced the concept of 'performance tables' designed to provide patients with information about hospitals and support their ability to choose services (National Health Service Executive 1991). These measures were largely financial and focused on 'processes' rather than 'outcomes' until 1997 when the re-organisation of the NHS resulted in a new emphasis on achieving quality as well as efficiency within health services. This introduced a requirement to assure 'clinical' as well as financial governance and the establishment of regional and national systems to monitor outcomes of care (Department of Health (DH) 1998). In 1995, the value of measuring HCAI and enabling hospitals to compare their rates was recognised by the Hospital Infection Working Group of the Department of Health and PHLS which recommended that '*a voluntary national reporting system should be established, which will enable hospitals to compare their data against aggregated anonymized data from other hospitals. Investigation by the hospital of areas where it appeared to differ significantly from the norm would then be possible*' (DH 1995, Cooke *et al* 2000). Initially there was reluctance to publish performance measures since it was perceived that the complexity of case-mix and other factors would make 'league tables' misleading (DH 1999). However, through the 2000s as other league tables, notably those applied to schools were developed these views changed and a range of performance measures or 'clinical indicators'

began to be published (DH 1999). The Department of Health began to suggest that improvements in data quality would enable meaningful comparison of HCAI data, and that action would be driven by their results (DH 2000). This approach was supported by the National Audit Office in its report on the management and control of HCAI that recommended the use of HCAI surveillance data for inter-hospital comparison and identifying poor performers (National Audit Office (NAO) 2000). In February 2002, the first league table of HCAI in acute NHS Trusts in England was published in the form of rates of meticillin resistant *Staphylococcus aureus* bacteraemia rates (Chief Medical Officer (CMO) 2006) Tables of performance in relation to SSI were first published by SSISS in late 2005 following the introduction of mandatory orthopaedic SSI surveillance in April 2004 (CMO 2003).

4.3.1.1 Concerns remained about the validity of healthcare performance measures, in particular whether the observed variation in performance can reasonably be attributed to variation in clinical practice (Nutley and Smith 1998) and key methodological issues that influence interpretation of comparisons (Goldstein and Spiegelhalter 1996; Davies and Lampel 1998; Goddard *et al* 2002; Adab *et al* 2002; Freeman 2002; Bird *et al* 2005).

These concerns included:

1. Variation in inherent risk of infection between different groups of patients exposed to different procedures and appropriate denominators that address this variation.
2. Comparability of methods used to capture denominator and numerator data.
3. Robust analytical methods that take account of the precision of point estimates and the effects of sampling and case-finding variation.
4. Mechanisms of representing data to non-expert audiences (ranging across the public, clinicians, manager and politicians) that make the results accessible whilst minimising the possibility of misinterpretation.

4.3.1.2 ***Mandation of SSI surveillance in orthopaedic surgery***: The national SSI surveillance system in England had been established on a voluntary, confidential basis in 1997. However, in response to the political imperative to measure performance the Department of Health made participation in surveillance of SSI in orthopaedic surgery mandatory for all NHS Trusts in England from April 2004 (CMO 2003). The data would be published annually, be made available to the public and used to inform patients about risk of SSI at individual hospitals via the NHS Choice website. The study described in this publication reports the analyses we used explore the issues surrounding these rate comparisons, factors that influence variability in the risk of developing SSI following hip prosthesis, and the development of robust methodologies to identify hospitals with outlying rates of SSI that would justify investigation.

4.3.2 Conceptual and methodological development

The mandatory orthopaedic SSI surveillance system had the advantage of being based on clearly defined methods and robust data quality management systems and whilst the intensity of case finding might vary between centres, unlike the inter-country comparisons, there were not major differences in approach to surveillance and healthcare delivery systems (see section 2.2.3). At the time these analyses were conducted, the methodology did not include post-discharge surveillance (PDS) and although the length of hospital stay for elective orthopaedic surgery had decreased significantly in preceding decade, it was fairly consistent across participating NHS hospitals (HPA 2005).

4.3.2.1 One of the difficulties in making comparisons in rates of SSI is disparity between centres in the number of procedures undertaken which results in variation in the precision of estimated rates and highly imprecise rates being generated where surgical throughput is low. As illustrated in figure 2.2 (section 2.3.1.2) our initial approach to identifying hospitals with outlying rates of SSI was the box and whisker plot where rates above the 90th percentile were deemed as outliers. However,

imprecise rates based on low number of procedures could not be reliably distinguished by this method and hospitals that had contributed data on less than 50 procedures were therefore excluded from the plot. Since the mandatory surveillance required performance data to be available for all hospitals, the first set of data were published in large table and based on CI rates of SSI (the proportion of 100 operations that developed SSI) as it was perceived that ID would not be readily understood or translated back into the more intuitive measure of risk. Confidence intervals around these rates were used to indicate the precision of the estimated rate and whilst they were accompanied by a simple description of how to interpret the rates of SSI presented in these tables; the concept was undoubtedly difficult for non-experts to comprehend. A different, more robust graphical method of discriminating hospitals with outlying rates of SSI was therefore required and my publication describes an approach based on the funnel plot that we subsequently developed.

4.3.2.2 ***The concept behind the funnel plot****:* Distinguishing exceptional results from those expected by normal chance variation had been recognised as a problem in manufacturing industry by Shewhart in the 1920s (Shewhart 1939). Shewhart developed the theory of statistical process control (SPC), which used the principles of statistical distribution to distinguish random or common cause variation from special cause (non random) variation (Berwick 1991). A core component of this methodology is the use of prediction values, or control limits. These are based on the principle that within a normal distribution, 95% of the measurements will fall with two standard deviations (SD) of the mean and 99% within three standard deviations (Berwick 1991, Lee and Sellick 1994). Measurements that fall outside these ranges therefore reflect non-random variation. One of the key advantages of this methodology is that charts can be created with minimal statistical analysis but can detect significant signals from the data in a powerful, graphical form (Benneyan 1998a and 1998b; Mohammed *et al* 2001; Benneyan *et al* 2003). Although SPC charts had largely been confined to industrial processes, in the late 1990s Benneyan began to apply the methodology to measuring and communicating healthcare improvements (Benneyan *et al* 1998, 2003; Curran *et al*

2006). Whilst the standard SPC chart was essentially a run chart with a series of measurements plotted in time order, a variation of this chart proposed that plotted observed events against the sample size as an indicator its precision in order to detect centres or units with outlying performance (Spiegelhalter 2002). In the case of healthcare events such as the deaths associated with the GP Harold Shipman the number of deaths were plotted against the denominator of GP case-load (Mohammed *et al* 2001). These funnel plots illustrate graphically the distribution of rates across several centres and superimpose thresholds at which the observed indicator is significantly different from the distribution mean that equate to the 95% (2SD) and 99.8% (3SD) control limits and equate to significance levels of $p<0.05$ and $p<0.001$. These control limits can then be used as a 'warning' or 'alarm' of poor performance and can be used to trigger investigation (Speigelhalter 2005a). Marshall *et al* illustrated the value of funnel plots in encouraging health-service decision-makers to reduce over-investigation of unusual performance when compared to standard league tables (Marshall *et al* 2004). This approach therefore seemed to offer a potential solution to the problem of presenting data on rates of SSI in such a way that would avoid inappropriate action but encourage investigation of poor performance. In addition to exploring the use of funnel plots as a method of identifying hospitals with outlying rates of SSI, this study also set out to describe the risk of SSI associated with THR and HH in England, using ID to illustrate that whilst the CI rate for HH was significantly higher than THR, this difference was markedly reduced if adjusted by the length of postoperative stay.

4.3.3 Summary of main methods and findings

A total of 22 160 hip prosthesis operations undertaken during a 12 months period and 430 SSI detected during the post-operative stay in 125 hospitals were included in the analysis. The CI indicated that the rate of SSI in HH (4.06%) was three times greater than the rate for THR (1.26%). However, using ID (see section 4.2.3.5) to account for differences in case finding period demonstrated that the rate in HH was only 1.7 times higher than THR when the longer length of hospital stay (median 14 days vs. 7 days) was accounted for. The rate of SSI was also significantly

higher following revision surgery and even higher at 11% (95%CI 6.5% - 16.9%; p<0.001) where the revision was due to infection. A chi^2 test for trend was used to confirm that in the 82% of records where complete risk factor data was available, there was a significant association between rate of SSI and the number of risk factors present, confirming the applicability of the risk index to this English dataset. Unlike other national surveillance systems we captured data on microorganisms found to be causing SSI and this data was available for 84% of the SSI. This provided evidence for the significant role of methicillin resistant *Staphylococcus aureus* as a cause of SSI, accounting for 36% of the infections, with 67% of the *S. aureus* causing SSI resistant to methicillin.

4.3.3.1 ***Identifying outlying rates of SSI using box and whisker plots***: The mandatory surveillance requirements were that hospitals were required to conduct a minimum of three months surveillance and participation by hospitals varied from all four quarters (28%) of hospitals to only one quarter (41% of hospitals). In order to explore the effect of ranking hospitals by cumulative incidence of SSI we plotted the rates for each hospital in a box and whisker plot where the lines in the box represent the rate of SSI at the 25^{th}, 50^{th} and 75^{th} percentile of the distribution, and the end of the lines (whiskers) the 10^{th} and 90^{th} percentiles (see figure 2.2; section 2.3.1.2). Hospitals with rates above the 90^{th} percentile were identified as outliers on the basis that a rate that was higher than 90% of other hospitals was more likely to reflect a problem that required investigation with sufficient margin for error to reduce the chance the rate was influenced by case-mix. We identified 19 hospitals with rates above the 90^{th} percentile but 10 of these were based on less than 50 operations in both categories. This reflected two factors, firstly that there is marked variation in orthopaedic surgical capacity between centres and secondly that hospitals undertook surveillance for between three and 12 months in any year and therefore accumulate different volumes of data. We used exact confidence intervals to measure the precision of these estimates, since normal approximation methods are unreliable for a dataset where the number of SSIs is less than 10 and can generate lower confidence intervals of less than zero (clearly an unrealistic value for an estimate of

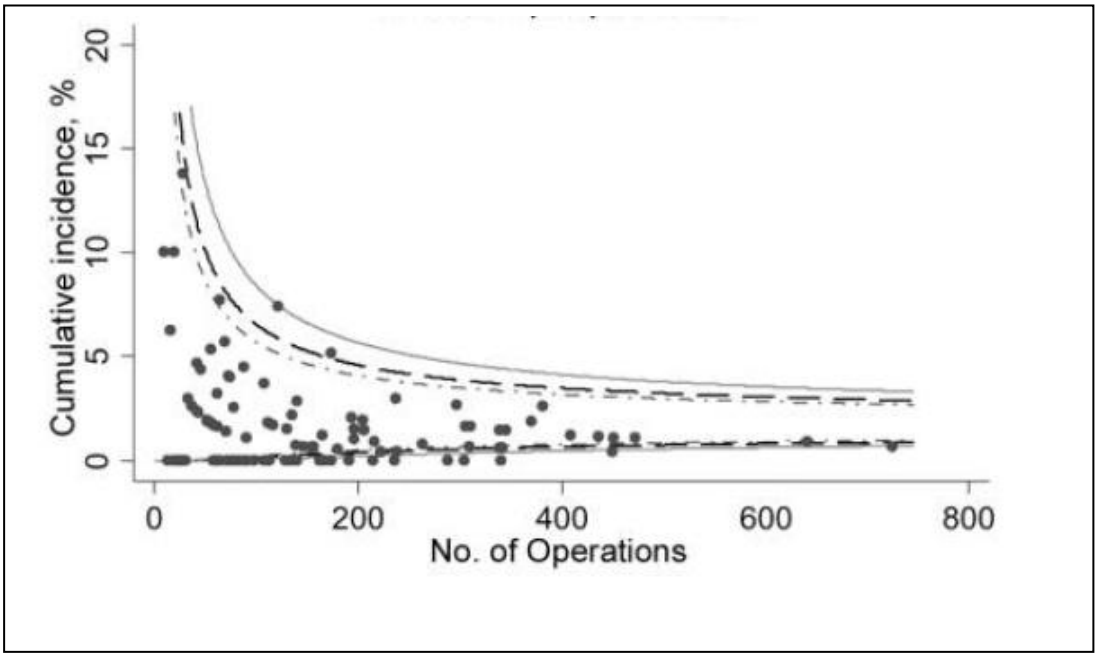
proportion). However, exact confidence intervals tend to be conservative and therefore generate intervals that are wider than necessary for a 95% confidence that they contain the true rate.

4.3.3.2 ***Identifying outlying rates of SSI using funnel plots***: We constructed funnel plots with the same data, plotting the incidence rate for each hospital against the number of operations (or number of postoperative patient days) on which the rate was based. We created 'warning' and 'action' limits based on exact 95% and 99% confidence intervals (CI) around the pooled incidence rate and used two-sided CIs so that hospitals with either unusually high or low rates could be identified. One phenomenon that is often observed with data in funnel plots is over-dispersion. This occurs when there is excess variability between centres, which is not explained by chance and which results in a disproportionate number of centres being labelled as above or below the control limits (Spiegelhalter 2005b). Such variability suggests a non-homogenous population and that other factors are contributing to the observed variation. Where over-dispersion is evident, mechanisms such as grouping or risk stratifying centres or including a random effect to account for variation between hospitals in calculating control limits are required to reliably identify outliers (Spiegelhalter 2005b; 2005c). In the case of healthcare events, variation in the size and nature of hospitals and the case-mix of patients that they treat commonly result in over-dispersion. In this SSI dataset there was no evidence of over-dispersion, probably because the data is based on groups of clinically similar procedures which minimises heterogeneity between centres. The control intervals therefore did not require adjustment for over-dispersion. Figure 4.3 illustrates the funnel plot for the cumulative incidence rates for THR with exact confidence intervals (control limits) set at 90%, 95% and 99%. This shows that only two hospitals identified as outliers by the Box and Whisker plot are identified as outliers with a rate above the 95% control limit on the funnel plot (see also Wilson *et al* 2008; Appendix 4.2). The imprecision of the rates for the other Box and Whisker plot outliers means that their position on the funnel plot is to the far left and below the control limits. A rate above the control limit should be perceived as a 'trigger for investigation' rather than indicating a poorly

performing hospital since the rate could still be explained by chance or by unusual case-mix. However, the value of this approach is that it focuses effort on those centres most likely to have unusually high (or low) rates and minimises resources being spent on the investigation of high rates of SSI that reflect chance variation. In addition, by varying the point at which the control limits are set it is possible to balance the certainty with which outliers will be defined and the trigger for investigation.

Figure 4.3: Funnel plot comparing rates of SSI in total hip replacement between hospitals.

Key: Dot = rate at a hospital; Dotted line 90%CL; Dashed line 95%CL; Solid line 99%CL

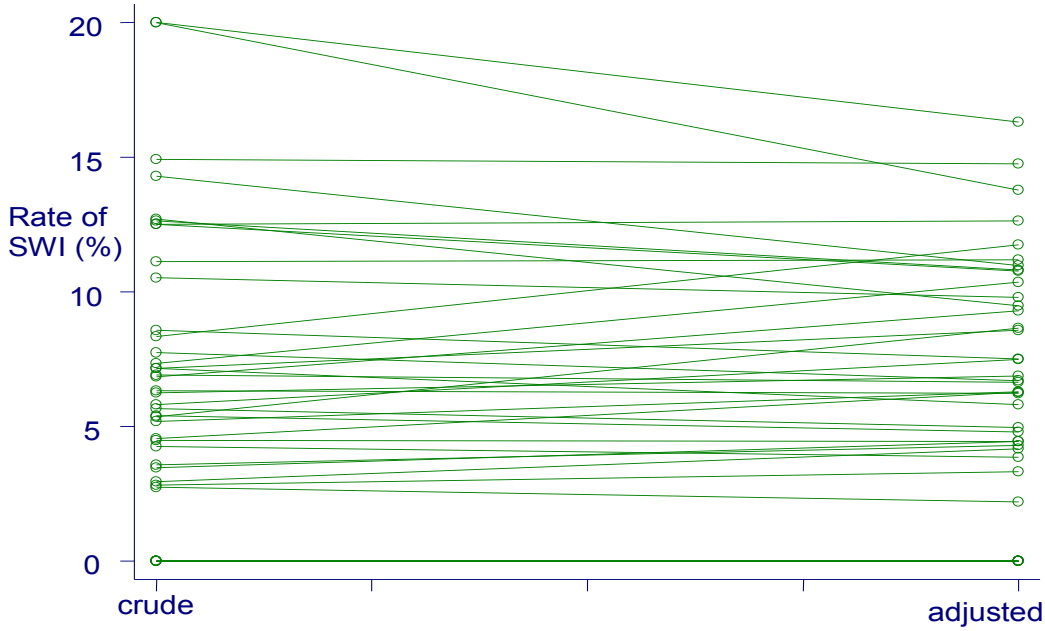


4.3.3.3 We also considered adjusting the rates for case-mix as this could account for high rates associated with case-mix variation. However, about 20% of records in the English surveillance dataset could not be allocated to a NNIS Risk Group because one or more of the contributory variables was missing, and these would have to be excluded from the analysis. This would make reduce the precision of the estimated rate still further. In a previous analysis exploring variation in rates of SSI in vascular surgery I had found that whilst there was some variation in the distribution of

risk index between centres, in the majority of hospitals adjusting rates by indirect standardisation did not significantly affect their relative position compared to the crude rates (Figure 4.4). This suggested that, in a UK setting where NHS hospitals are likely to have a broadly similar case-mix for this type of general surgery, there is limited benefit to risk-adjusting rates in the funnel plot and significant adverse impact associated with the reduction in eligible records to include in the rate. Provided that rates above the control limits are considered a trigger for investigation rather than punitive indicators of poor performance, then the role of risk factors in explaining a high rate can be explored in the subsequent investigation. Prior risk adjustment of rates would therefore add little benefit. In addition, others have pointed out the problems of using an indirect method of standardisation because it applies stratum specific rates of the reference population to different populations with the potential for confounding if the distributions are different (Delgado-Rodriguez and Llorca 2005).

Figure 4.4: Relationship between crude rate of SSI and rate adjusted for NNIS risk index and age of patients.

Source: Wilson 2002



Another important finding was the high number of hospitals with rates below the 10% control limits. Whilst this might reflect good performance, other likely explanations are inadequate surveillance methods and low sensitivity of case finding. This is a particular problem if rates are to be used for inter-hospital comparison and benchmarking (Tanner *et al* 2013a; 2013b).

4.3.4 Conclusions

This impact of this publication was that it presented a novel method of identifying outlying rates of SSI developing the funnel plots for a unique use in the national benchmarking system. In addition, we built on the analysis of risk factors for SSI following hip prosthesis described in Chapter 3 (Ridgeway *et al* 2005; Appendix 3.2) where we had identified the issue of variation in follow-up period between HH and THR procedures. We presented comprehensive data on risk factors for SSI with robust estimates derived from a uniquely large dataset. In applying the methodology for calculating rates of SSI that we had developed for surveillance reports and used in the analysis of HELICS data (HPA 2005; Wilson *et al* 2007; Appendix 4.1), we demonstrated the more robust comparison of risk of SSI based on ID rather than CI.

4.3.4.1 As acknowledged in the discussion, the presentation of variation in rates of SSI in a funnel plot might have been improved if rates could be adjusted the by risk factors for SSI, in particular the Risk Index factors, age and trauma which we had previously shown to significantly affect the risk of SSI (Ridgeway *et al* 2005; Appendix 3.2). However, the disadvantage of this approach was the lack of complete data on these risk factors. This meant that indirect standardisation could only be applied to the proportion of records with complete data and the precision of any standardised rates would therefore be markedly reduced. In addition, although the standardised infection ratio (SIR) was a standard feature of other national surveillance systems, our evidence was that there was insufficient between-hospitals variation in risk factors to explain most high rates of SSI (Wilson 2002). Evidence from other European surveillance systems suggested that risk adjustment does not substantially

alter the rank positions of individual centres because the risk factors are relatively uncommon and their distribution is similar across most acute care hospitals (Brümmer *et al* 2006). Although some authors consider risk adjustment essential if rates are used for public reporting, there needs to be a balance between the purpose and value of risk adjustment and the effort required to collect risk factor data (Geubbels *et al* 2006; Mu *et al* 2011). Evidence from the evaluation of inter-country comparisons suggested that variation in surveillance methodology might be a more important source of variation (Wilson *et al* 2007; Appendix 4.1). Indeed, the high proportion of low outliers identified by the funnel plots in this study suggested that variation in intensity of case finding might also be an important factor in the English data. This problem was explored in a survey we conducted of hospitals participating in SSI surveillance in 2006 where we found that 17% were using passive surveillance methods rather than the active case finding methods required by the surveillance protocol (McDougall *et al* 2007; Appendix 2.4). Funnel plots therefore provided an effective mechanism of identifying hospitals, which may not have adequately applied the surveillance protocol and could be selected for further investigation of their surveillance procedures.

4.3.4.2 A limitation of the SSISS surveillance at the time of this analysis was the lack of data on SSI that occurred after discharge. Whilst we made some adjustment for duration of follow-up using incidence density, this could not account for the changing risk of SSI in the days following the operation. With rapidly declining length of post-operative stays associated with elective surgery the need to establish robust methods of PDS that could provide reliable data on which to make inter-hospital comparisons became an important priority for the surveillance system. The next publication described in this chapter presents and evaluation of the efficacy of PDS systems and the implications for benchmarking (Wilson *et al* 2013; Appendix 4.3).

4.3.4.3 ***My contribution to this research***

As leader of the national SSI surveillance service I had an instrumental role in developing effective

methods of identifying hospitals with outlying rates of SSI. This was particularly relevant to orthopaedic data since the mandatory surveillance data was available to the public and rates based on small numbers of procedure were open to misinterpretation. I developed the concepts underpinning the research and wrote the publication in order to present a detailed analysis of rates of SSI in hip prosthesis and demonstrate or work the advantage of funnel plots as a mechanism of identifying outliers. I worked with the statistician to define the funnel plot methodology and supervised a junior scientist who then built them.

4.3.5 Contribution of this study to contemporary knowledge

This paper represented a unique, detailed analysis of data on rates of SSI following hip prosthesis from a large, multicentre surveillance system together with an innovative approach to performance monitoring. It has subsequently been cited by 30 other authors in relation to both rates of SSI in hip prosthesis and benchmarking of HCAI rates. In terms of the application of funnel plots, whilst standard SPC charts had been applied to HCAI data the use of funnel plots was uncommon. Mohammed *et al* (2001) and Spiegelhalter (2005a) proposed their use as a mechanism for discouraging inappropriate ranking in performance monitoring of health systems and had applied them to evaluating mortality and MRSA bacteraemia data as a mechanism of exploring whether the observed variation in rates reflected true differences or normal variation (Spiegelhalter 2005c). My publication was the first to demonstrate the value of funnel plots as a mechanism for displaying benchmarking data for SSI. The analysis reflected the unique position of the English surveillance system at that time of having a mandatory component of national SSI surveillance that both enabled and demanded methods to support the comparison of rates across all orthopaedic centres in England (Haustein *et al* 2011). Subsequently, funnel plots have become the standard approach to presentation of inter-hospital comparisons of SSI rates for the surgical site surveillance service and were subsequently adopted by other surveillance systems and for benchmarking other types of HCAI

such as ventilator-associated pneumonia in the German national surveillance system (Meyer *et al* 2009; Vrijens and Hulstaert 2010; Health Protection Scotland 2013).

4.3.6 Subsequent research contributions to the field

Funnel plots are now widely recommended for assessing quality of healthcare related to surgery and their advantage in drawing attention to those units that lie outside statistical control limits have begun to be recognised, albeit that encouraging both healthcare processionals and the public to understand and use them is challenging (Meyer *et al* 2009; Marshall *et al* 2004). We did not attempt to include risk adjustment in our funnel plots and there are no examples in the literature where this has been attempted with SSI data, possibly because there are few examples of SSI benchmarking systems where public reporting is required (Haustien *et al* 2011). In a development to the crude rates used in our funnel plots, Morton *et al* (2011) developed risk adjusted funnel plots for comparing rates of in-hospital bacteraemia. These rates are based on count data with a population level denominator such as occupied bed-days, rather than the binary data used in SSI rate comparisons, and may be prone to problems of 'over-dispersion' unless a method of adjusting for excess variability between institutions (e.g. size, services, activity) is applied (Morton *et al* 2011). They plotted observed counts against the expected counts (based on indirect standardization of rates from all institutions) and control limits calculated based on the weighted average of the risk adjusted rates. Whilst acknowledging their value as an improvement tool for discouraging inappropriate action, the authors cite a key disadvantage of this approach is bias associated with indirect standardisation where there is heterogeneity of denominators (Delgardo-Rodriguez and Llorca 2005; Morton *et al* 2011). Van Dishoeck *et al* suggest that differences in rates of SSI are explained by case-mix, however, their analysis was based on only 13,629 records in 34 Dutch hospitals and pooled data from a range of categories of surgery with major differences in intrinsic risk of SSI (Van Dishoeck *et al* 2013).

4.3.6.1 One example of a benchmarking surveillance system is the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) which captures data on morbidity and mortality up to 30 days post-surgery across a range of surgical specialties (Ingraham *et al* 2010). The standard mechanism of detecting 'outliers' in this system was based on the odds ratio (OR) of the *hospital-adjusted rate* and the *all hospitals-adjusted rate* (where an OR >1 is high outlier; OR <1 low outlier) combined with hospitals above and below the 10^{th} and 90^{th} percentile. Lawson *et al* 2011 compared this standard method with control charts in reliably identifying outliers and hospitals that had improved or worsened between 2008 and 2009. Among the 95 hospitals on which the analysis was based, the control chart method was better at discriminating hospitals with stable performance (specificity of 86.6%) than identifying those with worsening performance (sensitivity of 61.5%). Thus 57.9% of hospitals where the control chart indicated worsening performance were true and 6.6% of those hospitals with a worsening performance were not detected by the control chart. This study assumed that the standard method of detecting outliers is completely accurate, when in reality it is still prone to error. Our approach of using control limits in a funnel plot did not attempt to detect a trend in performance. The evidence from Lawson *et al* (2011) suggested that whilst their control chart methodology could provide a trigger mechanism for investigating potential problems, they should be used with caution to avoid outliers being labelled as poor performers without further investigation of other important factors that might explain the rate.

4.3.6.2 There have been few examples of the application of SPC chart methodology to multi-centre benchmarking systems for HCAI, however, there have been a number developments in this methodology applied to monitoring the performance of a health facility over time. These have included the CUSUM chart, where the difference between the benchmark and each binary outcome or event is cumulatively summed and deviation from the benchmark identified when the CUSUM value reaches a pre-determined 'decision value' (Noyez 2009). Methods of risk-adjusting the CUSUM chart have also been proposed so that the risk of 'failure' is taken account of in the

cumulative sum. Morton *et al* describe the use of cumulative 'observed-minus-expected' charts which are based on the CUSUM methodology. In these charts the rate of SSI is adjusted by the factors in the Risk Index to enable the observed (O) and expected (E) rate after adjustment of risk factors to be calculated. The O-E is then cumulatively summed and two standard deviation control limits added to indicate when the cumulated events differ from what would be expected (Morton *et al* 2010). This approach is based on the variable life-adjusted display (VLAD) method, which has been used for plotting trends in mortality in order to adjust for the risk of death following cardiac surgery, but is based on observation of trends rather than setting defined control limits to trigger action (Pagel *et al* 2013). As pointed out by Morton *et al* (2008) effective risk adjustment in relation to rates of SSI is limited by poor discrimination of variation in risk of SSI when the NNIS risk index is applied to clean and clean contaminated surgery. In our analysis we also identified that such adjustment depends on the availability of complete risk factor data and this, together with the limitations of adjustment in discriminating risk, mean that our approach of using control limits as triggers for investigation rather than definitive indicators of poor performance is probably the most effective approach.

4.3.6.3 Finally, I extended my own work in relation to monitoring performance in relation to rates of SSI in an analysis of overall trends in rates of SSI since the inception of mandatory surveillance for hip prosthesis in 2004 based on small area estimation methods (Wilson *et al* 2009; Appendix 4.5). We used this approach to adjust for small sample sizes for some hospitals (areas) by allowing their random effects to be correlated and adjusted for the major risk factors of ASA score and wound class. In order to determine whether the observed downward trend in rates of SSI was explained by the declining post-operative stay (and therefore case-finding) we also included length of hospital stay in the models. This analysis suggested that the introduction of mandatory surveillance was associated with a reduction in rate of SSI when the effects risk factors, hospital variation and reductions in length of post-operative stay are taken into account (Wilson *et al* 2009; Appendix 4.5).

This provided evidence that participation in this national benchmarking system was associated with a reduction in rate of SSI, although it was not possible to determine how such reductions might have been achieved or whether factors, such as changes in intensity of case-finding, may have played a part. These factors are explored in the next publication presented in this chapter which was developed in order to explore the feasibility of benchmarking rates of SSI following caesarean section delivery (Wilson *et al* 2013; Appendix 4.3). This category of procedures presented particular challenges because patients undergoing these procedures generally stay in hospital for less than four days. In these circumstances, the previous approach we had used of calculating the ID of inpatient SSI would clearly be very imprecise as most infections would occur after discharge. The alternative approach, to include SSI detected post-discharge required an evaluation of the reliability and reproducibility of the methods and their impact on detecting hospitals with high rates of SSI.

4.4 Published work 6: Inter-hospital comparison of rates of SSI following caesarean section delivery

Wilson, J., Wloch, C., Saei, A., *et al* (2013) Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. *Journal of Hospital Infection*. **84**:44-51 (Appendix 4.3)

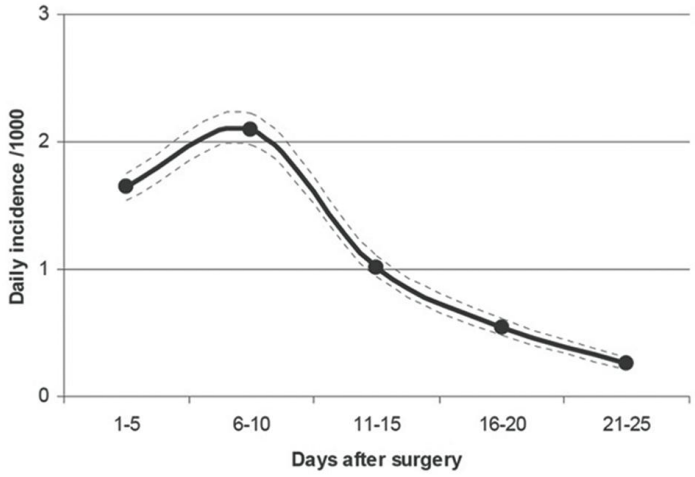
4.4.1 Background

Since a small number of microorganisms left behind in an operative wound take time to multiply and invade the surrounding tissue it can take several days after surgery for surgical site infections (SSI) to become apparent. In the analysis of the European HELICS data we modelled the relationship between time of operation and rate of SSI (Figure 4.5). Whilst this analysis could not account for the decline in intensity of case finding after discharge it did demonstrate a peak in incidence of SSI between six and 10 days after surgery. This illustrates that where the length of post-operative stay is short a high proportion of SSI will not be detected by inpatient surveillance alone. As discussed in section 4.2, this analysis of the European HELICS data also demonstrated the strong influence of post-discharge surveillance (PDS) on the cumulative incidence of SSI and the implications for comparing rates of SSI (HELICS 2005).

4.4.1.1 A number of different approaches to PDS have been reported in the literature and are summarised in Table 4.2. Common approaches include review of patients at out-patient visits, surgeon questionnaire and patient questionnaire, report cards or telephone interviews (see Table 4.2). However, they demonstrate some of the key challenges of PDS, in particular the difficulty in obtaining follow-up data on all cases and imprecision in detection of SSI from questionnaire surveys of both healthcare workers and patients (Whitby *et al* 2002). Active review by healthcare professionals has also been described, but has tended to be either part of a research project rather than routine surveillance, or focused on specific types of surgery such as breast or caesarean section

where follow-up by designated healthcare professionals was part of routine care (Reilly *et al* 2006, Johnson *et al* 2006; Ward *et al* 2008).

Figure 4.5: Incidence rate of surgical site infection by number of days since operation and 95% confidence curves (dotted lines) in 5-day analysis periods (smoothed). Source: HELICS 2005



Whilst it might be expected that healthcare workers could reliably identify SSI, evidence has suggested that sensitivity and specificity of case finding by healthcare professionals is low (Manian *et al* 1997; Whitby *et al* 2002; Taylor *et al* 2003; Sands *et al* 2003; Mannien *et al* 2006; McNeish *et al* 2007). This may reflect inconsistent interpretation of surveillance case definitions, which are generally complex and do not necessarily match to clinician expectation of SSI (Talbot *et al* 2013). The efficacy of some systems would also be strongly dependant on the healthcare system (Manian *et al* 1997). For example, in the largely private healthcare systems in the USA, surgeon questionnaires and review of administrative data may be more effective than in the NHS where responsibility for surgery is likely to be devolved across a surgical team rather than a single surgeon and availability of detailed computerised records is limited.

4.4.1.2 Another approach to PDS proposed by Reilly *et al* (2006) was to systematically capture SSI in patients readmitted with SSI. A study by Huotari *et al* (2006) indicated that readmission surveillance

Table 4.2: Evaluation of different methods of identifying surgical site infection after discharge from literature published between 1990 and 2010.

Method	Advantages	Disadvantages	Evidence
Direct examination of wound by trained surveillance healthcare professional	Active case finding; High sensitivity and specificity	Resource intensive	Used as Gold Standard (Whitby et al 2002, 2007) or research (Bailey *et al* 1992)
Direct examination of wound as part of routine care	Active case finding; data captured using established systems of clinical care	Case finding may not be complete and may be variable (Ward *et al* 2008)	Has been used for surveillance of caesarean section (Johnson *et al* 2006, Ward *et al* 2008, Reilly *et al* 2006) and breast surgery (Reilly *et al* 2006). No data on sensitivity and specificity.
Patient questionnaire (paper or telephone) • Combined with HCW questionnaire • Combined with visit by surveillance nurse or to GP	Active case finding; high response rates can be achieved (if include reminders); Requires limited resources. Increase reliability of diagnosis of SSI by combining with HCW review	HCW confirm 50-75% of patients reported symptoms as SSI (Reilly *et al* 2005, McNeish *et al* 2007, Taylor *et al* 2003). PPV variable (30-83%) but NPV high (98%) (Whitby *et al* 2002, 2007)	Response rates of over 90% where combined methods used (Stockley *et al* 2001, Mitt *et al* 2005). Response rate may vary according to patient characteristics (Noel *et al* 1997)
Surgeon questionnaire	Can be active or passive; inexpensive; response rate 50-70% (Fanning *et al* 1995, Manian & Meyer 1997)	Response rate may be highly variable (Manian & Meyer 1997); poor sensitivity/specificity (Whitby *et al* 2002, Sands *et al* 1996)	Efficacy probably dependant on healthcare system; monthly computer generated lists of patients work best (Manian & Meyer 1997)
Review wound at outpatient clinic (OPC) visits	High sensitivity and specificity if use trained observers	Delay between operation and attendance at OPC; now uncommon for many procedures and	68-94% reviewed at centralised OPC (Ferraz *et al* 1995) 11% of orthopaedic SSI detected by this method (Huotari *et al* 2006)
Review of administrative data (infection diagnoses or antibiotics)	Inexpensive once established	Limited evidence for sensitivity/specificity (Miner et al 2004, Sands *et al* 2003)	Efficacy dependant availability of data within healthcare system

following orthopaedic surgery detected 43% of post-discharge SSI, however this approach was biased towards the detection of more severe infections and would therefore underestimate the occurrence of superficial SSI where the patient is likely to be treated in the community. Several studies have based the PDS on reporting of SSI by the patient and have suggested that high response rates of approximately 80% are possible and associated with high negative predictive values, with over 90% of patients able to reliably indicate that they did not have an SSI (Whitby *et al* 2002, 2007; Reilly *et al* 2006). However, the positive predictive value of patient reporting of SSI appears to be much lower (between 30-50%). Other studies suggested that the reliability could be improved by using other methods to confirm patient-reported SSI, for example by contact with the GP or other healthcare personnel (Stockley *et al* 2001; Taylor *et al* 2003; McNeish *et al* 2007).

4.4.1.3 The literature provided limited evidence for the efficacy of different methods of PDS as most studies did not compare validity or reliability or had other methodological limitations that made it difficult to determine efficacy, in particular they did not determine the sensitivity and specificity of the method (Petherick *et al* 2006; Taylor *et al* 2003; McNeish *et al* 2007). Most examples of validation studies on SSI surveillance had involved single centres and therefore did not evaluate the efficacy of methods across multiple centres (Broderick *et al* 1990; Cardo *et al* 1993).

4.4.1.4 As discussed in 2.3.3.2, when SSISS was established in the late 1990s the surveillance was directed at SSI detected during the inpatient stay. However, the decline in length of hospital stay that occurred in England during the 2000s resulted in the length of post-operative stay after some types of elective surgery reducing to five days or less, and thus a high proportion of SSI were likely to be missed by inpatient based surveillance. To address this problem, in July 2008 we introduced a defined methodology for PDS that included both voluntary and compulsory elements (see Table 2.1). These included methods for detection of SSI on readmission to hospital, post-discharge patient questionnaires, and review by healthcare professionals post-discharge. However, a particular

concern for SSISS was the potential impact of PDS methods on inter-hospital comparisons as variation in both the length of postoperative stay and proportion of patients followed up post discharge could have a significant impact on the estimated rate of SSI. In order to explore the potential impact of PDS on benchmarking and the reliability of the surveillance methods we had implemented, I designed a study to determine the utility and validity of the methods in a set of hospitals conducting surveillance of SSI following caesarean section delivery (CSD), a category not previously included in SSISS. The results of this study were subsequently published in Wilson *et al* 2013 (Appendix 4.3).

4.4.2 Conceptual and methodological development

Surveillance for SSI following CSD would be heavily dependent on the efficacy of PDS since the median length of post-operative stay was only three days (Ward *et al* 2008). However, unlike most other types of surgery the routine follow up of all women for up to 10 days post delivery by a community midwife (CMW) enabled active surveillance by a healthcare professional for this period (Ward *et al* 2008). In addition to CMW follow-up, a patient questionnaire (PQ) was used to identify SSI that occurred between 10 and 30 days post operation or missed by the other surveillance methods. Since evidence from other studies indicated that patients were likely to over-report problems with their wound as SSI (Whitby *et al* 2002), our method did not require patients to identify if they had an SSI but to answer questions about the wound. Patients whose responses suggested a possible SSI were then phoned by the surveillance coordinator to check the symptoms and only those that met the definition of SSI were included. Since the wounds of these patients were not directly visualised by the surveillance personnel, the criteria for SSI had to be slightly adapted to account for the 'clinician diagnosis' of SSI being made by the GP. The study was therefore designed to evaluate the reliability of the combination of these surveillance methods for detecting SSI in inpatients and readmissions, and post discharge by CMW and patient questionnaire.

4.4.2.1 ***Recruitment of hospitals and data collection****:* This was a pragmatic study to assess the reliability of these methods applied by hospitals participating in SSISS. We therefore recruited hospitals to participate in the study from those already participating in SSISS, used the local hospital staff to collect the surveillance data and trained them to collect additional data required to evaluate the surveillance. Each hospital undertook either one or two three-month surveillance periods and established systems for implementing and coordinating the surveillance locally, based on the standard surveillance protocol and methods of case-finding described in Table 2.1. This approach enabled us to evaluate the reliability of the surveillance methods in detecting SSI and the feasibility of using methods based on PDS for benchmarking rates of SSI. Since SSIs reported by the patient might be considered as less reliable than those reported by a healthcare worker, we categorised rates into those reported only by healthcare professionals and those reported by both patient and healthcare professional; where the SSI was reported by a healthcare profession and the patient the latter took precedence in the classification of detection source.

4.4.2.2 ***Methods used to determine sensitivity and specificity of case finding****:* The optimal design for a study to validate the accuracy of diagnostic tests (such as the detection of SSI) has been suggested to contain three key features (Petherick *et al* 2006):

- Series of patients from an appropriate clinical spectrum
- Patients undergo both the test and a reference or Gold standard test regardless of the results of either test
- The reference or Gold Standard test should be measured independently of the study test

In designing our study we selected a random sample of four hospitals from the 14 participating in the study in which to validate the surveillance methods and used review of clinical records by two expert assessors as the Gold Standard test. Conventionally, the calculation of the parameters used to describe the reliability of a test (namely, the prevalence, sensitivity, specificity, positive predictive

value (PPV) and negative predictive value (NPV)) require the test to be measured against the Gold Standard for all negative and positive results. However, it was impractical to review all the surveillance reports from each of these hospitals against this Gold Standard since this would require assessment of over 1000 records. A random sample of 10% of reports from patients where no SSI was documented was therefore selected, together with all patients who were documented in the surveillance to have an SSI. However, since measurement of the parameters from this sample would be extremely biased we needed to take account of this when making our estimates. We chose to achieve this by treating test negative cases and test positive cases as two samples from two independent binomial distributions and applying a logistic linear mixed effect model to predict non-sampled cases. This method also enabled us to estimate 95% confidence intervals for each of the measures.

4.4.2.3 ***Evaluation of the impact of the surveillance methods on benchmarking:*** Other studies had reported the involvement of community midwives (CMW) in surveillance but had not explored variation in response rates of either CMW or patients, and had not considered the implications of variation in case-finding for a benchmarking system (Huotari *et al* 2006; Reilly *et al* 2006; Johnson *et al* 2006; Ward *et al* 2008). The second aim of this study was therefore to determine the utility of these surveillance methods in establishing benchmark rates of SSI and the implications for valid inter-hospital comparison of rates. Accurate data on both denominator and numerator are required to calculate reliable rates of SSI, we therefore aimed to determine the reliability of the denominator by comparing the number of CSD captured by the surveillance with the number captured by the routine administrative databases in each hospital. We evaluated the reliability of the numerator based on all SSI detected up to 30 days after CSD (in line with the definition of SSI) by exploring the proportion of women followed-up after discharge by the CMW and the proportion from whom data was captured in the PQ at each participating hospital. However, we also attempted to define this relationship statistically using a multinomial linear mixed model, which included category of PDS

detection method for SSI or no SSI and surveillance period as predictors, and added hospital as a random effect to take account of variation not explained by the detection method. This enabled us to develop more robust estimates of the impact of variation in case-finding on rates of SSI by adjusting for the effect of PDS method, hospital and surveillance period.

4.4.2.4 ***Resources required for surveillance and experience of establishing surveillance locally***: We gave a structured questionnaire to the surveillance coordinator at each participating hospital to capture data on staff time and other resources required to conduct the surveillance; the number of patients readmitted to hospital and how many of these had SSI; CSD identified in hospitals databases and not detected by surveillance; the method used to captured data on PQs, number followed up and how many were determined to have SSI; and their views on the efficacy of the surveillance. This combination of qualitative and quantitative data was used to draw conclusions about the value of the surveillance for benchmarking and contextual factors that might influence the efficacy of the surveillance and reliability of the rates of SSI.

4.4.3 Summary of main methods and findings

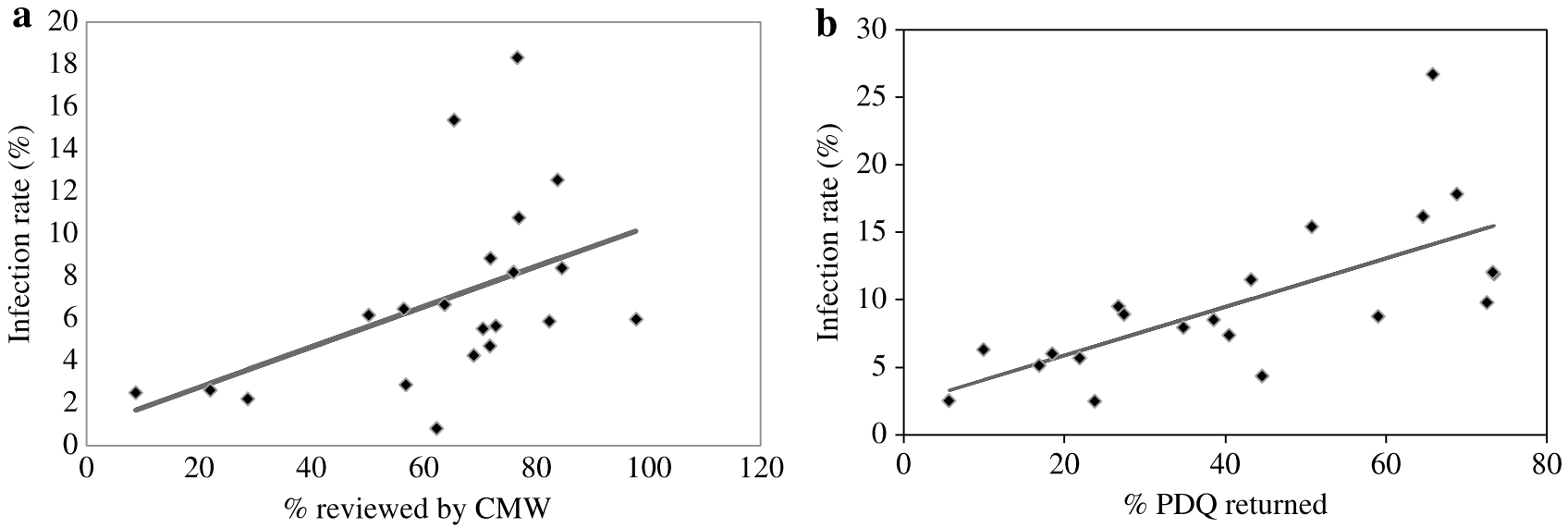
We recruited 15 hospitals to participate in the study, although one discontinued surveillance after six weeks and was subsequently excluded from the analysis. The remaining 14 hospitals captured data in a total of 21 surveillance periods on 4107 operations and 404 SSI. Overall, the surveillance identified an SSI rate of 9.8% following CSD; with 89% of the SSI detected post-discharge, 55% by the CMW and 34% by the PQ. If the SSI was based only on those SSI detected by healthcare workers then the rate of SSI was 6.5%. Not only were these rates of SSI relatively high compared to other types of clean contaminated surgery (Wloch *et al* 2012), but there was considerable variation in infection rate between hospitals, with the overall rates ranging from 2.5 to 26.7% and those based on healthcare-worker defined SSI ranging from 0.8 to 18.3%. A key criteria for a benchmarking system is that as far as possible sources of variation attributable to surveillance methodology and

case mix are eliminated so that observed differences are more likely to be attributable to variation in clinical practice. However, despite the standardised surveillance protocol and training programme for hospitals participating in the study, there was marked variation in completeness of follow-up by both CMW and PQ between hospitals. Whilst the median return rate for CMW surveillance record and PQs was 71% and 44% respectively, there was marked variation in return rate between hospitals. In terms of CMWs return rates ranged from 8.8% to 97.8% with a return rate of less than 70% in 48% of the surveillance periods. For PQs the range was 5.6% to 73.4% with only three hospitals achieving a return rate of over 70%.

4.4.3.1 The efficacy of PDS was clearly paramount for robust benchmarking since the majority of SSIs were detected after discharge from hospital. The linear relationship between the observed rate of SSI and the proportion of patients with a CMW surveillance report could be seen in a simple graph (Figure 4.6). However, the multinomial linear mixed model enabled us to more accurately determine the relationship between the PDS method and odds of detecting SSI. In the case of CMW follow-up, the odds ratio of detecting SSI increased significantly with each unit (percentage) increase in the proportion of patients reviewed above the mean of 62.4% (OR 1.02; 95%CI 1.005 – 1.026; p=0.003). With PDS based on PQ, the odds ratio of detecting SSI also increased significantly in response rates above the mean of 43.5% (OR 1.034; 95% CI 1.016-1.052; p=0.025). This finding had important implications for using a surveillance system based largely on method of PDS for benchmarking, since variation in rates of SSI detected by the surveillance were at least in part explained by inter-hospital variation in intensity of case-finding.

4.4.3.2 The data captured in the survey of surveillance coordinators pointed to some factors related to local organisation of the surveillance that affected the efficacy of case-finding and contributed to this variation. Hospitals that achieved greater than 70% return rates for PQs used a method based on phoning patients and surveillance periods.

Figure 4.6: Relationship between proportion of operations with post-discharge follow-up and rate of SSI (a) Percentage of community midwife (CMW) forms returned versus the rate of SSI (detected by healthcare professional) (b) Percentage of patient post- discharge patient questionnaire (PDQ) completed versus the rate of SSI (detected by all methods).



In addition, where the surveillance was coordinated by maternity rather than infection control, CMW return rates were significantly higher (79% vs 56%; p<0.001) but PQ return rates significantly lower (35% vs 47%; p<0.001). Other factors reported by the hospitals to support implementation of the surveillance were high quality information systems, a designated surveillance coordinator, specific training of CMW and involvement of a senior member of the maternity department. Interestingly, whilst the average resource requirement for surveillance of 200 CSD per quarter was estimated from the hospital survey to be 23 person-hours per week the median time ranged from 28 to 219 hours per week and more time spent of surveillance was not necessarily associated with better follow-up rates.

4.4.3.3 ***Results of the validation of the methods***: A total of 226 cases from the four hospitals chosen for the case-note were included in the validation study, 136 of which were SSI. In the linear predictor model developed to estimate the sensitivity and specificity of the surveillance methods we included a hospital random effect to account for the extra variation that was not explained by fixed effects. The estimated values from this model were used to predict non-sampled cases and these were added to sample cases to determine the best linear unbiased estimates for prevalence, sensitivity, specificity, PPV and NPVs and their associated 95% confidence intervals. This analysis found that the combined surveillance methods were very reliable in identifying patients without SSI with a high specificity and NPV of 99%, and did not mis-classify patients with SSI. Although the sensitivity of case finding and PPV was lower, at 91% was still good, and mis-classification of patients with SSI was largely attributable to misinterpretation of the patient questionnaire at one hospital. This finding was interesting because it illustrated that by using PQs as a trigger for detecting SSI we could reliably identify SSIs, but it also pointed to the potential for inter-hospital variation where the responses were not accurately validated by the surveillance coordinator. In addition, in a separate analysis of the PQ responses we found that in PQs where the patient had reported potential signs of SSI the follow-up by the surveillance coordinator resulted in 39% being found not to meet the criteria for

SSI. These findings resonated with those of Whitby *et al* (2002) who reported that whilst patients could not reliably identify symptoms that met the definition of SSI, their recall of antibiotics prescribed by the GP was the most valid proxy measure of SSI (Pearson correlation coefficient 0.76) and that the negative predictive value associated with patients reporting was very high (98%). This compares with our approach of using patients to report problems with wound healing potentially indicative of SSI but combining this with clinician assessment to improve the sensitivity of case finding.

4.4.3.5 Whilst the study was not designed to formally test reductions in rates of SSI associated with the surveillance, data from the hospital survey identified 10 that reported improvements in operative care made as a result of the focus provided by the surveillance. In five of the seven hospitals that participated in two surveillance periods, there was a decrease in rate of SSI with a mean decrease of 50% between the two periods.

4.4.4 Conclusions

This study confirmed the feasibility of the surveillance methods applied to CSD, where the length of postoperative stay was very short and therefore detection of SSI was largely reliant on PDS. It also demonstrated the high rates of SSI associated with CSD and the potential for surveillance to drive improvements in practice and reductions in rates of SSI. However, whilst the study demonstrated the reliability of the PDS methods to detect SSI, it also identified the major problem of achieving consistent follow-up after discharge across multiple centres and the limitations of benchmarking where surveillance is heavily reliant on PDS with these inherent difficulties. The variation in follow-up of cases was very marked, ranging from less than 10% to over 97% for CMW and less than 6% to over 73% for PQ, with only half of hospitals achieving CMW or PQ follow-up rates of more than 50%. This means that not only is PDS likely to miss a high proportion of SSI where follow-up rates are poor but that the rates reported will be strongly dependant on the efficacy of the surveillance. Local

organisation of the surveillance appeared to have an important effect in determining the efficacy of case-finding and thus the reliability of the estimated rate and this was not explained by resources allocated to the surveillance. Although clinical involvement in the surveillance was associated with better response rates, the study also demonstrated the practical challenges of accomplishing this across all centres in a devolved surveillance system. Whilst other authors have focused on the need to develop valid and reliable methods of case-ascertainment post discharge (Petherick *et al* 2006), this study was unique in highlighting the additional challenge of creating a method that produces consistent and reproducible results across a range of different centres.

4.4.4.1 ***My contribution to this research***

The introduction of methods of PDS to the SSI surveillance system prompted me to undertaken this study as a means of evaluating their efficacy. In addition, there was considerable demand for adding CSD as a surveillance category but in the light of my experience of inter-country differences in application of PDS, I was interested in investigating the potential effect of variation in intensity of PDS on rates of SSI and the implications for benchmarking. I therefore designed the study, developed the approach to analysis and sought advice from the statistician about how to handling the sampling strategy for assessing reliability of the methods and in estimating the effect of variation in case-finding on reported rates of SSI. I then used my knowledge and experience of SSI surveillance benchmarking to develop the discussion and consider the findings in the context of using SSI rates for performance measurement. I interpreted the data and took the lead on writing the paper.

4.4.5 Contribution of this study to contemporary knowledge

At the time of this study there were three examples in the literature of validation studies conducted on SSI surveillance systems, all of which had significant limitations. McCoubrey *et al* (2006) studied surveillance data collected by 27 hospitals participating in the national SSI surveillance programme.

They randomly selected 60 cases without SSI and the 15 most recent cases with SSI from each hospital. The presence or absence of SSI was validated by review of the case notes by a trained, independent member of staff. The main limitation was that the assessment was made on only a sample of cases rather than all cases independently of the test result, however it was not clear whether the calculations for sensitivity and specificity were adjusted in the analysis to account for the bias inherent in this approach. Secondly since the case definitions included a criteria for 'clinician diagnosis' which was frequently not documented, calculations of sensitivity and specificity were made on the assumption that SSI reported to the surveillance system were valid even if not documented in case records. This would tend to over-estimate the reliability of the method. A second study used a similar approach of sampling patient charts (10 with SSI and 40 without) and applied the results to the aggregated data without accounting for bias in the sampling method (Huotari *et al* 2007). A validation study conducted on the national SSI surveillance system in the Netherlands, involved validating the 20 most recently completed records of patients included in the surveillance regardless of SSI status and five most recently completed records of patients reported with SSI, with the judgement of the validation team considered to be the Gold Standard test (Mannien *et al* 2007). This study acknowledged the overestimation of sensitivity and specific associated with this method and reported only the NPV and PPV. However, because only a small number of records were evaluated at each hospital, the confidence intervals around these estimates would be very wide. Thus our research is important because it describes a practical approach to measuring reliability of PDS and a pragmatic analysis of the impact of variation in intensity of PDS on the reliability of rate comparisons.

4.4.6 Subsequent research contributions to the field

PDS has become a source of considerable controversy with some authors asserting it should be a required component of national benchmarking systems in order to capture data on the full burden of SSI (Tanner *et al* 2013; Leaper *et al* 2013). However, our study has clearly illustrated that this

approach is fraught with difficulty, that even within the environment of a research project complete follow-up of all surgical cases once they have been discharged from hospital is unrealistic (Lamagni *et al* 2013). As contested by Hall *et al* (2013) PDS is generally not cost-effective and rates of SSI based on PDS are not a good indicator for performance measurement and should therefore be used with caution in benchmarking. Similarly, linking incentives to SSI rates when variation in case-finding is either not considered or accounted for have been recognised as a significant danger associated with quality improvement programmes such as the Hospital Inpatient Quality Reporting system in the USA (Bratzler 2013). The solutions appear to lie either in developing focused, resource intensive but high quality data capture systems such as the American College of Surgeons NSQIP where data on a proportion of surgical procedures is captured by designated staff and subject to comprehensive validation and audit, or working with underestimated rates based on SSI detected in hospital or through incomplete post-discharge data, and using more complex methods of adjusting for cases the surveillance methods may have missed (Anderson *et al* 2008; Biscione *et al* 2009; Cohen *et al* 2013; Bratzler 2013).

4.5 Summary of chapter

The three studies included in this chapter illustrate some of the challenges associated with comparing rates of SSI. In both the European and English datasets one of the key difficulties is the lack of consistent follow-up after discharge from hospital and the profound effect that this has on the detection of SSI for procedures where the length of hospital stay is short (Wilson *et al* 2007; Appendix 4.1, Wilson *et al* 2013; Appendix 4.3). Whilst my research has not necessarily provided a simple solution to this problem it has illustrated the need for caution in making comparisons between rates of SSI and provided evidence to counter the argument that PDS is should be an essential component of benchmarking systems. I have also illustrated that there are other approaches to adjusting for variation in length of follow-up such as a metric based on incidence-density that maybe more appropriate for making comparisons where there is wide variation in

length of post-operative stay (Wilson *et al* 2007; Appendix 4.1). Whilst developing SSI surveillance systems that assure complete follow-up of all eligible patient both in hospital and after discharge is an unrealistic proposition, it is important to recognise that this is not essential when the value of benchmarking systems lies in their ability to identify potentially poor performance that can then be investigated further. The use of data to improve the quality of care was identified as a key benefit of the CSD surveillance, even though the variation in case-finding made it difficult to draw precise conclusions about variations in rates between hospitals (Wilson *et al* 2013; Appendix 4.3). In using funnel plots to support the detection of outliers we have developed a simple and visually effective method of supporting this aim that is now being increasingly recognized as useful for benchmarking. In Chapter 5, I will explore some of the different methodological issues that emerge when exploring trends in rates of infection using a different type of surveillance data captured on cases of bloodstream infection.

CHAPTER 5

Exploring the epidemiology of healthcare associated infection through the analysis of trends in national surveillance data

5.1 Introduction

The research presented in this chapter focuses on the analysis of trends emerging from national surveillance data. It includes two published works in which examine bloodstream infection (BSI) surveillance data from both a general surveillance system (LabBase) and a specific system for methicillin resistant *Staphylococcus aureus* (MESS). Key to these analyses were mechanisms to address methodological issues associated with using surveillance data for analysis of trends. Bloodstream infections cause significant morbidity and mortality. They affect two in every 1000 hospital admissions and are associated with an almost three time increased risk of mortality (OR 2.8; 95%CI 1.4 – 5.6) (Fabbro-Peray *et al* 2007). They are estimated to account for mortality in 6.22 per 1000 discharges (Pittet and Wenzel 1996). In the UK, BSI surveillance had been established as part of the Public Health Laboratory Service (PHLS) laboratory surveillance system since the 1940s although not in a comprehensive way until the 1990s when the centralised database (LabBase), electronic data capture and reporting systems were established (Grant and Eke 1993) (see section 2.2.4). This surveillance was 'microorganism' rather than infection focused and therefore cases were referred to as 'bacteraemia', since clinical data to support the diagnosis of infection was not captured. The PHLS (later the Health Protection Agency (HPA)) reported the number of cases of bacteraemia detected by this surveillance in the Communicable Disease Reports. These reports focused on a single genus or species of pathogen and tended to report actual number of cases and regional differences rather than trends over time, or the comparative

importance of difference pathogens. There were a number of problems with this bacteraemia surveillance that complicated the analysis of trends. Firstly, it was a passive surveillance system that relied on laboratories voluntarily reporting cases to the central system and was therefore vulnerable to variation in case ascertainment associated with changes in the number of reporting laboratories and the methods of reporting over time. The development in the early 1990s of software (CoSurv) to support the automatic transfer of data from local Laboratory Information Management Systems (LIMS) was particularly influential. This electronic reporting increased the quality, completeness and timeliness of reporting by enabling file outputs from the laboratory to be converted to a standard format (LabLink), exported into CoSurv and from there into LabBase (HPA 2008b). Secondly, whilst BSI are more easily identified than most other HCAI because the diagnosis is primarily based on a laboratory result (Horan *et al* 2008), the laboratory data includes little information about the clinical condition of the patient. This makes it difficult to determine the primary source of the BSI and reliably attribute it to a hospital or a community source. In addition, whilst laboratories would be expected to report 'clinically significant' isolates from blood, this was not based on defined criteria (HPA 2008b). Although the presence of any organisms in the blood is generally a significant finding, it is possible to contaminate a blood culture with skin microorganisms at the time the sample is taken (Thylefors *et al* 1998; Dhillon *et al* 2009). This produces a 'false positive' result that can be difficult to distinguish from a true infection without information on specific criteria such as presence of fever or hypotension (Horan *et al* 2008).

5.1.2 Despite these limitations, the surveillance of BSIs at a national level has the unique advantage of enabling changes in the epidemiology of pathogens causing serious infections to be detected, that would not be apparent from the relatively small number of cases available from single laboratories. The trends apparent in this bacteraemia surveillance

undoubtedly influenced the national policy. The year on year increase in the proportion of *Staphylococcus aureus* isolates resistant to methicillin that occurred during the 1990s (rising from 2% in 1990 to a peak of 43% in 2002) detected by this surveillance was one of the main factors that compelled the Government to establish a programme of activity aimed at reducing MRSA bacteraemia by 50%. This included the patient level, web-based reporting system called the MRSA bacteraemia Electronic Surveillance System (MESS) which was established in October 2005 and was the basis of data analysis presented in section 5.3 (Pearson *et al* 2009). The following research work describes the analysis of trends in pathogens causing bacteraemia in the 2000s, the factors influencing the changing epidemiology of these organisms and implications for public health.

5.2 Published work 7: Trends in pathogen causing bacteremia in England

Wilson, J., Elgohari, S., Livermore, D. *et al* (2011). Trends among pathogens reported as causing bacteraemia in England: 2004 – 2008. *Clinical Microbiology & Infection*. **17(3)**: 451-8 (Appendix 5.1).

5.2.1 Background

The central LabBase database in England and Wales was unique in capturing data on all bloodstream infections from microbiology laboratories at a large number of hospitals (see section 2.2.3). Most other surveillance systems were principally hospital or regionally based, focused on only primary bacteraemia or hospital-acquired bacteraemia, or targeted specific pathogens in sentinel hospitals (Wisplinghoff *et al* 2004; Perencevich *et al* 2008; Rojo *et al* 1999; Vrijens *et al* 2010; Gagliotti *et al* 2011). Nonetheless, the only comprehensive analysis of the pathogens causing bacteraemias reported to LabBase, and associated trends, had been published 10 years previously (Reacher *et al* 2000). Although the data was described in routine Communicable Disease Reports published by the PHLS/HPA, the focus of these was single pathogens or groups of related pathogens. Therefore, recent comparative trends in causative organisms particularly in the context of the marked decline of *Staphylococcus aureus* in the late 2000s, had not been investigated. Similarly, although by 2007 the annual report on HCAI surveillance mentioned that *Escherichia coli* had replaced *S. aureus* as the most common cause of bacteraemia it only included a crude analysis of case reports (HPA 2007; 2008a). My observation of the crude comparative trends of these pathogens that were apparent in this report prompted me to develop a methodology that could be used to analyse these trends, that would account for variation in case ascertainment over time and more fully investigate the epidemiology of the infections.

5.2.2 Conceptual and methodological development

Laboratories participating in the laboratory surveillance system in England reported all 'clinically significant isolates' from clinical cultures including blood to the national database (LabBase) via the local CoSurv modules. Records included a patient identifier, mostly the surname encoded as a Soundex code. These are used to assure the confidentiality of the report since the Soundex code is not unique to a surname but when combined with other patient data can be used to enable record matching and de-duplication. Laboratories were asked to make the reports as soon as possible after the organism was identified, preferably at the same time as the report was issued to the requester, however they had up to six months after identification for reports to be submitted (HPA 2008b). A record within CoSurv and LabBase is based on a principle called OPIE (Organism-Patient-Illness-Episode). This means that each OPIE record constitutes a distinct organism in a patient in a defined period of time. If a patient had been infected by two different organisms at the same time (including two different sub-types of a single species), there would be two distinct OPIEs. Similarly, an episode period is set at two weeks, therefore when the same organism is isolated from the same patient within two weeks it would be allocated to the same OPIE but after two weeks would be recorded as a new OPIE. Laboratories are expected to report all clinically significant isolates/infections, although in practice, without further investigation, the laboratory may not be able to distinguish whether some isolates from blood were 'clinically significant'. For each OPIE there was a limited set of data associated with the infection as shown in table 5.1. Whilst some OPIEs may have reflected blood cultures that were contaminated during collection, contamination is most likely to be due to skin microorganisms, such as *Staphylococcus epidermidis,* and most other pathogens isolated from blood are highly likely to reflect infection (Horan 1992; 2008; Nosocomial Infection National Surveillance Service 2001).

Table 5.1: Core dataset reported to the national laboratory surveillance system in England

Data item	Description
Source Lab	Required data item
Reporting Lab*	
Patient identification*	Soundex and initial; or surname and initial; or NHS number; or hospital number
Date of birth*	Or age if not available
Sex*	
Organism*	Full organism name and any typing results
Date of onset	Date of onset of the illness caused by the organism being reported
Specimen type(s)*	E.g. CSF, blood, sputum, serum (serology results)
Specimen date(s)*	Date the specimen was collected from the patient. If this is not known, use the date the specimen was received at the source laboratory
Identification method(s)	Method used to identify the organism
Postcode	Full postcode of the patient residence.
District of residence:	Patient's Health Authority and Local Authority of residence (or of GP if not available).
Ethnicity	Required under the Race Relations Amendment Act 2001.

5.2.2.1 ***Establishing an appropriate denominator:*** The approach to calculating and comparing rates of bloodstream infection is dependent of the population included in surveillance and the criteria used to define cases of infection. Although a positive blood culture result indicates a BSI, defining those associated with healthcare and capturing denominator data that corresponds to hospital patients at risk of BSI is much more problematic because not all healthcare is delivered in a hospital setting and the source of the primary infection may not be easily identified. Although 'hospital-acquired' was included as a field in the supplementary 'epidemiological features' dataset in LabBase, reporting this data was voluntary, there was no specific definition and their identification would require review of the patient by a clinician, it was rarely completed. The location of the patient when the blood culture was taken was available for 69% of episodes, although this was also not a reliable indicator of a hospital or community source since it would be likely that most patients would have the blood taken in hospital regardless of the origin of their infection. Whilst we could have attempted to calculate rates of BSI by the number of

patients admitted or the total number of 'patient-days' in the hospitals associated with the reporting laboratory, we chose instead to use a denominator derived from the Office for National Statistics mid-year population estimates. This was for two main reasons, firstly we could not be certain that all the cases were hospital acquired and secondly because some reporting laboratories processed specimens from more than one hospital and the source of the records could not be reliably distinguished (Anon 2001).

5.2.2.2 ***Methods used in trend analysis:*** Our primary interest was to establish if there was an increase in overall incidence of BSI and whether there was evidence of changes in the proportion of episodes attributable to different pathogens that might suggest an underlying changing epidemiology of these infections, whilst adjusting for changes in the number of cases over time. We used data from 2008 to describe the current distribution of pathogens causing bacteramia in England, since for some laboratories there could be a delay of up to six months before data was uploaded this was the most recent complete dataset available. The period we selected for review of trends was the five years prior to 2009. However, we noticed that although LabBase generally received approximately 100 000 bacteraemia reports annually from laboratories in England, there was a 20% increase in reports in the period between 2004 and 2008. Since this coincided with a major project by the HPA to extend participation by commissioning LabLink outputs from two major providers of LIMS which resulted in new laboratories contributing data and some existing laboratories increasing reporting, our analysis of trends needed to take account of these structural changes in order minimise potential bias associated with variation in case ascertainment. We sought to do this by excluding data from laboratories that had converted from annual to electronic reporting during this period, or where there was evidence of incomplete or inconsistent reporting.

5.2.2.3 In determining whether there was evidence of trends in the relative importance of different pathogens causing bacteraemia in England we chose to use a generalized linear model to compare the proportions of microorganisms responsible for bacteraemia between two rolling years. This model allows for the 'events' to have an arbitrary distribution rather than a normal distribution, and rather than assuming that the response to the predictor variables is linear, the model uses an arbitrary function of the dependent variable (a link function) that varies linearly with the predictor variables. Such models account for associations that may be geometric rather than constant and where the dependent variable is not normally distributed, for example it has fixed limits or varies by small amounts (Dobsen and Barnet 2002). Since we were modeling count data i.e. number of infections in a defined period of time, we used a Poisson log-link function since the occurrence of events over time would reflect a Poisson probability distribution. A similar Poisson regression model had been used in the previous analysis of trends in LabBase data (Reacher *et al* 2000), in the evaluation of secular trends in incidence in data on BSIs submitted to the communicable disease surveillance registry in Finland (Lyytikäinen *et al* 2005, Skogberg *et al* 2008), and in a time-series analysis exploring the association between season and number of infections in a hospital population (Perencevich *et al* 2008). Other studies had used less sophisticated approaches such as the Cochran-Armitage test for trends in categorical data to evaluate changes in annual proportion of Gram-negative organisms and differences across units (Albrecht *et al* 2006), or Chi^2 and two sample T tests as used by Wisplinghoff *et al* (2004) to evaluate secular trends in organisms causing hospital-acquired BSI.

5.2.2.4 Whilst other studies have evaluated trends in a wide range of clinical specimens (Perencevich *et al* 2008), this study focused only on bacteremia. This has the advantage of providing a greater precision of identification than might be the case with some specimens such as urines or wound cultures where the level of identification may not go beyond genus

or main group, such as coliforms, or be clearly indicative of infection. We defined the pathogens by a combination of species and genus depending on the predominance of the organism and conventional approach used in previous analyses of LabBase data (HPR 2008b).

5.2.3 Summary of main methods and findings

We found that in 2008 the overall rate of BSI was 189 per 100 000 population reported by the 210 (95% of all) laboratories in England reporting to LabBase at this time. This was higher than that reported by the only other study based on a national surveillance system in Finland which found an annualised incidence of 125 cases/100 000 population between 1995 and 2002 (Skogberg *et al* 2008). We were unable to compare the rate with the incidence in England in the previous analysis as this was not reported by Reacher *et al* (2000) although the validity of such comparison would be limited by changes in case ascertainment and completeness of reporting that occurred between the 1990s and 2008.

5.2.3.1 ***Age/sex distribution****:* We found that age and gender significantly affected the epidemiology of bacteremia. A higher proportion of cases occurred in males (54%) and they were more likely than females to have bacteraemia caused by *Staphylococcus aureus* (13% vs 10%; p <0.001) and less likely to have bacteremia caused by *E. coli* (19% vs 27%; P<0.001). The increased risk of *S. aureus* bacteraemia in males had been reported by the mandatory MRSA surveillance system, although without comparisons to other pathogens (HPA 2007; 2008a). Other studies on bacteraemia either did not report data on gender or did not explore differences in risk associated with different pathogens (Skoberg *et al* 2008; Reacher *at al* 2000; Wisplinghoff et al 2004). Our analysis was also able to describe the significant variation in risk of bacteremia by age, and demonstrated differences in causative pathogen among different age groups. More than half the bacteraemias (55%) occurred in people

over 65 years. As might be expected, the extremes of age were most vulnerable to these infections with the rate in the over 75 year old age group over four times higher than the average rate (857/100 000 population) and in the under one year olds over three times higher. Reacher *et al* (2000) also identified increased risk of bacteraemia in these age groups but much lower population rates (437 and 366 /100 000 respectively). The difference in distribution of pathogens between gender and age groups pointed to differences in in risk of for source infections, with the genitourinary tract being a primary source of *E. coli* bacteraemia and evidence that the risk of urinary tract infection increases with age especially in women (Mathews and Lancaster 2011; Wilson *et al* 2011). In the under one year-olds over a third of bacteraemia were caused by coagulase negative staphylococci (CNS), and this remained a common cause of bacteremia in all paediatric age groups, compared to adults where in the over 65s they accounted for less than 20% of the infections. Whilst some of these cases may have reflected blood cultures contaminated with skin organisms during collection, CNS bacteraemia are also commonly linked to device-associated infections in children and this analysis underlined the key importance of these as a source of infection in children (Favre *et al* 2005; Venkatesh *et al* 2006; Henderson *et al* 2010).

5.2.3.2 ***Trends in pathogens causing bacteraemia****:* We used the 2008 data to determine the predominant pathogens causing bacteraemia. We focused the analysis on the 12 most common pathogens, which accounted for 80% of the cases. We were able to demonstrate that whilst *S. aureus* bacteremia had been the predominant pathogen in the early 2000s, *E. coli* had now emerged as the major cause of bacteraemia accounting for 22% of cases by 2008. As a result *S. aureus* had moved into third place causing 11.6% of bacteraemias. Coagulase negative staphylococci, previously the third most common cause, had also increased in importance and in 2008 was the second most common pathogen accounting for

17% of cases. This analysis suggested that there had been major change in epidemiology of these infections in England the past decade. Clearly, the recent changes could have been explained by changes in the data capture systems, especially since the extension of electronic reporting had increased the number of participating laboratories and the move from manual to automated data imports could have could have altered the nature of reporting. We therefore identified a subset of laboratories to use for the analysis of trends that would enable us to minimise the risk of ascertainment bias. We did this by excluding those that during the period of analysis (2004 and 2008) had changed from manual to automated reporting, had not submitted complete datasets for one or more years, or demonstrated fluctuations in numbers of reports that were not explained by changes in reporting arrangements e.g. laboratory mergers. These criteria identified 137 of the total of 210 (65%) laboratories as being consistent reporters, although these laboratories actually accounted for almost 80% of the total episodes reported during the period of analysis. This approach enabled us to demonstrate that reports of bacteraemia had increased significantly by 7% ($p < 0.001$) during this period, but that this overall trend disguised a remarkable variation in trend over this time that was driven by changing epidemiology of different pathogens. Thus, whilst the number of episodes of bacteraemia increased by 15% between 2004 and 2006, it subsequently declined with over 90% of the decline between 2006 and 2008 attributable to *S. aureus* (58%) and CNS 34%.

5.2.3.3 ***The Poisson generalised linear regression model***: This enabled us to investigate trends in individual pathogens whilst adjusting for changes in the overall number of episodes and to determine the variation in trend over time by making rolling two-year comparisons of incidence rate ratios, generating confidence intervals and p values to identify significant differences. Using this method we identified that *E. coli* was the most common causative pathogen in each of five years included in the analysis, that the number of reports increased

by almost a third ($p< 0.001$), and the trend was especially prominent in the over 75 year-olds where by 2008 it accounted for 30% of bacteraemias. The analysis also provided evidence of significant increases in other Gram negative pathogens (Klebsiella spp 14%; Pseudomonas spp 24%; Proteeae 13%). Such trends would not be obvious in most blood stream infection surveillance systems which are focused on the detection of hospital-acquired primary (device-associated) rather than secondary infections (Anon 2000; Albrecht *et al* 2006), but are powerful early indicators of potential changes in epidemiology and associated implications for public health.

5.2.3.4 ***Exploration of potential contributory factors****:* Whilst it is difficult to determine a cause and effect relationship from surveillance data, it is important to consider the possible contributory factors to these observed trends. The significant decline in *S. aureus* from 2006, which by 2008 accounted for 3% of bacteraemia compared to 6% in 2004, appears to have been entirely due to the decline in MRSA. Similarly prior to 2000, *S. aureus* had not been the most common cause of bacteraemia and the rise in cases between 2000 and 2006 also appeared to have been related to MRSA rather than meticillin-sensitive (MSSA) strains (Johnstone *et al* 2001). Johnstone *et al* (2005) reported that the proportion of *S. aureus* bacteraemia resistant to meticillin rose from 2% in 1990 to 43% in 2002. We demonstrated that by 2008 this proportion had decreased to 23%. The decline in cases of MRSA from 2006 coincided with major national initiatives to tackle MRSA. Each NHS Trust was set reduction targets for MRSA bacteraemia, and strategies to reduce infections from invasive devices (such as intravenous and urine catheters), prevent cross-infection (such as enhanced hand hygiene, screening patient admitted to hospital for skin carriage and treating them to eliminate colonization) were actively promoted (Johnstone *et al* 2012). We contended that whilst some of these measures would specifically target MRSA (e.g. screening and decolonization), others such as invasive device could have been expected to have an equal

effect on MSSA and MRSA. Other evidence suggests that the increase in MRSA as a cause of bacteraemia emerged in the late 1990s with the spread of new epidemic strains (EMRSA 15 and 16) and that one of these strains started to decline in the early 2000s (Johnstone *et al* 2001; Ellington *et al* 2010; Wyllie *et al* 2011). The emergence and disappearance of EMRSA stains is not a new phenomenon (Murchan *et al* 2004) and we postulated that the ecology of *S. aureus* may, at least in part, explain the difference in trend between MSSA and MRSA. In contrast to *S. aureus*, CNS increased between 2004 and 2007 and then significantly declined between 2007 and 2008, although the trend was only apparent in adults. CNS bacteraemia are often associated with invasive devices as they have a propensity to form biolfilms on catheter surfaces (Raad 1998; O'Grady *et al* 2011) and as a common skin commensal they also readily contaminate the blood culture specimen if this is not taken aseptically (Beekman *et al* 2006). We suggested that the trend we observed may have been influenced by the guidance on taking blood cultures that was issued in 2006, in combination with improvements in the management of intravascular devices that was driven by the strategies to prevent MRSA bacteraemia (Department of Health 2007, Dawson 2014).

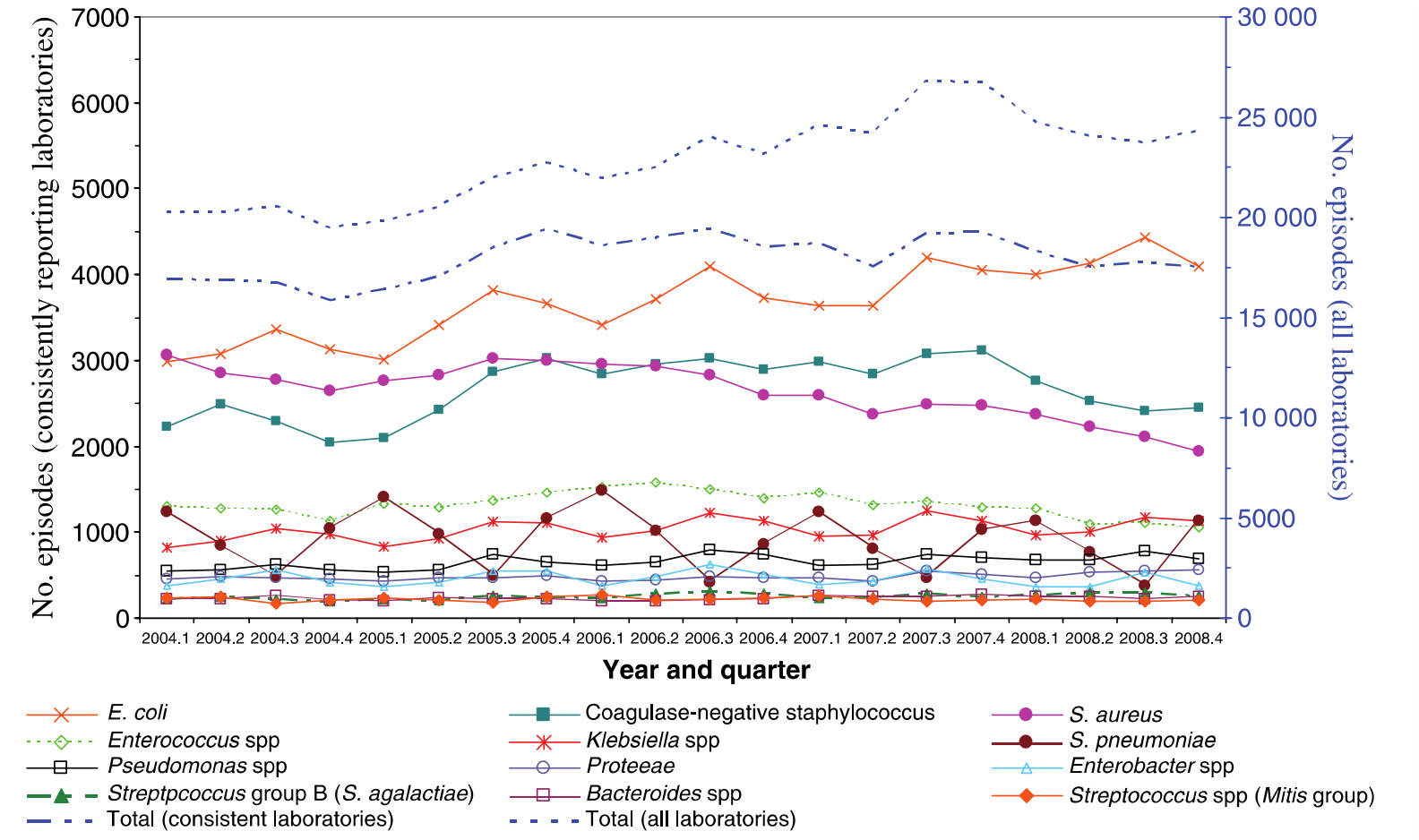
5.3.3.5 ***Evidence of seasonal trends***: Another remarkable finding in the trend analysis was the marked seasonal trend in cases of *E. coli* and other Gram negative pathogens (see Figure 5.1). Seasonal variation in infection rates are not uncommon but had previously been associated with the winter months and increased risk of respiratory tract infection. Winter peaks of MRSA bacteraemia, *Strepococcus pneumoniae* and *Clostridium difficile* were evident from other surveillance data (HPA 2008a; Ampofo *et al* 2008; Jansen *et al* 2008). Whilst our dataset could not provide data on the source of the bacteraemia, we considered evidence available from other datasets about the main cause of Gram negative and *E. coli* bloodstream infections. The British Society for Antimicrobial Chemotherapy (BSAC) operates a sentinel surveillance system to capture isolates of 12 pathogens (or groups of

pathogens) in order to study trends in antimicrobial resistance (Reynolds *et al* 2008). This data is captured by between 25 and 30 hospital laboratories, and whilst clinical data associated with the specimens is limited, the presumed focus of infection is reported. Although based on relatively small numbers of cases and over-represented by large, teaching hospitals,the focus of infection was reported as the genitourinary tract infections in 44% of cases of *E. coli* bacteraemias and accounting for 64% where a presumed focus was known (Livermore *et al* 2008). Whilst these infections often originate in community-based patients they are frequently linked to healthcare. Marshall *et al* found that over 80% of patients who had been hospitalised for less than 48hrs when bacteraemia due to Gram negative bacteria was identified had a history of recent hospital admission, outpatient treatment or were resident in long term care facility (Marshall *et al* 2009). The seasonal effect that we observed was particularly marked in the over 75 years age group who accounted for 30% of cases of *E. coli* bacteraemia. Since dehydration has been suggested to increase the risk of urinary tract infection (UTI) we postulated that during period of high temperature in the summer months, the elderly who due to deficits in thirst reflex and other underlying morbidity, are at increased risk of dehydration and subsequent UTI and that this could be a plausible driver of the observed increase in Gram negative bacteremia in the summer months (Phillips *et al* 1993; Abdulla *et al* 1994; Mentes 2006).

5.2.4 Conclusions

This publication was the first population-based investigation of the pathogens causing bacteraemia in England that attempted to define trends more accurately by attempting to address the affect of changes in case ascertainment. Whilst our methods provided a more robust analysis than Reacher *et al* (2000) there were limitations. Firstly, the selection of a subset of consistently reporting laboratories had the potential to introduce bias if these were different from the excluded laboratories. This risk was probably small given that whilst

Figure 5.1: Trends in total number of reported episodes of bacteraemia in England for all laboratories (n=210) and for the 12 most commonly reported pathogens in consistently reporting laboratories (n=137) between 2004 and 2008. Source: Wilson *et al* 2011.



the selected laboratories represented 64% of the laboratories they accounted for 80% of cases reported, suggesting that the excluded laboratories were mostly small. There was also an element of judgment in the identification of 'consistent reporting' since the many Trust, and therefore laboratory mergers that took place during the period under review made it difficult to establish whether a large period range in number of reports from a specific laboratory was due to inconsistent reporting or re-configuration of the service. We probably erred on the 'side of caution' in excluding data from laboratories where there was a wide variation in reports between periods indicative of incomplete data exports, but this was to some extent subjective as the volume of data varied widely according to the size of the laboratory and normal variation in number of 'events'. However, if anything this approach would have resulted in an underestimation of trends as those laboratories with sharp peaks in reports would have been excluded. By using a subset of laboratories to explore changes in the numbers and proportion of pathogens we were also not able to calculate the change in population incidence over this time, although it is unlikely that the trends observed would have been explained by changes in the population denominator.

5.2.4.1 The other main limitation of the dataset used for this analysis is the lack of clinical data associated with the reports. The surveillance system is reliant on laboratories reporting only bacteraemia considered to be 'clinically significant' and in reality these judgments may not be made with any consistency, especially when automated data downloads are used. That said, among the top twelve pathogens (which accounted for 80% of reports) all but CNS would be highly unlikely to be detected in the blood if the patient did not have infection. *E. coli* and other Gram negative pathogens, in particular, are unlikely to represent contaminants, and although a subsequent analysis of MRSA bacteraemia data demonstrated evidence for some of these cases being probable contaminants, this was in less than 10% of cases (Wilson *et al* 2011b; Appendix 5.2). However, in the trends we observed in CNS it is

difficult to distinguish changing epidemiology of the organism from changes in practice that may reduced the risk of blood culture contamination (Beekman *et al* 2005; Dhillon *et al* 2009, Henderson *et al* 2010).

5.2.4.2 The absence of clinical data meant that we were unable to determine the explanation for the trends observed, including the seasonal effect in Gram negative pathogens and whilst we drew on other sources of data to postulate on possible causes this needs to be the subject of future analytical studies. In addition, although in 80% of cases for which the data was available the blood culture was taken in hospital, without a date of hospital admission it is not possible to determine whether the patient acquired the infection in hospital or the community. However, the study also demonstrated the value of not focusing purely on HCAI by drawing attention to changing risks of infection in a wider, public health context.

5.2.4.3 ***My contribution to this research***

Whilst most of my research had been focused on data captured by SSI surveillance, the origins of this research were my curiosity about trends in pathogens causing bacteraemia that I first observed in the data included in an HPA annual report (HPA 2007). I subsequently devised the approach to minimsing case ascertainment bias by selecting consistently reporting laboratories and used my expert knowledge of microbiology, infection and surveillance data to develop the analysis, interpret the results and draw conclusions from the results. I was also mainly responsible for drafting the publication.

5.3 Application of these methods to other bacteraemia surveillance data

Published work 8: Analysis of trends in sources of MRSA bacteraemia

Wilson, J., Guy, R., Elgohari, S. *et al* (2011) Trends in sources of meticillin resistant *Staphylococcus aureus* bacteraemia: data from the National mandatory surveillance of MRSA bacteraemia in England, 2006 to 2009. *Journal of Hospital Infection*. **79**: 211-217 (Appendix 5.2)

5.3.1 Overview

Concerns about the proportion of *S. aureus* bacteraemia resistant to methicillin identified in LabBase and in sentinel surveillance data submitted to the European Antimicrobial Resistance Surveillance System (EARSS) emerged in the 2000s. This data indicated that the proportion of *S .aureus* that were resistant to meticillin (MRSA) had risen from 2% in 1991 to 42% in 2000 and were far more prevalent in the UK than most other countries in Europe (Duckworth *et al* 2002; Johnson *et al* 2005; Pearson 2009). In 2001 the Government announced that surveillance of methicillin resistant *Staphylococcus aureus* (MRSA) bacteremia would become mandatory, data would be captured separately from the routine LabBase reporting system, and a new MRSA bacteremia system would be established (see section 2.2.7). Initially, this system was based on aggregate quarterly reports of cases by each NHS Trust, but in October 2005, a patient level, web-based reporting system called the MRSA bacteraemia Electronic Surveillance System (MESS) was developed. All NHS Trusts in England were required to report each episode of MRSA bacteraemia via this system, together with a small dataset on the specialty and admission-type of the patient. Unlike the data in LabBase, the MESS system included an option to enter clinical data on the primary source of the bacteraemia. Using the methods that we developed for the analysis of trends in LabBase data, we evaluated trends in the reported sources of MRSA bacteraemia in cases entered into the system between 2006 and 2009. In common with the LabBase data, this

surveillance data had some key limitations, in particular that data on source was completed for only 40% of episodes and there were different levels of 'certainty' attached to the reported source and the sources were not based on precise case definitions. We therefore included data on the 4400 cases of infections (26% of all MRSA bacteraemia reported during this period) where the reported source was considered as 'certain', highly likely' or 'probable'. Using the same approach as described previously (see section 5.2.2.3), we developed a generalized linear model with a log link for the Poisson distribution, and made rolling two-year comparisons of incidence rate ratios of the proportions of cases attributable to each source adjusted for the total counts. This enabled us to demonstrate a significant decline in the proportion of episodes of MRSA bacteremia associated with central vascular catheters (IRR 0.42; 95%CI 0.29-0.61; p=<0.001), peripheral vascular catheters (IRR 0.69; 95%CI 0.48-0.99; p=0.042) and surgical site infections (IRR 0.42; 95%CI 0.25-0.72; p=0.001) in the context of a general decline in the rate of MRSA bacteraemia since 2006. This analysis therefore provided evidence that the strategy of improving practice surrounding the care of IV devices and the widespread adoption of screening and decolonization prior to surgery were instrumental to the significant decline in MRSA bloodstream infection in England since 2006. It also demonstrated that a significant proportion of cases of MRSA bacteremia attributed as community-acquired due to their detection within 48hr of admission to hospital were in fact associated with invasive devices or procedures linked to hospital care.

5.3.2 My contribution to this research

I used my previous experience in developing the bacteremia surveillance system for NINSS to develop the approach to this research. My clinical knowledge and experience was essential for informing the analysis and interpretation of the results. I also cleaned the data and grouped and classified the reported sources of bacteraemia, and then developed and wrote the publication.

5.4 Contribution of these publications to contemporary knowledge

At the time of this research limited data had been published on population trends in pathogens causing bacteraemia in adults. A recent analysis of trends in children had identified a markedly different picture to the one we identified, with *S. aureus* a predominant pathogen, an overall increase in reports of bacteraemia but declining trend in vaccine preventable infections such as *Strep. Pneumoniae (*Henderson *et al* 2010*).* Although no attempt to adjust for ascertainment bias was made in this analysis, *E. coli* accounted for only 5% of pathogens and an increasing trend was only apparent in children aged 1 – 11 months (Henderson *et al* 2010). In the USA the surveillance of BSI was focused on primary hospital-acquired infections and there was no national system for laboratory-based surveillance such as in the UK (Horan *et al* 2008). Analyses of trends were therefore concentrated on this limited group of essentially device-associated infections rather than considering BSI more broadly (Pittet & Wenzel 1995; Anon 2000; Warren *et al* 2001; Wisplinghoff *et al* 2004; Albrecht *et al* 2006). The rationale for this approach was that secondary BSI reflected an infection at another site and therefore did not merit targeted surveillance in their own right (Horan *et al* 2008). However, as our analysis has shown exploring trends in pathogens causing bacteraemia, whilst unable to establish cause and effect can identify important epidemiological trends that would not be apparent if limited to only primary BSI. The steady growth in systems that support the delivery of healthcare interventions in community settings means that focusing only on bloodstream infections acquired in the inpatient setting is an increasingly inappropriate approach.

5.4.1 Finland is one of few other countries to operate a population-based BSI surveillance system. Their analysis of trends in bloodstream infection between 1995 and 2002 found that the annual incidence of these infection had increased by 40% and, as in our analysis of

English data, approximately 30% of cases occurred in those aged 75 years or older (Skogberg *et al* 2008). *E. coli* was the most common pathogen followed by *S. aureus* although there were no changes in relative proportion observed during this time period (Skogberg *et al* 2008). Unlike the UK, the proportion of *S. aureus* that were resistant to meticllin was very low (less than 1%) and therefore the increase in proportion of bloodstream infections due to MRSA that probably explained the predominance of *S. aureus* bloodstream infections at this time in the UK did not occur in Finland (Lyytikainen *et al* 2005, Johnson *et al* 2005; Pearson *et al* 2009). In the absence of population-based studies of the incidence of bloodstream infection, our study was also unique in presenting data on the differences in risk associated with both age and gender. Whilst the HPA published crude reports of number of bacteraemias submitted to LabBase, the detailed analysis of trends had been focused only on MRSA bacteraemia which was the subject of a separate mandatory surveillance system during this period, and no previous analysis in the context of trends in other pathogens had been published (Johnson *et al* 2005; Pearson *et al* 2009).

5.4.2 The seasonal effect on the incidence of bacteraemia caused by Gram negative pathogens was a particularly striking finding. We identified only two previous references to this seasonal effect, the first included all types of cultures not only blood and was conducted in a single medical centre and in a time-series analysis found a 19% increase in *E. coli* infections in the summer months (Perenevich *et al* 2006). The second study was a population-level analysis of laboratory data captured across Minnestota in the USA and used Poisson regression methods to explore the association between incidence of *E. coli* and BSI and average monthly temperature adjusted for age and calendar year (Al-Hasan *et al* 2009). They identified a 35% increase incidence rates of *E. coli* bloodstream infection in the summer months and a 7% increase in risk for each 10^{o}F increase in average temperature. As in our analysis, neither of these observational studies were able to demonstrate the cause of

this association but speculated about food or water-borne sources, prevalence of clonal strains and human behavior such as sexual activity and water recreation, although the need for further studies to determine the precise reasons behind the seasonality of *E. coli* infections was recognised (Perenevich *et al* 2006; Freeman *et al* 2009).

5.4.3 At the time of our analysis of the trends in sources of MRSA bacteraemia, there had been limited research by others and the few other studies had been conducted had focused on specific patient groups or involved small case series (Big *et al* 2010; Das *et al* 2007). The unique nature of both the mandatory surveillance system for MRSA in the UK, and marked declining trend in MRSA bacteraemia after 2006 also provided a rare opportunity to explore factors that might underpin these changes based on clinical data about the cases as opposed to population level associations that infer a causal effect (Stone et al 2012; Wylie *et al* 2011).

5.5 Subsequent research contributions to the field

The significant decline in MRSA as a cause of bacteraemia in England has been mirrored in a number of other European countries. In 2002, data captured by the European Antimicrobial Resistance Surveillance System (EARSS) indicated many countries where MRSA accounted for more than 25% of *S. aureus* isolates from blood but by 2008 more countries were showing decreasing rather than increasing trends in prevalence of MRSA (Johnson *et al* 2011; de Kraker *et al* 2013). There has been much speculation as to the reasons for the marked decline in the UK which have included the action taken by the Government to set improvement targets, the package of guidance on preventing MRSA transmission and infection, widespread change in antimicrobial agent prescribing and change in epidemiology of the underlying epidemic strains (Ellington *et al* 2010; Livermore 2012; Wylie *et al* 2011; Johnson *et al* 2012). However, the studies that exist are largely descriptive or focused on a single institution and are unable to shed light on the underlying reasons for the changing

epidemiology of MRSA bacteraemia or extend knowledge on the sources of these infections (Johnson *et al* 2012).

5.4.1 In a study of bloodstream infections in an Australian tertiary referral hospital between 2001 and 2009 found a similar increasing trend in Gram negative pathogens as causative organisms linked to community-onset infections, with 53% of cases occurring in the over-70s and a significant age-dependant increase in E. coli infections (Aung *et al* 2012). The seasonal effect has also been confirmed in a study in Israel where rates of E. coli bloodstream infection were approximately 20% greater in the summer months compared to winter and autumn/spring and a link with urinary tract infection was suggested by the finding that the urinary tract was the source of 67% of the infections (Chazan *et al* 2011). Alcorn *et al* also observed an increase in episodes of healthcare associated bloodstream infection caused by Gram negative pathogens in summer months, but only in patients receiving care outside hospital the source was attributed to intravascular devices in 38% of cases (Alcom *et al* 2013). Further evidence for a relationship between high ambient temperature and gram negative BSI is provided by an analysis of data from 132 US hospitals found a significant increase in BSI due to Gram negative bacteria in summer months. They identified a 3.5% (95%CI 2.1-4.9) increase in frequency of *E.coli* BSI with each 10^{o}F increase in mean monthly temperature (Eber *et al* 2013).

5.5.2 The role of antimicrobial agents in driving the changing epidemiology of *E.coli* has also been highlighted. EARSS data (now EARS-Net) identified a 71% increase in *E.coli* bloodstream infection reported from 198 participating hospitals in 22 countries between 2002 and 2009, in comparison with a 43% increase in *S.aureus* infection during the same period. (Gagliotti *et al* 2011). During this time resistance to third-generation cephalosporins increased significantly from 1.7% to 8% and resistance to all four classes of agent

(aminoglycosides, aminopenicillins, fluroquinolones) from 0.6% to 3.4%. Siedelman et al found that previous antibiotic use and recurrent urinary tract infection were significant risk factors for both community and hospital-acquired bloodstream infection caused by resistant *E. coli* strains (Siedelman *et al* 2012). Extended-Spectrum beta-lactamases (ESBLs) began to emerge in Gram-negative pathogens in the UK in the early 2000s initially in Klebsiella species but spreading to *E. coli* (Livermore 2012). The predominate type of *E. coli* ESBL (ST131) has been found to carry a number of virulence factors that promote colonisation and invasion of bladder cells and this may explain the observed increase *in E. coli* bloodstream infections (Totsika *et al* 2011; Livermore 2012). This changing epidemiology is highly significant since UTI is a common infections, acquired by up to 50% of women and 5% of men in their lifetime (Ulett *et al* 2013). Not only is *E. coli* significantly increasing as a cause of severe infection, resistant strains are associated excess mortality. Patients with bloodstream infections caused by *E. coli* resistant to third-generation cephalosporin were found to be 2.5 times more likely to die within the first 30 days after infection than matched patients with sensitive strains (de Kraker *et al* 2011). However, prevention of these infections is likely to be challenging, as unlike other HCAI many emerge in patients living in community settings and hence receive lesser attention. As yet, no studies have been published on approaches to reduce the risk of these infections.

5.6 Summary of chapter

The methods that I have described in these two studies used observational data captured by surveillance systems to investigate the epidemiology of bacteraemia. As with any data derived by surveillance rather than research there are limitations in its interpretation and challenges in analysis created by partial data and incomplete records. In both studies we were presented with incomplete set of data. The first analysis addressed the effect of

potential case ascertainment bias on observed trends by focusing on a subset of consistently reporting laboratories used generalized linear models to adjust for variation in number of cases over time. In the second study, we identified a subset of cases where there was reasonable evidence of the source of bacteremia to investigate trends in causes of MRSA bacteremia and associated implications for practice. Whilst both studies illustrate the imperfections in surveillance datasets they also demonstrate the value of careful analysis of population-level data in identifying emerging problems that need to be addressed to protect the public from the risk of infection. They also provide important insights that can help to improve our understanding of potential causes of infection and inform the development of strategies that may help to prevent them.

CHAPTER 6

My professional development as a researcher

My initial introduction to, and interest in, conducting research was engendered through a research assistant post at the Nursing Practice Research Unit based at Northwick Park Hospital in London and funded by the Department of health and Social Security. My role was on a project investigating the risks of urinary tract infection associated with catheters, which allowed me to combine my experience from my honours degree in microbiology with a registered general nurse qualification. These were significant assets for this research, which required observation of clinical practice and collection of epidemiology data on patients who were catheterised and the UTI they acquired. As part of a small research team, this role enabled me to develop skills in study design and analysis, and the practical problems of capturing data on the use and management of urinary catheters in clinical settings. It also introduced me to the concept of healthcare associated infections and the challenges of assuring adherence to infection prevention practice and to some of the practical problems of surveillance and principles of data capture and analysis (Crow *et al* 1988).

My specific interest in surveillance developed in the late 1980s. At that time, surveillance of healthcare associated infections (HCAI) was not a widely recognised strategy for infection control specialists in the UK, but the evidence emerging from the Study of the Efficacy of Nosocomial Infection Control (Haley *et al* 1985a) highlighted the critical importance of surveillance in driving improvements in practice and reducing rates of HCAI. A keynote lecture about the role of surveillance in preventing HCAI given at the Infection Control

nurses Association annual conference in 1988 by Professor Robert Haley, who had been Director of the SENIC project, inspired my subsequent research interests. Through my contact with Professor Haley, who was then Director of the Division of Epidemiology at the Southwestern Medical Centre in Dallas Texas, I visited a number of hospitals in the USA that he recommended had expertise in using surveillance as part of their infection control programme. I was subsequently able to apply the knowledge I acquired from these visits about methodology, data capture and analysis to build surveillance into the infection control programme in my own institution. My clinical background and expertise has subsequently had an important influence on my development as a researcher, with my experience as a nurse playing a key role in both directing my interests in relation to the practical value of surveillance, and in providing a relevant clinical focus to how I have interpreted and analysed surveillance data.

In my next role as Programme Lead for surveillance Public Health Laboratory Service (later to become the Health Protection Agency) I was able to further develop my understanding of the application of surveillance methods to support infection control and reduce HCAI. I was involved in the design and development of a landmark project at the PHLS - the Socio-economic Burden of Healthcare Associated Infection project which has provided the framework for defining costs of HCAI both in the UK and Internationally for the last decade (Plowman *et al* 2001). This gave me important insights into the principles of determining the costs of HCAI and informed my contribution to our subsequent analysis of the costs associated with SSI (Coello *et al* 2005). My involvement in the design and delivery of a second major PHLS project – the Clinical Audit of Hospital Infection Control Activity (Glynn *et al* 1997) - developed my skills in research and project design, but also extended my knowledge of HCAI data capture, analysis and interpretation across several hospitals. I subsequently was able to apply this knowledge to the development of the first national HCAI

surveillance systems in the UK, which has formed the basis of the work described in this thesis.

In my role leading the national SSI surveillance system there were two key influences on my research strategy. Firstly, I was interested in exploiting the unique size of the surveillance dataset to improve understanding of the impact of SSI and the factors that affected its acquisition. I perceived that studies that define these relationships are essential to both direct effective prevention measures and to inform the design of appropriate surveillance systems. These same guiding principles influenced my subsequent research on bloodstream infections. My second research focus was exploring surveillance methodology, both to establish the robustness of its metrics and to enhance its impact in driving improvements in infection prevention practice.

My formal training in the principles and methods of epidemiology and statistics I gained from studying an MSc in Public Health. My dissertation for this MSc entitled *Surgical site infection following vascular surgery: risk factors for infection and the use of rates as performance indicators*. In this work I analysed SSISS data on 3901 vascular operations from 40 hospitals in order to identify significant risk factors and how these influenced variation in rates of SSI between hospitals. In addtion to a systematic review of the literature for evidence for potential risk factors for SSI, I used backwards stepwise logistic regression techniques to identify significant independent risk factors for SSI and used the risk adjusted rates generated from this model to indirectly standardise rates of SSI for each hospital. This grounding in these statistical methods was invaluable in developing my approach to the analysis of the large national surveillance datasets, particularly the SSI data where the structure of the dataset made it possible to use these techniques to clearly define risk factors for infection. This method of adjustment enabled us to make robust estimates of the

independent effect of SSI on length of hospital stay and mortality in Coello *et al* 2005, and determine the factors influencing the variation in risk between hip hemiarthroplasty and total hip replacement procedures by including the procedure type as a predictor (Ridgway *et al* 2005). This study was also the first time that I had sought to work in collaboration with an orthopaedic surgeon (S. Ridgeway) to analyse the data and write the publication. This collaboration was essential in ensuring we designed the data analysis appropriately and appraised the relevance of potential risk factors for SSI using his expert knowledge of the procedures. This collaboration as also invaluable for the interpretation of the results as it provided insight into the potential explanations for the observed risk factors and expert knowledge with which we could check the face validity of the regression models. This also illustrates the influence that working in teams and learning from others has had on my research. Key players in the teams I have worked with in developing my research have included statisticians, clinicians, scientists and epidemiologists. The analyses of these large surveillance datasets require complex statistics and I have learnt that bringing together my knowledge of the surveillance system/dataset and my experience of healthcare systems and HCAI with the statisticians' expert knowledge of statistical analyses was highly effective in developing a robust approach to analyzing and interpreting the data. Similarly, combining ideas and insights from members of the team with different knowledge and skills generates innovative ideas and approaches. These team relationships are wholly symbiotic with neither member able to conduct the study effectively without the input of the other, and I have continued to apply this philosophy throughout my subsequent research.

The knowledge I gained from undertaking the analysis for Ridgeway *et al* 2005, in particular the important differences in risk between hip hemiarthroplasty and total hip replacement procedures that could not be distinguished by the standard risk index, influenced research I subsequently undertook in exploring the relationship between duration of operation and risk

of SSI in which the segregation of hip hemiarthroplasty procedures was fundamental to the analysis (Leong *et al* 2006). The T time analysis was an important step in order to validate the national SSI surveillance methodology since common criticism was the use of US T times as these were seen to be out-dated and not representative of UK operation times. This analysis was important in developing my thinking about the key advantage of the T time in providing a stable indicator of increased duration of operation, although I now believe that recent studies indicate it is a strong extrinsic rather than intrinsic risk factor and its use for risk adjustment should therefore be reconsidered.

My findings from both these studies, as well as the in-depth knowledge of the structure of SSI dataset that I had gained through these analyses, informed my subsequent work with European colleagues on exploring inter-country variation in rates of SSI (Wilson *et al* 2007). I was an active participant in the Hospitals in Europe Linked through Infection Control network of HCAI surveillance networks and as a result gained a broad knowledge of methodology used by other national surveillance systems in relation to both SSI and HCAI in intensive care surveillance. The value of this collaboration was combining the technical proficiency of statisticians at the HELICS coordinating centre in Brussels with my expertise in understanding SSI surveillance data to shape the analysis. This enabled us to identify the key variables with which to investigate variation and interpret the implications for SSI surveillance methodology and inter-country comparisons. I prepared the analysis for a presentation on inter-country variation in HELICS data for the International Hospital Infection Society conference and subsequently wrote this first publication exploring variation between countries in rates of SSI data. On reflection, I could have improved this publication by incorporating greater detail about the methods and approach that we took to this analysis as this is key to understanding the results and our interpretation. As I have developed as a researcher I now have a greater appreciation of the importance of clearly

describing the methodology, especially for the complex approaches to modeling that are used in the analysis of surveillance data.

In leading the team responsible for managing the SSI surveillance system I was able to drive and direct the programme of research. One key aspect of the surveillance that I recognised needed more research was the mechanisms for reporting of results of the surveillance to participating hospitals. The scientific literature supported the fundamental role played by feedback of surveillance data in reducing infection rates and that benchmarking was an important driver of improvement (Taylor et al 1994; Gastemeier et al 2005; Geubels et al 2006). However, through my work with HELICS I realised that methods of benchmarking in national surveillance systems largely relied on comparisons between the pooled mean and individual hospital rates, with or without standardisation to account for case-mix variation but without consideration for the precision of estimated rates. Whilst we used this approach in the first reports of mandatory orthopedic surveillance, I sought to find a more effective means of accurately communicating variation in rates of SSI and detecting outlying rates of SSI, to clinical staff of hospitals participating in SSISS and those responsible for monitoring performance. My publication about funnel plots (Wilson *et al* 2008) again reflected a collaboration between statistical and surveillance expertise to create a novel application of a statistical method to solve a surveillance problem. My experience with exploring international comparisons had illustrated the effect that PDS exerted on rates of SSI and the difficulties of developing an accurate metric for comparing rates based on PDS where rates of follow-up differed. The analysis of HELICS data was limited because it was based only on data captured by the routine surveillance systems in each country and we had little data on the reliability of the methods used to capture it. In designing my study on surveillance following caesarean section delivery I sought to address these limitations by capturing data on the proportion of patients followed-up by PDS methods and estimating the reliability of

the methods in detecting SSI. Whilst this study still had its own limitations, in particular the practical problems of accurately measuring sensitivity and specificity, I was able to define differences in application of surveillance methods and their impact on rates, at least in this one category of surgical procedures.

Whilst I was initially less closely involved in developing methodology for bacteraemia surveillance after the NNISS surveillance was discontinued, my detailed knowledge of HCAI surveillance systems was invaluable in informing my work on designing the methods for the analysis of trends in sources of MRSA and pathogens causing bacteraemia. Whilst I was aware of limitations of using data captured by surveillance systems for drawing conclusions about 'cause and effect', my research interests were driven by recognition that these large national datasets presented unique opportunities not available in local small scale surveillance, to define and communicate HCAI problems, understand and influence factors that affect them and improve the data capture systems to support effective infection prevention efforts.

Building this body of research, I have developed and applied knowledge and skills in the analysis and interpretation of surveillance data. During this time my development as a researcher has been strongly influenced by the opportunities I have had to work with experts in epidemiology, surveillance and data analysis, at the HPA, in Europe and the USA who have shaped my ideas, triggered many of the questions that I have endeavored to answer and identified the challenges that my research has sought to address. These collaborations have enabled me to develop as a researcher with National and International recognition through my publications, presentations at conferences and invited lectures.

CHAPTER 7

Conclusions and future research

7.1 Introduction

In this thesis I have described the principles underpinning the development of HCAI surveillance systems in England, how my research has contributed to their development and how I have made use of the large datasets captured by these national surveillance systems to explore risk factors, outcomes for infection and epidemiology of pathogens that cause them. In this final chapter I will draw conclusions about my work and explore future directions for my research.

7.2 Conclusions from my programme of research

My research has provided new knowledge about risks of SSI in terms of mortality and increased length of hospital stay that have been widely used to provide evidence for the impact of SSI, derive costs associated with these infections and justify the benefits of strategies to prevent SSI. My work has also contributed to the body of knowledge on risk factors for SSI, with the large datasets captured by the SSI surveillance system providing the unique opportunity to determine significant independent risk factors for SSI following hip prosthesis and to provide robust evidence for the relationship between duration of operations and risk of SSI. Both these analyses have influenced the subsequent development of the SSI surveillance system in England and Europe and supported more accurate risk adjustment and comparison of rates. My research also comprises the first publication on inter-country comparisons of rates of SSI in data captured by the 14 countries participating in the European HELICS network. It highlighted key methodological issues and

at the time of its publication there were few examples of such inter-country comparisons in the literature. The limitations of the comparisons recognised by this analysis have helped to sustain and increase participation in the surveillance by highlighting heterogeneity between countries evident in the data the risk of unreasonable inferences about variation in performance being drawn can be reduced.

7.2.1 My unique, detailed analysis of data on rates of SSI following hip prosthesis together with an innovative approach to performance monitoring has demonstrated the value of funnel plots as a mechanism for supporting the comparison of rates of SSI and providing a robust mechanism for identifying outliers. The value of this approach has been recognised by other HCAI surveillance systems who now also use funnel plots for displaying inter-centre comparisons. My work has also provided evidence for the impact of post-discharge surveillance on benchmarking and the challenges of producing consistent and reproducible results across a range of different centres when most SSI are detected after discharge. This work is particularly important in the context of declining length of postoperative stay in hospital and has also provided a new, practical methodology for evaluating the reliability of SSI surveillance methods.

7.2.2 Finally, my research has highlighted important emerging trends in pathogens causing infection, with the striking findings on seasonal variation in *E. coli* bacteraemias providing important evidence about possible contributory factors and informing public health strategy to prevent them. My research on sources of MRSA bacteremia provided important insights into reasons why the strategies that were put in place to prevent these infections may have been effective which are highly relevant to understanding best practice in relation to infection prevention and control.

7.3 Proposals for future research

7.3.1 Reducing rates of HCAI through benchmarking

The establishment of the national surveillance system in the late 1990s provided a standard surveillance methodology that for the first time enabled hospitals in England to compare their rates of SSI (Cooke *et al* 2000). From its inception, SSISS identified variation between the lowest and highest rate of SSI, which was so large that it was unlikely to be explained by differences in case-mix (PHLS 2000). The ability to make these comparisons was highly valued by participating hospitals and was cited as being a key reason for their participation in the surveillance (Wilson *et al* 2002). However, whilst other national surveillance systems such as Germany, France and until latterly the USA, resisted publication of comparative rates the mandation of SSI surveillance in England made public reporting of such comparisons inevitable (Haustien et al 2011; Bratzler 2013). However, presenting this data in a way that focused attention on those hospitals most likely to have problems with infection prevention practice was a major challenge that had not been addressed by other national surveillance programmes (Haustien *et al* 2011). In using funnel plots to present institutional comparisons of rates of SSI, I was able to address the difficulty of presenting benchmarking data for the mandatory surveillance of SSI following orthopedic surgery and avoiding spurious ranking systems that did not allow for the effect of variation in volume of procedures. These visual methods have become an important development to support effective comparison of performance and act as triggers to take corrective action. In the four years following the introduction of mandatory surveillance in orthopaedic surgery and use of this funnel plot methodology to identify outliers, the rates of SSI across all four categories of orthopaedic procedures declined significantly (HPA 2009; European Center for Disease Prevention & Control 2009; Wilson *et al* 2009; **Appendix 4.5**). Whilst it is not

possible to directly attribute this decline to the measurement of performance through surveillance, it seems likely that it made a contribution since other studies have demonstrated a link between participation in national SSI surveillance systems and declines in rates of SSI (Gastmeier *et al* 2005; Guebbels *et al* 2006; Rioux *et al* 2007). However, one of my concerns in detecting outliers is the importance of not just focusing on those centres with unusually high rates but also considering those identified with unusually low rates. This is not an unusual outcome, in a study evaluating the interpretation of funnel plots by Directors of Public Health, the plots were found to increase the tendency to identify and recommend action on outlying rates however, the focus tends to be on identifying poor performance rather than exemplary practice (Marshall *et al* 2004). The relevance of low outliers in relation to SSI surveillance is two fold. As cited in our publication low rates '*may signify either an excellent performance worthy of emulation (ie, by sharing best practices) or inadequate surveillance methods and a low sensitivity of case finding'*. (Wilson *et al* 2008) Low sensitivity of case finding is a particular problem in the surveillance of SSI, because of the complexity of the definitions of infection and lack of routinely available data required to identify them. Indeed, Tanner et al (2014) have also pointed to variation in interpretation of the surveillance protocol as a factor in explaining variation in rates of SSI (Tanner *et al* 2013b). Therefore a key area for future research is exploring rates of SSI that lie below the lower 90 and 95% control limits and the extent to which they are explained by case-mix (patients at lower risk of SSI than at other centres), low intensity surveillance or high quality practice. I would intend to evaluate quality of practice at participating hospitals with low rates by adapting methods used by Campbell *et al* (2008). This study used a combination of survey questionnaire and review visits to determine the practice associated with low and high outlier status in hospitals participating in the American College of Surgeons – National Surgical Quality Improvement Program (ASC-NSQIP) and identified some important structural factors in American operating departments such as theatre efficiency and low

trainee to bed ratio that were linked to low outlier status (Campbell *et al* 2008). Similar research in the UK would contribute to improving understanding of what factors in the surgical patient care pathway reduce the risk of SSI and enable best practice to be shared. This would be an important area of research because whilst benchmarking of rates of SSI has been associated with marked decline in rates of SSI in England, there has been no research to determine how these trends are correlated with quality of care (Astagneau and L'Heriteau 2010, Wilson *et al* 2009; Appendix 7.1).

7.3.2 Developing data capture systems that support robust benchmarking

My second area of further research is focused on developing methods of SSI surveillance that enable robust comparison of SSI rates in the context of reducing post-surgical stay in hospital. The work on exploring comparison in rates of SSI between countries contributing data to the European SSI surveillance network (HELICS) illustrated the difficulties of drawing robust comparisons where differences in approach to surveillance had an important effect on the number of SSI reported, in particular methods of post-discharge surveillance (PDS) and application and interpretation of case-definitions (Wilson *et al* 2007; Appendix 4.1). The publication on surveillance following cesarean section delivery illustrated the difficulty of consistently identifying SSI that develop post-discharge and the key challenge that this presents to making both inter and intra-country comparisons since this publication demonstrated that, where post-operative hospital stay is short the rate of SSI is strongly associated with the intensity of PDS, and that the intensity of PDS varies markedly between hospitals even when they are using detailed, standard surveillance protocol (Wilson *et al* 2014; Appendix 4.3). This effect seriously hampers the ability of a benchmarking system to detect hospitals with high rates of SSI and use this to drive improvements in infection prevention practice. Whilst an ideal solution may be to ensure complete PDS (Tanner *et al* 2014; Leaper *et al* 2014), in a resource constrained a healthcare environment such as the

UK, adequate funds to conduct complete PDS of all surgical patients are unlikely to be available (Hall *et al* 2013). Therefore more efficient approaches to capturing and benchmarking surveillance data need to be developed which meet the key goal of identifying hospitals with high rates compared to other hospitals.

7.3.2.1 One approach that I would explore in order to address these problems identified with SSISS in terms of the robustness of benchmarking would be to develop a 'research quality surveillance system' such as the ASC-NSQIP. This system uses designated personnel at participating hospitals to capture data on a defined set of procedures to be used for benchmarking. Such a system is better able to reliably compare rates because they are then based on high quality, validated data from a systematic sample of surgical procedures and it follows all patients included in the sample up for 30 days post operation (Ingraham *et al* 2010). This methodology assures data quality and completeness and enables benchmarking and analysis of risk factors by capturing data on a range of post-operative adverse events not just SSI. However, whilst able to provide very high quality data on which to base benchmarking, its disadvantage is that is resource intensive, does not support surveillance for SSI on a wide range of surgical procedures and does not provide data that is easily interpreted by patients.

7.3.2.2 Another area of research that I propose to develop is the use of NHS data submitted to Hospital Episode Statistics as a source of comparative information on rates of SSI. Whilst the quality of this data was relatively poor in previous decades, the introduction of payment-by results has introduced a financial incentive for NHS Trusts to capture accurate clinical data on patient procedures and outcomes and as a result the quality of this data has improved in recent decades (Jenks *et al* 2014). Procedures are captured by their relevant OPCS codes and data on outcome can be gathered from ICD10 codes derived from operation

notes, laboratory data and discharge letters. Evidence suggests, that whilst this data has limitations it has an accuracy of around 83% for diagnostic and procedure codes (Mamidanna & Faiz 2012). The advantage of using such routinely captured data for surveillance is that it would considerably reduce the resources required to generate rates of HCAI and would also avoid the biases associated with variation in intensity of care finding. Rates for all NHS hospitals could be calculated by combining data on the number of specific operations performed in a designated period (the denominator) with cases of SSI detected in the electronic records (the numerator). Hospitals with high or low rates of SSI could then be identified using the funnel plot methodology developed in Wilson *et al* 2008 (Appendix 4.2) and those above or below control limits investigated to determine the cause. However, the value of this approach depends on the reliability of the coding in detecting cases of SSI and the extent to which there is inter-hospital variation in coding. The first stage in this research is to develop an algorithm to define a potential SSI from ICD10 codes that are indicative of a problem with wound healing or infection following an operation and apply these to records of patients who are identified to have undergone a specified surgical procedure. I am currently conducting a preliminary study to test the practicality and reliability of this algorithm, including measuring the sensitivity and specificity by comparing the cases of SSI it detects with prospective active, surveillance system at a single hospital. Further studies are then required to test the comparability of the method across several centres. Whilst such electronic data sources are unlikely to detect all cases of SSI, especially the less severe superficial case, if the method reliably detects a high proportion of severe SSI it may be possible to develop the system to provide a high level mechanisms of monitoring and comparing rates of SSI and detecting outliers that require further investigation. In addition, another advantage of developing methods of capturing data on SSI from these electronic records is the potential to better define the adverse effects associated with it. The analysis of costs and mortality we published in 2005 (Coello *et al;* Appendix 3.1) remains

the best available data. Currently, whilst all Trusts in England are required to conduct at least three months of SSI surveillance in orthopedics few Trusts undertake surveillance in other categories of surgical procedure (HPA 2005). This means that there is little data on the risk of infection available to patients, clinicians or health service managers and in the absence of evidence for the overall burden of SSI to those providing and receiving healthcare means that infection prevention measures, including surveillance, can be difficult to justify. As demonstrated by the SENIC study in the 1980s, the availability of such surveillance data is critical to driving improvements in surgical practice and assuring patient safety in terms of preventing SSI (Haley *et al* 1985). Analysis of HES data may provide an opportunity to increase address this problem by providing evidence on the risks of significant SSI following a wide range of surgical procedures.

7.3.3 Developing and testing validation systems

The evaluation of SSI surveillance in caesarean section delivery highlighted the need to develop efficient and effective validation systems that can be used to assure the reliability of hospital surveillance systems and accuracy of their reported rates (Wilson *et al* 2013; Appendix 4.3). This is particularly important where surveillance is associated with performance management, which generates perverse incentives to avoid reporting cases of SSI especially when linked to a message of 'zero tolerance' (Bratzler 2013). Tanner *et al* in a survey of Trusts participating in SSISS found variation in data quality and collection methods that had an affect on the rates that they reported (Tanner *et al* 2013). They also found that 10% of Trusts did not report superficial SSI, reflecting the problem of conflating surveillance definitions with clinical diagnosis. As pointed out by Talbot *et al,* the latter are in part based on subjective judgment and are used to guide treatment, whilst the latter are ideally based on objective criteria derived from readily accessible data (Talbot *et al* 2013). I propose that further work is therefore required that identifies mechanisms of validating case-finding by

participating hospitals, determines inter-rater reliability of case-definitions and defines effective systems for organising surveillance locally. This research could also explore the use of electronic data sources and the potential for integrating data from primary care with hospital-based surveillance systems. These developments are imperative to support effective, high quality HCAI benchmarking systems in the context of declining lengths of hospital stays and challenges of capturing data in community settings.

7.3.4 Determining factors contributing to the increasing trend in *E.coli* bacteraemia

Data captured by routine laboratory surveillance systems such as those I have described in Wilson *et al* 2011a and 2011b (Appendix 5.1 and 5.2) are useful in describing emerging trends but of limited value in identifying causative factors. The MRSA surveillance system had some data on sources of the infection that could be analysed to throw light on potential causative factors, but as illustrated in the publication, this data was limited and incomplete (Wilson *et al* 2011b; Appendix 5.2). However, the success in controlling MRSA as a cause of severe infection in the UK does illustrate the importance of reacting to emerging threats and the value of routine surveillance systems in providing early warning of changes in epidemiology. However, whilst the strategies targeting the reduction in MRSA bacteraemia were ultimately successful, it is difficult to know what factors contributed to the decline (Gagliotti *et al* 2011; Johnson *et al* 2012; Livermore 2012). In relation to *E. coli* bacteraemia, our analysis has highlighted the emergence of *E. coli* as the predominant pathogen causing bacteraemia (Wilson *et al* 2011a). The Department of Health has subsequently established a mandatory surveillance system for *E. coli* bacteraemia and is striving to drive prevention efforts (Department of Health 2011; Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) 2013). However, currently there is scanty evidence for the important drivers for these infections and little is known about the patients who acquire them and the factors that contribute to the acquisition of the primary infection.

Since over half of the cases appear to occur in individuals who have not had contact with healthcare (Public Health England (PHE) 2014) investigation of the underlying causes and contributory factors for these infections is more complex that might be the case for infections acquired in hospitals. Understanding these factors will be critical to developing effective strategies to prevent and control these infections, especially as interventions are likely to be required at a community level. A case control study would be an effective method of investigating these contributory factors, since the bacteraemia is relatively rare infection and matching cases with similar patients with a different type of bacteraemia would enable risk factors to be distinguished. A better understanding of the factors associated with *E. coli* bacteraemia would enable preventive measures to be more effectively targeted.

7.3.4.2 The seasonal trend in *E. coli* bacteremia that we clearly identified in our analysis may provide important clues for factors driving the increasing trend in infections (Wilson et al 2011a; Appendix 5.1). Evidence suggests that at least 50% of cases relate to infection of the urinary tract with a preponderance of cases in the elderly and a background of repeat urinary tract infections (UTI), sub-optimal antimicrobial prescribing and increasing prevalence of resistant *E. coli* strains with urinary tract virulence factors (PHE 2014, Livermore 2012, Totsika *et al* 2011). The peak of cases in the summer months that we observed suggests that dehydration may be a contributory factor to these infections, and whilst it is generally accepted that dehydration increases the risk of UTI currently there is little evidence to demonstrate this link especially in the elderly (Su *et al* 2006; Wang 2002; Rudaitis *et al* 2009). The elderly are particularly vulnerable to dehydration due to physiological changes associated with aging that result in a decrease in water volume in the body, including the loss of the thirst reflex, decline in kidney function and ability to concentrate urine, and loss of muscle tissue (Phillips *et al* 1991; Bossingham *et al* 2005;

Mentes *et al* 1999). In addition, cognitive and physiological impairments may affect the ability of the elderly to consume fluids and some may restrict fluid intake due to fear of incontinence (Mentes 2006). The population of the elderly in care homes would provide an opportunity to study the relationship between dehydration and risk of UTI. Since dehydration is acknowledged as being very difficult to diagnose (Chassagne *et al* 2006) I would take the approach of measuring the effect on morbidity (including UTI) of a strategy to optimize hydration of residents. I would use a stepped wedge, cluster randomised design (with a care home as the unit of randomisation) to minimise the risk of confounding. This approach would have the benefit of both establishing whether there was a relationship between hydration and UTI and determine whether a strategy aimed at optimising hydration was successful in reducing the associated morbidity. In addition, the effect of daily temperature on incidence of infection could also be explored in such a study.

7.4 Conclusion

In an editorial by Richard Platt in 2005, he commented on the current status of HCAI surveillance and its role in informing clinicians, healthcare providers and patients about risks of infection and quality of care (Platt 2005). He pointed to the benefits that the increased attention paid by society to these infections in relation to investment by healthcare institutions in HCAI reduction and improving patient safety. However, he also cited key challenges to preventing the burden of mortality, morbidly and costs of these infections. These included the lack of information held by hospitals on their own infection rates that they could use to measure their performance, monitor effectiveness of prevention strategies and define models for good care and the lack of information for patients about comparative risk of infection between institutions that they could use to inform their choices. Platt also pointed to the need for surveillance methods to be able to inform hospitals that have a high rate compared to other hospitals so that they can take corrective action, but to achieve this

as efficiently as possible to avoid excessive use of scarce resources. The work that I have described in this thesis has contributed to addressing some of these challenges. In particular it has added to the body of knowledge on outcomes of SSI that can be used to inform clinicians and patients about variation in practice and factors that are important when making comparison of rates. In addition, it has enhanced methods of benchmarking hospitals performance; informed the design and delivery of surveillance systems by identifying the impact of risk factors and case-finding methods on rates; and informed public health strategy by investigating emerging trends in rates of HCAI pathogens.

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