

**Healthcare associated infection surveillance: Examining influences on reliable and valid
data collection and analysis**

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Author Declaration and Statement of Authorship and Sources

This thesis contains no material published elsewhere or extracted in whole or in part from a thesis by which I have qualified for or been awarded another degree or diploma. No parts of this thesis have been submitted towards the award of any other degree or diploma in any other tertiary institution. No other person's work has been used without due acknowledgment in the main text of the thesis. All research procedures reported in the thesis received the approval of the relevant Ethics Committee (where required) or a relevant safety committee if the matter is referred to such a committee.

I can confirm that my thesis was copyedited for conventions of language, spelling and grammar by Katie Poidomani, Edge Editing and Proofreading. Editing was consistent with Standards D and E of the Australian Standards for Editing Practice (Council of Australian Societies of Editors, 2001).

I declare that I have received financial assistance from a number of organisations. Financial assistance was provided to support my doctoral studies. Organisations that have provided financial assistance are listed below. I declare that none of the organisations listed played any role in the conduct of my research.

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Publications

Peer review journals

Publications that have been published, accepted for publication or submitted to journals are listed below. For articles that have been published, a link to the online version is provided.

1. **Mitchell, B.**, Gardner, A., Collignon, P., Stewart, L., & Cruickshank, M. (2010). A literature review supporting the proposed national Australian definition for *Staphylococcus aureus* bacteraemia. *Healthcare Infection*, 15(4), 105-113.
 - <http://www.publish.csiro.au/paper/HI10030.htm>
2. **Mitchell, B.**, & Gardner, A. (2012). Prolongation of length of stay and *Clostridium difficile* infection: A review of the methods used to examine length of stay due to healthcare associated infections. *Antimicrobial Resistance and Infection Control*, 1(14).
 - <http://www.aricjournal.com/content/1/1/14>
3. **Mitchell, B.**, & Gardner, A. (2012). Mortality and *Clostridium difficile* infection: a review. *Antimicrobial Resistance and Infection Control*, 1(20).
 - <http://www.aricjournal.com/content/1/1/20/abstract>
4. **Mitchell, B.**, Gardner, A., & Stewart, L. (2012). The epidemiology of *Staphylococcus aureus* bacteraemia in Tasmania. *Healthcare Infection*, 17(3), 98-103.
 - <http://www.publish.csiro.au/nid/242/issue/6247.htm>
5. **Mitchell, B.**, Gardner, A., & McGregor, A. (2012). Healthcare associated infections: safety and quality vs. public reporting; getting the balance right. *Australian Health Review*, *Australian Health Review*, 36 (4), 365-366.
 - <http://www.publish.csiro.au/nid/270/paper/AH11200.htm>

6. **Mitchell, B.**, Gardner, A., & Hiller, J. (2012). *Clostridium difficile* infection and mortality in an Australian setting. Submitted to *Journal of Advanced Nursing*, Online early. DOI: 10.1111/jan.12078.
 - <http://onlinelibrary.wiley.com/doi/10.1111/jan.12078/abstract>

Peer review conferences

1. **Mitchell, B.**, Gardner, A., Barnet, A., Hiller, J., & Graves, N. (2012). *The prolongation of length of stay due to Clostridium difficile infection using a multistate model*. Oral presentation accepted for the Annual Scientific Conference of the Australasian College for Infection Prevention and Control, Sydney. Awarded best referred oral abstract.
2. **Mitchell, B.**, Gardner, A., & Stewart, L. (2012). *The labyrinth of infection prevention: new frameworks for using healthcare infection data*. Oral presentation accepted for the Annual Scientific Conference of the Australasian College for Infection Prevention and Control, Sydney.
3. **Mitchell, B.**, Gardner, A., & Hiller, JE. (2012). *Mortality and Clostridium difficile infection in an Australian setting*. Poster presentation accepted for the Annual Scientific Conference of the Australasian College for Infection Prevention and Control, Sydney.
4. **Mitchell, B.**, & Gardner, A. (2012). *Mortality and Clostridium difficile infection in an Australian setting*. Poster presentation at the Annual Scientific Meeting of the Australasian Society for Infectious Diseases, Fremantle.
5. **Mitchell, B.**, Gardner, A., & Stewart, L. (2011). *The epidemiology of Staphylococcus aureus bacteraemia in Tasmania*. Oral presentation at the 5th International Congress of the Asia Pacific Society for Infection Control, Melbourne, November 2011.

6. **Mitchell, B.** (2010). *Capturing the true incidence of Staphylococcus aureus bacteraemia*. Poster presentation at the 7th International Conference of the Hospital Infection Society. Liverpool, UK.

Additional Publications by Author Relevant to Thesis

The publications listed below were produced and submitted during my PhD Candidature and have been cited in my thesis.

Peer review journals

1. Grayson, L., Russo, P., Cruickshank, M., Bear, J., Gee, C., Hughes, C., Johnson, P., McCann, R., McMillian, A., **Mitchell, B.**, Selvey, C., Smith, R., & Wilkinson, R. (2011). 24 Month Outcomes from the Hand Hygiene Initiative. *Medical Journal of Australia*, 195(10), 615-619.
 - a. https://www.mja.com.au/journal/2011/195/10/outcomes-first-2-years-australian-national-hand-hygiene-initiative?0=ip_login_no_cache%3D292982aef4527d96e7403e79c05bd211
2. **Mitchell, B.**, Ware, C., McGregor, A., Brown, S., & Wells, A. (2011). *Clostridium difficile* infection in Tasmanian Public Hospitals 2006-2010. *Healthcare Infection*, 16(3), 101-106.
 - a. <http://www.publish.csiro.au/paper/HI11009.htm>
3. **Mitchell, B.**, McGregor, A., & Coombs, G. (2009). Prevalence of MRSA colonisation in Tasmanian rural hospitals. *Healthcare Infection*, 14(4), 159-163.
 - a. <http://www.publish.csiro.au/paper/HI09023.htm>

List of Abbreviations used in this thesis

Abbreviation	Term in full
AB	Antibiotic
ACSQHC	Australian Commission on Safety and Quality in Health Care
AGAR	Australian Group on Antimicrobial Resistance
ASA	American Society of Anesthesiologists
CA	Community associated
CCI	Charlson co-morbidity index
CDI	<i>Clostridium difficile</i> infection
CI	Confidence interval
df	Degrees of freedom
DRG	Diagnosis Related Group
EIA	Enzyme immunoassay
HAI	Healthcare associated infection
HAIs	Healthcare associated infections
HA	Healthcare associated
HCA HFO	Healthcare associated, healthcare facility onset
HICPAC	Healthcare Infection Control Practices Advisory Committee
HREC	Human Research Ethics Committee
ICD	International Classification of Diseases
LOS	Length of stay
MRSA	Methicillin resistant <i>Staphylococcus aureus</i> bacteraemia
n	Number of cases (subsample)
N	Total number of cases
NHMRC	National Health and Medical Research Council
OR	Odds ratio
PCR	<i>Polymerase chain reaction</i>
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RHH	Royal Hobart Hospital
RR	Relative risk
SAB	<i>Staphylococcus aureus</i> bacteraemia
τ	Kendall's rank-order correlation coefficient
TIPCU	Tasmanian Infection Prevention and Control Unit
χ^2	Chi-square distribution

Glossary of common terms used in the thesis

Term	Definition ¹
Colonisation	The term used to describe a sustained presence of replicating infectious agents on or in the body, without the production of an immune response or disease.
Diagnosis Related Group	Methods used to categorise and characterise episodes of care received by patients admitted to hospitals.
Healthcare associated infection	Infections acquired in healthcare facilities and infections that occur as a result of healthcare interventions.
Hospital acquired infection	An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other healthcare facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staff of the facility.
Nosocomial infection	Same as “Hospital acquired infection”, please see definition above.

¹ The definitions provided in this table are defined and referenced in the thesis. Definitions are provided in this glossary for ease of reference.

Abstract

Healthcare settings are dangerous places. Individuals who receive healthcare may be subject to unintended harm as a consequence. One potential adverse event is a ‘healthcare associated infection’. This contemporary term refers to any infection which is acquired in healthcare facilities or any infection that occurs as a result of healthcare interventions. This thesis is concerned with the topic of healthcare associated infections. The effects of healthcare associated infections are felt not only by individual patients through increased morbidity and mortality but also by health services faced with higher costs associated with infections. The prevention of infection requires a multifaceted approach which is underpinned by healthcare-associated infection surveillance. Surveillance is used to influence practice and policy as well as to evaluate the effectiveness of strategies to reduce healthcare associated infections. Surveillance of healthcare associated infections is a critical element of any infection control program and it is crucial that healthcare-associated infection surveillance data are reliable and valid. In this thesis, three individual studies are presented.

The three studies focus on two specific healthcare-associated infections: *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection. The aim of this thesis is to explore the epidemiology of these two infections and, in doing so, to examine methodological influences on reliable and valid healthcare associated infection data collection and analysis.

The first study – an examination of the epidemiology of *Staphylococcus aureus* bacteraemia in Tasmania, Australia – used a descriptive, observational, population-based study design. This is the first known Australian study to capture and analyse data from all cases of SAB at a population-based level and represent this as an incidence. Four key findings can be identified from this study. First, the incidence of *Staphylococcus aureus* bacteraemia at a population level was accurately determined for the first time in Australia and was found to be 21.26 per 100,000 population, with 42% of *Staphylococcus aureus* bacteraemia being healthcare associated. Second, 55% of healthcare associated *Staphylococcus aureus* bacteraemia was associated with intravascular device management. Third, case definitions for healthcare associated *Staphylococcus aureus* bacteraemia have an influence on detection. Sixty-eight per cent of healthcare associated *Staphylococcus aureus* bacteraemia occurred in persons hospitalised less than 48 hours but had other criteria which resulted in them being

defined as healthcare associated. Therefore, in cases where no criteria other than timeframe are used to define cases of SAB, approximately 30% of cases of SAB would be incorrectly identified as community associated. Fourth, 11% of *Staphylococcus aureus* bacteraemia were identified in private hospitals which fall outside the scope of almost all *Staphylococcus aureus* bacteraemia surveillance programs in Australia.

The second study examined mortality following *Clostridium difficile* infection in hospitalised persons at the Royal Hobart Hospital, Tasmania. Results from this study indicated that *Clostridium difficile* infection was associated with increased mortality, when compared to a comparable population who did not have *Clostridium difficile* infection. More specifically, mortality following *Clostridium difficile* infection was found to be statistically significant at 180 days post-admission to hospital, compared to persons who did not have *Clostridium difficile* infection, using a conditional logistical regression model. One potential explanation for the delayed effect was the manner in which exclusion criteria, more specifically the management of two or more positive laboratory tests, were applied to the study population. This is an important finding in itself, as this study highlights not only the impact of a *Clostridium difficile* infection on individuals but also the potential influence that case definitions may have on valid and reliable results.

The third study examined both the incidence of *Clostridium difficile* infection at Royal Hobart Hospital over a four year period and its impact on the prolongation of length of stay. The calculated incidence of 2.68 per 1000 admissions was higher than that found in other published Australian data but lower than internationally reported incidences. This study used multistate data analysis techniques to determine the potential prolongation of length of stay due to *Clostridium difficile* infection and is, to the best of the author's knowledge, the first study to do so. From the findings, it can be inferred that *Clostridium difficile* infection does not significantly contribute to a longer hospital length of stay, ($p = 0.51$). Conversely, the influence of CDI in a proportional hazard model was found to be statistically significant, with acquisition of CDI significantly reducing the discharge hazard ($p < 0.001$). In essence, the findings of this study demonstrate limitations of both existing and relatively new data analysis techniques. An unpublished model for multistate data analysis is proposed which could further enhance the reliability of data analysis.

Each of the three studies presented in this thesis provided a significant and unique contribution to the literature. In conducting these studies, an improved understanding of the epidemiology of these infections in Australian settings was achieved and four influences on reliable and valid data collection and analysis were identified. A new model summarising these influences is presented which has implications for future healthcare associated infection surveillance planning and evaluation.

Chapter 1: Introduction

1.1 Origins of the thesis: patient safety and healthcare

Healthcare settings are dangerous places. For those receiving care, the risk of unintended harm from healthcare failures continues to be excessive. The elderly fall and suffer fractures and other injuries; incorrect medications are administered with sometimes serious consequences; patients unable to move independently develop pressure injuries; and clinicians fail to respond to people whose condition deteriorates quickly enough to prevent further morbidity or sometimes death; healthcare associated infection (HAI) can cause increased morbidity and mortality. These adverse events have spawned an entire industry charged with attempting to keep people safe from the dangers associated with being the consumers of health care. These points are demonstrated in a landmark paper “*To Err is Human: Building a Safer Health System*” published in 1999 by the Institute of Medicine (IOM) (Kohn, 1999). Patient safety studies informing the IOM report suggested that the most frequent types of adverse events affecting hospitalised patients include adverse drug events and HAI (Brennan et al., 1991; Leape et al., 1991).

The IOM paper focussed the attention of policy makers, the public and healthcare workers on improving patient safety in healthcare facilities (Kohn, 1999; Yokoe & Classen, 2008). The authors reported that adverse events affected approximately two million patients each year in the United States, resulting in 90,000 deaths and an estimated \$4.5–5.7 billion per year in additional costs for patient care at that time (Kohn, 1999). Following the IOM report, the ‘blame game’ and the search for how to fix the problem commenced in the United States (Donaldson, 2008). Congressional hearings were subsequently held, while government agencies, professional groups, accrediting organisations and insurers responded with plans to define events and develop reporting systems (Donaldson, 2008).

In Australia, the themes of the IOM report and patient safety studies are evident through the establishment and work undertaken by the Australian Commission on Safety and Quality in

Health Care (ACSQHC). The ACSQHC is an independent statutory authority, under the *National Health and Hospitals Network Act 2011*. The purpose of the ACSQHC is to lead and coordinate improvements in safety and quality in health care across Australia. The remit of the ACSQHC includes medication safety, falls prevention, recognising and responding to clinical deterioration and the prevention of HAIs. This thesis is particularly concerned with one patient safety activity the prevention and control of HAIs.

1.1.1 The emergence of healthcare associated infections in patient safety

Healthcare associated infection is the contemporary term used to refer to infections acquired in healthcare facilities and infections that occur as a result of healthcare interventions (National Health and Medical Research Council, 2010). The effect of HAIs are not only felt by individual patients through increased morbidity and mortality, but also by a health service through higher costs associated with infections. The magnitude of the effect of HAIs on patients is evidenced by a report from the World Health Organisation, which suggests that 7.6% of hospitalised patients will acquire a HAI (World Health Organisation, 2011b).

Following the publication of the IOM report, further reports were published and strategies were developed to raise awareness across the world about the specific importance of HAIs and patient safety. In addition, there was a growing consensus that many HAIs were largely preventable (Adams, Corrigan, & Institute of Medicine Committee on Identifying Priority Areas for Quality Improvement, 2003; Department of Health, 2002, 2004; Yokoe & Classen, 2008). These developments led to an increase in interest in the area of HAIs from patients, the media, politicians, healthcare workers, regulators and government bodies (Flanagan, Welsh, Kiess, Hoke, & Doebbeling, 2011; H. Humphreys, Smyth, E T M., 2006; R. A. Weinstein, Edmond, & Eickhoff, 2008). In the United States, infection control programs have been regulated via legislative mandates and 32 states have HAI reporting laws (Association of Professionals in Infection Control and Epidemiology, 2011; Weinstein et al., 2008). In the United Kingdom, there has been extensive coverage of HAIs in the media (Turner, 2008). A British Broadcasting Corporation health reporter has stated, “There is probably no subject in health that has dominated the headlines as much as hospital infections” (Triggle, 2008).

In Australia, accreditation standards for hospitals have been strengthened in the area of infection control and new standards will be implemented in 2012 (Australian Commission on Safety and Quality in Health Care, 2011e); while public reporting of limited infection control data commenced during 2011 and 2012 (Australian Institute of Health and Welfare, 2012; B. Mitchell, McGregor, A., Brown, S., Wells, A., 2011b). Nationally, public reporting on hand hygiene compliance rates and reports on healthcare associated rates of *Staphylococcus aureus* bacteraemia (SAB) occurs, while in Tasmania data on other HAIs, such as *Clostridium difficile* infection (CDI), are recorded. At the time of writing, Tasmania is the only state in Australia that mandates public reporting of HAI data, additional to those that are required nationally. More broadly, on the issue of public reporting an expert advisory committee to the Centres for Disease Control and Prevention (CDC), the Healthcare Infection Control Practices Advisory Committee (HICPAC), argue that patients do have a right to know this information, but note concerns that the reliability of public reporting systems may be compromised by the variability in the definitions used for HAIs, or in the methods and resources used to identify HAIs (McKibben et al., 2005). The concerns raised by the HICPAC are themes that emerge through the three studies undertaken in this thesis and are discussed in more detail in Chapter 6.

The decision to move to public reporting in Tasmania came after considerable media and political attention on the issue. Patient advocate groups applaud the fact that politicians have legally mandated reporting of infection prevention and control measures, for example, the requirement of formal governance arrangements incorporating the role of senior level managers and executives in healthcare organisations. Conversely, others “lament the forced creation of more layers of bureaucracy instead of focusing on resolving root causes, root causes created by the same political forces that created these new requirements” (Birnbaum, 2004, p. 256). Regardless of individual views on political involvement in infection control, one key element in any infection prevention strategy, mandated or not, is the need to inform and evaluate strategies to reduce HAIs.

1.2 Surveillance of healthcare associated infections

To influence practice and policy and to evaluate the effectiveness of strategies to reduce HAIs, there is a need to collect HAI data and use these through a wider system of quality management, as demonstrated through the *Study of the efficacy of nosocomial infection control* project, often referred to as the SENIC study (Haley et al., 1985). As a consequence of the SENIC study and the IOM report, HAI surveillance programs have been established in numerous countries to monitor and control the occurrence of HAIs through internal quality improvement efforts (Cruickshank, 2009; Health Protection Agency, 2007; Jarvis, 2003; Yokoe & Classen, 2008). HAI surveillance data can be integrated into a quality improvement cycle, such as the ‘plan-do-check-act’ cycle developed by Shewhart (Cleghorn & Headrick, 1996). This cycle shares basic features of well-accepted theory about individual and organisational learning, including the concepts of change and action and or reflection (Cleghorn & Headrick, 1996). Surveillance for quality improvement in the area of HAIs can measure outcomes such as infections, or processes that are linked to outcomes, for example hand hygiene compliance (Collins, 2008). Regardless of whether outcome or process data are used, a critical element in using surveillance data for quality improvement is the need for it be of high quality (Clezy, 2008). Erroneous conclusions about healthcare problems in a given population may be drawn from poor quality data.

In this thesis, I undertake three individual pieces of research, referred to as studies. As well as providing new clinical findings related to the infection themselves, I demonstrate methodological challenges in common approaches to HAI surveillance. The themes relating to the methodological challenges are synthesised at the end of the thesis and a new framework is proposed incorporating the influences on reliable and valid HAI surveillance data.

The three studies in this thesis focus on two specific HAIs, namely, SAB and CDI. Each study is an individual piece of research that makes a significant contribution to the understanding and effect these two infections have in Australia. In addition the findings of these three pieces of work, brought together, provide an impetus for change and future research.

1.3 Setting for the studies in this thesis

The geographical location of the three studies is the Australian State of Tasmania. The State of Tasmania consists of an archipelago of more than 300 islands. It is located 240 kilometres south-east of mainland Australia. The state is home to a population of approximately 500,000 people, most of whom inhabit the main island.

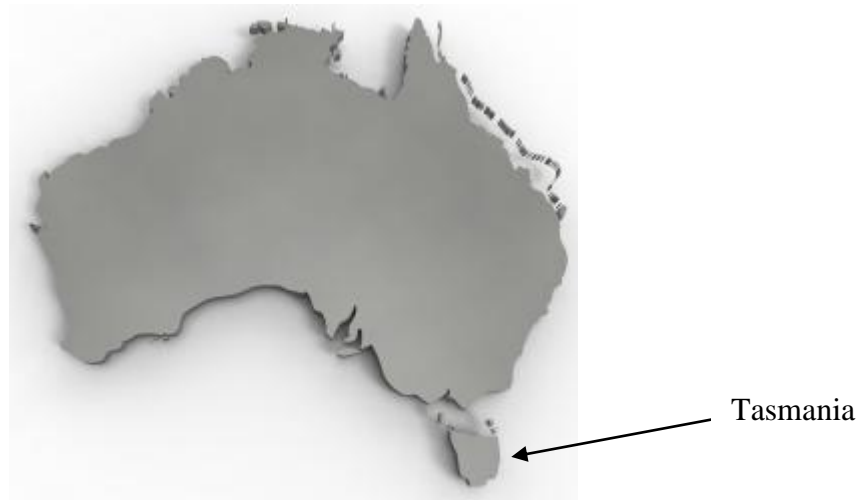


Figure 1. Map of Australia indicating Tasmania.

The first study is conducted at a population level, while the setting for studies two and three is the Royal Hobart Hospital (RHH). The RHH, located in Tasmania's capital city, Hobart, is a tertiary hospital and is Tasmania's largest public hospital. Like other Australian states and territories, Tasmania is facing the challenges of an ageing population, an increase in chronic disease and an increase in the costs of healthcare (Department of Health and Human Services, 2007; Taylor, 2008).

1.4 Background of the author

My interest in conducting this research emanated from 13 years of experience as a practising nurse working in both community and hospital settings, culminating in my present role as

Assistant Director of Nursing at the Tasmanian Infection Prevention and Control Unit (TIPCU), a departmental unit of the Department of Health and Human Services. In this role I take a lead in the strategic planning and management of HAI prevention in the Tasmanian public health system. As a result, many aspects of my work as Assistant Director and the research undertaken as part of this thesis are intrinsically linked. This is demonstrated by my involvement in Australia's national hand hygiene initiative, the development of the first HAI strategy for Tasmania, the development of national surveillance implementation guides, and my work on the National Health and Medical Research Committee (NHMRC) responsible for overseeing the national infection control guidelines (L. Grayson, Russo, R., Cruickshank, M., Bear, J., Gee, C., Hughes, C., Johnson, P., McCann, R., McMillan, A., Mitchell, B., Selvey, C., Smith, R., Wilkinson, I., 2011; B. Mitchell, Brown, S., Wells, A., McGregor, A., 2009; B. Mitchell, McGregor, A., Coombs, G., 2009; National Health and Medical Research Council, 2010). In each of the studies in this thesis, a clear delineation between my work as a researcher and my work in the TIPCU is made where necessary.

In my role as Assistant Director, I have developed and implemented a range of HAI strategies, including the establishment of surveillance programs in Tasmania. I am a current member on national committees, including the National Hand Hygiene Advisory Committee and the National Technical Surveillance Group (Australian Commission on Safety and Quality in Health Care, 2011c, 2011d). My work in the latter group required the translation of a concept, namely national surveillance of two HAIs into reality. This experience has provided me with insight into the current challenges in implementing national HAI surveillance programs. More specifically, I was faced with the dilemma of providing a national surveillance program that could be implemented across Australia in a variety of settings and at the same time attempting to maintain high quality, reliable and valid HAI surveillance data. This experience led me to question how I could build on existing Tasmanian HAI surveillance data to address key clinical questions relating to SAB and CDI, and at the same time articulate influences on reliable and valid data collection and analysis.

1.5 Aims of the thesis

There are two overarching aims for this thesis:

1. To explore the epidemiology of two serious HAIs namely SAB and CDI
2. To examine methodological influences on reliable and valid HAI data collection and analysis

1.6 Structure of the thesis

The thesis contains three studies on two HAIs, namely SAB and CDI. Each of these three studies has specific objectives that relate to the aims of the thesis. In addition, each study has specific research questions to address the stated objectives. The thesis contains six chapters, including this chapter. A brief summary of each of the chapters will now be provided.

The next chapter, Chapter 2, provides an introduction to the topic of HAIs, including a description of what HAIs are and the common types of infection that are implicated. The effects that HAIs have on an individual and on health services as a whole are also explored, in addition to current strategies to prevent HAIs in Australia. Theoretical frameworks and elements of HAI prevention programs, both of which underpin infection prevention activities, are then discussed.

The third chapter is concerned with SAB. This chapter provides a background to *S.aureus* infection generally and SAB, before a literature review analysing the epidemiology of SAB and elements of a SAB surveillance program are detailed. Following the literature review, the methods, results and interpretation of the first study are presented. The objectives for the first study are to describe the epidemiology of SAB in Tasmania and to understand the methodological influences on reliable and valid collection of SAB data.

The fourth chapter is concerned with CDI. This chapter initially provides background about the organism *C.difficile* and CDI, before a literature review analysing mortality and CDI is presented. Following the literature review, the second study of this thesis is described. The objectives for the second study are to describe the risk of mortality associated with CDI and to explore potential limitations in estimating mortality associated with CDI, when current international surveillance definitions for CDI are applied.

The fifth chapter is again concerned with CDI; however this chapter further explores the epidemiology of CDI in more detail, by examining the potential effect it has on prolonging the length of stay in hospital in persons who had this infection. As a background to CDI was provided in the previous chapter, it is not repeated again. A literature review analysing studies that have examined CDI and the prolongation of length of stay in hospital is provided. Then, the third and final study of this thesis is presented. The objectives of this piece of research were to explore the incidence of CDI and prolongation of length of stay due to CDI and to analyse potential influences of differing data analysis methods in the calculation of any prolongation of length of stay.

The final chapter, Chapter 6, commences by summarising and synthesising the key findings of the three studies presented in this thesis. In doing so, a model explaining the influences on reliable and valid HAI data—as identified through the studies conducted for this thesis—is presented and the implications for the proposed model discussed. The contribution to knowledge will then be presented, before concluding the thesis.

1.7 Conclusion

This chapter has provided an overview on the origins of this thesis, an introduction to the study setting for the three studies contained in the thesis and a summary of the structure of the thesis. Information on the background of the author of this thesis was presented to provide clarity about how this research aligns with employment and current infection prevention

activities of the author. The next chapter of the thesis will introduce the topic of HAIs and includes strategies for their prevention.

Chapter 2: An introduction to healthcare associated infections

2.1 Introduction to the chapter

While Chapter 1 painted an overall picture regarding HAIs, this chapter will provide comprehensive information about the topic. Initially, an explanation of what HAIs are, including common types of infections is provided. The impact that HAIs have on an individual and on health services as a whole will then be explored. Strategies for HAI prevention and the role of HAI surveillance are subsequently discussed. Then, existing theoretical frameworks for infection prevention and control will be presented. An extension of an existing theoretical framework that incorporates the role of surveillance will then be proposed with supporting arguments.

2.2 What are healthcare associated infections?

The prevention of infection in persons receiving healthcare stretches back over a century to the time of Ignaz Semmelweis in 1847 and Florence Nightingale in 1863. Semmelweis, a Hungarian physician, discovered that using chlorine in hand washing practice dramatically reduced the incidence of puerperal fever and mortality in obstetric practice (Pittet & Boyce, 2001). Similarly, Nightingale's ideas about infection were formed through improving environmental hygiene and sanitation (Nightingale, 1863). In the past hundred years, hand hygiene, environmental cleanliness and other practices—such as isolation of patients with specific conditions—as methods of preventing infection have been reinforced repeatedly. Regardless of the known efficacy of these practices, however, compliance with infection prevention activities by healthcare workers remains sporadic, which continues to contribute significantly to the incidence of HAIs.

‘Healthcare associated infection’ is the current term used to refer to infections acquired in healthcare facilities and infections that occur as a result of healthcare interventions (National Health and Medical Research Council, 2010). The terms ‘nosocomial infection’ and ‘hospital acquired infection’ are still often used in the infection control literature. Hospital acquired

infection and nosocomial infection are terms that are used to reflect a subcategory of HAIs, i.e. those that have arisen during a hospital stay. For the purpose of this thesis, the term 'HAI' is used in a manner consistent with that defined by Australia's main research body, the National Health and Medical Research Council (National Health and Medical Research Council, 2010). In this thesis, when other terms are used to describe subsets of HAIs, these terms are initially defined and subsequently used consistently throughout (see Glossary of common terms used in the thesis).

Healthcare associated infections are common and can be caused by a variety of organisms, triggering a range of symptoms and infections in various human systems. One of the most commonly cited prevalence studies was undertaken in the United Kingdom. Findings from this study suggested that in hospitals, the prevalence of HAIs is approximately 8% (D. Gravel, Taylor, G., Ofner, M., Johnston, L., Loeb, M., Roth, V., Stegenga, J., Bryce, E., 2007; H. Humphreys, Newcombe, R., Enstone, J., Smyth, E., McIlvenny, G., Fitzpatrick, F., Fry, C., Spencer, R., 2008; Smyth et al., 2008). The types and frequency of HAIs identified in this point prevalence survey of 75,694 persons in England, Wales, Northern Ireland, and the Republic of Ireland are listed in Table 1 and grouped by anatomical location of the infection (Smyth, et al., 2008).

Table 1

Frequency and causative agents of healthcare associated infections

Infection Type / Anatomical location	% of all HAIs	Main causative agent(s)
Gastrointestinal	20.6%	<i>C.difficile</i>
Urinary tract	19.9%	Gram negative bacteria
Surgical site	14.5%	<i>S.aureus</i> , Gram negative bacteria
Pneumonia	14.1%	<i>S.aureus</i> , Acinetobacter species
Skin and soft tissue	10.4%	<i>S.aureus</i>
Other (bone, joints, eyes, nervous system, cardiovascular, reproductive tract)	7.2%	Various
Bloodstream (bacteraemia)	7%	<i>E.coli</i> , <i>S.aureus</i>
Lower respiratory tract (other than pneumonia)	6.3%	<i>S.aureus</i>

Note: Adapted from Smyth et al. (2008). The information regarding main causative agents was adapted from the National Audit Office (2009), from data from the study conducted by Smyth et al. (2008). Gastrointestinal system includes gastroenteritis, hepatitis, and intra-abdominal infections. HAIs = healthcare associated infections.

The results of the study undertaken by Smyth et al. (2008) as presented in Table 1 not only demonstrate the distribution of HAIs by anatomical location, but also highlight that HAIs can be caused by a range of pathogens. Having provided background information, a description of the impact that HAIs have at individual and healthcare service levels will now be explored.

2.3 The impact of healthcare associated infections on individuals and the health service

Healthcare associated infections have a significant impact on patients through associated morbidity and mortality, and on the population as a whole through a negative effect on health services. These infections are deemed the most frequent adverse events threatening patients' safety worldwide (Bates, Larizgoitia, Prasopa-Plaizier, & Jha, 2009; Burke, 2003; Pittet &

Donaldson, 2005). It is important to note that the impact of HAIs on individuals varies significantly, due to the nature of the illness caused by the infection. For example, as a general rule, a urinary tract infection would not be considered as serious as a bacteraemia, because the former is localised and the latter is systemic. The variation in effect of an infection on a person is also influenced by the causative agent. Some microorganisms are of greater concern due to their high level of virulence or because antibiotic resistance reduces our ability to treat them. With this background in mind, the impact that bloodstream infections have on individuals will be used as an example of the seriousness of HAIs.

Bloodstream infections with bacteria (bacteraemia) or fungi (fungaemia) are common, and they are associated with significant morbidity and mortality. Although these are not the most common HAI, they are among the most important contributors to morbidity and mortality caused by HAIs (P. Collignon, Dreimanis, D., Ferguson, J., van Gessel, H., Taylor, P., Wilkinson, I., Worth, L, 2008). Many people who develop a healthcare associated bloodstream infection die during their hospital stay (Higuera et al., 2007; Pittet & Wenzel, 1995; Wey, Mori, Pfaller, Woolson, & Wenzel, 1988). Those who do survive often develop complications and stay in hospital longer than persons who do not contract an infection (Saint, 2000). To explore this more fully in an Australian context, a prospective cohort study over three years examined the mortality and health status of persons who had a bloodstream infection (Gardner, 2003). In this study, 9% died by the end of the first week, and 34.5% died by six months. Survivors were followed up post-discharge. The two main findings from this study were that bloodstream infections are important in contributing to the probability of death, and that survivors continued to have reduced health when followed up for six months (P. Collignon, Dreimanis, D., Ferguson, J., van Gessel, H., Taylor, P., Wilkinson, I., Worth, L, 2008; Gardner, 2003). The example of morbidity and mortality associated with bacteraemia is one way to demonstrate the impact HAIs have on patients. There are other instances in the literature, including the effects of surgical site infections (Bull, 2008; Kirkland, Briggs, Trivette, Wilkinson, & Sexton, 1999), urinary tract infections (Foxman, 2002), and pneumonia (Kollef et al., 2005).

A different approach to examining the impact that HAIs have on individuals is to explore the impact of a specific organism, such as methicillin resistant *Staphylococcus aureus* (MRSA),

an example of a multi resistant organism (Engemann et al., 2003). For example, a retrospective cohort study evaluated the risk of subsequent MRSA infection and death among patients known to have harboured MRSA for at least one year (Datta & Huang, 2008). The study identified 281 carriers of MRSA, 23% of whom went on to develop discrete and unrelated MRSA infections in the year following their identification as prevalent carriers. The most common infections were pneumonia (39%), soft tissue infection (14%), and central venous catheter infection (14%) (Datta & Huang, 2008).

The impact of HAIs is not limited to individuals. Treatment of HAIs consumes additional healthcare costs, through need for additional diagnostic procedures; interventions, such as surgery and antibiotic therapy; and longer lengths of stay in hospital (Rosenthal, Guzman, Migone, & Crnich, 2003). Additional length of stay is a major contributor to cost. One review identified 254 separate estimates of the length of stay attributable to a HAI and found that additional length of stay due to HAI varies according to infection type and causative agent, but it was clear that infections played a role in increased lengths of stay in hospital (N. Graves, Halton, K., Robertus, L., 2008). Costs associated with HAIs, however, are not limited to hospitals. The cost of HAIs also extends beyond the hospital, with post-discharge costs of persons with surgical site infections being one example. There has been one estimate that the post-discharge cost of surgical site infections in Australia is \$21 million per year (N. Graves, Halton, K., Robertus, L., 2008).

It is clear from the examples provided in this section that HAIs have a negative impact on individual patient outcomes, in addition to contributing to additional costs of a health service. With this in mind, the importance of preventing HAIs becomes clearer. The next section provides an overview of infection prevention activities and the role that surveillance plays in these activities.

2.4 The prevention of healthcare associated infections and the role of surveillance

In Australia, access to healthcare is universal through Medicare, Australia's publically funded healthcare system, which provides free or subsidised medical, optical, and hospital care. Private healthcare is also available; however, there are close links between public and private facilities. For example, a patient may choose to receive private healthcare, but be physically located in a public hospital. Australian state and territory governments are responsible for the governance and management of public hospitals, whilst private hospitals are managed by the relevant funding organisation. Until recently, strategies to prevent HAIs were solely undertaken by individual hospitals or led by state or territory government bodies, such as the Centre for Healthcare Related Infection Surveillance and Prevention in Queensland and the TPCU (Centre for Healthcare Related Infection Surveillance and Prevention, 2012; B. Mitchell, Brown, S., Wells, A., McGregor, A., 2009). Professional organisations, such as the Australasian College for Infection Prevention and Control (formally Australian Infection Control Association) and the Australasian Society for Infectious Disease, have also played key roles in infection control activities. The establishment of the ACSQHC in 2006 has changed the focus of HAI prevention in Australia to a more national and collaborative direction. The ACSQHC identified the prevention of HAIs as one of its key pieces of work, and commissioned a review of the infection control programs in Australia as part of the background work (Tropea, 2008).

The ACSQHC set five individual pieces of work as part of a strategy to reduce the risk of HAIs: 1) improvement in surveillance of HAIs (a main focus of this thesis), 2) the establishment of a national hand hygiene initiative, 3) commissioning of the National Health and Medical Research Council (NHMRC) to develop national guidelines for infection control, 4) building clinical capacity, and 5) antimicrobial stewardship (Australian Commission on Safety and Quality in Health Care, 2011a). At the time of the writing of this thesis, the national hand hygiene initiative was in progress, with the participation of over 500 hospitals in Australia, as well as agreement to the program by all state and territory health ministers (Russo, Pittet, & Grayson, 2012). In addition, the NHMRC has published national guidelines for infection prevention and control (National Health and Medical Research

Council, 2010). Furthermore, there have been publications on surveillance and antimicrobial stewardship, with agreement on national definitions for SAB and CDI, and agreement by all states and territories to undertake surveillance of these two infections (Australian Commission on Safety and Quality in Health Care, 2010; Duguidm, 2011). Clinical capacity has been expanded, through the development of a national committee and the provision of education through online learning modules and ‘road shows’.

On 1 July 2011, the ACSQHC became a permanent independent Statutory Authority under the National Health and Hospitals Network Act 2011. The ACSQHC’s primary function is to lead and coordinate improvements in safety and quality in healthcare across Australia. In September 2011, Australian Health Ministers endorsed new National Safety and Quality Healthcare Service Standards. These standards include infection prevention and control standards that are consistent with and support the work led by the ACSQHC (Australian Commission on Safety and Quality in Health Care, 2011b, 2011e). Infection prevention and control activities are monitored through approved accreditation agencies in Australia. Some of these initiatives are referred to throughout the thesis.

The prevention of infection requires a multifaceted approach. These various approaches are often summarised in an infection control management plan or program used to facilitate the prevention and control of HAIs through internal quality improvement efforts (Yokoe & Classen, 2008). In 2010, the World Health Organisation (WHO) summarised the core components of an infection control program (Seto, Otaíza, & Pessoa Silva, 2010). These components as outlined by the WHO are consistent with those subsequently suggested by the ACSQHC, the NHMRC, and Australian state and territory government led infection control units. The WHO and the ACSQHC have listed surveillance as a key component of an infection control program. Surveillance is the collection, collation, analysis, and dissemination of data regarding a health related event for action to reduce morbidity and mortality and improve health (Guidelines Working Group, 2001). The WHO suggested that surveillance programs include surveillance of infections and assessment of compliance with infection control practices (Seto et al., 2010).

There have been calls nationally and internationally for improved surveillance of HAIs so that the size, burden, and impact can be reduced, and to monitor the effect of interventions (Allegranzi et al., 2011). Likewise, there have been suggestions that surveillance itself can lead to a reduction in HAIs (Allegranzi et al., 2011; Gastmeier et al., 2006; Haley et al., 1985). Surveillance has an important role in healthcare as it can serve as an early warning mechanism, provide essential data for monitoring the effectiveness of interventions, detect trends, provide information for designing and planning future programs, provide a measure for evaluating interventions or programs, and provide a framework for performance management (M. Cruickshank, Jorm, C., 2008; Gregg, 2002). Furthermore, it has been suggested by Nelson (2007) that key attributes of an effective surveillance program include sensitivity, timeliness, representativeness, yielding a high positive predictive value, and being simple, acceptable, and flexible.

This section has provided a brief overview on HAI prevention strategies and introduced the importance of HAI surveillance. Surveillance, in the context of a revised theoretical framework for infection prevention and control, will be discussed in more detail later in this chapter. First, it is important to consider the current theoretical frameworks that underpin infection prevention activities. This is the focus of the next section.

2.5 Theoretical frameworks in infection prevention and control

Two frameworks related to infection prevention and control are explored in this section. The first, chain of infection, is a commonly cited framework used to describe methods of controlling and preventing infection as in the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council, 2010). The second framework discussed in this section describes a biopsychological approach to infection prevention incorporating the chain of infection model as one component.

2.5.1 Chain of infection

Three processes are required for infectious agents to cause infection. These processes are often grouped together and referred to as the chain of infection (Figure 2). The chain of infection describes the elements for transmission of infections: the presence of an infectious agent (source), a mode of transmission, and a susceptible host (National Health and Medical Research Council, 2010). The term ‘cross infection’, is often used to describe the spread of infection from one person to another.

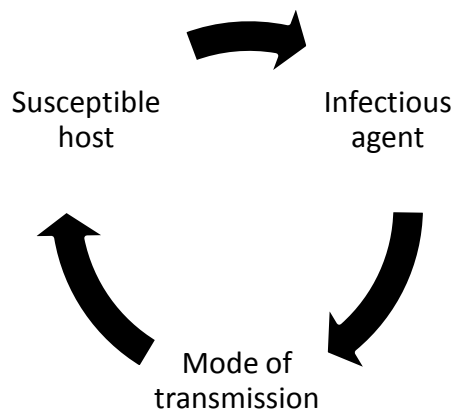


Figure 2. The chain of infection. This figure describes the elements required for a person to acquire an infection.

The sources of infectious agents primarily transmitted in healthcare settings are patients, healthcare workers, and visitors. The presence of an infectious agent on a human, however, does not necessarily mean infection. Individuals may carry an organism but display no symptoms for several reasons: the incubation period for the organism may be long, the carriage may be temporary, or the individuals may be chronic carriers without any symptoms. The term ‘colonisation’ is used to describe a sustained presence of replicating infectious agents on or in the body, without the production of an immune response or disease. Conversely, infection is the invasion of infectious agents into the body, resulting in an immune response, with or without symptomatic disease (National Health and Medical Research Council, 2010). There are two other sources of infectious agents: first, the endogenous flora of patients, and second, environmental sources, such as air, medical equipment, and other inanimate objects that have been contaminated. More detail regarding these latter two sources of infectious agents are provided in Appendix A.

Infectious agents can be transmitted from their sources to a susceptible host by a variety of methods, which include direct spread on the hands of healthcare workers, carriage on equipment, and through airflow. The prevention of transmission via these methods can be routinely prevented in healthcare settings using standard precautions. A more detailed description of standard precautions is provided in Appendix B. Other modes of transmission for infectious agents are via direct or indirect contact, mucous membrane contact with respiratory secretions (droplet transmission) or inhalation of infectious agents suspected in the air (airborne transmission) (National Health and Medical Research Council, 2010). These three processes fall under the umbrella term ‘transmission based precautions’ and more information is provided in Appendix C.

If transmission of an infectious agent does occur, infection is not necessarily certain. Infection is the result of a complex interrelationship between a host and an infectious agent and people vary in their response; not all people exposed to an infectious agent will develop symptomatic disease (National Health and Medical Research Council, 2010). The term ‘susceptible host’ is used in the chain of infection framework to describe this stage (Figure 2). A number of factors influence an individual’s outcome following exposure. These factors include age, immune status, existing co-morbidities, the presence of wounds and devices, and the pathogenicity of the infectious agent. Pathogenicity is further characterised by the organism’s virulence and invasiveness (Brachman, 1996).

The chain of infection has been referred to as using a biomedical or physical approach to infection prevention and control (Elliott, 2009). The terms ‘physical’ and ‘biomedical’ are often used interchangeably in the literature to describe the chain of infection approach. For the purpose of this thesis, the term ‘physical’ is used for consistency. The physical approach to health focuses on risk behaviours, emphasises health education, targets individual responsibility, and treats people in isolation. Considering the chain of infection approach and the examples of standard and transmission based precautions provided earlier, the suggestion that the chain of infection is physical in its orientation has some merit. However, there have been arguments recently that the chain of infection model, a sole approach, is out-dated

(Elliott, 2009). In the next section, the potential limitations of the chain of infection model are explored in the context of a different theoretical approach to infection prevention.

2.5.2 Biopsychosocial approach to infection prevention

A biopsychosocial approach, that is, an approach that considers the physical, social and psychological aspects to infection prevention, was documented by Elliott (2009). He considered that the chain of infection model was no longer an adequate framework. The basis for his suggestion was that the chain of infection is out-dated and that it is “biomedical in its orientation and in the absence of any empirical findings to substantiate it as a holistic and rigorous measure capable of contributing to long term reductions in healthcare-acquired infection, it must be concluded that the chain is neither valid nor reliable” (Elliott, 2009, p. 68). To elaborate further, he explained that this model is, at best, tenuous in its ability to purport what it is meant to, because they are developed by health and social care professionals who consistently demonstrate a propensity for being susceptible to dissonance effects, cognitively economic thinking and unrealistically optimistic beliefs in failing to recognise the necessity of adopting a biopsychological approach (Elliott, 2009). Examples of why the chain of infection has limitations as a physical approach, suggested by Elliott (2009), are provided in Appendix D. Elliott (2009) recognising the need to embrace a new theoretical framework for infection control proposed a biopsychosocial or united approach to infection prevention (Figure 3).

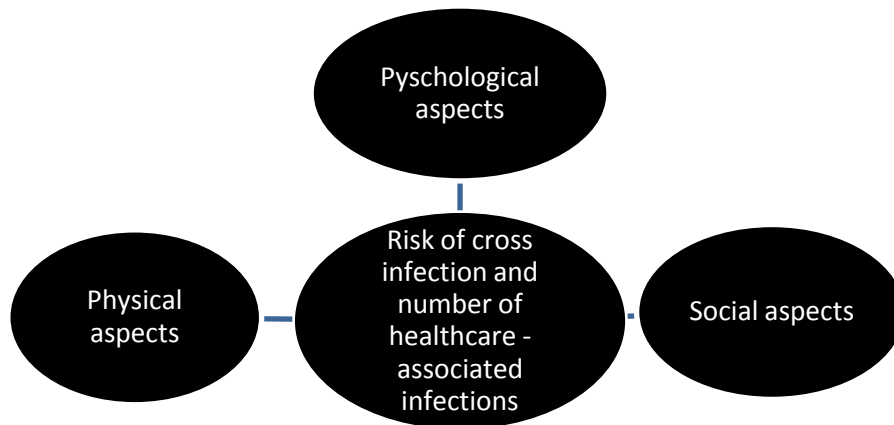


Figure 3. A biopsychosocial approach to the causal nature of cross infection and the number of HAIs. This model was proposed by Elliott (2009, p. 69). Failure to acknowledge and reflect upon all three aspects equally will serve to increase the risk of cross infection and the number of HAIs. The physical aspects approach in this figure refers to a biomedical approach (i.e. the chain of infection).

Elliott (2009) provides examples of each of the three aspects in the above model. Examples of the physical aspects reflect those in the chain of infection, i.e. reservoir, susceptible host, and mode of transmission. Psychological aspects include: rationalised beliefs, arrogance, stress, poor morale, and egocentric attitudes; while the social aspects include: elements of workload, management issues, fatigue, and peer pressure. In considering how infections are transmitted and the potential roles of social and psychological influences, theoretical frameworks for infection prevention and control and the subsequently developed programs need to be multifaceted. Such an argument is supported by Pittet, who suggested that “based on behavioural theories and reported experiences, multimodal intervention strategies have more chance of success than single approaches or promotion programmes focusing on one or two elements alone” (2004, p. 12). Despite this, explicit frameworks for infection prevention and control are rarely used or discussed in the infection control literature, as noted in a review conducted by Zimmerman, Yeatman and Jones (2012).

The authors of this review concluded that “there is an absence of literature on studies that have applied conceptual frameworks to describe and analyse the adoption of comprehensive infection control programs within healthcare settings” (Zimmerman et al., 2012, p. 130). The authors go on to suggest that frameworks which dominated the literature, “focussed on continuous quality improvement and diffusion of innovations” (Zimmerman et al., 2012, p. 130). The review identified four studies that used a diffusion of innovation theory (Abbott, Dremsa, Stewart, Mark, & Swift, 2006; Farrell & Petrik, 2009; Larson, Quiros, & Lin, 2007; Leu, 1995). Diffusion of innovation theory describes “the process by which an innovation is communicated through certain channels over time among the members of a social system” (Rogers, 1983, p. 5). Zimmerman et al. (2012), having identified four studies that used the principles of diffusion of innovation theory, supports the framework proposed by Elliott (2009).

2.6 A conceptual framework for infection control that incorporates the role of surveillance

Miles and Huberman (1994) defined a conceptual framework as a product that explains, either graphically or in narrative form, the main factors, concepts, or variables to be studied, as well as the presumed relationships. A conceptual framework, therefore, could be considered a group of concepts or ideas, broadly described and systematically organised to provide a guide for the interpretation of information. The successful use of conceptual frameworks to translate evidence into practice in various healthcare disciplines is well recognised in the literature (Atun, de Jongh, Secci, Ohiri, & Adeyi, 2010; Biron, Richer, & Ezer, 2007; Donaldson, Rutledge, & Ashley, 2004; Drolet & Lorenzi, 2011; Sudsawad, 2005). In the context of infection prevention and control, use of a conceptual framework has been supported by evidence suggesting that organisations with surveillance programs have seen a reduction in HAIs (Gastmeier et al., 2006; Haley et al., 1985). In this section I introduce an extension of the framework proposed by Elliott (2009) detailed in Figure 3 by incorporating the role of surveillance. Rationale for why surveillance should be included in a framework for controlling HAI is provided.

As discussed earlier, HAI surveillance programs and, to a broader extent, HAI research, allow for the collection, collation, analysis, and dissemination of data. Further, analysis of HAI data through surveillance and research enables evaluation of interventions (Gaynes, 1997). In Section 2.5.2, Elliott's theoretical model describing biopsychosocial influences on the number of HAIs was presented (Figure 3). The model, however, does not include of the role of HAI surveillance. Surveillance programs for HAIs usually focus on infections that occur most frequently in healthcare settings and on the types of infections that pose the greatest risks to patients, through increased morbidity and mortality. Other infections are monitored because they are validated indicators of a range of important healthcare processes, such as hand hygiene and environmental cleanliness. The results of surveillance programs provide measures of the standards of infection control practices in hospitals and other healthcare facilities (Gaynes & Platt, 2006). Reliable surveillance data and continuous monitoring can provide useful information for clinicians and patients alike, by identifying areas for improvement and demonstrating the effectiveness of interventions, such as a reduction in infection rates and, subsequently, patient morbidity and mortality (K. Guerin, Wagner, J., Rains, K., Bessesen, M., 2010; Haley, et al., 1985; Pronovost et al., 2006). With these concepts in mind, a conceptual framework that includes the role of surveillance in HAI prevention is presented in *Figure 4*.

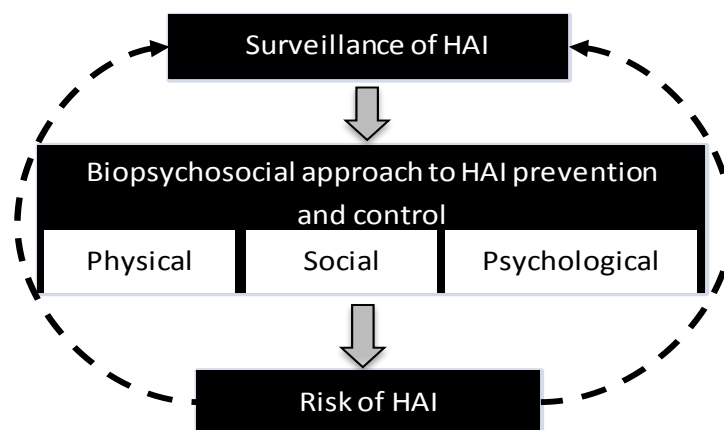


Figure 4. Conceptual framework incorporating the role of HAI surveillance in infection prevention and control. Surveillance refers to the collection, collation, analysis, and dissemination of data and, therefore, could include HAI research.

In the framework depicted in *Figure 4*, a relationship is shown between surveillance of HAIs and the physical, social, and psychological aspects influencing the risk of infection. The argument for the developed framework is that surveillance can be used to inform, influence, and evaluate all three aspects of infection prevention described by Elliott (2009). The evaluation component is represented by the broken line in *Figure 4*. Examples that demonstrate the rationale for inclusion of HAI surveillance in the framework proposed in *Figure 4* will now be explored.

Psychological aspects and role of HAI surveillance

The term ‘unrealistic optimism’ is used to describe a process whereby individuals behave in ways that put themselves or others at risk. In the context of infection control, an example may be failure to perform hand hygiene or failure to prepare a skin site appropriately prior to insertion of a device. In unrealistic optimism, an individual has a distorted belief of the risks involved in a type of behaviour. Using hand hygiene as an example, a healthcare worker may believe that either a) their practice is consistent with best practice, or b) failure to perform hand hygiene will not result in a person acquiring an infection. This statement is supported by a study that examined self-reported against observed hand hygiene compliance in healthcare workers (Jenner et al., 2006). The results indicated that observed hand hygiene practice was not predicted by self-reported measures of practice. Interpreting these findings, the authors propose that if people believe that their hand hygiene is much better than it is, then they are likely to be oblivious to current campaigns aimed at increasing hand hygiene compliance by changing their attitude (Jenner et al., 2006). Surveillance data can be used to correct the assumptions that individuals may have about their own practices or the way in which interventions affect patient outcomes. One example of this is the national hand hygiene initiative currently underway in Australia. Hand hygiene compliance data are used to inform healthcare workers of their level of adherence to correct hand hygiene, with early findings from the national hand hygiene initiative in Australia suggesting a reduction in SAB associated with improved hand hygiene compliance (L. Grayson, Russo, R., Cruickshank, M., Bear, J., Gee, C., Hughes, C., Johnson, P., McCann, R., McMillan, A., Mitchell, B., Selvey, C., Smith, R., Wilkinson, I., 2011).

Another aspect of a psychological approach to infection prevention is the concept of cognitive economy, where it is argued that individuals develop ‘tunnel vision’ and fail to take into account the wider implications of their behaviour. As stated by Reason, “humans, if given the choice, would prefer to act as context-specific pattern recognisers rather than attempting to calculate or optimize” (Reason 1998, p. 44). It is postulated that individuals prefer to be task orientated as opposed to considering the wider context and being person centred, with the reason being that being task orientated requires less cognitive effort; hence, the term cognitive economy (Elliott, 2009). The development and success of care bundles in reducing HAIs can be used as an example of how cognitive economy can be positively applied to the framework proposed in Figure 4. A care bundle approach is defined as the “bundling together of several scientifically grounded elements essential to improving clinical outcome” (Aboelela, Stone, & Larson, 2007, p. 105). One example used in infection control is a central line care bundle which specifies the key components required to reduce the risk of infection (Institute for Healthcare Improvement, 2012). Each component of the care bundle should be well defined and based on strong evidence from at least one systematic review of multiple well designed, randomised, controlled trials or from at least one properly designed, randomised, controlled trial (Fulbrook & Mooney, 2003). Evidence provided through HAI surveillance and research is used in development of care bundles as well as evaluating the effect of care bundles on reducing HAIs, as evidenced by studies showing a reduction in central line associated bacteraemia (Guerin, Wagner, Rains, & Bessesen, 2010; Schulman et al., 2011) and ventilator associated pneumonia (Resar et al.; Westwell, 2008).

Social aspects and role of HAI surveillance

Elliott (2009) suggests that social aspects include workload, management issues and peer pressure, and the presence of infection control professionals. On the issue of workload, there is evidence that inadequate staffing can increase the risk of HAIs (Hugonnet, Chevrolet, & Pittet, 2007). The purpose of these studies was to demonstrate to colleagues and policy makers the importance of workload in relation to safe, quality care. These studies were only possible because data on the occurrence of infections or errors were available.

A different example of the role surveillance plays in social strategies to prevent HAIs is the use of social cognitive theory. Social cognitive theory provides a framework for understanding, predicting, and changing human behaviour, and the theory identifies human behaviour as an interaction of personal factors, behaviour, and the environment (Bandura, 1977). The theory suggests that people learn not only through their own experiences, but also by observing others' actions and the results of those actions, as well as through modelling (Pittet, 2005). Such a theory supports strategies to engage clinical leaders and enrol senior management support in infection prevention strategies (Department of Health, 2003; B. Mitchell, Brown, S., Wells, A., McGregor, A., 2009; Welsh Assembly Government, 2004).

Using the framework of social cognitive theory, Pittet (2005) also suggests that social networks can play a role in infection prevention. He explains this further by stating that “the conceptual framework of community organization models is based on social networks and support, focusing on the active participation and development of communities that can help evaluate and solve health problems” (Pittet, 2005, p. 265). An example of community involvement is an initiative funded by the Department of Health in England called Service Users Research Forum (SURF). The purpose of SURF is to encourage greater patient and public involvement in infection research (Healthcare Associated Infection Research Network, 2012) .

Physical aspects and role of HAI surveillance

Surveillance plays a key function in the physical approach to HAI prevention. There are numerous studies that use surveillance to inform and evaluate interventions. The role of hand hygiene in infection prevention best demonstrates this point. Hand hygiene is used to prevent the transmission of infection. Transmission has already been identified as an element of the chain of infection (Figure 2). Surveillance has been used to monitor hand hygiene and the effect that increased hand hygiene compliance has on infections (L. Grayson, Russo, R., Cruickshank, M., Bear, J., Gee, C., Hughes, C., Johnson, P., McCann, R., McMillan, A., Mitchell, B., Selvey, C., Smith, R., Wilkinson, I., 2011; M. L. Grayson et al., 2008; Harrington et al., 2007; Victor D. Rosenthal, Guzman, & Safdar, 2005).

Another component of the physical approach to HAI prevention and the prevention of transmission of pathogen is the practice of isolating individuals with specific infections (Appendix C). Similar to hand hygiene, surveillance has been used to monitor compliance with isolation and the effect isolation practices have on reducing infections (Gastmeier, Schwab, Geffers, & Rüden, 2004; Huang et al., 2006; Klein, Perloff, & Maki, 1989).

A final example to demonstrate the role surveillance plays in the physical approach to HAI prevention is vaccination. Vaccination is an example of how infections can be prevented at the 'source of infectious agent' component in the chain of infection. Vaccination is a long standing and proven public health strategy for infection prevention (World Health Organisation, 2005).

2.7 Conclusion

Healthcare associated infections pose a serious threat to patient safety and are a common occurrence. They have a significant impact on morbidity and mortality for individual patients, in addition to increasing health service costs. This chapter explored a physical approach to infection prevention and control, namely the chain of infection. The chain of infection assists in explaining the ways that infections are transmitted and methods used to prevent and control infection.

A second theoretical framework, a biopsychosocial approach, was also presented. This framework incorporates the physical approach to HAI prevention, with psychological and social aspects. From the literature described in this chapter, it can be argued that the physical approach in isolation (chain of infection) and a biopsychosocial approach have merit, in that they both help facilitate an understanding of infection prevention and control. Arguments put forward by Elliott (2009) suggesting why a physical approach to infection prevention has limitations were presented. As a result, it became clear that there is a need to consider a biopsychosocial approach to HAI prevention.

Importantly, however, frameworks are rarely incorporated in the infection control literature, as evidenced by the recent review conducted by Zimmerman et al. (2012), and no framework incorporating the role of surveillance, a key element of infection prevention activities, was identified. A biopsychosocial framework for HAI prevention relies on the use of HAI data, underpinned by surveillance. A revised biopsychosocial framework explicitly incorporating the role of surveillance has been presented (Figure 4).

If HAI surveillance is a critical element of infection control strategies, it is imperative that surveillance is reliable and valid. Where this is not possible, limitations of the data should be clearly articulated. Returning to a point made in Chapter 1, the HICPAC believes that the reliability of HAI data may be compromised by the variability in the definitions used for HAIs, or in the methods and resources used to identify HAIs (McKibben et al., 2005). Through examining three studies in this thesis, I will demonstrate that the concerns of the HICPAC regarding reliability are valid. The first of the studies focuses on SAB and this is presented in the following chapter.

Chapter 3: *Staphylococcus aureus* bacteraemia

3.1 Introduction to the chapter

Some of the most serious HAIs are bloodstream infections, also known as bacteraemia. In the United States, bacteraemia is one of the leading causes of death (Wenzel, 2001). This chapter is concerned with the relatively uncommon, but serious bacteraemia, SAB. The chapter is divided into three main sections. The first section, background to SAB, describes pertinent clinical issues about *S.aureus* as an infectious agent and the development of SAB in particular. The second section is a literature review in which gaps in knowledge of the epidemiology of SAB at a population level are explored. Elements of population-based SAB surveillance programs, including detection, duplicates, classification, definitions of acquisition, focus of infection, validation, and reporting of data are examined. The third section of this chapter describes the first study of this thesis, the aim of which is to describe the epidemiology of SAB in Tasmania and influences on reliable and valid collection of SAB data.

3.2 Background to *Staphylococcus aureus* and bacteraemia

Staphylococcus aureus is a pathogen of significance, due to its ability to adhere, invade and develop antimicrobial resistance. Bacteraemia caused by *S.aureus* is one of the most common bloodstream infections and is associated with a high mortality. Worldwide, SAB is a serious cause of morbidity and mortality, regardless of whether the infection onset is in the community or in a hospital (P. Collignon, Wilkinson, I., Gilbert, G., Grayson, L., Whitby, M, 2006; Whitby, McLaws, & Berry, 2001). It is estimated that in Australia, there are around 7000 episodes of SAB each year, equating to an annual rate of 35 per 100,000 population (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005). Furthermore, it is estimated that a large proportion of SAB is directly related to healthcare interventions, with intravascular devices being the most common cause of bacteraemias (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A,

2007; P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005).

Colonisation of *S.aureus* is an important element of *S.aureus* infection pathogenesis. Approximately 20% of the general population are persistent carriers of *S.aureus* and up to 30% are intermittent carriers (Wertheim et al., 2005). A study undertaken by von Eiff (2001) found that a substantial proportion of cases of SAB appear to be of endogenous origin since they originate from colonies in the nasal mucosa. The results of this study support strategies to prevent *S.aureus* infections by eliminating nasal carriage of *S.aureus*.

Additional risk factors for SAB include individual person specific factors which pose an increased risk of developing SAB including previous MRSA infection or colonisation, skin ulcers or cellulitis, presence of intravascular devices, urinary catheter insertions, surgical site infection, injecting drug use, presences of immunosuppressive conditions, and liver disease (Naber, 2009; Tacconelli, Venkataraman, De Girolami, & Dagata, 2004). Within a healthcare facility, other factors which influence the prevention and control of infections such as SAB include appropriate hand hygiene and correct insertion and management of intravascular devices. Underpinned by surveillance and quality improvement processes, improvements in hand hygiene compliance and management of intravascular devices have been demonstrated to reduce the occurrence of SAB in hospital settings (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007; M. L. Grayson, et al., 2008).

Bacteraemia caused by *S.aureus* often results in other infections such as infective endocarditis (Corey, 2009). In a study undertaken by Fowler (2003), 246 (34%) patients with SAB developed metastatic infections and the 12 week mortality rate was 22%. In patients with bacteraemia originating from an intravascular catheter, the incidence of metastatic infections was 14% (Fowler, 2003). Similar to the findings of Fowler (2003), a multi-centre study in Australia and New Zealand found an all-cause mortality of 20.6% in 1994 episodes of SAB (J. Turnidge, Kotsanas, D., Munckhof, W., Roberts, S., Bennett, C., Nimmo, G., Coombs, G., Murray, R., Howden, B., Johnson, P., Dowling, K., Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis., 2009). It is clear that *S.aureus* is a

pathogen that is commonly involved in causing HAIs including bacteraemia. Factors that enable *S.aureus* to cause infection include its ability to adhere to and colonise the skin and nasal mucosa, to invade the bloodstream and cause host immunological response i.e. infection. The ability to disrupt the skin barrier by excreting exfoliative toxins and enzymes that destroy tissue, improve the ability of *S.aureus* to cause invasion. Invasion can also occur when the skin is compromised, for example following surgical procedures or when a break in infection control practices occurs (Naber, 2009). Given these characteristics, *S.aureus* is considered a highly successful and increasingly important Gram positive pathogen in humans (Naber, 2009).

The development of resistance to antibiotics is another important element of the pathogenesis of *S.aureus*. Antibiotics to which strains of *S.aureus* have become resistant include penicillin, methicillin, cephalosporins, linezolid and vancomycin (Naber, 2009). Resistance to penicillin occurs by *S.aureus* producing β -lactamase, while MRSA strains have acquired the *mec* gene which encodes penicillin binding protein 2a and the *fem* gene which confers resistance to methicillin and cephalosporins (Jansen et al., 2006; Naber, 2009). Resistance to vancomycin is believed to rely on the acquisition of the *vanA* gene and linezolid resistance occurs by a mutation in *S.aureus* ribosomal RNA (Appelbaum, 2006; Naber, 2009; Peeters & Sarria, 2005).

Studies within hospitals have shown that the incidence of SAB can be reduced with improvements in hand hygiene compliance and intravascular device management (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007; M. L. Grayson, et al., 2008). The seriousness of SAB coupled with the potential to reduce its occurrence, suggests that each case of SAB demands rigorous investigation.

The following section of this thesis identifies gaps in knowledge of the epidemiology of SAB at a population level through a comprehensive review of the relevant literature, focussing on surveillance of SAB.

3.3 Literature Review

3.3.1 Introduction to the literature review

This literature review explores elements of an effective SAB surveillance program capable of identifying the incidence of SAB at population level and suitable for application in all settings. Key criteria used to judge the suitability of a surveillance program in all settings includes ensuring adequate detection of SAB, adequate and accurate data collection and strong validation. Therefore, the literature review will examine the methods of detection, accounting for duplicates and classification of *S.aureus*, discuss ways to define the place of acquisition for SAB, and explore the challenges faced by surveillance programs in ensuring that data are valid.

3.3.2 Elements of a surveillance program

Surveillance has an important role in healthcare as it can serve as an early warning mechanism, provide essential data for monitoring the effectiveness of interventions, detect trends and provide a framework for performance management (Clezy, 2008). According to Gregg (2002), the former editor of the Centre for Disease Control's Morbidity and Mortality journal, surveillance programs should provide: an accurate assessment of the health status of a given population, an early warning system, measures to define specific priorities, information to design and plan future programs, and a measure to evaluate intervention or programs. The themes described by Gregg (2002) are similar to those by Nelson (2007) who describes sensitivity, timeliness, representativeness, positive predictive value, simplicity, acceptability and flexibility as key attributes of a surveillance system. These elements will frame the description of the components of a SAB surveillance program.

3.3.3 Search strategy

The literature was accessed from several sources. Database searches using Medline, Cinahl and Informit were undertaken, limited to the years 2002 to 2009 to ensure that the review is

based on current practices at the time of the review. Other limits included publication in English and studies involving humans. Key search words included “*Staphylococcus aureus* bacteremia, *Staphylococcus aureus* bacteraemia, *Staphylococcus aureus* bloodstream infection AND *Staphylococcus aureus* bloodstream infection”. The key word “surveillance” was added to the search however this did not yield any new results. Once the literature was retrieved, articles that did not directly relate to surveillance of SAB were removed. Articles were excluded if the primary focus was not surveillance. For example, research studies that were undertaken to look for a specific outcome were excluded. The rationale for such limits was to ensure that the review concentrated on research that was relevant to continuous surveillance and therefore had the potential to be implemented and sustained. An individual review of each article was performed.

Details of SAB surveillance programs undertaken at a jurisdictional or national level are often located in the grey literature. A further search of the English language grey literature was then undertaken, targeting government departments. This search involved identifying each Australian state and territory’s surveillance programs within Australia and targeting specific international surveillance programs from the United Kingdom, Europe (when published in English), Canada and the United States. This search yielded 14 additional documents.

In addition to searching government departments, professional organisations that have recommendations relating to surveillance programs relevant to the literature review were targeted. International professional organisations were difficult to locate, therefore, the search was limited to Australian based professional associations. Two associations were identified as having either made recommendations for SAB surveillance or undertaken multi-centred studies for SAB. These two organisations were the Australian Infection Control Association (AICA) and the Australian Group on Antimicrobial Resistance (AGAR). A summary of literature used in the review as identified in the database searches and the grey literature is detailed in Appendix E. Figure 5 provides a summary of the search strategy process using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as the basis for presentation (Moher, Liberati, Tetzlaff, Altman, & The, 2009). A total of 54 studies were included in this review.

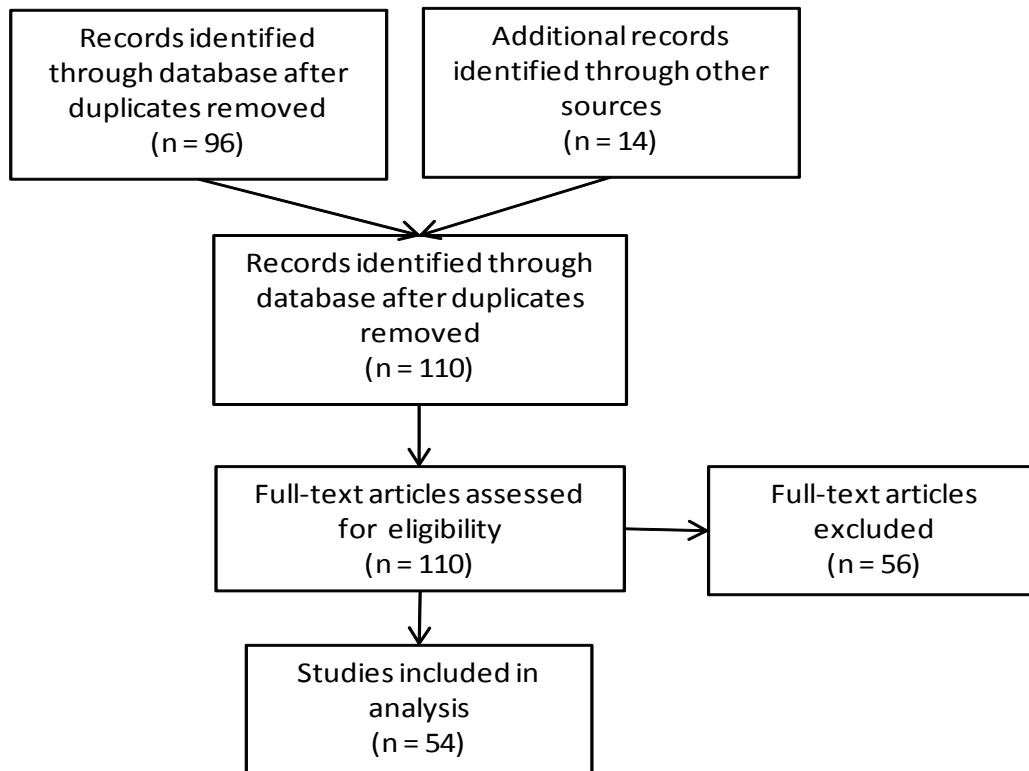


Figure 5. Summary of search strategy for *Staphylococcus aureus* bacteraemia.

As discussed earlier, the aim of this literature review is to describe the elements of a population-based SAB surveillance program that can be effectively applied in all settings. To address the aims described in the introduction, the topics of detection, duplicates, classification, definitions of acquisition, focus of infection, validation and reporting of data will be examined. In exploring each of these topics, the impact that varying practices have on the epidemiology of SAB will be discussed, where relevant.

3.3.4 Findings from the literature review

Detection

The majority of Australian state and territory surveillance programs assume that a positive blood culture for *S.aureus* indicates SAB (Chang et al., 2003; de Oliveira Conterno, 2002; Health Protection Agency, 2009; Lyytikainen, Ruotsalainen, Jarvinen, Valtonen, & Ruutu, 2005; Rezende, 2002; South Australian Infection Control Service, 2006; Tacconelli et al.,

2004). There are very few false positive *S.aureus* isolates from blood cultures (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007). The risk of this occurring remains low and in the context of developing a population-based surveillance program for SAB, it is not a significant issue.

There are a number of advantages of using a positive *S.aureus* blood culture as the detection method for SAB. This method allows easy data extraction from laboratories, linkage of laboratory data to software programs and utilisation of existing 'notification' processes often used in public health. A well-established example of direct extraction of laboratory data to a national surveillance program occurs in Wales, United Kingdom (Welsh Healthcare Associated Infection Program, 2009). In Tasmania, SAB was made a notifiable disease in 2009. The latter allows notification of SAB to occur direct from laboratories to public health officials and provides the trigger process for a SAB surveillance program (Mitchell, McGregor, & Wells, 2009).

Duplicates

The determination of SAB using a positive blood culture is simple to implement, however, it does raise the issue of managing multiple positive samples and the subsequent duplication (Healthcare Associated Infection Unit, 2009). It would be clinically incorrect to classify each and every positive blood culture as a single case of bacteraemia. Contemporary practice in research and surveillance programs is to remove subsequent positive blood cultures for a given individual within a specified time frame. The specified time frame in the literature does vary, but is generally between 14 and 30 days. The majority of studies and continuous surveillance programs for SAB use 14 days as the timeframe for which any subsequent positive sample should be excluded (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005; Dreimanis, 2005; Expert Working Group in surveillance of the Australian Infection Control Association, 2000; Health Protection Agency, 2009; Health Protection Scotland, 2009b; D. Jeyaratnam, Edgeworth, J., French, G., 2006).

Classification

Staphylococcus aureus can be resistant to any number of antibiotics. More commonly, surveillance programs classify *S.aureus* into either methicillin-sensitive (MSSA) or MRSA, based on the antibiotic sensitivities (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005; Health Protection Agency, 2009; Kuint et al., 2007; B. Mitchell, et al., 2009; van der Mee-Marquet, Domelier, Girard, Quentin, & Bloodstream Infection Study Group of the Relais d'Hygiene du, 2004). To effectively ensure that a surveillance program has the capacity to distinguish MRSA in addition to other emerging resistance patterns, it would be prudent for a surveillance program to capture a range of antibiotic sensitivities, but this does not happen consistently. Capturing this information in a population-based surveillance program would provide valuable information over time.

Similar incidence of SAB have been reported from areas with high and low prevalence of MRSA (Huggan et al., 2010). In Tasmania, the setting for the SAB research detailed later in this chapter, there are regional variations in the prevalence of MRSA (B. Mitchell, McGregor, A., Coombs, G., 2009). Whether these regional differences in the prevalence of MRSA are translated into regional differences in MRSA bacteraemia is explored in the study presented later in this chapter.

A number of studies have shown that MRSA bacteraemia is associated with poorer outcomes and increased mortality (Whitby et al., 2001). In contrast, a large, multi-centre study by Turnidge et al. (2009), indicates that MRSA bacteraemia is not an independent risk factor of mortality. The authors examine this finding in detail and suggest that sufficient patients infected with methicillin-susceptible strains were treated with vancomycin instead of a β -lactam and it was the use of vancomycin that demonstrated a higher 30 day mortality, compared with flucloxacillin treatment. The authors suggest that it may be “better to consider MRSA as a major threat, mostly because the drug of choice for serious invasive infection are less effective than β -lactams are against methicillin-susceptible strains” (J. Turnidge, Kotsanas, D., Munckhof, W., Roberts, S., Bennett, C., Nimmo, G., Coombs, G., Murray, R.,

Howden, B., Johnson, P., Dowling, K., Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis., 2009, p. 372).

Acquisition definitions

Overview

To understand the epidemiology of SAB, it is important to establish the place of acquisition. There are varying terms used in the literature to define the place of acquisition. Definitions of acquisition found in the literature can however, be broken into three general groups: those infections associated with the community, those associated with healthcare including hospitals, for example, outpatient settings, and those acquired in hospital. The latter is a subset of the second. Acquisition should not be confused with the 'strain' of *S.aureus*. For example, 'community acquired' SAB may refer to a specific strain of *S.aureus*. Conversely, the term 'community associated', often refers to an infection originating in the community. It is therefore vital that researchers undertaking surveillance of infections relating to healthcare define the criteria and the terminology they use to determine the place of acquisition of infection.

It appears from the literature that custom and practice has played a large part in defining what previously constituted 'hospital acquired' infections and definitions have evolved based on findings in the literature. Historically, hospital acquired infections were infections that occurred in patients in hospital for greater than 48 hours. This definition has a number of limitations, including neglecting patients who may have had recent hospital treatment with subsequent infection or patients who receive healthcare in the community. A study undertaken in Australia demonstrated this point and found that using the figure of 48 hours as the criterion for HAI substantially underestimates the number of episodes of bacteraemia that are healthcare associated (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005). In this multi-centred study, 971 episodes of SAB were reviewed, with a total of 64-75% found to be healthcare associated, however only 46-61% were acquired after the patient was in hospital more than 48 hours (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005).

Healthcare systems are now providing more treatment in settings other than inpatient settings, so it is vital to capture these patients when undertaking surveillance.

In 2002, Friedman suggested a new classification for bloodstream infections, using the terminology: hospital acquired, healthcare associated or community acquired. Lesens et al. (2005) undertook a multi-centred study to determine the usefulness of these definitions. The study supported the notion of having three different classifications, with particular emphasis on the point that some patients who acquire an infection in the community may do so as the result of healthcare exposure or treatment (recent or in the community). Therefore they could be incorrectly classified as community associated (Lesens et al., 2005).

The definitions as outlined by Friedman (2002) and supported by Lesens et al. (2005) are not the only definitions used in current literature to determine acquisition of bloodstream infections. In a paper outlining a range of surveillance definitions, the Centre for Disease Control (CDC) and the National Healthcare Safety Network (NHSN) are less specific about the exact definitions of acquisition in respect to bloodstream infections (Horan, 2008). They define a HAI as a “localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting” (Horan, 2008, p.310).

The definition as it stands by the CDC/NHSN requires a clinical review of the patient and is open to interpretation by less experienced staff undertaking surveillance. The CDC/NHSN definition is essentially the same as that defined by Friedman (2002) and Lesens et al. (2005) in that it is attempting to remove infections that are present or incubating on admission to a hospital from being classified as healthcare associated. Outlining specific criteria or timeframes is more suited for population-based SAB surveillance, as it will reduce the potential for variability in interpretation.

From the initial examples described above, it is clear there has been a blurring in the differences between hospital, healthcare and community associated acquisition. Length of stay in hospitals has reduced and increasingly people are managed in the community (Saginur

& Suh, 2008). To determine a definition for application of a state wide or national surveillance program suitable for all settings, it is important to review and critique the definitions used in current surveillance programs in more detail.

Hospital acquired

Worldwide, the majority of studies and surveillance programs define ‘hospital acquired’ SAB if a blood culture was taken greater than 48 hours after admission and/or there was no evidence of infection at presentation (Burke, Halpern, Baron, & Gutierrez, 2009; Chaves, Garc a-Mart nez, de Miguel, Sanz, & Otero, 2005; Chua et al., 2008; Denniston & Riordan, 2006; Dreimanis, 2005; Jeyaratnam, Edgeworth, & French, 2006; Nickerson et al., 2009; South Australian Infection Control Service, 2006; Wyllie, Crook, & Peto, 2006). In some studies however, a different definition of ‘hospital acquired’ is used, for example 72 hours (Guilarde, Turchi, Martelli, & Primo, 2006; Johnson, Bhan, Pawlak, Manzor, & Saravolatz, 2003; Perovic et al., 2006). No rationale is given in either study for the basis of using 72 hours as opposed to 48 hours and none was found in other literature examined. The greatest proportion of SAB surveillance programs described in the literature define an infection as hospital acquired if the blood culture was taken greater than 48 hours after admission and assuming there was no other recent positive blood culture.

Hospital acquired SAB is only one classification of acquisition. The issue of community associated or healthcare associated SAB in patients with a blood culture less than 48 hours after admission requires further discussion.

Community associated

Patients who have a SAB identified in a community setting or in hospital but less than 48 hours after admission can potentially have either community associated or healthcare associated SAB. Community associated SAB can also be referred to as ‘Community Onset’. Healthcare associated SAB could be caused by a recent hospitalisation or treatment received in a community or outpatient setting. It is therefore important to identify the different definitions currently being applied for determining community and healthcare associated SAB.

No specific continuous community associated SAB surveillance program was found in the literature. Surveillance or studies of community associated SAB are often undertaken for a limited period within a specific population group or occur as a result of undertaking surveillance within a specific population group, for example those who present or are admitted to hospital (Khairulddin, Bishop, Lamagni, Sharland, & Duckworth, 2004; Lin et al., 2009). The definitions used for determining community and healthcare associated SAB identified in the literature review vary considerably.

In a retrospective study at a tertiary hospital, Chaves et al. (2005) defined community onset SAB as “evidence of infection at the time of presentation or blood specimen positive for *S.aureus* collected less than 48 hours after admission” (p. 151). Similarly, a retrospective study undertaken by Chia, Hsu, Chai and Tambyah (2008) investigating the epidemiology and onset of community-onset MRSA bacteraemia, defined community onset bacteraemia as “a positive blood culture drawn \leq 48 hours after hospitalisation or if he/she remained symptomatic with no other cause of infection found in the event the blood cultures were positive $>$ 48 hours post hospitalisation” (p. 2). Chia et al. (2008) further classified this group into community acquired or healthcare associated cases based on the criteria proposed by Friedman (2002).

Friedman (2002) defines community associated SAB as “a positive blood culture obtained at the time of hospital admission or within the 48 hours after hospital admission for patients who did not fit the criteria for a health care–associated infection” (p. 792). Variability in definitions of community SAB is found throughout the literature. A retrospective study by Chi, Wong, Fung, Yu, and Liu (2004) investigating the epidemiology of community acquired SAB in Taiwan, defines community associated as:

A blood culture performed with the initial 48hours after hospital admission, the patient had not been hospitalized in an acute-care setting within one year before the isolation of MRSA; transfer from other hospitals occurred within 48 hours of admission; no history of renal dialysis, residence in a nursing home or surgery in the recent one year; no permanent indwelling catheter or percutaneous medical device present at the time of admission (p. 17).

The definition for community associated SAB is often made on the basis that the patient does not meet the criteria for hospital acquired or healthcare associated SAB. It is therefore important to finalise the definition of ‘healthcare associated’, in order for ‘community associated’ to be defined.

Healthcare associated

In 2002, Friedman defined a HAI as occurring in a person who has a positive blood culture obtained at the time of hospital admission (or within 48 hours of admission) and the patient fulfilled any of the following criteria:

1. Received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before the bloodstream infection. Patients whose only home therapy was oxygen use were excluded.
2. Attended a hospital or haemodialysis clinic or received intravenous chemotherapy in the 30 days before the bloodstream infection.
3. Was hospitalized in an acute care hospital for 2 or more days in the 90 days before the bloodstream infection.
4. Resided in a nursing home or long-term care facility (Freidman, 2002, p. 792).

The definitions described above were used in a study in Ireland (O’Connell, McMahon, Kelleher, & Rossney, 2007). Similar to the definitions used by Chia et al. (2008), O’Connell et al. (2007) and Friedman (2002), Chaves et al. (2005) used a different definition to classify HAIs. Chaves et al. (2005) defined ‘healthcare related infection’ if a patient had “documented evidence of hospitalization within the twelve months before collection of the current culture positive blood specimen, had undergone peritoneal dialysis or haemodialysis within the previous 12 months, or had used a vascular device at home immediately before hospital admission for the current infection” (p. 151). Those definitions unrelated to healthcare were strictly community acquired.

In Australia, a number of states undertake surveillance of SAB. The definitions developed by the expert working group in surveillance of the Australian Infection Control Association are often used by the various jurisdictions or researchers within Australia (Centre for Healthcare Related Infection Surveillance and Prevention, 2009; Cordova et al., 2004; Expert Working Group in surveillance of the Australian Infection Control Association, 2000; Healthcare Associated Infection Unit, 2009; Mitchell et al., 2009; South Australian Infection Control Service, 2006). The definitions used by these groups can be summarised as:

Health care associated criteria

Acquired during hospitalisation and not present or incubating on admission (in inpatient neonates ≥ 48 hours after delivery), **or** is a complication of the presence of an indwelling medical device (e.g. IV line, CSF shunt, urinary catheter), **or** occurs within 30 days of a surgical procedure, when related to a surgical site infection, **or** an invasive instrumentation or incision related to the bloodstream infection was performed within 48 hours (or longer if compelling evidence) before onset of the infection, **or** associated with neutropenia (< 1000 neutrophils $\times 10^6$ /L) contributed to by cytotoxic therapy.

Health care associated inpatient [IP]

Episode occurs > 48 hours after admission or within 48 hours of discharge.

Health care associated non-inpatient [NIP]

Patient is not an inpatient or episode occurs within 48 hours of admission.

(Expert Working Group in surveillance of the Australian Infection Control Association, 2000)

Although the definitions used in SAB surveillance may seem consistent, there are variations in how these data are analysed due to variations in reporting and validation processes. This will be discussed in more detail later.

In the United Kingdom, continuous mandatory surveillance of SAB occurs within England, Wales and Scotland. Although similar, the methodologies and definitions used for surveillance of SAB occasionally differ. From 2001 (2003 in the case of Scotland and

Wales), each of these countries has included all positive SAB identified in a hospital, regardless of place of acquisition in the hospital's (Trust) surveillance report. No delineation is made between hospital acquired, healthcare or community associated (Health Protection Agency, 2005; Health Protection Scotland, 2009b; Welsh Healthcare Associated Infection Program, 2009). Although very easy to implement, this reporting does not meet the objective of determining the most appropriate manner to undertake state wide surveillance as it only includes specimens taken in hospitals and fails to differentiate between the places of acquisition. Measures to reduce or eradicate infections cannot be implemented if the place of acquisition is not identified. More recently, in England, a voluntary enhanced surveillance program for SAB has been developed (Health Protection Agency, 2009). This program includes capturing admission date and therefore the ability to define hospital acquired for patients in hospital more than 48 hours after a blood culture is obtained. It still does not define or identify 'healthcare associated' infections.

Canada does not appear to have a continuous surveillance program specifically for SAB, although methicillin resistant MRSA bacteraemia would be included within their surveillance program for MRSA infections (Canadian Nosocomial Infection Surveillance Program, 2008). Despite the variations in approaches used worldwide to define hospital, community and healthcare associated SAB it is possible to draw out common themes.

The issue of defining healthcare associated bacteraemia appears to be dependent on the nature of the study and its intended aims (Lesse & Mylotte, 2006; Lin, Yeh, Peng, & Chang, 2004). For the purpose of population-based surveillance, the definition of healthcare associated needs to be easily applied. The difficulty with the definitions described by Friedman (2002), is with their application. Identifying whether a patient has been in a nursing or residential home in the past year or had received wound care treatment in the past 30 days is made more complex by the range of public and private entities providing healthcare, often with limited or no access to obtaining such information in a timely fashion. A data linkage system may be of use in obtaining such information. Alternatively, a person investigating a case of SAB could rely on information the patient provides, however this may still cause difficulties due to a patient's cognitive status and reduce the reliability of the information being provided.

Summary of acquisition definitions

From the literature reviewed, it is clear that the definition of hospital acquired (also called healthcare associated inpatient) can be summarised as an infection in a person who has a blood culture positive for *S.aureus* taken 48 hours after admission (or within 48 hours of discharge). The position for defining the acquisition of infections occurring within 48 hours of admission but that might have resulted from healthcare, i.e. healthcare associated (also called healthcare associated non-inpatient) does vary. The common themes for defining healthcare associated includes recent related surgery (usually 30 days) or invasive surgical procedure, association with an indwelling or intravascular device, association with neutropenia or the person is receiving hemodialysis. There is some debate as to whether patients in long term care or residential facilities should also be defined as having a HAI (Friedman, 2002). Figure 6 summarises the position described above.

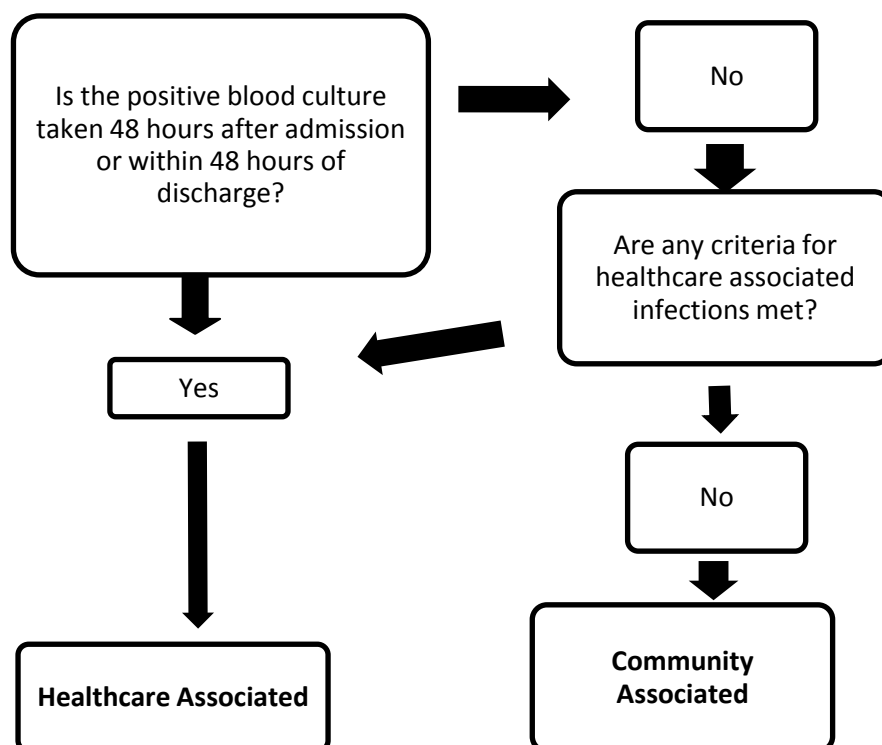


Figure 6. Criteria used to determine acquisition of cases of *Staphylococcus aureus* bacteraemia.

Figure 6 is consistent with recommendations made by the HAI Surveillance Committee, at the Australian Commission on Safety and Quality in Healthcare. These definitions have since been adopted at a national level (Australian Commission on Safety and Quality in Health Care, 2010). For the purposes of this review, the term healthcare associated refers to both healthcare associated inpatient and healthcare associated non-inpatient, unless otherwise stated. The acquisition of SAB is important but the questions used to determine the acquisition still do not provide definitive insight into the cause of the infection.

Focus / Cause of infection

To better understand and potentially prevent SAB, identifying the cause of infection is important. Causes of SAB are varied and it is not within the scope of this literature review to explore all causes. SAB can occur in any setting therefore data collection in a surveillance system may be sought from less experienced clinicians, or indeed, clinicians who rarely see SAB. In a paper describing SAB of unknown primary source, Saginur and Suh (2008) state that “there is no commonly held definition of bacteraemia of unknown source” (p. 21). This reinforces the need to consider ease of application when developing a system for identifying the cause of infection.

There is a strong indication that intravascular devices are the most common cause of healthcare associated bloodstream infections in developed countries (Coello et al., 2003; Munckhof, 2005; N. P. O’Grady et al., 2002). Specific population groups, such as patients in intensive care or haemodialysis patients are particularly at risk, given the frequency of intravascular device use. It would be prudent for any surveillance program to identify whether persons with SAB have intravascular devices and whether they receive haemodialysis. It would not be practical to request information on whether the intravascular device was the cause of infection, as that would potentially require further microbiological testing. Identifying whether a person had an intravascular device at the time of blood culture collection is straight forward and is consistent with earlier recommendations of determining whether this bacteraemia is healthcare associated. The limitation is the inability to confirm

that the intravascular device was the cause of the infection unless the tip of catheter is cultured. If a person with SAB did have an intravascular device, it would be prudent to identify which device/s the person had. The practice of identifying the device is consistent with surveillance programs being undertaken in the Canberra Hospital and in South Australia (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007; South Australian Infection Control Service, 2006).

In addition to identifying whether a person has an intravascular device, other potential sources or causes of infection could be identified. Within Australia, surveillance programs that seek to identify the cause of infection group these into five areas: catheter/intravascular device-related, source unknown, neutropenia, procedure related, or organ site focus (Centre for Healthcare Related Infection Surveillance and Prevention, 2009; Healthcare Associated Infection Unit, 2009; South Australian Infection Control Service, 2006). Procedure related or organ site focus infections have not yet been discussed.

When identifying whether the bacteraemia was procedure related, it is recommended that there must be compelling evidence that it was related to the bacteraemia, for example, identifying the same organism from the tip of a catheter through culture as identified in the blood culture. Similarly, organ site focus should only be identified when there is clinical or bacteriological evidence that the infection arose from the specific organ. The specific organ site is usually then identified (Centre for Healthcare Related Infection Surveillance and Prevention, 2009). Identifying whether a bacteraemia was procedure related or organ site focussed is made more difficult without the clinical support of infectious disease physicians or microbiologists (Jenkins, Price, Sabel, Mehler, & Burman, 2008). Therefore, in implementing a program suitable for all settings, identifying the cause of infections may cause some difficulties and raise issues regarding the reliability of the data.

Validation

Within Australia, South Australia, Western Australia, Queensland, and Tasmania conduct surveillance for SAB from hospitals participating on a voluntary basis within their respective states (P. Collignon, Dreimanis, D., Ferguson, J., van Gessel, H., Taylor, P., Wilkinson, I., Worth, L, 2008; M. Cruickshank, Ferguson, J., 2008; B. Mitchell, et al., 2009). The Australian Capital Territory has no territory wide surveillance unit as such, however at the Canberra Hospital, infection control staff use data from their laboratory department to commence the investigation of SAB cases (Dreimanis, 2005). This is a robust way of capturing all cases of SAB within their hospital. Each jurisdiction has variations in data collection, reporting and validation processes, for example, in South Australia, hospitals submit completed surveillance forms to the South Australian Infection Control Service, which collates and analyses the data. The voluntary surveillance data submitted to each jurisdiction's surveillance unit is often reliant on hospital staff (infection control practitioners) completing and submitting a surveillance form. Therefore the catalyst for commencing the data collection process is often outside the control of the state wide surveillance units and this has the potential of leading to an incomplete or inaccurate dataset.

One way of validating the number of surveillance forms received by the surveillance unit, is to have access to or receive a direct laboratory report from each of the hospitals outlining the number of *S.aureus* positive blood cultures identified in a given period. Although this may happen in practice, the process is not detailed in any of the jurisdictional surveillance programs protocols, other than Tasmania (Mitchell et al., 2009). It is also made more complicated by the use of a combination of private and public microbiology departments.

At the beginning of 2009, all Australian states and territories agreed to participate in a national surveillance scheme for SAB. All acute hospitals within the jurisdictions are expected to contribute. At the time the literature review was undertaken, no evidence was found of implementation or coordination of this program at the national level.

In the United Kingdom a mandatory SAB surveillance exists, and in Wales, Scotland and England SAB data derived directly from microbiology laboratories are compiled. As discussed earlier, this has some limitations in respect to determining acquisition. From a validation perspective, however, this system does provide a way to capture all SAB cases (Health Protection Agency, 2005; Health Protection Scotland, 2009b; Welsh Healthcare Associated Infection Program, 2009).

Reporting of rates

The manner in which SAB rates are reported is subject to variation and often dependent on the purpose or aim of the surveillance program or research undertaken. This section examines how rates are reported at a hospital level and also at a state or national level. Before doing so however, it is important to define some of the terms commonly used in surveillance.

The International Epidemiology Association defines the term ‘rate’ as the measure of the frequency of the occurrence of a phenomenon over a period of time and is an expression of the frequency with which an event occurs within a defined population, usually in a specified period (Porta, 2008, p. 207). Therefore, the rate equals the number of events in the specified period, divided by the average population size during the period. Not to be confused with the term rate, which the International Epidemiology Association also defines as ‘incidence’ and ‘incidence rate’. Incidence is defined as the number of instances of illness commencing or of persons falling ill during a given period in a specific population. It may be measured as a frequency count, a rate or a proportion (Porta, 2008, p. 124). An incidence rate is the rate at which new events occur in a specific period divided by the time persons were exposed to risk during the period.

The terms ‘rates’ and ‘incidence’ are often used in the literature when attempting to describe the disease burden of SAB (Chaves et al., 2005; Jeyaratnam et al., 2006; Turnidge et al., 2007). When considering the formula to express the rate of SAB cases appropriately, the

numerator and the denominator in the equation must be representing the same phenomenon and the time period must be specified.

Describing rates of SAB within hospitals choice of denominators

When reporting rates of SAB identified in hospitals, the choice of denominator varies not only within Australia, but also internationally making direct comparisons difficult. Examples of denominators used include 'patients at risk' days (Coello et al., 2003), occupied bed days (South Australian Infection Control Service, 2006) or separations (Grayson et al., 2008). Furthermore, each of these denominators requires a specific definition or clarification. For example, occupied days data may include or exclude day case patients in hospitals. It is therefore vital that the numerator used is relative to the denominator and is clearly defined. If a hospital is including healthcare associated SAB from their day case patients, then including patient bed days for this group in the description of the population at risk or denominator may be more suitable than separations for example.

Despite the issues raised above about the choice of denominator, the major purpose of surveillance, particularly in a hospital setting, is to inform quality improvement processes. Studies have shown that despite the choice of denominator, for example comparing occupied bed days and separations, the overall trend of the incidence remains the same (P. Collignon, Dreimanis, D., Ferguson, J., van Gessel, H., Taylor, P., Wilkinson, I., Worth, L, 2008; A. McGregor & Mitchell, 2009). Therefore, a further consideration in choosing a denominator may be the audience of a report and how easily they can understand the meaning of occupied bed days, separations or admissions. In Australia, the national data dictionary has stated that patient care days should be used as the denominator. Patient care days are essentially the same as occupied bed days and are the only hospital activity data that is collected in a standardised manner by jurisdictions in Australia (Australian Commission on Safety and Quality in Health Care, 2010).

Describing the incidence of SAB within a region, state or national level

Unless a surveillance program captures all SAB, in all settings, identifying the incidence of SAB accurately within a region, state or nationally is challenging (Laupland, Ross, & Gregson, 2008). One well recognised Australian study undertaken by the AGAR attempted to determine the incidence of SAB in Australia by extrapolating data from a number of hospitals.

The AGAR undertook a review of SAB cases in 17 hospitals (public and private) in Australia (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005) to quantify the number of cases, place of acquisition and the proportion caused by MRSA. Data were derived from microbiology departments that prospectively collected information on laboratory confirmed bacteraemia. Multiple or duplicate positive blood culture samples that occurred within the previous 14 days were considered a single episode. A case was classified as hospital onset if the positive blood culture was taken more than 48 hours after admission; all other cases were defined as community onset, including day only dialysis related cases. Published data relating to the number of hospital bed days and separations (referred to as admissions) were used to determine rates. In total, 3192 episodes of SAB were identified. The rates for both hospital and community onset SAB were determined for each hospital, using occupied bed days and admissions. The rates in different hospitals were extrapolated to estimate the incidence for Australia. Using the median bacteraemia rate of public and private hospitals surveyed, the AGAR estimated there are approximately 6900 episodes nationally each year or 35 per 100,000 population. The authors then used this figure to compare against data from Northern Ireland and the United States (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005).

The authors acknowledge the definitions of acquisition underestimate the rate of healthcare associated bacteraemia. Conversely, the authors may have overestimated the number of cases occurring in Australia because of the over inclusion of larger tertiary hospitals that have higher risk patient populations. Of note, is the AGAR comment that “if systems were in place

that better captured and reported on all bacteraemia episodes in well defined populations (e.g. all of Australia or a State) then this would give us a more accurate rate” (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005, p.558).

3.3.5 Summary of literature review

Throughout the review, elements of surveillance programs have been critiqued. These focussed on variations in the surveillance programs, particularly in reporting, validation and definitions of acquisition. Within Australia, each jurisdictional SAB surveillance scheme has focussed on assessing the number of cases within the context of a hospital environment and determining rates accordingly. These programs have a number of limitations that must be remembered when considering a program suitable for all settings. First, detection of SAB is primarily focussed on identifying those people who present or are associated with an acute hospital. This may include inpatients, those who present to emergency departments or those receiving healthcare directly from the hospital (e.g. haemodialysis patients). The population being sampled is therefore limited as it excludes people who may present to hospitals not participating in a coordinated surveillance program (public, private or less acute hospitals) or who receive healthcare in a community setting, for example a general practice or nursing home.

Second, the definition of acquisition needs to be such that clinicians not familiar with causes of SAB, principles of surveillance and infection control terminology can understand and accurately complete a surveillance form. Third, to ensure the validity of a surveillance program, it must capture all bacteraemias and not be reliant on an individual’s submission of a surveillance form. To overcome the challenges of capturing all data, a recommendation suggested by Collignon et al. (2006) was to make SAB a notifiable disease. The notification process will ensure that all SAB are captured and pursuant to each state’s Public Health Act, and provide the authority and mechanism for data collection. This process is currently being

used in Tasmania and allows all SAB to be captured, regardless of the patient's healthcare provider (Mitchell et al., 2009). Similarly, the direct data extraction method from laboratories used in the United Kingdom would provide a comparable method of obtaining all SAB. However, the complex network of public and private healthcare providers may make the latter more difficult in Australia.

The fourth consideration of a SAB surveillance program is the need to capture adequate information that is not only useful to acute hospitals, but also to understand the epidemiology of the infection within the wider population which includes the cause or focus of infection and antibiotic sensitivities.

To truly understand the epidemiology of SAB at a population level, a surveillance program must capture data from all SAB cases in a given population and have the ability to accurately identify cases of HA SAB and the healthcare facility to which the infection is attributable. Ensuring the validity of SAB data at a population level is challenging and inherently linked to the data collection process. For example, internationally, England and Wales capture all cases of SAB by obtaining data direct from laboratories; however, they collect limited additional information to identify an accurate picture of the burden of HA SAB and acquisition in comparison to methods currently used by Australian states and territories. Conversely, Australian states and territories fail to capture and report on data from all cases of SAB in a given population. By having such data, an improved understanding of the true incidence of SAB and relevant epidemiological data is possible, which can be used to inform future planning. It is evident that if the incidence of SAB is to be calculated in a meaningful way at a population-based level, a surveillance system must capture all episodes of SAB. Through this process, the ability to quantify the occurrence of SAB occurring outside of acute public hospitals will be possible and provide some evidence on which to base a decision on whether an expansion of current SAB surveillance is required.

3.4 Objectives and research questions

The objectives for the first study of this thesis are to describe the epidemiology of SAB in Tasmania and to understand the methodological influences on reliable and valid collection of SAB data in that state. To address these objectives, the author devised the following research questions:

1. In the general Tasmanian population for the calendar years 2009 and 2010:
 - a. What is the incidence of SAB?
 - b. What are the relative proportions of community associated and healthcare associated SAB?
 - c. What are the relative proportions of methicillin-sensitive (MSSA) SAB and of methicillin resistant (MRSA) SAB?

2. In the three geographical regions of Tasmania for the calendar years 2009 and 2010:
 - a. What is the comparative incidence of SAB?
 - b. What are the relative proportions of community associated and healthcare associated SAB?

3. What is the potential for under reporting of SAB where:
 - a. Data are only collected from public hospitals?
 - b. Different case definitions for HA SAB are applied?

3.5 Methods

3.5.1 Study design

The author chose a descriptive, observational, population-based study which facilitates the examination of rare occurrences of disease, provides a mechanism for determination of risk, and ensures that data collected represent the entire population (Friis, 2009). A prospective design ensured the research questions could be specifically tested.

3.5.2 Setting and timeframe

The study captured all Tasmanian cases of SAB identified by microbiology services between the 1st January 2009 and the 31st December 2010 (as defined by the collection date of blood cultures). As of the 30th June 2009, the estimated population of Tasmania, the smallest Australian state, was 503,292, representing the target population of the study (Australian Bureau of Statistics, 2011). More detail regarding the population of Tasmania is provided in Chapter 1. At the time of writing, there were three health services areas in Tasmania, namely the north, the north-west, and the south regions, which are recognised by the Australian Standard Geographical Classification. The northern area health service consists of one general hospital and nine rural hospitals with an estimated target population of 141,434. In Tasmania, the term ‘rural hospital’ refers to hospitals with a small number of inpatient beds, usually less than 20 and geographically located in towns with a small population. Rural hospitals in Tasmania may also provide a location for primary health services. The term ‘general hospital’ refers to a hospital that has an accident and emergency capacity, high dependency or intensive care unit and resident general specialities. The north-west region has an estimated population of 112,383 with one regional hospital, a community hospital, and ten rural hospitals. The southern region has a tertiary referral hospital, five rural hospitals, and an estimated population of 249,475 (Australian Bureau of Statistics, 2011). The term ‘tertiary hospital’ refers to a hospital that provides services requiring highly specialised skills, technology and support. Typically a tertiary hospital may include centres of excellence, research and development and will provide a leadership role of integrated clinical services. Health services in Tasmania are provided in a similar fashion to other states and territories, with a mixture of public and private hospitals providing acute care.

Different microbiology laboratories service each of the regions. A public hospital microbiology laboratory in each region services the public hospitals in the southern and northern regions, whilst in the north-west a private provider services the public hospital. There are four private microbiology laboratories in Tasmania, three of which are owned by the same parent company.

3.5.3 Definition and selection of cases

The definitions applied in this study were those developed by the ACSQHC, which have been accepted as national definitions in Australia (Australian Commission on Safety and Quality in Healthcare, 2009). The following operational definitions are provided for clarification.

One or more blood cultures positive for the bacterium *S.aureus* defined a case of SAB. Only the first isolate per patient was counted, unless at least 14 days had passed without a positive blood culture, after which an additional episode was recorded. Using blood cultures to define a case of SAB runs the risk of including false positives in the data; however, it is believed that there are very few false positive *S.aureus* isolates from blood cultures (P. Collignon, Wilkinson, I., Gilbert, G., Grayson, L., Whitby, M, 2006). Further, the use of blood cultures to define a case of SAB is standard practice in most research and surveillance programs as previously discussed in Chapter 3.

A case of SAB defined as healthcare associated (HA) depended on the following criteria:

- the first positive blood culture was collected more than 48 hours after hospital admission or less than 48 hours after discharge, or
- the first positive blood culture was collected 48 hours or less after admission and one or more of the following key clinical criteria was met:
 1. The SAB was a complication of the presence of an indwelling medical device (e.g. intravascular line, haemodialysis vascular access, cerebrospinal fluid shunt (CSF), urinary catheter).
 2. The SAB occurred within 30 days of a surgical procedure where the SAB was related to the surgical site.
 3. An invasive instrumentation or incision related to the SAB was performed within 48 hours.
 4. The SAB was associated with neutropenia ($<1 \times 10^9$) contributed to by cytotoxic therapy.

(Australian Commission on Safety and Quality in Health Care, 2010).

If none of these criteria applied, then the episode of SAB was considered community associated (CA).

3.5.4 Data collection

This section on data collection is divided into two parts. The first part describes the data collection process, including validation, and the second part outlines the specific data collected.

Data collection process

Staphylococcus aureus bacteraemia is a notifiable disease in Tasmania and has been since the end of 2008. At the time of writing, Tasmania is the only state in Australia that has SAB listed as a notifiable disease. The data collection process utilised the existing notification system as the catalyst for commencement of data collection. Data collection involved two main steps. First, laboratories notified Public Health (Tasmanian Department of Health and Human Services) regarding all cases of SAB. Second, the TIPCU, a departmental unit within Public Health, investigated all notified cases and sought additional information. Figure 7 illustrates the data collection process.

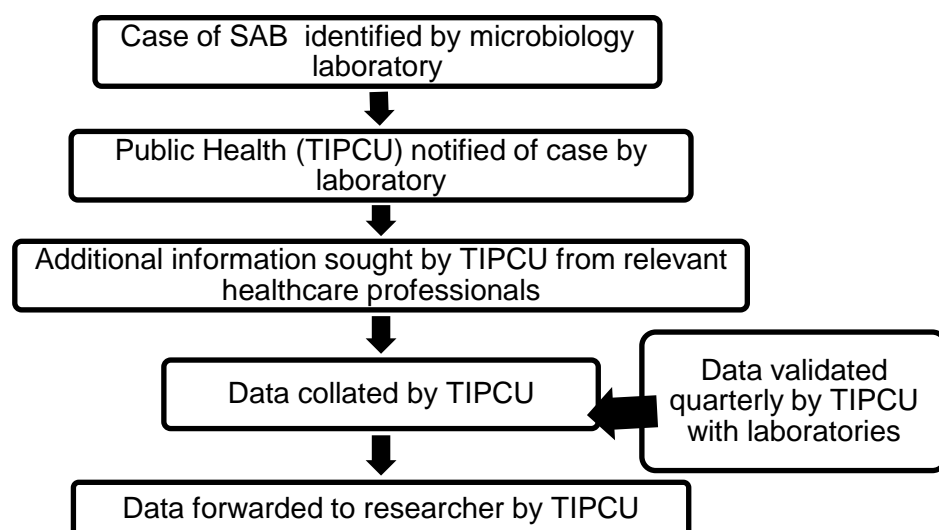


Figure 7. Flow chart illustrating the data collection process.

To collect additional information on each case of SAB, the TPCU used a data collection form¹ which was developed through modifications of an existing instrument used in South Australia at the time. The data collection sheet was piloted for a period of six months during 2008 and modifications were made following this pilot. Information obtained from microbiology laboratories and sent to the TPCU was entered onto the data collection form and then into a database. In Tasmania's larger public and private hospitals, the data collection form is forwarded to an infection control professional at the hospital where cases of SAB were identified. The TPCU staff supported the completion of the required information by infection control professionals where required. A developed protocol was used as the foundation for education material and ongoing reference (Mitchell et al., 2009) and education to infection control professionals was provided at face-to-face meetings, video conferencing, and discussions on the telephone. Where there was no infection control professional, such as non-hospital settings, the form was sent to the responsible healthcare professional for each case. In these circumstances, TPCU staff provided phone support to complete the form, which served to improve the reliability of the data collected. These processes ensured consistency of data quality given the range of experience of staff collecting and recording information.

Once the data were received by the TPCU, an initial interpretation of the data against available patient administration information was undertaken by the TPCU staff. One staff member at the TPCU classified the data as CA or HA SAB; where a case of SAB involved a hospital, the responsible infection control professionals discussed and reached agreement on the classification and attributable facility. The definition of attributable facility is discussed later in this chapter. In rare situations where agreement could not be reached, a senior TPCU staff member referred to the national surveillance definition, and made a final decision. During the study period, this only occurred once.

Upon completion of the process just described, data were entered into a Microsoft Excel spread sheet. To improve validation and ensure that all cases of SAB in Tasmania were captured, the TPCU received a data file containing all positive *S.aureus* blood cultures,

¹ The data collection form was developed by the researcher in his role working for the TPCU.

directly from every laboratory in Tasmania (public and private) on a quarterly basis. This was used to cross check against notifications received, ensuring a complete Tasmanian dataset.

Data items collected

The data items collected as part of the two-step data collection process described in section 3.5.4 are outlined in Table 2, including data sources. Further explanations for some of these data items are discussed below.

Table 2

Data items collected and the sources of these data

Data item	Source
Name	Laboratory
Date of birth	Laboratory
Sex	Laboratory
Postcode of affected individual	Laboratory
Patient identification number (if applicable)	Laboratory
MSSA or MRSA	Laboratory
Admission date (where applicable)	Laboratory
Specimen collection location	Laboratory
Laboratory	Laboratory
Antibiotic sensitivities for the antibiotics Flucloxacillin, Penicillin, Ciprofloxacin, Erythromycin, Fusidic acid, Gentamicin, Rifampicin, Tetracycline or Doxycycline, Trimethoprim or Trimethoprim / Sulphamethoxazole.	Laboratory
Collection date	TIPCU (via data collection form)
> or ≤ 48 hours in hospital at the time of blood culture collection	TIPCU (via data collection form)
Key clinical criteria met	TIPCU (via data collection form)
Device type. In a case where the SAB was a complication of the presence of an indwelling medical device, the device type was recorded.	TIPCU (via data collection form)

Note: Antibiotic sensitivities were collected by the TIPCU but were not analysed as part of this research.

For the purpose of data collection, any case of SAB that reported intermediate resistance to a particular antibiotic was reported as resistant. The data items listed in Table 2 include whether any key clinical criteria have been met. The key clinical criteria used to define a case of HA SAB were those agreed to nationally in Australia, as discussed previously:

1. the SAB is a complication of the presence of an indwelling medical device (e.g. intravascular line, haemodialysis vascular access, CSF shunt, urinary catheter);
2. the SAB occurs within 30 days of a surgical procedure where the SAB is related to the surgical site;
3. an invasive instrumentation or incision related to the SAB was performed within 48 hours;
4. the SAB is associated with neutropenia ($<1 \times 10^9$) contributed to by cytotoxic therapy.

(Australian Commission on Safety and Quality in Health Care, 2010)

3.5.5 Ethical considerations

The Tasmanian Human Research Ethics Committee (HREC) (H11130) and the Australian Catholic University (N20156) granted ethical approval for this research. Copies of ethics approvals are provided in Appendix N and Appendix O. The Tasmanian Director of Public Health granted access to data held by the TIPCU. The application for ethics approval included a request to have consent from participants waived. The justification for the waiving of consent submitted to the Tasmanian HREC is summarised in this section. As consent from participants was not obtained, compliance with the NHMRC research values and principles was paramount (National Health and Medical Research Council, 2007). More specifically, as consent was not obtained from participants, the privacy of participants' data was critical.

Section two of the NHMRC National Statement for Ethical Conduct in Human Research describes the risks and benefits to be considered when undertaking research and criteria for

waiving of consent (National Health and Medical Research Council, 2007). The ethics application approved by the Tasmanian HREC contained details on the justification for the waiving of consent. The application demonstrated that criteria set out in section 2.3.6 of the National Statement for Ethical Conduct in Human Research were met (National Health and Medical Research Council, 2007). Of the criteria stated in section 2.3.6, four main points supported the request. First, the study undertaken was deemed low risk as there were no interventions and no harm or discomfort likely to be caused by the study. Second, it was argued that it was in the community's interest to ensure access to information about SAB as the mortality of SAB has been reported between 25% - 35%, an unacceptably high level. Further epidemiological studies have identified potentially modifiable risk factors to reduce the number of SAB cases (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007; J. Turnidge, Nimmo, G., Pearson, J., Gottlieb, T., Collignon, P., Australian Group on Antimicrobial Resistance, 2007). Third, the obtaining of consent was impractical as there was a high likelihood that up to one third of participants would have since died (J. Turnidge, Kotsanas, D., Munckhof, W., Roberts, S., Bennett, C., Nimmo, G., Coombs, G., Murray, R., Howden, B., Johnson, P., Dowling, K., Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis., 2009). Finally, there were clear processes in place to ensure that the privacy of data was maintained. To ensure the privacy of data, a unique patient identifier was created for each person and all re-identifiable information removed (as described below) and the data collection spread sheet was password protected.

To remove the need for re-identifiable information storage, a unique identifier was developed for each case of SAB and re-identifiable information was removed from the spread sheet. The list was securely locked and was subsequently destroyed following data analysis. In conducting the research, there was no known breach of privacy and no known harm occurred from the study.

All other information related to this study will be kept for a period of five years at Australian Catholic University. This particular time frame was chosen to comply with the NHMRC Australian Code for the Responsible Conduct of Research, point 2.1.1 (National Health and Medical Research Council & Australian Research Council, 2007) .

3.5.6 Data management and analysis

After the provision of an overview on data management, this section describes the analysis plan for each research question.

Overview of data management

In preparation for analysis, some data collected in the Microsoft Excel spread sheet were recoded into numerical values, ensuring that date formats were consistently applied. Checks were performed to ensure recoding was undertaken correctly. Data from the Microsoft Excel spread sheet were then imported into IBM SPSS Version 19.0 for data analysis (International Business Machines Corporation, 2011). Further recoding and data cleaning in SPSS occurred, including checking codes for errors, detecting implausible values, and identifying missing values through frequency and cross tabulation calculations. New variables were computed in SPSS based on the data collected.

Table 3 provides details of these new variables (data fields) with explanations of their definitions.

Table 3

Operational definitions

Variable	Definition
Age	Age in years at the time of blood culture collection.
Age group	Age group (decade). The ages of cases were grouped into decades, consistent with descriptive epidemiology practices (Friis, 2009).
Australian Bureau of Statistics (ABS) age group	Age grouped according to available ABS population data for Tasmanian regions. Further discussed in section 3.6.3.
Infection number	Each infection occurring in the same patient was numbered in ascending order, with the first infection starting at '1'.
Postcode region	The geographical region of Tasmania based on the home address (postcode) of the participant.
Location of blood culture collection	The location where the positive blood culture was taken.
Region where blood culture was collected	The geographical region of Tasmania where the blood culture was collected.
Attributable facility	For HA cases of SAB, the attributable facility is the facility to which the infection was traced.
Attributable facility region	The geographical region of Tasmania where the attributable facility is located.
Attributable facility type	Defines the attributable facility type as a public hospital, private hospital, rural hospital, or other.
Final classification of source of infection	If a person had a blood culture taken more than 48 hours after admission to a hospital or any of the key clinical criteria described earlier were met (section 3.5.4), the case of SAB was defined as HA. All other cases were defined as community associated.

Table 3 includes references to geographical regions of Tasmania. The three regions of Tasmania are the south, north, and north-west, as defined by the Australian Standard Geographical Classification (Australian Bureau of Statistics, 2007). In relation to the grouping of postcodes into regions, two cases had an interstate postcode and another had a

postcode from a country other than Australia. These three cases were grouped and coded as 'non-Tasmania postcode'.

Data analysis

Data analysis addressed the three research questions posed. The statistical program SPSS was used to examine the frequency of SAB by gender, age group, SAB acquisition type (HA or CA), and the location where the SAB was attributed and identified. Occurrences of SAB in the same person were identified through exploring cases with the same date of birth and sex. Where this occurred, the unique patient identifier was used to identify whether these cases occurred in the same person. The incidence of SAB was determined by calculating the number of new cases of SAB during the two year study period and dividing that by the estimated at-risk population. For example, Tasmanian population data were used in calculating the incidence of SAB at a population level. Similarly, when the incidence of SAB was calculated at a regional level, population data for the relevant region was used. Population data for 2009, sourced from the Australian Bureau of Statistics, were used for data analysis, as data for 2010 were not available at the time. In the five years preceding 2009, the Tasmanian population increased by 1% or less each year. Age stratification for SAB was performed at both a population and regional level. Data from the Australian Bureau of Statistics contained population data only for the 0-14, 15-24, 25-39, 40-64, over 65, and over 85 age groups for each of the regions. Using these data, it was possible to calculate the population for the 65-84 and the over 85 age groups for each region. Confidence intervals for incidence were calculated using Fisher's Exact Test. As this is a cohort study, relative risks were calculated to compare risks between two groups, for example the risk of SAB in males compared with females.

Data analysis was performed on cases of SAB that met the national SAB surveillance definition and therefore included repeat cases that occurred in the same person more than 14 days apart. A number of factors influenced this decision. First, including cases of SAB occurring in the same person ensured that data could be compared to other published literature. Second, the approach taken was consistent with other national surveillance

programs examining infection incidence at a population level, for example, Chlamydia (National Notifiable Diseases Surveillance System Annual Report Writing Group, 2010; Public Health Laboratory Network, 2009). Therefore, cases of SAB that occurred in the same person, but more than 14 days apart remained in the dataset for analysis.

3.6 Results

3.6.1 Overview of results

Two hundred and fifteen cases of SAB were identified between the 1st January 2009 and the 31st December 2010. The 215 cases occurred in 202 different individuals. Of the 202 individuals identified with SAB, one hundred and twenty (59%) were male. The age of individuals varied from three weeks to 94 years (median 66.0 years). Of note was that 12 of the 18 cases (66%) of SAB occurring in individuals in the zero to nine age group occurred in persons aged less than one month. Figure 8 demonstrates the distribution of individuals with SAB by age group and sex.

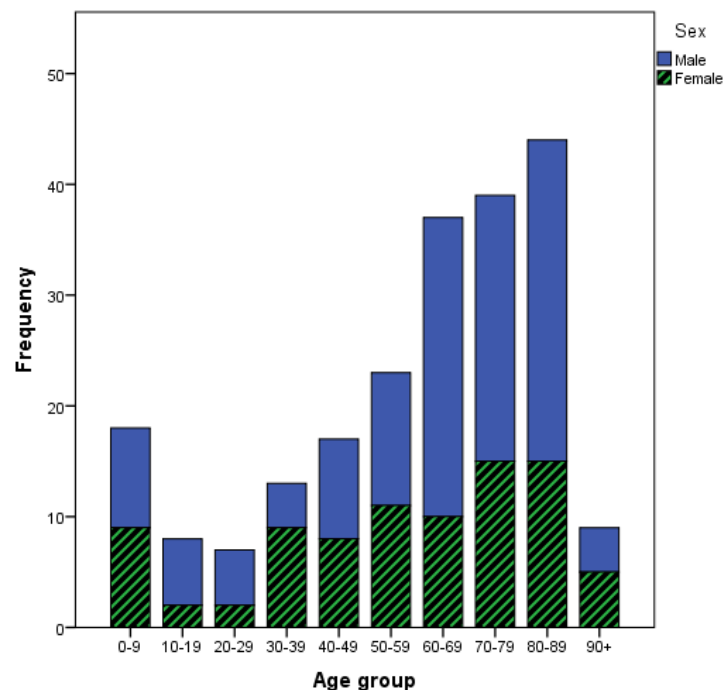


Figure 8. Distribution of *Staphylococcus aureus* bacteraemia by age group and sex. n = 202.

Of the 215 cases of SAB, one case of HA SAB was attributed to an interstate hospital. This case is not included in the following data analysis. Therefore, the total number of cases analysed was 214. As national surveillance definitions were applied, including the approach that a patient is included only once (unless at least 14 days had passed without a positive blood culture), it was assumed that each case of SAB was unrelated to a previous case. Therefore, cases of SAB occurring in the same person (but more than 14 days apart) were included. The data from persons who had more than one episode of SAB were examined. The results are detailed in Table 4. During the study period, 11 people had a second infection and one person had three infections (see Table 4). Most of the repeat infections occurred at least two months after the first episode. Such findings suggest that the likelihood of subsequent SAB being related to the first infection remains low.

Table 4

Infection characteristics in participants who had more than one case of Staphylococcus aureus bacteraemia

Participant	SAB occurrence	Stated region*				Date of SAB
		HA SAB		CA SAB		
		MSSA	MRSA	MSSA	MRSA	
1	1	-	-		North-west	April 2009
	2	-	-	North-west	-	November 2010
2	1	North	-	-	-	June 2010
	2	North	-	-	-	July 2010
3	1	-	-	North	-	November 2009
	2	-	-	North	-	November 2009
	3	South	-	-	-	January 2010
4	1	-	-	North	-	November 2009
	2	-	-	North	-	December 2009
5	1	North	-	-	-	June 2009
	2	North-west	-	-	-	July 2009
6	1	South	-	-	-	March 2010
	2	South	-	-	-	April 2010
7	1	North-west	-		-	March 2009
	2	-	-	North	-	May 2009
8	1	South	-	--	-	December 2009
	2	-	-	South	-	May 2010
9	1	-	-	North-west	-	April 2010
	2	-	-	-	North-west	September 2010
10	1	-		North	-	January 2009
	2	-	South	-	-	August 2009
11	1	-	-	North-west	-	June 2009
	2	-	-	North-west	-	July 2009
12	1	North-west	-	-	-	June 2009
	2	North	-	-	-	June 2010

Note: *Stated region refers to where the SAB was attributed. SAB = *Staphylococcus aureus* bacteraemia.

3.6.2 Incidence of SAB at the population level

Overview

Two hundred and fourteen cases of SAB were identified between the 1st January 2009 and the 31st December 2010. Of the 214 cases, 128 (60%) occurred in males. 194 cases (90.7%) of SAB were caused by MSSA.

The annual incidence of SAB within Tasmania was 21.26 per 100,000 population, 95% CI [18.51, 24.31], Fisher's Exact Test. The incidence was calculated on the assumption of a population of 503,282 per year during this period, indicating an at-risk population of 1,006,584 over the two years studied. In 2009, there were 112 cases of SAB equating to an incidence of 22.25 per 100,000 population, 95% CI [18.32, 26.78]. In comparison, 102 cases of SAB occurred in 2010, equating to an incidence of 20.27 per 100,000 population, 95% CI [16.53, 24.60].

The proportion of cases that were HA was 41.6%, with the remaining 58.4% being CA. The respective incidences of HA and CA SAB are detailed in Table 5. The majority of cases of SAB – 194, (90.7%) were caused by MSSA.

Table 5

Incidence of Staphylococcus aureus bacteraemia per year per 100,000 population within Tasmania.

Characteristic	Healthcare Associated		Community Associated		Total	
	Incidence (n)	95% CI	Incidence (n)	95% CI	Incidence (n)	95% CI
<i>S.aureus</i> type						
MRSA	0.89 (9)	0.32-2.04	1.09 (11)	0.44-2.32	1.98 (20)	0.95-3.65
MSSA	7.95 (80)	5.68-10.82	11.33 (114)	8.58-14.67	19.28 (194)	15.63-23.51
Total	8.84 (89)	6.52-11.74	12.42 (125)	9.62-15.79	21.26 (214)	17.42-25.69
Sex						
Male	10.88 (54)	7.17-15.82	14.90 (74)	10.49-20.54	25.78 (128)	19.85-32.92
Female	6.86 (35)	4.18-10.67	10.00 (51)	6.66-14.47	16.86 (86)	12.20-22.71
Age group						
0-9	7.80 (10)	2.53-18.20	6.24 (8)	1.7-15.98	14.04 (18)	6.42-26.66
10-19	1.46 (2)	0.04-8.65	4.39 (6)	0.96-13.62	5.85 (8)	1.69-15.91
20-29	0 (0)	N/A	4.99 (6)	1.03-14.59	4.99 (6)	1.03-14.59
30-39	8.90 (11)	3.56-18.89	1.62 (2)	0.04-9.02	10.52 (13)	4.55-21.11
40-49	3.51 (5)	0.87-10.15	8.43 (12)	3.09-18.34	11.94 (17)	5.78-22.14
50-59	7.89 (11)	3.15-16.73	8.60 (12)	3.16-18.72	16.49 (23)	8.89-28.21
60-69	11.90 (13)	5.15-23.91	21.97 (24)	11.35-38.38	33.87 (37)	20.95-52.09
70-79	25.93 (17)	12.55-48.09	33.56 (22)	16.75-60.04	59.49 (39)	37.27-90.51
80+	48.47 (20)	23.24-89.14	79.98 (33)	48.00-125.90	128.45 (53)	86.25-184.70

Note. Incidence = number of new cases of SAB per 100,000 population per year. n = number of cases. 95% CI = 95% confidence interval. Confidence intervals are expressed using the lower and upper limits. 95% confidence intervals calculated using Fisher Exact Test.

To explore the association between age and the risk of SAB, age specific incidence rates have been calculated and the results are shown in Table 6. Relative risks were calculated to compare the difference between groups. The relative risk of a male having an episode of SAB in comparison to a female was 1.52, 95% CI [1.15, 2.03]. Similarly, using the 60-69 age group as a reference category, the relative risk of SAB increases with age and represents a J shaped distribution. The relative risk of SAB by age group is displayed in Table 6. The 60-69

age group category was chosen as the reference group as the median age lies within this age group.

Table 6

Relative risk of Staphylococcus aureus bacteraemia by age group, Tasmania 2009-2010.

Age group	n	Relative risk	95% CI
0-9	18	0.41	0.22-0.75
10-19	8	0.17	0.07-0.38
20-29	6	0.15	0.05-0.35
30-39	13	0.31	0.15-0.60
40-49	17	0.35	0.19-0.64
50-59	23	0.49	0.28-0.84
60-69	37	1.0	Reference group
70-79	39	1.76	1.09-2.83
80+	53	3.79	2.44-5.94

Note. N = 214. 95% CI = 95% confidence interval. Confidence intervals are expressed using the lower and upper limits. 95% confidence intervals calculated using Fisher Exact Test.

Healthcare associated SAB and risk factors

Of the 89 cases of HA SAB, 61 (68%) occurred in patients who were hospitalised for more than 48 hours whilst 29 (32%) occurred in persons who were in hospital less than 48 hours but met clinical criteria defining a case of HA SAB. Key clinical data for all cases of SAB were collected. Of note was the proportion of cases associated with indwelling devices. Forty-one cases (46%) of HA SAB were solely associated with an intravascular device. There were 12 (13%) cases of SAB associated with a surgical procedure, five (6%) cases associated with a neutropenia, one (1%) case associated with an invasive procedure, and 22 (25%) instances where one of the four clinical criteria was not met, but the patient was in hospital more than 48 hours. There were eight instances (9%) where persons had intravascular devices but one other key clinical criterion was not met. Of the 49 (55%) instances where an intravascular device was implicated in some way, 27 (55%) of these devices were central

lines, 12 (25%) were a peripheral intravascular device, and ten (20%) were other devices that were not specified.

More than half of HA SAB were associated with an intravascular device in both persons who had been hospitalised more than 48 hours (n = 34, 55%) and in persons hospitalised less than or equal to 48 hours (n = 15, 52%).

3.6.3 Results by Tasmanian region

A total of 103, 69, and 42 cases of SAB were attributed to healthcare facilities in the southern, northern, and north-west regions of Tasmania, respectively. As CA SAB cannot be directly attributed to any one cause, the geographic region in which the case of community SAB was identified was used for the purposes of data collection. Table 7 outlines the incidence of SAB by region and characteristic. The percentage of population by age group and region is detailed in Appendix F.

Table 7

Annual incidence rate of Staphylococcus aureus bacteraemia per 100,000 population in each Tasmanian region

Characteristic	South (total population = 249,475)			North (total population = 141,434)			North-west (total population = 112,383)		
	HA (n) [95% CI]	CA (n) [95% CI]	All (n) [95% CI]	HA (n) [95% CI]	CA (n) [95% CI]	All (n) [95% CI]	HA (n) [95% CI]	CA (n) [95% CI]	All (n) [95% CI]
Type of <i>S.aureus</i>									
MRSA	1.00 (5) [0.25-2.89]	0.80 (4) [0.09-2.89]	1.80 (9) [0.65-4.10]	1.41 (4) [0.17-5.11]	0.71 (2) [0.01-3.94]	2.12 (6) [0.44-6.20]	0.00 (0) 0	2.22 (5) [0.55-6.43]	2.22 (5) [0.55-6.43]
MSSA	10.42 (52) [6.80-15.27]	8.42 (42) [5.21-12.87]	18.84 (94) [13.84-25.05]	6.36 (18) [2.91-12.08]	15.91 (45) [10.31-23.55]	22.27 (63) [15.48-31.11]	4.45 (10) [0.55-6.43]	12.01 (27) [7.47-18.65]	16.46 (37) [10.87-24.22]
Total	11.42 (57) [7.78-16.22]	9.22 (46) [5.84-13.83]	20.64 (103) [15.57-26.88]	7.77 (22) [3.88-13.92]	16.62 (47) [10.87-24.44]	24.39 (69) [17.24-33.59]	4.45 (10) [1.45-10.38]	14.24 (32) [8.14-23.12]	18.68 (42) [11.57-28.56]
Age group									
0-14	11.54 (11) 5.90-21.49	4.20 (4) 0.50-15.16	15.74 (15) 7.24-30.27	0.00 (0) 0	7.28 (4) 0.88-26.3	7.28 (4) 0.88-26.3	0.00 (0) 0	6.65 (3) 1.07-24.70	6.65 (3) 1.07-24.70
15-24	1.49 (1) 0.08-11.02	4.48 (3) 0.72-16.65	5.98 (4) 0.72-21.59	0.00 (0) 0	10.62 (4) 1.29-38.35	10.62 (4) 1.29-38.35	0.00 (0) 0	0.00 (0) 0	0.00 (0) 0
25-39	7.56 (7) 2.36-18.94	2.16 (2) 0.54-12.04	9.72 (9) 3.50-22.13	8.02 (4) 0.97-28.98	2.01 (1) 0.10-14.80	10.03 (5) 2.48-28.98	0.00 (0) 0	2.60 (1) 0.13-19.16	2.60 (1) 0.13-19.16
40-64	7.61 (13) 3.29-15.28	9.36 (16) 4.04-18.45	16.97 (29) 9.83-27.49	5.20 (5) 1.28-15.03	10.40 (10) 3.37-24.27	15.60 (15) 7.19-30.00	5.19 (4) 0.63-18.74	11.67 (9) 4.21-26.57	16.86 (13) 7.30-33.88
65-84	29.77 (19) 15.03-53.55	17.24 (11) 6.90-36.57	47.01 (30) 26.31-77.53	25.77 (10) 8.37-60.14	46.39 (18) 21.21-88.06	72.16 (28) 39.45-121.10	6.26 (2) 0.16-34.89	56.36 (18) 25.77-107.00	62.62 (20) 30.00-115.20
>85	63.53 (6) 13.10-180.57	105.89 (10) 34.38-247.10	169.42 (16) 73.15-333.80	55.11 (3) 8.90-204.70	183.69 (10) 59.64-428.70	238.80 (13) 103.40-479.80	91.70 (4) 11.10-331.30	22.93 (1) 1.16-169.10	114.63 (5) 28.37-331.30

Note: SAB = *Staphylococcus aureus* bacteraemia. N = 214. HA = healthcare associated; CA = community associated. Incidence = number of new cases of SAB per 100,000 population per year. HA cases are listed against the attributable region; CA cases are listed as the region in which the case of SAB was identified. 95% CI = 95% confidence interval. Confidence intervals are expressed using the lower and upper limits. 95% confidence intervals calculated using Fisher Exact Test. N/A = Not applicable as no data.

From the results provided in Table 7, a number of results were of interest. First, there was a higher overall incidence of SAB in the northern region compared to the southern and north-west regions, although not statistically significant. Second, there was a higher incidence of HA SAB in the southern region, compared to the other two regions. Consistent with data described in Table 7, it is also possible to see that the incidence of SAB generally increased with increasing age. Notably however, the incidence of SAB in the southern region was higher in the 0 to 14 age group, compared with the other two regions, before declining in the 15-24 age group and increasing again.

The incidence of SAB was homogenous among the three regions other than a large increase in CA SAB in the north and north-west regions in the 65-84 age group. The incidence of CA SAB in the north continued to increase in those aged 85 and over, whereas there was a decrease in the incidence of CA SAB in the north-west region for the same age group. However, there were small absolute numbers of cases and very wide confidence intervals in the highest age groups.

Finally, differences between the location (region) where a blood culture was taken and the region to which it was attributed were analysed. Four cases (4.5%) of HA SAB were attributed to a different region from that where the blood culture was taken. Three of the four cases were situations in which the blood cultures were collected in the north-west region, but were attributable to the southern (2) and northern (1) regions.

3.6.4 Results by hospital type

This section examines cases of SAB according to where they were identified and distinguishes the attributed locations by hospital type. For the purposes of this section, 'identified' refers to the locations where the positive blood cultures were collected. The reason for examining this, as opposed to only examining where a case of SAB was attributed to, is to answer the third research question for this study. Currently, the national surveillance program for SAB in Australia is concerned with cases of SAB associated with public hospitals. Therefore, the results described below sought to provide data to answer the

question of what proportion of SAB cases would be missing from the national surveillance program, when only data from public hospitals were included.

Table 8 shows the distribution of SAB cases found outside acute public hospitals. The majority of cases of SAB were identified in one of the four acute Tasmanian public hospitals. However, a small but potentially clinically significant proportion of SAB cases were identified in private hospitals.

Table 8

Identification of Staphylococcus aureus bacteraemia by healthcare facility type

Characteristic	Facility type where SAB was identified		
	Acute Public Hospital	Private Hospital	Public Rural Hospital
Total SAB	188 (88%)	24 (11%)	2 (1%)
Type of SAB			
MSSA	171 (88%)	22 (11%)	1 (1%)
MRSA	17 (85%)	2 (10%)	1 (5%)
Acquisition			
HA	80 (90%)	8 (9%)	1 (1%)
CA	108 (86%)	16 (13%)	1 (1%)

Note: SAB = Staphylococcus aureus bacteraemia.

A similar percentage of MRSA bacteraemia and MSSA bacteraemia were identified in public and private hospitals. The percentage of HA SAB was lower, however, in private hospitals, compared to public hospitals. The calculation of relative risk of SAB comparing public and private hospitals was not possible, as data on the number of persons exposed in private hospitals were not available.

Table 8 demonstrates where cases of SAB were identified. Not all of the 89 cases of HA SAB were identified in and attributed to the same facility. Five cases (5.6%) of HA SAB were

attributed to different hospitals from those where the blood culture was taken and one case of HA SAB was identified in a public hospital but attributed to a private hospital.

3.6.5 Summary

Two hundred and fourteen cases of SAB were identified in this study. Of the 214 cases, 128 cases (60%) occurred in males. Over 90% of cases (194, 90.7%) were caused by MSSA. The incidence of SAB within Tasmania was 21.26 per 100,000 population per year. The proportion of cases that were HA was 41.6%, with the remaining 58.4% being CA.

Of the 89 cases of HA SAB, 61 (68%) occurred in patients who were hospitalised more than 48 hours whilst 29 (32%) occurred in persons who were in hospital less than 48 hours but met clinical criteria defining a case of HA SAB. Of the 49 (55%) instances where an intravascular device was implicated in some way, 27 (55%) of these devices were central lines, 12 (25%) were a peripheral intravascular device and 10 (20%) were from all other devices.

The incidence of SAB was relatively homogenous among the three regions at around two cases per 100,000 population per year; with 11% of SAB identified in private hospitals. Five cases (5.6%) of HA SAB were attributed to different hospitals from those where the blood culture was taken and one case of HA SAB was identified in a public hospital but attributed to a private hospital. The next section of this chapter will discuss the findings of this study.

3.7 Discussion

3.7.1 Introduction

This study provides useful insights into the epidemiology of SAB. It is the first reported study in Australia to capture data from all cases of SAB in a discrete population. Tasmania is an island state in Australia with a relatively stable population. Results from the study were analysed at the population level, by region, and by hospital type. The discussion focuses on three main elements consistent with the research questions guiding the study: the overall incidence of SAB at a population level, regional variation of SAB, and the potential for under reporting SAB by only collecting data from public hospitals. In particular the overall incidence and its contributing proportions highlight many key points and therefore these are explored in more detail in the discussion. After exploring each of the three elements in more detail, the reliability and validity of the data and the limitations of the research are discussed. To conclude the discussion recommendations are identified regarding policy, practice, and further research.

3.7.2 Incidence of SAB at a population level

Three main results were of particular note when looking at the incidence of SAB at the population level. First, the study was unique, in that it collected data from all cases of SAB occurring in Tasmania. As such, I can confidently report the incidence of SAB as 21.26 per 100,000 population, with approximately 40% of cases being HA. Second, my study suggests that the risk of SAB increases with age, with the exception of the first decade. Third, results suggest that males are more likely than females to suffer from SAB. Finally, my results suggest that there are a number of potentially modifiable risks for HA SAB. In this section, comparisons are drawn between the current findings and those published in the literature for each of these three findings.

Comparing the incidence of SAB

Only a few reports describe the population-based incidence of SAB (Asgeirsson, Gudlaugsson, Kristinsson, Heiddal, & Kristjansson, 2011; P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005; Easton, 2010; Huggan, et al., 2010; Lamagni et al., 2011; Lessa et al., 2010; J. Turnidge, Nimmo, G., Pearson, J., Gottlieb, T., Collignon, P., Australian Group on Antimicrobial Resistance, 2007). Of these reports, only one study captured all cases of SAB in a defined population (Asgeirsson et al., 2011). In the study undertaken in Iceland, the annual incidence of SAB was reported as 24.5 per 100,000 population between the years 1995 and 2008 (Asgeirsson et al., 2011). There are a number of similarities between the study undertaken by Asgeirsson et al. (2011) and the current study. Both had a clearly defined population and employed similar methodology in that they identified all cases of SAB in the population. Further, in the Icelandic study, 721 episodes of SAB were identified, with 4% of the episodes being re-infection, a figure that compares to that of the present study (6%). Although the re-infection rates are similar between the studies, the Icelandic study was conducted over 13 years and therefore the potential for new infections in the same person is higher. Both studies had exclusion periods for duplicate cases of SAB. In my study, consideration was given to excluding all cases of SAB occurring in the same person, for the purposes of calculating a population incidence. In deciding whether to remove duplicate cases occurring in the same person but outside the 14 days exclusion period as described in 3.5.3, other population-based studies were reviewed. Following this process it was clear that like my study, other population-based infection surveillance programs do not remove second cases of infection occurring in the same patient in the same year. One example of this in Australia was the nationally notifiable disease Chlamydia (National Notifiable Diseases Surveillance System Annual Report Writing Group, 2010; Public Health Laboratory Network, 2009).

The similarities between the current study and that conducted by Asgeirsson et al. (2011) continue. On initial review, it also appears that both studies have a similar proportion of HA SAB, with 46% and 42% of SAB being HA in the Icelandic study and this study, respectively. However, different case definitions for HA SAB were used. It is likely that the study undertaken in Iceland underestimated the occurrence of HA SAB. Asgeirsson et al.

used patient administration data to define cases of nosocomial SAB and all cases of SAB occurring after 48 hours were classified as HA. In contrast to the current study, no clinical or other assessment criteria were used to determine cases of SAB that were HA, but were in hospital less than two days. In this study, 32% of persons defined as having HA SAB were in hospital less than 48 hours, a finding that is comparable to Dendle's study performed over a 27 month period in a single Australian hospital (Dendle et al., 2009). This study found that 26.7% of HA SAB occurred in non-inpatients, using the same clinical criteria applied in my study (section 3.5.4). Assuming that by only including persons in hospital more than 48 hours in a HA definition misses other cases of HA SAB, then the true occurrence of HA SAB in Iceland is probably higher than in Tasmania. Such a finding is important, as many studies examining SAB, including those describing the incidence of SAB at a population level, use the simple criterion of a case of SAB occurring more than 48 hours after hospitalisation to define HA SAB (Easton, 2010; Huggan et al., 2010). These studies, therefore, underestimate the true occurrence of HA SAB.

The advantages of using a timeframe such as 48 hours to define a case of HA SAB were explored in detail in Chapter 3. The use of well-defined terminology is important when describing study results to facilitate accurate comparisons. For example, the term 'hospital onset' SAB has been correctly used in several studies to describe instances of SAB occurring in patients hospitalised for more than 48 hours (Lessa, et al., 2010; J. Turnidge, Nimmo, G., Pearson, J., Gottlieb, T., Collignon, P., Australian Group on Antimicrobial Resistance, 2007). The use of recognised terminology not only makes comparing results between studies easier to interpret, but also ensures that those without an in-depth understanding of these issues, including the wider public, do not misinterpret the data. Such issues become more critical when data on HA SAB are publicly reported or used as a performance measure.

A similar incidence of SAB was found in a study undertaken by Huggan et al. (2010), which determined the population-based incidence of SAB in a region of New Zealand. Similar to the current study, population census data were used to calculate the incidence of SAB, which was found to be 21.5 per 100,000 population. One limitation of the New Zealand study was that data from community laboratories were not collected. Therefore, it is possible that it under-represented the true number of cases. Further, it only examined one region in New

Zealand, not the entire New Zealand population. Challenges in accounting for a dynamic population and the potential crossover of persons receiving healthcare between regions would have been difficult to quantify, an issue also faced in my study.

Compared to my study, a much higher incidence of SAB for Australia has been reported in a study undertaken by the AGAR which estimated the incidence of SAB at 35 per 100,000 persons per year in Australia, with approximately 6900 cases of SAB occurring each year (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005). Following this study, the figure of an estimated 7000 cases of SAB occurring in Australia each year has been widely used. This incidence was estimated using the median SAB rate from the 17 participating hospitals. The current data suggest that the SAB incidence suggested by the AGAR, and used in numerous publications since, is an overestimate. The authors acknowledge the limitations of their methodology and call for a program that captures all bacteraemia in a well-defined population (P. Collignon, Nimmo, G., Gottlieb, T., Gosbell, I., Australian Group on Antimicrobial Resistance, 2005). My study addresses this issue: extrapolating from an incidence of 21.26 per 100,000 population in Tasmania, there would be approximately 4800 cases of SAB in Australia each year, based on a population of 22.7 million.

This discussion so far has compared the peer reviewed literature with the current study. However, government or professional organisations undertake many surveillance programs for SAB, as described in Chapter 3. These are reported through various websites and in other grey literature. A voluntary SAB surveillance program in England, Wales, and Northern Ireland attempted to report on the incidence of SAB at a population level and included stratification for age and sex (Health Protection Agency, 2011b, 2011c). Data from 185 laboratories were used to collate the occurrence of SAB. One significant limitation of this three country program is that it is not clear what proportion of all laboratories contributed data. In 2010, 10,070 cases of SAB were reported in the three countries. The annual incidence of SAB was not reported in this study, but rather, it was reported in a bar graph comparing the total number of SAB cases by year, making a statement about an exact figure difficult (Health Protection Agency, 2011c). The authors stated that they used population data from the Office of UK Statistics. Using this data, it is possible to estimate the incidence of

SAB in these three countries combined to be 17.9 per 100,000 population, with 15.5% of SAB reported as MRSA (2.77 per 100,000 population in 2010). These results suggest a lower incidence of SAB in the United Kingdom than in Tasmania but a higher proportional incidence of MRSA. However, a published study by Lessa et al. (2010) seems to cast doubt on the MRSA results published by the Health Protection Agency and this will now be examined in more detail.

Lessa et al. (2010) compared the incidence of MRSA bacteraemia in the United States and England using population-based surveillance in these countries. Data from the United States used sources from eight metropolitan areas and one state, comprised of 162 hospitals under surveillance with an approximate population base of 16 million people. In England, the reporting of MRSA bacteraemia is mandatory and the information source was microbiology laboratories. The estimated population under surveillance in England was 56 million people. Hospital onset bacteraemia was defined as a positive blood culture three days after hospital admission. All other cases were defined as community onset. The total incidence of MRSA bacteraemia was 29.1 and 11.3 per 100,000 population for the United States and England, respectively. In the case of England, such a result was not consistent with the HPA results discussed earlier (Health Protection Agency, 2011b). The HPA data suggests the incidence of MRSA bacteraemia in the United Kingdom was only 2.77 per 100,000 population and therefore there is a significant discrepancy between this data and that reported by Lessa et al. (2010). One possible explanation is that England has a considerably higher incidence of MRSA bacteraemia compared with Wales and Northern Ireland, although some doubt is cast in this assertion as the percentage of SAB caused by MRSA is reported to be 28.8% in Wales (Welsh Healthcare Associated Infection Program, 2009). These points demonstrate the challenges in comparing data when definitions are inconsistent, catchment populations are not clearly defined, and a validation process is limited. I am confident that, in this study, data from all cases of laboratory confirmed SAB in Tasmania were collected using an open and consistent process with robust validation procedures. Issues relating to the validation of data are discussed later in this section.

The study by Lessa et al. (2010) did highlight some points of interest. The incidence of community-onset MRSA bacteraemia was 21.9 per 100,000 population in the United States,

compared to 3.5 in England (Lessa et al., 2010). These results suggest that the majority (75%) of MRSA bacteraemia in the United States is community onset. Comparisons of MRSA bacteraemia between my study and others should be undertaken with caution, given the relatively low prevalence of MRSA bacteraemia identified. For this reason, comparisons are not provided.

I argue that by having a robust process for capturing data from laboratories on SAB, it is possible to improve the identification of cases of SAB in a defined population. This can be achieved by making SAB a notifiable disease, as is the case in Tasmania, or by having a robust data linkage system among all laboratories and a central agency. The latter must also be supported by a relevant structure that enables this to occur, for example a legislative or contractual requirement. Without this requirement, it would be possible for laboratories to refuse to be part of a co-ordinated data program.

Healthcare associated SAB and risk factors

The discussion in this section only refers to data pertaining to healthcare associated SAB. The collection of data on the potential causes of HA SAB identified important clinical problems. Forty-one cases (46%) of HA SAB were solely associated with an intravascular device and an intravascular device was implicated in some way in 55% of all HA SAB cases.

Such a finding suggests that a considerable proportion of HA SAB can be prevented by improved processes relating to the insertion and maintenance of intravascular devices. Interventions proven to reduce the occurrence on intravascular device-associated bacteraemia include active surveillance and review of cases of SAB with feedback to clinical staff about potentially modifiable risk factors (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007). An example of a process aimed at reducing the risk of infection such as SAB is the promotion of correct hand hygiene prior to any interventions, such as intravascular insertion. Improved hand hygiene compliance has been demonstrated to reduce the occurrence of HA methicillin resistant SAB (L. Grayson, Russo, R., Cruickshank, M., Bear, J., Gee, C., Hughes, C., Johnson, P., McCann, R., McMillan, A., Mitchell, B., Selvey,

C., Smith, R., Wilkinson, I., 2011). A second example of an intervention aimed at reducing the risk of SAB is correct intravascular device insertion practices. Correct skin preparation with alcohol (70%) prior to intravascular device insertion has been shown to reduce the risk of bacteraemia and to lessen severe localised infections (Maki, Ringer, & Alvarado, 1991). Other measures to reduce the risk of intravascular device-related bacteraemia include the selection of the best entry point for the device, and the choice of device used. Each of these processes are themselves subject to considerable research and debate, which have led to guidelines from notable organisations such as the Centres for Disease Control and the NHMRC (National Health and Medical Research Council, 2010; N. O'Grady, Alexander, M., Burns, L., Dellinger, P., Garland, J., Heard, S., Lipsett, P., Masur, H., Mermel, L., Pearson, M., Raad, I., Randolph, A., Rupp, M., Saint, S., and the Healthcare Infection Control Practices Advisory Committee., 2011). The NHMRC are not alone in the issuing of guidelines aimed at reducing HAIs, such as HA SAB (L. Grayson, Russo, R., Ryan, K., Bellis, K., Havers, S., Heard, K., Simpson, P., 2010; Health Protection Scotland, 2011b; National Patient Safety Agency, 2010; World Health Organisation, 2011a).

The findings from the current study demonstrate that HA SAB represents approximately 41% of all cases of SAB, meaning that CA SAB is more common than HA SAB. In comparison to the prevention of HA SAB, CA SAB appears to receive little attention and prevention strategies seem sparse. In light of this, more attention should be paid to understanding the risk factors for CA SAB, and where possible, to identifying strategies for prevention.

Risk of SAB related to increasing age and male sex

The research results presented in this chapter demonstrate that the risk of SAB increases with age. Similar results have been found in a number of studies (Asgeirsson, et al., 2011; Laupland, et al., 2008; Morin & Hadler, 2001; J. Turnidge, Nimmo, G., Pearson, J., Gottlieb, T., Collignon, P., Australian Group on Antimicrobial Resistance, 2007). My study also identified that the relative risk of SAB was higher in males, compared to females. The same finding has also been reported in other studies (Easton, 2010; Huggan et al., 2010).

3.7.3 Regional variation of SAB

There were three key points of interest when reviewing the incidence of SAB among the three regional areas of Tasmania. The first was a higher incidence of SAB in the northern region and a higher incidence of HA SAB in the southern region in inter-regional comparisons, although these differences are not statistically significant. The second was a noticeable increase in the incidence of CA SAB in the three regions in the 65-84 age group from the 40-64 age group, but a decline in the north-west region for the 85 and over age group. Third, there were only minor differences when the study compared the numbers of cases of SAB by the region in which they were attributed to against the region in which they were identified. Each of these three issues is discussed in more detail.

The higher incidence of CA SAB in the northern region of Tasmania is difficult to explain. The difference could be chance as the higher incidence is not statistically significant. Conversely, the higher incidence could be real but would require a longer study period to confirm. There are no published research papers in Australia examining or comparing the incidence of SAB at a regional level. Therefore, it is not possible to compare the current study with other published literature. Potential risk factors for CA SAB include intravenous drug use. In the case of my study, there is no known difference in the prevalence of intravenous drug use among the regions. Further, should intravenous drug use be a factor in the higher incidence of CA SAB, it would be more likely to appear in a younger age group than seen in my study. Other potential reasons that would require further research include whether health issues such as smoking, obesity, and diabetes play a role in CA SAB. Aged standardised mortality for diabetes is higher in the north compared to the other two regions; however, data are not available for the prevalence of smoking or for body mass indices for the regions (Population Health Epidemiology Unit, 2008).

The increasing incidence of CA SAB with age is consistent among the regions, except for a decline in the 85 years and over age group in the north-west. Little weight should be attached to this result given the relatively low numbers of SAB occurring in this region. For example, if there were two more cases of SAB occurring in this age group and region, a continual increase in the incidence of CA SAB by age group would be seen, consistent with the north

and south. In the south, the incidence of HA SAB in the 0-14 age group is higher than in the other regions. Such a finding can be explained by this region containing a tertiary referral centre, with the state's only neonatal intensive care and paediatric unit.

The final point of interest in this section is the difference between where a case of SAB was identified compared to where it was attributed. Exploration of this point is important, as surveillance units and infection control professionals often spend considerable time debating whether a case of SAB should be attributed to their facility. This issue is also explored in more detail at a hospital level in the next section. Results from the study suggest that approximately 5% of HA SAB should be attributed to different regions from the origins of the blood cultures. Importantly however, this particularly affected the north-west region, where two cases of SAB were attributed to a hospital in the south and one to a hospital in the north. If these three cases had been included in the data analysis for the north-west region, it would have potentially overestimated the incidence of SAB in this region. Importantly however, given the small numbers of SAB occurring in the north-west, the addition of two extra cases of SAB can markedly change the incidence, in comparison to other regions with higher cases of SAB.

The national SAB surveillance program in Australia seeks to attribute cases of HA SAB to a particular facility (H. Van Gessel, McCann, R., Peterson, A., Cope, C., Wilkinson, I., Mitchell, B., Wells, A., Kennedy, B., Hall, L., Gallard, J., Lee, R., Cooley, L., Cruickshank, M., Greig, S., Hanley, E., Willows, K., Board, N., 2011). Results from the current study suggest that approximately 5% of HA SAB cases identified in one facility were attributed to another. Furthermore, among this 5%, there were instances where a hospital may attribute a case of SAB to another facility, but have a case identified in a different facility attributed to them. Such findings would appear to influence further debate on whether the time spent on attributing HA cases of SAB to a particular facility is a suitable use of resources, since the level of incorrect attribution is likely to be cancelled out.

3.7.4 Potential for under reporting

This research study captured data on all cases of SAB. Therefore, for the first time in Australia, it was possible to accurately quantify the proportion of cases of SAB that occurred outside public hospitals. Since the commencement of this study, an Australian national surveillance program for SAB has been established for cases of SAB associated with public hospitals. The results detailed in section 3.6.4 provide quantitative data on the proportion of SAB cases that is potentially missed in the national surveillance program because of its limited focus on public hospital data.

This study's results indicate that approximately 11% of cases of SAB were identified in healthcare settings other than public hospitals. Such a finding is important, given the current national focus on public hospitals only and provides valuable insight into whether the national SAB surveillance program should be formally extended to private hospitals. Such findings open the door for further debate on whether the time spent capturing data from private hospitals is a valuable use of resources. Capturing data from private hospitals would enable a more accurate understanding of the epidemiology of SAB, including CA SAB. Conversely, as private hospitals differ significantly in structure and size, and use a variety of microbiology services, a one size fits all policy may not be suitable.

The development of a surveillance definition and program for HA SAB in Australia was initially proposed as part of a safety and quality agenda. Therefore, HA SAB data could be used as part of a framework (Chapter 2) to drive interventions that can reduce its incidence. At the time of writing, HA SAB surveillance data were also being used in a performance management agenda. In using these data in such a way, the challenges of ensuring the data are valid, comparable, and reliable become more of an issue. This particular point is addressed further in Chapter 6. In Australia, HA SAB data at the hospital level were recently made public on the *MyHospitals* website (Australian Institute of Health and Welfare, 2011). This information is now available to media and members of the public. How these data are used and interpreted varies, as limitations are not fully necessary appreciated by the end users. This is not unique to HA SAB surveillance as will become evident throughout this

thesis. Themes from the challenges faced in HAI surveillance and its use are described in more detail in Chapter 6.

To improve the application of surveillance definitions, guidelines to interpret definitions should be developed. Such a process ensures all cases are treated and classified in the same manner. In the case of HA SAB, the Australian Commission on Safety and Quality in Health Care has developed guidelines for infection control professionals and clinicians for the interpretation of SAB surveillance definitions (H. Van Gessel, McCann, R., Peterson, A., Cope, C., Wilkinson, I., Mitchell, B., Wells, A., Kennedy, B., Hall, L., Gallard, J., Lee, R., Cooley, L., Cruickshank, M., Greig, S., Hanley, E., Willows, K., Board, N., 2011). Conversely, the use of strict and simplistic definitions potentially negates clinical interpretation and may result in disengagement by healthcare professionals. Such issues underscore the importance of using a psychosocial approach to infection control, as described in Chapter 2.

As this study is concerned with SAB at the population level, individual hospital results are not presented. Further, bed occupancy data for individual private hospitals were not available, and therefore, such data analysis was not possible. In the case of Tasmanian public hospitals, although HCA SAB is reported by the TIPCU, bed occupancy data are not. Only summary rates are published (B. Mitchell, McGregor, A., Brown, S., Wells, A., 2011a). Therefore, comparisons between the incidence of SAB in public and private hospitals are not possible.

3.7.5 Reliability of the data

A number of steps were put in place to ensure the inter-rater reliability of data used in this study. First, mandatory reporting greatly increased the likelihood of all cases of laboratory diagnosed SAB being reported. As SAB is a notifiable disease in Tasmania, laboratories have a legal requirement to report all blood cultures that contained *S.aureus*. All but one laboratory in Tasmania established an electronic means for this to occur, meaning that when a blood

culture was reported as growing *S.aureus*, a report was automatically generated by the computer and sent to the Public Health Department. This reduced the risk of human error associated with a manual reporting process. The one laboratory that did not have an electronic method of notification relied on laboratory staff faxing a copy of the result to the Public Health Department, which may reduce the reliability of all results being notified. To overcome this issue and to provide a secondary check, each laboratory was required to provide the Public Health Department with a monthly manual download of all blood cultures positive for *S.aureus*, as described in Figure 7. This download was then cross checked against previously submitted notifications, enhancing reliability by ensuring that all cases of SAB were reported.

For the second important step, a number of processes were established at the commencement of data collection, to ensure that the data collected on each case of SAB were accurate and these processes were discussed in section 3.5.4. Some methods used in my study, such as monthly laboratory extracts to cross check against reported cases of SAB and the use of clear protocols and education are reproducible and are not labour intensive. However, one key element underscoring the processes of capturing all data was that SAB was a notifiable disease in Tasmania. The process for making SAB a notifiable disease in Tasmania was relatively straight forward and did not result in significant changes or workload for the Public Health Department. As each state and territory's public health legislation differs in Australia, the key mechanism used in my study to ensure all cases of SAB were identified may not be possible elsewhere.

3.7.6 Validity of the data

The current study applied national surveillance definitions. Chapter 3 examines the issue of whether the surveillance definitions measure what they are supposed to measure. Since the development of the national SAB surveillance definitions, there has been a publication endorsing them (B. Mitchell, Gardner, A., Collignon, P., Stewart, L., Cruickshank, M. , 2010). During this study, the national surveillance definition for SAB was found to be clear, concise, and easily applied. There were very few situations where the definition was not

explicit enough to enable easy application or where there was disagreement between a TIPCUC classification of SAB and infection control professionals or clinicians. Where these situations occurred, in all circumstances, the issue was resolved by careful review of the individual person's details to come to a mutually agreed position on the classification of SAB.

3.7.7 Limitations

The study does have limitations. First, the population of Tasmania is relatively small; thus, firm conclusions about the representativeness of the Tasmanian data at an Australian level require caution. Second, the calculation of incidence over the two year period was based on 2009 population data, as data for 2010 were not available at the time of data analysis. The magnitude of any overestimation is unlikely to be significant, given that in the five years preceding 2009, the Tasmanian population increased by 1% or less each year (Australian Bureau of Statistics, 2011). Finally, the prevalence of MRSA in healthcare settings in Tasmania has already been established as generally low (B. Mitchell, McGregor, A., Coombs, G., 2009). Therefore, caution should be taken when comparing the incidence of MRSA SAB to other Australian settings where MRSA prevalence is higher.

The incidence of SAB is based on laboratory confirmed cases of SAB. Cases where *Staphylococcus aureus* was not present at the time of blood culture or where a blood culture was not taken will be missed.

3.8 Recommendations

A number of recommendations can be made based on the finding of my study. Consistent with other research, my study found that half of HA SAB was associated with an intravascular device. This provides evidence of a need to have a system in place to monitor and evaluate HA SAB trends and their potential causes. Further, data from my study

suggested that if timeframes are the sole criteria used to determine cases of HA SAB, approximately 30% of cases of HA SAB will be incorrectly identified as CA SAB.

With these two points in mind, the following policy and research recommendations are made:

1. Continued surveillance of HA SAB in Australia is required
2. Surveillance of HA SAB should include the ability to collect data on its potential causes
3. The definition of HA SAB should include clinical criteria

The findings of this study also suggest that approximately 11% of cases of SAB were identified in healthcare settings other than public hospitals. In order to inform a debate about whether the national SAB surveillance program should be formally extended to private hospitals occurrences, I recommend:

4. This population-based study be replicated in another Australian state, with the aim of comparing the incidence of SAB in private hospitals.

While there is a strong policy focus in Australia on reducing HA infections including HA SAB, it is important to note that results from this study suggest that CA SAB is more common than HA SAB. An improved understanding of CA SAB in Australia is vital, in particular, improving our understanding of risk factors for CA SAB. Therefore, future research in the following areas is recommended:

5. Research that examines risk factors for CA SAB in Australian settings.

3.9 Conclusion

This chapter started by providing background to a common hospital pathogen, *S.aureus* and to a serious HAI, namely SAB. A literature review was undertaken to explore the epidemiology of SAB in current SAB surveillance programs. Through this review of the literature, it was identified that no SAB surveillance system captured enhanced data from all

SAB cases in a given population and reported on these findings. Such a program would allow for an improved understanding of the epidemiology of SAB and to explore potential influences for under reporting of SAB.

In response to the literature review, the first piece of research for this thesis was presented. This study examined the epidemiology of SAB at a population level using a descriptive, observational, population-based study design. All cases of SAB occurring in Tasmania between the 1st January 2009 and 31st December 2010 were explored. This is the first known Australian study to capture and analyse data from all cases of SAB at a population-based level and represent this as an incidence. In doing so, three main areas were explored, namely the incidence of SAB at a population level, the incidence of SAB at a regional level and the potential for under reporting for SAB where data is collected from public hospitals only and where different case definitions are applied.

The findings from this study can be summarised into four themes. First, the incidence of SAB at a population level has been accurately determined for the first time in Australia. The annual incidence of SAB was found to be 21.26 per 100,000 population. Using the incidence of SAB in Tasmania, it was estimated that there are approximately 6800 cases of SAB occurring each year in Australia. Both the incidence of SAB and the estimate of the total number of cases of SAB in Australia are lower than that reported in other Australian studies. Second, a large proportion of HA SAB was associated with intravascular device management. Third, case definitions for HA SAB will influence its detection. If only timeframe from admission to hospital and infection onset are used to determine cases of HA SAB, approximately 30% of HA SAB will be incorrectly classified as CA SAB. Fourth, 11% of SAB were identified in private hospitals and these fall outside the scope of almost all SAB surveillance programs in Australia. Such a finding enables an informed debate on whether data on cases of SAB occurring outside public hospitals should be captured.

Chapter 4: *Clostridium difficile* infection and mortality

4.1 Introduction to the chapter

In the first section of this chapter, issues relating to CDI are explored through a critical review of the literature. Initially, background on CDI will be provided, with a particular emphasis on CDI pathogenesis, detection and issues commonly faced when undertaking research or surveillance of CDI, namely, how to define cases and the location of CDI acquisition. An exploration of the risk factors associated with CDI is also provided in this section. A literature review related to mortality and CDI will then be presented. Through an exploration of the literature, current gaps in the understanding of CDI and mortality in the southern hemisphere are identified. The findings from this review indicate that CDI has a significant adverse effect on hospitalised patients. Further, no published study was identified examining CDI and mortality in the southern hemisphere. Studies investigating the mortality of CDI in settings outside of Europe and North America are needed so that the epidemiology of CDI in these regions can be understood and appropriate decisions regarding infection prevention strategies made. The second study of this thesis addresses this deficit by examining CDI and associated mortality in an Australian setting, more specifically, the Royal Hobart Hospital, Hobart, Tasmania. Following the literature review, this study is presented. To conclude this chapter, recommendations are made.

4.2 Background to *Clostridium difficile* infection and surveillance

All members of the genus *Clostridium* are anaerobic bacteria and all have the ability to form endospores, one of the most highly resistant life forms on earth (Cartman, Heap, Kuehne, Cockayne, & Minton, 2010). There are over 100 identified *Clostridium* species, however 90% of clinical disease is caused by just 12 (Cartman et al., 2010). *Clostridium difficile* is a bacterium that is commonly the cause of diarrhoea in hospitalised patients. The spectrum of disease caused by *C.difficile* ranges from uncomplicated diarrhoea through to pseudo membranous colitis and toxic megacolon and is often termed “*Clostridium difficile*-associated diarrhoea” or “*Clostridium difficile* infection” (Heinlen & Ballard, 2010; L. Clifford McDonald et al., 2007; Stuart & Marshall, 2011; H. Van Gessel, Riley, T., McGregor, A, 2009). For the purposes of this thesis, the term CDI is used.

Clostridium difficile can be cultured from the faeces of 3% of healthy adults, 16-35% of hospitalised inpatients and up to 80% of healthy newborns and infants (Aslam, Hamill, & Musher, 2005; Bartlett, 1992). There is however, a widely held belief that *C.difficile* is not pathogenic in neonates (Kuijper, Coignard, & Tull, 2006). It is on the basis of this assumption, that the majority of CDI research and surveillance excludes people of less than two years of age (Australian Commission on Safety and Quality in Health Care, 2010).

Around the world, the incidence of CDI has been increasing since 2002. Explanations for this increase may in part be explained by a change in circulating strains of *C.difficile*, in particular the emergence of a strain known as polymerase chain reaction (PCR) ribotype 027 (Bauer, van Dissel, & Kuijper, 2009). This strain has been implicated in hospital outbreaks of CDI in the northern hemisphere (Goorhuis et al., 2007; Loo et al., 2005).

This section of the chapter explores the pathogenesis, detection and diagnosis of CDI and related issues encountered when undertaking research or surveillance of CDI, namely, how to manage relapses of CDI in surveillance and how to determine the location of CDI acquisition. This section concludes by exploring the risk factors for CDI.

4.2.1 Pathogenesis and treatment diagnosis

Individuals colonised with *C.difficile* may remain asymptomatic carriers or they may exhibit symptoms. In healthy adults, colonisation with *C.difficile* does not usually result in infection due to the protective effects of colonic flora (Cartman et al., 2010). Disruption of the normal flora can occur following exposure to antibiotics, leading to a loss of colonisation resistance and an enabling of *C.difficile* to proliferate and cause symptoms (Cartman et al., 2010).

Colonisation resistance is the term used to describe the process where the indigenous anaerobic flora limit the concentration of potentially pathogenic (mostly aerobic) flora in the digestive tract (Vollaard, 1994). The ability of antibiotics to alter bowel flora depends on the mechanism and characteristics of the antibiotic, such as degree of absorption, binding

properties and rates of elimination. The risk of CDI due to antimicrobial exposure is explored in more detail later in this chapter. Chemotherapy, antiperistaltic drugs and gastroenterological surgery are other factors that have the potential to influence colonic flora (Cartman et al., 2010; Kuijper et al., 2006).

In CDI, inflammation of the bowel is caused from the production of two protein toxins; toxin A and toxin B. Isolates of *C.difficile* that do not produce either of these toxins are non-pathogenic (M. Bauer, van Dissel, J., Kuijper, E, 2009). Whether differences between toxin A and toxin B are associated with variation in disease severity remains unknown (M. Bauer, van Dissel, J., Kuijper, E, 2009; Warny et al., 2005). Toxins A and B are endocytosed by enterocytes and as a result, damage the intestinal mucosa. The damage to enterocytes causes an inflammatory response in the bowel mucosa and clinical symptoms ranging from mild diarrhoea to toxic megacolon can result (M. Bauer, van Dissel, J., Kuijper, E, 2009; Kelly & LaMont, 2008). In addition to toxins A and B production, a small number of isolates produce a binary toxin; however the role of this third toxin remains unknown.

Treatment of symptomatic CDI usually involves the prescribing of either vancomycin or metronidazole. There is ongoing debate as to which of these two antibiotics is the most efficacious. It is not within the scope of this chapter to explore this particular issue. The immune response plays an important role in CDI and in particular its recurrence, so immunotherapy has also played a role in the treatment of recurrent CDI. As normal pooled immunoglobulin can neutralise toxins A and B, intravenous immunoglobulin has been used to treat recurrent infection (Kelly & LaMont, 2008). Although no randomised control trials have been undertaken, immunoglobulins appear to be effective (Kelly & LaMont, 2008). Probiotics such as lactobacillus species and *Saccharomyces boulardii* have also been used to treat CDI. They have shown efficacy in reducing antibiotic associated diarrhoea but prevention of CDI has been inconsistent. Probiotics have not been shown to be effective as a solo treatment option for CDI (Kelly & LaMont, 2008).

A person who has recovered from CDI may suffer a relapse. Whether the relapse is due to endogenous re-infection or re-infection from the environment remains unclear (Bauer et al., 2009; O'Neill, Beaman, & Riley, 1991; Rupnik, Wilcox, & Gerding, 2009). Regardless, a major risk factor for CDI relapse may be inadequate humoral response (Bauer et al., 2009).

Relapse of CDI is associated with older age, co-morbidity and duration of previous episodes of CDI (McFarland, Elmer, & Surawicz, 2002; Pepin, Routhier, Gagnon, & Brazeau, 2006). The specific issue of managing relapses (potential duplicate cases) of CDI in the same individual is explored in section 4.2.3.

4.2.2 Diagnosing and defining CDI

This section provides detail on CDI diagnosis. The issues related to CDI diagnosis are important to understand, as they have implications for case definitions and ascertainment bias. Consensus criteria for CDI diagnosis are being developed, with the majority of researchers and clinicians utilising diagnostic definitions proposed by McDonald et al. (2007). More specifically, laboratory detection of *C.difficile* is the most common method used to define a case of CDI (Australian Commission on Safety and Quality in Health Care, 2010; Boyd, 2007; A. McGregor, Riley, T., Van Gessel, H, 2008).

The diagnosis of CDI occurs through testing of faecal samples at a microbiology laboratory. Laboratory diagnosis of CDI is made through detection of *C.difficile* by culture and/or by detection of its toxins. The sensitivity of culture is high, however this method lacks specificity. Similarly, culture does not produce any information about the toxigenicity of isolates (toxin A or B) and time to a result can be delayed due to the need to perform a further test to determine the presence of a toxin (DuPont, Garey, Caeiro, & Jiang, 2008; Kufelnicka, 2011).

The detection of *C.difficile* toxin A or B (CDT) in faeces is a common method used by laboratories. Compared to culture, the identification of CDT and hence CDI, is faster due to the availability of commercial CDT assays. Laboratories generally test for CDT using an enzyme immunoassay (EIA) that detects both CDT A and B, or by a neutralised cell cytotoxicity assay (Planche et al., 2008). More recently, other detection methods for *C.difficile* such as PCR, which ensures a rapid sensitive result, or the detection of the presence of glutamate dehydrogenase (GDH), are being used (DuPont et al., 2008; Reyes et al., 2007; van den Berg et al., 2007). The sensitivity of GDH is very high, i.e. it accurately

identifies the presence of *C.difficile* and it provides a rapid result. Conversely, the specificity of the GHD assay is poor (Sharp et al., 2010).

In a systematic review examining diagnosis of CDI by toxin detection kits, the authors reported that the positive predictive value of a range of assays was unacceptably low when the prevalence of CDT A and B was less than 10% in the population at large (Planche et al., 2008). This is not unique to CDI testing, but is a feature of screening in populations with a low prevalence of the disease (Grimes & Schulz, 2002). The low positive predictive value has a direct impact on clinical management and the reliability of data. The authors suggest that to improve diagnosis, a two-stage testing strategy for CDT occur by using a highly sensitive rapid screening test initially, with a confirmation by reference method for positive samples (such as culture) (Planche et al., 2008).

One issue faced when using a laboratory based method for the detection of CDI relates to choosing which faecal samples should be tested for *C.difficile*. A positive test in an asymptomatic patient proves colonisation, not necessarily infection. It has been suggested that any diarrhoeal sample in a hospitalised patient should be tested for *C.difficile* (A. McGregor, Riley, T., Van Gessel, H, 2008). Surveillance definitions proposed by McDonald et al. (2007) recommend that a case of CDI is defined as diarrhoea (i.e. unformed stool that conforms to the shape of a specimen collection container) or toxic megacolon (i.e. abnormal dilation of the large intestine documented radiologically) without other known aetiology that meets one or more of the following criteria:

- (1) the stool sample yields a positive result for a laboratory assay for *C. difficile* toxin A and/or B, or a toxin-producing *C. difficile* organism is detected in the stool sample by culture or other means or;
- (2) pseudomembranous colitis is seen during endoscopic examination or surgery or;
- (3) pseudomembranous colitis is seen during histopathological examination

(McDonald et al., 2007)

Within Australia, the surveillance definition used to define CDI is similar to that proposed by McDonald et al. (2007). As summarised in Table 9, a CDI case is defined as a case of diarrhoea (that is, an unformed stool that takes the shape of the container) that meets the following criteria:

- (1) the stool sample yields a positive result in a laboratory assay for *C. difficile* toxin A and/or B, or
- (2) a toxin-producing *C. difficile* organism is detected in the stool sample by culture or other means.

(Australian Commission on Safety and Quality in Health Care, 2010)

The advantage of using the definition proposed and adopted by all states and territories in Australia is the ability to obtain data from laboratories, rather than rely on a combination of laboratory and clinical evaluation and subsequent reporting as per criteria two and three proposed by McDonald et al. (2007).

Internationally, laboratory based CDI programs are used in a number of countries including England, Scotland, Wales, and Belgium. In England, a case of CDI is defined as a toxin positive result for CDI detected by the Health Care Trust whose laboratory processes the specimen (Health Protection Agency, 2011a). In Wales, the detection of *C.difficile* toxins in diarrhoeal stool samples is used to define a case of CDI. Surveillance in Wales is restricted to *C.difficile* occurring in inpatients with diarrhoea, however laboratories are unable to ascertain information on faecal consistency (Welsh Healthcare Associated Infection Programme, 2010). The Scottish CDI surveillance program defines a case of CDI as:

Someone in whose stool *C.difficile* toxin has been identified at the same time as they have experienced diarrhoea not attributable to any other cause, or from cases of whose stool *C.difficile* has been cultured at the same time as they have been diagnosed with PMC (pseudomembranous colitis).

(Health Protection Scotland, 2009a, p. 4).

Essentially, the programs in the United Kingdom are the same as those in Australia.

In France, a patient based voluntary surveillance program is used, which is reliant on hospitals and nursing homes notifying severe cases of CDI. Similarly, the Netherlands use a patient based surveillance program for severe or cluster cases of CDI, in addition to periodic laboratory based studies. In the United States, there is no nationally co-ordinated surveillance program (A. McGregor, Riley, T., Van Gessel, H, 2008). Belgium commenced CDI surveillance in 2006 and used definitions proposed by the European Centre for Disease

Prevention and Control (ECDC) (Kuijper et al., 2006; Lambert, Mertens, Ramboer, Delmee, & Suetens, 2009). Canada undertakes laboratory based CDI surveillance which is mandatory for all hospitals participating in the Canadian Nosocomial Infection Surveillance Program (CNISP). In Canada, a case of CDI is defined as:

1. diarrhoea or fever, abdominal pain and/or ileus AND laboratory confirmation of a positive toxin assay for *C.difficile*; **OR**
2. diagnosis of pseudomembranes on sigmoidoscopy or colonoscopy, or histological/pathological diagnosis of CDAD.

(Boyd, 2007)

Although there are differences in the criteria used to define a case of CDI, there is broad agreement that a person who is displaying symptoms of infection, such as diarrhoea, and whom has *C.difficile* toxin detected from faeces, has CDI. As we have seen, some literature suggests that a diagnosis of pseudomembranous colitis could also be used to define CDI, however this requires additional diagnostic techniques and it is difficult to obtain accurate and consistent information on all cases of CDI.

On a practical level, the use of laboratory diagnosed CDI is relatively easy, noting that different laboratory testing methodologies and definitions for diarrhoea pose some inconsistencies when attempting to compare data. In addition, multiple samples of faeces from the same patient can be sent for testing and this raises the specific issue of how to exclude such patients when using laboratory diagnosed CDI for research or surveillance. This issue will now be discussed further.

4.2.3 Managing duplicate samples with laboratory diagnosed CDI

Recurrent positive laboratory tests for *C.difficile* toxin pose a challenge for interpretation. For the purposes of research and surveillance, duplicate episodes for a given individual within a defined period are often excluded (Health Protection Agency, 2011a; Welsh Healthcare Associated Infection Programme, 2010). In Australia, cases are excluded where a known previous positive test has been obtained within the last eight weeks (that is, cases are only

included once in an eight week period) (Australian Commission on Safety and Quality in Health Care, 2010).

Table 9 provides a summary of the CDI surveillance definitions used in Australia. The approach taken in Australia is consistent with CDI surveillance definitions proposed by McDonald et al. (2007) and by ECDC (Kuijper et al., 2006). In some countries that undertake CDI surveillance, duplicates at four weeks are discarded (Health Protection Scotland, 2009a). Research that uses laboratory diagnosed data to determine cases of CDI, generally applies the surveillance definitions described by the ECDC and McDonald et al. (Chung et al., 2010; Goorhuis et al., 2007). In some instances however, no mention of the management of duplicate samples is discussed (Dubberke et al., 2008; Gasperino, Garala, Cohen, Kvetan, & Currie, 2010).

As *C.difficile* is assumed not to be pathogenic in neonates and the risk of CDI increases with age, CDI surveillance programs often make age specific exclusions. The ECDC does not make any specific age related exclusions, however it does comment that depending on the population and the reasons for surveillance and reporting, some restrictions may be warranted (Kuijper et al., 2006). Similarly to the ECDC, definitions proposed by McDonald et al. (2007) do not define any age restrictions. Despite these recommendations, Australia, England and Wales exclude persons under two years old identified with *C.difficile* in their surveillance programs (Australian Commission on Safety and Quality in Health Care, 2010; Health Protection Agency, 2011a; Welsh Healthcare Associated Infection Programme, 2010). In Scotland, only persons aged 15 years or older are included and in Canada, only persons aged less than one month old are excluded (Boyd, 2007; Health Protection Scotland, 2009a).

In summary, there is a variation in criteria used to exclude cases of CDI in surveillance and research. There is however, a broad acknowledgement that duplicate cases within a given period need to be excluded. A timeframe of between four and eight weeks is most commonly used to exclude duplicate samples in laboratory based CDI research and surveillance, with authors of notable publications calling for a consistent approach of eight weeks (Kuijper et al., 2006; McDonald et al., 2007). On the issue of excluding cases of CDI based on age,

practices vary. Despite both the ECDC and McDonald et al. (2007) not stating an age for which cases should be excluded, practices across the world do apply some form of age limit. Most commonly, persons aged less than two years old are excluded from laboratory based CDI surveillance and research.

Table 9 provides a summary of the CDI surveillance definitions used in Australia. The use of laboratory based CDI surveillance and research does have limitations, particularly when trying to differentiate between healthcare associated and community associated cases of CDI. Further information is required to determine such differences and this will be explored in more detail in the next section.

Table 9

Australian Clostridium difficile infection surveillance definition

A CDI case is defined as a case of diarrhoea (that is, an unformed stool that takes the shape of the container) that meets the following criteria:

- the stool sample yields a positive result in a laboratory assay for *C.difficile* toxin A and/or B, or
- a toxin-producing *C.difficile* organism is detected in the stool sample by culture or other means.

A hospital identified CDI case is:

- a case diagnosed in a patient attending an acute care facility (that is, it includes positive specimens obtained from admitted patients and those attending the emergency department, and outpatient departments).

Exclusions:

- cases where a known previous positive test has been obtained within the last eight weeks (that is, only include cases once in an eight week period).
- patients less than two years old.

Note: Adapted from “*Data Dictionary and Collection Guidelines for the Surveillance of Healthcare Associated Infections: Staphylococcus aureus bacteraemia & Clostridium difficile Infection,*” Australian Commission on Safety and Quality in Health Care (2010), p.15.

4.2.4 Defining the location of CDI acquisition

Surveillance for CDI primarily focuses on the hospital environment, yet not all cases of CDI occur in hospitals nor are necessarily attributable to the hospital in which CDI has been identified. To overcome this issue, a range of definitions to determine the place of acquisition of CDI has been proposed. These can broadly be summarised as healthcare associated healthcare facility onset; healthcare associated community onset; community associated; indeterminate; and unknown (Australian Commission on Safety and Quality in Health Care, 2010; Kuijper et al., 2006; McDonald et al., 2007).

Hospital identified CDI, is an Australian term used to define cases of CDI that are identified in persons who are admitted patients or those attending the emergency department and outpatients departments at the time a specimen is collected (Australian Commission on Safety and Quality in Health Care, 2010). Hospital identified CDI is the same classification as the term 'healthcare facility onset', proposed by McDonald (2007). The term hospital identified CDI, reflects a practical approach to CDI surveillance by acknowledging the limitations of information systems which are unable to merge patient admission data with laboratory data. It also removes the need for individual case review, and for allocating CDI cases to other hospitals. Such an approach is used in Wales and England (Health Protection Agency, 2011a; Welsh Healthcare Associated Infection Programme, 2010). A limitation of using this definition is the inability to distinguish between cases of CDI identified at a hospital, but occurring as a result of healthcare outside of that hospital or those that are community associated.

Healthcare associated healthcare facility onset (HCA HFO) CDI is defined when the onset of symptoms occurs at least 48 hours following admission. A person is classified as having healthcare associated community onset (HCA CO) CDI when symptom onset (or date and time of stool specimen collection if a laboratory system is used) occurs in the community or within 48 hours of admission to a healthcare facility, provided that symptom onset was less than four weeks after the last discharge from a healthcare facility. A person is classified as having community associated (CA) CDI when symptom onset (or date and time of stool specimen collection if a laboratory system is used) occurs in the community or within 48

hours of admission to a healthcare facility, provided that symptom onset was more than 12 weeks after the last discharge from a healthcare facility. Indeterminate onset refers to a person that does not fit any of the other criteria for exposure setting, for example onset in the community but within four and 12 weeks of discharge from a healthcare facility. The unknown classification is used when the exposure setting cannot be determined because of a lack of data (Kuijper et al., 2006; McDonald et al., 2007). Figure 9 provides a summary of the acquisition definitions in graphical form.

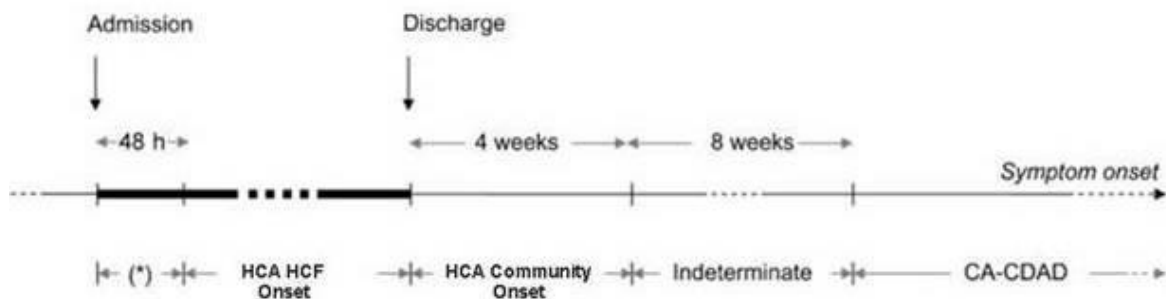


Figure 9. Timeline for *Clostridium difficile* infection acquisition definitions. *refers to a window period. Cases of CDI during this period could be classified as HCA community onset, CA CDI or intermediate disease. Adapted from “Recommendations for surveillance of *Clostridium difficile*-associated disease,” by L. McDonald, B. Coignard, E. Dubberke, X. Song, T. Horan, P. Kutty, and et al., 2007, *Infection Control & Hospital Epidemiology*, 28(2), p.141. Copyright 2008 by The University of Chicago Press.

4.2.5 Risk factors for *Clostridium difficile* infection

This section will broadly discuss the risk factors for CDI, before explaining two risk factors in more detail, namely the roles of antimicrobials and the healthcare environment. The risk factors for CDI can be broken into two categories, host and non-host factors summarised in Table 10. Non host factors include the presence of spores and associated transmission to other individuals, hospitalisation, exposure to drugs such as antimicrobials, proton pump and

H2 receptor drugs. Host risk factors affecting the risk of CDI include advancing age and the presence of co-morbidity (DuPont et al., 2008).

There is some debate about the role of proton pump inhibitors (PPI) and CDI. Use of proton pump inhibitors may be a risk factor for CDI because survival of spores is facilitated by elevated gastric pH levels. In addition, PPI may have an effect on the immune function or toxin production of the organism (Vaishnavi, 2009). Studies have shown contradictory results when trying to determine the influence that PPI has on CDI. A case control study demonstrated an increased risk of CDI in hospitalised patients who had received PPI compared to those who did not (Cunningham, Dale, Undy, & Gaunt, 2003). Conversely, a study by Pepin (2005) reported an elevated risk of CDI with PPI occurring in univariate analysis but not after adjustment for co-morbidities on multivariate analysis. These two studies are examples of the conflicting evidence on the role that PPI may have in CDI. There is however, more clarity about the role of antimicrobials, such as antibiotics and CDI.

Table 10

Potential risk factors for Clostridium difficile infection

Host	Non host
Advancing age (DuPont et al., 2008)	Hospitalisation (Bignardi, 1998; McDonald, Owings, & Jernigan, 2006)
Co-morbidity (Vaishnavi, 2009)	Exposure to antimicrobials (J. Pépin, Saheb, N., Coulombe, M., Alary, M., Corriveau, M., Authier, S., Leblanc, M., Rivard, G., Bettez, M., Primeau, V., Nguyen, M., Jacob, C., Lanthier, L, 2005; Polgreen et al., 2007; Thomas, Stevenson, & Riley, 2003) Healthcare Environment (Best, Fawley, Parnell, & Wilcox, 2010; Dubberke et al., 2007; Dumford, Nerandzic, Eckstein, & Donskey, 2009) Proton Pump / H2 receptor drugs (Cunningham et al., 2003; Vaishnavi, 2009)

Antimicrobials and *Clostridium difficile* infection

Antibiotics are thought to be an important risk factor for CDI because they reduce the colonisation resistance of the bowel (Bignardi, 1998). There are a large number of studies reporting an association between antibiotic use and CDI (J. Pépin, Saheb, N., Coulombe, M., Alary, M., Corriveau, M., Authier, S., Leblanc, M., Rivard, G., Bettez, M., Primeau, V., Nguyen, M., Jacob, C., Lanthier, L, 2005; Polgreen, et al., 2007; Thomas, et al., 2003). It has been suggested however, that despite this large number of studies there is a lack of well-designed epidemiological research (Thomas et al., 2003). In a systematic review examining the role of antibiotics in the acquisition of hospital acquired CDI, Thomas et al. (2003) suggests that methods used in the majority of studies demonstrating a link between antibiotics and CDI estimated the risk of CDI in hospitalised patients when exposed to a number of factors, rather than to antibiotic therapy alone. Similarly, a lack of *a priori* sample size calculation, incorrect control groups, inadequate control of confounders and diagnostic bias were particular threats to validity of the data (Thomas et al., 2003). The conclusion of the systematic review was that only two studies in the review McFarland, Surawicz and Stamm (1990) and Chang and Nelson (2000) were considered valid in providing evidence of the role of antibiotics in development of hospital acquired CDI (Thomas et al., 2003).

The cohort study undertaken by McFarland et al. (1990) found an increased risk of CDI after exposure to cephalosporins for 1 - 7 days (RR 2.82) and exposure to penicillin (RR 3.52) for 8-14 days, after adjusting for age and severity of illness (McFarland et al., 1990). The study by Chang and Nelson (2000) examined the risk antibiotics pose in causing CDI by using a retrospective cohort study design. After multivariate analysis, exposure to the antibiotic clindamycin (RR 4.22) and the number of antibiotics taken (RR 1.49) were found to be significant risk factors for CDI (Chang & Nelson, 2000). In the majority of studies, regardless of their methodological imperfections, clindamycin, fluroquinolones, third-generation cephalosporins, and penicillins have been considered to pose the greatest risk for CDI, however nearly all classes of antimicrobials have been implicated (Owens, Donskey, Gaynes, Loo, & Muto, 2008; Thomas et al., 2003). The final risk factor for CDI explored in this section focuses on the healthcare environment and its role in the transmission of CDI.

The healthcare environment and transmission of *Clostridium difficile*

The primary mode of transmission of *C.difficile* is person to person via the faecal-oral route (National Health and Medical Research Council, 2010). *Clostridium difficile* can exist in a vegetative or spore form, with spores acting as a reservoir through persistence in the environment for several months. In turn, this places patients at risk through contamination of healthcare workers' (HCWs) hands and of regularly touched items or fomites (Dumford et al., 2009; Mayfield, Leet, Miller, & Mundy, 2000; Stuart et al., 2011).

Individuals with symptomatic CDI shed *C.difficile* spores into the environment. In heavily contaminated environments spores may be aerosolised by movement of HCWs and patients, allowing widespread dissemination (Best et al., 2010). Environmental contamination may in turn play a role in CDI transmission through colonisation pressure. Similar theories have been used to explain transmission of organisms such as MRSA and vancomycin-resistant enterococcus (VRE) (Bonten et al., 1998; Eveillard et al., 2005; Merrer et al., 2000; Puzniak, Mayfield, Leet, Kollef, & Mundy, 2001). *Clostridium difficile* is transmitted in a similar fashion to VRE and hence it is thought that colonisation pressure and the environment play an important role in CDI transmission.

To prove that colonisation pressure is a risk factor in CDI transmission, a cohort and nested case control study of 36,000 admissions was undertaken. Following multivariate logistic regression, the authors suggest that the greater the number of patients with CDI there are on a hospital ward, the more likely it is that other patients will acquire the organism (Dubberke et al., 2007). Environmental contamination with spores is now well accepted as a risk factor for the acquisition of *C.difficile*. It is thought that as the level of environmental contamination increases, so too does the amount of *C.difficile* on the hands of healthcare workers and frequently touched items, posing a risk of transmission (Dancer, 2009). Contamination of the environment can act as a reservoir, leading to potential transmission and subsequent ingestion of spores by susceptible persons. In turn, *C.difficile* spores can germinate and cause asymptomatic carriage. Events that subsequently alter the bowel flora, such as antimicrobial exposure, can trigger alteration in bowel flora and CDI. Therefore, the role of environmental cleaning is increasingly becoming recognised as an important factor in CDI prevention, given

its potential role in breaking the cycle of CDI transmission. The cycle of CDI is summarised in Figure 10.

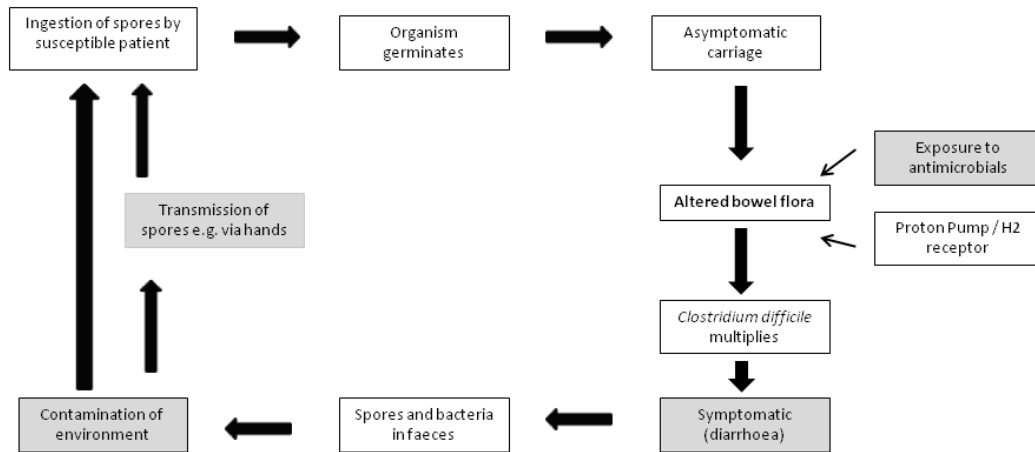


Figure 10. The cycle of *Clostridium difficile* infection. Shaded boxes denote the stages where infection can be potentially prevented.

Summary

Having explored the background to CDI in section 4.2 and the risk factors for CDI in this section, it is evident that there are opportunities for prevention of CDI as seen in Figure 10. Improved antimicrobial usage and control, often termed ‘antibiotic stewardship’ is one strategy in CDI prevention. The use of contact precautions, such as isolating symptomatic individuals and the use of gloves and gowns, also has the potential to minimise contamination of *C.difficile* bacteria and spores. Two further strategies to prevent CDI include the prevention of spore transmission among patients by healthcare workers, through processes such as hand hygiene and cleaning the environment, to minimise colonisation pressure and the risk of subsequent transmission. In Chapter 2, the impact that HAIs have on individuals and the health services was briefly discussed (section 2.3). To explore this further, the next section of this chapter presents the literature examining mortality and CDI.

4.3 Literature review

4.3.1 Introduction to the literature review

As already stated, the incidence and severity of CDI appears to be increasing, particularly in the northern hemisphere (Khanna & Pardi, 2010). In the United Kingdom, the number of death certificates in England and Wales citing *C.difficile* rose from 1416 in 2002 to 6480 in 2006 (Office for National Statistics, 2008). The increase in incidence appears to be driven by a number of factors, including large outbreaks of CDI in hospitals, a change in circulating strains of *C.difficile*, such as *C.difficile* ribotype 027 and 006 and other host and environmental factors as described in section 4.2.5 (Cartman et al., 2010; Healthcare Commission, 2006, 2007; Healthcare Inspectorate Wales, 2009; Kelly & LaMont, 2008).

This section presents a review of studies that have investigated mortality and CDI in hospitalised patients. The purpose of this section is to describe current gaps in the literature and the various methods used to examine mortality in this population.

4.3.2 Search strategy

The literature was accessed through searches on Medline and Pubmed limited to the period from 1st January 2005 to 30th April 2011. The review was limited to these years to reflect the recently changing epidemiology of *C.difficile*. Other limits included only searching literature published in English and studies involving humans. Key search words used were “*Clostridium difficile* AND mortality” and “*Clostridium difficile* AND death”. These searches were combined with duplicate studies removed. The initial search yielded 362 articles. A first review of these articles was undertaken. Only case control, cohort designs or reviews were included. Additionally, articles were only included if they examined mortality of all hospitalised patients and were not limited to a CDI in a specific patient group (for example a person with cancer) and did not use CDI as a comparison group, for example mild versus severe CDI and related mortality. The rationale for excluding such articles was to ascertain a better understanding of CDI in the general hospitalised population, not restricted to those with a specific illness. Following this first review, a total of 303 articles were excluded and

59 articles remained. In a second review of these 59 remaining articles, studies which did not examine CDI mortality at fixed intervals, for example 30 or 90 days, were excluded. The inclusion of studies that documented mortality at fixed intervals was chosen in an attempt to assist in the pooling of data during data analysis. A total of 26 articles remained after the second review. Figure 11 provides a summary of the search strategy process using the PRISMA as the basis for presentation (Moher et al., 2009). Table 11 provides a list of the included articles.

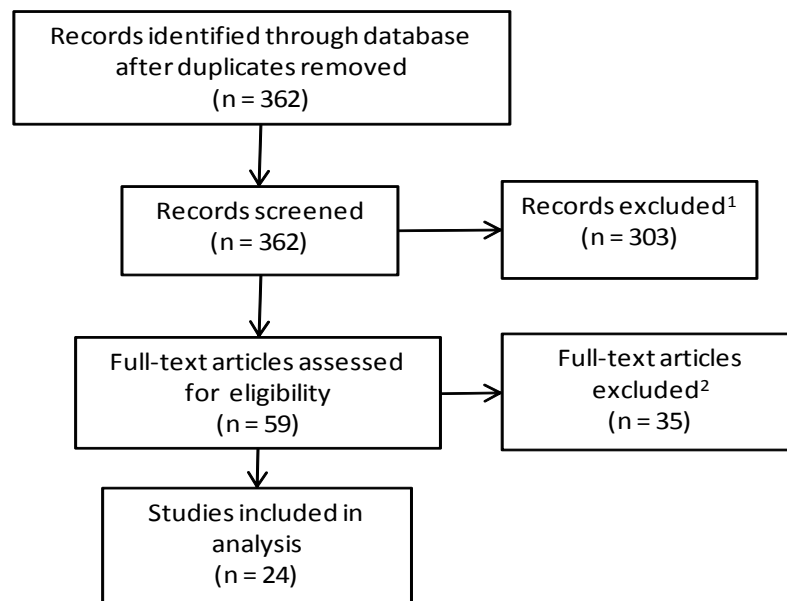


Figure 11. Summary of the search strategy used in the review examining mortality and *Clostridium difficile* infection. ¹ Articles were excluded if they were not case control, cohort or reviews or did not examine mortality in hospitalised patients. ² Articles were excluded if they did not examine mortality at fixed intervals.

A review of mortality due to CDI was recently published, however this only included studies from 2000 to March 2010 that contained data on attributable mortality or circumstances where attributable mortality could be calculated from the data included (Karas, Enoch, & Aliyu, 2010). All articles identified in the review published by Karas et al. (2010) and published since 2005 were identified through the search strategy described above and were included in this review.

4.3.3 Findings from the literature review

The section commences by providing an overview of the characteristics of the included studies, before discussing the reported mortality. To appreciate the reported mortality and to inform future research examining mortality and CDI, strengths and weaknesses of the study design, data analyses, case definitions and the data items collected from the included studies are also discussed. These particular topics are important considerations for future research on mortality when attempting to control for bias in primary research, and for future systematic reviews (Karas et al., 2010).

Overview

Of the 24 articles included, one was a review. Eighteen studies reported mortality at 30 days or less, with 11 studies reporting mortality at further end points, predominantly 90 or 180 days. One study which reported 30 days mortality, used 30 days post-discharge as the definition (Outi Lyytikainen et al., 2009). The choice of 30 days post-discharge as the method to examine mortality was made due to limitations in available data and should be noted when considering results from this study. Four studies examined in-hospital mortality, in addition to 30-day mortality. The reported mortality in each of these studies is detailed in Table 11 and is explored in more detail later in this section.

The majority of studies were undertaken in the United States (9), United Kingdom (7) or Canada (3). No studies were included from an Australian setting. As there are different circulating strains of CDI in different countries, this is an important issue because mortality from persons with CDI in Australia may differ from these countries. A higher incidence of CDI compared to other countries with data on CDI incidence including Australia, coupled with an increased focus on CDI due to high profile hospital outbreaks, may provide insight into explaining the number of included articles from these countries. These studies did not meet my inclusion criteria and were excluded as the participants were from a selected clinical group. For example, they had a specific strain of CDI or had severe CDI. Conversely, my review did identify and include 14 studies not used by Karas et al. (2010). The primary

reason for this discrepancy is the inclusion of more recent publications, with 11 of these 14 published in the past two years. Also, the review by Karas et al. (2010), was limited to studies that calculated attributable mortality.

Table 11

Summary of included articles in the review examining mortality and Clostridium difficile infection

Author	Study type	Country	30 day all-cause mortality (population to which mortality refers)	Mortality at any other endpoint (population to which mortality refers)
Arvand, Hauri, Zaiss, Witte, & Bettge-Weller, 2009	Case series	Germany	25% (persons who had CDI)	-
Bhangu, Bhangu, Nightingale, & Michael, 2010	Case series ¹	UK	38% (persons who had CDI)	-
Bishara, Peled, Pitlik, & Samra, 2008	Cohort	Israel	15% (persons who had CDI) 11.5% (persons who didn't have CDI)	-
Cadena et al., 2010	Cohort	US	16% (persons who had CDI)	45% at 90 days (persons with relapsing CDI) 23% at 90 days (persons with non-relapsing CDI)
Chung et al., 2010;	Cohort	Taiwan	23.5% (had CDI and mild diarrhoea) 25.8% (had CDI and prolonged diarrhoea) 23.3% (all persons who had CDI)	37.2% IHM (all persons who had CDI)
Cloud, Noddin, Pressman, Hu, & Kelly, 2009	Cohort	US	-	12.1% IHM (all persons who had CDI) 13.6% IHM (persons who had CDI and NAP-1 strain) 12.4% IHM (persons who had CDI and non-NAP-1 strain)
Dubberke et al., 2008	Cohort	US	-	38% at 180 days (persons who had CDI) 12% at 180 days (persons who didn't have CDI)
Fenner et al., 2008	Case series	Switzerland	9% (persons who had CDI)	-
Gasperino et al., 2010	Cohort	US	16% (persons who had CDI) 5% (persons who didn't have CDI)	20% (persons who had CDI) 8% (persons who didn't have CDI)
Gravel et al., 2009	Case series	Canada	16.3% (persons who had CDI) 5.7% attributable mortality*	-
Gulihar, Nixon, Jenkins, & Taylor, 2009	Cohort	UK	19% (persons who had CDI) 12%(persons who didn't have CDI)	67% at 180 days (persons who had CDI), 27% at 180 days (persons who didn't have CDI)
Karas, Enoch, & Aliyu, 2010	Review	UK	Review	Review
Kenneally et al., 2007	Cohort	US	36.7% (persons who had CDI) 30.6% (persons who didn't have CDI) 6.1% attributable*	-
Labbe et al., 2008	Cohort	Canada	16% (persons who had CDI with a non 027 ribotype) 29% (persons who had CDI with a 027 ribotype)	-

Loo et al., 2005	Cohort	Canada	23.9% (all persons who had CDI) 24.8% (persons who had CDI) Not stated for controls (persons without CDI) 6.9% attributable**	-
Lyytikainen et al., 2009	Case series	Finland	--	14% at 30 days post-discharge
Marra, Edmond, Wenzel, & Bearman, 2007	Case series ¹	US		17.2% at 14 days 27.6% IHM
McGowan et al., 2011	Cohort	UK	3.4% (persons who had CDI, aged <40 years) 11.9% (persons who had CDI, aged 40-49) 10.1% (persons who had CDI, aged 50-59) 28.8% (persons who had CDI, aged 60-69) 27.6% (persons who had CDI, aged 70-79) 36.2% (persons who had CDI, aged 80-89) 41.2% (persons who had CDI, aged <90)	
Musher et al., 2005	Case series	US	-	27% at 90 days
Pant et al., 2010	Case series	US	13.6% (persons who had CDI)	-
Shears, Prtak, & Duckworth, 2010	Case series	UK	24.7% (persons who had CDI)	30.0% at 90 days (persons who had CDI)
Sundram et al., 2009	Cohort	UK	14.4% (persons who had CD) at 28 days ***	
Wilson et al., 2010	Cohort	UK	35.1% (persons who had CDI with a non O27 ribotype) 38.2% (persons who had CDI with a O27 ribotype)	-
Zilberberg, Shorr, Micek, Doherty, & Kollef, 2009 [#]	Cohort	US	26.9% (persons who had CDI aged < 65 years) 45.2% (persons who had CDI aged ≤ 65 years)	-

Note: IHM = in hospital mortality. US = United States. UK = United Kingdom.¹ The authors state their study was a cohort study. Listed as a case series in this table as only persons with CDI were included in the study population. *Attributable mortality was defined by the authors as crude mortality in persons who had CDI minus crude mortality in persons who had CDI. ** Attributable mortality was determined by two physicians who judged independently whether CDI was an attributable cause. *** Attributable mortality was determined by an assessment by a hospital epidemiologist or a physician to determine whether the death was attributable to CDI. ~ This figure was calculated from data presented. Data for controls was not reported and could not be calculated. # Secondary analysis of Kenneally et al., 2007.

Mortality at fixed intervals

Despite limiting inclusion criteria to studies with fixed endpoints, as previously described, there was considerable variability in the study designs, exclusion criteria and data collected. This made the pooling of data for analysis impossible and limited the interpretation. All-cause mortality at 30 days varied considerably among the included articles, with reported mortality ranging from 9% to 38% as shown in Table 11. Three studies reported all-cause mortality at 90 days with a range of 27% to 30% (Cadena et al., 2010; Musher et al., 2005; Shears, Prtak, & Duckworth, 2010). Similarly, three studies reported attributable mortality at 30 days, varying from 5.7% to 6.9% (Gravel et al., 2009; Kenneally et al., 2007; Loo et al., 2005). In-hospital mortality was reported in four studies and ranged from 8% to 37.2% (Chung et al., 2010; Cloud, Noddin, Pressman, Hu, & Kelly, 2009; Gasperino et al., 2010; Marra, Edmond, Wenzel, & Bearman, 2007).

Eighteen studies documented all-cause mortality at 30 days, or 28 days in the case of the study undertaken by Sundram et al. (2009). The study undertaken by Sundram et al. (2009) examined two strains of *C.difficile* (027 and 106) and their respective associated mortality. The total cohort size was larger than these two groups combined and therefore it was unclear whether participants with other strains of CDI died. Acknowledging the limitations of different study designs and excluding the study undertaken by Sundram et al. (2009), a total of 2041 out of 7774 persons (26.3%) died within 30 days of CDI diagnosis. These figures include those persons identified with CDI in these studies who died within 30 days (all-cause mortality) (Arvand, Hauri, Zaiss, Witte, & Bettge-Weller, 2009; Bhangu, Bhangu, Nightingale, & Michael, 2010; Bishara, Peled, Pitlik, & Samra, 2008; Cadena et al., 2010; Chung et al., 2010; Fenner et al., 2008; Gasperino et al., 2010; Gravel et al., 2009; Gulihar, Nixon, Jenkins, & Taylor, 2009; Kenneally et al., 2007; Labbe et al., 2008; Loo et al., 2005; McGowan et al., 2011; Pant et al., 2010; Shears et al., 2010; Wilson et al., 2010; Zilberberg, Shorr, Micek, Doherty, & Kollef, 2009).

Data analysis and presentation of results

The manner in which mortality was analysed and presented in the studies differed, however there were some similarities. In two cohort studies, participants were divided into those with CDI and those without (Gasperino et al., 2010; Loo et al., 2005). Other cohort studies divided participants into two groups: survivors and non-survivors (Bhangu et al., 2010; Kenneally et al., 2007; Wilson et al., 2010). Regardless of the methods used, similar data analyses occurred and involved using 30 day mortality as the primary outcome and using logistic regression for the controlling of potential confounders. Commonly, the use of Chi squared or Fisher's Exact Test were used for categorical data analysis and Student *t* test for continuous variables (Cadena et al., 2010; Chung et al., 2010). Kaplan-Meier survival analysis was used in a study undertaken by Bishara et al. (2008). Several studies used adjusted odds ratios to make comparisons between groups, following multivariate analysis (Fenner et al., 2008; Kenneally et al., 2007; Labbe et al., 2008; Marra et al., 2007; Wilson et al., 2010). Not all studies undertook adjustment for variables when determining mortality rates. Despite collecting basic demographic data on cases, Charlson co-morbidity data and exposure to recent medication such as antimicrobials, the study undertaken by Chung (Chung et al., 2010) did not adjust for any variables in the calculation of hospital mortality and all-cause mortality.

In addition to studies comparing survivors with non-survivors or those with and without CDI, some studies enhanced comparisons by stratifying analyses by age group (Zilberberg et al., 2009). In a retrospective cohort study, McGowan et al. (2011) examined the difference in mortality by age groups divided into decades, with all aged less than 40 years old grouped together. A significant difference in 30 day mortality was found for the age groups (decades) above 60 years old, using the <60 years old as the reference group ($X^2 = 65.82$; df: 2; $P < 0.05$). However, the study did not examine the effect of co-morbidity on outcomes and the authors made a recommendation for inclusion of this in future research (McGowan et al., 2011). Similar to McGowan et al. (2011), a prospective multi-centred study of 1430 participants demonstrated that age specific mortality attributed to CDI increased sharply after 60 years of age (Gravel et al., 2009). These two studies demonstrate the importance of collecting and analysing data related to age.

Some studies presented data comparing groups based on the causative strain of the CDI (Labbe et al., 2008; McGowan et al., 2011; Sundram et al., 2009). The retrospective cohort study undertaken by Labbe et al. (2008) found that patients affected by *C.difficile* ribotype 027 were twice as likely to die within 30 days of diagnosis than patients affected with other ribotypes. Similar results were demonstrated in a study comparing persons with CDI caused by ribotype 027, 106 and all other ribotypes (Sundram et al., 2009). Importantly not all studies comparing the effect of different *C.difficile* strains have found an effect on mortality (Cloud et al., 2009). It is therefore important for any studies examining mortality and CDI to include data on the relevant strains of *C.difficile* wherever possible.

Regardless of how participants were grouped, some commonalities were found in the way in which data were analysed. The majority of studies used a statistical model involving univariate analysis, followed by the development of a multivariable or regression model. Survival analysis was also used frequently in some studies.

Case definitions

The majority of studies used the identification of toxin A or B via EIA or ELISA as the case definition of CDI. There were variations in the approach taken as to which faecal samples were tested for *C.difficile*, however the majority only tested patients suffering diarrhoea (Bishara et al., 2008; Chung et al., 2010; Dubberke et al., 2008; Gasperino et al., 2010; Gravel et al., 2009; Marra et al., 2007; McGowan et al., 2011; Sundram et al., 2009; Wilson et al., 2010). The CDI case definitions varied and the impact such variation has on reported mortality remains unknown. It would, however, be logical to assume that a less sensitive laboratory detection approach may identify fewer cases in a given population and this has the potential to underestimate the incidence of CDI and thus the total number of persons who died after having CDI.

Similar to variation in CDI definitions, the data collected in each of the studies varied considerably. Data collected include gender, age, co-morbidities, length of stay in hospital prior to CDI, exposure to drugs including antimicrobials, clinical symptoms and whether the person was a resident of a nursing home. In the vast majority of studies, gender and age of participants was collected.

Data collection

A co-morbidity score such as the Charlson co-morbidity index, was calculated in a limited number of studies (Chung et al., 2010; Cloud et al., 2009; Dubberke et al., 2008; Kenneally et al., 2007; Labbe et al., 2008; Loo et al., 2005; Marra et al., 2007; Wilson et al., 2010). A number of studies used another tool such as the American Society of Anaesthesiologists (ASA) grade, or Acute Physiology and Chronic Health Evaluation (APACHE) II, and a number of studies collected data on co-morbidities but did not specify how or why they choose these co-morbidities (Bishara et al., 2008; Cadena et al., 2010; Fenner et al., 2008; Goorhuis et al., 2007; Gravel et al., 2009; Sundram et al., 2009; Zilberberg et al., 2009). The admitting diagnosis was collected for two studies (Loo et al., 2005; Marra et al., 2007). This variation in the use of co-morbidity data makes comparison between studies challenging and potentially limits the validity of results. Co-morbidities were shown to influence mortality in patients with CDI (Bishara et al., 2008; Kenneally et al., 2007). In one instance where co-morbidity data were not collected, the researchers recognise this limitation and suggest this is an area to be included in future research (McGowan et al., 2011). Conversely, one study used electronic data to attempt to collect ASA grades, but acknowledged that information was found to be incomplete (Gulihar et al., 2009). Patients with incomplete data were censored, therefore this may have introduced an element of bias as only persons with an ASA grade, that is, had anaesthesia, were included.

The length of stay in hospital prior to CDI was collected in a number of studies (Fenner et al., 2008; Goorhuis et al., 2007; Gravel et al., 2009; Kenneally et al., 2007; Labbe et al., 2008; Zilberberg et al., 2009). In one study there was a trend of increasing mortality with increasing length of stay (Shears et al., 2010). Several studies collected data on exposure to antibiotics

(Bishara et al., 2008; Cadena et al., 2010; Chung et al., 2010; Fenner et al., 2008; Labbe et al., 2008; Loo et al., 2005; Musher et al., 2005; Sundram et al., 2009; Zilberberg et al., 2009). Some of these studies reported an association between antibiotics exposure and increased risk of CDI (Cadena et al., 2010; Chung et al., 2010; Loo et al., 2005). Exposure to other drugs such as proton pump inhibitors or steroids and information on interventions such as surgery or the use of a nasogastric tube were reported in some studies (Bishara, et al., 2008; Cadena, et al., 2010; Chung, et al., 2010; Fenner, et al., 2008; Goorhuis, et al., 2007; Loo, et al., 2005; Sundram, et al., 2009; Zilberberg, Shorr, et al., 2009). The manner in which data were collected on drug therapy, surgery and nasogastric tube exposure was not reported consistently, with different time periods and a range of procedures used. Further, in these studies, mortality was one outcome being examined alongside other variables, such as risk factors for CDI. If a study was to examine mortality following CDI as the single outcome, then the efficacy of including data on some of the data described above could be limited, particularly as there is no standardised method or definition used.

Three studies collected data on whether participants were nursing home residents (Bishara et al., 2008; Gasperino et al., 2010; Wilson et al., 2010). If a study was to only examine healthcare associated/healthcare facility onset CDI, the usefulness of collecting these data becomes questionable. Clinical symptoms such as temperature, white cell count or severity of disease were collected in a number of studies in various ways (Bhangu et al., 2010; Fenner et al., 2008; Gasperino et al., 2010; Kenneally et al., 2007; Labbe et al., 2008; Marra et al., 2007; Musher et al., 2005; Wilson et al., 2010). The purpose of some of these studies was to examine mortality according to clinical risk factors such as albumin level and urea, explaining why such data was collected (Bhangu et al., 2010).

4.3.4 Summary of literature review

There was considerable heterogeneity among the studies included in this review. Differences were found in study design, patient groups and data collected from participants. Some studies lack demographic and co-morbidity data, a similar finding to the review undertaken by Karas (2010). In general, all-cause 30 day mortality appeared to be high, with 15 studies indicating

a mortality of 15% or greater. Several studies demonstrated that age was a risk factor for mortality indicating the need to adjust for such data in future studies.

There were no articles from an Australian setting or a setting from the southern hemisphere included in this review. Even accepting all-cause mortality at the low end of the included studies in this review, CDI clearly has a significant impact on hospitalised patients. Studies investigating the mortality of CDI in an Australian setting are needed so that a picture of this disease in this region can be understood. Future studies examining the mortality of CDI should include basic demographic data, reporting of mortality at seven days, 30 days and 90 days after the first diagnosis of CDI, the use of exclusion criteria and acquisition definitions as recommended in the international literature, and the studies should use a co-morbidity index score such as the Charlson co-morbidity index. In doing so, pooling of data becomes possible and comparisons between studies will be easier. Similarly, the addition of data on antibiotic exposure will assist future meta-analysis on the role of antibiotics and CDI. The second study of this thesis, examining mortality and CDI in an Australian setting, will now be presented.

4.4 Objectives and research questions

The objectives for the second study are to describe the risk of mortality associated with CDI and to explore potential limitations in estimating mortality associated with CDI when current international surveillance definitions for CDI are applied. To address these objectives, the following research questions were devised:

1. During the calendar years 2007 to 2010, for patients hospitalised in a Tasmanian acute public hospital for more than 48 hours and aged two years or older:
 - a. What percentage of people who had an episode of CDI died within 30, 60, 90 and 180 days of admission to hospital?
 - b. What is the risk of a person diagnosed with CDI during their hospital stay dying within 30, 60, 90 and 180 days, compared to persons without CDI?

2. What are the potential limitations of using CDI surveillance definitions when examining the risk of death in people who had an episode of CDI?

4.5 Methods

4.5.1 Study design

To address the research question, a non-concurrent cohort study design was used.

4.5.2 Setting and timeframe

The RHH in Hobart, Australia, was the setting for this study. The RHH is the only tertiary hospital in Tasmania and consists of approximately 500 inpatient beds. An overview of Tasmania and the health services available was detailed in Chapter 1. The RHH is a publicly funded hospital and is serviced by one microbiology department. The timeframe for the study was the calendar years 2007 to 2010.

4.5.3 Definition and selection of cohort

The source population for the study cohort included all persons hospitalised for 48 hours or greater and aged two years or older between 1st January 2007 and 30th December 2010. The exposed group included all patients in the source population who had CDI during their hospitalisation between 1st January 2007 and 30th December 2010. A comparison group was sampled on a two to one basis from among those members of the source population without CDI at any time during their stay, matching on sex, age group (decade of life) and date of hospital admission of patients in the exposed group.

The selection of the exposed and non-exposed groups will now be explored individually.

Selection of the exposed (persons with CDI)

As discussed in the previous chapter, there are several ways to define an episode of CDI. In Australia, a national surveillance definition for CDI was developed by ACSQHC (Australian Commission on Safety and Quality in Health Care, 2010). *Clostridium difficile* infection is defined as an infection in a hospitalised patient who has a positive stool sample result for *C.difficile*, using either a laboratory assay (Enzyme immunoassay or *polymerase chain reaction*) detecting toxin A and or toxin B, or culture, resulting in the isolation of *C.difficile* that is subsequently shown to produce toxin A and/or toxin B.

During the full study period, the RHH microbiology department tested all diarrhoeal samples from hospitalised patients, regardless of reason for hospitalisation for *C.difficile*. Diarrhoea was defined as an unformed stool that took the shape of the container.

Until 30 August 2007, the RHH microbiological department cultured all faecal samples. Faeces samples that grew *C.difficile* were tested for toxin B using a cell culture cytotoxin assay (CCNA). From September 2008, samples that were culture positive, but CCNA negative then had a further CCNA performed on the organism, that is to say that the same test was performed specifically on the organism (McGregor, 2011).

In September 2010, the RHH microbiology department implemented a further change to the testing methodology for *C.difficile*. While all diarrhoeal samples from hospitalised patients at the RHH were still tested for *C.difficile* and all were still cultured, from 1st September, faecal samples were tested for glutamate dehydrogenase (GDH) antigen assay using Quik Check (Techlab). Those samples that were GDH positive and toxin positive were considered to be diagnostic of CDI. Samples that were GDH positive but toxin negative were subsequently tested using PCR. Samples that were PCR positive were reported as having pathogenic CDI, whilst those that were negative were considered to have the organism, but not the toxin, and therefore were considered as having non-pathogenic *C.difficile*. Samples that were GDH negative, toxin negative but culture positive were tested using PCR, whilst samples that were GDH negative, toxin positive were also tested using PCR. In both these situations, samples

that were PCR positive were considered to have CDI (Cooley, 2011; McEwan, 2011). Figure 12 summarises the *Clostridium difficile* testing process at the RHH microbiology department.

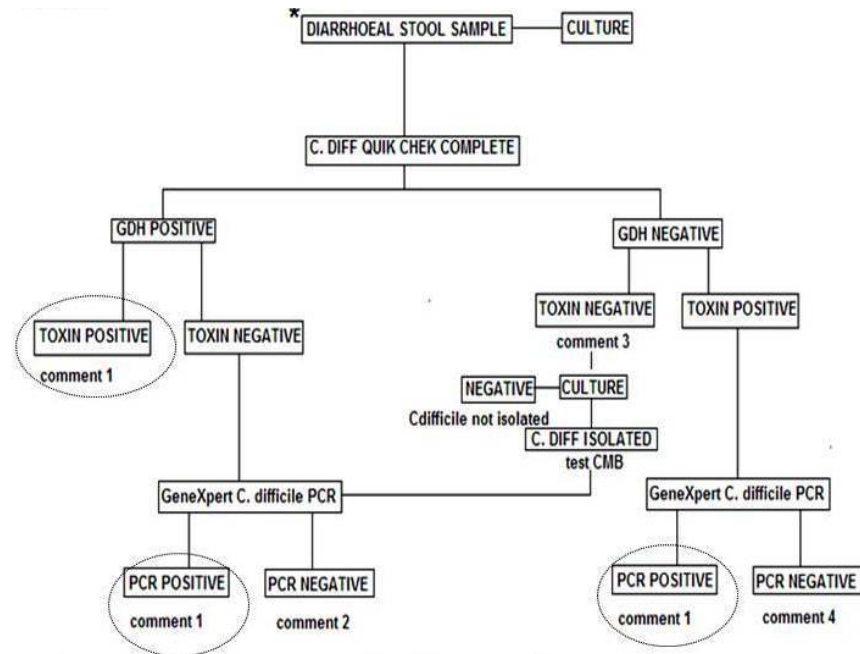


Figure 12. Algorithm for *Clostridium difficile* testing at the Royal Hobart Hospital. Adapted from McEwan (2011). Comment 1 = *Clostridium difficile* detected and toxin producing. Comment 2 = *Clostridium difficile* detected but has not been shown to be toxin producing. Comment 3 = preliminary report, initial screening tests for *Clostridium difficile* are negative. Comment 4 = indeterminate result and a repeat test is requested. GDH = glutamate dehydrogenase. PCR = polymerase chain reaction. CMB = cooked meat broth. Dotted ovals indicate situations where the test indicates *Clostridium difficile* infection. *Diarrhoeal stool sample refers to faeces that take the same shape as its container.

Despite the changes in testing methodology, there are two important points for noting. First, all the methods employed by the RHH microbiology during this study period are highly sensitive, particularly as all diarrhoeal faecal samples are cultured for *C. difficile*. Second, in all situations, the laboratory was testing for *C. difficile* toxin using an assay, either CCNA or PCR. Issues relating to the detection of CDI were described in more detail in section 4.2.2. Therefore, the change in methodology is not likely to have increased or decreased sensitivity or specificity in diagnosing the exposed.

For the purposes of this study, the exposed group were all persons hospitalised at the RHH for more than 48 hours between 1st January 2007 and 30th December 2010 inclusive, and who were diagnosed as having CDI using the national definition for CDI described earlier. The laboratory processes for identifying persons with CDI at the RHH enabled a direct translation of a laboratory result into defining an exposed individual. As discussed in section 4.2.2, episodes of CDI that occur more than 48 hours after admission are often referred to as healthcare associated, healthcare facility onset (HCA HFO) episodes of CDI (L. Clifford McDonald, et al., 2007; H. Van Gessel, McCann, R., Peterson, A., Cope, C., Wilkinson, I., Mitchell, B., Wells, A., Kennedy, B., Hall, L., Gallard, J., Lee, R., Cooley, L., Cruickshank, M., Greig, S., Hanley, E., Willows, K., Board, N., 2011). Any positive stool sample for *C.difficile* occurring in patients less than two years old or occurring within eight weeks of the last positive test was excluded (Australian Commission on Safety and Quality in Health Care, 2010). All infectious episodes included in this study are HCA HFO episodes.

In this study, the term ‘persons who had CDI’ may be used to describe the exposed, in situations when the use of this term would make the sentence unclear.

Selection of the non-exposed (persons who did not have CDI)

From the study cohort a subset of non-exposed persons was selected to assess the relationship between CDI and increased mortality above that which would be expected among hospitalised individuals of the same age and sex. For each person exposed to CDI, two persons from the source population who did not have CDI at any time during their stay were chosen, matching on sex, age group (decade in which a person was born) and period of hospital admission of patients who had CDI. If the matching process resulted in more than two persons without CDI being identified from the source population, then a random selection process was used to limit the selection to two individuals. The choice of matching criteria was decided following substantial consideration of the relevant issues. As discussed in the background to this chapter, age is a risk factor for CDI, therefore it was considered that matching by age group was important. The study period covered several years, therefore,

potential changes which may affect the risk of CDI and mortality needed to be considered. Such changes include variation in staffing, differing infection control policies and priorities, and variations in processes that may affect CDI such as hand hygiene and antimicrobial prescribing. Therefore, if the admission date for the non-exposed were to be substantially different to the exposed, controlling for a range of additional variables would be required. This would be inherently difficult to undertake, given the inability to obtain accurate and consistent data on additional variables. The relative importance of each of these variables is difficult to quantify. With these issues in mind, matching by admission period occurred, with each admission period being one quarter and representing a season, as there is strong seasonal weather variation in Tasmania. The final matching criterion used was sex as this has been reported as a potential risk factor for CDI (Dial, 2005). More details regarding the matching process are detailed in section 4.5.4.

4.5.4 Data collection

This section on data collection is divided into two parts. The first part describes the data collection process and the second section outlines the specific data items collected during each step of the process and the rationale for collecting these items.

Process

Data were retrieved from four different sources. These sources comprised data from:

1. the TIPCU
2. the Clinical Coding department of the RHH
3. a review of the patient administration system
4. a review of medical records of each participant by the researcher.

Figure 13 provides a summary of the data collection process and sources of data. Each of the data collection steps will now be explored in more detail.

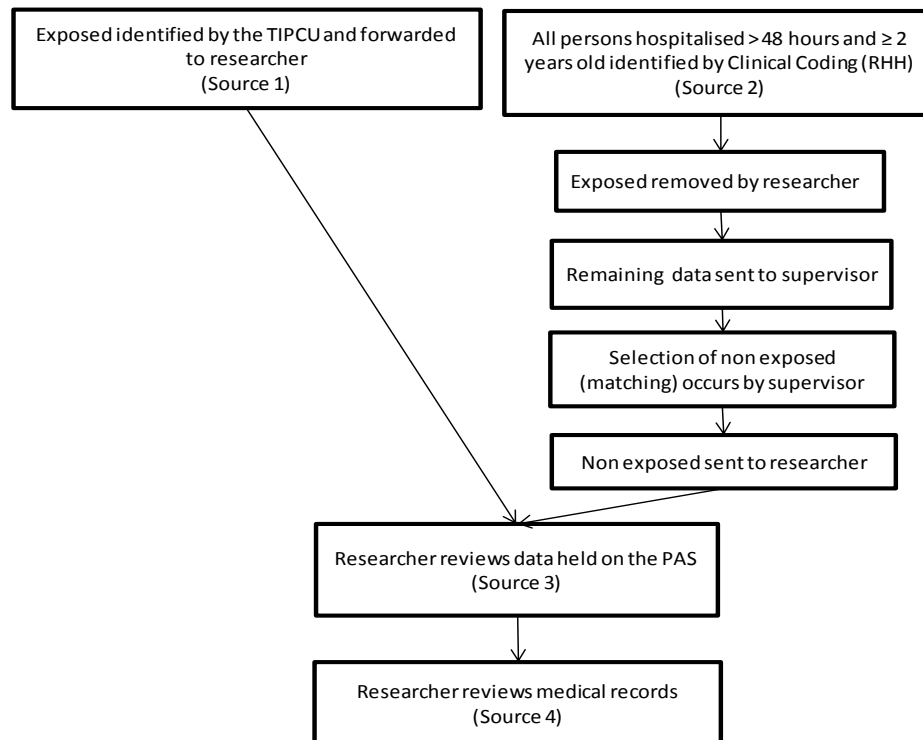


Figure 13. Flow chart illustrating the data collection process and sources of data. PAS = patient administration system. CDI = *Clostridium difficile* infection. RHH = Royal Hobart Hospital.

The TIPCU is a unit of the Tasmanian Health and Human Services department and is a data repository for all episodes of CDI occurring at the RHH. Data on episodes of CDI were provided to the TIPCU direct from the RHH microbiology department using definitions described in section 4.5.3. The TIPCU provided me with data on all persons who had CDI identified at the RHH between the 1st January 2007 and the 30th December 2010. Only infections occurring in persons who had been hospitalised greater than 48 hours and aged two years or older were provided by the TIPCU.

To select the non-exposed, all persons admitted to the RHH for more than 48 hours during the study period, were identified by the Clinical Coding department at the RHH at my request. Data were provided in an Excel spread sheet and comprised all patient admissions, including the exposed. The exposed were identified and removed. I then copied the data from the Excel spread sheet into SPSS and sent this database to my supervisor. The process of

matching was then undertaken independently by my supervisor to ensure no potential bias was introduced.

The matching process involved the removal of a number of entries because their recorded admission period was in January or February 2007, when there were no episodes of CDI. Further entries were excluded because their gender was intersex or unknown. Cross tabulation for both the exposed and non-exposed databases was performed, enabling the identification of the number of exposed in each sub group that were being matched (i.e. admission period, age group and sex). Three potential non-exposed persons were then randomly selected, using a computerised random selection process, to match each exposed person. Two potential non-exposed were sent to myself from my supervisor, and the third retained as a backup, if required. The third was used in situations where the medical records of either of the first two persons could not be located or where the same person had been readmitted (to prevent the same control being used more than once).

Once I had obtained the list of the exposed from the TIPCU and the non-exposed from my supervisor, a review was performed of the records held on the RHH patient information system for both the exposed and non-exposed. Similarly, I undertook a review of the medical records relating to the admission period at the RHH for the study group. Therefore, I was aware of whether the medical record belonged to an exposed or non-exposed person i.e. this process was not blinded. The review of the medical records for admission period data was a quality assurance check against the data provided by the TIPCU and Clinical Coding department (Table 12). The data items collected during this process and the rationale for collecting some of the items are provided shortly.

Data collected

This section will contain information on the specific data items collected from each of the various sources of data, as previously described. The rationale for the manner in which some data items were collected will also be explained in this section. More specifically, the manner in which the Charlson co-morbidity (CCI) index was calculated, and the determination of

exposure to antibiotics will be discussed in more detail. Table 12 provides a summary of the items collected during the data collection process, the manner in which they were defined and the source of each item. The data were collated in Microsoft Excel.

Table 12

Data collected and source

Data field	Definition	Source of data	
		Exposed	Non-exposed
Date of birth	Date of birth	TIPCU**	RHH Clinical Coding*
Sex	Defined as male, female or intersex	TIPCU**	RHH Clinical Coding*
Age	Age in years at time of specimen collection	TIPCU**	RHH Clinical Coding*
Admission date	Date of admission to the RHH	TIPCU**	RHH Clinical Coding*
Discharge date	Date of discharge from RHH or date of death (whichever is first)	Researcher- review of medical records & PAS	Researcher- review of medical records & PAS
Date of death (if applicable)	Date of death up to 180 days post-admission date [^]	Researcher- review of medical records & PAS	Researcher- review of medical records & PAS
CCI score	Charlson co-morbidity index score. Described in section 4.5.4	Researcher- review of PAS	Researcher- review of PAS
Diagnosis Related Group	Methods used to categorise and characterise episodes of care received by patients admitted to hospitals.***	Researcher- review of PAS	Researcher- review of PAS
Date infection commenced	Date of specimen collection	TIPCU	N/A
Strain of <i>C.difficile</i>	Ribotype of <i>C.difficile</i>	TIPCU	N/A
Exposure to antibiotics	Received oral or intravenous antibiotics during admission period, up to date of infection commencement for cases.	Researcher- review of medical records	Researcher- review of medical records

Note: PAS = Patient administration system. *Sourced from the patient admission system by Clinical Coding. **Originally sourced from the PAS by the TIPCU and cross checked by the researcher. ***Adapted from "Australian Refined Diagnosis Related Groups Version 6.0 Definitions Manual Volume One," by Australian Government. Copyright 2008 by the Commonwealth of Australia. [^]The RHH are notified of dates of death by the Births, Deaths and Marriages department and these are recorded on the patient administration system.

Charlson co-morbidity index (CCI)

The CCI is often used by health researchers to measure co-morbid disease. The CCI was originally developed through a review of hospital medical records and used to assess the relevance of a number of diseases in the prediction of one year mortality (Charlson, Pompei, Ales, & MacKenzie, 1987). A weighted score was assigned to each of the 17 co-morbidities. The score was based on the relative risk of one year mortality. The total CCI therefore is an indicator of disease burden and provides a strong estimate of mortality risk. Since the initial development of the CCI many studies have validated its use and demonstrated it as a valid prognostic indicator (Gabriel, Crowson, & O'Fallon, 1999; Zhang, Iwashyna, & Christakis, 1999). Further, algorithms using the International Classification of Disease (ICD) coding data have been developed to match the Charlson Index variables (Deyo, Cherkin, & Ciol, 1992).

My study used ICD-10 coding data to calculate a CCI score using a validated algorithm developed by Sundararajan et al. (2004). The decision to use ICD-10 coding data as opposed to ascertaining a CCI score from a review of medical notes was undertaken following a pilot study. The pilot study involved the researcher reviewing the notes of ten persons included in the study to calculate a CCI score (Charlson et al., 1987). The score was then compared against a score derived using ICD-10 codes and the algorithm published by Sundararajan et al. (2004). The algorithm proved more accurate as the review of the medical notes by the researcher failed to identify all co-morbid disease identified by clinical coders. In situations where the researcher failed to identify co-morbid disease, a further review of the notes was conducted to check the accuracy of the coding. Following this process, it was clear that the clinical coding was superior at identifying co-morbid disease when compared to the researcher. Therefore, the algorithm published by Sundararajan et al. (2004) to match the coding to the CCI was subsequently used for this study. There was no missing ICD-10 coding data, therefore CCI could be calculated for each exposed and non-exposed person.

The Clinical Coding department at the RHH codes patients' data using ICD-10-AM codes. The algorithm developed by Sundararajan et al. (2004) and used in my study, matched ICD-10-AM codes against CCI variables and is detailed in Appendix G (Charlson et al., 1987).

Antibiotic exposure

The final data collection element to be explored in more detail in this section is antibiotic exposure. As discussed in Chapter 5, antibiotic exposure is a risk factor for CDI. It is unclear as to whether antibiotic exposure plays any prognostic element in mortality and length of stay in hospital. Therefore, a decision to collect data on antibiotic exposure was made. Antibiotic exposure was defined as receipt of one or more doses of oral or intravenous antibiotics during an admission period. If the medication prescription chart was signed by a health professional as having administered the antibiotic, a person was considered to have received the antibiotic and subsequently, the variable was coded as “yes” to antibiotic exposure. Further, when these data were collected, the class of antibiotic that a person received was also recorded.

For the exposed, data collection on antibiotic exposure ceased on the date of CDI infection commencement estimated as the date of faeces collection. Antibiotic data from the non-exposed continued until the end of their hospitalisation. Topical antibiotics were not included in data collection as they are not a risk factor for CDI. The approach taken in collecting data on antibiotic exposure in my study was consistent with the approach taken in other studies examining CDI mortality (Fenner et al., 2008; Zilberberg et al., 2009).

4.4.5 Ethical considerations

Ethical approval for this research was granted by the Tasmanian HREC (H0011484) and by Australian Catholic University (N201150). Copies of ethics approvals are provided in Appendix P and Appendix Q. The application for ethics approval included a request to have consent from participants waived. The justification for consent being waived was as previously described in Chapter 3 and the principles remained the same for this research. One major difference between the first study (Chapter 3) and this study is the higher level of access to personal information. This study involved the review of medical notes and patient information system. At all times confidentiality was maintained and the only data reviewed and collected was that relevant to this study. I undertook the review of medical records and

the patient administration system using a secure Department of Health and Human Services computer and under the supervision of staff from the TIPCU.

This research also involved the sending of data to the researcher's supervisor for the purposes of the selection of controls, as described in section 4.5.3. All records were permanently deleted by the supervisor once matching had occurred. There were no adverse events related to this study because no persons were contacted and no breaches of confidentiality occurred.

4.5.6 Data analysis

After providing an overview of data management, this section will conclude by describing the analysis plan for each research question.

Overview of data management

Datasets of the exposed and non-exposed were merged once the collection of data concluded. The data collected in Microsoft Excel was coded from text into numerical values; ensuring date formats were consistently applied. Data from the Microsoft Excel spread sheet was then imported into IBM SPSS Version 20.0 for data analysis. Further data cleaning in SPSS occurred. New variables were computed in SPSS based on the data collected. The variables (data fields) used in this study are detailed in Table 13, with an explanation of how these were defined.

Table 13

Operational definitions

Variable title	Categories (where applicable)	Detail
Patient identifier	N/A	The number applied to each individual person.
Episode number	N/A	A number applied in ascending order for every infection occurring in the same patient.
Group	Exposed or non-exposed	Exposed is a person who had CDI during their hospital stay. Non-exposed is a person who did not have CDI during their hospital stay. See section 4.5.3 for full details.
Age group	2-9 yo, 10-19 yo, 20-29 yo, 30-39 yo, 40-49 yo, 50-59 yo, 60-69 yo, 70-79 yo, 80-89 yo, ≥ 90 yo	The decade in which a person's age falls. The categories applied were grouped in a manner consistent with descriptive epidemiology practices (Friis, 2009). The first decade was for the 2-9 year age group given no participants less than 2 years old were included.
Admission period	Pre-Jan 2007, Jan 2007-Feb 2007, Mar 2007-May 2007, Jun 2007-Aug 2007, Sep 2007-Nov 2007, Dec 2007-Feb 2008, and continuing until the last category of Dec 2010	An admission period is the period in which a person was admitted to hospital. The admission periods correspond to the four seasons of each year of data collection. A total of 18 categories applied to this variable.
Admission season	Summer, Autumn, Winter or Spring	The season in which a person was admitted i.e. summer, autumn, winter or spring.
Length of stay	N/A	The difference in days between the admission date and discharge date.
Length of stay group	Length of stay <7 days Length of stay ≥7 days	A length of stay < 7days or ≥7 days.
Date of study exit	N/A	Defined as the date of death or 30 th June 2011, whichever is first.
Days to study exit	N/A	Days from admission date to 30 th June 2011.

Discharge outcome	Alive Dead	Defined as whether the person was discharged dead or alive. A person was coded dead if the admission date was the same as the date of death.
Kaplan survival	Alive or Dead	Defined as whether the person was dead or alive as at the 30 th June 2011, coded by the researcher
DRG category – Nervous	Yes / No	The person had an AR DRG category defined in the “Nervous system” category (Australian Government, 2008).
DRG category – Respiratory	Yes / No	The person had an AR DRG category defined in the “Respiratory system” category (Australian Government, 2008).
DRG category – Circulatory	Yes / No	The person had an AR DRG category defined in the “Circulatory system” category (Australian Government, 2008).
DRG category – Musculoskeletal	Yes / No	The person had an AR DRG category defined in the “Musculoskeletal system” category (Australian Government, 2008).
CCI score group	Charlson score = 0, Charlson score >0	A total CCI score = 0 or > 0.
Any antibiotics use	Yes / No	Defined as whether a patient had any antibiotic exposure or not.

Note: yo = years old. DRG = Diagnosis Related Groups. AR = Australian Refined.

Statistical analysis

Overview

This section provides the statistical methods used for data analysis. Data analysis for this study involved two steps. Data were initially analysed using descriptive statistics before survival analysis was used. These two elements of data analysis will now be explored in more detail. All data analysis was performed in IBM SPSS Version 20.0 (International Business Machines Corporation, 2011).

Descriptive statistics

Univariate analysis comparing the characteristics of the exposed and non-exposed was performed. To test for normal distribution, data were analysed using Q-Q plots and the Kolmogorov-Smirnov test. As this was a matched cohort study, Mantel-Haenszel methods were used to estimate the differences between the exposed and non-exposed (Kirkwood, 2003). Continuous variables were compared using the Mann Whitney *U* test, as all continuous variables were non-normally distributed. The median Charlson score for exposed and non-exposed was zero. Similarly, the median Charlson score for exposed and non-exposed combined was zero. For these reasons, the Charlson co-morbidity index was recorded into two categorical variables for data analysis, those with a score equal to and those with a score greater than zero. Length of stay was grouped into length of stay greater or equal to seven days or less than seven days. Seven days was chosen as the dividing point as the median length of stay for the two groups combined was seven days.

Survival analysis

Following univariate analysis, survival analysis using the Kaplan-Meier method was performed to examine mortality at 30, 60, 90 and 180 days. A log rank Mantel-Cox test was used to compare survival between exposed and non-exposed. The time from admission date was used for both exposed and non-exposed when examining mortality at fixed periods. Further analysis, using Kaplan-Meier survival analysis techniques, was undertaken

controlling for categorical variables found to be significant at the 0.1 level in univariate analysis. Kendall's tau rank correlation was used to determine the correlation between individual antibiotics found to be significant in univariate analysis and the variable 'any antibiotic use'. Similarly, correlation between individual co-morbidities and the 'CCI group' was undertaken. A correlation was found in all instances. Therefore, survival, controlling for the individual categorical variables of length of stay group, CCI group and any antibiotic exposure were undertaken using Kaplan-Meier.

Risk of death comparing exposed and non-exposed

A conditional logistic regression model was used to estimate the risk of a person with and without CDI dying at 30, 60, 90 or 180 days, while controlling for confounders. The conditional logistic regression analysis was performed using Cox Proportional Hazard data analysis in IBM SPSS (International Business Machines Corporation, 2011). The same three variables found to be significant in univariate analysis, namely: any antibiotic exposure, length of stay longer than seven days, and CCI score greater than zero, were entered into the model.

Exploratory analysis was also undertaken on non-survivors up to 180 days post-admission to investigate potential association with strains of *C.difficile*. This analysis breaks the matching; therefore analysis included comparison of age and admission period.

4.5.7 Summary of methods section

In the methods section provided above, details on the study design, data collection, ethical considerations and data analysis of my study examining the relationship between patients who had CDI (exposed) and a subset of the non-exposed population were provided. The next section of this thesis will outline the results of the study.

4.6 Results

4.6.1 Overview of results

A total of 484 persons were included in this study. In section 4.5.3 the methods used to select cases and controls were discussed. Figure 14 summarises how the cohort for this study was derived.

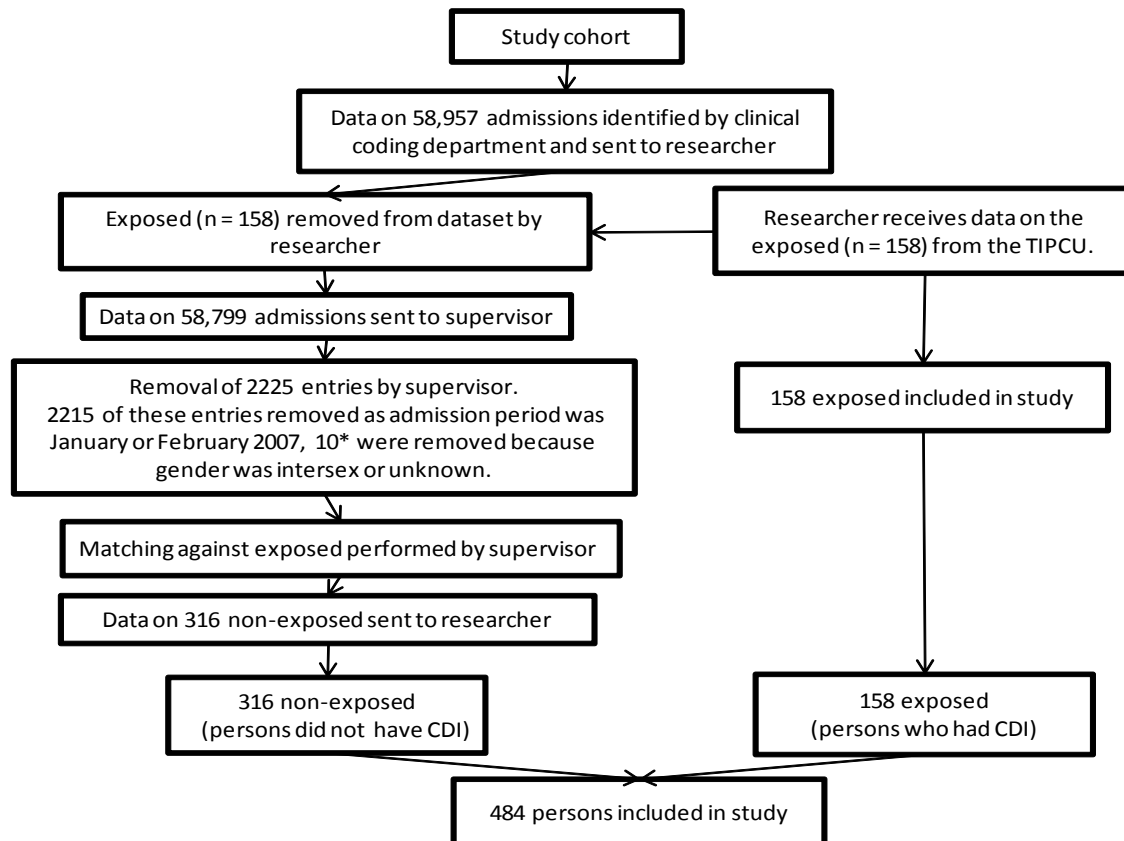


Figure 14. Summary of selection of cohort. *Three of these ten entries were admitted during January or February 2007.

A total of 158 episodes of CDI occurred between the 1st January 2007 and the 30th December 2010. Of the 158 cases, 79 (50%) were male. The median age of cases was 67 years, with a range between two and 102 years. As discussed earlier, non-exposed for the study were matched two to one, by age group, sex and admission period. Figure 15 demonstrates the age distribution of the study group, whilst Figure 16 illustrates the season and year in which the exposed were admitted to hospital.

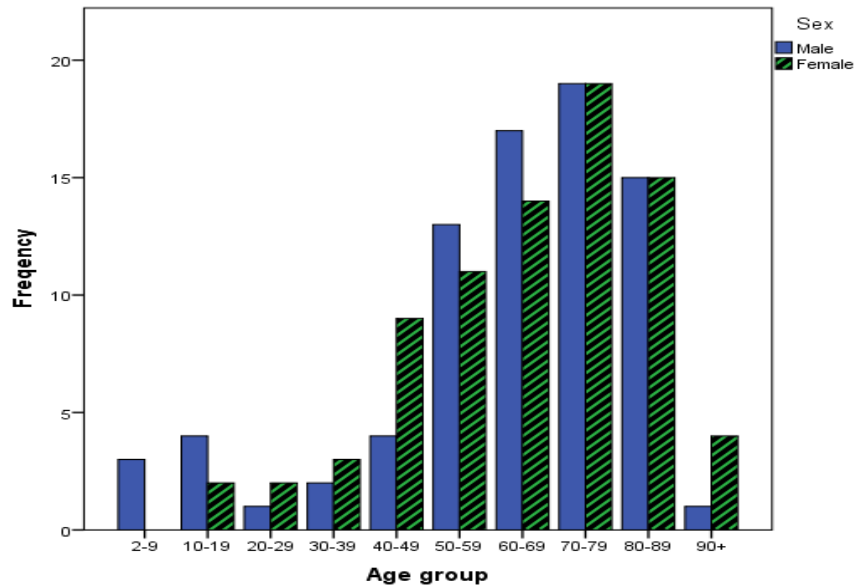


Figure 15. Age distribution of the exposed, 1st January 2007 to 30th December 2010. The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old.

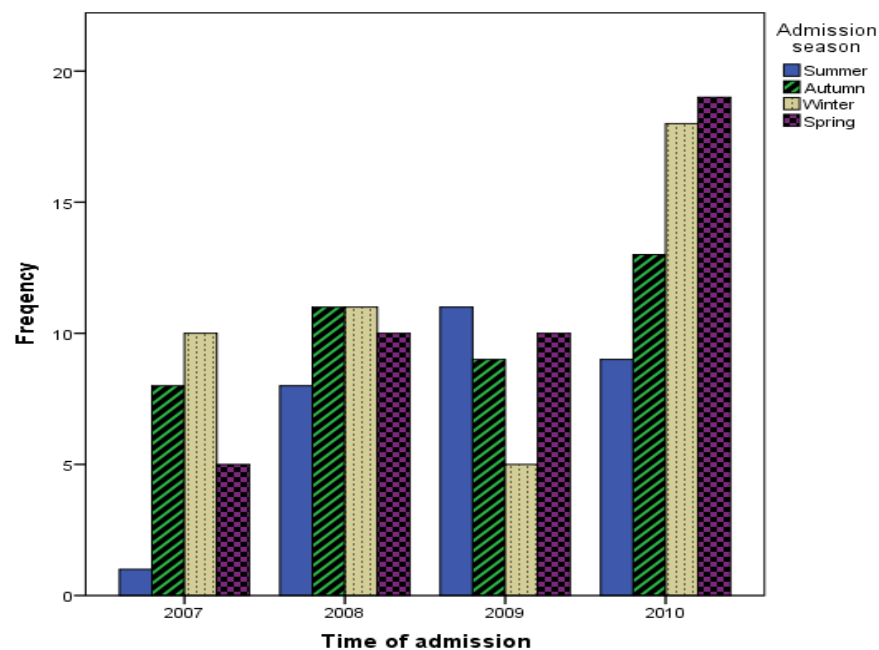


Figure 16. Distribution of admission to hospital for the exposed, 1st January 2007 to 30th December 2010. The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old.

Despite removing duplicate samples occurring within eight weeks of the previous positive sample, as outlined in Chapter 4, there were five instances of a second infection occurring in the same person during the four year study period. Further analysis of these five individuals suggests that second cases were unrelated to the first episode. There was at least four months between the first and second infection, with one person having a second episode of CDI three years after the first. These results are summarised in Appendix H. With this in mind and given that the study has used international and national definitions for exclusion of duplicate cases, data from these five episodes were included in this study. The non-exposed were matched on each individual episode. Therefore it was possible that an individual with multiple hospitalisations may have been a control on multiple occasions, however this did not occur.

4.6.2 Clinical characteristics of exposed and non-exposed

Table 14 summarises and compares the characteristics of the exposed and non-exposed. There was a statistically significant difference between exposed and non-exposed in relation to the CCI group, with the exposed having a CCI group score of greater than zero, with the non-exposed having a CCI group score of zero. There was also a difference in the length of stay between the two groups. Using the Kolmogorov-Smirnov test, length of stay was found not to be normally distributed for both exposed and non-exposed (0.20, $df = 158$, $p < 0.01$ and 0.28, $df = 316$, $p < 0.01$) respectively. The range of the length of stay was three to 214 days for cases and two to 109 days for controls. The median length of stay for exposed and non-exposed combined was seven days. For the exposed, the median time to infection after admission was eight days, with a range of two to 104 days. The range is important to note, as the upper limit of length of stay in cases was found to be higher than the non-exposed.

Table 14

Univariate analysis of exposed and non-exposed characteristics (N = 474)

Characteristic	Exposed (n = 158)	Non-exposed (n = 316)	OR	95% CI	p value
Charlson category					
Cancer (yes)	26	29	1.95	1.10-3.44	0.029
Cerebral accident (yes)	19	11	3.79	1.76-8.18	0.001
Chronic pulmonary disease(yes)	7	13	0.65	0.28-1.56	0.449
Congestive heart failure (yes)	10	13	1.58	0.68-3.68	0.406
Connective tissue (yes)	3	1	6.10	0.63-59.10	0.214
Dementia (yes)	4	8	1.00	0.30-3.38	1
Diabetes (yes)	3	1	6.10	0.63-59.10	0.214
Diabetes complications (yes)	11	8	2.88	1.14-7.31	0.039
HIV (yes)	1	0	-	-	-
Liver disease (yes)	0	3	-	-	-
Metastatic cancer (yes)	11	14	1.61	0.72-3.65	0.345
Myocardial infarct (yes)	4	12	0.66	0.21-2.07	0.653
Paraplegia (yes)	6	11	1.09	0.40-3.02	0.93
Peptic ulcer (yes)	2	1	4.04	0.36-44.88	0.539
Peripheral vascular disease (yes)	1	1	2.00	0.13-32.29	0.802
Renal disease (yes)	11	16	1.40	0.64-3.10	0.529
Severe liver disease (yes)	2	0	-	-	-
CCI group (score >0)	98	120	2.67	1.80-3.95	<0.001
Length of stay					
Median	17	4	N/A	N/A	<0.001*
Length of stay group (> 7 days)	137	90	16.38	9.74-27.56	<0.001
Persons who received antibiotic					
Any other AB (yes)	56	48	3.07	1.96-4.80	<0.001
Any penicillin (yes)	69	77	2.41	1.60-3.61	<0.001
Any cephalosporin (yes)	64	76	2.16	1.43-3.24	<0.001
Any fluoroquinolone (yes)	14	11	2.70	1.19-6.09	0.024
Any aminoglycoside (yes)	20	23	1.85	0.98-3.48	0.08
Any macrolide (yes)	11	16	1.40	0.64-3.10	0.529
Any antibiotic (yes)	121	158	3.27	2.13-5.02	<0.001

Note: The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period. OR = odds ratio. OR calculated using conditional logistic regression. 95% CI = 95% confidence intervals. *Mann-Whitney U test. N/A = Not applicable. AB = antibiotic.

Exposure to antibiotics for exposed and non-exposed were compared by antibiotic class and whether they had received any antibiotic. When comparing antibiotic exposure between the groups, there are two points to note. First, there was a significant difference between the exposed and non-exposed in their exposure to all of the individual classes of antibiotics, other than the macrolide and aminoglycoside groups. Second, there was a significant difference in ‘any antibiotics’ use.

4.6.3 In-hospital mortality

In section 4.3, the literature surrounding mortality and CDI was explored. Many authors calculated in-hospital mortality, despite the risk period for in-hospital mortality varying due to different lengths of stay. Thus, so comparisons between the current and the literature can be undertaken in-hospital mortality was calculated. Among persons with CDI, five (3.2%) died whilst in hospital, compared to ten (3.2%) among controls.

4.6.4 *Clostridium difficile* infection and mortality using Kaplan-Meier

Table 15 demonstrates the numbers of exposed and non-exposed who were dead at 30, 60, 90 and 180 days following admission to hospital, using Kaplan-Meier survival analysis. A significant difference in mortality between the exposed and non-exposed at 60, 90 and 180 days were identified. Figure 17 demonstrates the Kaplan-Meier survival curve up to 180 days post-admission.

Table 15

Kaplan-Meier death rates with and without Clostridium difficile infection

Timeframe	Exposed (n = 158)	Non-exposed (n = 316)	Chi-square	p value
Mortality up to 30 days (%)	11 (7.0%)	13 (4.1%)	1.70	0.191
Mortality up to 60 days (%)	20 (12.6%)	20 (6.3%)	5.32	0.021
Mortality up to 90 days (%)	23 (14.6%)	23 (7.3%)	6.37	0.012
Mortality up to 180 days (%)	37 (23.4%)	29 (9.2%)	17.72	<0.001

Note: The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period. Log rank test (Mantel-Cox); df1.

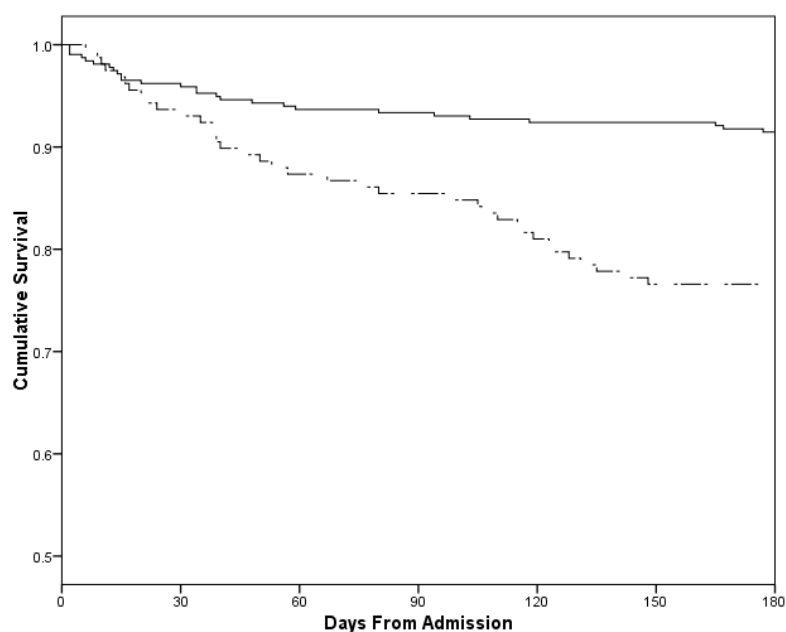


Figure 17. Survival up to 180 days following hospital admission. Non-exposed = unbroken line. Exposed = dashed line. The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period.

To control for differences between the exposed and non-exposed, three categorical variables found to be significant in univariate analysis were individually added to the Kaplan-Meier analysis. These three variables were any antibiotic exposure, length of stay group and CCI group. As described in section 4.5.6, the CCI group indicated those participants with a CCI score greater than zero, whilst the length of stay group represented those with a length of stay greater than seven days in hospital.

Table 14 demonstrates a significant difference between the exposed and non-exposed for the individual CCI variables of cerebral accident, cancer and diabetes. These variables were not included in future models as a significant correlation was found using Kendall's tau rank correlation, between the CCI group and the following variables: cerebral accident ($\tau= 0.28$, $p<0.001$); cancer ($\tau= 0.39$, $p<0.001$); and diabetes complications ($\tau= 0.22$, $p<0.001$). Similarly, for antibiotics, the variables of penicillin ($\tau=0.56$, $p<0.001$), cephalosporin ($\tau=0.54$, $p<0.001$), other antibiotics ($\tau=0.44$, $p<0.001$), fluoroquinolone ($\tau=0.20$, $p<0.001$), and aminoglycoside ($\tau=.0.26$, $p<0.001$) were all found to be significantly correlated to the variable any antibiotic use.

Table 16 outlines the results of Kaplan-Meier analysis, controlling for the three variables of any antibiotic use, length of stay and CCI group. A significant difference in mortality between exposed and non-exposed remained at 180 days, after controlling for any one of the three variables. Mortality at 60 and 90 days only remained significantly different after controlling for any antibiotic use ($\chi^2 5.95$, $p=0.02$ and $\chi^2 6.89$ $p=<0.01$, respectively).

Table 16

Adjusted Kaplan-Meier death rates with and without Clostridium difficile infection

Timeframe	Covariate		Exposed (n = 158)	Non-exposed (n = 316)	Chi - square	p value
Mortality up to 30 days	Any AB use	No	6	6	2.67	0.104
		Yes	5	7		
	LOS	≤ 7days	2	6	0.09	0.762
		> 7days	9	7		
CCI Score	0	1	1	0.05	0.827	
	> 0	10	12			
Mortality up to 60 days	Any AB use	No	8	9	5.95	0.015
		Yes	12	11		
	LOS	≤ 7 days	4	11	1.90	0.168
		> 7 days	16	9		
CCI Score	0	3	4	1.28	0.257	
	> 0	17	16			
Mortality up to 90 days	Any AB use	No	9	10	6.89	0.009
		Yes	14	13		
	LOS	≤ 7 days	5	11	2.81	0.094
		> 7 days	18	10		
CCI Score	0	3	5	1.57	0.209	
	> 0	20	18			
Mortality up to 180 days	Any AB use	No	13	14	18.97	0.001
		Yes	24	15		
	LOS	≤ 7 days	6	15	5.87	0.015
		> 7 days	31	14		
CCI Score	0	7	8	8.18	0.004	
	> 0	30	21			

Note: The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period. Log rank test (Mantel-Cox); df1. AB = antibiotic. LOS = length of stay.

To further explore the association between CDI and mortality, a Cox regression model was developed.

4.6.5 *Clostridium difficile* infection and mortality using logistic regression

A conditional logistic regression model was developed in SPSS to estimate the hazard of death at 30, 60, 90 and 180 days using Cox regression data analysis. All models had exposed

or non-exposed entered as a forced step. Consistent with the results in section 4.6.4, a significant difference in mortality was found between the exposed and non-exposed at each timeframe, when no additional variables were added to the equation. For each of these four timeframes, three variables—antibiotic use, length of stay longer than seven days and CCI score lower than zero—were then included in the model using a forward stepwise conditional (likelihood ratio) process. The results are displayed in Table 17. There are two important points to note from this table. First, no model that included any of the three variables was found to be significant at the 30, 60 and 90 day endpoints. Second, the most parsimonious model was at 180 days, which included the variable of a CCI score higher than zero and demonstrated a significant difference between exposed and non-exposed, controlling for CCI.

Table 17

Conditional logistic regression models for mortality at four timeframes post hospital admission (n = 474)

Timeframe and final model	Variables in the equation	Partial OR	95% CI	p value	Variables not in the equation (p value)
30 day model	Group (exposed) ¹	1.09	0.49-2.46	0.827	Any AB use (0.224)
	CCI Score >0 ²	13.22	3.07-56.90	0.001	LOS > 7 days (0.472)
60 day model	Group (exposed) ¹	1.44	0.77-2.70	0.257	Any AB use (0.433)
	CCI Score >0 ²	5.48	2.39-12.56	<0.001	LOS > 7 days (0.852)
90 day model	Group (exposed) ¹	1.46	0.81-2.62	0.209	Any AB use (0.473)
	CCI Score >0 ²	5.63	2.59-12.22	<0.001	LOS > 7 days (0.957)
180 day model	Group (exposed) ¹	2.04	1.24-3.36	<0.005	Any AB use (0.254)
	CCI Score >0 ²	3.83	2.13-6.89	<0.001	LOS > 7 days (0.384)

Note: OR = odds ratio. The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period. AB = antibiotic. LOS = length of stay. CCI = Charlson co-morbidity index.¹ The non-exposed were the reference category. ² CCI score = 0 was the reference category.

4.6.6 Characteristics of non-survivors

Exploratory analysis was undertaken on non-survivors up to 180 days post-admission. A total of 66 persons (37 exposed, 29 non-exposed) died within 180 days post-admission. Univariate analysis was performed comparing characteristics of non-survivors, as detailed in Table 18.

Table 18

Characteristics of non-survivors 180 days post-admission

Characteristic	Exposed (n = 37)	Non-exposed (n = 29)	Total (n = 66)	Statistic (p value)	p value
Sex					
Male (%)	19 (51.4%)	19 (65.5%)	38 (57.6%)	1.33 [^]	0.248
Female (%)	18 (48.6%)	10 (34.5%)	28 (42.4%)		
Median age (range)	67 (2-102)	76 (48-97)	74 (2-102)	2.13 [^]	0.145
CCI group (score >0) (%)	30 (81.1%)	21 (72.4%)	51 (77.3%)	0.70 [^]	0.404
Median length of stay (range)	14 (5-77)	6 (2-60)	11(2-77)	5.27 ^{**}	0.022
Length of stay group (LOS > 7 days)	31 (83.8%)	14(48.3%)	45 (68.2%)	9.45 [^]	0.002
Any antibiotic exposure (yes)	24 (64.9%)	15 (51.7%)	39 (59.1%)	1.16 [^]	0.281
Day from admission to infection					
Median	5	N/A	N/A	-	-
Range	2-29				
Year of admission					
2007	5 (13.5%)	5 (17.2%)	10 (15.2%)	N/A [*]	0.738
2008	7 (18.9%)	5 (17.2%)	12 (18.2%)	0.03 [^]	0.861
2009	10 (27.0%)	13 (44.9%)	23 (34.8%)	2.27 [^]	0.132
2010	15 (40.6%)	6 (20.7%)	21 (31.8%)	2.95 [^]	0.086

Note: [^]Chi-square. ^{*}Fisher's Exact Test. ^{**}Mann Whitney U test. N/A = Not applicable. LOS = length of stay. The exposed were persons who had *Clostridium difficile* infection identified ≥ 48 hours after hospital admission and aged ≥ 2 years old. Non-exposed were matched by age group, sex and admission period.

In Table 18 of particular note is the year of admission. For the exposed group, there was an increase in the number of deaths each year (between 2007 and 2010). During 2010, there was a large, but not statistically significant, difference in the number of people who died when comparing the exposed and non-exposed.

The results in section 4.6.4 indicated a statistically significant difference in mortality between the exposed and non-exposed from 60 days after admission. Exploratory analysis was performed on those who died up to 30 days after admission to identify any possible explanation for this. No significant differences were found between the two groups when comparing their length of stay, age or CCI group (>0).

4.6.7 Strains of *Clostridium difficile*

Data on the strain of *C.difficile* affecting the exposed was available in ten persons, and these data are presented in Table 19. Strain data were not available for all cases of CDI as typing was only undertaken on isolates that had been kept in frozen storage. Storage of isolates was not undertaken routinely by the RHH laboratory.

Table 19

Strains of *Clostridium difficile* affecting exposed

Status at 180 days	Strain of <i>Clostridium difficile</i>		
	Ribotype 014	Ribotype 078	Not available
Dead	2	0	35
Alive	7	1	113

Note: Typing of strains was undertaken by a reference laboratory, namely PathWest Laboratory, Western Australia.

4.6.8 Summary of results

The study cohort consisted of 474 persons, 158 exposed to CDI and 316 non-exposed. In-hospital mortality was reported as 3.4% for both the exposed and non-exposed. There was a statistically significant difference between the exposed and non-exposed in mortality from 60 days and beyond using Kaplan-Meier analysis. Using conditional logical regression, at 180 days, a significant difference in mortality between the exposed and non-exposed remained after controlling for variables.

4.7 Discussion

4.7.1 Introduction

As the first known study to examine CDI mortality in Australia in over a decade, this research provides interesting insights into the mortality associated with CDI in hospitalised patients in Australia, as well as the opportunity for robust comparison with studies in other countries. This study also provides results indicating that persons who had CDI have a higher all-cause mortality compared to persons without CDI. Further, one key finding from my study is that mortality is significantly higher from 60 days after admission and beyond. These two points are explored in the first two sections of this discussion. The next section of the discussion reviews the characteristics of the exposed and non-exposed further, with a focus on potential confounders. This point is explored in the context of reflecting on the data collected in my study and informing future research approaches examining mortality and CDI. Finally, some limitations of the study are presented in section 4.7.5.

4.7.2 Mortality

The first research question for this study had two parts. The first was to determine the percentage of persons who died within 30, 60, 90 and 180 days following admission and who had an episode of CDI during the incident admission. The second was to examine the risk of persons diagnosed with CDI dying at the same fixed periods compared to persons without

CDI. Mortality was reported in a number of different ways in the results section of this chapter, in order to answer these two research questions. There were significant differences in mortality between the cases and controls at various endpoints, even after adjusting for other factors. The risk of dying at 180 days was twice as high in cases, compared to controls, OR 2.04, 95% CI [1.24, 3.36]. In this section I will discuss mortality and CDI in relation to the research questions and explore why mortality is higher at a relatively late stage following admission to hospital.

Mortality at fixed timeframes

Mortality increased steadily in cases and was reported as 7.0%, 12.6%, 14.6% and 23.4% at 30, 60, 90 and 180 days following admission to hospital. There were statistically significant differences in mortality between the exposed and non-exposed at 60, 90 and 180 days post-admission using Kaplan-Meier analysis. It is important to remember that, as a result of being a matched cohort study, these data are inherently adjusted for the matching variables of age group, sex and admission period. After additional adjustment for antibiotic exposure at 60, 90 and 180 days, these differences in mortality remained. Similarly, at 180 days, adjusting for any one variable—antibiotic exposure, length of stay and CCI—using Kaplan-Meier analysis, significant differences remained.

Using a conditional logistic regression model, the risk of dying by 180 days following admission to hospital was twice as high in cases compared to controls. In this final model, the only variable that was retained was a CCI score of greater than zero. Indeed, a CCI of greater than zero was associated with mortality at all endpoints examined. This reinforces the need for studies to collect and analyse the effect of co-morbidities, thereby enabling a more accurate statement about the association between CDI and mortality (Karas et al., 2010).

There are a number of ways that mortality associated with CDI is reported in the literature. In some published case control studies, statistically significant differences in all-cause 30 day mortality have been reported as 5% vs. 16% and 9% vs. 19% for controls and cases

respectively (Gasperino et al., 2010; Gulihar et al., 2009). Thirty day mortality adjusted for age and sex remained significantly different in the study conducted by Gasperino et al. (2010). In the study undertaken by Gulihar et al. (2009) controls were matched to cases by age, sex, residential status and ASA score where known. This study design was similar to that used in my study. At six months, a significant difference in mortality remained between the exposed and non-exposed (67% vs. 29%, $p < 0.001$) (Gulihar et al., 2009).

It is also interesting to note the reported percentage of persons with CDI who died at various endpoints. As previously stated, mortality at 30 days has been reported as being 16% and 19% at 30 days, and as high as 67% at 180 days (Gasperino et al., 2010; Gulihar et al., 2009). A number of cohort studies have reported all-cause mortality in persons with CDI. In these studies, all-cause mortality ranged from 9% to 38% at 30 days (Bhangu et al., 2010; Fenner et al., 2008) and between 27% and 30% at 90 days (Musher et al., 2005; Shears et al., 2010). The reported mortality as a percentage is higher than that reported in the present study (7% and 23.4% at 30 and 180 days, respectively). The numbers of cases used in the studies performed by Gulihar et al. (2009) and Gasperino et al. (2010) were 170 and 108, respectively with similar numbers of controls. In the study undertaken by Fenner et al. (2008) there were 78 persons with CDI.

Similar to my study, one study reported a non-statistically significant difference between persons who had CDI (exposed) and persons who did not (non-exposed) in examining all-cause mortality at one month (15% vs. 11.5%) (Bishara et al., 2008). The sample size of this study was limited to 52 persons who had CDI and 165 without CDI; only persons with CDI who had been exposed to antibiotics in the previous 40 days were included in the study. In a matched case control study, significant differences in mortality between those with and without CDI were reported at 90 and 180 days (Dubberke et al., 2008). By 180 days after hospital admission, 127 (36%) persons who had CDI had died, compared with 107 controls (30%). Similar to the present study, persons who had CDI were no more likely to die than those without, at 60 days after hospital admission, but a divergence became apparent more than 60 days after hospital admission (Dubberke et al., 2008). The hazard ratio for death was reported as 2.0, 95% CI [1.47, 2.72] from 60 to 180 days after death.

The findings of my study, which indicate a divergence in survival between the exposed and non-exposed at 60 days, support previous findings. As discussed earlier, the study undertaken by Dubberke et al. (2008) demonstrated a delayed impact on death. My previous suggestion that studies examining CDI and mortality may be influenced by the methodologies used (and, in particular, exclusion criteria) is supported by Dubberke et al. (2008), who comments that delayed death caused by CDI may not be easily recognised as related to the initial CDI episode and CDI may contribute to a decline in patient function and overall illness over time, ultimately leading to death in many patients. This particular point is explored in more detail later in this section. Analysis is also included examining the characteristics in persons who died (non-survivors) and more specifically, any differences between the exposed and non-exposed. In my study, in those persons who died, the only significant difference between the exposed and non-exposed found after applying univariate analysis was length of stay.

Of interest from this analysis was the comparison of death by exposed and non-exposed and the year of admission. For the exposed, there was an increase in the number of deaths each year (between 2007 and 2010). During 2010, there was a large, but not statistically significant, difference in the number of people who died when comparing exposed and non-exposed ($p = 0.086$). This increase in the number of deaths in cases may result from a changing epidemiology of *C.difficile*, such as a change in the circulating strain. My study was only able to obtain limited data on the strain of *C.difficile* affecting the exposed. Nonetheless, these data are important as they can be used to pool with data from other studies. In doing so, conclusions about whether specific strains of *C.difficile* result in different levels of mortality may be possible. Due to the limited data available from my study, no conclusions can be drawn with respect to the influence that different strains of *C.difficile* may have on death. Further, there are no published data on the circulating strains of *C.difficile* across Australia at the time of writing.

In-hospital mortality

An in-hospital mortality of 3.2% was found for both the exposed and non-exposed. This proportion is lower than reported mortality from a number of studies, which has ranged between 8% and 37% (Chung et al., 2010; Cloud et al., 2009; Gasperino et al., 2010; Marra et al., 2007). Comparisons between my study and those reported elsewhere however should be undertaken with caution. There are a number of issues inherent in comparing in-hospital mortality data amongst studies for CDI. The circulating strains (and therefore virulence) of *C.difficile* vary not only among institutions, but also among countries (McDonald et al., 2005; Warny et al., 2005). In-hospital mortality for CDI reported in the literature does not adjust for this difference. A further challenge when comparing in-hospital mortality, which is not limited to CDI, is the case-mix of the participants in the study (Ansari, Ackland, Jolley, Carson, & McDonald, 1999; Iezzoni, Ash, Shwartz, & Mackiernan, 1997). As demonstrated by the results in the present study and others, co-morbid disease plays a role in CDI, yet in-hospital mortality data may not account for this (Vaishnavi, 2009). The size of the hospital can also play a part in the calculation of in-hospital mortality which can become less precise in smaller hospitals, with fewer deaths as a function of fewer admissions (Scott, Brand, Phelps, Barker, & Cameron, 2011). Given the issues with reporting in-hospital mortality, I suggest comparisons using this method are not made in examining mortality associated with CDI.

4.7.3 A limitation of surveillance definitions

The second research question for this study was to examine the potential influences of using CDI surveillance definitions when examining the risk of death in people who has an episode of CDI. One question the findings from my study poses is why CDI is associated with mortality at a relatively late stage following admission to hospital. Earlier, in section 4.6.2, data on the time from hospital admission to infection was discussed. Eight persons had an episode of CDI commence more than 30 days after admission; but none of these persons died. Therefore, the timing of infection commencement during a hospital stay may not fully explain the higher occurrence of mortality at 60 days and beyond. One potential reason for the results seen could be the use of exclusion criteria applied to the study population.

In clinical practice, a person may suffer several relapses of CDI before recovering or dying, and relapses often occur within a few weeks of initial recovery (Pépin et al., 2005). For example, it has been suggested that CDI will recur in 33-65% of persons who have had more than two relapses (Barbut et al., 2000; Gerding, Muto, & Owens, 2008). In situations where a person has a relapse within eight weeks of the previous episode of CDI, data relating to this relapse were not captured in my study. Any episodes of CDI occurring within eight weeks of the previous episode were excluded, in accordance with national surveillance definitions. This would include persons who have been discharged from hospital. Figure 18 seeks to illustrate this point graphically.

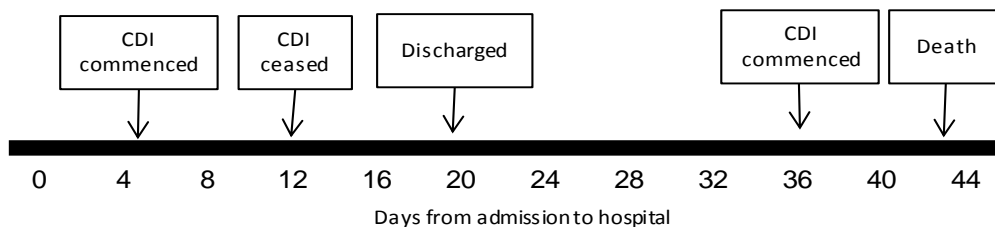


Figure 18. Scenario of a person who had *Clostridium difficile* infection dying 43 days following initial admission to hospital. The second episode of CDI would not be included in data as it occurred within eight weeks of the previous episode. If the second episode of CDI was included, the person would have died seven days following the second episode of CDI.

Any study that uses exclusion criteria to remove duplicate cases may run into the same issue. In section 4.2.3, the literature surrounding the management of duplicate samples of CDI was explored. In my study, episodes of CDI occurring within eight weeks of the previous, as defined by a laboratory diagnosis, were excluded, consistent with national and international surveillance definitions. My study is not alone in encountering this issue (Sundram et al., 2009). Similarly, a study by Kenneally et al. (2007) only included an index case in their data analysis.

Findings from previous research on CDI suggest that the more relapses a person has, the poorer the outcome for the person (Musher et al., 2005). This scenario may go some way in explaining a higher mortality at 60 days post-admission and beyond. If this is the case, it demonstrates a potential weakness in using exclusion definitions for CDI surveillance programs as this goes to the heart of what constitutes a case of CDI. Whether episodes of CDI occurring within eight weeks of the previous case are relapses or new infections is an important point to consider, not only when considering mortality as described in the section above, but also when determining the incidence of CDI. In the case of the latter point, failure to account for these could result in under reporting of CDI. Further work is required on refining how duplicate episodes of CDI occurring in the same person in a defined period are managed and classified for the purposes of data analysis.

4.7.4 Exploration of length of stay, co-morbidities and antibiotic exposure

In univariate analysis, a number of differences in length of stay in hospital, co-morbidities and exposure to antibiotics in hospital between the exposed and non-exposed were identified. In this section these differences are discussed. There also appeared to be more exposed in the last year of this study, and more people with CDI in older age groups. These points are explored in more detail in Chapter 5 using a different study design and so are not explored further here.

The length of stay differed significantly between the exposed and non-exposed. It was not the purpose of the present study to attribute length of stay to CDI as this is the focus of the next study of this thesis. Rather, the exploration of length of stay in the exposed and non-exposed is interesting in the context of interpreting survival at different endpoints which is discussed later in this section. The median length of stay was 17 days for the exposed and four days for the non-exposed. This is consistent with other studies examining mortality and HAIs that have also demonstrated a significant difference in the length of stay between those with and without infection (Askarian & Gooran, 2003; Laupland, Lee, Gregson, & Manns, 2006; Leleu, Aegerter, & Guidet, 2002; Piednoir et al., 2003). Mortality was measured according to the number of days after admission to allow comparisons to other studies that used the same methodology. For example, if a person does not acquire an infection until day 30 of their

hospital stay and dies on day 40, they will be recorded as having died within 60 days or admission, not 30 days. In my study, the median time to infection after admission was eight days, with a range of 2-104. Further analysis of the study group showed that for the exposed who died up to 180 days following admission, the median time to infection from admission was five days (range 2-27 days). Therefore it appears that time of infection did not play a significant role in explaining why mortality was higher at 60 days and beyond.

There were also significant differences in co-morbidities between the exposed and non-exposed. Given the differences found in my study and evidence that the CCI is a valid prognostic indicator for mortality, the inclusion of these data are a particular strength of this study (Gabriel et al., 1999; Zhang et al., 1999). This is further supported by a review in which the authors call for future studies to include co-morbidities when examining mortality and CDI (Karas et al., 2010). Findings from my study suggest that more people who had CDI had had a cerebral accident, cancer or diabetes complications compared to those who did not have CDI. Dubberke et al. (2008) found a difference in the number of people with diabetes complications ($p = 0.06$), cancer ($p < 0.001$), congestive heart failure ($p < 0.001$), chronic pulmonary disease ($p < 0.001$), and leukaemia ($p < 0.001$) when comparing the exposed and non-exposed. Conversely, a study by Gasperino et al. (2010) did not identify any difference in co-morbidities between persons who had CDI and persons without CDI.

There were also notable differences in exposure to antibiotics between the exposed and non-exposed in my study. As discussed in section 4.2.5, exposure to antibiotics is thought to be an important risk factor for CDI (Bignardi, 1998). There are a large number of studies supporting the association of antibiotic exposure and CDI (J. Pépin, Saheb, N., Coulombe, M., Alary, M., Corriveau, M., Authier, S., Leblanc, M., Rivard, G., Bettez, M., Primeau, V., Nguyen, M., Jacob, C., Lanthier, L, 2005; Polgreen, et al., 2007; Thomas, et al., 2003). Results from this study were consistent with the literature in suggesting that a larger proportion of people who had CDI were exposed to antibiotics, compared to those who did not have CDI. When exposure to antibiotics was divided into antibiotic class, there were significant differences in exposure to all classes other than macrolides ($p = 0.50$) and aminoglycoside ($p = 0.08$). It was not the primary purpose of the present study to examine the relationship between antibiotic exposure and CDI, except as a potential confounder. The

results suggest that antibiotic exposure played little role in mortality as adjusting for this variable made no difference to survival under the Kaplan-Meier survival analysis. Further, antibiotic exposure was excluded in the final conditional logistic regression models for the four timeframes examined in this study (Table 17).

Given the reported mortality associated with CDI in the present study, the importance of infection prevention activities, such as antibiotic stewardship, were underlined. Antibiotic stewardship is the term used to describe an effective approach to improving antimicrobial use in hospitals (Duguid & Cruickshank, 2011). The RHH has had an active antibiotic stewardship program since late 2010. The hospital also monitors the use of antimicrobials through the National Antibiotic Utilisation Surveillance Program. At a national level in Australia, there has been a growing push for hospitals to have an antibiotic stewardship program in place (Duguid & Cruickshank, 2011). With CDI being associated with increased mortality, the need is increased for CDI prevention strategies, such as antibiotic stewardship programs and surveillance programs to monitor their effectiveness.

Antibiotic exposure was only one of several potential confounders that were considered in this study. Consideration of other potential confounders was attempted either through the data analysis or through the study design (i.e. matching). Further detail regarding the rationale for the collection of specific data items and the criteria used for matching are described in detail in section 4.5.4. Nevertheless, when discussing and interpreting the results below, the relationship that variables have with both CDI and subsequent mortality needs to be understood, particularly when reviewing results from the regression model. The relationship between variables considered in the design and interpretation of the present study is displayed in Figure 19.

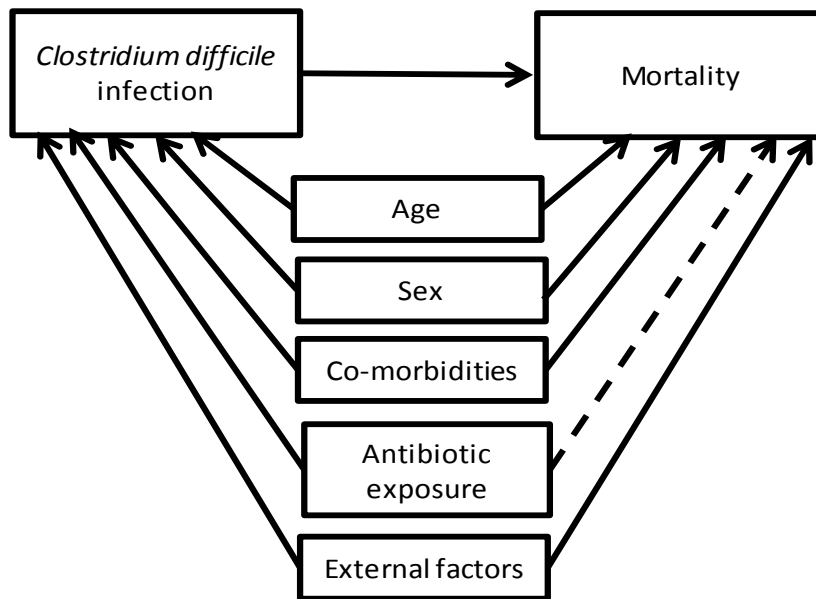


Figure 19. Relationship between variables and *Clostridium difficile* infection and mortality. Note: Broken line indicates an uncertain relationship. “External factors” represents those factors that were attempted to be controlled for through matching by admission period. These are described in the methods section.

In my study, the final conditional logistic regression model explaining mortality at 180 days only included co-morbidities. As age and sex were used as part of the matching process for controls, this study is unable to draw conclusions on their role in CDI and mortality. In the next chapter, the influence of age and sex on CDI is explored.

4.7.5 Limitations

There are some limitations to this study. Caution should be applied when comparing this research to other published studies: based on conditions in the northern hemisphere the circulating strains of *C.difficile* and their effect on mortality may be different (Loo et al., 2005; Miller et al., 2010). Also, as with all retrospective studies, the number of variables are limited by the existing range of data collected. For this study, this limited the number of potential explanatory variables that could be introduced in the regression modelling and therefore other factors affecting mortality may have been missed.

4.8 Recommendations

From the findings, a number of recommendations can be made. First, in my study, data were not captured on the time between CDI diagnosis and treatment. This variable may be important in understanding the effect that CDI has on mortality. Second, my study also demonstrated the importance of considering co-morbidities when examining mortality. As identified in the literature review not all studies examining the influence of CDI on mortality capture data on co-morbidities. Unlike co-morbidity data, data on the strains of *C.difficile* affecting all cases was not available, thus the role that different strains play should be considered for future studies. Often such data are limited, therefore it becomes even more important that studies include strain data where possible, to allow for future meta-analysis. With these points in mind, the following recommendation is made for future research:

1. Future research examining the association between CDI and mortality should include collection of data on:
 - a. co-morbidities of individuals in the cohort
 - b. strains of *C.difficile*.

Findings from my study suggest that CDI is associated with increased mortality but only a considerable time after initial infection commencement. Efforts to better understand the epidemiology of CDI in Australia are required and infection prevention and control strategies for CDI need to be enhanced given that these findings suggest mortality in persons who had CDI is higher compared to persons who did not have CDI. With this in mind, the following recommendations are made:

2. Surveillance programs for CDI are enhanced to include collection of:
 - a. The date of death up to 180 days following infection (where relevant)
 - b. Examination of strains of *C.difficile* where possible
3. The use of exclusion criteria for duplicate cases of CDI, in both surveillance data and in research, needs further refinement to consider how new infections within an eight week period of the previous episode are managed.

4.9 Conclusion

This chapter presented an overview of CDI, including risk factors and the association between CDI and mortality. No published study examining CDI and mortality in the southern hemisphere was identified. This finding informed the second study for this thesis, presented in this chapter which examined mortality following CDI at the Royal Hobart Hospital, Tasmania. Results from this study indicated that CDI was associated with increased mortality, compared to persons who did not have CDI. More specifically, mortality following CDI was significant at 180 days post-admission to hospital and a considerable time after initial infection commencement. One potential reason for the result seen could be the use of exclusion criteria applied to the study population. This is an important finding in itself, as this study not only highlights the impact the CDI has on individuals, but also the potential influence that case definitions may have on valid and reliable results.

This study has the potential to influence local, state and national policy in CDI prevention by demonstrating the late impact that CDI may have on hospitalised individuals, compared to persons without CDI. Based on the findings of this research, specific recommendations have been made that are relevant to policy makers, infection control professionals and researchers. The next chapter discusses the third study contained within this thesis which examines the prolongation of length of stay due to CDI in hospitalised persons.

Chapter 5: Examining length of stay and *Clostridium difficile* infection

5.1 Introduction to the chapter

In the previous two chapters, the epidemiology of SAB and CDI in an Australian setting was discussed by presenting the first two studies of this thesis. In doing so, methodological influences on reliable and valid data have been highlighted. The third and final study of this thesis, presented in this chapter, continues this theme. In this chapter, the epidemiology of CDI is explored further in addition to estimating the prolongation of hospitalisation due to CDI.

In this chapter, the prolongation of length of stay in hospital is initially explored through a critical review of the literature which informed data analysis methods used for the third study of this thesis, examining the incidence of CDI and prolongation of length of stay due to CDI at the RHH in Hobart, Tasmania. The findings and recommendations from this study extend beyond CDI and have wider ramifications for examining other HAIs and their impact on length of stay.

In Chapter 4, background on *C.difficile* and CDI was presented. Reference can be made to Chapter 4, section 4.2 for details on pathogenesis, diagnosis, management of duplicate episodes of CDI, CDI acquisition and risk factors for the infection. The next section of this chapter details the literature surrounding CDI and prolongation of length of stay in hospital.

5.2 Literature review

5.2.1 Introduction to the literature review

Through exploration of epidemiology and mortality in the second study (Chapter 4), a picture emerges of the impact that CDI has on health services and patients. One important element in understanding the burden that CDI has on a health service is the additional economic cost of CDI in hospitalised patients. By having data on the prolongation of hospitalisation due to a

HAI, it is possible to inform basic economic analysis of the costs associated with a particular infection.

Determining the additional length of stay due to a HAI, including CDI, is challenging due to the need to manage time-dependent bias, that is, the longer a person stays in hospital, the greater the risk of acquiring an infection. Therefore, managing issues such as time-dependent bias and sampling bias are important. Through a review of the literature, this section will examine what is known about the impact CDI has on extending the length of stay in hospital, what gaps there are in our knowledge, and the different study designs used to determine this issue.

5.2.2 Search strategy

To evaluate the methodologies used to determine the excess length of stay caused by CDI in hospitalised patients, the literature was accessed through searches on Medline and Pubmed, limited to the years 2000 to 30th April 2011. Other limits included only searching literature published in English and studies involving humans. Key search words used in the search were “*Clostridium difficile* AND economic”, “*Clostridium difficile* AND length of stay”, “*Clostridium difficile* AND cost” and “*Clostridium difficile* AND burden”. These searches were combined, with duplicate studies removed. The initial search yielded 330 articles. After a subsequent review of these articles, case control, cohort or reviews were included if they examined the length of stay from hospitalised patients with CDI. Following this step, interventional studies, for example the effect of immunoglobulin treatment on length of stay were excluded.

Figure 20 summarises the search strategy used in this review and uses the PRISMA as the basis for presentation (Moher et al., 2009). A total of 16 articles remained and were included in the review and are summarised in

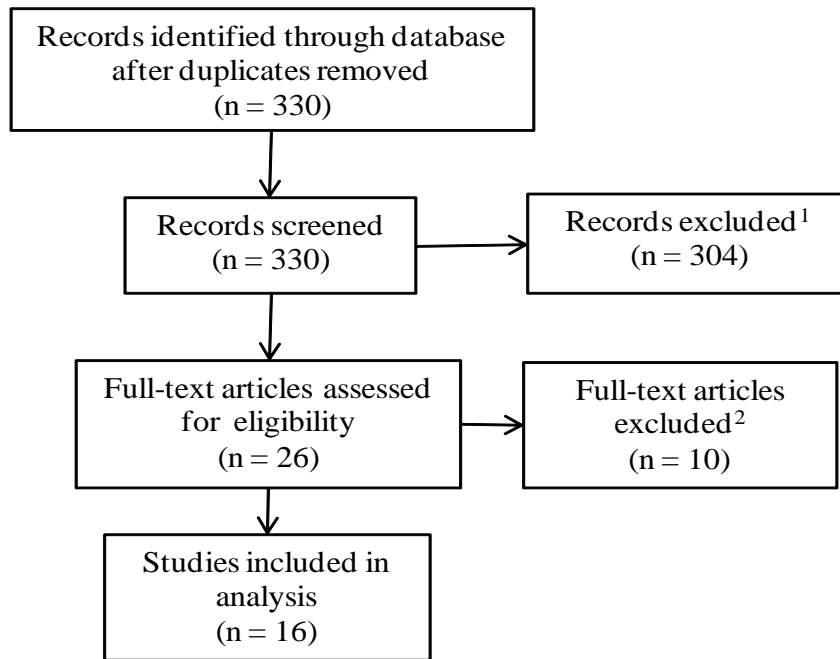


Figure 20. Summary of the search strategy used in the review examining length of stay and *Clostridium difficile* infection. ¹Articles were excluded if they were not case controlled, cohort or reviews or if they did not examine length of stay in hospitalised patients. ²Interventional studies were excluded.

5.2.3 Findings from the literature review

Overview

The majority (n = 12) of the 16 studies identified through the search strategy were retrospective in design. Two reviews were identified in addition to two prospective studies. The manner in which participants were identified differed, with several studies using ICD codes to identify episodes of CDI (Ananthakrishnan, McGinley, & Binion, 2008; Nguyen, Kaplan, Harris, & Brant, 2008; O'Brien, Lahue, Caro, & Davidson, 2007; Zerey et al., 2007; Zilberberg et al., 2009), whilst others used laboratory diagnosis. The use of ICD codes to identify participants has the potential to reduce the sensitivity and specificity of identifying cases of CDI. In addition, coding practices can vary among hospitals and therefore multi-centred studies have a greater potential for variation in sample selection. Further, the timing of the episode of *C.difficile* is unable to be determined when using such an approach.

The search strategy used to identify articles for this review did not identify the exact articles as those included in the latest review published by Ghantaji et al. (2010). Two articles included in the review by Ghantaji et al. (2010) were not included in my review, whilst my review identified and included eight studies not used by Ghantaji et al. (2010). The primary reason for these discrepancies is that my review examined the prolongation of length of stay, whereas the focus by Ghantaji et al. (2010) was economic cost. Similarly my review did not include two articles identified by the review conducted by Dubberke and Wertheimer (2009), but did identify a further 11 articles not used by Dubberke and Wertheimer (2009). The reasons for this are the same as those just described in addition to the inclusion of recent publications. Nine articles were common to both reviews. The review by Ghantaji et al. (2010) identified four articles not used by Dubberke and Wertheimer (2009). Conversely, Dubberke and Wertheimer (2009) identified five articles not used by Ghantaji et al.(2010).

Table 20

Summary of included articles in the review examining length of stay and Clostridium difficile infection

Author	Study type	Country	Statistical analysis	Results
Ananthakrishnan, McGinley, & Binion, 2008	Cohort	US	Linear regression	Three times LOS in person who had CDI and who have IBD compared to persons with IBD
Bajaj et al., 2010	Cohort ¹	US	Logistic regression	Mean LOS = 12.7 days in persons who had CDI Mean LOS = 6.7 days in persons with cirrhosis (no CDI)
Dubberke et al., 2008	Cohort	US	Logistic regression	Median LOS = 9.6 days in persons who had CDI Median LOS = 5.8 days in persons who did not have CDI
Dubberke & Wertheimer, 2009	Review	-	Review	Review
Ghantaji et al., 2010	Review	-	Review	Review
Kenneally et al., 2007	Cohort	US	Logistic regression	Mean ICU LOS = 13.7 in persons who had CDI Mean ICU LOS = 11.5 in persons who did not have CDI Mean hospital LOS = 27.3 in persons who had CDI Mean hospital LOS = 22.8 in persons who did not have CDI
Lawrence et al., 2007	Cohort	US	Linear regression	Median ICU LOS = 6.1 in persons who had CDI Median ICU LOS = 3.0 in persons who did not have CDI Median hospital LOS = 10.1 in persons who had CDI Median hospital LOS = 24.5 in persons who did not have CDI
Lumpkins et al., 2008	Cohort	US	Linear regression	Hospital LOS ¹ = 34.9 day LOS in persons who had CDI Hospital LOS ¹ = 19 in persons who did not have CDI
Miller et al., 2002	Case series	Canada	Not discussed	9% participants with CDI deemed to have mean extension of LOS of 10 days (median = 7 days)
Nguyen, Kaplan, Harris, & Brant,	Cohort	US	Linear regression	Mean hospital LOS = 9.9 days in persons who had CDI

2008				Mean hospital LOS = 6.7 days in persons who had ulcerative colitis
O'Brien, Lahue, Caro, & Davidson, 2007;	Cohort	US	Descriptive	Mean hospital LOS attributed to CDI = 6.4 days in patients with primary CDI as primary diagnosis Mean hospital LOS attributed to CDI = 2.9 days in patients with CDI as secondary diagnosis
Pepin, Valiquette, & Cossette, 2005	Cohort	Canada	Not discussed	Mean hospital LOS = 33.7 days in persons who had CDI Mean hospital LOS = 23.1 days in persons who did not have CDI
Song et al., 2008	Cohort	US	Linear regression	Median hospital LOS = 22 days in persons who had CDI Median hospital LOS = 18 in persons who did not have CDI
Vonberg et al., 2008	Cohort ²	Germany	Descriptive	Median hospital LOS = 27 days in persons who had CDI Median hospital LOS = 20 days in persons who did not have CDI
Zerey et al., 2007;	Cohort	US	Logistic regression	16 days longer LOS (with CDI)
Zilberberg et al., 2009	Cohort	US	Logistic regression	CDI correlated significantly with longer LOS (16.0 days, $p < 0.0001$) compared to persons without CDI

Note: CDI = *Clostridium difficile* infection. LOS = length of stay. DRG = Diagnosis Related Group. IBD = Inflammatory bowel disease. ¹Study did not state whether the LOS was mean or median LOS. ¹The authors of this study state their study design as case controlled. However persons in this study were selected by their study factor i.e. persons who had CDI, persons who had cirrhosis or persons who had both cirrhosis and CDI. Therefore, this study is a cohort study. ²The authors of this study state their study design as case controlled. However, all persons were included in this study if they had CDI and a selected (match) group of persons without CDI were included. The outcome, LOS was then examined. Therefore, this study is a cohort study.

Study settings

Excluding the reviews, only three of the remaining 14 studies were undertaken in countries other than the United States. There were no studies identified from an Australian setting. The systematic review examining the economic costs of CDI undertaken by Ghantaji et al. (2010) also reported that only four of the 13 included articles were not from the United States and no study was identified from Australia. In the review undertaken by Dubberke and Wertheimer (2009) one Australian study, published as a letter to the editor, was identified (Riley, Codde, & Rouse, 1995). A separate search for Australian studies examining length of stay and CDI confirmed this to be the last published study examining this topic in an Australian setting.

Data collection

The data collected in the various studies differed considerably. The majority of studies collected basic demographic data such as age and gender. Some studies collected data on co-morbidities and used a severity index such as the Charlson co-morbidity index (Dubberke et al., 2008; Nguyen et al., 2008; Pepin, Valiquette, & Cossette, 2005). Data collected on variables such as antibiotic exposure or other drug therapy were limited (Kenneally et al., 2007; Lawrence et al., 2007; Pepin et al., 2005).

Clostridium difficile infection and association with length of stay

Findings from all the studies suggested that CDI contributes to a longer length of stay in hospital. It was not possible to pool data as studies varied considerably in design, sampling and data analysis. In studies that used a comparison between persons with CDI and those without, the difference in the length of stay between the two groups ranged from 2.8 days to 16.1 days (Dubberke et al., 2008; Lumpkins et al., 2008). These data suggest that CDI may play a role in increasing the length of stay in hospital even after adjustment for confounders such as age.

In a cohort of over 18,000 non-surgical patients hospitalised for more than 48 hours, Dubberke et al. (2008) undertook an analysis of the nested subset of this population (persons who had CDI and did not have CDI) using a matched pairs analysis. The authors found that the length of stay attributable to CDI was 2.8 days. Persons without CDI were matched to persons who had CDI using a developed propensity score. The propensity score was developed by applying logistic regression to the data to predict the variables suspected to impact the risk of developing CDI. Median length of stay was determined for persons who had and did not have CDI, with the different median pairwise length of stay compared using the Wilcoxon signed ranked test. Attributable length of stay was calculated as the median pairwise difference between persons who had CDI and those who did not (Dubberke et al., 2008). As this study did not include surgical patients it is possible that those with severe CDI, requiring colectomies, were excluded leading to bias. A propensity score was used for matching, to reduce confounding between controls and cases in determining attributable length of stay.

A study undertaken by Lumpkins et al. (2008) suggested a considerably higher length of stay in hospital due to CDI, compared to the study undertaken by Dubberke et al. (2008). In a cohort study consisting of critically injured trauma patients admitted to an intensive care unit, those with and without CDI were analysed prospectively. A logistic regression model was used for data analysis in comparing the two groups and associated variables. The mean hospital length of stay was 15.9 days greater in patients who developed CDI, compared to those who did not (34.9 days vs. 19.0 days, $p = 0.003$). When persons who had CDI were compared by extent of antibiotic exposure, those with minimal exposure were found to have a shorter length of stay in hospital, however antibiotics exposure prior to injury was not obtained in this study (Lumpkins et al., 2008). Such a finding would suggest the need to collect data on antibiotic exposure in future studies employing a similar methodology to that used.

Data analysis

The methods of data analysis varied. In the majority of studies, a regression model was developed to attempt to determine the impact that CDI had on length of stay (Ananthkrishnan et al., 2008; Bajaj et al., 2010; Dubberke et al., 2008; Kenneally et al., 2007; Lawrence et al., 2007; Lumpkins et al., 2008; Nguyen et al., 2008; Song et al., 2008; Zerey et al., 2007; Zilberberg et al., 2009). The studies did not report the timing of onset of CDI and therefore it is not possible to exclude the possibility of reverse causality, in which longer lengths of hospitalisation may have increased the risk of CDI. The issues associated with controlling for a potential time-dependent bias caused by the length of stay in hospital raises some significant concerns. In order to explore this particular issue in more detail, literature, specifically in relation to this issue will now be explored.

Controlling for length of stay prior to infection onset

Some literature suggests that previously applied models to determine the additional length of stay in hospital due to infection result in an overestimation compared to newer statistical models (Barnett et al., 2009; Beyersmann, Gastmeier, Wolkewitz, & Schumacher, 2008; Beyersmann, Kneib, Schumacher, & Gastmeier, 2009; Beyersmann, Wolkewitz, & Schumacher, 2008; Graves et al., 2010; Graves et al., 2007). The prolongation of hospitalisation due to any infection is an element in estimating cost (N. Graves, Halton, K., Jarvis, W., 2009). It is therefore vital that studies are designed to evaluate and analyse this effectively. Methods used to evaluate costs associated with HAIs are discussed in more detail in Appendix I. The method used to determine length of stay should account for the fact that a HAI, such as *C.difficile*, can occur at any point during a hospitalisation and that length of stay is affected by other variables such as co-morbidity and primary diagnosis (Graves et al., 2010). Matched cohort studies suffer from two types of bias. First, some patients are predisposed to a longer length of stay and matching is unable to control all bias. Second, in an attempt to control for all bias, increasing matching criteria often causes individuals to be selected out of the study (Graves et al., 2010).

The time varying nature of infection also poses an issue in matched studies. Infections can occur at any time however data analysis in matched studies often compares infected and uninfected patients by their total hospital stay, as evidenced by the findings of this review. If the timing of infections is not taken into account, costs associated pre and post infection are included and can dramatically amplify confounding and lead to time-dependent bias (Graves et al., 2010). Statistical models can be used to address this issue at the data analysis stage, rather than at the design stage. A model can be built to describe the relationship between length of stay and the predictors of that outcome (Beyersmann, 2007; Graves et al., 2010). Previously, models that ignored the time of infection often used a linear model assuming a gamma distribution of length of stay and an independent variable of infected (yes/no) (Barnett et al., 2011).

Methods have recently been developed to address this issue when estimating length of stay and HAIs. These methods include a multistate model in which the infection is the intermediate event between admission and discharge and patients are given three states: non-infected, infected, and discharged (Barnett et al., 2009; Barnett et al., 2011; Beyersmann et al., 2006). Therefore, for future research examining the prolongation of length of stay in persons with a HAI such as CDI, data collected on the commencement and completion of infection will enable the potential to use a multistate model in data analysis.

5.2.4 Summary of literature review

Studies examining length of stay attributable to CDI vary considerably in their design and data collected. Several studies used administrative codes, such as ICD codes, to identify cases of CDI. The use of administrative data for this purpose does have some limitations, including the potential for ascertainment bias and lack of sensitivity and specificity. A limited number of studies captured data on co-morbidities which

influence the length of stay in hospital and thus this information should be collected where possible.

Despite these differences, there was a clear indication that CDI plays some role in the prolongation of length of stay in hospitalised patients. As length of stay in a hospital is a major contributor to healthcare cost, it is a logical assumption that CDI has an economic cost to the health system, a view shared by Ghantaji et al. (2010). None of the studies identified in the literature review or in the two published reviews by Ghantaji et al. (2010) and Dubberke and Wertheimer (2009) examined the length of stay caused by CDI in an Australian setting. The last published study in an Australian setting was published 17 years ago (Riley et al., 1995). The provision of health services and the epidemiology of CDI vary among countries and therefore it is vital that future studies examining length of stay and CDI are undertaken in a variety of countries.

Potential issues in data analysis were identified, as no study fully addresses the issue of time-dependent bias when examining the length of stay caused by CDI. More specifically, no study identified the onset and cessation of CDI infection and used these data to inform data analysis. Recent literature suggests that a multistate model should be used to manage the issue of time-dependent bias. In order for a multistate model to be used, the timing of CDI infection must be captured. No study identified in the literature search undertaken, including the two published reviews examining the economic cost of CDI, used or identified a multistate model design. The third study to be presented in the next section was informed by the findings of the literature review just described.

5.3 Objectives and research questions

The objectives for the third and final piece of research for this thesis were to explore the incidence of CDI and prolongation of length of stay due to CDI and to analyse potential influences of differing data analysis methods in the calculation of any prolongation of length of stay. To address these objectives, the following research questions were developed:

In the period 1st January 2007 to 30th December 2010, for all admissions for hospitalised patients aged two years or older in a Tasmanian acute public hospital:

1. What is the incidence of CDI?
2. What impact does CDI have on the prolongation of length of stay, when managing time-dependent bias?

In order to answer the second research question, data were available to enable the incidence of CDI to be explored. Describing the incidence allowed for a logical flow in this study.

5.4 Methods

5.4.1 Study design

To address the research questions, an observational design, with dynamic population was applied.

5.4.2 Setting, timeframe and selection of the population

All persons hospitalised more than 48 hours aged two years or older, between the 1st January 2007 and the 30th December 2010 at the RHH, Hobart, Tasmania, formed the study population. In this chapter, persons in the study population will be referred to as “admissions” from this point forward. A description of the characteristics of the RHH was provided Chapter 4, section 4.5.2. From the available data, those persons who developed CDI during their hospital stay were subsequently identified. A person was defined as having CDI, based on the national surveillance definition for CDI and as previously described in Chapter 4, section 4.5.3.

5.4.3 Data collection

This section on data collection is divided into two parts. The first describes the data collection process and the second outlines the specific data items collected during each step of the process and the rationale for collecting specific items.

Data collection process

Data were retrieved from four different sources. These sources comprised data from the Clinical Coding department of the RHH, the TIPCU, the Infection Prevention and Control Unit at the RHH, and through a review of the patient administration system and medical records of each member of the study population by the researcher.

To identify the population, all admissions aged two years and older admitted to the RHH for more than 48 hours during the study period were identified by the Clinical Coding department at the RHH at the request of the researcher. To allow for the identification of persons who developed CDI during their hospital stay, the TIPCU provided the researcher with details on all admissions who had an episode of CDI occurring at the RHH during the study period. The identification of admissions with CDI was described in more detail in Chapter 4, section 4.5.3.

Once the researcher had obtained information on the admissions with CDI from the TIPCU, further data were collected through a review of the records held on the RHH patient information system and medical records of those with CDI. The data items collected during this process, including the rationale for collecting some of the items are detailed shortly.

The Infection Prevention and Control Unit at the Royal Hobart Hospital collects data on the timeframe a person with CDI is isolated under contact precautions. The researcher reviewed data provided by this unit for when persons with CDI had contact precautions ceased. The rationale for using the cessation of contact precautions as a marker for infection cessation is described in more detail in the following section. Data using this process were only available from the 1st July 2009 until the 30th December 2010, as the RHH infection control unit did not collect this data prior to the 1st July 2009. There were 11 instances within this timeframe where data were not available from the RHH infection control unit. Subsequently, specific review of the medical notes of these 11 admissions was conducted by the researcher and resulted in the date a person was removed from isolation being identified for another six admissions. Therefore, data on when a person was removed from isolation could not be obtained in five instances. Data on isolation periods for a total of 72 persons (1st July 2009 until 30th December 2010) were obtained.

Data items collected

This section contains information on the specific data items collected from each of the various data collection sources. The rationale for the choice of how data on the cessation of CDI was collected will be explored in more detail. Table 12 provides a summary of the data items collected, the manner in which they were defined and the source from where these data were obtained. The data collected were collated in Microsoft Excel.

Table 21

Data collected and source

Data field	Definition	Source of data	
		Admission with CDI	Admissions without CDI
Date of birth	Date of birth	TIPCU**	RHH clinical coding*
Sex	Male, female or intersex as stated on the PAS	TIPCU**	RHH clinical coding*
Age	Age at time of specimen collection	TIPCU**	RHH clinical coding*
Admission date	Date of admission to the RHH	TIPCU**	RHH clinical coding*
Discharge date	Date of discharge from the RHH or date of death (whichever is first)	Researcher - review of medical records & PAS***	RHH clinical coding*
Date of death (if applicable)	Date of death up to 180 days post-date of infection commencement	Researcher - review of medical records & PAS***	RHH clinical coding*
Date infection commenced	Date of specimen collection	TIPCU	N/A
Date infection ceased [^]	Date contact precautions were ceased	RHH Infection Prevention & Control Unit records	N/A
Diagnosis Related Group (DRG)	Methods used to categorise and characterise episodes of care received by patients admitted to hospitals ****	RHH clinical coding*	RHH clinical coding*

Note: PAS = patient administration system. *Sourced from the PAS by clinical coding. **Originally sourced from PAS by the TIPCU and cross checked by the researcher. ***Described in more detail in Chapter 6. ****Adapted from “*Australian Refined Diagnosis Related Groups Version 6.0 Definitions Manual Volume One*,” by Australian Government. Copyright 2008 by the Commonwealth of Australia. [^]Only available for the period 1st July 2009 to 31st December 2010 as described in section 5.4.3.

The issue of defining CDI cessation in an individual is challenging. As *C.difficile* may continue to be detected from asymptomatic colonisation, laboratory testing for clearance of CDI is not recommended (Stuart et al., 2011). The researcher undertook a review of 20 medical notes of admissions with CDI and found that medical records

failed to document a formed stool or cessation of diarrhoea reliably. Based on the findings from the review of the 20 medical records, it was considered that the cessation of contact precautions for persons with CDI was a simple, reliable and practical method of determining cessation of CDI and was consistent with literature (Cohen et al., 2010; National Health and Medical Research Council, 2010).

The decision to cease contact precautions at the RHH at the time of the study was consistent with recommendations made by the Australian Infection Control Association, the National Health and Medical Research Council and the Infectious Disease Society of America (Cohen et al., 2010; National Health and Medical Research Council, 2010; Stuart et al., 2011). Additionally, the decision to cease contact precautions was made after a review by an infection control professional at the time of making this clinical decision.

5.4.4 Ethical considerations

Ethical approval for this research was granted by the Tasmanian HREC (H0011484) and by Australian Catholic University (N201150). Copies of ethics approvals are provided in Appendix P and Appendix Q. The application for ethics approval included a request to have consent from participants waived. The same justification for consent being waived as described in the previous two case studies was accepted.

The study population for this study differed from that described in study two (Chapter 4). All persons admitted to the RHH for more than 48 hours, aged two years and older were included in this study. Therefore, the size of the study is considerably higher than that presented in Chapter 4. Conversely, less personal data were required to be obtained for this study.

De-identified data were analysed in this study. All patient identifiable information was removed from the database immediately after data collection was complete.

5.4.5 Data analysis

After the provision of an overview on data management, this section will be structured by describing the analysis plan for the research questions.

Preliminary data management

Data entered into Microsoft Excel were coded by the researcher from text into numerical values ensuring date formats were consistently applied. Data from the Microsoft Excel spread sheet were then imported into IBM SPSS Version 20.0 for initial data analysis. Further data cleaning in SPSS occurred and included checking codes for errors, detecting implausible values and identifying missing values through frequency and cross tabulation calculations. New variables were computed in SPSS based on raw data collected. These new variables were grouped: CDI or no CDI, length of stay, and discharge outcome. The definition and detail regarding these three variables have been previously discussed in Chapter 4 and can be reviewed in Table 13, Chapter 4.

Statistical analysis

Descriptive analysis on the characteristics of the admissions was performed in IBM SPSS Version 20.0 (International Business Machines Corporation, 2011). Data analysis included determining the median length of stay and age for all admissions. The distribution of length of stay and age were analysed using Q-Q plots and tested using the Kolmogorov-Smirnov test. Univariate data analysis was performed comparing those with and without CDI. The calculation of relative risk was performed to compare occurrence of CDI in different groups. Time to discharge (crude length of stay) was described using Kaplan-Meier survival curves. A log rank (Mantell-Cox) test was used to compare crude length of stay between persons who had CDI and those who did not. Data analysis was then undertaken to determine the

prolongation of length of stay due to CDI. This specific analysis is described in more detail in the remainder of this section.

To determine the prolongation of length of stay due to CDI, data were analysed using a multistate model, undertaken in the statistical software program *R*, version 2.13.2 (R Development Core Team, 2011). Multistate models are models for a process, for example describing a life history of an individual, which at any time occupies one of a few possible states. They can be used to explore several possible events for one individual, or the dependence among several individuals (Hougaard, 1999). Events are transitions between the different states that a person may undergo. Multistate models are useful for modelling different events, which have an event-related dependence, like occurrence of HAI (Hougaard, 1999).

The first step in determining the prolongation of length of stay using a multistate model is to consider the possible state and paths a person may undergo i.e. the multiple states a person may go through during their admission. As described in the literature review presented earlier in this chapter, studies have traditionally performed data analysis where CDI was considered a time-dependent covariate. The approach used in other studies does not permit the calculation of length of stay due to CDI explicitly as retrospective stratification of cases (infected) and controls (non-infected) are likely to overestimate the effect of CDI, as described in the earlier literature review. Even the inclusion of time to infection as a baseline covariate in Cox proportional hazard model does not adjust for time-dependent bias as the time to infection itself is a time-dependent covariate (Beyersmann et al., 2009). These issues are explored in more detail shortly.

In this study, all admissions were considered to be admissions without infection and only progressed to an infected state if and when they were confirmed as having CDI. In principle, every individual can move between different states (Wolkewitz, Allignol, Schumacher, & Beyersmann, 2010). In the case of my research, individuals could have three states: susceptible (infection free), infected, and discharged. All admissions

in the study were considered as being susceptible to infection until they were either discharged or they succumbed to infection. The discharged state could be either discharged alive or discharged died. Figure 21 demonstrates the different states that an admission in the study could progress through.

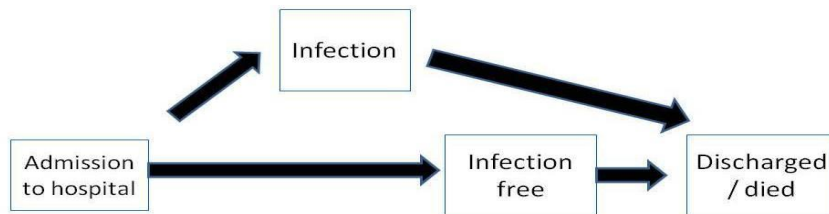
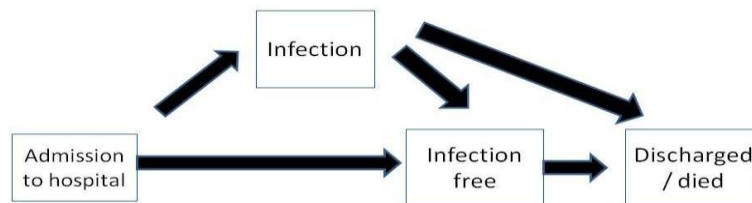


Figure 21. Model demonstrating the different states a person can transition through in my study.

In finalising the above model, a number of other models were explored. The two most plausible models are displayed in Figure 22.

Model A



Model B

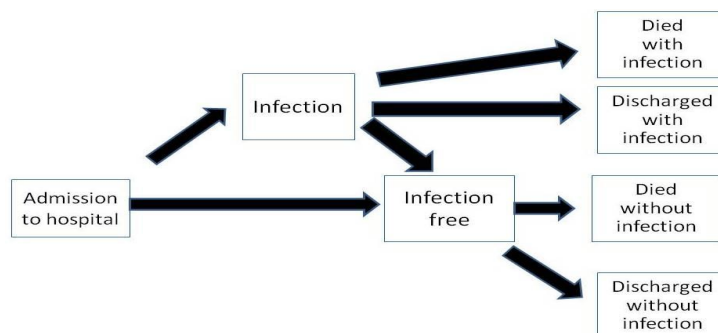


Figure 22. Potential multistate models. These models were explored before deciding on the final model for my study.

Model A (Figure 22) was more accurate in describing the path of a person with CDI in hospital, compared to that described in Figure 21. Once a person has ceased having CDI, they may either be discharged or they may go back into the 'no infection' state. In Chapter 9, the number of persons who are discharged the day CDI ceases is described and was relatively low in number. The majority of persons with CDI move back into a state of 'no infection'. The researcher had discussions with leading biostatisticians responsible for developing multistate models that examine prolongation of length of stay due to HAIs. They were unable to assist in the development of a code for R that could have been used for data analysis that reflected Model A. Therefore, despite being the optimal model, Model A was not able to be used for data analysis.

Model B displayed in Figure 22, is an extension of Model A. Model B divides the discharged status into discharged alive or discharged died and allows for the transition of those persons who had an infection, back into a non-infection status.

The developed model used for this study (Figure 21) assumed that the movements between states were Markovian, i.e. the future state only depends on the present state. Therefore, analysis on each episode of CDI was considered to represent a separate patient. If a person had two episodes of CDI during the study period, they were analysed as data for two independent individuals (Beyersmann et al., 2006; Gastmeier et al., 2003). The model described in Figure 21 is referred to as a three state model in the published literature and has been summarised in the manner displayed in Figure 23. Despite not being the optimal model, the three state model has been shown to be superior in estimating the length of stay due to HAIs, when compared to other methods as demonstrated in the literature review conducted to inform this research.

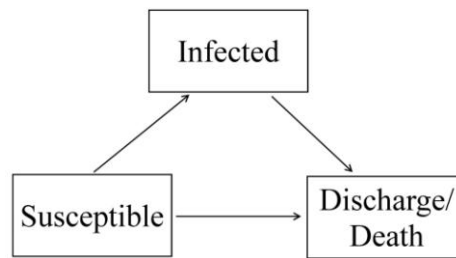


Figure 23. Three state model. The term ‘susceptible’ refers to persons who are susceptible to the given infection. In the case of my study, ‘susceptible’ refers to inpatients of a hospital.

The hazard used in data analysis for this study was estimated using the multivariate Nelson-Aalen estimator (MVNA) in *R*. Multistate models require specialised software and a multistate model package is available in *R* (Meira-Machado, de Uña-Álvarez, Cadarso-Suárez, & Andersen, 2009). Infection was modelled as a time-dependent covariate to avoid time-dependent bias which over-estimates any increased length of stay due to infection. This particular issue is discussed in more detail shortly. A technical explanation for a multistate model is provided in Appendix J.

The use of a multistate model provides a framework for the display and management of length bias and time-dependent bias, which can distort the statistical analysis through a misclassification of ‘at risk time’ (Wolkewitz et al., 2010). Using the multistate model for my study (Figure 23), a Lexis diagram, displayed in Figure 24 with fictional data, was developed to demonstrate the potential for length and time-dependent bias. Lexis diagrams visualise complex survival data, where individuals are displayed as lines on a calendar time. Lexis diagrams are particularly useful in displaying time-dependent study entries into a study population and exposures (Lund, 2000).

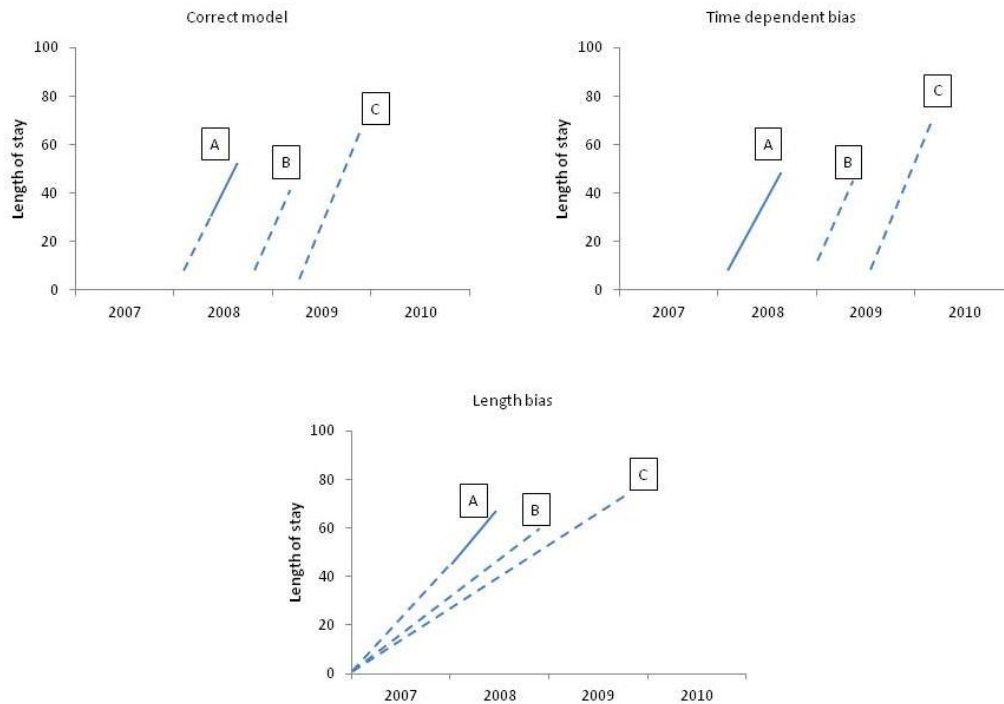


Figure 24. Lexis diagram demonstrating the potential for time-dependent and length bias in my study. Each line represents an individual person's time in hospital and the data they contribute to the study. Three individuals are presented in this diagram, labelled A, B and C. Individuals B and C do not ever have CDI during their hospital stay. Solid lines indicate the time a person has CDI. Dotted lines the time a person does not have CDI. Data are fictitious.

If the time between admission and infection is ignored, then the study has the potential to introduce length bias. Length bias occurs if it is incorrectly assumed that individuals enter the study at the time of study commencement, that is, the time interval between the date of study entry and discharge is incorrectly longer than the actual time interval (Asgharian, M'Lan, & Wolfson, 2002). Length bias can be overcome by the correct application of data analysis techniques, such as Cox Proportional hazards models, assuming data are coded correctly. In my study this issue is overcome by persons entering the study on their actual date of hospital admission and leaving the study on their discharge date. My study does not assume all admissions entered the study on the 1st January 2007. Time-dependent bias occurs in data analysis when a time-dependent exposure is incorrectly analysed as a baseline covariate (Wolkewitz et al., 2010). This type of bias is related to a time-dependent

exposure or an intermediate event. In the case of my study the event is CDI. To explain how time-dependent bias was managed in my study, the following was considered.

All persons who were admitted to the RHH were at risk of CDI. In persons who had CDI, their data contributed to the risk sets (length of stay) of persons without CDI, between the date of admission and infection commencement. Via truncation, persons with CDI were then followed up from the time of commencement until discharge (Wolkewitz et al., 2010). If the time between admission and infection commencement was ignored, it would have incorrectly assumed that a person with CDI contributed to the risk set before their infection commenced, thereby resulting in time-dependent bias (Wolkewitz et al., 2010). This is represented in the graph labelled “Time-dependent bias” in Figure 24. The code used in *R* for data analysis is detailed in Appendix K.

In addition to the use of a multistate model, data were analysed using a Cox proportional hazard model in IBM SPSS Version 20.0 (International Business Machines Corporation, 2011). This was undertaken to demonstrate how different data analysis techniques influence results. A Cox proportional hazard regression model was developed to estimate the proportional hazard of discharge. Variables found to be significant in univariate analysis were entered into the model using a forward stepwise condition process.

Summary of methods

This section provided an overview of data management and described the analysis plan for the research questions. Descriptive statistics and a Cox proportional hazard model were undertaken in IBM SPSS Version 20.0. Traditionally, studies that calculate excess length of stay due to a HAI do not permit the calculation of length of stay due to the infection explicitly. Retrospective stratification of persons with and

persons without infection is likely to overestimate the effect of CDI. Even the inclusion of time to infection as a baseline covariate in Cox proportional hazard models has been shown not to adjust for time-dependent bias as the time to infection itself is a time-dependent covariate. Therefore, to determine the prolongation of length of stay due to CDI using a multistate model, data were analysed using a multistate model, undertaken in the statistical software program *R*, version 2.13.2 (R Development Core Team, 2011). Different multistate models were explored in this section and the model used for data analysis in this study provided.

5.5 Results

5.5.1 Population size and incidence of infection

During the study period, there were 58,942 admissions of persons aged two years and older to the Royal Hobart Hospital (RHH) who stayed for 48 hours or longer. These 58,492 admissions equated to a total of 493,626 bed days, defined as the sum of each individual person's length of stay in hospital. The total number of admissions per annum to the RHH increased from 14,055 in 2007 to 15,185 in 2010, representing an 8% increase over the four years, as demonstrated in Figure 25. Within this four year period, the largest seasonal increase in admissions occurred in spring, with a total of 16.5% more persons being admitted in 2010 compared to 2007.

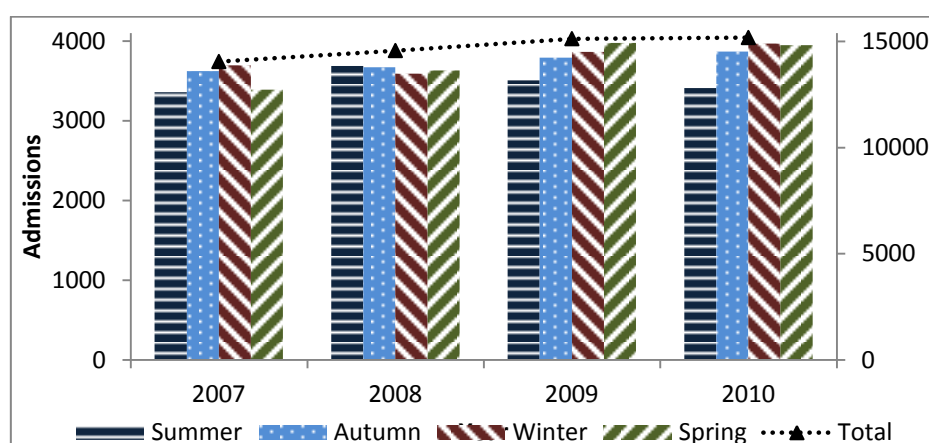


Figure 25. Distribution of hospital admission dates. Admissions = admissions to the RHH hospitalised ≥ 48 hours and aged ≥ 2 years old. Total admissions per year = 14,055 in 2007, 14,571 in 2008, 15,131 in 2009, and 15,185 in 2010.

As described in Chapter 4, there were 158 admissions with an episode of CDI in the calendar years 2007 to 2010. Despite removing duplicate samples occurring within eight weeks of the previous positive sample, there were five instances of a secondary infection occurring in the same person during the four year study period. Further analysis of these five individuals suggests that secondary cases were unrelated to the first case. More information regarding these secondary cases of CDI was provided in Chapter 4, section 4.6.1.

The annual incidence of CDI per 1000 admissions for the calendar years 2007 to 2010 ranged from 1.71, 95% CI [1.12, 2.50] to 3.89, 95% CI [2.96, 5.01] (Figure 26). Raw data informing this figure are provided in Appendix L. The incidence of CDI per 1000 admissions for the entire study period was 2.68, 95% CI [2.28, 3.13]. There was a statistically significant increase in the incidence of CDI in 2010 compared to 2007 ($p < 0.001$).

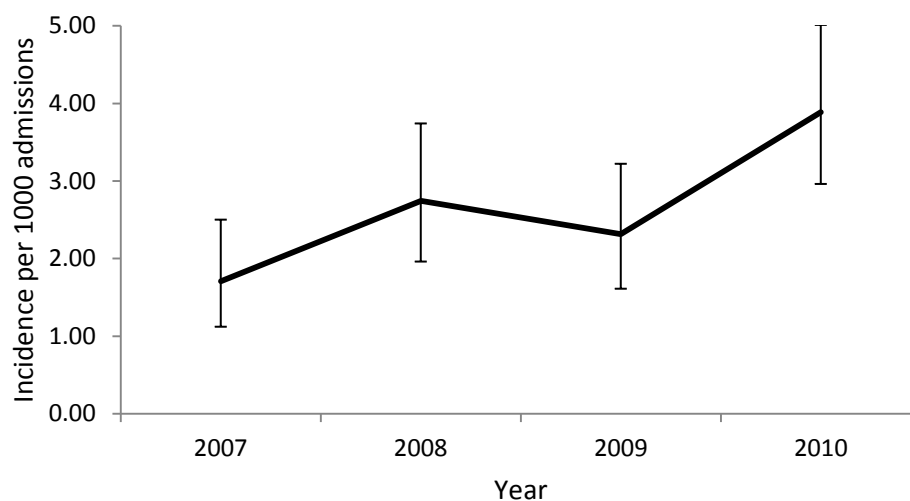


Figure 26. Incidence of *Clostridium difficile* infection (CDI) per annum at the Royal Hobart Hospital between 2007 and 2010. Admissions = total admissions hospitalised ≥ 48 hours and aged ≥ 2 years old. Admissions with CDI occurring ≥ 48 hours after hospital admission in persons aged ≥ 2 years old. Errors bars denote 95% confidence intervals. Total admission with CDI = 158.

5.5.2 Demographic characteristics of the study population

The distribution of age for the study population was not normal: $D(58,784) = 0.08$, $p < 0.001$ (Kolmogorov-Smirnov test). As the size of the study is large, the distribution of age was confirmed as non-normally distributed using Q-Q plots. Table 22 displays the age and sex characteristics of admissions.

Table 22

Demographic characteristics of those with and without Clostridium difficile infection

Characteristic	Admissions that developed CDI (n = 158)	Admissions that did not develop CDI (n = 58,784)	Total (N = 58,942)
Sex			
Male	79 (50%)	25,915 (44.1%)	25,994
Female	79 (50%)	32,857 (55.9%)	32,936
Intersex**	-	11 (<1%)	11
Not specified	-	1 (<1%)	1
Age			
Median	67	55	55
Range	2-102	2-106	2-106
Age group			
2-9	3 (1.9%)	1523 (2.6%)	1526 (2.6%)
10-19	6 (3.8%)	3471 (5.9%)	3477 (5.9%)
20-29	3 (1.9%)	7977 (13.6%)	7980 (13.5%)
30-39	5 (3.2%)	6928 (11.8%)	6933 (11.8%)
40-49	13 (8.2%)	5748 (9.8%)	5761 (9.8%)
50-59	24 (15.2%)	6759 (11.5%)	6783 (11.5%)
60-69	31 (19.6%)	8609 (14.6%)	8640 (14.7%)
70-79	38 (24.1%)	9159 (15.6%)	9197 (15.6%)
80-89	30 (19.0%)	7057 (12.0%)	7087 (12.0%)
≥90	5 (3.2%)	1553 (2.6%)	1558 (2.6%)

Note: CDI = *Clostridium difficile* infection.

Age stratification, examining the incidence of CDI per 1000 admissions, was performed. The results displayed in Figure 27 and Table 23 demonstrates the incidence of CDI by age group. The incidence of CDI increases from the 30-39 year age group until the 80-89 year age group. The incidence of CDI stratified by sex and age group is provided in Table 23.

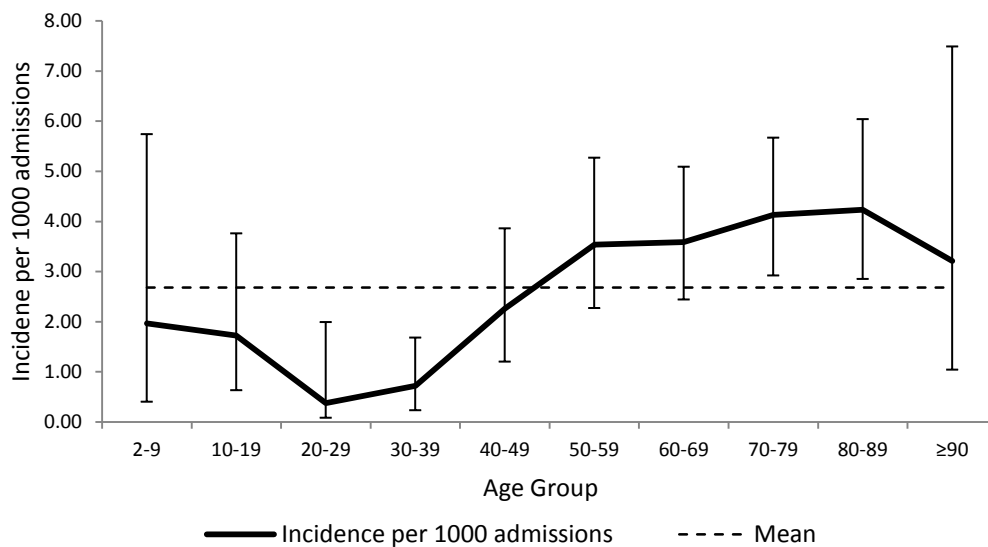


Figure 27. Incidence of *Clostridium difficile* infection (CDI) per annum at the Royal Hobart Hospital between 2007 and 2010 by age group. Admissions = total admissions hospitalised ≥ 48 hours and aged ≥ 2 years old. Admissions with CDI occurring ≥ 48 hours after hospital admission in persons aged ≥ 2 years old. Mean = incidence of CDI over the entire study period. Errors bars denote 95% confidence intervals.

Table 23

Incidence of Clostridium difficile infection stratified by sex and age group

Characteristic	Incidence per 1000 admissions	95% confidence interval
Sex		
Male	1.34	1.07-1.66
Female	1.34	1.07-1.66
Age group		
2-9	1.97	0.40-5.74
10-19	1.73	0.63-3.76
20-29	0.38	0.08-1.99
30-39	0.72	0.23-1.68
40-49	2.26	1.20-3.86
50-59	3.54	2.27-5.27
60-69	3.59	2.44-5.09
70-79	4.13	2.92-5.67
80-89	4.23	2.85-6.04
≥90	3.21	1.04-7.49

Note: Admissions = total admissions to the RHH hospitalised ≥ 48 hours. Admission with *Clostridium difficile* infection occurred ≥ 48 hours after hospital admission in persons aged ≥ 2 years old. Study period = 2007 to 2010 calendar years.

The probability of a person admitted to the RHH during the study period having CDI relative to their age group is displayed in Table 24. In calculating the relative risks displayed in Table 24, reference groups were persons aged less than the stated age group. Results are displayed in this manner to demonstrate the graduating relative risk. The graduating relative risk displayed in this manner can inform a decision as to the age groups CDI surveillance should be performed in. This point is discussed further in section 5.6.2.

Table 24

Comparison of relative risk of Clostridium difficile infection by age group

Age group	Incidence	Admissions that developed CDI /		
		Admissions	RR	95% CI
≥80 years old*	4.06	35 / 8610	1.66	1.14-2.40
≥70 years old*	4.11	73 / 17,769	1.98	1.44-2.70
≥60 years old*	3.94	104 / 26,378	2.36	1.70-3.27
≥50 years old*	3.86	128 / 33,137	3.29	2.21-4.90
≥40 years old*	3.63	141 / 38,885	4.23	2.56-7.00
≥30 years old*	3.19	146 / 45,813	3.44	1.91-6.19
≥20 years old*	2.77	149 / 53,790	3.53	1.80-6.88
≥10 years old*	2.71	155 / 57,261	1.36	0.43-4.24

Note: *Reference group are persons aged less than the stated age group. RR = relative risk. CDI = *Clostridium difficile* infection. Admissions with CDI = number of admission with CDI occurring ≥48 hours after hospital admission in persons aged ≥2 years old. Admissions = number of admissions to the Royal Hobart Hospital in persons aged ≥2 years old with a length of stay in hospital ≥48 hours. 95% CI = 95% confidence interval. Confidence interval calculated using Taylor series.

Comparisons were made between the DRG category assigned to persons with and without CDI (Table 25) Table 25 only details DRG categories where the P value was ≤0.10. The comparison of all DRG categories is provided in Appendix M.

Table 25. Comparison of Diagnosis Related Group in person with and without *Clostridium difficile* infection at the Royal Hobart Hospital, 2007-2010

DRG category	Admissions that developed CDI (%)	Admissions that did not develop CDI (%)	Total (%)	Chi sq. statistic	p value
Pregnancy	1 (0.6)	7898 (13.4)	7899 (13.4)	22.26	<0.01
Nervous	20 (12.7)	5007 (8.5)	5027 (8.5)	3.46	0.06
Digestive	21 (13.3)	4709 (8.0)	4730 (8.0)	5.95	0.02
Mental health	1 (0.6)	3894 (13.4)	3895 (6.6)	9.17	<0.01
Kidney	10 (6.3)	1577 (2.7)	1587 (2.7)	8.00	<0.01
Neoplastic	8 (5.4)	795 (1.4)	803 (1.4)	16.15	<0.01

Note: DRG = Diagnosis Related Group. Only DRG categories with a p value of ≤ 0.1 were included in this table. All DRG categories are provided in Appendix M. Those admissions with an “Error” or “Pre” DRG classification were excluded from this table. These categories are artefacts of the way DRG are coded and clinically do not fit with the above analysis.

5.5.3 Timing and duration of infection

For admissions that had an episode of CDI, the median time to infection from admission was eight days, with a range of two to 104 days (75th percentile = 13 days). As described in the methods section, available data about the length of time admissions had infection was incomplete. The time an admission was in isolation in hospital was only identified for 72 of the 158 instances of infection. For these 72 infections, the median time an admission had CDI was five days, with a range of one day to 47 days. Twenty-five per cent of these admissions had CDI for 11 days or more. The total number of bed days for the time between infection cessation and discharge was 286.

5.5.4 Length of stay using univariate analysis

Using the Kolmogorov-Smirnov test, the length of stay was not normally distributed ($p < 0.001$) and this distribution was confirmed by Q-Q plots. The median length of stay for all admission was five days. The median length of stay for those who did not have CDI at any time during their hospitalisation was five days (range 2-312). For those persons who had an episode of CDI during their hospitalisation, the median length of stay was 17 days (range 2-214).

Using the Mann Whitney U test, a significant difference was found between the median length of stay in those who had an episode of CDI, compared to those who did not ($\chi^2 = 178.3$, $p < 0.001$). A Kaplan–Meier survival graph demonstrating the crude length of stay in hospital up to 100 days for admissions with and without infection CDI is displayed in Figure 28. The proportion of cases with a length of stay of 100 days or less was 99.8%. There was a significant difference in the length of stay between those who had CDI, compared to those who did not ($\chi^2 = 141.6$, $p < 0.001$).

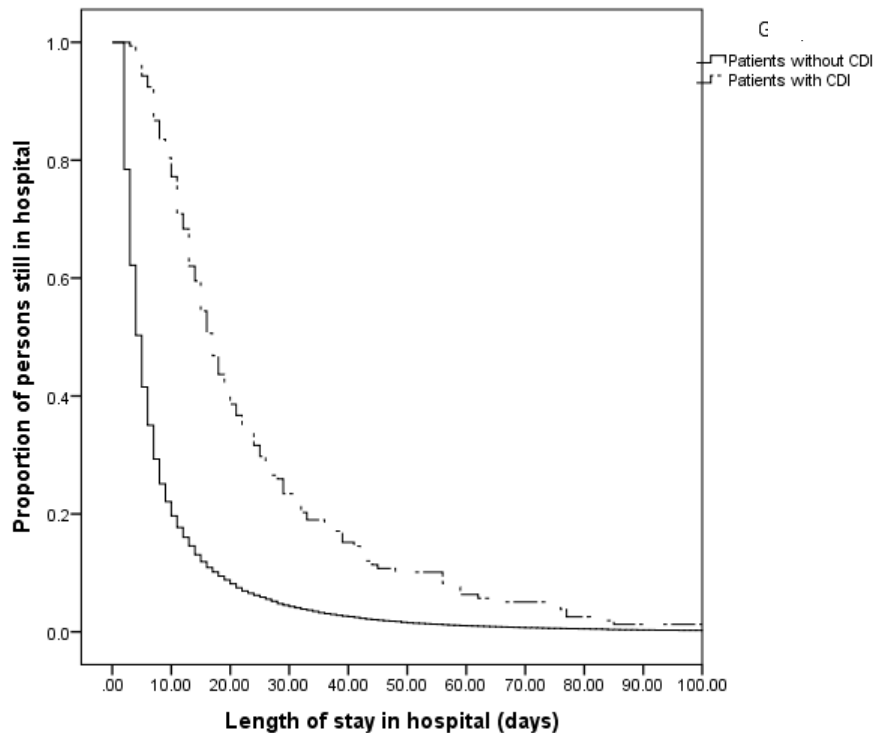


Figure 28. Unadjusted length of stay for persons with and without *Clostridium difficile* infection at the Royal Hobart Hospital, 2007-2010. CDI = *Clostridium difficile* infection.

5.5.5 Prolongation of length of stay using a multistate model

A multistate model was developed to estimate the prolongation of length of stay due to CDI. The multistate model used for data analysis was described in section 5.4.5 and enabled the time-dependent nature of CDI to be taken into account. Using a multistate model, the mean extra length of stay due to infection was calculated to be 0.9 days, $p = 0.51$, 95% CI [-1.8, 3.6] using the empirical transition matrix in the statistical package R. Therefore, the increase in length of stay for people who had CDI was not statistically significant at the 0.05 level. Figure 29 displays the estimated length of stay by each day of infection.

The extra length of stay for patients who were ultimately discharged and for those who ultimately died was 0.9 days and 0 days, respectively. In considering these results however, death was only measured as death on discharge from hospital (in-hospital mortality). The study presented in Chapter 4 provides a more thorough explanation of mortality and CDI.

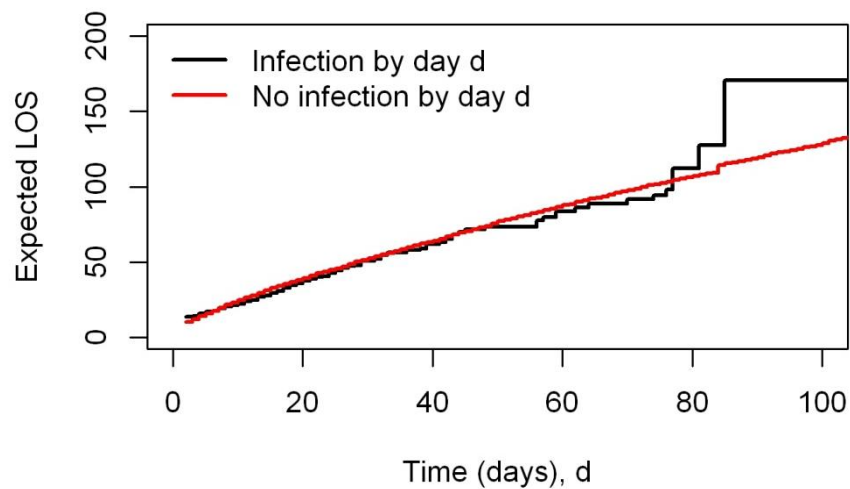


Figure 29. Estimated length of stay by each day of *Clostridium difficile* infection in persons admitted to the Royal Hobart Hospital, 2007-2010. The red line shows the expected length of stay in hospital for each increasing day along the x-axis. The black line shows the difference from this length of stay for those with an infection. Only person's aged ≥ 2 years old admitted to hospital ≥ 48 hours are included.

Figure 29 demonstrates divergence in the expected length of stay in persons with and without CDI from around 80 day's post-admission to hospital. Further exploration of these data indicates that only 308 persons out of 58,942 admissions remained in hospital more than 80 days. Of these 308 persons, four had an episode of CDI.

5.5.6 Prolongation of length of stay using a Cox proportional hazard model

A Cox proportional hazard model was developed to estimate the hazard of discharge (dead or alive), comparing those with and without CDI. The proposed null hypothesis was that CDI does not increase the hazard of discharge. In univariate analysis, there was a statistically significant difference for six prognostic variables, when comparing those with and without CDI. The six variables were age and the DRG categories of digestive, neoplastic disease, mental health, kidney, and pregnancy, which were included in the model using a forward stepwise conditional (likelihood ratio) process. In contrast to the results in section 5.5.5, the influence of CDI in a proportional hazard model was found to be statistically significant, with acquisition of CDI significantly reducing the discharge hazard (i.e. it prolonged the length of stay) (Table 26 and Figure 30). Overall the model varied from the null hypothesis $\chi^2 = 7216$, $p < 0.001$.

Table 26

Cox regression model for the hazard of discharge (N= 58,942)

	Adjusted hazard ratio	95% CI	p value
Person with CDI	0.42	0.36-0.49	<0.0001
Age	0.989	0.989-0.999	<0.0001
DRG Mental health (yes)	0.59	0.57-0.61	0.0001
DRG Pregnancy (yes)	1.55	1.51-1.59	0.0001
DRG Kidney (yes)	1.32	1.26-1.39	0.0001
DRG Digestive (yes)	1.26	1.22-1.30	0.0001

Note: The Diagnosis Related Group category of neoplastic disease was excluded in the final model as $p = 0.20$. CDI = *Clostridium difficile* infection. Age was entered as a continuous variable; therefore this hazard ratio represents the risk for each additional year of age. Only one admission with a DRG category “Mental Health” had an episode of CDI.

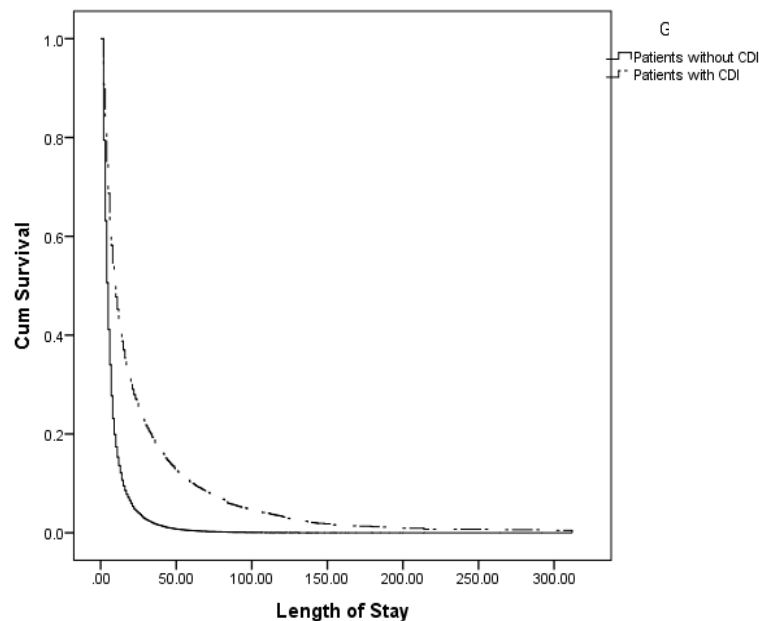


Figure 30. Effect of *Clostridium difficile* infection on the hazard of discharge in persons admitted to the Royal Hobart Hospital, 2007-2010 as estimated using Cox proportional hazard model. Only person's aged ≥ 2 years old admitted to hospital ≥ 48 hours are included.

5.5.7 Summary of results

The incidence of CDI per 1000 admissions for the entire study period was 2.68. The annual incidence of CDI increased from 2007 to 2010. When comparing the relative risk of CDI by age group, persons aged 40 years and above were at greater risk of CDI, compared to persons less than 40 years old. The median length of stay for all admissions was five days. For those persons who had an episode of CDI during their hospitalisation, the median length of stay was 17 days. Using a multistate model, the mean extra length of stay due to infection was calculated to be 0.9 days and this was not significant. Applying a proportional hazard model on the same data, acquisition of CDI significantly reduced the discharge hazard ($p < 0.001$).

5.6 Discussion

5.6.1 Overview of section

This study examined the incidence of CDI and whether there is prolongation of length of stay in hospital in persons with CDI. The challenge faced in determining the length of stay due to a healthcare-associated infection was to tease out the independent effect that the infection has on outcomes, and make necessary allowances for measured confounders. This was achieved using a multistate model for data analysis. The data from my study suggest that the incidence of CDI increased during the study period and that CDI did not significantly increase the prolongation of length of stay in hospital in persons hospitalised at the RHH during the years 2007 to 2010. The latter conclusion was made after undertaking data analysis using a multistate model and is contrary to findings of other studies. When the same dataset was analysed using a Cox proportional hazards model, CDI was associated with an increase length of stay. These conflicting findings support recent literature suggesting that data analysis methods that do not account for the timing of infection lead to differences and arguably a bias in findings when examining infections and length of stay in hospital. This is the first known study to examine CDI and prolongation of length of stay in hospital using a multistate model.

In the discussion to follow, three distinct areas are explored. First, the incidence of CDI at the RHH will be discussed in the context of potential influences on that incidence. Second, the effect that CDI has on the prolongation of length of stay will be explored through comparisons between the findings of my study and the published literature. The significance of length of stay in relation to the economics of HAIs will be discussed and the implications for future research. To conclude the discussion, the limitations of my study will be noted.

5.6.2 Incidence of *Clostridium difficile* infection at the Royal Hobart Hospital

The following section discusses the incidence of CDI at the RHH. Comparisons between the incidence of CDI at the RHH and other Australian hospitals will be made, in addition to examining the incidence of CDI in Europe and North America. In comparing data from my study to other published literature, challenges and influences on the rates of CDI, such as different testing methodologies and exclusion criteria will be explored. This section will also examine the age and its impact on the risk of CDI.

Incidence of *Clostridium difficile* infection and comparisons to the literature

The incidence of CDI among persons aged two years and older and hospitalised more than 48 hours at the RHH increased during the study period. At the same time, the number of persons who had a CDI episode increased. When comparing the incidence of CDI per 1000 admissions between 2007 and 2010, a significant increase was found. These findings were consistent with reports published by the TPCU, which also indicate an increase in healthcare-associated, healthcare facility onset (HCA HFO) CDI at the RHH (B. Mitchell, McGregor, A., Brown, S., Wells, A., Wilson, F, 2011; B. Mitchell, McGregor, A., Wells, A., Wilson, F., 2012). Importantly however, there are some distinctions between the reports produced by the TPCU and the research conducted as part of my study. First, the TPCU do not report on any of the characteristics of the persons included in their CDI surveillance, such as age, gender or DRG. My study has collected and analysed such data and consequently has enabled relative risks to be calculated – according to demographic characteristics. Second, the analysis of the characteristics in my study has enabled a robust comparison to the literature, whereas the reports by the TPCU, limited by the data reported, do not provide robust comparisons. Third, reports by the TPCU do not provide denominator data nor confidence intervals for individual hospitals, therefore, it is not possible to tell from these reports whether the increase at the RHH was statistically significant, as demonstrated in my study. Future reports developed by the TPCU could be improved by adding the capacity to report these data.

Reports from the TIPCU suggest that the increase in CDI is not isolated to the RHH. In Tasmania's four acute public hospitals, there has been an increase in HCA HFO CDI from 1.87 per 10,000 patient care days in 2006-2007 to 3.38 per 10,000 patient care days in 2010-2011 (B. Mitchell, McGregor, A., Brown, S., Wells, A., Wilson, F, 2011). The increase in CDI in Tasmania has been reported in peer reviewed literature confirming the results of the TIPCU (Mitchell, Ware, McGregor, Brown, & Wells, 2011a). In comparing the incidence of CDI in Tasmania to other Australian states and the international literature, Mitchell et al. (2011a) highlight inconsistencies in study duration, denominator selection, testing effort, and testing methodology. The authors concluded that there is a need for national standards for CDI testing and reporting (Mitchell et al., 2011a). This is an important point. If HAI data are used to underpin infection prevention programs and strategies as discussed in Chapter 2, it is imperative that data are collected and reported using consistent and reproducible methods. Failure to do so will make the evaluation of interventions to reduce HAIs more challenging as it will be difficult to decipher the impact of interventions against the effect of issues such as changes in testing methodologies and testing effort.

The incidence of CDI at the RHH appears to be higher than that reported in other Australian hospitals. The incidence at the RHH across the four year study period was 3.20 per 10,000 patient days, 95% CI [2.72, 3.74]. A study examining CDI in nine Western Australian hospitals in 2006 found the incidence of CDI to be 1.2 per 10,000, 95% CI [0.9-1.6] occupied bed days, however the authors note that the short study period and marked variations in laboratory diagnostic practices were limitations (Van Gessel, 2008). There are limited data with which to compare the incidence of CDI in Australia. However, it can be noted that the incidence of CDI at the RHH is lower than that reported in many CDI surveillance systems in Europe.

In England, the reported rate for 2009-2010 was 3.7 per 10,000 bed days, down from 5.5 per 10,000 bed days in 2008-2009 (Health Protection Agency, 2011a). It is important to note, however, that only samples from persons hospitalised for four or more days are reported in this figure for the English surveillance scheme. If this criterion were applied to my study, 25 persons would be excluded from data analysis, which would result in an incidence of 2.26 per 1000 admissions, or 2.69 per 10,000

patient days. This demonstrates the importance of paying attention to exclusion criteria when comparing CDI data and the need for a more standardised approach (Freeman et al., 2010). The higher incidence of CDI is not only seen with England, Scotland had a reported rate of 7.6 per 10,000 occupied bed days for 2010 (Health Protection Scotland, 2011a) and there was a reported rate of 4.7 per 1000 admissions in Germany in 2007 (Gastmeier, Weitzel-Kage, Behnke, & Eckmanns, 2009). Other reported incidence rates of CDI in Europe include Belgium, with 1.52 per 1000 admissions in 2010 (Viseur, Lambert, Delmée, Broeck, & Catry, 2011) and 1.8 per 1000 admissions in the Netherlands in 2007 and 2008 (Hensgens, Goorhuis, Notermans, Benthem, & Kuijper, 2009). Consistent with my findings, the incidence of CDI has been reported as increasing in the majority of these studies in the past decade.

The incidence of CDI is also higher in North America, where researchers have reported an incidence of 22.5 cases of CDI per 1000 admissions (Loo et al., 2005). A more recent study in New Jersey demonstrated an increase in CDI from an annual rate of 3.7 per 1000 admissions in 2000 to 7.7 per 1000 admissions in 2004 ($p = 0.05$) (Tan, 2007). Increases in the incidence of CDI over the past decade have been reported in a number of studies from North America (Chandler, Hedberg, & Cieslak, 2007; Kazakova et al., 2006; McDonald et al., 2006). Data on the incidence of CDI in Asia is limited (Ekma, Yee, & Aziz, 2012), demonstrating the increasing importance of this infection worldwide.

Potential influences on an increasing incidence of *Clostridium difficile* infection

In the literature review presented in this chapter, issues relating to variations in laboratory testing and the potential impact these have in research and surveillance were discussed. In the methods section I discussed the various methodologies that could be applied to the testing of the effects of CDI on length of stay. There are two important factors to be taken into account when considering whether an increase in the incidence of CDI is 'real': the testing effort and testing methodology (Mitchell, Ware, McGregor, Brown, & Wells, 2011b). Testing effort refers to how many stool

samples received by a laboratory are tested for CDI. This is dependent on what criteria are used before a test for CDI is performed. At the RHH, all diarrhoeal samples in hospitalised persons were tested for *C.difficile* during the study period, so this is unlikely to have played a role in the calculated increase in CDI. However, the process of testing for CDI can vary considerably among institutions. For example, private microbiology laboratories may only test for *C.difficile* if the test is requested. This has the risk of ascertainment bias and is not often accounted for in CDI surveillance (Freeman et al., 2010; Mitchell et al., 2011a). Testing methodology or the sensitivity of testing can play a role in identifying cases of CDI. This issue was discussed in detail in Chapter 4, section 4.2. At the RHH, the methodologies used for testing for *C.difficile* were highly sensitive and, in all situations, the laboratory tested for the *C.difficile* toxin using an assay. Therefore, the increase in HCA HFO CDI over time at the RHH was unlikely to have been caused by changes in testing effort or testing methodology. Alternatively, given the rigorous testing, there is also little chance of underestimation of infection in my study.

Age and risk of *Clostridium difficile* infection

The findings from my study indicate that the incidence of CDI increases with age, from 30 years old, up until the age of 90. The reason for the incidence of CDI not continuing to increase past 90 years of age is almost certainly an artefact of the small number of admission with CDI occurring in this age group in this study. Consistent with my study, increasing age is a well-established risk factor of CDI, if there is variation in the proportion of a hospitalised population that is older, this may affect the incidence of CDI (McFarland et al., 1990; Starr, Martin, McCoubrey, Gibson, & Poxton, 2003; Vaishnavi, 2009).

Internationally, there are some surveillance programs that specifically focus on CDI in persons aged 65 years and over. The reported incidence of all CDI in this age group in England was 9.0 per 10,000 bed days for 2009-2010 (Health Protection Agency, 2011a). In Wales, a rate of 8.9 per 1000 admissions has been reported for persons

aged 65 years and older for 2010-2011 (Welsh Healthcare Associated Infection Programme, 2011). In both countries, the incidence of CDI in persons aged 65 and over is higher than in all persons aged two years and over. The relative risk of CDI, comparing those aged 65 and over to those aged less than 65 years in England was 2.27 $p < 0.001$, 95% CI [2.20, 2.34]. The relative risks were calculated using raw data provided by the Health Protection Agency (Health Protection Agency, 2011a). Due to insufficient admission data in persons less than 65 years old from Wales, it was not possible to calculate risk by age in this country. The trend of a higher incidence of CDI in persons aged 65 and older is repeated in my study, which reports an incidence of 4.22 per 1000 admissions, 95% CI [3.41, 5.16] for this age group. The relative risk of CDI in persons aged 65 and over in my study, compared to persons less than 65 years old is 2.42, $p < 0.001$, 95% CI [1.75, 3.38], a similar finding to that from CDI surveillance in England.

In my study, relative risks of CDI by age group were compared for each decade of life (Table 24). The groups with the highest relative risk were persons aged 40 years and older, compared to persons less than 40 years old. The calculated relative risk was 4.23, 95% CI [2.56-7.00]. It was not possible to calculate the relative risk of CDI in different age groups for England and Wales from the available data. Nonetheless, the findings of my study pose the question as to whether the '65 and over' age group is the most appropriate age group for targeted CDI surveillance because it appears that the risk of contracting CDI begins to increase significantly for patients as young as 40 years of age.

Summary

Noting limitations in comparing incidence of CDI, the incidence of CDI at the RHH is lower than that reported in most countries in the northern hemisphere, but higher than reports from limited Australian data. The increase in CDI at the RHH is part of a trend experienced internationally in recent years. These points are significant as my findings suggest that the impact of CDI is not yet fully realised in Australia as we may

yet experience increases in CDI as have occurred in other countries. In order to better interpret trends and the epidemiology of CDI, the issue of variation in microbiological testing methodologies becomes an important issue. Differences in testing methodologies make comparisons intrinsically difficult and there is a need for standardised practice in this area both in Australia and internationally. This point is taken up in the recommendations section.

5.6.3 Estimating the effect of *Clostridium difficile* infection on length of stay

My study found no significant increase in the length of stay in hospital caused by CDI if a multistate model was used for estimation. At the time of writing, no reports of studies examining the prolongation of length of stay due to CDI using multistate modelling were found in the peer reviewed literature; however, one study did use the principles of managing time-dependent bias in their study (Forster et al., 2012). This study is explored in more detail later in this section. As no other study has explored length of stay and CDI using multistate modelling, limited comparisons between my study and others were possible. There are many studies that examine the prolongation of length of stay due to CDI using different approaches; these are discussed below. Furthermore, studies have examined length of stay caused by other HAIs using multistate modelling and where relevant to this discussion, they are explored.

All the studies identified in the literature review presented earlier in this chapter, suggested that CDI contributes to a longer length of stay in hospital for patients when compared to people without infection. In studies that used a comparison between persons with CDI and those without, the difference in length of stay between the two groups ranged from 2.8 days to 16.1 days (Dubberke et al., 2008; Lumpkins et al., 2008). In the majority of studies a regression model was used in examining the impact that CDI had on length of stay, (Ananthakrishnan et al., 2008; Bajaj et al., 2010; Dubberke et al., 2008; Kenneally et al., 2007; Lawrence et al., 2007; Lumpkins et al., 2008; Nguyen et al., 2008; Song et al., 2008; Zerey et al., 2007; Zilberberg et al., 2009). None of these studies reported on the timing of CDI infection relative to admission period in hospital. Therefore, these studies may suffer from reverse

causality as a longer length of stay in hospital may increase the risk of CDI. Reverse causation ordinarily refers to situations where the outcome precedes and causes the exposure instead of the exposure preceding and causing the outcome (Flegal, Graubard, Williamson, & Cooper, 2010).

A retrospective cohort study was undertaken in Canada to determine the effect that hospital acquired CDI had on length of stay and attempted to manage CDI as a time-varying covariate (Forster et al., 2012). Only persons who had CDI that commenced 72 hours after admission were included in the study; persons less than 15 years old were excluded. The authors attempted to account for the time varying nature of CDI onset by describing times to discharge from hospital by *C.difficile* status using Kaplan–Meier curves. The authors employed two different processes for data analysis to demonstrate the impact of not accounting for the timing of infection.

First, a patient who acquired CDI had two items of data collected: the time between admission and acquisition of *C.difficile*, and the corresponding time to discharge or death. Acquisition of CDI was censored; therefore, median times to discharge and the probabilities of remaining in hospital at various endpoints could be calculated. Using this first method, the authors calculated the crude median length of stay by CDI status and found that length of stay was 34 days in persons with CDI, and eight days without.

The second method used in data analysis in this study was the calculation of median times for length of stay. Only days between CDI acquisition and discharge were attributed to the group with CDI (Forster et al., 2012). In persons with CDI, the time from admission to CDI was attributed to the group that did not ever acquire CDI whilst in hospital. All persons who did not have CDI had all days between admission and discharge counted as not having CDI. The unadjusted and adjusted associations between CDI and time to discharge were estimated using Cox proportional hazards regression models (Forster et al., 2012). Using this process, CDI was still found to significantly decrease the hazard of discharge (i.e. increased the length of stay in hospital). On day seven, the hazard ratio measuring the association between CDI and

discharge was 0.55, 95% CI [0.39, 0.70] (Forster et al., 2012). The median increase in length of stay attributed to CDI was six days.

Although not stated as a multistate model, the authors in this study clearly used a process that attempted to control for the time varying nature of infection. Similar to my study, they demonstrated that not accounting for the time to infection could result in an overestimation of the length of stay attributable to CDI. However, in contrast to my study, even when accounting for timing of infection, they found that CDI did significantly increase length of stay in hospital. The findings from both Forster's study (Forster et al., 2012) and mine suggest the failure to account for the time varying nature of infection can lead to bias, are confirmed by others. Studies have demonstrated the same over-estimation of effect using other HAIs as examples (Barnett et al., 2009; Beyersmann et al., 2008).

The challenge faced in determining the length of stay due to a healthcare-associated infection is to tease out the independent effect that the infection has on outcomes, and make necessary allowances for observable confounders. This challenge can be addressed to some extent by using data collected from a cohort of hospitalised patients and either selecting a subset of infected patients or building multivariable statistical regression models that describe the relationship between HAI and cost outcomes, while controlling for other factors thought likely to affect outcomes (Katz, 2003). Such a process is called comparative attribution (Graves & Weinhold, 2006). All of the studies identified in the literature review informing this research used a comparative attribution approach. In contrast to my study however, these studies did not use a statistical method to control for the time varying nature of CDI in data analysis. Like my study, several of these used administrative data to evaluate the effect that CDI has on length of stay (Lesperance, Causey, Spencer, & Steele, 2011; Nguyen et al., 2008). In doing so, there are limitations on the amount of information available from administrative databases and, therefore, the ability to control for potential confounders. This demonstrates the need to have robust and preferably prospective data collection that includes influences on HAI data. These influences could be either characteristics of the infection itself, for example the time of infection onset, or characteristics about the affected person that may influence length of stay,

for example co-morbidities. The limitations for my study and their implications are discussed later.

One alternative to comparative attribution is direct attribution of length of stay. This requires an expert reviewer to assess the extra cost of each case of a healthcare-associated infection. An example of a study using this method examined the direct costs of healthcare associated catheter associated urinary tract infection (CAUTI). In this study, researchers prospectively reviewed patient's records and made a judgment on which diagnostic tests, treatments and length of stay could be reasonably ascribed to the episode of CAUTI (Tambyah, Knasinski, & Maki, 2002). This method has been criticised as being subjective and not reproducible. Accordingly, comparative attribution studies have been preferred by the research community (Graves et al., 2007; McGowan, Jr., 1981). The criticism that direct attribution is subjective and not reproducible would only have merit in situations where definitions used were not clear.

The multistate models used in my study and that of others (Bajaj et al., 2010; Barnett, Graves, Rosenthal, Salomao, & Rangel-Frausto, 2010; Beyersmann et al., 2006; Beyersmann et al., 2009; Graves et al., 2010), do not account for variables such as co-morbidity. This is a limitation of multistate models. Further, comparisons between regression models such as Cox proportional hazards and multistate models need to be undertaken with some caution, as regression models may account for confounders that multistate models do not consider. The issue of not adjusting for other variables such as co-morbidity in a multistate model may not necessarily be relevant to all HAIs.

5.6.4 Contribution of length of stay as part of the economics of healthcare associated infections

There are different methods used to evaluate the economic cost of HAIs (Appendix I), the accountants' model and the economists' model. The accountants' model for determining the cost of HAIs is to count fixed and variable costs. According to Graves et al. (2009), using such a model is not suitable for economic appraisal or

informing decisions as the assumption of an accountant model is that by reducing or eradicating a specific infection, a fixed figure could be saved. This model does not account for the increased investment associated with reducing infections and fails to consider what costs actually change with infections where many fixed costs remain (N. Graves, Halton, K., Jarvis, W., 2009). An economist's approach in evaluating the cost of HAIs is supported by the argument that the majority of the costs associated with hospital care are fixed (Plowman, 1999; Roberts et al., 1999). Therefore, in describing how costs change in relation to HAIs, it is important to demonstrate the number of bed days caused by HAIs (N. Graves, Halton, K., Jarvis, W., 2009). A decision on how these additional bed days will be utilised can then be considered. For example, the consumables may be reduced with a reduction in HAIs. The capacity gains associated with reduction in HAIs are valuable as this creates an opportunity for savings or for redeployment of resources. The redeployment of resources could be used for tasks such as elective surgery and, in turn, cause other variable costs to increase (N. Graves, Halton, K., Jarvis, W., 2009). In using either the accountants' or economists' model for evaluating costs of HAI, a fundamental issue is that an accurate assessment of the prolongation of length of stay due to the infection must occur.

Reviews examining the economic costs of CDI have primarily focussed on studies that have evaluated costs through the eyes of an accountant, primarily because studies included in these reviews have used this approach (Dubberke & Wertheimer, 2009; Ghantaji et al., 2010). Both of these reviews acknowledged this limitation and called for a more accurate measure of the cost of CDI. To address this issue, an economic computation simulation model was developed by McGlone et al. (2011) to evaluate the costs of CDI from three different perspectives: hospital, third party payer, and societal. The hospital perspective determines the opportunity cost of lost bed days from extended length of stay and considered a model proposed by Graves (2004). The third party payer perspective considers only direct costs, whilst the societal perspective includes both direct and indirect costs. As such, the study by McGlone et al. (2011) was the first known study to determine the cost of CDI from different perspectives. Results from this study suggest that the cost of CDI ranges from \$US2000 to \$US72,000 per case and varies with co-morbidities (McGlone et al.,

2011) . These figures are consistent with previous reports and suggest that, regardless of severity and the method used to evaluate cost, there are significant costs associated with CDI (Ananthkrishnan et al., 2008; Dubberke & Wertheimer, 2009; Ghantaji et al., 2010; Zerey et al., 2007).

The use of accurate methods to determine length of stay due to CDI and HAIs more generally, combined with specific economic models used to evaluate cost, can assist decision makers in formulating informed choices about investing in infection prevention and control prevention activities. The use of direct costs may be valuable in helping healthcare managers with insurance related issues and reimbursement decisions. These reimbursement decisions may evolve, as is the current trend in the United States, where there has been a decision not to reimburse for certain HAIs (Rosenthal 2007; Stone et al., 2010). Finally, having accurate information on the cost of CDI and other HAIs may assist manufacturers and drug companies in their decision to invest in products, and the choice of price for these products and treatments (McGlone et al., 2011). All these points highlighted in this paragraph demonstrate the need for accurate data to influence and shape infection prevention and control programs and strategies as discussed in Chapter 2.

Using a multistate model for data analysis, the findings of my study suggest that CDI has little impact on length of stay in hospital, noting my study did not adjust for other variables in this model. As these findings contradict published literature, it can be argued that this work is not supportive of infection prevention and control activities. On the contrary, I believe my study aims to present data to policy makers that is credible and able to withstand critical examination. Overinflated suggestions of the impact that CDI has on length of stay may have short-term benefits; however once it becomes clear that these data have limitations, there is a risk of loss of credibility in the broader field of infection prevention and control research. In turn, this may have effects for future investment in infection control activities. The use of sound data analysis techniques and study design that account for time-dependent bias are required for studies that evaluate the impact that HAIs have on length of stay in hospital. It is also important to consider that my study only examines the impact that

CDI has on length of stay and does not consider the human cost, which is difficult to quantify. The impact the CDI has on mortality was found to be significant, as described the second study of this thesis.

5.6.5 Implications for future studies examining length of stay

Various statistical models were discussed in the data analysis section 5.4.5. One model, suggested as optimal, Figure 22 on page 174 of this thesis, was not viable because code for this data analysis technique had not yet been developed in R. Further, it became clear after data collection that the infection cessation data for all admissions with CDI in the study was incomplete. Even if this model was available, given that my study only had data on CDI cessation from 72 persons, the value in its use could be questionable. This model accommodated the possibility of an infected person returning to a susceptible state upon infection cessation prior to discharge from hospital. This is important as in many instances of HAIs there is little or no immunity. Therefore, a person who recovers from an infection may be susceptible to being infected again. Five people in the current study had more than one infection, although these occurred during different admissions to hospital so did not pose an issue with respect to this point. Further, research examining the prolongation of length of stay due to a HAI typically focuses on one infection, such as CDI and the current multistate models do not account for multiple or concurrent infections during the same admission period.

Future studies may wish to examine the impact of more than one infection in a study cohort. For this to occur, a model not only needs to allow a person who had an infection to return to a susceptible status again, but also allow for the possibility of other or concurrent healthcare-associated infections. Specific patient groups such as those who are severely immuno-compromised are at a greater risk of infection, therefore multiple infections are possible. There were 30 instances where CDI ceased prior to discharge that could be identified in my study, equating to 286 bed days, These 30 instances are considered an underestimate as data on infection cessation was only available for 18 months of study period as described in section 5.4.3. Therefore,

it is possible that up to 762 patient days across the entire study period, were attributed to an 'infected status' when the person may in fact have recovered from CDI.

Although small relative to the total number of bed days under observations, it does underline the potential for improvement in the multistate modelling techniques used. Further, with improvements in data aggregation and surveillance programs collecting data on more and more HAIs, the need for data analysis to consider this model is becoming more important. As datasets become larger through increased surveillance and improved data aggregation, the effect of using substandard methods for data analysis will compound bias further.

A future consideration for the development of future multistate models is the need to adjust for other variables, such as co-morbidity, in the model. This is a limitation of current multistate models. Until such time, direct comparisons between regression models and multistate models should be undertaken with caution, as the methods used analyse the data differently. To the best of my knowledge, this point has not yet been articulated in the peer reviewed literature. Paradoxically, the use of multistate models does account for the timing of infection and the potential bias this can lead to when not managed in data analysis.

My study has contributed to testing relatively new statistical methods, namely multistate modelling and in doing so has proposed that these models can be further enhanced through an ability to account for persons returning to a non-infective status and to adjust for other variables such as co-morbidity.

5.6.6 Limitations

My study does have some limitations. First, the inability to identify the infection cessation date on all admissions that had CDI was a limitation. This did not affect the results however, as the multistate model used for data analysis did not require this information. Further, the study used a novel approach to determine infection cessation dates by using data held by the RHH Infection Prevention and Control Unit, as

discussed in section 5.4.3. In deciding to cease contact precautions, staff members from the RHH Infection Prevention and Control Unit examined each person with CDI and the decision was made after consultation with the Director of the unit. Therefore, there was a level of consistency in the data. Although infection cessation data were not required for data analysis, if the multistate model included the timing of infection cessation, as proposed in Figure 22 (Model B), there may be value in using the approach taken in this study to collect these data.

In my study, variables such as age and co-morbidities were not included in the multistate model. As previously discussed in this chapter, this issue is not unique to this study but is a broader limitation of using multistate modelling for data analysis.

A further limitation in this study is ascertainment bias, caused by approaches taken in laboratory testing and therefore subsequent identification of admissions with CDI. The effect of ascertainment bias in this study is low due to two main points. First, the RHH microbiology department tested all diarrhoeal samples from hospitalised patients for *C.difficile*. Second, all the methods employed by the RHH microbiology department during this study period are highly sensitive.

In this study, the date of infection commencement was obtained using the collection date of faeces subsequently found to be positive for *C.difficile*. It is possible that persons with CDI did not have a faecal specimen taken immediately, although there is no way of quantifying this. If this has occurred, the infection commencement dates in some persons with CDI may have been earlier therefore extending the time a person had infection. The effect this would have in calculating the prolongation of length of stay is unknown. This limitation is not unique to this study.

Finally, this study only examined admission with CDI occurring in persons hospitalised for more than 48 hours, i.e. healthcare associated, healthcare facility onset CDI. There would be admissions with HCA CDI that were not included in this

study, for example persons who acquired *C.difficile* from a recent admission or visit to hospital and subsequently succumbed to infection. Therefore, we cannot determine the wider impact that HCA CDI may have on length of stay. Paradoxically, the use of data from admissions with HCA HFO CDI is also a key strength of this study, as this study had a very succinct and clear dataset. Further, interventions can be put in place to reduce the incidence of healthcare associated, healthcare facility onset CDI; therefore, the findings of this study are relevant when determining the cost benefit of any intervention given the closed population.

5.7 Recommendations

From the findings of this study, a number of recommendations can be developed. Not accounting for the timing of infection can result in spurious results i.e. an overestimation of the prolongation of length of stay due to CDI. With this in mind, several recommendations are made for future research examining CDI and HAIs:

1. Future research examining the length of stay caused by a healthcare-associated infection must take into account the timing, including both onset and end of infection.
2. Data analysis must account for the time varying nature of infection.

Interventions aimed at reducing or preventing healthcare-associated infections are often implemented for two reasons: to improve the quality of care and to improve efficiency (reduce cost). As resources in healthcare are limited, a decision to implement an intervention to reduce a healthcare-associated infection should include a cost benefit analysis. Currently, the data used to inform a decision may not be as accurate or complete as possible and the limitations of data analysis techniques need to be understood. The following recommendation is made:

3. Policy makers and healthcare managers must carefully critique the data that underpin decisions relating to interventions that have a potential cost benefit. Where policy makers and managers do not have the necessarily skills to

undertake this, healthcare epidemiologists and biostatisticians should be employed to assist in analysing and interpreting data.

In the methods, potential multistate models were identified but could not be used as specific codes for these models have not yet been developed. In considering a multistate model that examines HAIs and length of stay, there are infections other than CDI that result in a person moving back to susceptible status once an infection has ceased. Future studies may wish to examine the effect of more than one infection on length of stay in a given timeframe. In both these examples, there is a need for a multistate model to be able to return to a susceptible state. Additionally, in the discussion section of this chapter, a further limitation of multistate models, not yet explored in the literature was identified. This limitation refers to the current inability of these models to adjust for other variables, such as co-morbidity. Noting the limitations of multistate models described in the paragraph, the following recommendations for future research and development are now provided.

4. A code for the following multistate model needs to be developed to better reflect how healthcare-associated infections affect hospitalised patients.

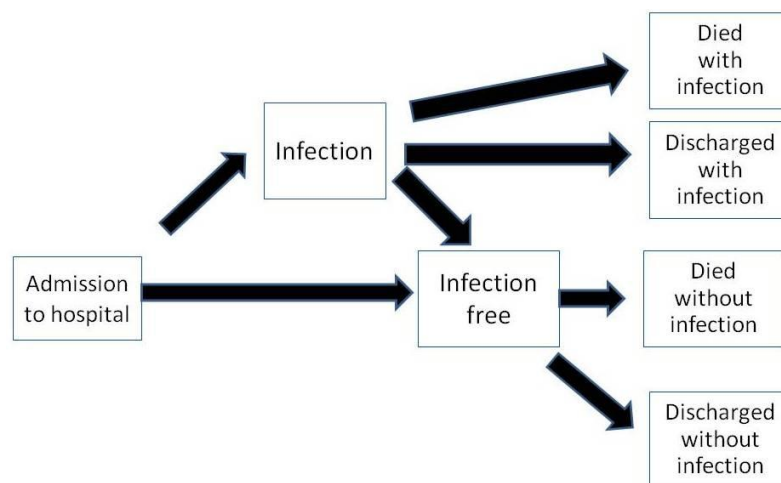


Figure 31. Suggested multistate model for future studies examining length of stay due to a healthcare associated infection. Identical figure presented in section 5.4.5 but is provided again in this section for clarity.

5. Multistate models that have the capacity to adjust for variables such as co-morbidity need to be developed and evaluated.

5.8 Conclusion

This chapter presented the results and discussed findings from the third piece of research for this thesis. The research questions addressed in this chapter reported both the incidence of CDI at RHH over a four year period and the potential impact of CDI on prolongation of length of stay in hospitalised persons. The calculated incidence was higher than other published Australian data but lower than internationally reported incidence. This study is, to the best of the author's knowledge, the first to use multistate data analysis techniques to determine the potential prolongation of length of stay due to CDI. From the findings, it can be inferred that *Clostridium difficile* infection does not significantly contribute to a longer hospital length of stay, ($p = 0.51$). Conversely, the influence of CDI in a proportional hazard model was found to be statistically significant, with acquisition of CDI significantly reducing the discharge hazard ($p < 0.001$). These findings have a number of implications for future researchers exploring the consequences of HAIs and for senior healthcare managers responsible for policy and practice in this area. In essence, the findings of my study demonstrate limitations of both data collected and data analysis techniques currently available. Multistate models may manage the issue of time-dependent bias, but there is further refinement still required in these methods. Nonetheless, in this chapter, a new model for data analysis was proposed to further enhance the reliability of conclusions.

Chapter 6: Conclusion

6.1 Introduction to the chapter

There were two overarching aims for this thesis: to explore the epidemiology of two serious HAIs and to examine the methodological influences on reliable and valid HAI data collection and analysis. This final chapter summarises the key findings of the three studies addressing these aims. A model is presented which elaborates influences on reliable and valid HAI data and implications for use of the proposed model are discussed. Finally, contributions made as a result of this work are presented.

6.2 Findings from the studies

This section summarises the key findings of the three studies presented in this thesis. Through an exploration of the epidemiology of SAB and CDI and the examination of mortality and prolongation of length of stay associated with CDI, key methodological influences on reliable and valid HAI data collection and analysis were identified. Additionally, a model that summarises these influences is proposed and the implications for this model are discussed. The purpose of this discussion is to elicit the themes relating to the burden of disease from SAB and CDI, and the potential methodological influences on reliable and valid HAI data collection and analysis – a foundation of many HAI prevention activities.

The burden of healthcare associated infections

The studies presented in this thesis clearly identify a proportion of the burden that HAIs pose in an Australian setting. For SAB, the burden of HA SAB remains high with 41.6% of SAB being HA. The findings from the first study indicate that of these HA cases of SAB, an intravascular device was implicated in some way in 55% of instances. Such a finding supports the need for improvements in intravascular device

management, an argument supported in the literature (P. Collignon, Dreimanis, D., Beckingham, W., Roberts, J., Gardner, A, 2007; Maki, et al., 1991). For CDI, the burden of this infection is demonstrated in the findings from the second study, suggesting that CDI is associated with increased mortality. However, the findings from the third study call into question the extent to which length of hospital stay is influenced by CDI.

The second aim of the thesis was to examine methodological influences on reliable and valid HAI data collection and analysis. Through the three studies, four broad influences on reliable and valid HAI data were identified: ‘host’, ‘definitional’, ‘environmental’ and ‘data analysis’. These four influences will now be explored in more detail.

Host influences

The term ‘host’ has been assigned to describe individual intrinsic patient risks that may in turn influence the interpretation of incidence data, because they are potential confounders. From the studies conducted three host influences were identified: age, sex, and co-morbidities.

In the study examining SAB, age was identified as a risk factor. This finding has been supported by other studies examining SAB (Asgeirsson, et al., 2011; Laupland, et al., 2008; Morin & Hadler, 2001; J. Turnidge, Nimmo, G., Pearson, J., Gottlieb, T., Collignon, P., Australian Group on Antimicrobial Resistance, 2007) and was also identified in the third study in which the risk of CDI increased with age. In the first study, gender was identified as a risk factor with males at greater risk of SAB than females. This finding has been reported in other studies (Easton, 2010; Huggan et al., 2010). The second study also identified other important ‘person specific’ issues that influenced outcomes. In this study, co-morbidities were identified as playing an important role in mortality. Given the findings of this study, the inclusion of co-

morbidity data is something that should be considered for future HAI surveillance. The ability to control for co-morbidities permits an assessment of the independent effect of HAIs and allows for the potential of risk adjustment. Where co-morbidity data are not available, this should be noted when interpreting results.

These examples demonstrate that there are individual (host) factors that can influence the likelihood of acquiring and surviving a HAI. The need to measure and adjust for patient risk in HAI surveillance has been previously identified in the literature (Haley, 1995). In targeted research, the influence of these host factors is often explored as a matter of course. However, in HAI surveillance programs, such data are not always collected or reported, as was evidenced through the three literature reviews presented in this thesis.

Definitional influences

‘Definitional’ is the broad term used to describe factors such as case definitions and laboratory testing. Case definitions, comprising inclusion and exclusion criteria, have been recognised as important elements in surveillance programs.

In the first study examining SAB, 42% of all 214 cases of SAB were HA. Of these HA cases of SAB, 68% occurred in people hospitalised for more than 48 hours, whilst 32% were hospitalised less than 48 hours but had other clinical criteria which resulted in them being defined as HA. Therefore, in cases where there were no criteria other than timeframe used to define cases of SAB, approximately 30% of HA SAB cases would not be identified and could in turn be incorrectly identified as CA. The practice of using timeframes to define cases of HA SAB is used in both surveillance and research, as identified in the SAB literature review in Chapter 3. This finding demonstrates how the application of different case definitions can cause significant variation. The impact of case definitions was also identified in the second study of this thesis.

The second study identified that CDI was associated with mortality at a relatively late stage. I argued that the removal of cases of CDI occurring within eight weeks of the previous case from data analysis may explain this (Chapter 4, section 4.7.3). The removal of cases occurring within eight weeks of the previous case is common in CDI surveillance as identified in the CDI literature review in Chapter 4 and is consistent with international CDI surveillance definitions. Nonetheless, findings from this second study raise the question that even accepted and commonly used case definitions may influence results.

Making comparisons is challenging, where case definitions vary, as demonstrated in the third study. In this study, admissions with healthcare associated, healthcare facility onset CDI were identified, i.e. infections that commenced more than 48 hours after admission. This surveillance definition of healthcare associated, healthcare facility CDI is internationally accepted and was the basis for the calculation of the incidence of CDI. In comparing the incidence of CDI in this study with the literature, it was found that not all CDI programs use the same case definition. For example, if the same case definition criteria were applied to data in this study as they are in England, persons would have been excluded from data analysis, leading to a reduction in the incidence of CDI. This demonstrates the importance of carefully monitoring exclusion criteria when comparing CDI data. It also demonstrates the need for a more standardised approach in this area (Freeman et al., 2010).

Data analysis

The third study, which explored the incidence of CDI and the prolongation of length of stay due to CDI, identified influences that differing data analysis methods have in the calculation of any prolongation of length of stay associated with a HAI. The major issue faced in studies examining length of stay and HAIs is controlling for the time-dependent nature of infections. Relatively new data analysis techniques such as multistate models—have been used to manage this issue at the data analysis stage.

When conducting this study, I identified that multistate models have limitations. One limitation that was current at the time of writing was that these models could not adjust for possible additional risk, such as co-morbidities. Until this can occur, direct comparisons between regression models and multistate models should be undertaken with caution because these methods analyse data differently. In this study, it was possible to demonstrate different results using different data analysis techniques applied to the same data—each had advantages and disadvantages. Importantly, the results between the two different techniques—namely, the prolongation of length of stay due to CDI—varied considerably.

Environmental influences

The term ‘environmental’ is used to encapsulate other factors identified in the three studies that may influence the reliability and validity of HAI surveillance data. The study examining CDI and mortality identified notable differences in exposure to antibiotics between persons who had and did not have CDI. This supported the argument that antibiotics influence the likelihood of acquiring CDI. Such an argument is supported by the wider literature suggesting antibiotics are an important risk factor for CDI (Bignardi, 1998; J. Pépin, Saheb, N., Coulombe, M., Alary, M., Corriveau, M., Authier, S., Leblanc, M., Rivard, G., Bettez, M., Primeau, V., Nguyen, M., Jacob, C., Lanthier, L, 2005; Polgreen, et al., 2007; Thomas, et al., 2003).

6.3 A model displaying influences on reliable and valid healthcare associated infection surveillance

Using the three studies presented in this thesis, this section brought together influences on reliable and valid HAI data. The four broad themes that arose were identified, namely: host, definitional, data analysis, and environmental. A model that displays the four influences on reliable and valid HAI data is presented below (Figure 32).

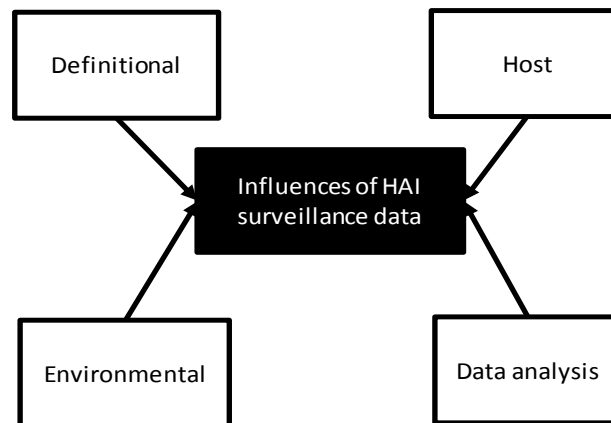


Figure 32. Model demonstrating the influences on reliable and valid healthcare associated infection surveillance data. HAI = healthcare associated infection.

The four themes identified and discussed above have similarities to the areas of concern proposed by Masterton (2000) in which he suggested that there are three areas of dilemma in surveillance programs: laboratory, organism source, and patient selection. ‘Laboratory’ describes variables such as laboratory performance and quality assurance. ‘Organism source’ refers to clinical factors, environmental factors, repeat isolates and organism species. ‘Patient selection’ refers to inclusion and exclusion criteria and community versus hospital acquisition. The model proposed in Figure 32 builds on that proposed by Masterton (2000). Further, in describing the National Nosocomial Infection Surveillance System of the Centre for Disease Control and Prevention (R. Gaynes, Richards, C., Edwards, J., Emori, G., Horan, T., Alonso-Echanove, J., Fridkin, S., Lawton, R., Peavy, G., Tolson, J., National Nosocomial Infection Surveillance (NNSI) System Hospitals, 2001), it has been suggested that a successful system must satisfy three requirements, each of which have been addressed in the model proposed in this thesis. A successful system must:

1. Have a clear purpose;
2. Use standard definitions, data fields and protocols;
3. Use an institution (specialist unit) to standardise definitions, assess for quality, risk adjust and interpret and disseminate data (R. Gaynes, Richards, C., Edwards, J., Emori, G., Horan, T., Alonso-Echanove, J., Fridkin, S., Lawton,

R., Peavy, G., Tolson, J., National Nosocomial Infection Surveillance (NNSI) System Hospitals, 2001).

The four methodological influences on HAI data presented in this section—as a result of the three studies conducted—will require further refinement and validation by future researchers and commentators. However, the model proposed presents a method for articulating the major influences on the reliability and validity of HAI data. The potential implications of this model will now be discussed.

Implications for a model describing the importance of reliable and valid healthcare associated with infection surveillance data

In Chapter 2, surveillance was described as the collection, collation, analysis and dissemination of data in order to improve health. Improvements in the surveillance of HAIs, such as more surveillance and improved processes and definitions have been called for, so that the size, burden, and understanding of the effect of HAIs can be improved. Improving the rigor of surveillance of HAIs makes it possible to provide more valid and reliable information, to design and plan future programs, as well as provide a measure for evaluating interventions. The biopsychosocial framework for infection prevention and control proposed in Chapter 2 relies on the use of HAI data underpinned by HAI surveillance. If the role of HAI surveillance is deemed so important that it is identified as a critical element for infection prevention, then it would be logical to assume that an understanding of the influences on reliable and valid HAI—as proposed in Figure 32—is also important. To the researcher's knowledge, no one has yet arranged the influences on reliable and valid HAI data in a model.

There are four main implications for displaying the influences on HAI data, as undertaken in Figure 32. First, having a clear, succinct model that describes the

influences on HAI data permits infection control professionals, researchers and planners of surveillance to consider how these elements can be best managed when designing a surveillance program or piece of research.

Second, when attempting to compare existing surveillance data or HAI research, the model can serve as a prompt for potential factors that need to be considered. Indeed, this concept can be extended further to the case of public reporting. The general public and media, who are unaware of the complexities that surround HAI data collection and analysis, should be provided with the necessary information to demonstrate that data are not always comparable, and to inform them of the reasons for this. Consequently, for professionals responsible for producing reports that are made publically available, the model may serve as a useful reference tool for informing the public about reports' potential limitations.

Third, as described in Chapter 2, HAI data are often used within a safety and quality framework to drive improvements in practice, and reduce the risk of HAIs. The data can also be used in performance management, with targets set for specific HAIs (Duerden, 2009). For those health planners responsible for developing and monitoring HAI as part of a performance management framework, it is vital, at both the design stage and monitoring stage, that limitations of the data are articulated and appreciated. For example, there is no credibility in holding hospital executives accountable for apparently excessive levels of HAIs that are beyond their control due to the application of inconsistent case definitions.

Finally, by considering influences on reliable and valid HAI data, risk adjustment may be possible to make the data more comparable, as happens in surgical surveillance undertaken by the VICNISS coordinating centre (Russo et al., 2006). Further, considering as many influences as possible on the data may enable their relative importance to be determined, thereby informing priorities for future strategies.

The value of surveillance in infection control programs is crucial, as was discussed in detail in Chapter 2. Importantly, regarding the issue of reliability and validity of data, healthcare professionals must also perceive value in the data. They are more likely to rely on data when making decisions and will hopefully alter their behaviour in order to reduce the risk of HAIs (R. Gaynes, Richards, C., Edwards, J., Emori, G., Horan, T., Alonso-Echanove, J., Fridkin, S., Lawton, R., Peavy, G., Tolson, J., National Nosocomial Infection Surveillance (NNSI) System Hospitals, 2001).

6.4 Thesis contribution

This thesis has made four significant contributions to the broader understanding of HAIs:

- First, a revised framework for HAI prevention that incorporates the role of surveillance in infection prevention and control activities was proposed in Chapter 2.
- Second, the first known Australian study to capture and analyse data from all cases of SAB at a jurisdictional level was undertaken, allowing for an accurate representation of the incidence of SAB. As a result, the burden of HA SAB at a population level was articulated, in addition to being able to identify the potential for under reporting of SAB where data are only collected from public hospitals. This has implications not only for SAB but for the design of future national HAI surveillance programs in Australia.
- Third, a study examining mortality and CDI was undertaken in the southern hemisphere for the first time in 15 years. The findings suggested CDI is associated with increased mortality and the findings have the potential to influence local, state and national policy direction in the area of CDI prevention by demonstrating the impact that CDI may have on hospitalised individuals.
- Fourth, the third study examining CDI and its impact on prolongation of length of stay in hospitalised persons, is, to the best of the author's knowledge, the first to apply multistate data analysis techniques to CDI data. Findings from this study suggest that the application of different data analysis

techniques produce significantly different results. These findings have a number of implications for future researchers exploring the consequences of HAIs and length of stay more broadly. In conducting this study refinements for multistate models were proposed to enhance the reliability of data analysis. Finally, by conducting three studies, influences on reliable and valid HAI data collection and analysis were articulated and a new model proposed that demonstrates these influences.

6.5 Conclusion

The two overarching aims for this thesis were to explore the epidemiology of two serious HAIs and to examine methodological influences on reliable and valid HAI data collection and analysis. At the beginning of this thesis, I discussed the emergence of HAIs as a safety and quality issue, explored strategies to reduce the effect of HAIs and examined the role of surveillance in HAI prevention and control activities. In this thesis I proposed a revised framework that incorporated the role of surveillance into a biopsychosocial framework for infection prevention and control. Three studies, which examined two HAIs, were presented in Chapters 3 to 5. Each of the three studies had objectives and research questions related to the aims of the thesis.

The first study explored the epidemiology of SAB using a descriptive, observational, population-based study design. This is the first known Australian study to capture and analyse data from all cases of SAB at a jurisdictional level and represent this as an incidence. The findings of this study can be summarised into four themes:

- First, the incidence of SAB at a population level could be accurately determined for the first time in Australia.
- Second, a large proportion of HA SAB was associated with intravascular device management.

- Third, case definitions for HA SAB influence detection, for example, if only timeframe from admission to hospital and infection onset are used to determine cases of HA SAB, approximately 30% of HA SAB will be incorrectly classified as CA SAB.
- Fourth, that a measurable proportion of SAB were identified in private hospitals and these fall outside the scope of almost all SAB surveillance programs in Australia.

The second and third studies were conducted on CDI. Results from the second study indicated that CDI was associated with increased mortality a considerable time after initial infection commencement, although the exact relationship between infection and subsequent mortality is still not clear; this was the first known study in 15 years to examine CDI and mortality in the southern hemisphere.

The third study examined the incidence of CDI and prolongation of length of stay in hospitalised patients. This study is, to the best of the author's knowledge, the first to use multistate data analysis techniques to determine the potential prolongation of length of stay due to CDI. In doing so, the calculations suggest that CDI does not significantly contribute to a longer hospital length of stay. Conversely, when other methods for data analysis were used on the data, a significant increase in length of stay was found for people infected with *C.difficile*. These findings have a number of implications for future researchers exploring the consequences of HAIs and for senior healthcare managers responsible for policy and practice in this area. In essence, the findings demonstrate the limitations of both data collected and data analysis techniques currently available. Multistate models may manage the issue of time-dependent bias, but there is further refinement still required in these methods. Nonetheless, in this chapter, a new model for data analysis was proposed to further enhance the reliability of data.

The three studies each provided a significant and unique contribution to the literature, with each presenting implications for practice, policy and research. In conducting

these studies, as well as new epidemiological knowledge, influences on reliable and valid data collection and analysis were identified. A new model summarising influences on reliable and valid HAI surveillance has been presented in this chapter. Overall, this thesis made a number of significant contributions to the broader understanding of HAIs.

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Appendix A

Sources of infectious agents in the chain of infection model

Exploring endogenous transmission further, it has been shown that persons with nasal carriage of *Staphylococcus aureus* have an increased risk of HAI caused by this organism, compared to persons without or with low level carriage (Kluytmans et al., 1995; Luzar et al., 1990; Nouwen et al., 2006). Further, more than 80% of HAIs caused by *Staphylococcus aureus* are thought to be endogenous (von Eiff et al., 2001; Weinstein, 1959; Wertheim et al., 2005).

The role of other source of infections, namely from environmental or other inanimate objects remains less clear, however there is increasing evidence of its role in infection transmission. From the data available, it has been suggested that contaminated surfaces can lead to HAIs indirectly (Weinstein & Hota, 2004). This is possible as microorganisms can survive for long periods in the environment (Kramer, 2006; Wagenvoort, 2011) and unless processes such as cleaning are performed, these microorganisms can persist in the healthcare environment and hence pose a source of infection, for example, via the hands of healthcare workers, as described earlier in this section (Barker, Vipond, & Bloomfield, 2004; Bhalla et al., 2004; Dancer, 2011; B. Mitchell, Wilson, F., McGregor, A., Dancer, S. , 2012). To demonstrate this point further, studies have shown that persistence of organisms in the environment leads to an increased risk of acquiring an infection in a patient who is admitted to a room previously occupied by a patient colonised or infected with that particular organism (Dancer, 2011; Huang, Datta, & Platt, 2006).

Appendix B

Further detail on standard precautions and their application

Standard precautions are used because:

- people may be placed at risk of infection from others who carry infectious agents;
- people may be infectious before signs or symptoms of disease are recognised or detected, or before laboratory tests are confirmed in time to contribute to care;
- people may be at risk from infectious agents present in the surrounding environment; and
- there may be an increased risk of transmission associated with specific procedures and practices.

(National Health and Medical Research Council, 2010)

Standard precautions consist of hand hygiene, the use of personal protective equipment, the safe use and disposal of sharps, routine environmental cleaning and reprocessing of reusable medical equipment and instruments, respiratory hygiene and cough etiquette, aseptic non-touch technique, waste management and appropriate handling of linen. Standard precautions should be used in the handling of blood, all other body substances, secretions and excretions (excluding sweat), non-intact skin and mucous membranes (National Health and Medical Research Council, 2010).

Appendix C

Examples of applying transmission based precautions

Contact precautions refer to processes that should be implemented when there is a risk of direct or indirect contact with an infectious agent, such as MRSA. Droplet precautions are intended to prevent transmission of infectious agents that are spread through close respiratory or mucous membrane contact with respiratory secretions, whilst airborne precautions prevent transmission of microorganisms that remain infectious over time and distance when suspended in the air (National Health and Medical Research Council, 2010). The modes of transmission vary by type of organism; some organisms, such as influenza, can be transmitted by more than one route (National Health and Medical Research Council, 2010). If the agent is transmitted to another person, infection can result. The table below provides examples of applying contact, droplet, and airborne precautions. These three processes fall under the umbrella term called ‘transmission based precautions’.

Type of transmission based precaution	Examples of processes that need to be applied
Contact precautions*	<ol style="list-style-type: none"> 1. When working with patients who require contact precautions. Contact precautions include performing hand hygiene; use of gloves and gown upon entry to the patient-care area; ensuring clothing and skin do not contact potentially contaminated environmental surfaces; and removing gown and gloves and performing hand hygiene before leaving the patient-care area. 2. Use patient-dedicated equipment or single-use non-critical patient-care equipment. 3. If common use of equipment for multiple patients is unavoidable, clean the equipment and allow it to dry before use on another patient. 4. A single-patient room is recommended for patients who require contact precautions. 5. Limit transfers of a patient on contact precautions to

	reduce the risk of environmental contamination.
Droplet precautions*	<ol style="list-style-type: none"> 1. When entering the patient-care environment, put on a surgical mask. 2. Patients on droplet precautions should be placed in a single-patient room. 3. When transfer of a patient on droplet precautions within or between facilities is necessary, the patient should wear a mask while they are being transferred and to follow respiratory hygiene and cough etiquette.
Airborne precautions*	<ol style="list-style-type: none"> 1. Use of P2 respirators (mask). Mask should be applied before entering the patients' room and removed upon leaving the room. 2. Patients on airborne precautions should be placed in a negative pressure room or in a room from which the air does not circulate to other areas. 3. When transfer of a patient on airborne precautions within or between facilities is necessary, the patient should wear a mask while they are being transferred and follow respiratory hygiene and cough etiquette.

Note: Adapted from “*Australian Guidelines for the Prevention and Control of Infection in Healthcare*,” by National Health and Medical Research Council.

Copyright 2010 by the National Health and Medical Research Council. *Standard precautions always apply, in addition to the examples listed in the table. Transmission based precautions are applied to patients suspected or confirmed to be infected with agents transmitted by the contact, droplet or airborne routes. A person with an infection can have a combination of transmission based precautions applied to prevent the transmission of infection. For example contact and droplet precautions can be applied in the case of a person with influenza.

Appendix D

Relating the biomedical model to infection control

Concept	Infection control example
The concepts of health and illness are seen to exist separately.	HAI and the interventions made by health and social care professionals are seen as existing in isolation; they are not perceived as impacting upon each other.
Disease or infection is external to the body and is not the result of an individual's behaviour.	The behaviour of health and social care professionals has no impact upon the risk of cross infection.
Individuals have no responsibility to ensure the maintenance of their own or others' health and wellbeing.	Despite failing to adopt standard precautions, health and social care professionals are not responsible for the consequences of such a failure.
Although it is acknowledged that they exist, the mind and body are perceived as being separate, with neither having consequences for the other.	A health professional who is experiencing stress will demonstrate a greater propensity toward becoming cognitively economic and unrealistically optimistic in his/her perception of the importance of standard precautions. Despite this, there will be no impact upon his/her behaviour. Therefore, a failure to carry out standard precautions according to a biomedical perspective is not a consequence of the way a health professional thinks, but simply a physical action.
Psychosocial factors have no part to play and healthcare intervention should centre around the physical aspects in isolation.	HAI has nothing to do with how health and social care professionals think or the social context within which they are practising. Cross infection is simply a consequence of physical factors, such as the cleanliness of equipment or the environment.

Note: Adapted from “*Infection Control a psychosocial approach to changing practice*”, by P. Elliott. Copyright 2009 by Radcliff Publishing, p.78.

Appendix E

Literature identified in *Staphylococcus aureus* bacteraemia literature review

Article	Comment
Burke, R. E., Halpern, M. S., Baron, E. J., & Gutierrez, K. (2009). Pediatric and neonatal <i>Staphylococcus aureus</i> bacteremia: epidemiology, risk factors, and outcome. <i>Infection Control & Hospital Epidemiology</i> , 30(7), 636-644.	
Canadian Nosocomial Infection Surveillance Program. (2008). Surveillance for Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) in Patients Hospitalized in Canadian Acute-Care Hospitals Participating in CNISP 2006-2007. Preliminary Results. Retrieved 2 October 2009, from http://www.phac-aspc.gc.ca/nois-sinp/pdf/mrsa-sarm-eng.pdf	Identified in grey literature
Chang, F.-Y., Peacock, J. E., Jr., Musher, D. M., Triplett, P., MacDonald, B. B., Mylotte, J. M., et al. (2003). <i>Staphylococcus aureus</i> bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. <i>Medicine</i> , 82(5), 333-339.	
Chaves, F., Garcia-Martinez, J., de Miguel, S., Sanz, F., & Otero, J. R. (2005). Epidemiology and clonality of methicillin-resistant and methicillin-susceptible <i>Staphylococcus aureus</i> causing bacteremia in a tertiary-care hospital in Spain. <i>Infection Control & Hospital Epidemiology</i> , 26(2), 150-156.	
Chi, C.-Y., Wong, W.-W., Fung, C.-P., Yu, K.-W., & Liu, C.-Y. (2004). Epidemiology of community-acquired <i>Staphylococcus aureus</i> bacteremia. <i>Journal of Microbiology, Immunology & Infection</i> , 37(1), 16-23.	
Chia, J. W.-Z., Hsu, L.-Y., Chai, L. Y.-A., & Tambyah, P. A. (2008). Epidemiology and outcomes of community-onset methicillin-susceptible <i>Staphylococcus aureus</i> bacteraemia in a university hospital in Singapore. <i>BMC Infectious Diseases</i> , 8, 14.	
CHRISP. (2009). Surveillance Manual 3rd. Retrieved 2 September 2009, 2009, from http://www.health.qld.gov.au/chrisp/surveillance/surveillance_manual.asp	Identified in grey literature
Chua, T., Moore, C. L., Perri, M. B., Donabedian, S. M., Masch, W., Vager, D., et al. (2008). Molecular epidemiology of methicillin-resistant <i>Staphylococcus aureus</i> bloodstream isolates in urban Detroit. <i>Journal of Clinical Microbiology</i> ,	

46(7), 2345-2352.

Coello, R., Charlett, A., Ward, V., Wilson, J., Pearson, A., Sedgwick, J., et al. (2003). Device-related sources of bacteraemia in English hospitals--opportunities for the prevention of hospital-acquired bacteraemia.[see comment]. *Journal of Hospital Infection*, 53(1), 46-57.

Collignon, P., Wilkinson, I., Gilbert, G., Grayson, L., & Whitby, M. (2006). Health care-associated *Staphylococcus aureus* bloodstream infections: a clinical quality indicator for all hospitals. *Medical Journal of Australia*, 184(8), 404-406.

Collignon, P., Dreimanis, D., Beckingham, W., Roberts, J., & Gardner, A. (2007). Intravascular catheter bloodstream infections: an effective and sustained hospital-wide prevention program over 8 years. *Medical Journal of Australia*, 187(10), 551-554.

Collignon, P., Dreimanis, D., Ferguson, J., van Gessel, H., Taylor, P., Wilkinson, I., & Worth, L. (2008). Bloodstream Infection. In M. Cruickshank, Ferguson, J. (Ed.), *Reducing harm to patients from healthcare associated infections: the role of surveillance*, 53-89. Sydney: Australian Commission on Safety and Quality in Health Care.

Collignon, P., Nimmo, G. R., Gottlieb, T., Gosbell, I. B., & Australian Group on Antimicrobial, R. (2005). *Staphylococcus aureus bacteremia*, Australia. *Emerging Infectious Diseases*, 11(4), 554-561.

Cordova, S. P., Heath, C. H., McGeachie, D. B., Keil, A. D., Beers, M. Y., & Riley, T. V. (2004). Methicillin-resistant *Staphylococcus aureus* bacteraemia in Western Australian teaching hospitals, 1997-1999: risk factors, outcomes and implications for management. *Journal of Hospital Infection*, 56(1), 22-28.

Cruickshank, M., Jorm, C. (2008). Introduction. In M. Cruickshank, Ferguson, J. (Ed.), *Reducing Harm to Patients from Healthcare Associated Infection: The Role of Surveillance* (pp. 19-25). Sydney: Australian Commission on Safety & Quality in Healthcare.

de Oliveira Conterno, L., Wey, S., & Castelo, A. (2002). *Staphylococcus aureus* bacteremia: comparison of two periods and a predictive model of mortality. *Brazilian Journal of Infectious Diseases*, 6(6), 288-297.

Denniston, S., & Riordan, F. A. I. (2006). *Staphylococcus aureus*

Identified in grey literature

Identified in grey literature

<p>bacteraemia in children and neonates: a 10 year retrospective review. <i>Journal of Infection</i>, 53(6), 387-393.</p>	
<p>Dreimanis, D., Beckingham, W., Collignon, P., & Roberts, J. (2005). <i>Staphylococcus aureus</i> bacteraemia surveillance: a relatively easy to collect but accurate clinical indicator on serious health-care associated infections and antibiotic resistance. <i>Australian Infection Control</i>, 10(4), 127-130.</p>	
<p>Expert Working Group in surveillance of the Australian Infection Control Association. (2000). Introduction to Australian surveillance definitions: surgical site infections and blood-stream infections. <i>Australian Infection Control</i>, 5, 25-31.</p>	<p>Identified in grey literature</p>
<p>Friedman, N., Kaye, K., Stout, J., McGarry, S., Trivette, S., Briggs, J., & Lamm, W., et al. (2002). Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections. <i>Annals of Internal Medicine</i>, 137(10), 791-797.</p>	
<p>Grayson, M. L., Jarvie, L. J., Martin, R., Johnson, P. D. R., Jodoin, M. E., McMullan, C., et al. (2008). Significant reductions in methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia and clinical isolates associated with a multisite, hand hygiene culture-change program and subsequent successful statewide roll-out. <i>Medical Journal of Australia</i>, 188(11), 633-640.</p>	<p>Not included in <i>Healthcare Infection</i> paper, but identified in literature review.</p>
<p>Guilarde, A. O., Turchi, M. D., Martelli, C. M. T., & Primo, M. G. B. (2006). <i>Staphylococcus aureus</i> bacteraemia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. <i>Journal of Hospital Infection</i>, 63(3), 330-336.</p>	
<p>Health Protection Agency. (2005). <i>Mandatory Enhanced MRSA Surveillance Protocol</i>. Health Protection Agency.</p>	<p>Identified in grey literature</p>
<p>Health Protection Agency. (2009). Mandatory <i>Staphylococcus aureus</i> bacteraemia surveillance scheme. Retrieved 2 September 2009, from http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1191942169773</p>	<p>Identified in grey literature</p>
<p>Health Protection Scotland. (2009). Scottish Surveillance of Healthcare Associated Infection Programme Quarterly report on <i>Staphylococcus aureus</i> bacteraemias in Scotland. Retrieved 1 October 2009, from http://www.hps.scot.nhs.uk/haiic/ic/wrdetail.aspx?id=41928&wrtype=6</p>	<p>Identified in grey literature</p>
<p>Healthcare Associated Infection Unit. (2009). Surveillance Manual Version 3. Retrieved 3 September 2009, from</p>	<p>Identified in grey literature</p>

<p>http://www.public.health.wa.gov.au/cproot/813/2/Revised%20Surveillance%20Manual%20July2009.pdf</p> <p>Horan, T., Andrus, M., & Dudeck, M. (2008). CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. <i>American Journal of Infection Control</i>, 310(5), 309-332.</p> <p>Jenkins, T. C., Price, C. S., Sabel, A. L., Mehler, P. S., & Burman, W. J. (2008). Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of <i>Staphylococcus aureus</i> bacteremia.[see comment]. <i>Clinical Infectious Diseases</i>, 46(7), 1000-1008.</p> <p>Jeyaratnam, D., Edgeworth, J., & French, G. (2006). Enhanced surveillance of methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia in a London teaching hospital. <i>The Journal of Hospital Infection</i>, 63(4), 365-373.</p> <p>Johnson, L. B., Bhan, A., Pawlak, J., Manzor, O., & Saravolatz, L. D. (2003). Changing epidemiology of community-onset methicillin-resistant <i>Staphylococcus aureus</i> bacteremia. <i>Infection Control & Hospital Epidemiology</i>, 24(6), 431-435.</p> <p>Khairulddin, N., Bishop, L., Lamagni, T. L., Sharland, M., & Duckworth, G. (2004). Emergence of methicillin resistant <i>Staphylococcus aureus</i> (MRSA) bacteraemia among children in England and Wales, 1990-2001. <i>Archives of Disease in Childhood</i>, 89(4), 378-379.</p> <p>Kuint, J., Barzilai, A., Regev-Yochay, G., Rubinstein, E., Keller, N., & Maayan-Metzger, A. (2007). Comparison of community-acquired methicillin-resistant <i>Staphylococcus aureus</i> bacteremia to other staphylococcal species in a neonatal intensive care unit. <i>European Journal of Pediatrics</i>, 166(4), 319-325.</p> <p>Laupland, K. B., Ross, T., & Gregson, D. B. (2008). <i>Staphylococcus aureus</i> bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. <i>Journal of Infectious Diseases</i>, 198(3), 336-343.</p> <p>Lesens, O., Hansmann, Y., Brannigan, E., Hopkins, S., Meyer, P., O'Connell, B., et al. (2005). Healthcare-associated <i>Staphylococcus aureus</i> bacteremia and the risk for methicillin resistance: is the Centers for Disease Control and Prevention definition for community-acquired bacteremia still appropriate? <i>Infection Control & Hospital</i></p>	<p>literature</p> <p>Not included in <i>Healthcare Infection</i> paper, but identified in literature review.</p> <p>Not included in <i>Healthcare Infection</i> paper, but identified in literature review.</p>
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<p><i>Epidemiology</i>, 26(2), 204-209.</p> <p>Lesse, A. J., & Mylotte, J. M. (2006). Clinical and molecular epidemiology of nursing home-associated <i>Staphylococcus aureus</i> bacteremia. <i>American Journal of Infection Control</i>, 34(10), 642-650.</p> <p>Lin, C., Wang, J., Lin, C., Chen, S., Wang, J., Wu, K., et al. (2009). Methicillin-resistant <i>Staphylococcus aureus</i> bacteremia in patients with end-stage renal disease in Taiwan: distinguishing between community-associated and healthcare-associated strains. <i>Infection Control & Hospital Epidemiology</i>, 30(1), 89-92.</p> <p>Lin, J.-C., Yeh, K.-M., Peng, M.-Y., & Chang, F.-Y. (2004). Community-acquired methicillin-resistant <i>Staphylococcus aureus</i> bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome. <i>Journal of Microbiology, Immunology & Infection</i>, 37(1), 24-28.</p> <p>Lyytikäinen, O., Ruotsalainen, E., Jarvinen, A., Valtonen, V., & Ruutu, P. (2005). Trends and outcome of nosocomial and community-acquired bloodstream infections due to <i>Staphylococcus aureus</i> in Finland, 1995-2001. <i>European Journal of Clinical Microbiology & Infectious Diseases</i>, 24(6), 399-404.</p> <p>McGregor, A., & Mitchell, B. (2009). Tasmanian Acute Public Hospitals Healthcare Associated Infection Surveillance Report. Retrieved from http://www.dhhs.tas.gov.au/__data/assets/pdf_file/0009/39384/74320_PROOF.pdf</p> <p>Mitchell, B., McGregor, A., & Wells, A. (2009). <i>Staphylococcus aureus</i> bacteraemia surveillance protocol. Department of Health and Human Services. Retrieved from http://www.dhhs.tas.gov.au/__data/assets/pdf_file/0003/33564/SAB_surveillance_March_2009.pdf.</p> <p>Munckhof, W. J. (2005). Intravenous catheter-associated <i>Staphylococcus aureus</i> bacteraemia: a common problem that can be prevented. <i>Internal Medicine Journal</i>, 35(6), 315-318.</p> <p>Nickerson, E. K., Hongsuwan, M., Limmathurotsakul, D., Wuthiekanun, V., Shah, K. R., Srisomang, P., et al. (2009). <i>Staphylococcus aureus</i> bacteraemia in a tropical setting:</p>	<p>Not included in <i>Healthcare Infection</i> paper, but identified in literature review.</p> <p>Identified in grey literature</p> <p>Identified in grey literature</p>
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<p>patient outcome and impact of antibiotic resistance. <i>PLoS ONE [Electronic Resource]</i>, 4(1), e4308.</p> <p>O'Connell, B., McMahon, G., Kelleher, M., & Rossney, A. S. (2007). Methicillin-resistant <i>Staphylococcus aureus</i> blood-stream infection among patients attending the emergency department of an urban tertiary-referral hospital. [see comment]. <i>Irish Medical Journal</i>, 100(4), 433-435.</p> <p>O'Grady, N. P., Alexander, M., Dellinger, E. P., Gerberding, J. L., Heard, S. O., Maki, D. G., et al. (2002). Guidelines for the prevention of intravascular catheter-related infections. <i>American Journal of Infection Control</i>, 30(8), 476-489.</p> <p>Perovic, O., Koornhof, H., Black, V., Moodley, I., Duse, A., & Galpin, J. (2006). <i>Staphylococcus aureus</i> bacteraemia at two academic hospitals in Johannesburg. <i>South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde</i>, 96(8), 714-717.</p> <p>Rezende, N. A., Blumberg, H. M., Metzger, B. S., Larsen, N. M., Ray, S. M., & McGowan, J. E., Jr. (2002). Risk factors for methicillin-resistance among patients with <i>Staphylococcus aureus</i> bacteremia at the time of hospital admission. <i>American Journal of the Medical Sciences</i>, 323(3), 117-123.</p> <p>Saginur, R., & Suh, K. N. (2008). <i>Staphylococcus aureus</i> bacteraemia of unknown primary source: where do we stand? <i>International Journal of Antimicrobial Agents</i>, 32 Suppl 1, S21-25.</p> <p>South Australian Infection Control Service. (2006). Bloodstream infection definitions Retrieved 2 September 2009, from http://www.health.sa.gov.au/INFECTIONCONTROL/Default.aspx?tabid=24</p> <p>South Australian Infection Control Service. (2006). <i>South Australian Statewide Nosocomial Bloodstream Infection Report 2005 - amended</i>. Government of South Australia. Retrieved from http://www.health.sa.gov.au/INFECTIONCONTROL/Default.aspx?PageContentID=18&tabid=147.</p> <p>Tacconelli, E., Venkataraman, L., De Girolami, P. C., & Dagata, E. M. C. (2004). Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains. <i>Journal of Antimicrobial Chemotherapy</i>, 53(3), 474-479.</p>	<p>Identified in grey literature</p> <p>Identified in grey literature</p>
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<p>Turnidge, J. D., Nimmo, G. R., Pearson, J., Gottlieb, T., Collignon, P. J., & Australian Group on Antimicrobial, R. (2007). Epidemiology and outcomes for <i>Staphylococcus aureus</i> bacteraemia in Australian hospitals, 2005-06: report from the Australian Group on Antimicrobial Resistance. <i>Communicable Diseases Intelligence</i>, 31(4), 398-403.</p>	
<p>van der Mee-Marquet, N., Domelier, A.-S., Girard, N., Quentin, R., & Bloodstream Infection Study Group of the Relais d'Hygiene du, C. (2004). Epidemiology and typing of <i>Staphylococcus aureus</i> strains isolated from bloodstream infections. <i>Journal of Clinical Microbiology</i>, 42(12), 5650-5657.</p>	
<p>Welsh Healthcare Associated Infection Program. (2009). <i>Staph. aureus</i> blood stream infection surveillance. Retrieved 3 September 2009, from National Public Health Service for Wales http://www.wales.nhs.uk/sites3/page.cfm?orgid=379&pid=13124</p>	<p>Identified in grey literature</p>
<p>Wyllie, D. H., Crook, D. W., & Peto, T. E. A. (2006). Mortality after <i>Staphylococcus aureus</i> bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study [corrected] [published erratum appears in <i>BMJ</i> 2006 Sep 2;333(7566):468]. <i>BMJ: British Medical Journal</i>, 333(7562), 281-284.</p>	
<p>Total</p>	<p>54 (14 grey literature)</p>

Appendix F

Percentage of population by age group and region in Tasmania

Age group	Region		
	South	North	North-west
0-14	19.10%	19.43%	20.07%
15-24	13.41%	13.32%	12.35%
25-39	18.55%	17.62%	17.13%
40-64	34.25%	33.99%	34.30%
65-84	12.79%	13.72%	14.21%
>85	1.89%	1.92%	1.94%

Note: Adapted from “*Tasmanian State and Regional Indicators*” by Australian Bureau of Statistics, 2011. Copyright 2011 by Australian Bureau of Statistics.

Appendix G

Algorithm used to match ICD-10-AM codes against Charlson co-morbidity index

Condition	Weight	ICD-10-AM Codes
Acute myocardial infarction	1	I21, I22, I252
Congestive heart failure	1	I50
Peripheral vascular disease	1	I71, I790, I739, R02, Z958, Z959
Cerebral vascular accident	1	I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Dementia	1	F00, F01, F02, F051
Pulmonary disease	1	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65
Connective tissue disorder	1	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353
Peptic ulcer	1	K25, K26, K27, K28
Liver disease	1	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745
Diabetes	1	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complication	2	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Paraplegia	2	G81 G041, G820, G821, G822
Renal disease	2	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25
Cancer	2	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96
Metastatic cancer	3	C77, C78, C79, C80
Severe liver disease	3	K729, K766, K767, K721
HIV	6	B20, B21, B22, B23, B24

Note: Charlson diagnostic categories and corresponding ICD-10 AM codes. Adapted from “*New ICD-10 version of the Charlson co-morbidity index predicted in-hospital mortality*,” by V. Sundararajan, T. Henderson, C. Perry, A. Muggivan, H. Quan, and W. Ghali, 2004. *Journal of Clinical Epidemiology*, 57, p.1290. Copyright 2004 by Elsevier B.V.

Appendix H

Time between first and second cases of *Clostridium difficile* infection for persons with more than one infection

Person	Time between first and second infection
1	3 years
2	9 months
3	4 months
4	6 months
5	4 months

Appendix I

Models used to evaluate the cost of healthcare associated infections

This appendix briefly explores the different models used to evaluate the economic cost of a HAI. By exploring these models, it becomes evident that length of stay in hospital is an important element of cost and that this variable underpins models used to evaluate cost. As demonstrated in a recent published systematic review examining the economic costs of CDI, the focus of many studies is to view costs through the eyes of an accountant (Ghantaji et al., 2010). An accountant's model for determining the cost of HAIs is to count fixed and variable costs. Variable costs may include items such as dressings, personal protective equipment and costs of laboratory test materials. Fixed costs include such things as salary, electricity and heating. As fixed costs are often jointly shared, for example one doctor does not treat one patient, the accountants' model determines a measure of usage for these fixed costs (cost per unit) and allocates this to patients or the health provider accordingly. Comparisons between the average cost per infected patient and average cost per non-infected patient are often used to attribute the cost of HAIs, however this may be misleading (N. Graves, Halton, K., Jarvis, W., 2009). According to Graves, using such a model is not suitable for economic appraisal or informing decisions on the best use of scarce healthcare resources. An implication of the accountant model is that by reducing or eradicating a specific infection, a fixed figure could be saved. An accountant model ignores the cost of increased investment associated with reducing infections and fails to consider what costs actually change with infections, where many fixed costs remain (N. Graves, Halton, K., Jarvis, W., 2009).

An economist model uses a cost analysis approach to determine any savings. For example, the consumables may be reduced with a reduction in HAIs. The capacity gained by a reduction in HAIs is valuable and should thus be redeployed for other uses. The redeployment of resources could be used for tasks such as elective surgery which in turn may cause other variable costs to increase (N. Graves, Halton, K., Jarvis, W., 2009). An economist's approach in evaluating the cost of HAIs is supported by the argument that the majority of the costs associated with hospital care

are fixed (Plowman, 1999; Roberts et al., 1999). Therefore, in describing how costs change in relation to HAIs, it is important to demonstrate the number of bed days caused by HAIs (N. Graves, Halton, K., Jarvis, W., 2009) before deciding who will utilise these extra bed days released. This concept of accurately determining the prolongation of length of stay due to CDI will assist in developing an economic model for its prevention and control.

Appendix J

Technical explanation of a multistate model

A technical explanation for a multistate model is provided by Wolkewitz et al (2010):

The hazard (u) depends on time u and is considered to be the probability of changing states in the next short time interval divided by the length of the interval, noting that individuals have been in the current state up to that time. In the equation below, $Y(u)$ is denoted as the size of the risk sets and $N(u)$ as the number of observed events at time u . The time-dependent cumulative hazard can be estimated by the following formula (Nelson–Aalen estimator). The formula shows that the size of the risk sets (denominator) is crucial to estimate the death hazards. Survival analysis is based on hazards because the cumulative hazard (and the hazard itself) remains ‘undisturbed’ by right censoring/left-truncation if the truncation as well as the censoring time is independent of the event time.

$$\hat{\Lambda}(t) = \sum_{u=0}^t \frac{\Delta N(u)}{Y(u)} = \sum_{u=0}^t \frac{\# \text{ events at } u}{\# \text{ at risk at } u-}.$$

(p. 207)

Appendix K

Code used for multistate model data analysis in R

```

# MVNA3state.R
# september 2011
# analyse Brett's data using MVNA, use a 3 state model (Susceptible, infected,
death/discharge)
setwd(lib$brett) # move to the folder
load('Brett.RData') # load the data
library(mvna) # R library to run multistate models

# split data by infected / not infected
index=is.na(data$Infection.start)==T
not.infected=data[index,]
infected=data[!index,]
## set up entry and exit times
# susceptible -> death/discharge
not.infected$entry=0 # start at time zero
not.infected$exit=as.numeric(not.infected$Discharge-not.infected$Admission) # exit
at discharge, add 0.001 day for same day entry/exit
not.infected$from=0 # from susceptible
not.infected$to=2 # to death/discharge
not.infected=subset(not.infected,select=c(id,from,to,entry,exit)) # remove extra
variables from the data
# susceptible -> infected
StoI=infected
StoI$entry=0 # start at time zero
StoI$exit=as.numeric(StoI$Infection.start-StoI$Admission)# exit at infection date
StoI$from=0 # from susceptible
StoI$to=1 # to infected
StoI=subset(StoI,select=c(id,from,to,entry,exit)) # remove extra variables from the
data
# infected -> death/discharge

```

```

ItoD=infected
ItoD$entry=as.numeric(ItoD$Infection.start-ItoD$Admission)# entry at infection date
ItoD$exit=as.numeric(ItoD$Discharge-ItoD$Admission) # exit at discharge
ItoD$from=1 # from infected
ItoD$to=2 # to death/discharge
ItoD=subset(ItoD,select=c(id,from,to,entry,exit)) # remove extra variables from the
data
# concatenate the three data sets
for.analysis=rbind(not.infected,StoI,ItoD)
with(for.analysis,table(from,to)) # table of the transitions

# Modification for patients entering and leaving a state at the same date
for.analysis <- for.analysis[order(for.analysis$id, for.analysis$entry,
for.analysis$exit), ]
for (i in 2:nrow(for.analysis)) {
  if (for.analysis$id[i]==for.analysis$id[i-1]) {
    if (for.analysis$exit[i]==for.analysis$exit[i-1]) {
      for.analysis$exit[i-1] <- for.analysis$exit[i-1] - 0.5 # move forward in time by half
a day
      for.analysis$entry[i] <- for.analysis$entry[i] - 0.5 # change to match above move
    }
  }
}
# quickly check a few patients
subset(for.analysis,id==23060)
subset(for.analysis,id==23042)

# Matrix of logical giving the possible transitions
tra <- matrix(ncol=3,nrow=3,FALSE)
tra[1, 2:3] <- TRUE
tra[2, 3] <- TRUE

# Computation of the Nelson-Aalen estimates
na <- mvna(for.analysis,c("0","1","2"),tra,'cens')

```

```

# plot to a jpeg
jpeg(filename = "3State.jpeg", width = 9, height = 9, res=300,
      units = "cm", pointsize = 12, quality = 100, bg = "transparent")
par(mai=c(0.9,0.9,0.05,0.2),las=1) # set up margins
plot(na, tr.choice=c("0 2", "1 2"), xlab = "Days in hospital",xlim=c(0,80),ylim=c(0,6),
     ylab = "Cumulative Hazard", lwd=2, curvlab=c("Not infected","Infected"))
dev.off()

### Biased estimate based on ignoring time-dependence
glm.data=subset(for.analysis,to==2) # just examine the discharge/death time
model=summary(glm(exit~from,data=glm.data,family=Gamma(link='log')))
tdep <- exp(model$coefficients[1,1]+model$coefficients[2,1])-
exp(model$coefficients[1,1])
z<-qnorm(0.975)
lower<-model$coefficients[2,1]-(z*model$coefficients[2,2])
upper<-model$coefficients[2,1]+(z*model$coefficients[2,2])
tdepLower <- exp(model$coefficients[1,1]+lower)-exp(model$coefficients[1,1])
tdepUpper <- exp(model$coefficients[1,1]+upper)-exp(model$coefficients[1,1])
cat('Mean=',tdep,', CI=[',tdepLower,', ',tdepUpper,']\n',sep=")

```

Appendix L

Incidence of *Clostridium difficile* infection per 1000 admissions by calendar year at the Royal Hobart Hospital

Year	Number of cases of CDI	Incidence per 1000 admissions	95% confidence interval
2007	24	1.71	1.12-2.50
2008	40	2.75	1.96-3.74
2009	35	2.31	1.61-3.22
2010	59	3.89	2.96-5.01
Total	158	2.68	2.28-3.13

Note: Admissions = total admissions to the RHH hospitalised ≥ 48 hours. CDI = *Clostridium difficile* infection.

Appendix M

Comparison of Diagnosis Related Group in person with and without *Clostridium difficile* infection at the Royal Hobart Hospital, 2007-2010

DRG category	Persons with CDI (%)	Persons without CDI (%)	Total (%)	Statistic	p value
Pregnancy	1 (0.6)	7898 (13.4)	7899 (13.4)	22.26 [^]	<0.01
Circulatory	12 (7.6)	6851 (11.7)	6863 (11.6)	2.52 [^]	0.11
Musculoskeletal	16 (10.1)	5877 (10.0)	5893 (10.0)	0.003 [^]	0.96
Nervous	20 (12.7)	5007 (8.5)	5027 (8.5)	3.46 [^]	0.06
Respiratory	9 (5.7)	4711 (8.0)	4720 (8.0)	1.15 [^]	0.28
Digestive	21 (13.3)	4709 (8.0)	4730 (8.0)	5.95 [^]	0.02
Health status	15 (9.5)	4278 (7.3)	4293 (7.3)	1.15 [^]	0.28
Mental health	1 (0.6)	3894 (13.4)	3895 (6.6)	9.17 [^]	<0.01
Injury	3 (1.9)	1957 (3.3)	1960 (3.3)	N/A [*]	0.50
Skin	3 (1.9)	1799 (3.1)	1802 (3.1)	N/A [*]	0.64
Endocrine	3 (1.9)	1623 (2.8)	1626 (2.8)	N/A [*]	0.81
Kidney	10 (6.3)	1577 (2.7)	1587 (2.7)	8.00 [^]	<0.01
Hepatobiliary	4 (2.5)	1525 (2.6)	1529 (2.6)	N/A [*]	1.00
ENT	1 (0.6)	1477 (2.5)	1478 (2.5)	N/A [*]	0.20
Female reproduction	2 (1.3)	1190 (2.0)	1192 (2.0)	N/A [*]	0.78
Infectious	4 (2.5)	895 (1.5)	899 (1.5)	N/A [*]	0.31
Neoplastic	8 (5.4)	795 (1.4)	803 (1.4)	16.15 [^]	<0.01
Blood	3 (1.9)	615 (1.0)	618 (1.0)	N/A [*]	0.23
Male reproduction	0 (0.0)	601 (1.0)	601 (1.0)	N/A [*]	0.42
Alcohol	0 (0.0)	335 (0.6)	335 (0.6)	N/A [*]	1.00
Burns	0 (0.0)	288 (0.5)	288 (0.5)	N/A [*]	1.00
Eye	0 (0.0)	165 (0.3)	165 (0.3)	N/A [*]	1.00
Pre	19 (12.0)	547 (0.9)	566 (0.9)	203.95 [^]	<0.01
Error	3 (0.3)	170 (1.9)	173 (0.3)	13.95 [^]	<0.01

Note: [^]Chi squared. ^{*}Fisher's Exact Test.

Appendix N

Ethics approval from the Tasmanian Human Research Ethics Committee for *Staphylococcus aureus* bacteraemia study

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
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HUMAN
RESEARCH
ETHICS
COMMITTEE
(TASMANIA)
NETWORK



21 July 2011

Mr Brett Mitchell
Sent via email

Dear Mr Mitchell,

REF NO: H11130

TITLE: The epidemiology of *Staphylococcus aureus* bacteraemia in Tasmania

- Updated NEAF to reflect changes in Prof Gardner and Mr Mitchell's employment

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above amendment documentation following its meeting on 14 July 2011.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on Ethical Conduct in Human Research* (NHMRC 2007).

Should you have any queries please do not hesitate to contact me on (03) 6226 1956.



Yours sincerely,

Adele Kay
Ethics Officer, Health and Medical
On behalf of the Executive Officer
HREC (TAS) Network




Appendix O

Ethics approval from Australian Catholic University for *Staphylococcus aureus* bacteraemia study


<p>Human Research Ethics Committee Committee Approval Form</p>
<p>Principal Investigator/Supervisor: Professor Anne Gardner Canberra Campus Co-Investigators: Dr Lee Stewart (JCU) Student Researcher: Mr Brett Mitchell Canberra Campus</p>
<p>Ethics approval has been granted for the following project: The epidemiology of <i>Staphylococcus aureus</i> bacteraemia in Tasmania for the period: 8 August 2011 to 30 June 2012 Human Research Ethics Committee (HREC) Register Number: N2011 56</p>
<p>Special Condition/s of Approval</p> <p><i>Prior to commencement of your research</i>, the following permissions are required to be submitted to the ACU HREC:</p> <p>Tasmania Health and Medical HREC</p> <p>The following standard conditions as stipulated in the <i>National Statement on Ethical Conduct in Research Involving Humans (2007)</i> apply:</p> <ul style="list-style-type: none"> (i) that Principal Investigators / Supervisors provide, on the form supplied by the Human Research Ethics Committee, annual reports on matters such as: <ul style="list-style-type: none"> • security of records • compliance with approved consent procedures and documentation • compliance with special conditions, and (ii) that researchers report to the HREC immediately any matter that might affect the ethical acceptability of the protocol, such as: <ul style="list-style-type: none"> • proposed changes to the protocol • unforeseen circumstances or events • adverse effects on participants <p>The HREC will conduct an audit each year of all projects deemed to be of more than low risk. There will also be random audits of a sample of projects considered to be of negligible risk and low risk on all campuses each year.</p> <p>Within one month of the conclusion of the project, researchers are required to complete a <i>Final Report Form</i> and submit it to the local Research Services Officer.</p> <p>If the project continues for more than one year, researchers are required to complete an <i>Annual Progress Report Form</i> and submit it to the local Research Services Officer within one month of the anniversary date of the ethics approval.</p>

<p>Signed: Date: ... 08.08.2011.... (Research Services Officer, McAuley Campus)</p>
<p><small>C:\Users\Brett\Documents\My documents\ACU\SAB Research\Ethics\Approvals\N2011 56 Gardner Approval Formbris.doc</small></p>

Appendix P

Ethics approval from the Tasmanian Human Research Ethics Committee for the *Clostridium difficile* infection studies

<p>Office of Research Services University of Tasmania Private Bag 1 Hobart Tasmania 7001 Telephone + 61 6 8225 1470 Facsimile + 61 6 8225 3148 Email: Human.Ethics@utas.edu.au http://research.utas.edu.au/human_ethics/</p>	<p>HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK</p>	
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7 December 2010

Professor Anne Gardner
C/- Brett Mitchell
Population Health
DHHS
GPO Box 125
Hobart TAS 7001

Dear Professor Gardner,

REF NO: H11484
TITLE: The impact of *Clostridium difficile* infection (CDI) on mortality and length of stay in an Australian setting

- *Application Form- NEAF*
- *Letter of support, Duncan McKenzie, Royal Hobart Hospital Pharmacy*
- *Letter of access, Dr Tara Anderson, Director Royal Hobart Hospital Infection Prevention and Control Unit*
- *Research Proposal*
- *Letter of Support, Dr Roscoe Taylor*


The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on 7 December 2010.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct of Human Research* (NHMRC 2007).

Therefore, the Chief Investigator's responsibility is to ensure that:

- (1) The individual researcher's protocol complies with the HREC approved protocol.
- (2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.
- (3) Section 5.5.3 of the National Statement states:
Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.research.utas.edu.au/human_ethics/medical_forms.htm



A PARTICIPATING INSTITUTION IN THE AUSTRALIAN NETWORK OF HEALTH AND HUMAN RESEARCH ETHICS AND THE UNIVERSITY OF TASMANIA

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **7 December 2011**. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 1956.

Yours sincerely




Adele Kay
Health and Medical HREC Ethics Officer
On behalf of the Executive Officer
HREC (Tas) Network



Appendix Q

Ethics approval from Australian Catholic University for the *Clostridium difficile* infection studies



Human Research Ethics Committee
Committee Approval Form

Principal Investigator/Supervisor: Prof Anne Gardner Canberra Campus Co-Investigators: Dr Lee Stewart (JCU) Student Researcher: Mr Brett Mitchell Canberra Campus
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Ethics approval has been granted for the following project: The impact of <i>Clostridium difficile</i> infection (CDI) on mortality and length of stay in an Australian setting for the period: 8 August 2011 to 30 June 2014 Human Research Ethics Committee (HREC) Register Number: N2011 50
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Special Condition/s of Approval

Prior to commencement of your research, the following permissions are required to be submitted to the ACU HREC:

Tasmania Health & Medical HREC


The following **standard** conditions as stipulated in the *National Statement on Ethical Conduct in Research Involving Humans (2007)* apply:

- (i) that Principal Investigators / Supervisors provide, on the form supplied by the Human Research Ethics Committee, annual reports on matters such as:
 - security of records
 - compliance with approved consent procedures and documentation
 - compliance with special conditions, and
- (ii) that researchers report to the HREC immediately any matter that might affect the ethical acceptability of the protocol, such as:
 - proposed changes to the protocol
 - unforeseen circumstances or events
 - adverse effects on participants

The HREC will conduct an audit each year of all projects deemed to be of more than low risk. There will also be random audits of a sample of projects considered to be of negligible risk and low risk on all campuses each year.

Within one month of the conclusion of the project, researchers are required to complete a *Final Report Form* and submit it to the local Research Services Officer.

If the project continues for more than one year, researchers are required to complete an *Annual Progress Report Form* and submit it to the local Research Services Officer within one month of the anniversary date of the ethics approval.



Signed: Date: ... 08.08.2011....
(Research Services Officer, McAuley Campus)

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