AN ECONOMIC EVALUATION OF ANTIMICROBIAL STEWARDSHIP PROGRAMS IN METROPOLITAN AUSTRALIAN HOSPITALS

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Keywords

Antimicrobial stewardship; bloodstream infection; clinical decision making; clinical decision support system; cost-effectiveness; economic evaluation; health economics; health resource allocation; hospital; rapid diagnostics

Abstract

Background:

The misuse of antimicrobials leads to the development of antimicrobial resistance (AMR) and the adverse consequences of this situation is under reported and the cost to society vastly under estimated. It has been established that effective Antimicrobial Stewardship (AMS) programs reduce the inappropriate use of antimicrobials in hospitals. AMS programs are mandated by the Commission on Safety and Quality in Health Care in all Australian hospitals.

Objectives:

The aim of this research is to use an economic framework to evaluate if the individual AMS interventions including the additional strategies of rapid diagnostics specifically Matrix Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) technology and Clinical Decision Support Systems (CDSS) at the hospitals under consideration are cost-effective in that setting.

1. To estimate the costs of implementing AMS interventions at two Australian hospitals.
2. To value the health benefits in terms of changes in mortality and length of stay (LOS) for patients with bloodstream infections (BSI) and equate to quality adjusted life years (QALYs).
3. To describe the cost-effectiveness of each competing AMS strategy and consider the uncertainty associated with decision making in this area.

Methods:

A decision analytic model based economic evaluation was undertaken to evaluate the cost-effectiveness of AMS interventions at two Australian hospitals, Royal Brisbane and Women's Hospital (RBWH) and the Mater Health Service (MHS). A decision tree was constructed in conjunction with a panel of experts to best represent the clinical pathway of patients with Bloodstream Infections (BSIs)

admitted to a hospital. The relative risk of mortality (logistic regression) and hospital length of stay (ANCOVA) related to these infections were captured to parameterise the model. Information on costs and the strategies adopted for each individual AMS intervention were identified using a questionnaire sent to the AMS team at each hospital. This information was used to populate the model and evaluate the cost-effectiveness of the AMS interventions. At the RBWH the economic evaluation compared the AMS intervention first in conjunction with rapid diagnostics and then with the addition of the CDSS to the baseline. At the MHS the evaluation compared rapid diagnostics prior to the implementation and the AMS intervention and then the AMS intervention in conjunction with rapid diagnostics to the baseline. The quality of the data used and the sensitivity of the data to modelling assumptions in terms of its impact on decisions making was assessed.

Results:

The AMS interventions at both hospitals resulted in cost savings compared to the baseline. At the RBWH the AMS intervention incorporating rapid diagnostics was the most optimal with a Net Monetary Benefit (NMB) of $24,877 and at the MHS rapid diagnostics prior to the implementation of AMS was the optimal choice with a NMB of $25,673. When the probability of cost-effectiveness was determined, all options implemented as part of the AMS intervention at both hospitals were more cost-effective than those during the period prior to AMS. When the GP&GN organism groups were combined, strengthening the estimates of mortality at each hospital, the AMS intervention including rapid diagnostics at the RBWH was found to be cost effective 46.7% of the time and the MALDI-TOF intervention at the MHS 51.4% of the time. The addition of the CDSS at the RBWH did not add to the cost-effectiveness of the intervention at the RBWH. The addition of AMS at the MHS was less cost effective than the intervention with rapid diagnostics alone.

Conclusion: This is the first time a cost-effectiveness analysis of an AMS intervention has been performed in Australia. The message for policy makers is that AMS interventions are cost-saving from a hospital perspective. This research also indicates that the interventions are cost-effective particularly if teamed with rapid

diagnostics in the laboratory. However the uncertainty in the mortality estimates does not allow for a high level of confidence in the decision. While BSI mortality is a useful metric, the morbidity associated with these serious infections due to inappropriate prescribing should be collected in hospital databases over a longer period of time to capture the true benefits of AMS interventions.

The research found that rapid diagnostics such as MALDI-TOF technology is cost-saving and provides good value for money for the small monetary investment per patient required. The AMS strategies used in each healthcare environment needs to be selected with care to ensure that the needs of that particular health care environment are met. Unless careful consideration is given to the design of AMS programs the large investment in particular due to human resource costs can quickly become a burden for small facilities.

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List of Abbreviations

AMS	Antimicrobial Stewardship
ACSQH	Australian Commission for Safety and Quality in Healthcare
BSI	Bloodstream infection
CDC	Centre for Disease Control
CDI	*Clostridium difficile* infection
CDSS	Clinical Decision Support System
CEA	Cost Effectiveness Analysis
CEAC	Cost effectiveness acceptability curve
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
ESBL	Extended spectrum beta lactamases
EVPI	Expected value of perfect information
GMS	Guidance MS
GP	Gram-positive
GN	Gram-negative
HAI	Healthcare associated infections
ICU	Intensive care unit
ICER	Incremental cost effectiveness ratio
IV	Intravenous
LIS	Laboratory Information System
LOS	Length of stay
LYG	Life years gained
MALDI-TOF	Matrix-Assisted Laser Desorption Ionisation - Time-Of-Flight
MHS	Mater Hospitals and Health Services
MDR	Multi Drug Resistant

MDRO	Multi Drug Resistant Organism
MRSA	Methicillin Resistant *Staphylococcus aureus*
MSSA	Methicillin Susceptible *Staphylococcus aureus* (MSSA)
NICE	National Institute for Clinical Excellence
NMB	Net monetary benefit
OECD	Organisation for Economic Co-operation and Development
PAIF	Prospective audit with intervention and feedback
PCR	Polymerase Chain Reaction
PFR	Preauthorisation formulary restriction
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QHAPDC	Queensland Hospital Admitted Patient Data Collection
RBWH	Royal Brisbane and Women's Hospital
RCT	Randomised controlled trial
SSI	Surgical site infection
TAT	Turnaround times
VAP	Ventilator Associated Pneumonia
VRE	Vancomycin Resistant Enterococci
WHO	World Health Organization
WTP	Willingness to pay

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature: QUT Verified Signature

Date: 19th February 2018

Dedication

In memory of my son Aaron whose compassion and unconditional love will always inspires me to be the best that I can be

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encouragement. And last but not least my faithful PhD companion Iggy-pup for always being by my side.

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Chapter 1: INTRODUCTION TO ANTIMICROBIAL STEWARDSHIP PROGRAMS

This chapter introduces the Cost-effectiveness Analysis (CEA) of Antimicrobial Stewardship Programs and provides background and context to highlight the value of this research (Section 1.1). Section 1.2 & 1.3 describes the specific research objectives with reference to significance and scope. Section 1.4 provides a list of the contributions of this thesis to the literature and the scientific community. Section 1.5 provides a summary of the thesis to follow and includes an outline of the content in the remaining chapters of the thesis.

1.1 INTRODUCTION

The global crisis of antimicrobial resistance and the cost to society of the inappropriate use of antimicrobial agents is well established (1, 2). This resistance to antimicrobials causes significant morbidity and mortality in hospitalised patients. Antimicrobial Stewardship (AMS) programs have been shown to reduce the inappropriate use of antimicrobials in hospitals (3-6). In Australia as of January 2013, it is mandatory for all hospitals to have implemented an AMS program in accordance with Standard 3 of the Australian Commission for Safety and Quality in Healthcare (ACSQHC) guidelines on preventing and controlling healthcare associated infections. Section 3.14 of this standard relates to the developing, implementing and regularly reviewing the effectiveness of AMS programs (7).

There are many different models of AMS in the literature. In Australia, a guidance document was developed by experts in the field to provide information on the core requirements of an AMS intervention (8). However, each hospital environment is unique with a varied case-mix of patients, making it difficult to identify which additional tools and strategies might be helpful in each setting. While

the design and implementation of AMS interventions are complex there is even less information on the best ways to evaluate these interventions.

While several studies have reported on the cost savings achieved by the reduction of antimicrobial utilisation due to AMS interventions only a few studies have reported on the clinical outcomes. There is only limited research on the cost effectiveness of AMS interventions. An early study in 2009, performed in Chicago USA, reported that AMS interventions were cost-effective in that setting (9). A more recent study compared a bundled AMS strategy with a more traditional approach in Brazil and found that the bundled strategy was more cost-effective(10). The bundled strategy adopted a more one-on-one education approach to AMS with greater success. To date there has been no cost-effectiveness analyses performed on AMS programs in Australia.

While there are many competing priorities in healthcare delivery and finite health resources to be invested, decision makers need to evaluate the best available options to achieve maximum health benefits. This research aims to assess the impact of AMS programs from a cost-effectiveness perspective in Metropolitan Australian hospitals with particular focus on the value of rapid diagnostics in the microbiology laboratory specifically Matrix Assisted Laser Desorption Time of Flight (MALDI-TOF) technology and clinical decision support systems (CDSSs) as additions to AMS. Both the hospitals evaluated in this research have adopted a combination of these strategies in their AMS intervention.

1.2 RESEARCH OBJECTIVES

This research aims to examine the change in costs and benefits of the AMS interventions implemented in two Brisbane metropolitan hospitals and evaluate the cost-effectiveness of the strategies used. AMS programs are complex and there is some doubt as to the combinations of individual strategies that may produce the best outcomes in different healthcare environments. In today's healthcare environment it is crucial that the value for money of these interventions are clearly stated using the best available information so that decision makers can be confident

that limited health resources are suitably allocated, and the optimal intervention is implemented.

The three main types of strategies used in AMS interventions are persuasive, restrictive and structural. Persuasive interventions include strategies such as audit and feedback measures as well as educational meetings and materials. Restrictive interventions include selective reporting of antimicrobials from the laboratory, restricting the use of antimicrobials without prior authorisation and use of automatic stop orders. Some examples of structural interventions are rapid diagnostics and CDSSs (11). In this cost-effectiveness evaluation, each individual hospital and the combination of strategies used in each setting will be considered using a decision analytic model.

The objectives of this research are as follows:

1. To estimate the costs of implementing AMS interventions including structural tools such as CDSSs and MALDI-TOF technology at two Australian hospitals.
2. To value the health benefits in terms of changes in mortality and length of stay (LOS) for bloodstream infections (BSI) and equate to quality adjusted life years (QALYs).
3. To describe the cost-effectiveness of each competing AMS strategy with respect to the change in both costs and health outcomes associated with the intervention accounting for uncertainty in the available data.

A cost utility analysis will be performed and a decision analytic model constructed to evaluate the cost-effectiveness of these programs in metropolitan Australian hospitals. The assumptions made in this research will be that there are potentially significant clinical implications for the treatment of BSI with early use of targeted antimicrobials guided by rapid diagnostics in the microbiology laboratory (MALDI-TOF). The timely delivery of these results to the treatment team may increase the likelihood of an improved outcome for the patient. The delivery of the result alone without the appropriate action from the clinician and the AMS team would mean that the timeliness of the rapid result had no benefit. For example a

patient with a BSI caused by *E. coli* where the susceptibility of this organism is not may be started on empiric meropenem. However if the rapid diagnostics suggest that the organism was fully susceptible to the antimicrobials tested, then the appropriate action would be to discontinue the meropenem and commence the patient on ampicillin. Ampicillin is a better option in this case because it reserves the use of carbapenems for patient with infections caused by resistant organisms and potentially reduces the emergence of resistance from a societal perspective.

A decision analytic model was developed to assess the cost-effectiveness of AMS programs in adult patients with BSIs in Brisbane metropolitan hospitals. The setting for this research was the Royal Brisbane and Women's Hospital and the Mater Health Service located in Brisbane. Both of these metropolitan hospitals had recently commenced AMS interventions and also had introduced novel technologies in the microbiology laboratory (the MALDI-TOF system for organism identification). The RBWH had implemented Guidance MS (GMS), a CDSS designed by infectious diseases physicians in Victoria, Australia, to enhance their AMS program.

The target population was adult patients admitted to both these hospitals with significant BSIs with a Gram-negative (GN) or Gram-positive (GP) pathogens. The clinical information for this patient cohort was collected and analysed for the relative risk of mortality and the LOS in hospital. The costs of the interventions and costs of antimicrobial usage were also included. The changes in cost and clinical outcomes were incorporated as input parameters into the cost-effectiveness model and the AMS intervention at each of the hospitals were evaluated.

The research questions that are required to be answered are whether the AMS program is value for money and whether the additional investment in a CDSS and novel technologies in the laboratory are cost effective.

1.3 SIGNIFICANCE, SCOPE AND DEFINITIONS

It has been proposed that AMS programs will significantly improve prescribing practice and as such reduce adverse outcomes related to inappropriate use of antimicrobials in hospitals. There is a perception that these programs will increase costs in terms of staffing and, if adopted, technology in the laboratory. The purpose

of a CEA is to quantitate the costs incurred and saved and the benefits resulting from these intervantions. Currently there is limited evidence on the metrics that are most effective to capture the clinical impact of AMS interventions.

This research will inform decision makers on whether the metrics used for the evaluation of these interventions adequately reflect the impact on patient outcomes. By quantifying not only the costs saved but the health benefits gained decision makers will be informed on the cost-effectiveness of the interventions evaluated. This information will be useful for clinicians leading AMS interventions as well as prescribers to see the value for money of the strategies used at their hospital. This research will be valuable to gain an insight in to how the interventions at each hospital can be improved to achieve a more cost-effective outcome. While the initial investment can be costly, an effective healthcare intervention can recoup the cost of the intervention in a relatively short time and continue to save money from the prevention of adverse events to patients.

Each hospital can allocate resources depending on the case-mix and their individual requirements. There are many decisions that need to be made as there are significant advances in technology in all areas of medicine and health resources are scarce. For example, a CDSS may be advantageous in a high acuity setting but may not add value for money in a general hospital or vice versa. It also may be that novel technologies in the laboratory may not represent value for money unless delivered to the treating clinician in a timely manner. Also a laboratory with a high throughput of testing may be able to recoup money spent on equipment while a laboratory with a smaller throughput may need to be more careful when investing in technology. Evaluation of the cost effectiveness of AMS, with and without CDSS and with novel technologies in the microbiology laboratory will enable decision makers to allocate these resources in a way that is appropriate for each setting.

1.4 CONTRIBUTION OF THIS RESEARCH TO THE LITERATURE AND THE SCIENTIFIC COMMUNITY

1.4.1 PUBLISHED PAPERS FROM THIS THESIS:

- S Coulter, JA Roberts, K Hajkowicz, K Halton. The use of Bloodstream Infection (BSI) mortality to measure the impact of antimicrobial stewardship (AMS) interventions: assessing the evidence. Infectious Disease Reports 2017; volume 9:6849. [Refer to Appendix D for the full article]

- S Coulter, K Merollini, JA Roberts, N Graves, K Halton The need for cost-effectiveness analyses of antimicrobial stewardship Programs: a structured review. International Journal of Antimicrobial Agents, 2015; 46(2): 140-9. PMID: 26058776. [Refer to Appendix D for the full article]

1.4.2 PLANNED PAPERS:

- S Coulter, N Graves, JA Roberts, K Hajkowicz, P Griffin and K Halton. An economic evaluation of AMS interventions in Metropolitan Hospitals in Brisbane, Australia.

- S Coulter, N Graves, G Nimmo, S Schlebusch and K Halton. A CEA of MALDI-TOF technology in conjunction with AMS interventions in Metropolitan Hospitals in Brisbane, Australia.

1.4.3 CONFERENCE PRESENTATIONS RELATED TO THESIS

- 2018: Invited Speaker European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Madrid, Spain.

- 2016: Speaker Australian Society for Antimicrobials Conference “An Economic Evaluation of an Antimicrobial Stewardship (AMS) intervention at a Brisbane Metropolitan Hospital” Melbourne, Australia.

- 2015: Invited Speaker Australian Society for Antimicrobials Conference “Getting Bang for Buck: Quantifying Benefits of AMS programs” Brisbane Australia.

- 2014: Invited Speaker Australian College for Infection Prevention and Control Conference “Antimicrobial Stewardship: An economic evaluation” Adelaide Australia.

- 2014: Invited Speaker Sri Lankan Society for Microbiology Conference "An economic evaluation of antimicrobial stewardship programs in metropolitan Australian hospitals" Colombo, Sri Lanka.
- 2013: Speaker Institute of Health and Biomedical Innovation Inspires Student Conference "An economic evaluation of antimicrobial stewardship programs in metropolitan Australian hospitals" Brisbane Australia.
- 2013: Oral Presentation PhD Candidature confirmation seminar for examination by panel review "An economic evaluation of antimicrobial stewardship programs in metropolitan Australian hospitals" Brisbane Australia.
- 2012: Oral Presentation at the Launch of the Centre for Research Excellence in reducing HAI (CRE-RHAI) in Sydney NSW as part of the PhD program.

1.4.4 PEER REVIEWER FOR THE FOLLOWING JOURNALS:

- International Journal of Antimicrobial Agents
- PLOS One
- Infectious Disease Reports
- Clinical Microbiology and Infection

1.4.5 INTERNATIONAL COLLABORATIONS LINKED TO THESIS:

- Sri Lanka 2014: Invited to present at the National Microbiology Conference Sri Lanka on the Cost-effectiveness Analysis of AMS programs.
- Netherlands 2016: Invited to submit a paper for a special Antimicrobial Stewardship edition for the Infectious Diseases Reports by Jan-Willem Dik (Guest Editor and researcher, in the area of cost-effectiveness of AMS interventions in the Netherlands).
- WHO Western Pacific regional office (WPRO) 2015: Provided feedback on a report written by the WHO reviewing the use of carbapenems in Fiji hospitals.

1.4.6 LOCAL COLLABORATIONS 2016 TO DATE:

- Preparation of an Options Paper for use by decision makers, at the public health unit in Brisbane, on options available to deliver Queensland hospital antimicrobial utilisation data to the National Antimicrobial Utilisation Surveillance Program (NAUSP).
- Currently employed by the department of health to report on antimicrobial utilisation and resistance for Queensland hospitals utilising two reporting tools, OrgTrx (antimicrobial resistance surveillance) and MedTRx (antimicrobial utilisation surveillance). These reports are used by the Queensland state wide AMS team and individual hospital AMS teams to monitor antimicrobial utilisation and resistance.
- Implementation and support of users of the Queensland OrgTRx program as the national antimicrobial resistance surveillance tool for the Antimicrobial Utilisation and Resistance Australia (AURA) project.

1.5 THESIS OUTLINE

The thesis is presented in nine chapters and the first chapter provides background, research objectives and the scope and rationale for the project.

Chapter 2 is a literature review where the historical background on antimicrobial resistance (AMR) and the rationale for AMS is described. The current evidence on AMS programs is critically reviewed and focuses on the factors important in the design of AMS interventions, the factors to consider when implementing an AMS intervention and reviews AMS in Australia. This chapter also discusses the metrics available to assess AMS interventions and highlights the gaps in the current research in relation to the cost and cost-effectiveness of these programs.

Chapter 3 reviews methods used in economic evaluations and appraises the most suitable methods to perform an economic evaluation of AMS programs. This chapter also discusses methods available for measuring health outcomes in economic evaluations. The decision analytic model to be used is discussed in terms

of evidence used, characterising uncertainty in the parameters and decision making in the presence of uncertainty.

Chapter 4 presents the findings from the questionnaire sent to the two Metropolitan Brisbane Hospitals that are evaluated in this thesis. This chapter discusses the design of the questionnaire and describes the AMS intervention at the RBWH and the MHS, the strategies used and the timeline for the implementation of the program. The chapter also describes the data sources used to measure the impact of the AMS intervention at each of the hospitals.

Chapter 5 presents the detail with regard to the derivation of the costs of the intervention. This chapter concludes with a comparison of the costs related to the strategies used at the two hospitals.

Chapter 6 outlines the clinical outcome data for patients at the two Metropolitan Brisbane Hospitals. The rationale for choosing BSIs as the metric to assess the impact of the AMS intervention in adult populations is presented. This chapter also sets out the method used to prepare the data for analysis and calculate the relative risk of mortality and the difference in hospital length of stay post AMS intervention at both hospitals.

In Chapter 7, the models used in the cost effectiveness analysis are described. This chapter focuses on the model development and validation as a result of consultation with an expert panel. The models including the structure and the point estimates to be used at each hospital is presented for the RBWH and MHS. The method used to calculate the QALYs in order to value the health benefits from the BSI data derived from each of the hospitals is described.

Chapter 8 presents the results from the cost-effectiveness analysis of each of the strategies used at the hospitals in terms of health benefits gained and costs saved. The results are presented in terms of the fixed value analysis and accounting for the uncertainties in model parameters using probabilistic sensitivity analysis. Further analysis is provided by presenting results from scenario and Net Monetary Benefit analysis.

Chapter 9 provides a discussion of the results in terms of the objectives of the research set out in Chapter 1. Further discussion on how this

evidence can be used for decision making in Australian hospitals. The chapter presents the value of rapid diagnostics, how this information may be used by decision makers, the limitations and strengths of the research. Finally the chapter concludes by discussing the future research opportunities highlighted by this work and the conclusions and recommendations resulting from this body of work.

The following chapter provides a summary of the current literature around AMS interventions in terms of composition, designing and implementing in hospital environments. It also critically appraises the currently available measures in evaluating AMS interventions in terms of effectiveness and cost-effectiveness.

Chapter 2: **LITERATURE REVIEW**

2.1 ANTIMICROBIAL RESISTANCE (AMR)

Antimicrobials are unlike other therapeutic agents because, whilst their effects benefit the individual patient, the emergence of resistance has consequences to all of society (12). A single patient infected with an antimicrobial-resistant pathogen can spread this organism in either the hospital environment or the community in a short period of time. The impact of antimicrobial resistance on patient care is to necessitate the use of expensive or adverse event prone antimicrobials which are second and third line treatment options, which in themselves further contribute to increased morbidity and mortality.

The societal cost of AMR is immense, and the true cost in terms of lives lost and the depletion of a precious natural resource is difficult to estimate. The overall extra healthcare costs due to AMR and productivity losses has been estimated by the CDC to be at least 1.5 billion Euros and 20 billion USD per year in Europe and the USA respectively(13).

In the same report, the societal cost of excess healthcare in the USA has been estimated to be $35 billion USD per year. In the USA at least 2 million people acquire infections caused by organisms that are resistant to one or more antimicrobials. The best available estimates suggest that multidrug resistant (MDR) infections, each year result in 25,000 deaths in Europe and 23,000 deaths in the USA. The lack of reliable estimates of AMR and related mortality and morbidity, grossly underestimates the global cost of resistant infections.

Whilst the emergence of resistance in GP pathogens such as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant Enterococci (VRE) is significant, the issues of GN resistance in the *Enterobacteriaceae* group is currently of great concern (14). The emergence of resistance specifically in *Escherichia coli* (*E coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) with an ability to produce enzymes such as extended spectrum beta lactamases (ESBLs) and

carbapenemases have posed a major threat to the effective treatment of infections worldwide. It needs to be noted that not all antimicrobial agents are equal when it comes to encouraging resistance development, one of the unintended consequence of antimicrobial use. For example cephalosporin use leads to selection of vancomycin resistant enterococci (VRE), extended spectrum beta-lactamase producers (ESBLs) and *C. difficile*, whereas carbapenem usage can lead to the development of fungaemia, *C. difficile* and methicillin resistant *Staphylococcus aureus* (MRSA).

The Infectious Diseases Society of America (IDSA) has raised the issue of a specific group of organisms described as the ESKAPE pathogens at the core of resistant infections in hospitals. They are *Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter species* (ESKAPE)(15). In addition to these organisms, an expert group in 2008, agreed to include Enterococcus *spp*. and *Enterobacteriaceae* (other than Salmonella and Shigella), because of the epidemiological significance, the emerging antimicrobial resistance and the importance of these bacteria as causative agents of health care associated infections (16). The suggestion from the IDSA is that the key efforts to reduce AMR could focus on these organisms as markers for any improvements due to interventions in this area. This would provide clear goals and direction and streamline the focus efforts in this field.

A number of resistant HAIs are caused by this group of organisms and are commonly known to form biofilms and escape the body's defences. A biofilm is when slower growing bacteria (sessile) form an extracelluar matrix or slime that together with the microorganisms form a biofilm(17). These organisms in biofilms make it difficult for antimicrobials to reach the microorganism in sufficient quantities to kill it.

A recent report by the Centre for Disease Dynamics, Economics and Policy (CDDEP) stated that in some resource limited settings almost sixty percent of the infections caused by *K*. *pneumoniae*, were found be resistant to carbapenem antimicrobials(18). These antimicrobials are one of the last resort options for the treatment of resistant GN infections. This is in contrast to the United States and

Europe where resistance to carbapenems in *K. pneumoniae* is between five to ten percent. Easy access to trade and tourism bring individuals with varying levels of endemic resistance into close contact and makes AMR a global concern that can no longer be viewed in geographical isolation.

The World Health Organization (WHO) has called upon the global community to commit to a common goal to prevent the further development of resistance by issuing a call to action in 2011(19). At the 68th World Health Assembly Meeting in May 2015 the WHO achieved agreement to develop national action plans to address the crisis of AMR. The focus centres on a "One Health" framework combining information on AMR and antimicrobial use from humans, animals and agriculture to inform the national action plan to preserve effectiveness of antimicrobial agents.

To ensure that a true and accurate estimate is obtained on the magnitude of the global burden of AMR it is essential that the best available surveillance systems are used and resources are employed to provide this evidence globally. In the UK in 2011, Professor Dame Sally Davies in her role as the chief medical officer called for AMR to be placed on the national risk register(20). This action helped raise awareness and gain political attention to the crisis of AMR. The UK was able to achieve great success in this area due to the commitment of its leaders to reduce the burden of AMR in their healthcare environment.

There are many factors that hinder the progress of initiatives to address the issues related to AMR globally. A recent study evaluated the governmental, economic and social factors and their impact on AMR in 28 European countries. They concluded that despite all efforts, the quality of governance and corruption in each country, has a significant impact on AMR (21). A similar study has not been conducted in resource-limited settings but could be justifiably extrapolated to arrive at similar conclusions. The buy-in of governments to support a national action plan and ensure that the infrastructure is provided is essential to achieve success in the control of AMR.

In hospital environments, the efforts to control AMR through the judicious use of antimicrobial agents, is not a recent phenomenon (22, 23). Although the

management of the appropriate use of antimicrobials in some form has existed in Australian hospitals since the 1970s, resistance to antimicrobials has continued to develop. It is of great concern that despite previous efforts, up to 50% of antimicrobial courses prescribed in Australian hospitals and those around the world are considered inappropriate in choice, dose or duration of therapy (8). The cost to the hospital from a complicated infection is very large, for example a case of mitral valve endocarditis has been estimated to be $46,000 per case in the USA in 1990 (24). The cost of hospitalisation of a patient with a joint infection in 2002 was estimated at $24,000 in the USA (25). These figures have not been adjusted to today's costs but would have escalated significantly. In addition, if the dosage and appropriateness of therapy was not optimal, the costs would only increase due to more serious long term complications resulting in poorer outcomes.

Inappropriate antimicrobial use in the community, in long term care facilities and hospitals, significantly impacts all of society in terms of economic cost. There are a number of unintended consequences of antimicrobial therapy regardless of the appropriateness of use. These include the emergence of AMR, development of pseudomembranous colitis due to *Clostridium difficile* infection, nephrotoxicity, hepatotoxicity, IV line infections and increased morbidity, mortality and LOS in hospitals. The increased LOS in turn, increases the risk of acquisition of healthcare associated infections (HAIs), delayed recovery and treatment failure. Patients infected with the same organism, but a resistant strain have an associated longer LOS in hospital and have a higher risk of death than patients with a non-resistant strain (26, 27).

In Australia in April 2012, the AMR Standing Committee (AMRSC) was established to bring together expert representatives from human, animal and agricultural contexts to formulate a plan of action to address issues impacting on the more appropriate use of antimicrobials. In keeping with the WHO national action plan requirements, the Antimicrobial Use and Resistance in Australia (AURA) project was established, with an aim to provide an accurate estimate of antimicrobial usage and resistance in Australia.

The AURA project reports on antimicrobial usage data in hospitals and the community in a number of different ways. The National Antimicrobial Prescribing Survey (NAPS) is an online audit performed by hospitals to assess antimicrobial prescribing practices and appropriateness of prescribing within the hospital system. The National Antimicrobial Utilisation Surveillance Program (NAUSP) reports on the use of antimicrobials at the hospital level. Participating hospitals receive bimonthly reports of their own data, and national reports are prepared annually. The NPS MedicineWise Medicine Insight program collects data on antimicrobial prescribing in general practice to provide information on the appropriateness of antimicrobial prescribing in the community.

The data on AMR in the hospital and community is also collected by the AURA program. The Australian Group on Antimicrobial Resistance (AGAR), connected by a network of 27 laboratories nationwide, started performing surveillance on resistance in GN and GP BSIs in 1986 and continues to collect this information to date. The Queensland Health program OrgTRx, links to the laboratory information system in Pathology Queensland laboratories (AUSLAB) and is used to provide antibiogram data and to monitor trends in resistances in key pathogens. The OrgTRx system has been adopted as the national AMR surveillance tool and has now been rolled out to include a large private sector laboratory service in Queensland and also includes data from ACT Pathology, New South Wales, Tasmania, Victoria, Western and South Australia. There are plans to include the Northern territory and some other private laboratories in the near future to provide a more representative sample on AMR surveillance in Australia.

In March 2016 a national alert system for reporting Critical Antimicrobial Resistances (CARalert) was established as part of the AURA project (28).

Table 2.1 Critical resistances reported in the CARalert system (adapted from report)

Species	Critical resistance
Enterobacteriaceae species	Carbapenemase-producing, and/or ribosomal methyltransferase-producing strains
Enterococcus species	Linezolid non-susceptible
Mycobacterium tuberculosis	Multidrug-resistant– at least rifampicin- and isoniazid-resistant
Neisseria gonorrhoeae	Ceftriaxone non-susceptible or azithromycin non-susceptible
Salmonella species	Ceftriaxone non-susceptible
Shigella species	Multidrug-resistant
Staphylococcus aureus	Vancomycin, linezolid or daptomycin non-susceptible
Streptococcus pyogenes	Penicillin reduced susceptibility

This report enables public health units to follow up on the management of these resistances in hospitals and the community. This alert system can be used to identify the source of potential outbreaks ahead of time. There continues to be efforts in this area as part of the AURA project to achieve the call to action to reduce the burden of AMR in Australian hospitals and the community.

2.2 ANTIMICROBIAL STEWARDSHIP (AMS)

There is a rapidly growing body of evidence to suggest that an antimicrobial stewardship (AMS) program, is effective in reducing the inappropriate use of antimicrobials in hospitals and healthcare facilities (1). The goals of an AMS program are defined as optimizing clinical outcomes while minimising unintended consequences of antimicrobial use including toxicity, the selection of pathogenic organisms (such as *C. difficile*) and the emergence of AMR (1). In recent times there has been suggestion that the term “antimicrobial stewardship” is misleading and may not be easily understood by hospital administrators as well as the public and may be better replaced by “antimicrobial safety” (29). Whichever term is preferred the intention of AMS is the delivery of optimal care to patients undergoing antimicrobial therapy for infectious diseases. Patient outcomes are less often

collected when evaluating AMS interventions and yet, these outcomes may best reflect the impact of the interventions.

However, the aspect that is not always shared with the patient is the risk of adverse events due to the use of antimicrobial agents (30). While antimicrobials are essential for the treatment of serious infections, if they are not required, the risk of harm may be higher than the likelihood of benefit. Therefore, it may be of value that all hospitals collect more accurate information on infection-related mortality and adverse events related to antimicrobial therapy. The choice to use an antimicrobial comes with the potential risk of unintended adverse events that needs to be documented as part of patient safety requirements (31). This may increase accountability and prevent clinicians prescribing antimicrobials when not required. The collection of adverse event data is the forgotten aspect of AMS interventions and needs to be pursued as part of the AMS activities of hospitals. This adverse event information should not only be collected when patients are in hospital but should be monitored for a longer period after discharge.

AMS interventions have been reported to have reduced antimicrobial consumption by 22-36% and led to a reduction of costs of between $200,000-900,000 per annum in some hospitals in the USA (3). This outcome is the primary focus of the majority of studies that have evaluated AMS interventions to date. Significant savings can be made by addressing the common errors that occur in prescribing, often referred to as the "low hanging fruit" (6). For example, a policy that ensures a timely transition from intravenous (IV) to oral antimicrobial treatment. This would not only reduce possible adverse events to the patient such as the acquisition of HAIs and emboli due to IV therapy, but also allow the patient to be discharged from the hospital sooner. Jones et al (32) estimated significant cost savings not only by reducing unnecessary IV antimicrobial use but also savings from the prevention of adverse events of IV lines and the reduction in nursing time required for these patients.

However, the reduction of antimicrobial usage does not necessarily translate to optimal use of antimicrobials. Some infections may require more expensive potent antimicrobials for a shorter duration or at a higher dose to clear the

infections. Effective AMS relies on good communication, and sustainable systems and processes to be set up from the outset of the program. Many areas in a hospital need to interact effectively and efficiently to produce the desired end result which is the appropriate use of antimicrobials leading to improved patient outcomes. It is often said that hospital departments work very efficiently and effectively as individual units but sometimes fail to communicate with each other to improve efficiencies. It is paramount to the success of AMS interventions that this communication is improved.

Figure 2.1, is a schematic that represents the complex nature of AMS interventions in hospital settings. Theoretically a successful AMS intervention is intended to improve patient outcomes by reducing inappropriate prescribing. To achieve this, many departments and teams are required to work in synchrony. The intervention needs executive support and to be led by someone able to influence clinicians into sustainably adopting changes to prescribing in the hospital environment. In Australian metropolitan hospitals, infectious disease physicians take on this lead role, however it is acknowledged that other countries may not have easy access to infectious disease physicians and clinical microbiologists and senior clinicians may take on this role. Effective communication between the pharmacy, the microbiology laboratory and the patient care team is crucial to ensure that the optimal antimicrobial choices are made in the most efficient manner. An AMS team must act to amalgamate this approach and ensure all members of the team work together.

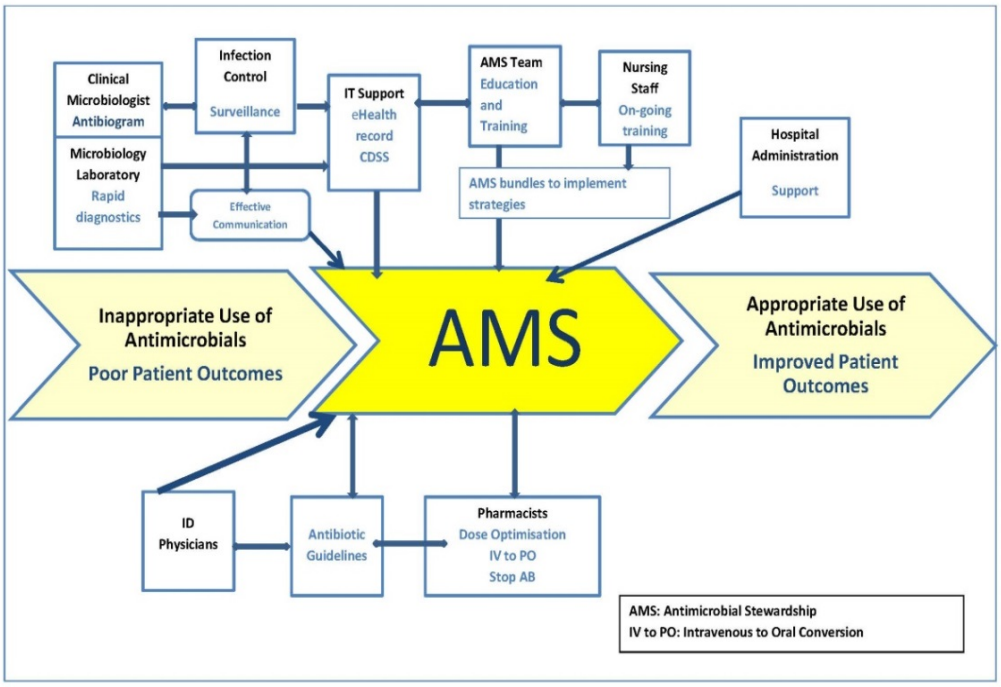

Figure 2.1 The complex interdependencies of an AMS intervention

The desired outcome is that by improving the communication and cohesion of the AMS team the AMS intervention would reduce inappropriate use of antimicrobials and push patient outcomes from the left of Figure 2.1 to the right and result in improvements in patient safety and care.

2.3 DESIGNING AN AMS INTERVENTION

When designing an AMS intervention "one size does not fit all" because hospitals vary in resource availability, size, patient demographic and access to specialist services. The first step in designing a program for a particular institution is to understand the specific issues in each setting. It is imperative that the program is rolled out to ensure as many healthcare professionals as possible are able to take ownership of the intervention.

There are different types of strategies to choose from when designing an AMS program for an individual hospital. Davey and colleagues (11) describe these

strategies as persuasive, restrictive and structural. The first type is a persuasive method where audit and feedback mechanisms are employed to provide information and education to prescribers. This can be in the form of education sessions, distribution of educational material and probably the most effective form being individual detailing where one-on-one feedback is provided. This mechanism is seen as collaborative and inclusive of other clinicians' point of view but the AMS team provides guidance for better prescribing practice.

The second strategy is restrictive and can be in the form of restricting the formulary of the hospital and establishing requirements for prior authorisation to prescribe certain antimicrobials. The laboratory can also selectively report antimicrobials that are most suitable for the 'drug'-'bug' combination. This method is sometimes not accepted as easily as persuasive methods but has been reported to achieve significant results (11). Ritchie (33) found that by restricting the use of ceftriaxone and co-amoxyclav and increasing the use of amoxicillin and gentamicin in their AMS intervention, that there was a reduction in mortality due to GN infections and to the rate of *C. difficile* infections (CDI) with no change to adverse events. However, it is important to note that there is very limited data on clinical outcomes due to AMS interventions, restrictive or persuasive, and as such it is difficult to conclude that there are no adverse effects related to the changes.

Structural methods are described as aids to enhancing AMS interventions such as CDSSs and rapid diagnostics in the laboratory. A small number of Australian studies (34-36) have examined the value of CDSS on the implementation of AMS programs. While CDSSs have certainly proven valuable in some settings, the size of the hospital and available resources may need to be considered to evaluate if they are required.

There has been a significant body of research supporting the role of rapid diagnostics in the microbiology laboratory in combination with AMS interventions (37, 38). It is fundamental to ensure that the treating clinician has access to the best available information when choosing empirical therapy for a patient with a serious infection. A rapid result from the laboratory with information on the identification

and susceptibility of the causative agent will then enable the clinician to either stop antimicrobial therapy or select a more appropriate targeted antimicrobial.

A combination of all of the above strategies maybe used depending on the size and complexity of the hospital setting to achieve a successful AMS intervention. It is also pivotal to the success of the program that hospital leaders are engaged and committed to the AMS goals (39). This will ensure administrative support for the program and the resources allocated to the AMS team. The involvement of an infectious diseases physician in program development will ensure patient safety in the clinical aspects of the treatment of diseases. It is an advantage if the AMS team is led by an infectious diseases physician that is well regarded and respected in the field (40-42). This may be of value when program implementation encounters blocks that can only be negotiated by a respected authority in the area. When designing an AMS program all these factors need to be taken into consideration and the needs of each hospital should be individually assessed. The components categorised under structural strategies also play a significant role in conjunction with an AMS intervention.

2.3.1 THE COMPOSITION OF THE AMS TEAM

The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) guidelines suggest that ideally the core members of an AMS team should consist of an infectious diseases physician and a clinical pharmacist with infectious diseases training. In addition the rest of the team can vary and typically should comprise of a clinical microbiologist, an information technology (IT) specialist, an infection control professional and a hospital epidemiologist (1).

There is evidence that the patient outcomes are vastly improved if an infectious diseases physician is involved in the management of patients with infections. A recent systematic review and meta-analysis concluded that in *S. aureus* BSIs that evidence based, clinical management enforced by the infectious diseases team improved outcomes for patients (43). However, while most metropolitan hospitals have access to an infectious diseases physician other specialities do not always consult the expertise of these clinicians prior to prescribing antimicrobials.

Pharmacists and other health care professionals need to advocate the value of a consultation with an infectious diseases physician when prescribing errors are detected. This is one of the advantages of a CDSS where errors in prescribing can be detected electronically and acted on in a timely manner. It is inconsistent that the prescription of anti- cancer treatments are limited to specialist oncologist, but the prescription of antimicrobials, requires no formal training in infectious diseases (12). This might be one of the reasons that antimicrobial prescriptions are still associated with a high rate of inappropriateness in hospitals. There is an urgent need to educate prescribers in infectious diseases, microbiology, pharmacokinetics and pharmacodynamics for the selection of optimal therapy for patients.

The pharmacists play a central role in AMS and need to be recognised as champions of these interventions and allowed to make strong recommendations and be supported by the clinical teams. However, once a program is established, having an infectious disease physician may not be as essential for the success of an AMS program (44). A cohesive team that is committed to patient safety with access to expert advice can ensure the success of these interventions. In some settings, when a senior infectious disease physician is not available, the clinical pharmacists with infectious disease training performed better at AMS than infectious disease fellows or registrars (40). This may be a good alternative when considering hospitals that are regional and remote.

Clinical pharmacists in consultation with clinical microbiologists and infectious diseases physicians are a pivotal link between the laboratory and the prescriber, so that the transition from empirical therapy to more targeted therapy is as efficient as possible (45). Empowering pharmacists led to success reported by Gaffin et al, where pharmacists were able to review antimicrobial orders and make recommendations (46). If these recommendations were disputed by prescribers, an infectious diseases specialist was automatically consulted. While medical officer training ensures a high turnover of doctors, this is not the case with pharmacists, laboratory scientists and nursing staff where a more stable pool can be accessed. These health professionals can be trained to support AMS and junior doctors with greater success. Being at the frontline of dispensing medications and guiding new

doctors, the value of nursing staff being on board from the beginning cannot be overstated (47, 48).

A direct line of communication between pharmacy and the microbiology laboratory may be a first step in improving the sustainability of AMS interventions. Once the team that is suitable for the hospital environment in question has been decided then the tools and strategies used can be considered. Rapid diagnostics and CDSSs and their value in AMS interventions will be discussed more fully in the following sections.

2.3.2 ROLE OF THE MICROBIOLOGY LABORATORY IN AMS

The microbiology laboratory plays an important role in AMS, the first and the most evident is in the rapid diagnosis of the causative agents of infectious diseases (49). Secondly, the microbiology laboratory produces information on the resistance patterns of key pathogens for the surveillance of resistant organisms (50). The pre- and post-analytical phases are equally important as the quality and integrity of the specimens collected and the access to resources in terms of equipment, reagents and adequate training of the personnel in the laboratory are paramount to the quality of the results generated from the laboratory.

The difficulty arises when the clinician has to interpret whether the result issued by the laboratory is significant or not depending on the specimen quality and site of infection. If the specimen that is sent to the laboratory is collected in theatre or from a sterile site the results are easier to interpret. However, if the specimen is from a site where commensal organisms are common and may not be the source of an infection, assistance interpreting the data is required. The role of the clinical microbiologists and laboratory scientists is to assist the clinician in interpreting the significance of the organisms isolated. This may be by suggesting repeat testing or by using other available clinical information such as inflammatory indicators to decide the significance of a particular result.

Infectious diseases physicians and clinical microbiologists may need to be consulted with regard to antimicrobial therapy. The laboratory can also assist by including relevant comments in the report to aid the interpretation of the results. However, the results need to be interpreted in conjunction with clinical

information. The information derived from the microbiology laboratory needs to be disseminated to the clinician looking after the patient in a timely manner. It is helpful if there is an established laboratory information system (LIS) in place as this database allows clinicians to access test results in real time. The result however high in quality is of no value if not easily accessible by the treating team.

The role of the laboratory can be underestimated and historically the resources needed to strengthen laboratory capacity can be overlooked when the budget is allocated. This is a key area that needs to be targeted if the goal is to reduce global AMR. The fast and accurate detection of infectious agents and reliable information on their resistance profile, play an important role in the optimal treatment of infectious diseases.

In recent years there have been a number of new technologies available for the rapid diagnosis of bacterial pathogens (51-53). One of the important functions of the microbiology laboratory is to perform culture and susceptibility testing on bacterial and fungal pathogens. This enables clinicians to either select the most appropriate antimicrobial or to change from empirical therapy to targeted therapy sooner and in turn improve the outcomes for the patient. The clinical microbiology laboratory can also detect non-bacterial or fungal pathogens causing disease, such as viruses, protozoa and helminths. If a bacterial or fungal cause is not found, empirical treatment may also be discontinued sooner.

Some studies have assessed the benefits of new technologies in the microbiology laboratory and found that rapid detection of pathogens, leads to better decision-making through more appropriate antimicrobial prescribing (54). Rapid diagnostics together with AMS interventions can reduce the time patients spend in hospital by reducing LOS and improving the quality of care provided (37). Rapid detection of the key resistance genes such as the MecA gene that codes for methicillin resistance in *S. aureus,* resistance to third generation cephalosporins or carbapenems in *Enterobacteriaceae* or rifampicin and isoniazid resistance in *Mycobacterium tuberculosis* can reduce the time to effective therapy and produce better patient outcomes.

Rapid diagnostics using the GeneXpert ™ technology and other PCR based methods for the detection of the MecA gene for Methicillin Resistant *Staphylococcus aureus* (MRSA) may have a significant impact on the ability of doctors to change to more targeted prescribing in a shorter time period (55, 56). Brown et al (57), performed a CEA based on an economic model in 2009 including a rapid Polymerase Chain Reaction (PCR) based method to detect MRSA which was compared to traditional methods available at the time. They found the PCR approach improved clinical outcomes for the patients at a reduced cost and found it to be cost-effective in terms of life years gained in both the USA and Europe.

Another study also evaluated the impact of PCR based screening to differentiate MRSA from MSSA to optimise pre-emptive antibiotic therapy (58). They found when the rate of MRSA in their population was at 24.5% this technology led to improved empirical choices for patients with *S. aureus* bacteraemia. The use of PCR technology for the rapid detection of coagulase negative *Staphylococci* in conjunction with a pharmacy driven initiative to reduce inappropriate prescribing was found to be successful in reducing LOS in hospital (59).

Knowing the identification of microorganisms can also be helpful in selecting appropriate therapy in a timely manner even when susceptibility results are unavailable. This is particularly relevant in organisms belonging to the *Enterobacteriaceae* group or Candida *spp.* Heil (60) described the impact of rapid diagnostics on the identification of Candida *spp.* in BSIs. Traditional methods of identification of Candida *spp.* can take up to 5 days and can cause significant delays in selecting targeted therapies for these infections. Some Candida *spp.* such as *Candida albicans* are generally quite susceptible to antifungals whilst others such as *Candida glabrata* can be quite resistant. In their study, Heil et al identified significant cost savings due to the implementation of rapid diagnostics in conjunction with an AMS intervention in the selection of appropriate antifungal therapy.

Of the recent advances in technology in diagnostic microbiology the MALDI-TOF (Matrix Assisted Laser Desorption Time of Flight) instrument which uses mass spectrometry has significantly changed the speed with which microbiology results

can be issued. Identification of organisms that took 5 to 48 hrs can now be reported in minutes (61). The identification to the genus for GN organisms can provide a significant amount of information regarding the antimicrobials that they are predictably resistant to. For example *K. pneumoniae* are predictably resistant to Ampicillin whereas Enterobacter *spp.* are resistant to a number of first line antimicrobials due to intrinsic resistance mechanisms. When the susceptibility is unavailable this information is invaluable in guiding therapy in GN infections.

Another major advantage of MALDI-TOF technology is that it can identify a wide range of organisms such as bacteria, yeasts, moulds and mycobacteria. The rate limiting step is the databank of organisms already in the database. The protein fingerprints produced by the instrument can be matched and identified using the information already stored in the systems database. It also does not rely on a large inoculum of the organism as one colony is sufficient for the analysis. The technique used with this instrument is very simple and does not require a high level of skill. This is quite different to the level of skill required to perform some molecular microbiology testing.

A small portion of the colony is placed on the sample tray and the matrix solution is applied to the plate and allowed to dry. The tray is then moved to the ionisation chamber where multiple short laser pulses are generated, which releases ionized proteins that travel through an electromagnetic field that send the ions into the flight tube. The ions travel at a speed relative to their size and they are detected and a spectrum is generated (Figure 2.2).

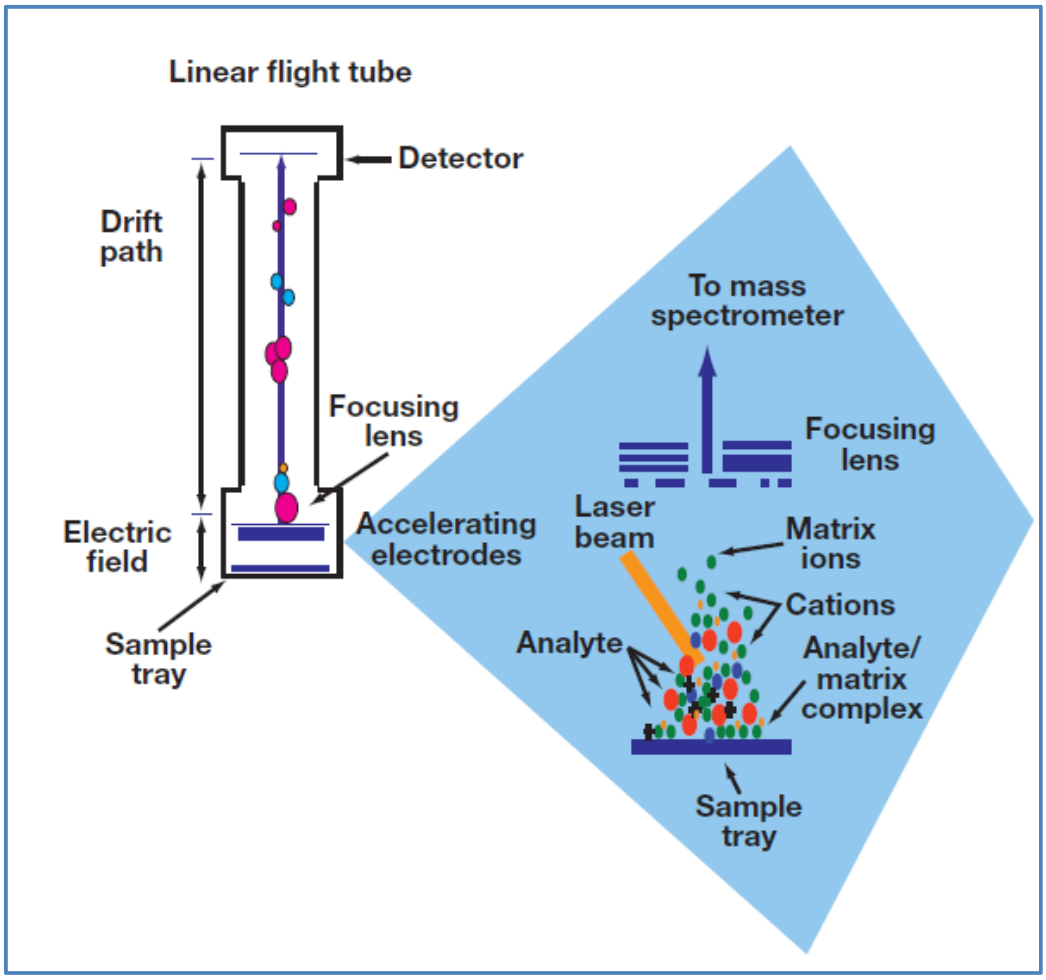

Figure 2.2 Schematic representing the mechanism of action of the MALDI-TOF (Matrix Assisted Laser Desorption Time of Flight) instrument (62)

A number of studies (63-67) have evaluated MALDI-TOF technology in conjunction with an AMS intervention. They have reported an improvement in patient outcomes in terms of reduction in LOS in hospital. Three studies also found cost savings post intervention when using rapid diagnostics combined with an AMS intervention (65-67). One study evaluated the impact of this technology and AMS on bloodstream infections caused by resistant GN organisms and found a statistically significant reduction in LOS from 23.3 to 15.3 days post intervention ($p \leq 0.0001$) and mortality from 21% to 8.9%, $p \leq 0.01$) and a cost savings of $26,298 per inpatient(67).

A recent study in the USA by Patel et al(68), reported a decrease in mortality from 21% to 12% ($p \leq 0.01$) and a reduced LOS (not statistically significant) for patients with bloodstream infections and a resultant cost savings of $2439 per BSI resulting in a total costs savings of $2.34 million per annum after the implementation of MALDI-TOF technology in conjunction with an AMS intervention.

Whilst the initial outlay for the technology can be significant the additional cost per test in an institution that performs a moderate number of identifications per year can be minimal. The significant cost savings and improvements in patient outcomes must always be considered by decision makers when allocating the health care budget in a hospital.

A secondary role of the laboratory is also to provide up to date information on resistance trends to inform surveillance systems and generate information by way of an antibiogram specific to each hospital. An antibiogram typically provides information on the proportion of resistance in the key pathogens in the patient population specific to that healthcare environment (69). This information provides a snapshot of the most likely drugs the bacteria would be susceptible to in that healthcare environment. The hospital antibiogram could be a useful tool for the selection of the most appropriate empirical antibiotics for the treatment of infections.

2.3.3 ROLE OF CDSSS AND ELECTRONIC HEALTH RECORD IN AMS

A CDSS is software that integrates patient information from databases and presents alerts, interpretations, recommendations in real time to assist with clinical decision making (70, 71). Thursky et al (72) identified at an early stage the importance of linking laboratory and pharmacy databases. For effective prescribing, it is considered valuable to identify an organism and provide susceptibility information together with appropriate dosing information concurrently. It is crucial for successful AMS that all areas that are involved in providing information relevant to optimal patient care make a co-ordinated effort to communicate with each other. If this information is available in an integrated manner to the treating clinician then it would significantly aid the appropriate selection of antimicrobials.

The advent of information technology has allowed the impact of AMS programs to have more far reaching effects reducing overall antimicrobial use by 22.8% (70).

In Australia CDSSs have been used for some time, primarily to triage patients that require infectious disease consults as well as alerts to review patients that might need deescalating following empirical therapy for an agreed duration. ADVISE was a CDSS tool developed in Victoria, Australia for use in the ICU for antimicrobial prescribing (73). This system resulted in a 10.5% reduction in total and broad spectrum antimicrobial use and an increase in the switching from broad to narrow spectrum antimicrobials. ADVISE has been further developed over the years and has evolved into an updated version known as Guidance MS which is now being implemented in many hospitals in Australia as a tool for AMS interventions. The system has the advantage of having been designed by infectious diseases physicians with a thorough understanding of antimicrobial therapy.

Chen et al (74) reported that the pivotal resource for the successful implementation of AMS programs in Australia would be the nationwide implementation of a CDSS such as IDEAS (another CDSS also developed in Victoria) or Guidance MS. Although the initial outlay is significant Chen et al suggests that they would be cost-effective in the long run. A recent study by Nault et al(75), reported on the longer term benefits of a CDSS resulting in sustained savings in terms of antimicrobial usage and savings due to reductions in LOS. There was also evidence of improved uptake of the intervention by prescribers. Scheetz et al (9), has established that CDSSs in the USA was cost-effective in an economic evaluation performed in 2009. His study suggested that when used in conjunction with an effective AMS program the gains were estimated at US$ 7368 per Quality Adjusted Life Year (QALY).

In a study performed in Victoria, Australia, all junior doctors as well as senior registrars identified the need for assistance in interpreting the significance of pathogens reported by the laboratory and dosing information from pharmacy(76). This study identified the need for an effective microbiology browser as viewing and collating results proved to be very laborious to clinicians. Other information relating to the patient such as allergy status, renal function and other pathology results as

well as the antibiogram for that specific institution could be integrated to recommend the best possible choice of therapy (35). The patient's past microbiology results could also be of great benefit when deciding on possible empirical therapy. For example if the patient had a resistant organism such as an ESBL isolated from the same or similar site of infection previously there would be a high likelihood that the same organism may be responsible this time.

The Electronic Medical Record (EMR) is rapidly gaining popularity in modern health care and being incorporated into the hospital system worldwide. Clinical decision support tools have been developed to be used with the EMR that are suitable for AMS. A recent study by Kullar et al, discussed the merits of combining an electronic health record with AMS (77). There are distinct advantages of an EMR to track patient outcomes overtime and consequences of antimicrobial therapy. This could be a vital resource for monitoring outcomes of healthcare interventions. If aligned with good principals of data collection with the input of medical statisticians this valuable information can be collected for various analytical purposes.

A recent study by Dik et al (5) highlights the importance of an integrated approach to AMS including rapid diagnostics and CDSS. The authors refer to a theragnostic approach integrating the key elements that are essential for the successful treatment of infection. Whilst we are aware that rapid diagnostics in the microbiology laboratory are crucial for the timely and effective treatment of infections without an integrated approach the technology does not necessarily lead to improved outcomes for patients.

2.4 FACTORS TO CONSIDER WHEN IMPLEMENTING AMS IN HOSPITALS

The successful implementation of an AMS program in hospital settings relies on the approach taken by the governing body in each country. The global picture on the implementation of AMS Programs is varied. In the USA for example, AMS has been promoted since 1997 but is not mandatory except in the State of California

where all acute care hospitals must implement AMS (78). It follows that a significant proportion of hospitals do not have an AMS program implemented in the USA.

The United Kingdom started their AMS programs in 2008 when the Health and Social Care Act was introduced (79). The UK has made significant advances in AMS and led the way in reducing inappropriate prescribing. The “start smart and focus” antimicrobial care bundle, an initiative to educate and encourage clinicians to prescribe antimicrobials more effectively, was introduced in 2011, by the National Health Service in the UK (79). Dame Sally Davies, the Chief Medical Officer, played an important role in promoting and leading the national action plan to successfully lead the nation to achieve some success in the area of improved antimicrobial prescribing(20).

In Europe one of the major initiatives for AMS was the “project ABS international” which was initiated at a European Union meeting in Austria in September 2006 for the development of appropriate strategies for the use of antimicrobials in hospital for the countries belonging to the European Union(EU) (80). The EU is committed through its European Centre for Disease Control to pool expertise and standardise the collection of surveillance data to make it easier to address the problem of AMR(81).

Cooke et al (82) proposed the development of a care bundle for prescribing antibiotics in both the acute setting and as part of surgical prophylaxis. It is proposed that these bundles be checklists for the important factors that need to be considered when prescribing antibiotics. The clinical rationale for initiation of therapy, appropriate specimens sent for analysis to the clinical microbiology laboratory and discontinuation of antibiotics when appropriate are some of these check points. Also, other measures would include the removal of foreign bodies and the drainage of pus as required. De-escalation of therapy from IV to oral administration as well as therapeutic drug monitoring was also proposed for inclusion in the care bundle.

This concept would be a practical approach to ensure that a checklist was followed and junior staff made accountable when initiating antimicrobial therapy. The value of nursing staff in ensuring compliance with these care bundles would

ensure an efficient and effective implementation of AMS. Once the core elements are established other tools such as the use of rapid diagnostics and CDSSs to enhance AMS programs can be considered.

The Australian Commission on Safety and Quality in Health Care (ACSQHC), has recognised that AMS programs need to be implemented in Australian hospitals to ensure optimal care is provided to patients(8). Section 3.14 of this standard relates to the developing, implementing and regularly reviewing the effectiveness of the AMS programs (7). Whilst Australia is still in its early stages of AMS implementation all hospitals have started some form of an AMS program ranging from complex to simple models depending on the size, remoteness of location and available resources.

2.5 AMS IN AUSTRALIA

A team of experts were consulted and in 2011 guidelines for the implementation of AMS in Australia were developed and published. Strategies that are considered essential by the Australian Guidelines for the implementation of AMS programs are as follows(8):

- The implementation of clinical guidelines that is consistent with the latest version of therapeutic guidelines and the local antibiogram for the health care institution.
- Establishing formulary restriction and approval systems
- Establishing prescription audit and feedback interventions
- Auditing of antimicrobial usage
- Ensuring that the clinical microbiology laboratory uses selective reporting of susceptibility results consistent with the treatment guidelines.

There are a few more suggestions that may be useful dependent on local priorities and resources(83):

- Educating prescribers, pharmacists and nursing staff about prescribing practices and implications of AMR

- Using point of care interventions to assist with streamlining therapy
- Use of technology such as electronic prescribing with CDSSs
- Publishing facility specific antimicrobial susceptibility data annually.

First and foremost encouraging clinicians to take responsibility for prescribing antimicrobials by justifying the need for an antibiotic in the patient's clinical notes and then outlining the logic behind the choice of agent, route of administration, dose and duration of treatment must be a requirement.

Each Australian hospital differs in their internal structure and resource allocation models. Although a framework exists for elements that are required for AMS there is no standard AMS program that would suit all hospitals. While the larger metropolitan hospitals are more advanced in their AMS implementation the less resourced regional and rural hospitals are less advanced. The needs in the many different environments are varied, where metropolitan hospitals have microbiology, pharmacy services and access to infectious disease services on site the remote and rural hospitals may not. In Queensland, a state-wide AMS program led by an infectious diseases physician was established in 2016 with a sole purpose of supporting all of the state's hospitals to implement suitable AMS interventions.

The AMS team plays an important role to ensure that all communications are melded into one cohesive team effort to improve patient care. Electronic health records have been found to be useful in improving prescribing practices in the Australian setting (72). The easy access to antibiotic guidelines, antibiograms, laboratory test results and surveillance data for the patient of interest leads to better prescribing.

Australia also has a standardised manual for antimicrobial therapy (Therapeutic Guidelines – Antibiotic) for the prescription of antibiotics. This guide was first published in 1978 and whilst there is agreement in principal on best practice there is an ongoing education requirement to ensure our prescribers are familiar with and adhere to these guidelines. Improved adherence and compliance to these guidelines may be facilitated by the use of tools such as smartphones and

tablet apps. Goff found that these tools were useful to ensure stewardship activities were more attractive and easy to comply with for the busy clinician (84).

The barriers to implementation of AMS interventions in Australia have been summarised in a recent survey of pharmacists, infectious diseases physicians and infection control nurses (74). The perceived barriers were the inadequate education about AMS, the lack of access to resources in rural and remote hospitals, the inadequate feedback to doctors regarding prescribing practices in their institution compared to a national benchmark and the lack of key performance indicators to measure the outcomes of the intervention.

A more recent survey conducted in Queensland also identified significant barriers to implementation of effective AMS programs in regional and rural hospitals (85). The major barriers identified in this report were the lack of education in the appropriate use of antimicrobials of the prescribers. The lack of communication between disciplines was also highlighted despite the availability of a state-wide antibiogram program which provides access to antibiotic resistance data. A larger study in Victoria including metropolitan, regional and private hospitals also reported similar findings, and the top three barriers were identified as being lack of access to resources in pharmacy, infectious diseases and clinical microbiology services(86).

With this knowledge AMS interventions need to be designed to ensure equal access in metropolitan as well as rural and remote settings. Strategies that work in the city may not be the same ones that work in remote areas. Access to services via the internet, skype and telehealth might be options to consider in remote areas. Another consideration is that the use of IT such as the electronic medical record and CDSSs may be valuable in settings where remote access to these systems is an option.

Due to the complex requirements of AMS it is important to note that there is no correct way to go about AMS in hospitals. A recent article by Hamilton et al (87), stressed the importance of AMS ward rounds where a more interpersonal approach is adopted. The AMS ward round can allow for discussions between the treating team of more complicated cases with an infectious diseases specialist and the AMS

team. These ward rounds not only provide a collegiate and more visible AMS team but also gives the team a true insight as to the barriers encountered every day to appropriate prescribing. This real-time approach will improve communication and inspire trust in the AMS intervention than just a phone call or electronic message. However depending on the availability of resources a combination of strategies may need to be employed. The AMS ward round would also be a good time to discuss results from the laboratory and their interpretation and the importance of correct duration and dose of antimicrobials for each individual case.

2.6 MEASURING THE SUCCESS OF AMS INTERVENTIONS IN HOSPITALS

Kaki et al (88) performed a systematic review of AMS interventions implemented from 1996-2010 in critical care settings. Twenty-four studies from nine countries including three from Australia were included. Of these 71% only assessed the savings achieved from the reduction in antimicrobial usage. The studies also reported a trend where restriction policies reduced the use of that specific antimicrobial but caused a phenomenon referred to as “squeezing the balloon” and resulted in the increase in use of other antimicrobials of a similar spectrum of utility. They found that strategies such as involvement of infectious diseases consultants, CDSS and prospective audit and feedback interventions reduced the consumption of antimicrobials. This work was further supported by a second systematic review performed by Wagner et al (89), which concluded that the studies were short in duration and of generally poor quality in terms of study design. The clinical outcome data was lacking and the majority of the information reported on was process measures such as antimicrobial use and appropriateness of prescribing.

In general, AMS interventions may be evaluated using process or outcome measures. Process measures are an audit of the strategies used in AMS such as information on antimicrobial utilisation, appropriateness of therapy, conformance with guidelines and other details such as time to initiation of therapy. Walsh et al(90) suggested the development of an International Antimicrobial Stewardship

index scoring system where the focus would be on scoring the national activities on AMS. This idea could be adopted nationally or by each hospital or community health centre and each state or hospital can then have their very own accreditation score. To be able to score against a minimum standard while useful, maybe difficult to establish considering the various healthcare settings.

While process measures ensure that the intervention is being implemented effectively, for the purposes of a cost-effectiveness evaluation outcome measures are required to adequately reflect the impact of the intervention on patients. Outcome measures can be divided into microbiological, patient and financial (91). The measures used to evaluate the intervention will vary based on the perspective of the evaluator. Generally, hospital administrators are more interested in the financial cost savings, while the clinicians focus would be the appropriateness of the choice of antimicrobial and the reduction in the adverse clinical outcomes associated with antimicrobial therapy.

From a financial cost-savings perspective, the reduction in antimicrobial usage and the reduction in hospital LOS can be directly translated to a large cost savings. The majority of AMS evaluations have reported significant cost savings as a result of reduced antimicrobial utilisation. However, the costs saved due to reduction in unintended consequences of antimicrobial use are less well captured. These clinical outcomes could be the rate of *C. difficile* infections, AMR development, mortality and hospital LOS.

C. difficile infections are a good indicator of the impact of effective AMS programs as these infections are associated with antimicrobial therapy. Antimicrobials disrupt the gut bacteria and cause the colon to become colonised by *C. difficile* which produces toxins that lead to the development of *C. difficile* associated diarrhoea (CDAD). There is a direct relationship between clindamycin, third generation cephalosporin and fluoroquinolone use and the development of *C. difficile* in hospitalised patients (92, 93). A restrictive strategy on antimicrobial use in a hospital in Glasgow provided evidence that there was reduction in *C. difficile* infections by 50% percent following this intervention(33). While a good indicator

the methods of testing and confirming these infections have changed overtime and this makes comparison between institutions difficult.

While it makes sense that the impact on clinical outcomes are the most important measure of success of an AMS intervention, the metrics actually collected depend on the perspective of the evaluator. A survey conducted including physicians and pharmacists found that, while the infection related mortality and hospital LOS is the most valued metric to be measured from the perspective of an infectious diseases specialist, other groups favour the collection of antimicrobial cost and usage data (94).

A recent systematic review on the clinical and economic outcomes of the implementation of hospital based AMS programs suggests that there was an overall reduction of antimicrobial consumption by 20% after AMS and this effect was doubled in the ICU setting. They reported a decrease in cost and LOS but that 30-day all-cause mortality and infection rates were not affected. The authors suggested that longitudinal studies greater than 3-years may be needed to fully review the benefits of AMS(95).

Strengthening this argument a recent study by Cook (96), reported the benefits of assessing AMS interventions over a 13 year period with a specific mention on the benefit of e-health records (EHR) in improving the ability to review prescriptions by pharmacists to provide advice on more effective options. A reduction in AMR was also reported overtime particularly with the restriction of fluoroquinolone use.

However a recent systematic review and meta-analysis on the available evidence for assessing the impact of AMS interventions revealed that there is only low quality evidence particularly for evidence on clinical outcomes, adverse events and costs (97). Cairns (98), found that the impact of a multidisciplinary antimicrobial stewardship team on the timeliness of antimicrobial therapy in patients with positive blood cultures was significant. They also found that active review of patients with BSIs by their AMS team improved the timeliness of appropriate therapy. A study by Niwa 2016 (99), found that the daily review of antimicrobial use resulted in a significant reduction in time to antimicrobial therapy and the rate of

de-escalation. The rate of 30 day mortality associated with BSI reduced from 11.4% to 5.4% (p=0.030) and the incidence of adverse events also were significantly reduced from 28% to 7.7% (p<0.001). While there is evidence to indicate that there is definite value in implementing AMS interventions, the best metric to measure the effectiveness of these interventions is not clear. Since many publications have targeted patients with BSIs to measure the impact of AMS interventions the literature to date published to link inappropriate prescribing and the impact on mortality was reviewed and published by the author of this thesis. This publication and the findings are discussed in the section below.

2.6.1 THE USE OF BLOODSTREAM INFECTION (BSI) MORTALITY TO MEASURE THE IMPACT OF ANTIMICROBIAL STEWARDSHIP (AMS) INTERVENTIONS: ASSESSING THE EVIDENCE.

Summary of peer-reviewed publication:

S Coulter, JA Roberts, K Hajkowicz, K Halton. *Infectious Disease Reports* 2017; 9:6849.

PMID: 28458799.

Refer to Appendix D1 for the complete article (100).

To determine the impact of inappropriate, delayed and inadequate therapy on BSI mortality, a systematic review of the current literature was conducted on studies up to July 2015. Only primary studies in English, of adult inpatients in hospital settings in countries belonging to the OECD with a sample size greater than 99 were considered. The risk of mortality related to BSI was required to be expressed as an odds ratio, relative risk or hazard ratio and the organisms reported also needed to belong to the ESKAPE group of organisms. The ESKAPE pathogens included are *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter species* (ESKAPE)(15). In addition to these organisms, an expert group in 2008, agreed to include Enterococcus spp. and Enterobacteriaceae (other than Salmonella and Shigella), because of the epidemiological significance, the emerging antimicrobial resistance and the importance of these bacteria as causative agents of health care associated infections (16).

Forty six studies were included and two were large multi-centre studies: one including data from USA, Canada and Saudi Arabia (101); and the second including data from nine European countries (102). Thirteen studies were from the USA,(101, 103-114) eight from Spain (115-122), five from Italy(123-127), four from Korea(128-131), three each from Turkey(132-134) and Israel(135-137), two each from the Netherlands(138, 139) and the UK(140, 141), and single studies from Denmark(142), Germany(143), Norway(144), and Australia (145).

While the quality of the studies were overall poor and the definition of inappropriate therapy varied the review concluded that inappropriate therapy was associated with a higher risk of mortality in patients with BSIs. The risk of mortality was highest in patients with BSIs caused by GN organisms especially if these BSIs were caused by resistant GN organisms (the risk of death ranging from 3 to 25 fold depending on the resistance status of the pathogen). Also in patient with BSIs caused by GP organisms, patients with BSIs caused by MRSA had a higher risk of mortality than those with BSIs caused by MSSA.

The ESKAPE organisms are the main pathogens in hospital settings. BSI-associated mortality in patients caused by these organisms resulted in an increased risk of mortality; this finding suggests a link between inappropriate prescribing and an increased risk of death in BSI. Since the largest impact of inappropriate prescribing was seen in resistant GN BSI, these may be a suitable metric to describe the impact of an AMS intervention on patient outcomes. However, little is known on the longer term impacts of BSI that are treated with inappropriate antimicrobials and future longitudinal studies would provide better information on morbidity and quality of life impacts on patients receiving inappropriate therapy for BSI.

2.7 COST ANALYSES AND THE NEED FOR COST EFFECTIVENESS ANALYSIS (CEA)

Decision makers constantly battle with competing priorities when allocating the healthcare budget. Historically this process has often been performed by hospital administrators employing a silo mentality where each department is considered in isolation. For example rapid diagnostics for the identification of a

multi resistant organism such as MRSA may prevent an outbreak, but the budget allocated to the pathology department does not take into account the impact on the broader hospital budget where an infected patient may cost several thousand dollars in terms of a hospital bed in the infection control ward per day. While cost analyses have their place in allocating hospital budgets cost-effectiveness analyses take into account the change in health outcomes as well as the change in costs brought about by an intervention.

Stevenson et al (146) reviewed the overall hospital costs in terms of asset and capacity management, and optimising investment in fixed costs when reviewing AMS programs. Hospitals have a high fixed cost that remains relatively stable, but if efficiency is improved then that fixed cost is utilised to treat more patients in a given period of time. The authors (146), also discussed the use of technology such as PCR to improve turnaround times of blood culture results to improve the efficiency of appropriate antibiotic therapy, which in turn reduced the LOS and decreased the cost of treatment. This study does not evaluate the cost-effectiveness of AMS programs but instead looks at ways in which the efficiencies can be improved in hospital settings.

There are considerable savings that may be achieved through the prevention of resistant infections to sustain an already overburdened healthcare system. Resistant infections require more expensive treatments, extended hospital stays, additional specialist care and can result in greater disability and death compared to susceptible infections(147). The current evidence on cost-effectiveness of AMS interventions does not capture the significant cost savings that are achievable with more appropriate use of antimicrobials.

Two systematic reviews performed one by Dik et al (5) and the second by Coulter et al (148) concluded that the current evidence on cost and cost-effectiveness analyses available were difficult to compare due to the heterogeneity of the methods used in the studies. The majority of studies only assessed the pharmacy cost savings gained from AMS interventions and only a few assessed the clinical outcomes as a result of AMS. There is a clear need to standardise the evaluation of AMS interventions from a cost-effectiveness point of view. The

current evidence on cost and cost-effectiveness analysis of AMS interventions is summarised below as published by the author of the thesis.

2.7.1 THE NEED FOR COST-EFFECTIVENESS ANALYSES OF ANTIMICROBIAL STEWARDSHIP PROGRAMMES: A STRUCTURED REVIEW.

Summary of peer-reviewed publication:

S Coulter, K Merollini, JA Roberts, N Graves, K Halton *International Journal of Antimicrobial Agents*, 2015; 46(2): 140-9. PMID: 26058776.

Refer to Appendix D2 for the complete article (148).

Of 36 studies included in the review all but one reported that AMS resulted in a reduction in pharmacy expenditure(9, 32, 40, 55, 57-60, 66, 149-175). Among 27 studies measuring changes to health outcomes, either no change was reported post-AMS, or the additional benefits achieved from these outcomes were not effectively quantified. AMS programs achieved a reduction in pharmacy expenditure, but there was a lack of consistency in the reported cost outcomes making it difficult to compare between interventions. The failure to capture complete costs in terms of resource use makes it difficult to determine the true cost of these interventions.

Due to AMS interventions being greatly varied in composition depending on the combination of strategies implemented by each healthcare institution, comparison is difficult. Not only are they varied in composition but also in the amount of resources invested at each institution.

There is limited evidence on the cost effectiveness of AMS programs with only two studies that have looked at the costs and benefits of AMS programs and one of these performed a comparison between two approaches to AMS(9, 10). Davey et al (2013), in a recent update to a Cochrane review first published in 2005, clearly pointed out the need to fill the significant gap in the literature with regard to the cost effectiveness evidence on AMS interventions (11, 176).

The first study to perform a full economic evaluation on AMS is the study by Scheetz et al (9) where the impact on patient outcomes due to an AMS Program in terms of QALYs was evaluated. Scheetz et al (9), reported that the AMS intervention at their hospital was cost effective and expressed the value of this intervention in terms of incremental cost effectiveness ratios (ICERs) as a cost per QALY gained. The AMS intervention was cost effective at a cost of US$2367 per QALY gained and when a CDSS was introduced the cost per QALY gained was US $7368 and was also found to be cost effective in this setting. A second more recent study by Okumura et al(10) compared two approached to AMS and found that a bundled approach achieved a more cost effective result.

While the true impact of AMS interventions on prescribing are difficult to measure it is clear from the evaluations performed so far that there is a significant reduction in antimicrobial use and no increases in 30 day mortality due to these interventions. However the more subtle impacts of poor prescribing are not reported and collected as comprehensively in hospitals. The number of adverse events due to allergic reactions or nephrotoxicity or hepatotoxicity due antimicrobial therapy is less well documented.

The effectiveness measures in these interventions need to reflect the true impact of inappropriate antimicrobial use on patients in hospitals. This information needs to be collected accurately and over longer periods of time to measure the benefits of AMS interventions and the safe use of antimicrobials. To truly evaluate AMS interventions the change in costs and effectiveness pre and post intervention needs to be quantitated and presented to decision makers as a cost per health benefit achieved.

While the overall cost savings as a result of these interventions are encouraging decision makers need to be aware that the most important consideration is patient safety and the avoidance of patient harm. The decision to choose one antimicrobial over another should not be based on cost but the most optimal choice for the treatment of the infection. In some instances these choices to reduce AMR and adverse patient outcomes may result in an increase in drug acquisition costs initially but result in a better overall outcome for patients.

2.8 SUMMARY

While this body of work is focused on the hospital perspective when evaluating the cost effectiveness of an AMS intervention, a societal perspective is preferred. The view that the development of AMR is seen as an externality and that the short-term effect is not felt by either the patient, prescriber or supplier is a significant issue in our society. AMS interventions should have a long-term perspective and continuous quality improvement in healthcare environments needs to be their goal. CEAs measure the impact of an intervention in terms of the change in costs compared to the health gains achieved. The true challenge is being able to convince decision makers that the initial investments in interventions to improve patient safety may not be cost saving in the short term but have significant long term societal benefits.

The methods that are employed in this thesis will be discussed in Chapter 3 with regard to the type of decision analytic model used, and how this analysis will be applied to evaluating AMS interventions. The chapter will also address how the costs and health benefits will be measured and provide the theoretical background for how the results will be analysed characterising uncertainty in the estimates used in the model.

Chapter 3: ECONOMIC EVALUATION AND DECISION MAKING

This chapter provides background on the benefit of cost effectiveness analyses for decision making in healthcare as well as describing the methods available for performing these analyses (3.1). Section 3.2 describes CEA in the context of AMS interventions and section 3.3 on the methods available for the measurement of health outcomes. The decision analytic models available and the choice of the type of model for this analysis are discussed in section 3.4. The following section (3.5) provides information on how the results generated by economic modelling can be used and interpreted by decision makers and the information on valuing the hospital bed day, and points out the difference between the accounting costs and economic costs of hospital stays. Section 3.6 summarises the methods that are relevant for the economic evaluation of AMS interventions.

3.1 DECISION MAKING IN HEALTHCARE

CEAs are an accepted tool to inform decision makers on the value-for-money of healthcare interventions. A decision to adopt one healthcare initiative will take away resources that might have been allocated to another. Economic evaluations provide decision-makers a framework where the initiative that provides the maximum "opportunity cost" can be chosen. A standardised approach to measuring health outcomes and health costs can significantly improve how we allocate potentially scarce health resources in national and international programs. This ensures that the decision made warrants that scarce resources are used efficiently and provides a benefit to society as a whole.

Australia has led the way in performing cost-effectiveness analyses in the areas of reimbursements for new drugs and health technology assessment (177). The Pharmaceutical Benefits Advisory Committee (PBAC) for new drugs and the Medical Services Advisory Committee (MSAC) for new technologies are well

established in Australia as a formal means of performing cost-effectiveness analyses.

While CEAs are important in healthcare decisions, a poorly performed analysis can be misleading. Therefore, the methods used and the way in which results are reported needs to be standardised. For example, the Bill and Melinda Gates Foundation generate high quality information to inform their own global health resource allocation decision-making (177). They are a major funder of economic evaluations globally and have generated impetus to develop standardised methodological guidance on economic evaluations in healthcare. A collaboration between the National Institute for Clinical Excellence (NICE), the Centre for Health Economics at the York University in the UK and the Health Intervention and Technology Assessment Program in Thailand has proposed eleven principles to address the key components of a comprehensive CEA (177).

The essence of these principles is to have transparency in the decision problem and a comparator for the new intervention. All available evidence needs to be accurately identified and measured. Health outcomes need to be captured and the cost difference carefully and accurately measured. The time horizon, discount rate and perspective of the evaluation clearly defined, ensuring heterogeneity and any other population biases are stated and considered. The uncertainty associated with the parameters used in the analysis needs to be identified and the constraints and equity issues relevant to the analysis should be taken into consideration.

The need for standardised reporting of economic evaluations by researchers and biomedical journal editors has also been identified. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), founded in 1995 developed guidelines in the form of a checklist of what needs to be included in a complete economic evaluation (177). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) provides recommendations for the optimal reporting of health economic evaluations (178).

3.1.1 TYPES OF ECONOMIC EVALUATION

A full economic evaluation involves identifying, measuring and valuing all changes that occur as part of implementation of an intervention (179). CEA is useful when comparing intervention outcomes in terms of costs in monetary units and results in health benefits such as life years gained or lives saved. For example treatments or interventions to assess the highest number of cases of breast cancer detected by alternative methods can be assessed in terms of incremental cost-effectiveness ratios (ICERs). These ICERs are calculated by determining the change in the cost of the intervention divided by the change in the effect measured, in this case 'cases detected'. The ICER is used to compare the additional cost incurred to achieve greater health benefits or case detection with one intervention when compared to another (180). Some of the limitations in CEAs are that they are unable to compare interventions that have more than one outcome or different terms of measurement (181).

Cost utility analysis (CUA) is a sub branch of CEA and is used to compare the incremental cost with the incremental health effects of a program. In CUA, the multiple outcomes can be valued and the incremental health improvement can be measured in Quality Adjusted Life Years (QALY) gained or another variant such as Disability Adjusted Life Years (DALY) gained.

Cost-utility analysis, allows a broad range of outcomes to be combined into one expression in the form of a QALY or a DALY. Drummond et al (181) stated that CUA is useful when health related quality of life is an important outcome and where one unit that can measure the effect of a program on morbidity and mortality needs to be used for the sake of comparison. It is useful when comparing interventions to be able to use a common measure of cost-effectiveness. This allows decision makers to allocate resources to programs that maximize health benefits across all disciplines in healthcare.

This research aims to answer the question as to whether making an investment in an AMS program is a good decision. Although implementing an AMS program may increase health costs initially, it is expected that in the longer term

AMS programs will decrease costs by reducing antimicrobial utilisation and improving health outcomes of patients in hospital (88, 89, 95).

3.2 APPLICATION OF ECONOMIC EVALUATION IN ASSESSING ANTIMICROBIAL STEWARDSHIP INTERVENTIONS

AMS interventions are now well established as one of the strategies to reduce inappropriate prescribing of antimicrobials and reduce antimicrobial costs in hospitals (32, 147, 149). These interventions impact on patient care on two levels. The first and immediate impact, is relevant to the individual patient, and consists of getting the drug, dose and duration of therapy optimised, leading to reduction of adverse events and the best outcome for the patient. The second, which relates to the societal impact, is less considered. However this impact is far reaching and relies upon the reduction of antimicrobial misuse leading to the prevention of AMR and improving the long-term utility of antimicrobials. Unlike other medications antimicrobials have the potential to adversely impact on the health of patients that are not even exposed these drugs due to AMR.

Coast et al (182) suggests that economic evaluations should focus on measuring the impact of interventions on patient outcomes such as mortality and hospital length of stay than merely on the change in antimicrobial usage. Ideally, the impact of inappropriate antimicrobial use should be evaluated from an individual and societal viewpoint.

The true cost of resistance is difficult to estimate as the intangible costs to society are not well characterised. In a recent review by Smith et al (183) the estimated cost of resistance varied from $5 to $55,000 per patient episode, and the highest estimate per annum from resistance was estimated at $55bn ($20bn in health service costs and $35bn in lost productivity) in the USA. The best estimates available in the contemporary literature are still likely to be a gross underestimate of the true costs of resistance in terms of the inability to perform surgical interventions, transplantation and other advanced health care interventions because of the lack of access to effective antimicrobials. Most commonly, the

various data collection restrictions and the time horizon for local research, means that the impact of AMR will be measured from a hospital perspective and will under estimate any subsequent societal effects. However, if AMS is cost-effective from a hospital perspective it may be extrapolated to be cost-effective from a societal perspective.

It is difficult to accurately estimate the true monetary benefits of AMS interventions as they are complex and utilise differing strategies and tools. They are also interwoven with other healthcare initiatives that often occur at the same time. There is ample evidence that the investment in AMS programs in hospitals reduces costs due to the reduction of antimicrobial usage (6, 32, 149), but there is little evidence in terms of cost-effectiveness of these interventions.

The hypothesis in this research is that AMS will lead to better prescribing of antimicrobials, which in turn would reduce the adverse events related to inappropriate therapy. As a consequence of better prescribing, patients would have reduced LOS in hospital which would in turn reduce their risk of acquisition of HAIs. Initiatives such as hospital in the home where the patient is cared for in their own home even while on IV antimicrobials, and converting patients to oral antimicrobials as soon as is safe, are part of a more efficient transfer of patients from a hospital environment to their home. These initiatives result in reductions in hospital LOS and potentially in further hospital cost savings.

However, costs from an economic perspective are different to accounting costs. Graves et al (184), explain that accounting costs are mainly the fixed costs in hospitals in terms of budget allocation and these constitute infrastructure such as resources and staff costs. The fixed costs constitute the larger portion of costs often between 80 to 90 percent of the hospital budget. The variable costs are the marginal costs of bed days and other resources released when available resources are allocated in the most efficient way. This savings can be better allocated as resources to be utilised to improve patient care in other initiatives.

For example a Dutch study evaluated the impact of the implementation of an AMS team in a urology ward in their teaching hospital using a cost minimisation model (5). The AMS intervention, while limited to one ward for 12 months, included

only 114 patients, but still resulted in a cost savings of €60,306. The cost of the intervention was calculated to be €17,732. This is an example of how a conservative and targeted investment resulted in significant savings achieved by an AMS intervention. This additional savings could be reallocated to other interventions to improve patient safety and care.

3.3 MEASURING CONSEQUENCES IN HEALTHCARE INTERVENTIONS

To measure health benefits due to healthcare interventions, it is important to value the effects of the intervention in terms of health related quality of life measures that take into account not only mortality but morbidity associated with the intervention (179). The benefits from a course of action are valued as the extra years of life it gives individuals adjusted for the quality of life they live those years in (185). The quality adjusted life year (QALY) is used to measure the effectiveness of an intervention where every QALY is equivalent to one year of life in full health. The purpose of the health utility measurement is to provide the quality adjustment weight in order to calculate the QALY. If life years gained (LYG) are adjusted for health utility scores between zero and one, then QALY gains or losses can be estimated as a result of the intervention.

Multi-attribute utility scales (MAUS) are commonly used tools to retrieve these scores (186). Health related quality of life (HRQoL) represents the impact of various conditions on the quality of an individual's life. These utility scores are generic preference based measures (GPBMs) that are derived from responses to questionnaires from patients or members of the general public to assign them to unique health states. There are a number of these GPBMs available for different countries and for patients suffering particular health conditions. There are a number of GPBMs available and some examples are EQ-5D (the EuroQoL 5 dimensions, the Short Form 6 dimensions (SF-6D) and the Assessment of Quality of Life 8 dimensions (AQOL-8D)).

3.3.1 HEALTH OUTCOMES

The number of years an individual has to live is the simplest measure of health (179). This information can be found by consulting life tables published by the WHO or country specific tables such as those published by the Australian Bureau of Statistics (ABS). The average life years gained for an intervention under consideration can then be calculated.

To perform a CUA in patients with bloodstream infections (BSIs) the QALY is calculated by working out the life expectancy for the population after BSIs and adjusting this by the QoL post infection. This QoL measure is ascertained using a questionnaire and is usually collected 6-8 months post discharge from hospital after sepsis (187). The long term impact on life on a patient who does not enter critical care is assumed to be the same as the general population.

There is little published evidence as to the long term quality of life for those who survive sepsis in general wards. There is some evidence that patients in ICU with severe sepsis that survive, have a lower quality of life (QoL) than the age and sex adjusted population even 1.5 years after their stay (187). This morbidity related to serious infection reflects the significant reduction in QoL in patients who have complicated infections with MDR organisms and other complications of long hospital stays. Adverse consequences of hospital stays such as healthcare associated infections (HAIs) and other adverse events related to antimicrobial therapy are less well captured in the literature and in hospital datasets. Most studies report on 28-30 day mortality and hospital LOS associated with BSIs. Because infection is a short and acute health condition the impact of weighting years of life by utility score on the conclusions is likely to be small. However, for the ease of comparison with other studies QALYs are used in this thesis. The recently published population norms for the AQoL derived from the 2007 Australian National Survey of Mental Health and Wellbeing were used in this study (188)

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3.4 DECISION ANALYTIC MODEL BASED ECONOMIC EVALUATIONS

A decision analytic model is defined as a means of expressing a mathematical relationship as a series of possible consequences that would flow from a set of alternative options being evaluated (189). This form of analysis in health care has been advocated for some time by the NICE in the UK (189).

Healthcare decisions regarding the implementation of various interventions need to be made regardless of the strength of the available evidence. Decision analysis provides an analytical framework within which this can be achieved (181). One of the key phases of developing a model framework involves considering the question or the decision problem being addressed. There needs to be careful definition of the research question with regard to patient population, perspective and setting (181).

3.4.1 EVIDENCE USED IN DECISION MODELS

One of the most obvious sources of effectiveness data is the existing medical literature which always needs to be assessed for relevance and quality (181). Ideally data from randomised controlled trials are preferred but in the absence of this, good quality clinical data on effectiveness can be used. Meta analyses of existing evidence can be performed to obtain best estimates for the parameters required for economic models.

For the evaluation of AMS interventions the nature of the subject matter is not suitable for RCT methodology as it would be unethical to randomise any patient or patient group to inappropriate therapy. In the absence of RCT data there are a number of factors to consider when finding the best data to populate a decision analytic model. It is important to assess the implication of the uncertainty in some of the parameters that may be used in terms of impact on the final result.

The model inputs are expressed in terms of the relative risk for that particular outcome to occur based on the likelihood of that outcome occurring. This method allows for extrapolation of data beyond a finite trial period. The disadvantages of this type of modelling is that the models are subject to uncertainty in terms of

variability, parameter and model uncertainty and heterogeneity of the information used (189).

When developing a cost-effectiveness model, primary data is the best source, with a requirement for sourcing high quality, rigorously collected data with minimal sources of bias. The evaluation of an intervention in individual healthcare settings may rely on access to the data that exists in hospital databases. If this data is unavailable the medical literature will need to be relied upon, publicly available databases and expert opinion can also be used. Cohort studies or disease registries can provide valuable information regarding the natural history of a disease but can also take time and resources to achieve the best results (179).

3.4.2 CHARACTERISING THE UNCERTAINTY IN ECONOMIC EVALUATIONS

There can be a variety of sources of uncertainty in economic evaluations, this may be due to the heterogeneity of the patient population used, the assumptions made while developing the model structure and the parameter uncertainty when estimating point estimates for the likelihood of the outcomes in the model.

3.4.2.1 **Heterogeneity**

In a clinical situation individual patients will differ from one another in the clinical events that they experience and the associated health impacts in terms of quality of life (189). These events occur between individuals by chance, and are known as variability in the parameters. Heterogeneity is the differences that occur between individuals such as a parameter that has an increased risk of occurring depending on the age of the cohort.

3.4.2.2 **Model based uncertainty**

The uncertainty in the model comes about if the assumptions made in the development of the structure of the model are not accurate. This may be due to a lack of understanding of the natural progression of the disease or process that is being evaluated. Scenario analysis can be used in this setting in conjunction with experts to help develop and validate the model. Scenario analysis uses the base

case, best case and worst case scenarios to assess the impact of some of the assumptions made in the model (181).

3.4.2.3 **Parameter based uncertainty**

The lack of data when estimating the input parameters into a model will create uncertainty in that parameter. The more evidence that can be gathered the less uncertain the parameter. So to circumvent this situation additional evidence needs to be gathered (189). In general, it is assumed that the data informing the parameter of interest will follow a distribution that is appropriate for the type of parameter. For example a transition probability takes values from 0-1 and a beta distribution is very common for this type of parameter. These parameters will also have a 95% confidence interval or standard error associated with them. Parameter uncertainty can be evaluated by using a few different approaches. Sensitivity analysis can be performed by varying individual input parameters and assessing this impact on the model(181). This approach is known as one way sensitivity analysis where one parameter is varied at a time.

A more efficient method that can be used since the advent of powerful computer technology is probabilistic sensitivity analysis (PSA). PSA involves defining the best estimate for the parameter plus a range. The second stage of PSA is to undertake a simulation exercise involving a random draw from the parameter distribution and generating a large number of expected costs and effects. The final step is to present these results as a mean overall cost and effect for the intervention being evaluated (181). This information can also be presented as a scatterplot of the simulation on the cost-effectiveness plane. In a well-designed probabilistic model uncertainty in the parameters can be adequately reflected and presented to the decision maker for consideration (189).

3.4.3 STRUCTURE OF DECISION MODELS – DECISION TREES

There are two main types of decision analytic models that may be used when performing a full economic evaluation, Decision trees and Markov models. Markov Models are useful when decision trees are unable to be used due to the complex or chronic nature of the disease process evaluated. They allow movement back and forth between health states unless the state is an absorbing state where it is not

possible to reverse such as death. In a Markov model a cycle length needs to be selected to represent the amount of time the transition occurs between these health states according to the disease process or infection modelled. When evaluating outcomes due to effective or ineffective antimicrobial stewardship interventions it was clear that a state based model was not required and so for these reasons a parsimonious approach of using a decision tree was adopted in this research.

The decision tree is the simplest form of decision analysis and differs from Markov models in that they only allow movement in one direction along the branch or clinical pathway. When a decision problem is being evaluated by considering two or more alternatives a simple decision tree can be constructed. The branches of the tree represent the different courses that can be followed in two alternative decisions. The decision node is the square box at the beginning of the decision tree and represents the question being answered in the analysis. There can be only one square node per analysis and at the end of the analysis when the tree is "rolled back" this question will be answered. The pathways that emanate from this point are mutually exclusive. The chance node is the circle along the branches of the tree and these points represent different possible pathways in the decision problem that patients can experience.

The likelihood of the different pathway occurring is estimated by the branch probabilities. This varies depending on the natural history of the clinical condition under evaluation. Branch probabilities are the possible events patients may experience at a specific point of the tree. The probabilities of subsequent events are conditional probabilities because they only relate to those who have undergone previous events in that pathway. The final probability at the end of that pathway is achieved by multiplying the initial branch probability by all the conditional probabilities.

Figure 3.1 refers to a schematic representation of a decision tree model where intervention A is compared to Intervention B. At the end of each branch the terminal node has a cumulative cost and health benefit for each pathway based on

the pathway and is conditional upon each of the events occurring in that clinical event.

The related costs and outcomes are allocated at the terminus of the decision pathway leading from the beginning on the left to the end on the right. Each pathway has a cost associated with it. This is obtained by summing all the costs associated with each of the events experienced by the patient along each clinical pathway. Cost and health outcomes are allocated to the end point or terminal node of the clinical pathway and an incremental cost-effectiveness ratio (ICER) is calculated for each alternative in the decision model. This can be achieved by "rolling back" the tree. This is achieved by working from the right to left of the decision tree and calculating expected values using the costs and the probabilities for each pathway or alternative. The ICERs are usually expressed as costs per QALY or LYG for each intervention or the incremental cost per incremental outcome measured.

The two fundamental drawbacks of decision trees is that they are best used to evaluate events occurring in an instantaneous and discrete period of time and they are not useful if used to evaluate complicated processes that can make the decision tree too large(189).

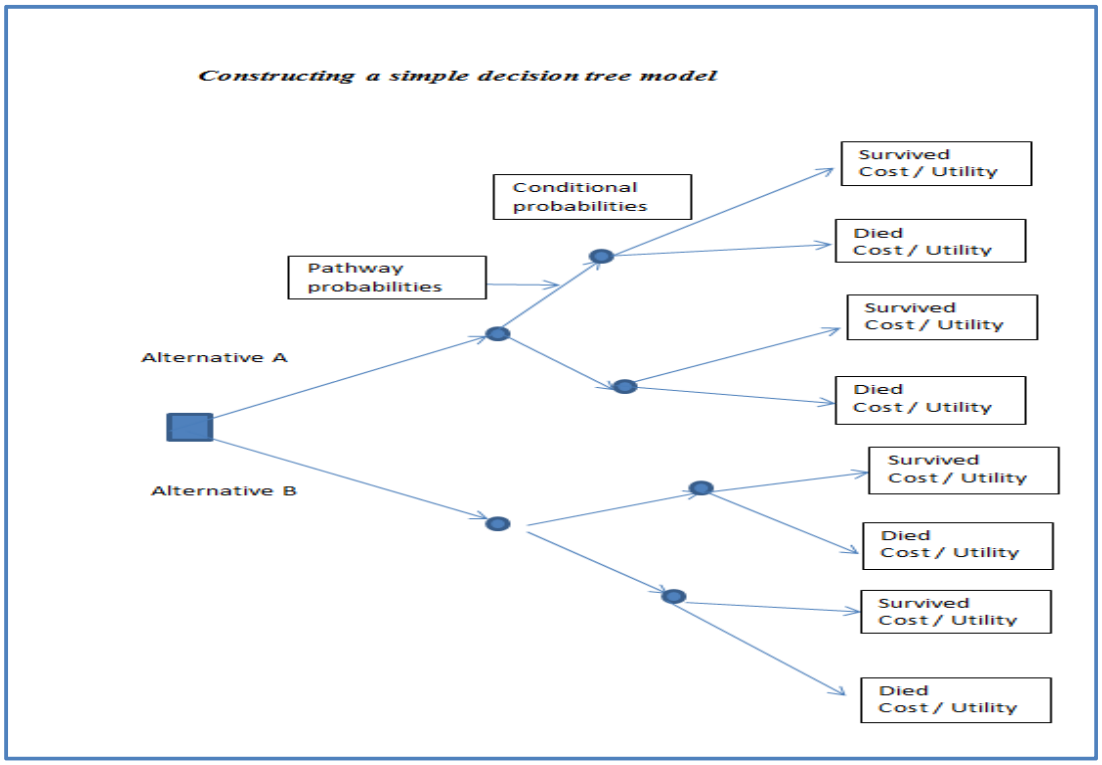

Figure 3.1 Schematic of a simple decision tree

3.5 ANALYSIS OF RESULTS FROM THE DECISION TREE MODEL

When the decision tree is "rolled back" a cumulative cost per health unit gained can be calculated for each of the alternatives that are being considered. This information then can be expressed as a cost-effectiveness ratio and plotted on a cost-effectiveness plane. When point estimates are used for the costs and effects in a CEA, it is referred to as a deterministic or a fixed value analysis (181).

3.5.1 FIXED VALUE RESULTS

This initial fixed value analysis is performed using values that have been estimated as a mean and the uncertainty in the estimates has not been taken into consideration.

The outputs from the model will be expressed in terms of ICERs :

$$\text{ICER A} = \frac{\Delta C}{\Delta E}$$

ΔC= Change in the cost of intervention A compared to current practice

ΔE=Change in the effectiveness of intervention A compared to current practice

When single data points are used and these values are inputted into the model single ICERs will be generated. These values can then be plotted on a cost-effectiveness plane as a single point. ICERs may be generated for all of the alternatives being considered in the analysis and can be calculated and plotted on a cost-effectiveness plane (Figure 3.2).

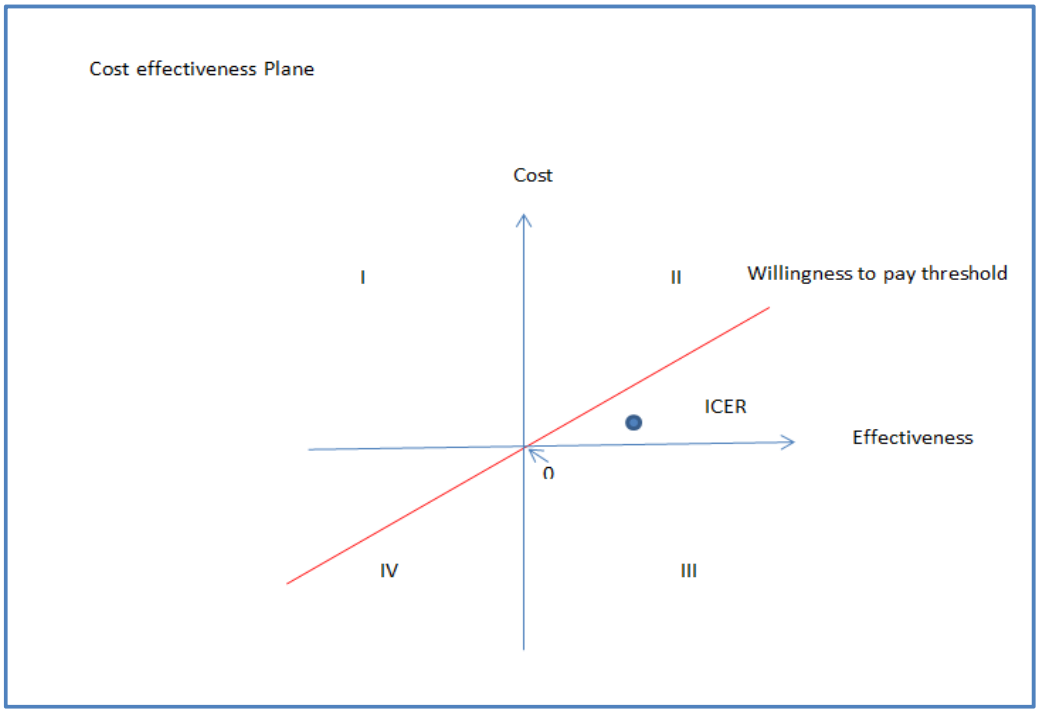

Figure 3.2 The cost-effectiveness plane

In Figure 3.2 the cost-effectiveness plane is divided into four quadrants I, II, III and IV with 0 representing the point of origin which is most often the current position. If the ICER is in Quadrant I or IV the intervention that is being assessed is less effective when compared to the current practice and should not be considered.

If the ICER is in Quadrant IV this means that the new intervention is less costly but still less effective than current practice. The ICER in Quadrant I means that the intervention is not only less effective but costs more than current practice. Both options are not an improvement from current practice in terms of effectiveness and could cause harm to patients and should not be adopted.

Ideally a CEA would generate an ICER in Quadrant III which means that the new intervention is not only more effective than current practice but also less expensive. However most often in cost-effectiveness analyses the ICER falls into Quadrant II where the new intervention is more effective but also more costly. In this scenario decision makers need to consider how much the increased effectiveness is worth. The willingness to pay for an additional health benefit varies depending on a number of factors and will be discussed in detail in section 3.5.3

3.5.2 INTERPRETING THE UNCERTAINTY IN ECONOMIC EVALUATIONS

All economic evaluations are based on the best available information at the time of performing the analysis. A decision needs to be made and the uncertainty surrounding the parameters used to inform the model needs to be considered. This may be done using a few different techniques.

3.5.2.1 **Parameter distributions**

Model parameters are estimates at the very best and the uncertainty surrounding these estimates needs to be quantified. Depending on the type of parameter a suitable distribution may be selected (189).

Once the point estimates with a 95% confidence interval is established these parameters are inputted into the model of choice and the results obtained maybe interpreted using a form of sensitivity analysis. For example probabilities of events occurring will be binomial and take the form of a beta distribution. Costs most commonly would take the form of counts and take either a lognormal or Gamma distribution but uniform distributions may also be considered (9).

3.5.2.2 **One way sensitivity analysis**

One way sensitivity analysis can be helpful to pinpoint which parameters have the highest impact on the final result. One parameter can be varied across a range of values and all other parameters are kept fixed. This information may be presented in a tornado diagram with the parameter with the greatest uncertainty at the top.

3.5.2.3 **Probabilistic sensitivity analysis**

Probabilistic sensitivity analysis is performed to quantify the uncertainty around the final result. To examine the impact of uncertainty on the final results, simulation modelling techniques are used to present uncertainty around the estimates in the analysis. To perform this analysis a simulation technique is undertaken that produces a large number of sets of expected costs and expected effects using parameters drawn at random from a range of values that reflects the uncertainty in each parameter. This can then achieve a range of results as each random draw generates one estimate plotted on the cost-effectiveness plane (Figure 3.3). This output after the probabilistic sensitivity analysis may be plotted on a cost-effectiveness plane as a scatter plot.

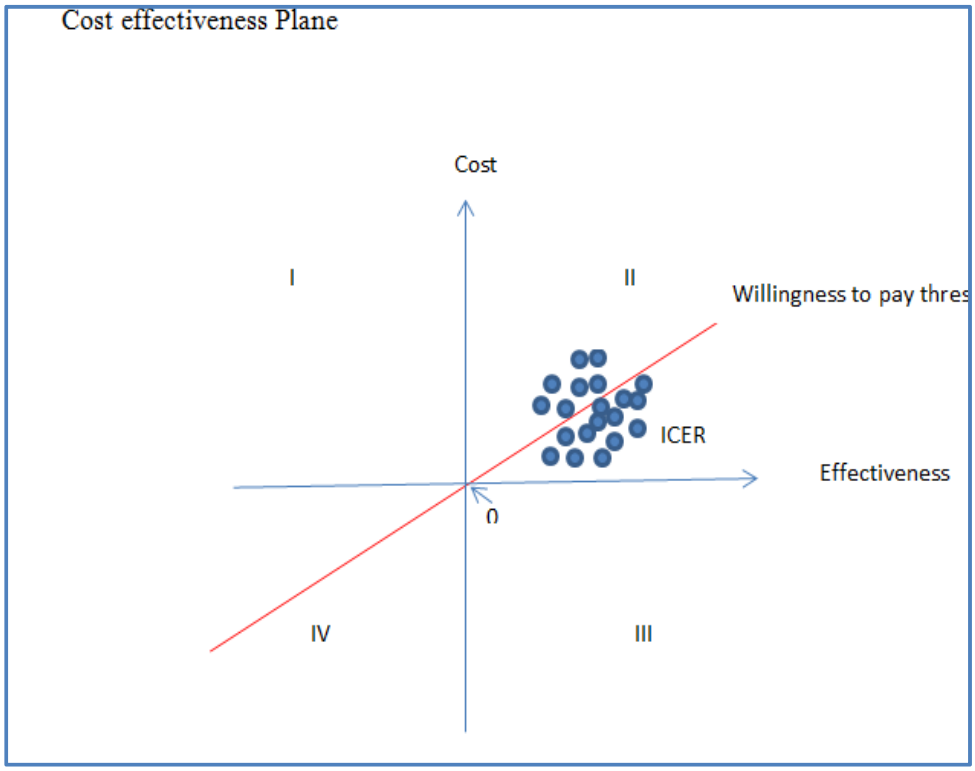

Figure 3.3 The same cost-effectiveness plane with multiple iterations of an ICER known as a scatter plot

In the example above the results of 20 simulations of the probabilistic sensitivity analysis is plotted on a CE plane as a cloud of point estimates from multiple draws from parameter distributions at random. The red line represents the cost per unit of effectiveness decision makers are willing to pay. So values under the red line are cost-effective but values above the red line are not. In this example 13 of 20 simulations were cost-effective, which means this intervention is cost effective 65% of the time.

3.5.3 DECISION MAKING IN THE PRESENCE OF UNCERTAINTY

Once the final results are obtained, a decision needs to be made as to whether the intervention under consideration is cost-effective. To achieve this, a number of factors need to be taken into account. The decision needs to be made even if maximum data is unavailable. The level of uncertainty in the parameters

used in the decision model will reflect the confidence with which the decision can be made. There is also only a finite amount that decision makers are willing to pay for a QALY. This amount may vary depending on the severity of the condition and whether the intervention will improve quality of life, or extend or even save lives(190).

3.5.3.1 **Willingness to pay**

Determining the amount a decision-maker is willing to pay for a defined unit of health is a highly controversial area. Gray 2016 (177) discussed the current controversies on what the cost-effectiveness threshold should be. Australia has not made public a formal cost-effectiveness threshold, but observations suggest that of the studies conducted in 1991-96 that were submitted to the PBAC, that ones under $39,800 were never rejected but studies over $75,300 per life year gained were never accepted. A recent systematic review (190), also alludes to the fact that the willingness to pay threshold for Australia is more transparent than that of some countries. In this review the range of willingness to pay for a QALY in Australia was estimated to be between $50-68,000. The WHO recommended that a cut off for their threshold is one to three times the GDP per capita per disability adjusted life year (DALY). The Australian GDP in 2015 was USD 54,718 which is equivalent to AUD 71,889 today.

Some countries have a flat value that is used for all decision making such as the USA where the CE threshold is $50,000. Other countries the CE varies depending on whether the interventions are for quality improvement or saving lives (190). Shirowa et al(191) in 2013 randomly sampled 2400 respondents on an on-line panel to assess the willingness to pay for one additional QALY for eight patterns of health states. They found that the WTP did change according to the severity of the health state in this analysis. In an earlier study with 5500 respondents the willingness to pay for Australia was calculated as AUD 64,000 based on estimates in 2009 and will be used in this analysis (192). The rationale for using this value is that the societal impact of inappropriate use of antimicrobials will result in a serious economic burden to the healthcare system in Australia if left unaddressed. There is also a global initiative strongly encouraging governments to address the rise in AMR

by developing a national action plan. The reduction of inappropriate use of antimicrobials and in turn addressing AMR is high on the agenda of healthcare initiatives in Australia.

3.5.3.2 Cost-effectiveness acceptability curve (CEAC)

The CEAC represents the decision uncertainty in the cost-effectiveness analysis. In the example below in Figure 3.4 at a willingness to pay of $35,000 the probability of the intervention being cost-effective is 100%. The curve provides the decision maker with information on how confident the decision maker can be that the intervention is cost-effective. The CEAC can be a useful tool for decision makers to graphically review the impact of the investment on the outcome of the intervention.

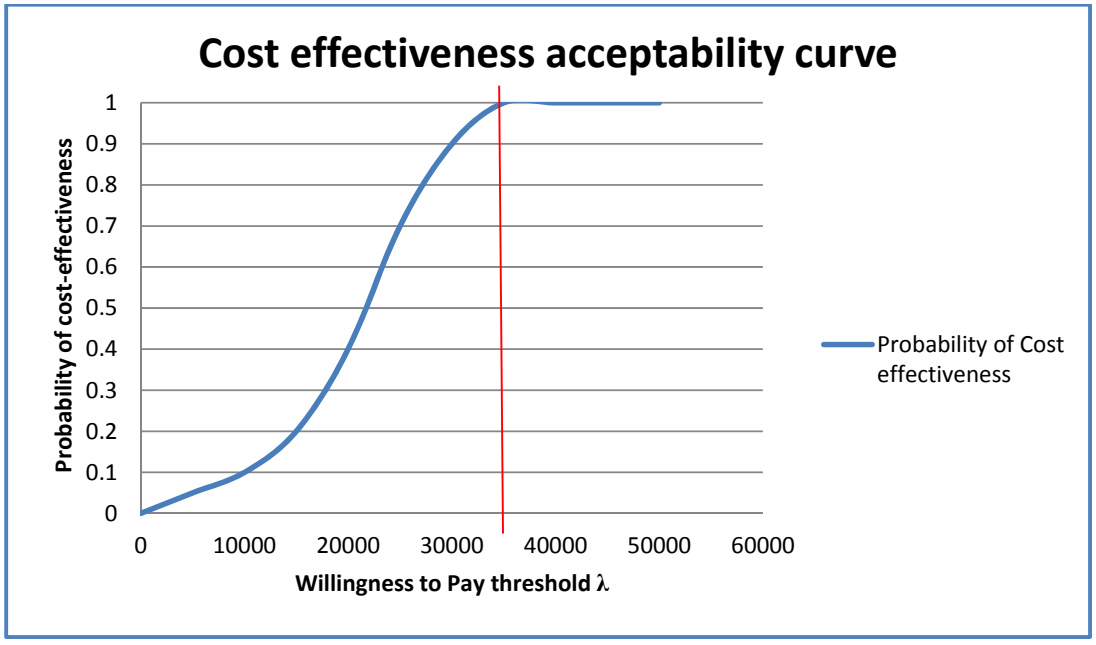

Figure 3.4 The cost-effectiveness acceptability curve

3.5.4 NET MONETARY BENEFIT

The NMB is purely the change in effectiveness multiplied by the willingness to pay for the intervention under consideration. This value needs to be greater than

the change in cost. In other words a program is deemed cost-effective if the NMB is greater than 0. The intervention with the greatest NMB is the most cost-effective.

When considering healthcare interventions this can be expressed as a net health benefit (NHB) where NHB = $\Delta E - (\Delta E/ \lambda)>0$

For a healthcare intervention to be acceptable then the health gain needs to be greater than that in the alternative being considered.

The NMB can be most valuable when the ICER is negative and is difficult to use in healthcare initiatives. A more linear analysis provides better evidence for decision making.

3.5.5 THE COST OF A BED DAY

One of the measurable impacts of a successful AMS intervention is how quickly the patients with BSIs are treated and discharged from hospital without compromising the quality of care. This reduction in LOS in hospital reflects an improvement in patient outcomes and produces a cost saving. The magnitude of this saving depends on the value placed on the cost of a bed day. A recent Australian study valued the economic cost of a non-ICU bed day at $216 AUD based on data collected in 2013 (193). This is in contrast to some economic evaluations using the accounting cost of a bed day for a non-ICU bed of $843 AUD which can make some interventions appear more cost-effective (194). The recent study represents the opportunity cost of a hospital bed day and possibly reflects better the value placed on a bed day by hospital executive. This is because regardless of whether patients occupy a bed or not there will be fixed costs in hospitals that will remain. Using a more conservative estimate for the value of a bed day will allow for a more realistic estimate of the cost savings achieved by the implementation of the AMS intervention at each of the hospitals. For our analysis the cost of a bed day of $216 AUD was used to provide a more moderate approach to the CEA.

3.6 SUMMARY

This chapter has provided a framework for the performance of a CEA on AMS programs and highlights the importance of considering the cost of the intervention in terms of the health benefits gained. An economic evaluation using a decision analytic model allows the decision maker to consider all options and make the best decision in the presence of uncertainty. While AMS programs do little harm a decision needs to be made to establish whether the benefits to patients are worth the funds that are invested. Or could these funds be better invested in an alternative strategy in that healthcare environment to improve patient care.

Chapter 4 provides background information on the two hospitals chosen in this evaluation with regard to each of the strategies used in their AMS intervention and the timeline of the implementation of these strategies. Information on the pre AMS antimicrobial management plan to set the baseline and the workflow of the laboratories at each setting is also provided.

Chapter 4: COMPOSITION OF AMS INTERVENTIONS AT TWO METROPOLITAN HOSPITALS

This chapter presents the composition and the components of the AMS interventions at two Australian metropolitan hospitals. Section 4.1 provides the rationale for the selection of the two Brisbane hospitals for the analysis. Section 4.2 describes the questionnaire that was designed to collect the information required for the analysis from the lead personnel at each of the hospitals evaluated. The information gathered included the composition of antimicrobial management program that existed prior to the introduction of the AMS program which provides the baseline for the economic analysis. It also included information regarding the strategies used in the AMS intervention, as well as the composition in terms of HR of the AMS teams. Section 4.3 presents the AMS interventions at the Royal Brisbane and Women's Hospital (RBWH) and section 4.4 the AMS intervention at the Mater Health Service (MHS). Section 4.5 compares, contrasts and summarises the composition of the interventions, and section 4.6 provides information on the origins of the data sources and section 4.7 describes the data preparation process. Section 4.8 provides a summary of findings.

4.1 RATIONALE FOR THE SELECTION OF THE TWO METROPOLITAN BRISBANE HOSPITALS

The overall objective of this research is to evaluate the cost-effectiveness of AMS interventions in the metropolitan hospital setting in Australia with a view that this model would be generalisable to other similar Australian hospitals. The two hospitals included in the evaluation are different from each other, firstly in size, in the way they are funded and governed and the case-mix of patients and services provided. These factors were thought to have an impact on the efficiency and effectiveness of the intervention in each setting.

RBWH is a 1024 bed teaching hospital, which is the largest tertiary referral hospital in Queensland, Australia. The RBWH belongs to one of 16 Hospital and Health Services and provides a large range of services. The Mater Adult Public Hospital has 197 beds is jointly funded by Queensland government grants and revenue generated by the Mater private hospitals and is governed by an executive committee of 12. The Mater Hospitals are owned and operated by the Mater Health Services, originally established by the Sisters of Mercy in Brisbane but in 2013 transferred to Mercy Partners Catholic Ministry. The Mater hospital provides a range of medical, surgical and oncology services.

The types of strategies used for AMS at each setting depends upon the laboratory providing the service to the hospital, the management structure of the hospital administration and the funding allocated to the AMS intervention. AMS interventions need to be tailored to each specific hospital depending on their size, geographical location and complexity of patient case mix.

4.2 DESIGN OF QUESTIONNAIRE AS A DATA GATHERING TOOL

The questionnaire was sent to the lead personnel of the AMS program, the Infectious Diseases (ID) Physician, the Clinical Microbiologist, the Microbiology Laboratory Manager and Director of Pharmacy at each hospital. It contained a series of questions pertaining to laboratory practice, antimicrobials utilised in each environment and reporting practices pre and post each of the strategies implemented as part of their AMS intervention (See Appendix C). Information was requested about the timeline of the intervention, the composition of the core AMS team (including the proportion of Full-time Equivalents (FTE) and additional resources dedicated to this service), and any support tools or technology used in conjunction with the intervention. Respondents were also asked to detail any barriers to the implementation of the program.

The survey tool consisted of tables listing organisms included in the analysis and lists of empirical and targeted therapy for BSIs caused by the most common pathogens. The ESKAPE pathogens are defined by the IDSA as the main pathogens that cause resistant infections in healthcare environments (15). The AMS team was

asked to comment on any differences to the listed antimicrobials at their specific institution. Only the antimicrobials used to treat ESKAPE organisms were taken into account for the costing component of antimicrobial usage in defined daily doses (DDD)/1000 occupied bed days (OBDs).

The impact of new technology in the form of the MALDI-TOF instrument with regard to cost, hours of operation, timing from positive report to delivery of result to treating clinician and methods of communication of positive blood culture results were gathered using the survey tool. Information was gathered pre- and post-AMS intervention to identify the differences in cost.

To ascertain the cost of the AMS intervention, information related to the composition of the AMS team and the dedicated hours for each member of the team and their wage rates were gathered. Information regarding the composition of the AMS committee and the duration and frequency of the meetings were also requested. Details of any AMS tools such as CDSSs and other resources consumed as part of the AMS program were also requested.

The purpose of the questionnaire was to gather detailed information at each of the hospitals evaluated so that an accurate cost of the AMS intervention and the rapid diagnostics used could be ascertained and included as part of the analysis. The summary of the information received for each of the hospitals included in the analysis are presented in the following sections.

4.3 HOSPITAL SETTING 1: ROYAL BRISBANE AND WOMEN'S HOSPITAL (RBWH)

RBWH has a staff of 1031 doctors, 3167 nurses and 932 health practitioners as at the end of March 2015. The hospital offers a range of specialities including medicine, surgery, orthopaedics, psychiatry, oncology, transplantation, obstetrics, gynaecological, neonatal and trauma services.

The RBWH is a leader in the provision of patient care and general medical and surgical services to the community in Brisbane. The RBWH is one of five hospitals that belong to the Metro North Hospital and Health Services (MNHHS). In

Queensland, public hospitals are governed by the Hospital and Health services (HHS) and are divided into 16 individual boards across the State.

4.3.1 ANTIMICROBIAL MANAGEMENT PRIOR TO AMS

Prior to the AMS intervention the adherence to core activities set out by the ACQSHC was well established at the RBWH. All clinicians had access to the Therapeutic Guidelines – Antibiotic and some formulary restriction and selective reporting from the laboratory had been in place for some time. However, reviewing of prescribing and direct feedback to the prescribers was only occurring on a regular basis in ICU and not in a structured format in the general wards.

At the time of the AMS intervention a new initiative the "hospital in the home" program had also commenced and patients that were able to be sent home for IV treatment were included as part of this program. Staff from the hospital visited patients in their homes, reducing the time spent in hospital for these patients and reducing the potential risk of acquisition of hospital acquired infections. The clinicians at the RBWH had access to up-to-date antibiograms for their specific wards for some time prior to the AMS intervention. The system in place to obtain approval for restricted antimicrobials was in the form of a pager managed by the infectious diseases physicians and was considered quite labour-intensive but functional.

The RBWH AMS initiative was fully supported by the management team at the hospital through funding received from a business case that was approved for this purpose. The funding was approved for staff, Information technology (IT) licence and annual support fee and total non-recurrent funding for the integration and training costs, for the CDSS Guidance MS (GMS).

4.3.2 COMPOSITION OF THE AMS INTERVENTION

The core elements of the AMS intervention at the RBWH consisted of an AMS team and an AMS committee and the intervention commenced in March 2012. There was a staged introduction of a number of strategies that formed the AMS intervention at the RBWH and is represented schematically in Figure 4.1. The committee met every second month for the duration of 1.5 hours. Stage one of the AMS intervention was formulary restriction for fluoroquinolones and carbapenem

antimicrobials. Approval was obtained by a laborious manual system of paging/calling the infectious diseases physician on call and emailing a central pharmacy email (ICU, haematology and neonates were exempt). For the analysis of the intervention at the RBWH, a 9 month dataset 14 months after the implementation of the intervention was collected to assess this phase of the intervention from May 2013 to Feb 2014 (9 month data set). The AMS intervention at the RBWH was formalised with the implementation of the CDSS hospital wide excluding ICU and haematology oncology wards in February 2014. Data for this part of the evaluation was collected 6 months after the implementation of the CDSS at the RBWH from August to December 2014 (a 4 month dataset).

Along with the implementation of the CDSS a number of antimicrobial restrictions were also implemented which helped to reduce use. Guidance MS was used to enforce the restrictions as well as provide education to junior staff. The Red/Yellow/Green (R/Y/G) 'traffic-light' system was used at this time. R needed infectious diseases physician approval in all cases, Y meant that the antimicrobial could only be prescribed for certain agreed indications listed in Guidance MS and an approval code needed to be generated from the system, and G had no restrictions. Some antibiotics that had an overlap in spectrum for example, dicloxacillin oral were retained and flucloxacillin and cephalothin were removed from stock. These changes were part of a strategy to streamline antimicrobial use at the hospital.

There were some significant reductions in antimicrobial utilisation noted following the AMS intervention. They were in particular gentamicin usage which was restricted to 24 hour use only, and amoxycillin-clavulanic acid usage which became yellow listed. There was also a notable increase in the prescribing of green antibiotics, showing a shift to narrow spectrum prescribing. The AMS ward rounds occurred each day, Monday to Friday on all non-exempt wards of the hospital. This was a marked improvement to the service provided previously to non-ICU wards.

In addition rapid diagnostics was introduced in the microbiology laboratory with the implementation of the MALDI-TOF instrument in November 2012. A dataset collected 6 months after the implementation of the MALDI-TOF instrument represents the combination of strategies of AMS and rapid diagnostics and was

collected to include May 2013 to February 2014(9 month data set). Pathology Queensland Central laboratory a large referral centre is located at the Herston campus at the RBWH and provides the major component of microbiology services to the RBWH and other hospitals with centralised pathology services across Brisbane.

4.3.3 WORKFLOW IN THE LABORATORY

The hours of operation at the Pathology Queensland Central Microbiology Laboratory at RBWH, is 24 hours, seven days a week and has been consistent throughout and prior to the AMS intervention. The impact of accurate and rapid results reaching the prescribing clinician is paramount for the effective management of BSIs. Therefore, the process undertaken to report a positive blood culture result from detection by the blood culture system to being reported to the treating team is crucial. At the RBWH, between the hours of 0800-1700 Monday to Friday and 0900-1200 Saturday and public holidays a clinical microbiology registrar telephones all positive blood cultures to the treating team and is able to provide clinical advice on antimicrobial treatment. Outside these hours results are communicated via telephone by scientific staff in the laboratory without clinical advice. Follow up calls are made to the treating team if identification and susceptibility results are unexpected and this may require a change to therapy. There is an on-call infectious disease service for after-hours queries regarding treatment options.

Before the AMS intervention, the same day results for a positive blood culture specimen are a Gram stain (1 hour) to decipher if the organism is GP or GN, and a tube coagulase test (within 4 hours) to differentiate *S. aureus* from other Staphylococcal *species*. The time taken for the identification of a GP organism is 8 hours and a GN organism is 6-8 hours.

The major change to the workflow was achieved by the introduction of the MALDI-TOF instrument to perform identification tests in the microbiology laboratory in November 2012, not long after the preliminary AMS intervention was rolled out. This instrument significantly changed the workflow of the laboratory by

changing the turnaround time for identification of both GP and GN organisms to less than an hour from setting up the test.

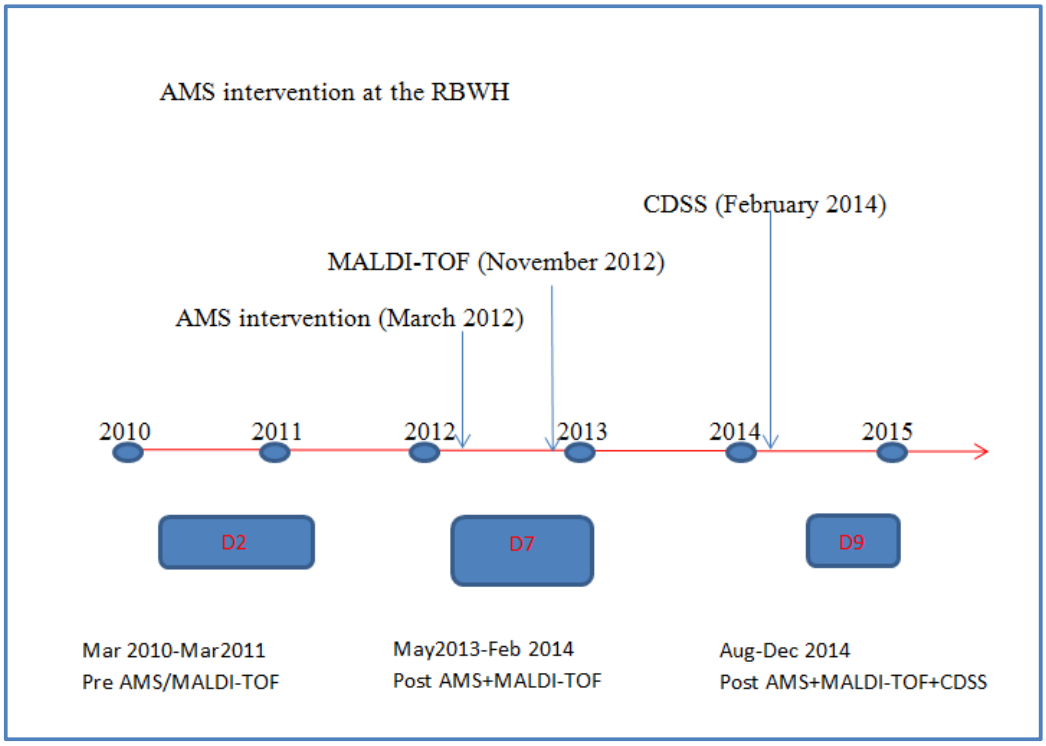

Figure 4.1 The AMS intervention at the RBWH

The impact of this new technology is that the identification results are made available significantly earlier. The identification of all organisms was available 5-12 hours from when the blood culture is flagged positive. The largest impact is for GN organisms as a significant amount of information regarding the selection of empirical treatment can be obtained from an organism's identification. In the case of the group of GN organisms belonging to the group *Enterobacteriaceae,* Enterobacter *species* are more resistant than say an *E. coli* and while Ampicillin and first generation cephalosporins are generally effective in the case of *E coli* this is not the case with Enterobacter *species*. *K pneumoniae* for example is intrinsically resistant to Ampicillin and the identification can provide timely information for therapy. In GP organisms *Enterococcus faecium* is usually resistant to ampicillin whereas ampicillin is the treatment of choice for *Enterococcus faecalis*. The

identification of the organism can be very valuable in selecting empirical therapy and switching to targeted therapy sooner.

4.3.4 PRELIMINARY EVALUATIONS

Following the implementation of the intervention a report was compiled by an external body to assess the impact of the intervention from an antimicrobial usage and cost point of view(195). The MedTRx system extracts dispensing and distribution data from pharmacy databases and produces a rate of antimicrobial utilisation as DDD per 1000 OBDs for Queensland Hospitals. The data is captured and categorised into total for smaller hospitals and non-ICU and ICU categories for larger facilities. The MedTRx system was used to capture the antimicrobial usage figures for the period between Jan 2010 to May 2014 for the RBWH. This report confirmed a steady decline in antimicrobial usage since the commencement of the AMS intervention and a related reduction in cost represented in Figure 4.2.

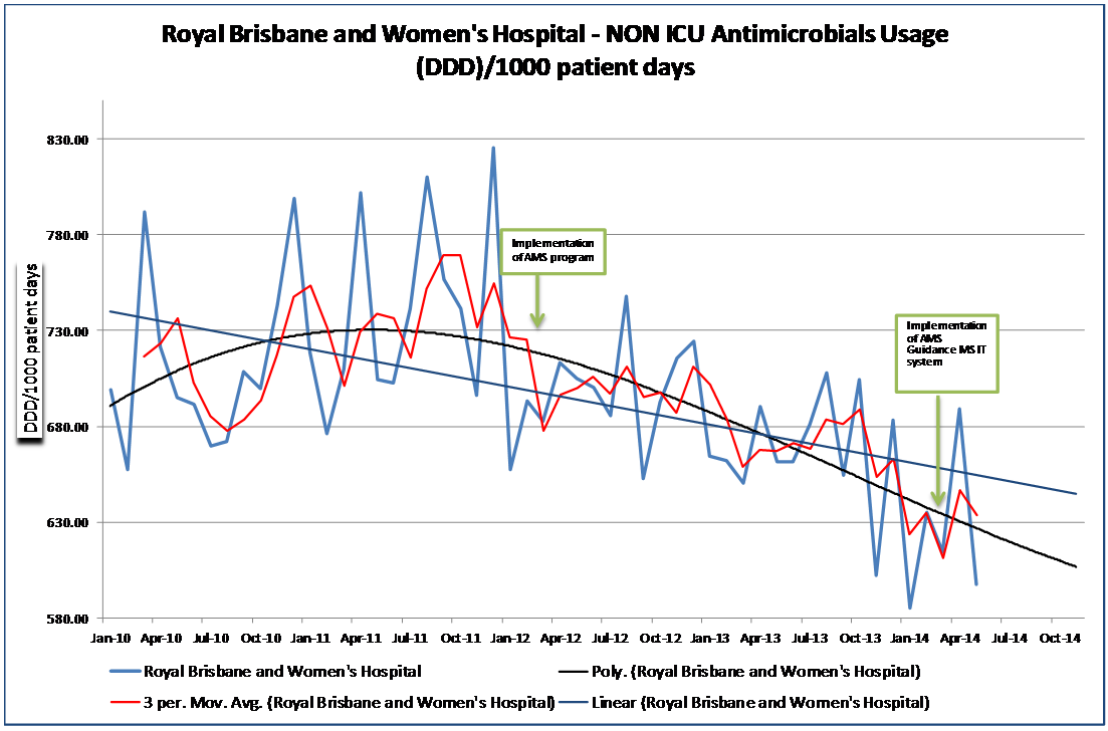

Figure 4.2 Illustrates the step change in the average monthly utilisation of antimicrobials DDD/1000 OBD for RBWH for the period January 2010 to May 2014 (extracted from the post implementation review of the AMS program at the RBWH report with consent (195))

Antimicrobial utilisation rates provided in this report are for inpatients calculated using the number of DDD of the antimicrobial agent, or class, consumed each month per 1,000 occupied bed days (OBD). DDD/1000 OBD is the internationally accepted standard that enables comparison of usage data for antimicrobial agents. This independent evaluation found that the AMS intervention at the RBWH was cost saving in the non ICU setting. The ICU antimicrobial usage was not included in this analysis as the AMS intervention was only rolled out in the non ICU setting. When this cost savings was monetised using a constant drug cost to determine a notional savings it was found to be equal to $379,000 since the implementation of the AMS intervention at that hospital (195). Since the majority of antimicrobials are used in ICU patients it is predicted that once the AMS intervention is rolled out in ICU there would be larger cost savings to be achieved.

This analysis was performed independent to this thesis and only took into consideration the cost saved due to antimicrobial utilisation. However, the cost of the AMS intervention was not included in this analysis.

4.4 HOSPITAL SETTING 2: MATER HEALTH SERVICE (MHS)

The Mater Adult Public Hospital was established in 1911 to provide care to the Brisbane community. The Mater Adult Hospital has 197 beds, and the number of ICU beds prior to May 2015 was 11 but has expanded to 16 since then. The hospital provides 63 surgical beds, 91 medical beds and 27 haematology/oncology beds.

4.4.1 ANTIMICROBIAL MANAGEMENT PRIOR TO THE AMS INTERVENTION

At the MHS adherence to core activities set out by the ACQSHC prior to the implementation of AMS was reasonably well established. The prescribers were able to access the Therapeutic Guidelines – Antibiotic; formulary restrictions existed on specific antibiotics such as linezolid, daptomycin and ertapenem but relied on self-regulated clinician compliance. No enforcement or monitoring of compliance with the antimicrobial restrictions or any AMS based approval system, was in place prior to the implementation of the AMS program. However the use of antimicrobials that

was not on formulary required approval from the director of the infectious diseases service.

Weekly infectious disease ward rounds in ICU where antibiotics were reviewed and modified were in place prior to AMS. On the general wards, feedback regarding antibiotic prescribing was only provided on patients referred to the infectious diseases service for consultation. The infectious disease consultants were available on-call 24 hours, seven days a week for antibiotic advice.

Education regarding appropriate use of antimicrobials had commenced with grand round presentations related to infectious diseases cases and associated discussion around antimicrobial prescribing. Infectious diseases and microbiology registrars presented at the journal club and "bug of the week" discussions for continuing education. Tutorials were also conducted to medical students and interns on basic prescribing principles several times a year based on a teaching roster. Therapeutic drug monitoring and dose adjustment advice was provided by Pharmacy for aminoglycosides and vancomycin. Recommendations to adjust dosing towards published or local guidelines were conducted as a standard clinical pharmacist activity only. Prior to AMS infectious diseases involvement in dose optimisation occurred only during consultation either by telephone or ward consultation.

4.4.2 MHS: COMPOSITION OF AMS INTERVENTION

The information gathered from the questionnaire sent to the AMS lead indicated that the AMS intervention at the MHS gained executive support and appropriate funding has been ongoing. The AMS program at the MHS has generally experienced good engagement with prescribers but also some opposition to change. Strong executive support has meant that this has not become a significant barrier to implementation of the program. The AMS intervention at this hospital was implemented in stages with a more formalised intervention being implemented in August 2013 (Figure 4.3). Initial work focussed on the hospital-wide point prevalence study and subsequent awareness sessions with clinical staff across the campus.

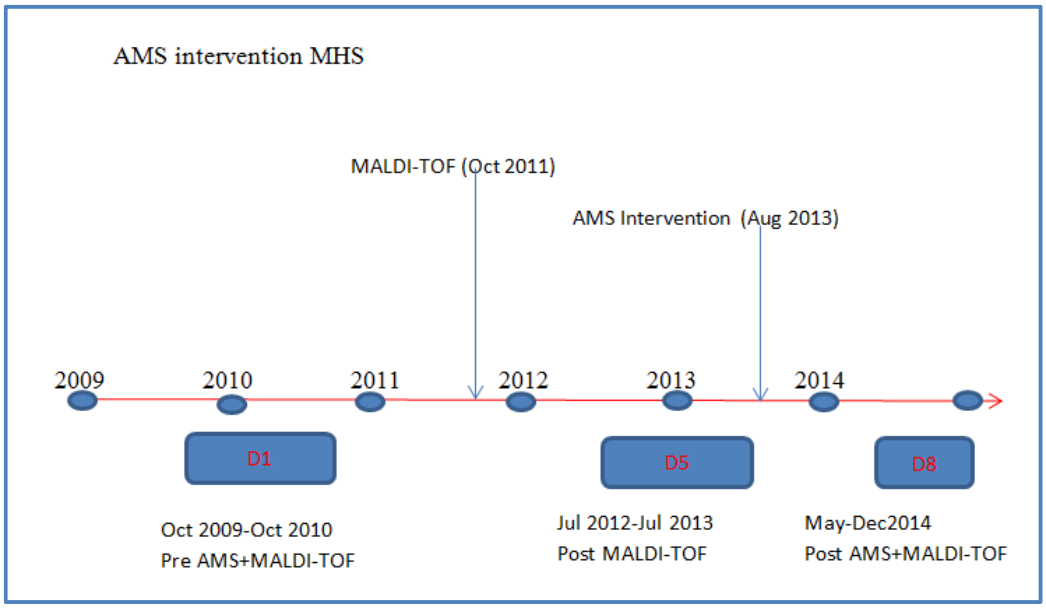

Figure 4.3 The AMS intervention at the MHS

From the results of that study, work was focussed towards the development of local guidelines in the area of urinary tract infection management and on the implementation of enforced restriction of meropenem. The surgical prophylaxis point prevalence study was completed in March 2014 and discussions and awareness sessions were held with prescribers and other key stakeholders. Activities focussed on improving documentation of antimicrobial administration in procedural areas and on further guideline development. Grand round education sessions were conducted twice per year, intern education conducted 4 times a year and education sessions for clinical pharmacists were conducted as required.

AMS ward rounds were commenced in the inpatient medical wards as a once weekly activity whereas at RBWH these AMS ward rounds occurred every week day. A database for collection and subsequent analysis of the effectiveness of this intervention was created by the IT specialists in Pharmacy. Gentamicin and meropenem audits were started in response to consideration of the National Antimicrobial Utilisation Surveillance Program (NAUSP) data which indicated a trend to increased utilisation rates in these antimicrobials by the AMS Working Party.

A MALDI-TOF platform to perform identification tests in the microbiology laboratory had been established in October 2011 which was prior to the AMS intervention. This instrument significantly changed the workflow of the laboratory by changing the turnaround time for identification of both GP and GN organisms to less than an hour from when a culture was available. The impact of this new technology is that the identification results were made available significantly earlier. The identification of most organisms was made available 5-12 hours from when the blood culture was flagged positive.

4.4.3 WORKFLOW IN THE LABORATORY

Mater Pathology is located on site at the MHS and the hours of operation of the Microbiology laboratory increased to 24 hours 7 day a week in July 2013 just before the AMS intervention was implemented. This is different to the RBWH as their laboratory operating hours had been 24-hours 7 days a week prior to the implementation of the AMS intervention.

The introduction of the MALDI-TOF prior to the AMS intervention at this hospital will provide the unique opportunity for the analysis of the impact of the rapid diagnostics without an AMS intervention at this hospital. There is evidence in the literature that rapid diagnostics in the laboratory without effective delivery of results to prescribing clinicians would not be of benefit to patient outcomes (49). At MHS, in July 2013 the opening hours of the laboratory became 24 hours a day 7 days a week, prior to this date the laboratory hours were 0730 – 2215 each week day. The treating clinician at MHS was contacted when Gram stain result were available and a follow up call made if additional information from direct testing such as positive tube coagulase, or culture reveals unexpected findings. Before the AMS intervention the same day results were the Tube coagulase test (within 4 hours), and the pneumococcal test (15 minutes).

4.4.4 PRELIMINARY EVALUATIONS

There were no independent evaluations performed by an external body at the MHS.

4.5 COMPARISON OF THE STRATEGIES USED AT EACH OF THE HOSPITALS

Table 4.1 summarises each of the interventions at both the hospitals in terms of resources used and the composition of the interventions.

Table 4.1 Summary of the AMS intervention at each of the hospitals

AMS initiative and related details	RBWH	MHS
Number of Beds	• General ward beds: 960 • ICU 26 beds	• ICU – 11 beds until May 2015, then expanded to 16 beds • Surgical – 63 • Medical – 91 (plus 27 haematology/oncology)
AMS Team **Recommendation ACSQHC** **Every 100 acute beds 0.3 FTE senior pharmacist and 0.1FTE lead clinician dedicated to AMS activities**	• ID Physician 0.3 FTE • AMS Pharmacist 0.6 FTE	• ID Physician 0.2 FTE + 0.05 FTE • AMS Pharmacist 1.0 FTE +0.05 FTE • Clinical Microbiologist 0.05 FTE • IT specialist 0.01 FTE • ICP (Infection Control) 0.1 FTE
AMS Committee	• Met every two months for 1.5hrs = 9hrs per year • Cost = $8182 • Personnel (11) • ID physician MO1 • ID physician MO4 • Clinical pharmacists HP5 • Clinical microbiologist MO4 • IT specialist AO7/AO8 • Hospital administrator MO4 • Infection control practitioner • 4x senior medical officers MO3	• Met every month for an hour = 12hrs per year • Cost $32,000 • Personnel (21) • 3x ID Physician • 1x AMS Pharmacist • 1x Clinical Microbiologist • 1x IT specialist • 1x Hospital Administrator • 1x Infection control practitioner • 3x Director of Nursing/Assist. Directors • 2x Director of Pharmacy/Assist. Director • 8x Senior Medical Staff (various

		specialties)
AMS intervention	• Started March 2012 • June 2013 interim approvals required for carbapenems and fluoroquinolones • Gentamicin usage restricted to 24 hours use only • Augmentin usage became yellow listed. • IV azithromycin was added to list which needed ID approval in all cases (except for ED first dose for severe pneumonia or ICU admission). • February 2014 daily AMS ward rounds Monday to Friday on all wards of the hospital • February 2014 Guidance MS (GMS) • The R/Y/G list in GMS where R needed infectious diseases (ID) approval in all cases, Y meant that it could only be prescribed for certain agreed indications listed in GMS and an approval code needed to be generated from the system and G had no restrictions.	• Started August 2012 • February 2014, Meropenem prescribing beyond 24hours requires ID/Micro approval. • As of Sept 2015, Gentamicin prescribing beyond 24 hours will also require ID/Micro approval for adult patients • AMS ward rounds are conducted weekly (Wednesdays) on general medical wards only - currently a pilot program introduced in May 2015 (after data collection) • ICU/ID wards rounds have been increased to twice weekly (Monday/Thurs) as of August 2015(not included in the data collected for this analysis).

The main differences in the two settings were that at the RBWH the intervention employed less than the recommended number of infectious disease (ID) physicians (0.3FTE) and AMS pharmacists (0.6FTE). The recommended number for that size of hospital was 1.0 FTE ID physician and 3.0 FTE senior pharmacists. At the MHS the AMS team consisted of slightly more than the recommended number of personnel (0.2FTE ID physician and 1FTE AMS pharmacist). For the MHS the

recommended number was 0.2FTE ID physician and 0.6FTE AMS pharmacist. The intervention at the MHS also started 5 months later and was implemented in a less formalised manner. The AMS team was also larger at the MHS but the AMS ward rounds were less frequent (weekly at MHS and daily at RBWH).

4.6 DATA SOURCES AND METHODOLOGY TO MEASURE IMPACT OF AMS INTERVENTIONS

To measure the impact of the AMS intervention at each of the hospitals the cost of each intervention needed to be gathered in as much detail as possible. Information regarding the composition of the AMS team and hours of contribution of each team member needed to be quantified in terms of cost. The information on the antimicrobials used for the treatment of BSI at each hospital was derived from the answers to the questionnaire by the ID physician and director of pharmacy at each hospital.

The second component to determine the impact of the intervention is the detailed collection of information on the clinical impact of the intervention. At both hospitals the laboratory information system (LIS) was used to access all positive BSI for each of the pre and post intervention periods as detailed in Figure 4.1 and Figure 4.3 above.

HR costs for both hospitals were calculated using the wage rates from Queensland Health (Appendix B). These rates were used to calculate the cost per annum for the intervention in total at both hospitals in terms of HR. The MHS provided a unit cost for their AMS Committee and AMS Steering Committee.

At the RBWH, the amount of antimicrobials used for each intervention period was obtained from the QH database MedTRx which collects information from the iPharmacy database on antimicrobial usage in terms of DDDs. The cost of each antimicrobial used for the treatment of ESKAPE organisms were estimated using the information provided by the RBWH pharmacy. The average dose for an 80kg person was used in the calculation of the DDD per OBDs.

All BSIs during the designated periods before and after each bundle of strategies (AMS intervention) were collected. This data was retrieved

retrospectively from the LIS which at the RBWH is AUSLAB. The AMS intervention at the RBWH was implemented in its initial form in March 2012. The pre AMS dataset was collected 2 years prior to the AMS intervention and consisted of 12 months of BSI data (March 2010-2011). The next strategy implemented at the RBWH was the MALDI-TOF instrument in November 2012 (8 months after the AMS intervention). This period (D7 in Figure 4.1) included all data from May 2013 to Feb 2014 for evaluation of the impact of the AMS intervention including rapid diagnostics. To capture the impact of both these interventions meant collecting data 15 months after the AMS intervention was implemented and only 6 months after the MALDI-TOF system was in place. The CDSS was implemented at the RBWH in February 2014 and D9 (Figure 4.1) represents the data collected from August to December 2014, six months after the implementation of this system. This dataset was the smallest in this analysis as the lag period of acquiring the admission and discharge data from the Queensland Health Admitted Patient Data Collection (QHAPDC) database was 6 months. This issue made it difficult to extend the data collection beyond this point. The data collection and linkage for the RBWH was completed in July 2015.

As for the RBWH, at the MHS all bloodstream infections during the designated periods before and after each bundle of strategies (AMS intervention) were collected. This data was retrieved retrospectively from the Laboratory Information System (LIS) which at MHS is Kestrel. The AMS intervention at the MHS was implemented in August 2013, but prior to this in October 2011 the MALDI-TOF system had been implemented in the laboratory. Data for the Pre AMS and MALDI-TOF scenario was collected two years prior to the implementation of MALDI-TOF and greater than three years prior to the implementation of AMS at the MHS. D1 which was the Pre AMS+ MALDI-TOF dataset was from October 2009-October 2010, included a full 12 months of data (Figure 4.3). The second dataset D5 was collected 9 months after the implementation of MALDI-TOF July 2012-July 2013 and consisted of 12 months of BSI data. D8 was collected 9 months after AMS was implemented at the MHS from May 2014-Dec 2014. This dataset consisted of 7 months of BSI data and was the smallest dataset in this setting. Original data for the periods requested

were sent by the Mater LIS team as de-identified blood stream infections with a unique identification number for each individual patient including the dates of blood culture collection, organisms isolated with their susceptibilities.

These datasets were then sent to QHAPDC where this information was used to find the corresponding patient admission and discharge information for each unique identifier provided. Patient information such as LOS, mortality, ward and outcome for each patient with a BSI was extracted.

4.7 DATA PREPARATION, CLEANING AND LINKAGE

This research focused on obtaining reliable primary data on BSIs from each hospital laboratory database and then linking this de-identified patient data with admission and discharge information. This involved acquiring ethics approvals from the QUT Research Ethics Unit, each individual Health Research Ethics Committees (HREC) at each hospital included in this evaluation. This process required individual ethics applications to be signed off by their respective executives and departmental heads. The AUSLAB data request form was signed off by the Director of the State-wide Microbiology Service prior to submission to the Laboratory Information Systems and Solutions (LISS) where it was signed off by the executive director of Pathology Queensland. A similar process was undertaken for the access to laboratory data at the MHS.

The laboratory data needed to be linked with patient admission and discharge data to decipher age, sex, discharge status, length of hospital stay and ward for the individual patients included in the analysis. To procure this information the Public Health Act (PHA) from 2006 required a formal application approved by the Director-General. The PHA application was prepared with the assistance of the data custodians of each jurisdiction. Following this approval, the required patient demographics pertaining to each of the patients with a BSI in the period of interest was extracted from the QHAPDC database. Approval was obtained from the following Ethics Committees and Gatekeepers to access hospital data from RBWH and the Mater Health Service (letters attached in Appendix A).

1. Queensland Government Department of Health, Health and Medical Human Research Ethics Committee, HREC reference number: HREC/13/QHC/33, approved 3 September 2013.

2. Queensland University of Technology, University Human Research Ethics Committee, UHREC reference number: 1300000719, approved 12 November 2013.

3. Queensland Government Department of Health, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Research Governance HREC/13/QHC/33 approved 25 November 2013.

4. Queensland Government Department of Health, Release of Confidential Information for the Purposes of Research under the provision of Section 280 of the Public Health Act 2005, reference RD004843, approved 12 December 2013.

5. Queensland Government Department of Health, Release of Confidential Information for the Purposes of Research under the provision of Section 280 of the Public Health Act 2005, reference RD004844, amendment approved by data custodian 6 July 2015.

In addition to the Queensland Government approvals listed above, an approval was obtained from the MHS (Letter attached at Appendix A).

1. Mater Health Service & Mater Medical Research Institute, Site Specific Assessment Authorisation, Mater Research Governance reference: RG-80A, approved 20 February 2014.

The dataset selection for the analysis was based on when each of the AMS strategies were implemented at each hospital under consideration as well as the timeline for the completion of this research (The RBWH Figure 4.1 and the MHS Figure 4.3.). Ideally the intervention was allowed 12 months or greater to establish prior to data collection. A dataset would include 12 months of data where possible for analysis. This was not always possible due to the timeline of the interventions. The lag of 6 months to the availability of admission and discharge data from QHAPDC once the data was collected from the laboratory information system (LIS) was also a factor to be taken into consideration when selecting the datasets for the analysis.

Following ethics approval the Bloodstream infection data from the LIS from both hospitals were extracted from two different systems, at the RBWH (AUSLAB) and MHS (Kestrel). The data was presented in slightly different formats and contained positive blood cultures for stipulated periods, pre and post intervention. Microbiological information as to the type of organisms isolated and their susceptibility to relevant antimicrobials were provided.

The two datasets were linked using the program R by the unique identifier and blood culture collection dates. The linked files were then manually examined to only include adult inpatients (i.e. patients in hospital for >48 hours) with only one unique organism for each date of collection if multiple blood cultures were collected. Organisms were then grouped into categories first if they were significant (ESKAPE pathogens, Anaerobes or Candida *species*) or non-significant. If poly-microbial cultures were encountered these were classified into a mixed category.

In our patient cohort, the number of BSIs that were largest belonged to the ESKAPE organisms that cause the majority of significant infections in hospitals. GP significant organisms that were either MRSA or VRE were further classified as GPR, and GN significant organisms that were classified as extended spectrum beta-lactamase producers (ESBLs) or carbapenem resistant organisms were classified as GNR.

4.8 SUMMARY

Each hospital had a well-established formulary and local guidelines derived from the Therapeutic Guidelines – Antibiotic prior to the implementation of the AMS intervention. RBWH is larger with approximately 1000 beds and the MHS with approximately 200 beds. In Australia, the ASQHSC guidelines recommend that at the bare minimum the AMS team needs 0.3 Full-Time Equivalents (FTE) senior pharmacists, and 0.1 FTE infectious diseases (ID) physician or lead clinician for every 100 acute beds. The MHS complied with these guidelines with slightly more than the required number of AMS pharmacist FTE easily meeting the requirement. The

RBWH however, fell short of meeting the requirement by 0.7 FTE ID physician and 2.0 FTE pharmacists.

Another major difference in the AMS strategies used at the RBWH compared to the MHS was the introduction of a daily AMS ward round in all wards of the hospital as opposed to a weekly ward round in general wards and twice a week in ICU at the MHS. Also, RBWH enforced more antimicrobial restrictions earlier in the intervention when compared to the MHS. The CDSS also had a structured list of antimicrobials on the red, yellow and green list and was managed via the CDSS.

Chapter 5 uses the information provided in the questionnaire for the HR component, the rapid diagnostics implemented in the laboratory and the antimicrobial usage at each hospital to cost each of the interventions.

Chapter 5: **COSTING OF AMS INTERVENTIONS**

This chapter presents the process of costing of the AMS interventions. Section 5.1 presents the cost information for the intervention at the RBWH and 5.2 the cost information for the intervention at the MHS. Section 5.3 provides a comparison of the costs of the two interventions including the additional tools used at each of the hospitals. And finally Section 5.4 provides a summary of the cost of AMS at both hospitals in terms of the human resource use, antimicrobial usage, and laboratory expenditure.

5.1 THE RBWH

To estimate the cost of the AMS interventions, the information from the questionnaire was used to allocate the hours each member of the team spent of their FTE hours on AMS activities. Table 5.1 lists the role of each member of the team and Queensland Health Wage rates as of 2015 were used to calculate the cost per annum for the intervention in total. The core AMS team was estimated to cost $133,439 in HR costs alone. The AMS committee met every two months for 2hrs at a time and as such based on a 40 hour week the FTE for each member of the committee was estimated to be 0.0043 per annum. The cost of the AMS committee was estimated to be $8181.70. The cost of additional resources for training was estimated at $1200 (by the AMS team) and the CDSS used at the RBWH was estimated at $26,298.40 per annum, the total intervention cost $169,118.70 (Table 5.1).

The new technology introduced into the laboratory soon after the implementation of the AMS intervention was part of the strategy used at the RBWH to improve patient care through delivery of organism identification in a much shorter time. This reduction in time to identification allows for the selection of more

appropriate antimicrobials for the treatment of patients with BSIs and other serious infections.

Table 5.1 Detailed costs of the AMS intervention at the RBWH (2015 QH wage rates)

Elements	HR	FTE	Cost per annum AUD
AMS team	ID physician	0.3	$49,988.10
	Pharmacist	0.6	$67,121.10
	Clinical microbiologist	0.1	$16,329.40
			$133,438.60
AMS committee	ID physician MO1	0.0043	$702.16
	ID physician MO4	0.0043	$883.37
	Clinical pharmacists HP5	0.0043	$481.02
	Clinical microbiologist MO4	0.0043	$883.37
	IT specialist AO7/AO8	0.0043	$481.08
	Hospital administrator MO4	0.0043	$883.37
	Infection control practitioner	0.0043	$463.50
	4x senior medical officers MO3	0.0043	$3,403.83
			$8,181.70
Training resources			**$1,200**
Decision Support System	Instrumentation discounted over 10 years	$33,744.91/10years	$3,374.40
	License and set up fee over 10 years	$69200 +GST =$76120/10	$7,612
	Annual support fee	$13920 + GST=$15312	$15,312
			$26,298.40
Total cost			**$169,118.70**

Prior to the implementation of the AMS intervention and for some months after, the laboratory performed identification and susceptibility testing using the Vitek 2XL instrument. All throughout the intervention at the RBWH the methods used to perform susceptibility testing did not change and as such were not included in the analysis. Table 5.2 provides detailed information on the cost of the Vitek 2XL identification and the subsequent implementation of MALDI-TOF technology and the costs involved. The estimated life span and the number of identifications per annum of each instrument were obtained from the Chief Scientist of the laboratory (personal communication, Dr Jacqueline Harper 2015). The estimated costs for the post MALDI-TOF period was lower than the pre MALDI-TOF period due mainly to the large reduction in the cost of consumables and a small reduction to the cost of labour due to the ease of performing the testing utilising the MALDI-TOF instrument.

Table 5.2 Laboratory cost pre and post implementation of the MALDI-TOF instrument per test

Item	Pre MALDI-TOF	Post MALDI-TOF
Cost of processing a blood culture	$25.60	$25.60
Cost of instrument	Vitek 2XL $140,000 (estimated life span 10 years) 72000 identifications per annum = 0.19 per test ($140,00/72,000 = 1.94/10 = .19)	MALDI-TOF $150,000 (estimated life span 5 years) 72000 identifications per annum = 0.42 per test ($150,00/72,000=$2.083/5 = 0.42)
Cost of consumables	$7	$0.60
Cost of Labour	$6	$4.00
Total cost	**$38.79**	**$30.81**

The total cost of antimicrobials for each intervention period per annum is included in Table 5.3. There is a gradual decrease in the cost of antimicrobials following the AMS intervention in the non-ICU wards. However, the AMS

intervention had not been rolled out in ICU at the time of data collection. There is an increase in antimicrobial usage in ICU in the time period immediately following the AMS intervention.

Table 5.3 Annual antimicrobial costs for each intervention period at the RBWH

	Pre AMS	AMS+M	AMS+M+G
Non ICU	$92,266.45	$86,603.62	$76,125.02
ICU	$221,579.91	$331,220.24	$122,924.00
Total	$313,846.36	$417,823.86	$199,049.02
Abbreviations: M: MALDI-TOF; G: Guidance MS			

Table 5.4 presents a summary of all the costs pertaining to pre- and post-implementation of the AMS intervention at the RBWH. While there is a decrease in costs due to antimicrobial utilisation post AMS, the AMS intervention incurred additional costs due to the HR component and the additional costs due to the CDSS but the laboratory costs decreased due to reduction in labour and consumable costs related to the MALDI-TOF instrument.

Table 5.4 Annual costs of antimicrobials, laboratory testing, and the AMS intervention in the pre and post intervention time periods evaluated

Cost per annum	Pre AMS	AMS +M	AMS+M+G
Antimicrobials	$92,266.45	$86,603.62	$76,125.02
Laboratory	$16,834.86	$14,573.13	$13,494.78
AMS intervention		$142,820.30	$142,820.30
CDSS			$26,298.40
Total	$109,101.31	$243,997.05	$258,738.50
Difference in cost compared to Pre AMS		$134,895.74	$149,637.19
Abbreviations: M: MALDI-TOF; G: Guidance MS.			

To include this information in the decision analytic model each of these costs needs to be converted into a unit cost per BSI. To do this an average number of BSIs was estimated for the institution per annum by adding the number for each intervention period and dividing that number by the number of periods in this analysis. The number of BSIs in each intervention period was 939 Pre AMS, 869 (AMS+MALDI-TOF), 987 (AMS+MALDI-TOF +Guidance MS) and the average of these is n=932. The final estimates of costs used in the model for the RBWH is represented in Table 5.5 as the cost per patient with a BSI.

Table 5.5 Costs per patient included in each intervention period for antimicrobials, AMS intervention and laboratory testing

Cost per patient (n=932)	Pre AMS	AMS+M	AMS+M+G
Antimicrobials	$99.00	$92.92	$81.68
AMS intervention	nil	$153.24	$153.24
CDSS			$28.22
Laboratory	$38.79	$30.81	$30.81
Total	$137.79	$276.97	$293.95

The initial AMS intervention at the RBWH cost $142,820.30 and $169,118.70 including the CDSS. The investment in MALDI-TOF technology in the microbiology laboratory, resulted in an overall cost savings. Pre-AMS the cost of processing a positive blood culture was $38.79 and post AMS the cost was $30.81, a cost savings of $7.98 per test.

The major cost savings due to the AMS intervention was in antimicrobial utilisation. Pre-AMS, the total annual cost of antimicrobials was $313,846.36, 12 months after the AMS intervention was in place the cost of relevant antimicrobials was $417,823.86 which was an increase in utilisation and six months after the CDSS

was introduced the cost of antimicrobials was reduced to $199,049.02 per annum. But in the non-ICU setting which is where the AMS intervention was implemented there was a gradual decrease in antimicrobial utilisation from $92,266.45 to $76,125.02. Table 5.5 presents these costs at a patient level for the non-ICU group ranging from $99 per patient in the pre AMS period down to $81.68 per patient at the end of the data collection period.

The increase in antimicrobial utilisation in the initial intervention period was due to an increase in the ICU consumption of antimicrobials. This increase may not necessarily mean less appropriate use of antimicrobials. A closer look at the data confirmed that there were changes to prescribing in the ICU to less potent antimicrobials that in fact cost more. For example there was a reduction in the use of vancomycin but an increase in the use of flucloxacillin. At the same time there was the implementation of the beta-lactam therapeutic drug monitoring service which resulted in 50% of patients receiving higher than standard doses of antimicrobials (personal communication Professor Jason Roberts May 2017).

It is difficult to establish what this significant reduction in antimicrobial utilisation in the final dataset was due to as there were many likely causes. At the time the third data set was collected the AMS intervention had been in place for a period of almost two years and an AMS ward round had been in place auditing antimicrobial use every weekday. Education and awareness of the benefits of appropriate prescribing had also been improved over time. While there has been published evidence indicating the CDSSs together with effective communication can improve outcomes it is difficult to conclude that the improvement was solely due to the implementation of CDSS at the RBWH. It takes time for a prescribing intervention to become embedded for resident physicians in an institution, especially where the workforce is constantly shifting due to the intake of junior doctors each year. It is more likely that the bundle of interventions was more effective at the time the final dataset was collected.

5.2 THE MHS

To estimate the costs of the AMS intervention the information from the questionnaire was used to allocate the hours each member of the team spent of their FTE hours on AMS activities. Table 5.6 lists the role of each member of the team. The core AMS team was estimated to cost $172,634.44 in HR costs alone. The cost of the AMS steering committee was estimated independently by the MHS as costing $4,725 per annum and the AMS working party at $27,300. The total cost of the AMS intervention was estimated to be $204,659.44.

The MALDI-TOF instrument was implemented prior to the AMS intervention at the MHS and an accurate cost per test was not available. . The cost of a test prior to the introduction of MALDI-TOF technology at the RBWH was 20% more than post MALDI-TOF; this cost saving was mainly due to the reduction in labour and consumable costs. This estimate obtained from the RBWH was used to extrapolate the cost Pre-AMS at the MHS since the equipment used in the laboratory was the same at both hospitals prior to the introduction of MALDI-TOF technology. The cost per BSI was estimated by the laboratory at the MHS to be $44.28 per BSI post MALDI-TOF. A 20% increase in cost was applied to that estimate pre MALDI-TOF to bring the laboratory costs to $53.14 per BSI pre MALDI-TOF.

Table 5.6 Cost of the AMS intervention

Intervention	Components	Costings
AMS Team	0.2FTE ID physician	0.2FTE ID physician MO4.1 $205,435 x0.2 =$41087
	Additional 0.05 ID Physician	0.05FTE M04.1 $205,435 x0.05 =$10271.75
	1.0 FTE Pharmacists	1.0 FTE Pharmacist HP4 Av wage $96,786 x 1.0 = $96,786
	0.05 FTE Additional Pharmacist	0.05 FTE x $96,786 = $4839.30
	0.05 FTE Clinical Microbiologist	0.05FTE Clinical Microbiologist MO1-6 $167,245 x 0.05 = $8362.25
	0.01FTE IT specialist	0.01FTE IT specialist AO7 $102,724 x 0.01 = $1027.24
	0.1FTE ICP	Nurse Grade 7 $102,609 x 0.1 = $10260.90
	Total	= $172,634.44
AMS Steering committee		$4,725
AMS working party		$27,300
AMS intervention Mater total cost	AMS Team +AMS committee+ AMS working party	$204,659.44
Abbreviations: FTE: Full time equivalent; ID: infectious diseases; MO: medical officer; IT: information technology; ICP: infection control practitioner; HP: health practitioner		

A summary of the costs in each intervention period is presented in Table 5.7. The total antimicrobial costs were also provided by the pharmacy department for the MHS. In this scenario, the costs of antimicrobial utilisation gradually decreased as the intervention became more established. However, the overall costs were reduced post MALDI-TOF but increased in the intervention period post AMS due to the cost of the AMS intervention.

Table 5.7 Summary of costs MHS

Costs per Annum	Pre AMS+MALDI-TOF	Post MALDITOF	Post AMS+MALDI-TOF
Antimicrobials	$699,866.77	$358,636.07	$321,399.44
Laboratory costs	$24,315.20 ($53.14 per BSI)	$23,114.16 ($44.28 per BSI)	$22,715.64 ($44.28 per BSI)
Cost of AMS intervention	Nil	Nil	$204,659.44

To include this information in the decision analytic model each of these costs needed to be converted into a unit cost per BSI. To do this an average number of BSIs was estimated for the institution per annum by adding the number for each intervention period and dividing that number by the number of periods in this analysis. The number of BSIs in each intervention period was 455 (D1), 522 (D5), 513 (D8) and the average of these is n=497. The final estimates of costs used in the model for the MHS is represented in Table 5.8 representing the cost per patient with a BSI.

Table 5.8 Summary of cost estimates per BSI

Parameters (n=497)	Pre AMS+MALDI-TOF	Post MALDITOF	Post AMS+MALDI-TOF
Cost of antimicrobials	$1383.82	$721.60	$646.69
Cost of AMS	Nil	nil	$411.79
Cost of Laboratory	$53.14	$44.28	$44.28
Total	$1436.96	$765.88	$1102.76

The AMS intervention at the MHS cost $204,659.44 and consisted of an AMS team and an AMS working party. The strategies used were the same as the RBWH with formulary restriction and a prospective audit and feedback intervention. The difference was that the MHS did not use a CDSS as part of the AMS tools and that the MALDI-TOF instrument was established prior to the AMS intervention. Due to

this, it was possible to assess the impact of rapid diagnostics in the laboratory with and without the AMS intervention.

The pharmacy costs at the MHS reduced in a more gradual way between pre AMS and MALDI-TOF $788,359.20 to post MALDI-TOF $431,046.30 and post AMS and MALDI-TOF $376,620.21. Overall there were cost savings of $357,579.56 post implementation of MALDI-TOF technology and a savings of $206,814.85 in the post-AMS and MALDI-TOF period when compared to a time without rapid diagnostics and AMS.

5.3 COMPARISON OF THE COST OF AMS INTERVENTION AT RBWH VERSUS MATER

At the RBWH the AMS intervention including the HR component, and the laboratory cost was $142,820 and with the addition of CDSS a total cost of $169,118. The AMS intervention at the RBWH employed less than the specified number of infectious diseases physician and pharmacist FTE recommended for a hospital of its size. This resulted in the AMS intervention costing less than the one at the smaller hospital MHS costing $204,659 which employed a slightly higher than recommended proportion of FTEs for their AMS intervention (detailed in, Table 5.6). Overall the HR component both in the AMS team and the AMS committee were greater at the MHS as compared to the RBWH. The RBWH did add a CDSS which added to the cost of their intervention. However, the overall cost of the intervention including CDSS was less at the RBWH compared to the intervention at the MHS. The MHS also had a substantial AMS committee that cost more than the CDSS adopted by the RBWH.

Table 5.9 summarises the costs for both RBWH and MHS for the treatment of a BSI with an ESKAPE organism in each intervention period. The average number of significant BSIs for each institution per annum was used as the denominator in the calculation per hospital. Only the antimicrobials used to treat ESKAPE organisms were included in the cost evaluation.

Table 5.9 Cost for the treatment of BSI per episode at the RBWH and at the MHS in each intervention period

Parameter	RBWH (non-ICU)			MHS (ICU and non-ICU)		
	Pre AMS	**Post AMS+MALDI-TOF**	**Post AMS+MALDI-TOF+CDSS**	**Pre AMS**	**Post MALDI-TOF**	**Post AMS+ MALDI-TOF**
Cost of Antimicrobials	$99.00	$92.92	$81.68	$1383.82	$721.60	$646.69
Cost of Laboratory	$38.79	$30.81	$30.81	$53.14	$44.28	$44.28
Cost of AMS	nil	$153.24	$181.46	nil	nil	$411.79
Total cost	**$137.79**	**$276.97**	**$293.95**	**$1436.96**	**$765.88**	**$1102.76**

The costs of the interventions at the two hospitals are different and this might be due to a number of reasons. The number of BSI experienced at each hospital and the throughput of testing performed in the laboratory are different and this could account for some of the differences in the cost of laboratory tests. The RBWH is a large referral centre and has a higher throughput of tests per annum.

The costs of antimicrobials at each institution for the treatment of infections due to pathogenic organisms also showed substantial differences. This was largely due to the ICU antimicrobial costs being excluded from the RBWH costings. It is encouraging that both hospitals showed a reduction in antimicrobial utilisation costs post-AMS. As would be expected the number of total BSI at the MHS was less than at the RBWH and would account for the difference in the cost per BSI.

The AMS intervention at the RBWH, where additional tools were used overall, was the least expensive. The AMS intervention at the MHS was less well established and started a little later than the one at the RBWH. The MHS is smaller and did not rely on a CDSS however the cost of the AMS intervention was higher than the RBWH even without the CDSS. This confirms the large human resource costs in AMS interventions. Since there were cost savings in terms of the reduction in

antimicrobial utilisation the question as to whether these cost savings are sustainable in the long run needs to be considered.

5.4 SUMMARY

While the implementation of the AMS intervention and rapid diagnostics at each of the hospitals resulted in reduced pharmacy expenditure, the HR component of the AMS intervention required greater investment than the rapid diagnostic infrastructure in the laboratory.

However, a cost-analysis does not capture changes in health outcomes that occur due to AMS. Given the stated aim of AMS programs is to optimise prescribing in order to improve patient outcomes, Chapter 6 aims to evaluate potential health benefits achieved as a result of the AMS interventions at both the hospitals assessed in this research. BSI data from both the hospitals are used to measure these health benefits in terms of the relative risk of mortality and length of stay in hospital in these patient populations over time.

Chapter 6: MEASURING EFFECTIVENESS OF AMS INTERVENTIONS

This chapter presents the information on clinical outcomes for each of the interventions examined in this research. Section 6.1 provides the rationale for selecting BSIs as the clinical indicator or metric to represent the impact of each AMS intervention. Section 6.2 provides the process employed to decipher the risk of mortality and hospital LOS for the patients in the pre and post intervention periods at both hospitals. Section 6.3 presents the scenario analyses conducted in this research and the information on how the estimates were derived for each hospital. Section 6.4 provides a summary of findings for the relative risk of mortality and LOS for each of the interventions at the two hospitals.

6.1 THE EFFECTIVENESS EVIDENCE FOR THE ASSESSMENT OF AMS INTERVENTIONS

Both hospitals implemented rapid diagnostics in the microbiology laboratory by way of a MALDI-TOF instrument to enable better turnaround times with identification of bacterial pathogens. Rapid diagnostics in conjunction with AMS interventions have been shown to improve patient outcomes, in terms of reduction in hospital LOS and mortality (64, 67, 68). The two hospitals assessed in this analysis have different approaches to AMS and as such it was important to assess the impact of these differences on patient outcomes. Clinical outcomes such as patient mortality and LOS in hospitals have been suggested as good metrics to measure the impact of AMS interventions (196). While it is recommended that AMS interventions should be evaluated there is no clear guidance as to which metrics are optimal (197). A number of metrics were considered such as AMR, *C. difficile*, LOS, and infection related mortality due to infectious diseases and clinical indicators such as urinary tract infections (UTIs), ventilator associated pneumonia (VAP), surgical site infections (SSI) and bloodstream infections (BSIs). While all of these were valid

metrics, the settings, the patient population and the availability of data needed to be taken into consideration when selecting the most appropriate metric for this research.

Choosing an appropriate clinical condition to measure the success of an AMS intervention poses significant difficulty. As with many hospital interventions other factors to improve patient safety might have been implemented at the same time, which makes it difficult to conclude that all the changes to patient outcomes are due to the intervention being evaluated. At the selected hospitals improvements in catheter care (RBWH) and implementation of the sepsis care bundle (not clear when this might have occurred at either hospital) may have a concurrent impact on LOS and mortality in this patient cohort.

Nonetheless, if the goal of an AMS intervention is to bring about more appropriate prescribing of antimicrobials then this improvement to patient outcomes, should be able to be measured. Invasive bacterial infections are often life-threatening to patients and need to be treated in a timely manner with the most appropriate antimicrobial, at the correct dose for the required duration. Ideally all infections should be considered however the compromise between the quantity and quality of the data needed to be taken into consideration.

The use of clinical conditions such as ventilator associated pneumonia (VAP), surgical site infection (SSI) or bloodstream infection (BSI) to measure the success of AMS interventions have been suggested in a study by Morris et al (196). The assumption is that if the AMS intervention is successful all of these infections will be managed better post intervention. While all of these clinical conditions need to be improved in terms of appropriateness of antimicrobial therapy the data available in each healthcare institution may determine the choice of condition available to evaluate AMS interventions.

While UTIs have been used as a clinical indicator for appropriate prescribing(5), the mortality related to this infection would be difficult to capture as it is generally not life-threatening. For this reason, we did not consider UTIs as a clinical indicator for this research. SSIs are a very heterogeneous assortment of conditions based on the surgical procedure performed and are complex to classify

(198). While infection control services routinely document the occurrence of these infections it is difficult to access this information in hospitals as they are not always consistently recorded and classified. Whilst SSIs would be a good indicator of appropriate use of antimicrobials, and is an area that needs to be targeted by AMS teams, it is difficult to access well classified good quality data for analysis. Therefore, SSIs were not considered an ideal indicator to measure the effectiveness of the AMS intervention for the hospitals under consideration.

VAP is one of the most common hospital acquired infections in the ICU due to a high proportion of patients in ICU that receive mechanical ventilation (199). The key issue that makes VAPs difficult to use as a clinical indicator is the classification of VAP. When patients in ICU develop VAP-like symptoms it is not always due to a bacterial infection. The difficulty in collecting samples to confirm the causative agent can also be challenging in this setting. This results in difficulties diagnosing VAP and therefore like SSIs these data sets are not helpful as clinical indicators to assess the impact of AMS programs in hospital settings. In addition the AMS intervention had not been rolled out into the ICU at the time of data collection.

It is expected that an effective AMS intervention will result in better outcomes for community and hospital acquired BSIs due to more appropriate prescribing behaviours. Data on BSIs are routinely collected in most hospital settings and may be used for the assessment of the impact of better prescribing. A number of recent studies have used 30 day mortality in patients with BSIs as a measure of the impact of their AMS interventions (33, 98, 99, 200).

While using BSIs as the clinical indicator was challenged by the experts consulted during the design of the AMS model for this research, it was agreed that the data for BSI were available in most hospitals and that the model would be more generalisable if this was the clinical indicator as opposed to say surgical site infections (SSIs), VAPs or UTIs. Most Australian hospitals collect information on BSIs routinely and *S. aureus* BSI (SAB) is the chosen quality indicator for the assessment of patient safety in hospitals by the ACSQHC. Since it is mandatory to collect this information in Australian hospitals it was thought to be a more accessible source of patient level outcome data for this research.

When selecting a metric to measure the impact of AMS, AMR and *C. difficile* infections in patients with BSIs would be of value as a measure of morbidity in this patient cohort. However, this impact would only be effectively captured over a longer period of time. Dik et al (201) highlights further issues, being the requirement for a large patient cohort to see the trends in the data and the longer period of time required to do this would lead to the influence of confounders such as the environmental cleaning bundle and other infection control interventions becoming more relevant. For this reason AMR and *C. difficile* rates were not included as a metric in this research due to the short time frame of the analysis.

BSIs from both hospitals were collected from the LIS and linked to specific admission and discharge information. Only patients with significant BSIs caused by ESKAPE organisms were included and as such only Gram Positive (GP) and Gram Negative (GN) infections were included in the model. While the earlier versions of the model included resistant GP and GN infections as a sub group, the final model included these organisms under the banner of GP or GN instead of drilling down to whether they were resistant or not to estimate attributable mortality and hospital LOS.

6.2 ANALYSIS

The aim of the analysis was to first establish an outcome baseline for patients with GP and GN BSIs. The inclusion of gender and sex covariates is to adjust for any potential effect of these two covariates on mortality. The outcomes chosen in this analysis to determine the impact of the intervention are the average LOS and mortality, for patients with BSIs caused by GP and GN organisms. The analysis was performed separately for each hospital. The statistical analysis was performed using SPSS (version 22), and R for the Cox proportional hazards model analysis.

The baseline risk of mortality was calculated for the patients with GN BSIs for the pre intervention period using logistic regression analysis, adjusting for age and sex. Subsequent mortality estimates were obtained using a Cox proportional hazards model to mitigate time dependent bias. A Cox proportional hazards model

was fitted to the mortality data for each hospital with organism group, intervention periods, gender and sex included as covariates. The model parameters of interest here are the hazard ratios for organism group and intervention period.

The average hospital LOS estimates for patients in the various intervention periods were analysed using an ANCOVA, adjusting for age and sex. An ANCOVA is performed to assess if the dependent-variable had statistically equal means across levels of a categorical independent variable, controlling for covariates that are not of primary interest. In this case, the average LOS of patients with BSIs was compared across intervention periods and organism groups, adjusting for the impact of sex and age of the patient cohort.

6.2.1 THE RBWH

Table 6.1 represents the total number of BSIs once duplicates were removed for the RBWH for all intervention periods (n=1847). This number included ICU patients as well as patients in general wards. The total number of ICU patients in the dataset was 60. Since the AMS intervention at this hospital had not commenced in the ICU these patients were excluded from the analysis (n=1787).

The next stage was categorising these BSIs by organism into significant and non-significant groups. Table 6.1 represents all non-duplicate BSIs that are caused by ESKAPE organisms (GP&GN) as well as Candida species (CN), poly-microbial infections (Mixed) and anaerobic infections (AN). Once likely contaminants and organisms not considered significant were removed (n=892) the remaining number of significant bloodstream infections equalled n=895.

The organisms were separated into intervention periods, the pre AMS period, the AMS intervention after the implementation of rapid diagnostics in the laboratory (AMS and MALDI-TOF), and the AMS intervention after rapid diagnostics and the CDSS Guidance MS was implemented (Post AMS, MALDI-TOF and Guidance MS). As is evident in Table 6.1 the number of organisms in the categories other than the ESKAPE organisms are small and were excluded from the regression analysis in this study.

Table 6.1 Total number of organisms in the RBWH data set in non-ICU patients who survived

Intervention period (n=1787)	AN	CN	GN	GP	Mixed	Non SIG	Total
Pre AMS intervention	15	23	227	98	71	471	905
Post AMS and MALDI-TOF	8	6	126	111	64	248	563
Post AMS, MALDI-TOF and Guidance MS	4	4	75	41	22	173	319
Total	**27**	**33**	**428**	**250**	**157**	**892**	**1787**
Abbreviations: AN**: Anaerobes;** CN**: Candida species;** GN**: GNs;** GP**: GPs;** Mixed**: Mixed infections;** Non SIG**: Non significant infections**							

Table 6.2 represents the number of ESKAPE organisms included in this analysis (GP BSIs =250& GN BSIs =428, total = 678). The overall level of resistance in the organisms that were included in the analysis was also relatively low (Figure 6.1). For this reason the regression analysis for mortality and LOS was calculated for GP and GN not differentiated for resistance status. The percentage of deaths in each intervention period varied from 8.6-12.3% with the highest being in the Pre AMS intervention period.

Table 6.2 ESKAPE organisms included in the analysis at the RBWH

Intervention period (n=678)	GN	GP	**No: Dead (%)**	Total
Pre-AMS intervention	227	98	40 (12.3%)	325
Post-AMS and MALDI-TOF	126	111	21 (8.9%)	237
Post-AMS, MALDI-TOF and Guidance MS	75	41	10 (8.6%)	116
Total	**428**	**250**	**71 (10.5%)**	**678**
Abbreviations: GP: Gram Positive; GN: Gram Negative				

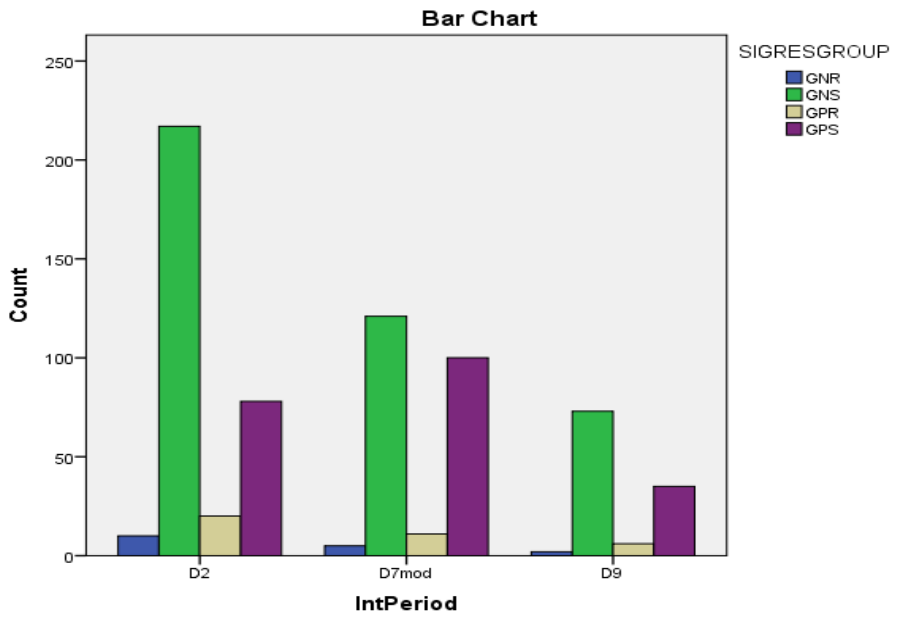

Figure 6.1 Plot of Gram Positive resistant (GPR) and susceptible(GPS) and Gram Negative resistant(GNR) and susceptible (GNS) BSIs per annum in the intervention periods; D2: pre AMS, D7 mod (AMS+MALDI) and D9 (AMS+MALDI-TOF +Guidance)

In this analysis the comparator was the mortality due to GN BSIs. This baseline estimate was obtained by performing regression analysis as described earlier. Table 6.3 summarises the impact on mortality in GP organism groups in each intervention period as compared to GN organisms.

Table 6.3 Relative Risk of Mortality due to a GP BSI compared to GN BSI and the RR in each intervention period at the RBWH

Intervention period	Relative Risk of Mortality
Pre AMS	1.6 (CI 0.99-2.6)
AMS+ MALDI-TOF	0.84 (CI 0.48-1.45)
AMS+ MALDI-TOF+ Guidance MS	0.93(CI 0.46-1.87).

The proportion of GP BSIs pre and post intervention was also calculated using the primary data obtained from the RBWH datasets. Using the baseline mortality calculated for GN BSIs pre AMS of 0.09692 the probability of death for GP and GN BSIs for each intervention group was calculated as described in Table 6.4 below. These parameters are the point estimates to be used in the economic model.

Table 6.4 Method used to calculate the probability of death in each intervention period for the RBWH

Intervention period	Parameter		Point estimate
Pre AMS	Proportion of GP BSIs		98/325=0.30
	Probability of death	GP BSI	0.09692* 1.6=0.156
		GN BSI	0.09692 (baseline)
Post AMS and MALDI-TOF	Proportion of GP BSIs		167/356=0.47
	Probability of death	GP BSI	0.09692* 1.6*0.84 =0.13
		GN BSI	0.09692*0.84 =0.081
Post AMS, MALDI-TOF and Guidance MS	Proportion of GP BSIs		123/348=0.35
	Probability of death	GP BSI	0.09692*1.6*0.93=0.14385
		GN BSI	0.09692*0.93= 0.09
Abbreviations: HR: hazard ratio;			

The hospital LOS for patients with BSIs in each intervention period was derived from the data collected. The LOS for patients with BSIs due to GP organisms that survived in that time period is presented in Table 6.5 below. There is no notable difference in the LOS in each of the intervention periods compared to the mean LOS pre AMS.

Table 6.5 LOS estimated for GP BSI of patients who survived

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	36.61	4.31	30.12	47.10
Post AMS + MALDI-TOF	32.82	3.92	25.09	40.55
Post AMS + MALDI-TOF + Guidance MS	34.10	6.39	21.52	46.69

The hospital LOS for patients with GP BSIs that died is presented in Table 6.6. The mean LOS for patients with GP BSIs who died is more randomly distributed in possibly due to the small number of deaths in our patient cohort.

Table 6.6 LOS estimates for GP BSI of patients who died

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	26.59	9.28	8.31	44.87
Post AMS + MALDI-TOF	19.30	10.35	-1.09	39.70
Post AMS + MALDI-TOF + Guidance MS	30.12	17.12	-3.59	63.83

In the patients with BSIs due to GN organisms that survived however there was a difference to the mean LOS. The pre AMS intervention period resulted in a mean LOS was 31.60 and with the addition of the AMS+ MALDI-TOF the mean LOS reduced to 26.30. A further reduction of the mean LOS to 20.44 was noted when the CDSS Guidance MS was introduced at the RBWH (Table 6.7).

Table 6.7 LOS estimates for GN BSIs of patients who survived

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	31.60	2.49	26.71	36.49
Post AMS + MALDI-TOF	26.30	3.27	19.87	32.74
Post AMS + MALDI-TOF + Guidance MS	20.44	4.23	12.14	28.75

In patients who died the LOS is more random and less predictable possibly due the smaller number of death in the patient cohort in the analysis (Table 6.8). While there was a trend to a reduction in LOS in the patients who survived, there was not a significant difference in the mean LOS in each of the intervention periods for either patients who survived or died.

Table 6.8 LOS estimates for GN BSIs of patients who died

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	25.73	7.56	10.87	40.59
Post AMS + MALDI-TOF	39.55	13.38	13.25	65.86
Post AMS + MALDI-TOF + Guidance MS	14.80	15.85	-16.36	45.96

Overall there is a small decrease in the probability of death in both GP and GN organisms after each of the interventions. While there is a trend towards a reduced LOS for GN organisms, the overall GP LOS did not change. However none of these changes were statistically significant.

6.2.2 THE MHS

Table 6.9 summarises the number of organisms in each intervention period at the MHS. Once non-significant BSIs were removed the numbers for each intervention were almost halved.

Table 6.9 Summary of the total organisms for each of the intervention periods

Intervention period n=653	Total number positive BSIs	Adjusted to 12 months	Total numbers of significant BSI	Adjusted to 12 months
Pre AMS (12 months)	455	455	245	245
Post MALDI-TOF (12 months)	522	522	288	288
Post AMS and MALDI-TOF (7 months)	299	513	175	300
Total	1276	1490	708	833

The organisms were sorted by organism group and Table 6.10 presents the summary of this information. Overall the number of organisms that belonged to non GP and GN groups was small and excluded from this analysis.

Table 6.10 Summary of the total number of organisms in each intervention period sorted by organism group

Intervention period	AN	CN	GN	GP	Mixed	Total
Pre AMS intervention	1	12	170	49	13	245
Post MALDI-TOF	0	11	185	79	13	288
Post AMS and MALDI-TOF	0	5	126	44	0	175*
Total	1	28	481	172	26	708

Abbreviations: AN**: Anaerobes;** CN**: Candida species;** GN**: GNs;** GP**: GPs;** Mixed**: Mixed infections;** Non SIG**: Non significant infections**

*The data set for post AMS and MALDI-TOF was only 7 months and was adjusted to an estimate for 12 months (n=300) for this analysis.

Similar to the analysis for the RBWH only ESKAPE organisms were included in the regression analysis (Table 6.11). The percentage of deaths in each intervention period ranged from 6.1-10% the highest being in the post AMS intervention period.

Table 6.11 ESKAPE organisms used in analysis

Intervention Period n=653	GP Total	GN total	No: dead (%)	Total
Pre AMS (12 months)	49	170	19 (8.7%)	219
Post MALDI-TOF (12 months)	79	185	16(6.1%)	264
Post AMS and MALDI-TOF (7 months)	44	126	17 (10%)	170
Total	**172**	**481**	**52(8%)**	**653**
Abbreviations: GP: Gram Positive; GN: Gram Negative				

As can be seen in Figure 6.2 the number of organisms that were resistant to antimicrobials in this dataset was very small and grouped in with the susceptible organisms.

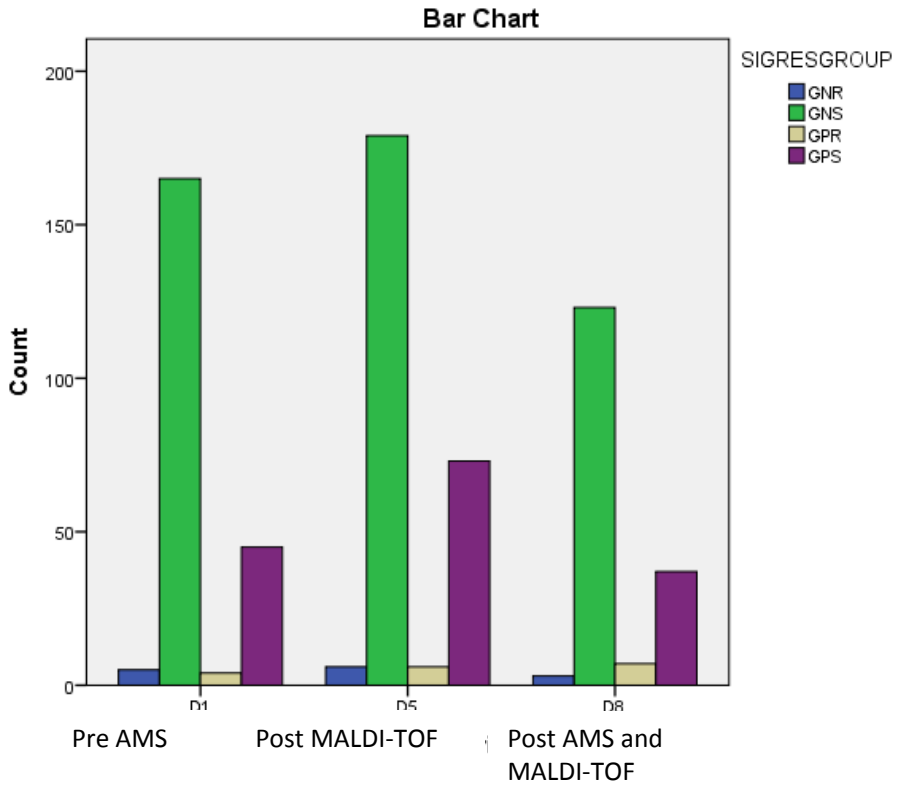

Figure 6.2 Plot of Gram Positive resistant (GPR) and susceptible(GPS) and Gram Negative resistant(GNR) and susceptible (GNS) BSIs per annum in the intervention periods at the MHS

As for the RBWH in this analysis the comparator was the mortality due to GN BSIs calculated by performing regression analysis adjusted for age and sex. These estimates were further adjusted for time dependence using the Cox proportional analysis. Table 6.12 summarises the relative risk of mortality in patients with GP BSI compared to GN BSIs in each of the intervention periods.

Table 6.12 Relative Risk of Mortality from a GP BSI compared to GN BSI and each intervention period

Intervention period	Relative Risk of Mortality
Pre AMS	1.053 (CI 0.59-1.89)
MALDI-TOF	0.749 (CI 0.37-1.49)
AMS+ MALDI-TOF	1.28 (CI 0.65-2.5)

Using the Baseline mortality calculated for GN BSIs pre AMS of 0.0765 the probability of death for GP and GN BSIs for each intervention groups is calculated as described in Table 6.13 below. These parameters are the point estimates to be used in the economic model.

Table 6.13 Final estimates adjusted for time dependence

Description	Parameter		Point estimate (probability)
Pre AMS	Proportion of GP BSIs		49/219=0.22
	Probability of death	GP BSI	0.0765* 1.053=0.0805
		GN BSI	0.0765
Post MALDI-TOF	Proportion of GP BSIs		75/291=0.26
	Probability of death	GP BSI	0.0765*1.053*0.749 =0.060
		GN BSI	0.0765*0.749 =0.0573
Post AMS and MALDI-TOF	Proportion of GP BSIs		79/264=0.30
	Probability of death	GP BSI	0.0765* 1.053*1.28 =0.1031
		GN BSI	0.0765*1.28=0.0979
Abbreviations: GP: Gram Positive; GN: Gram Negative; BSI: Bloodstream Infection			

The LOS estimates for the MHS once adjusted for age and sex, show very little difference. Unlike at the RBWH there is no trend to reduction in LOS estimates, in any of the organism groups. The values varied erratically for the patients who died, probably due to the small numbers in the dataset used in this analysis (Table 6.14&6.15).

Table 6.14 LOS estimates for GP organisms in patients who survived at the MHS

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	25.11	3.65	17.90	32.32
MALDI-TOF	26.07	2.85	20.46	31.69
Post AMS + MALDI-TOF	27.93	4.00	20.04	35.83

Table 6.15 LOS estimates for GP organisms in patients who died at the MHS

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	14.72	9.80	-4.63	34.07
MALDI-TOF	39.56	9.77	20.26	58.85
Post AMS + MALDI-TOF	19.87	9.26	1.59	38.16

The values for BSI related LOS for GN organisms unlike at the RBWH where patients who survived demonstrated a trend to a reduction of LOS in this data showed no significant difference for patients who survived or who died (Table 6.16 and Table 6.17).

Table 6.16 LOS estimates for GN organisms in patients who survived at the MHS

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	16.40	1.54	13.37	19.44
MALDI-TOF	16.24	1.46	13.37	19.11
AMS + MALDI-TOF	14.94	1.80	11.39	18.48

The estimates for LOS for patients who died (Table 6.17) with GN BSIs showed more erratic changes than those for patient who survived (Table 6.16).

Table 6.17 LOS estimates for GN organisms in patients who died at the MHS

Intervention Period	Mean LOS	Std Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Pre AMS	44.29	5.36	33.76	54.83
MALDI-TOF	22.11	6.11	10.10	34.11
AMS + MALDI-TOF	38.08	6.11	26.08	50.08

An option to strengthen the statistical analysis for these estimates was to combine the GP & GN BSI and repeat the calculation of these estimates. The value of a bed day was also explored to assess the impact on the final result. And finally the existing literature was assessed to find the best estimates for the impact of an AMS intervention on patient mortality and these scenarios are considered in the following section.

6.3 SCENARIO ANALYSIS

In order to look at the impact of the cost of a bed day and the result of strengthening the analysis by combining the estimates for GP&GN BSI an additional analysis was performed and presented below for both hospitals included in this analysis. A number of factors have an impact on the CEA at both hospitals. The BSI data were first categorised into ESKAPE organisms and then further grouped into GP & GN before the statistical analysis was performed. The original analysis was based on these estimates and the scenarios described below will be tested to determine the impact on the final conclusions:

1. The impact of combining GP&GN BSIs at the RBWH and the Mater hospitals to see if this strengthened the analysis.
2. The impact of the cost of a bed day from a conservative estimate of $216 to $0.

3. The impact of using literature based estimates of mortality to reduce the uncertainty in those parameters, while the other parameters remained the same for each hospital.

6.3.1 LITERATURE BASED ESTIMATES

While this research focuses on using primary data for the analysis, a scenario where a literature based estimate for mortality was substituted to provide an estimate that may have less uncertainty associated with it was sourced. Four recent studies that evaluated the impact of an AMS intervention and measured hospital mortality as an outcome were identified, with mortality reported as probability of death in table 6.18.

Table 6.18 Recent studies measuring the impact of AMS on mortality

Study	p(death 95% CI) Pre AMS	Standard Error	p(death 95% CI) Post AMS	Standard Error
Huang 2013 (64)	0.203 (0.154-0.252)	0.025	0.127(0.085-0.168)	0.021
Okumura 2015 (202)	0.380 (0.325-0.435)	0.028	0.272(0.209-0.335)	0.032
Perez 2014 (67)	0.210 (0.146-0.274)	0.033	0.089(0.037-0.142)	0.027
Patel 2017 (68)	0.211 (0.160-0.261)	0.026	0.120(0.078-0.162)	0.021

Three studies evaluated the impact of an AMS intervention coupled with MALDI-TOF technology on mortality using a pre and post quasi experimental study design, Huang et al(64), Perez(67) and more recently Patel(68). The first study included adult patients with a BSI identified by the MALDI-TOF in a three month period and compared them to BSIs in the same calendar months the previous year when conventional testing was performed. They included 501 patients in total with 245 in the intervention group and 256 in the pre-intervention group. The difference in the probability of death in the Pre AMS group was found to be 0.203 and post AMS 0.127. The second study observed the impact of AMS and MALDI-TOF on resistant GN BSIs, 153 patients in the pre-intervention group and 112 in the post

intervention group. The impact on the probability of death was to reduce the baseline probability of 0.210 to 0.089 post intervention. The third study reported a significantly different impact on mortality due to the intervention changing the baseline from 0.211 to 0.120. The study was performed in Michigan USA and included 247 adult patients in the pre-intervention group and 233 in the post intervention group. This study reported similar findings to Huang et al but was more recent.

The final study published by Okumura and colleagues (202) examined two different approaches to the implementation of an AMS intervention, one a traditional strategy and the second a more bundled approach to AMS performed in Brazil. The AMS strategy did not include MALDI-TOF technology. The baseline mortality in this study was higher than the previous studies at 0.38. In their setting, the bundled AMS intervention made a significant impact on mortality in the group post intervention and reduced to 0.272.

Figure 6.3 presents the probabilities of death with the uncertainty associated with each estimate. Of the three studies one study evaluated the impact of resistant GN organisms (67). The other two studies reported a similar baseline mortality to our population and the intervention included patients with BSIs and included MALDI-TOF technology (64, 68).

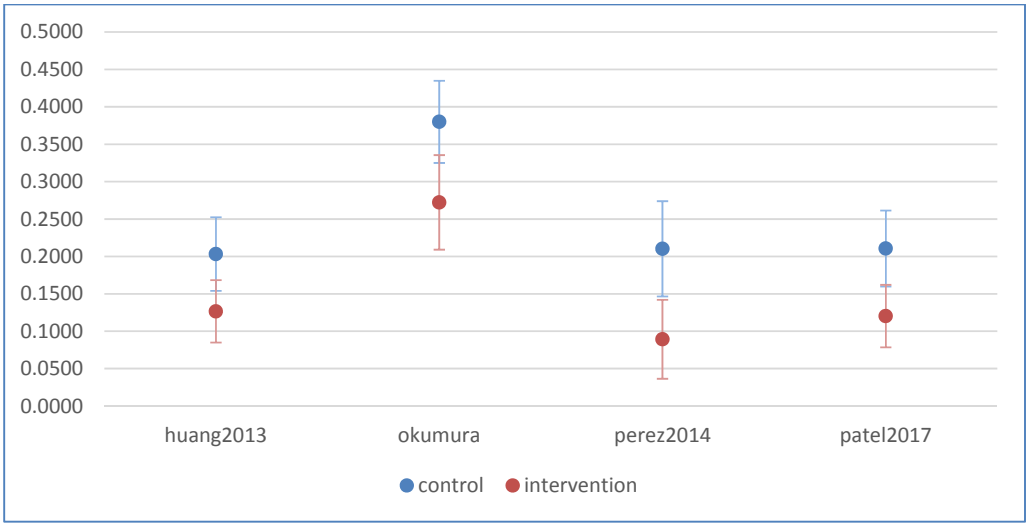

Figure 6.3 Pre and post intervention probabilities of death

In the scenario analysis the study published by Patel in 2017, was selected because the study is the most recent and reflects a similar patient population to our cohort of adult patients at the two Brisbane hospitals, and is not limited to resistant GN BSIs (68). There is less uncertainty in the estimate of the probability of death compared to the estimates derived in our study from either hospital. This estimate will be used instead of the values calculated from the raw data from the two hospitals to demonstrate the difference in the cost-effectiveness results with a more statistically significant estimate. The rest of the parameters for both hospitals will remain unchanged in the analysis.

6.3.2 RBWH

For the RBWH organism groups were combined in order to strengthen the statistical analysis of the data used in the model. The relative risk of mortality in each intervention period is calculated using the program R for the Cox proportional hazards model analysis. The relative risk of mortality for each intervention period compared to the baseline mortality is presented in Table 6.19 below.

Table 6.19 The relative risk of mortality compared to pre AMS when GP&GN organism groups were combined for the RBWH

Intervention period	Relative Risk of Mortality
AMS+ MALDI-TOF	0.93 (CI 0.54-1.59) = Probability of death 0.786
AMS+ MALDI-TOF+ Guidance MS	0.99 (CI 0.49-2.00) = Probability of death 0.985

In the original analysis when the GP and GN organism groups were individually assessed the probability of death in the GP group was 0.1302 for the AMS+M period and 0.1439 for the AMS+M+CDSS period. For the GN group AMS+M the probability of death was 0.0811 and AMS+M+CDSS were 0.0897.

Table 6.20 presents the new baseline probability of death for the combined GP&GN organism groups and the impact of each intervention period on the likelihood of mortality.

Table 6.20 The probability of death in each intervention period at the RBWH

Description	Point estimate
Probability of death Pre AMS(baseline)	0.123077
Probability of death post AMS and MALDI-TOF	0.123077*.93 = 0.114462
Probability of death post AMS, MALDI-TOF and Guidance MS	0.123077*0.99 = 0.121846

In the original analysis in patients who survived the LOS for GP organisms ranged from 36.6 in the Pre AMS period, 32.82 in the AMS+M period and 34.10 in the AMS+M+G period. In the GN patients who survived the LOS ranged from 31.60 Pre AMS, 26.30 AMS+M and 20.44 in the AMS+M+G.

Table 6.21 & 6.22 present the LOS estimates when the organism groups were combined for patients who survived and patients who died respectively.

Table 6.21 LOS estimates when the GP&GN organism groups were combined for patients who survived at the RBWH

Intervention Period	Mean LOS(alive)	Std Error	95% Confidence Interval	
			Lower Bound	**Upper Bound**
Pre AMS	33.466	2.176	29.193	37.739
Post AMS + MALDI-TOF	29.095	2.509	24.168	34.021
Post AMS + MALDI-TOF + Guidance MS	24.802	3.545	17.841	31.763

There was a much more erratic variation in the GP and GN LOS estimates for patients who died ranging in the GP group from 26.59 in the Pre AMS period, 19.30 in the AMS+M period and 30.12 in the AMS+M+G period. In the GN group similar variation was observed, in the Pre AMS period 25.73, AMS+M 39.55 and AMS+M+G 14.82. The number of patients who died in each intervention period was low and

accounts for this variation in the numbers. When the GP& GN groups were combined in patients who survived & died there seems to be a gradual reduction in the mean LOS.

Table 6.22 LOS estimates when the GP&GN organism groups were combined for patients who died at the RBWH

Intervention Period	Mean LOS (dead)	Std Error	95% Confidence Interval	
			Lower Bound	**Upper Bound**
Pre AMS	26.578	5.831	15.129	38.028
Post AMS + MALDI-TOF	25.499	8.007	9.778	41.221
Post AMS + MALDI-TOF + Guidance MS	23.490	11.551	.810	46.169

The same process was undertaken for the datasets from the MHS and the organism groups were combined and the results are presented in the following section.

6.3.3 MHS

For the MHS as with the analysis for the RBWH the organism groups were combined in order to strengthen the statistical analysis of the data used in the model. Table 6.23 presents the relative risk of mortality for the combined organism groups and the probability of death for each intervention period in this analysis.

Table 6.23 The relative risk of mortality compared to pre AMS when GP&GN organism groups were combined for the MHS

Intervention period	Relative Risk of Mortality
MALDI-TOF	0.75 (CI 0.38-1.49) = Probability of death of 0.420
AMS+ MALDI-TOF	1.29 (CI 0.66-2.5) = Probability of death of 0.458

Table 6.24 presents the probability of death for each intervention period compared to the Pre AMS period. In the original analysis the probability of death in the GP group Pre AMS was 0.0805, MALDI-TOF 0.0573 and AMS+M 0.0603 and GN Pre AMS was 0.0765, MALDI-TOF 0.099 and AMS+M 0.1031. It can be seen that the lowest probability of death is in the MALDI-TOF period for this analysis at 0.06507.

Table 6.24 The probability of death in each intervention period at the MHS

Description	Point estimate
Probability of death Pre AMS	19/219 = 0.08676
Probability of death post MALDI-TOF	0.08676*0.75=0.06507
Probability of death post AMS, MALDI-TOF	0.08676*1.29=0.11192

Table 6.25 and 6.26 present the LOS estimates in the combined analysis for patients who survived and patients who died at the MHS respectively. In the original estimates for the different organism groups that ranged from 25.11 Pre AMS, 26.07 MALDI-TOF, 27.93 for AMS+M for the GP organisms and 16.40 Pre AMS, 16.24 for MALDI-TOF and 14.94 for AMS+M for GN organisms.

Table 6.25 LOS estimates when the GP&GN organism groups were combined for patients who survived at the MHS

Intervention Period	Mean LOS(alive)	Std Error	95% Confidence Interval	
			Lower Bound	**Upper Bound**
Pre AMS	18.211	1.498	15.269	21.153
MALDI-TOF	19.291	1.344	16.652	21.931
Post AMS + MALDI-TOF	18.009	1.724	14.624	21.393

Table 6.26 LOS estimates when the GP&GN organism groups were combined for patients who died at the MHS

Intervention Period	Mean LOS(dead)	Std Error	95% Confidence Interval	
			Lower Bound	**Upper Bound**
Pre AMS	35.141	4.862	25.593	44.689
MALDI-TOF	28.569	5.295	18.172	38.966
Post AMS + MALDI-TOF	30.774	5.151	20.658	40.890

There appears to be no significant difference to the mean LOS estimates for either group in this analysis.

6.4 SUMMARY

At the RBWH, the total number of BSIs included in the analysis due to only GP&GN BSI was 678. In this analysis the probability of death pre AMS for GN BSIs was 0.097, AMS+M 0.081 and AMS+M+G 0.09. The probability of death for GP BSIs Pre AMS was 0.156, AMS+M 0.13 and after the addition of CDSS 0.144.

The LOS estimates at the RBWH, the estimates in the group of people that died were erratic in all groups due to the small number of deaths in this cohort of patients. However in the patients that survived while there were no statistically significant differences the LOS in the GN group reduced from 31.6 Pre AMS to 26.3 post AMS+M and 20.44 in the period after the addition of the CDSS.

In order to strengthen the statistical analysis the GP and GN organism groups were combined and as a result of this the probability of death Pre AMS was 0.1231 and AMS+M decreased to 0.1145 and the addition of CDSS was 0.1219. The LOS estimates in patients who survived reduced from 33.47 to 29.10 with the addition of AMS+M and 24.80 with the addition of CDSS. In the patients that died the LOS

also reduced from 26.57 pre AMS, 25.49 post AMS+M and 23.49 after the addition of CDSS.

At the MHS, the total number of BSIs that were non-duplicate and due to only GP&GN organisms included in the analysis was 653. The baseline probability of GN BSIs was 0.0765 and after the introduction of the MALDI-TOF instrument the probability of death estimate decreased to 0.057, but the addition of AMS increased this probability to 0.098. In GP BSIs the baseline probability was 0.0805 and the addition of MALDI-TOF reduced the probability of death to 0.060 and the addition of AMS to 0.103.

When GP&GN BSIs were combined for the analysis at the MHS, the probability of death Pre AMS was 0.09 and post MALDI-TOF was reduced to 0.065 and the addition of AMS increased the likelihood of death above the baseline of 0.09 (pre AMS) to 0.112. The LOS in this analysis did not vary much due to the interventions in either the patients who survived or died.

The point estimates on mortality and length of hospital stay calculated in this chapter and the cost estimates calculated in the previous chapter will be used to populate the decision analytic model discussed further

Chapter 7: AN ECONOMIC MODEL TO EVALUATE COST-EFFECTIVENESS OF AMS INTERVENTIONS

This chapter outlines the factors considered in the development of the decision analytic model to evaluate the impact of an AMS intervention on patients with BSIs. Section 7.1 discusses the rationale used for the design and choice of the model type and the decision problem under consideration. Section 7.2 describes the design of the model at the RBWH and section 7.3 the model at the MHS. The process of valuing the health outcomes in terms of QALYs is described in section 7.4 and Section 7.5 discusses methods used for result analysis. Section 7.6 presents the rationale for the scenario analysis and 7.7 a summary of the process of model development in this analysis.

7.1 MODEL DEVELOPMENT AND VALIDATION

"All models are a simplification of reality and it will never be possible to include all the ramifications of the problem being considered" Briggs 2006(189).

It is futile in economic modelling to try to include every detail of the research problem which inevitably will produce an unwieldly result. As suggested by Briggs, only the essence of the research problem needs to be captured in the evaluation. AMS interventions are challenging to evaluate as there is little consistency in the design and implementation of individual programs. While there is broad consensus that the main strategies in the intervention are formulary restriction and prospective audit intervention and feedback, the tools that are chosen to assist in this process are dependent on the preference and the availability of resources at each healthcare institution.

The two hospitals included in this research adopted different approaches to the way in which the AMS intervention was implemented in each of the individual

settings. The RBWH being a larger hospital included a CDSS as part of the tools. Whereas the MHS being a smaller hospital assumed a more conservative approach and decided to await the implementation of their Electronic Health Record (EHR) to ascertain the value of this addition at a future date to assist with prescriber education. Both hospitals either already had rapid diagnostics implemented in the hospital prior to the AMS intervention (MHS) or were about to implement rapid diagnostics (RBWH). Both hospitals had selected MALDI-TOF technology as their rapid diagnostic platform to improve turnaround times in the microbiology laboratory.

The early stages of the model once developed was validated at an expert advisory meeting at the RBWH on 9th October 2013 and included a team of infectious disease specialists, medical microbiologists and pharmacists from both hospitals. The structure of the model in its initial form and a plan for the evaluation was presented and a discussion encouraged at the end of the presentation regarding the choice of metrics to measure the impact of the intervention.

As discussed in Chapter 2 section 2.6, there is evidence to suggest that inappropriate antimicrobial therapy can result in poor outcomes in patients with severe infections. There is evidence that a higher rate of mortality is associated with patients with BSI that were not receiving active therapy as opposed to those who are receiving active therapy based on antimicrobial susceptibility testing (203). This evidence supports the need to treat patients with BSI quickly with the optimal antimicrobials in the shortest space of time from diagnosis.

If the pathogen is multi-drug resistant (MDR), the likelihood of getting the empirical antimicrobial therapy right may be reduced. BSI infections due to GN organisms have worse outcomes due to inadequate or delayed treatment (204). Patients with infections caused by resistant organisms have higher costs and worse outcomes than those caused by susceptible organisms (205). A large well designed multi-centre observational study conducted using data from 24 countries and 162 ICUs involving 1156 patients limited to hospital acquired BSIs, found that mortality due to MDR organisms compared to susceptible organisms had an odds of death of 1.49 (95%CI 1.07-2.06) and if the infection was not treated that odds increased to

5.86 (95%CI 2.5-13.9) (26). This data was supported by Niwa et al in 2016(99), who found that the daily review of antimicrobials used to treat patients with BSIs resulted in a significant reduction from 11.4% to 5.4% (p=0.030) in 30 day mortality.

A systematic review was also conducted to support the use of BSI mortality as a metric for assessing the impact of AMS interventions (100). Based on this reasoning BSIs were selected as the metric for assessing the impact of AMS interventions at both hospitals. The easy accessibility of this data in most hospital laboratory information systems makes this a more pragmatic choice as a metric to measure the impact of AMS interventions. While the total infections per year would have provided a larger dataset, the classification of the severity of the infections would have been difficult. The collection and organising and linking of a large diffuse dataset from the laboratory with patient admission and discharge information would have proven to be highly labour intensive and beyond the scope of this research.

The decision analytic model was developed taking into account the natural progression of a BSI in a patient entering the hospital. Patients with BSIs could have acquired them in the community or the hospital and depending on the severity of the illness and other comorbidities would enter the ED, general ward or ICU. A decision tree is the simplest form of a decision model and is well suited to evaluating the impact of an AMS intervention. This is because the duration that a patient is in hospital for antimicrobial therapy is usually short term unlike following a patient with a chronic disease. The model assumes that an effective AMS program would result in better outcomes for patients with BSIs. Access to rapid results from the microbiology laboratory (MALDI-TOF) would improve the turnaround time for the delivery of information regarding the identification of the organism causing the BSI. This in turn would aid in more appropriate selection of narrower spectrum antimicrobials for the optimal treatment of BSIs(68).

TreeAge Pro software was used to construct the model (*TreeAge Software 2015, R1.0, Williamstown, MA; software available at https://www.treeage.com*.) and the early stages of the model were reviewed by Dr Marc Scheetz (Professor of Pharmacy, Mid-western University, Chicago USA) Dr Jose Leal (Health economist

Oxford University London U.K) Dr Kate Halton (Lecturer QUT and Principal Supervisor) and Professor Nicholas Graves (Professor of Health Economics QUT, Associate Supervisor).

7.2 MODEL 1 RBWH

The first model applies to the RBWH (Figure 7.1) and the first arm of the decision tree represents the Pre AMS period and captures GP and GN BSIs in that time period. The impact of the AMS intervention and the MALDI-TOF instrument is represented in the second arm of the model (AMS+M) and the third arm takes into account the impact of the CDSS (Guidance MS) in addition to AMS and MALDI-TOF (AMS+M+G). Both these arms are compared to the situation prior to AMS, MALDI-TOF and CDSS. This decision tree represents Bloodstream infection datasets collected from March 2010 (Pre AMS) to December 2014 (Post AMS+M+G).

7.2.1 STRUCTURE OF THE DECISION TREE

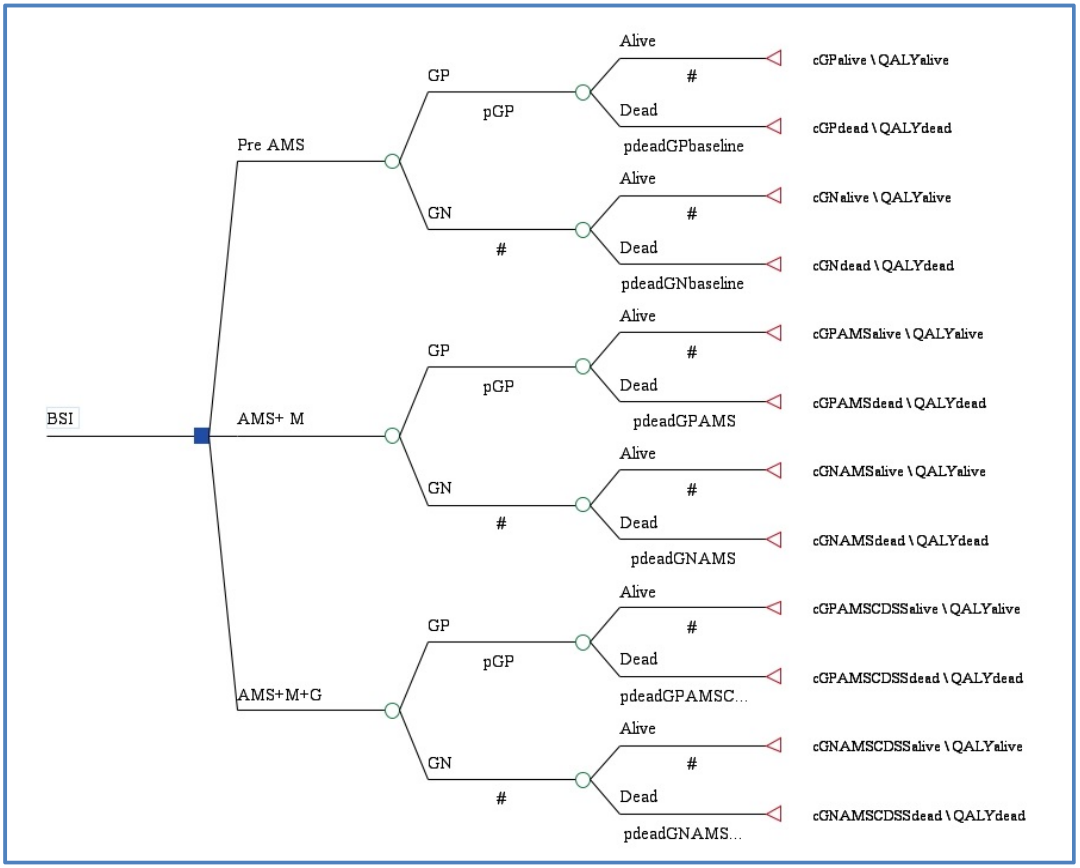

Figure 7.1 Schematic diagram of decision-analysis model RBWH

To estimate the proportion of GP BSIs in each dataset the proportion of GP in each intervention period was calculated and the average was included in the model (Table 7.1). The proportion of GP BSIs remains constant in each arm as this is not a variable that should impact the end result. The low and high values used in the table below are a binomial confidence interval.

Table 7.1 Proportion of GP in each intervention period

GP&GN	D2	D7	D9	Average	Low	High	SD
Not GP	227	126	75				
GP	98	111	41				
P(GP)	0.302	0.468	0.353	0.369	0.3327	0.4055	0.0185
Abbreviations: D2: Pre AMS; D7: AMS+MALDI-TOF; D9: AMS+MALDI-TOF+CDSS; P(GP) Proportion of GP							

7.2.2 POINT ESTIMATES FOR THE MODEL AT THE RBWH

Table 7.2 presents a combination of the point estimates for the cost of each of the components of the AMS intervention at the RBWH calculated in Chapter 5 and the point estimates for effectiveness achieved in Chapter 6. A suitable distribution for each type of parameter was selected and a standard deviation (beta-distributions), standard error (gamma distributions) and minimum and maximum values (uniform distributions) were derived for each of the variables.

Table 7.2 Point estimates and distribution type and ranges used in Model at the RBWH

Beta Distribution	Point estimate	Standard deviation	Source
Proportion of GP	0.369	0.0185	RBWH
Probability of death GP BSI Pre AMS	0.15546	0.03660	RBWH(D2)
Probability of death GN BSI pre AMS	0.09692	0.01964	RBWH(D2)
Probability of death GP post AMS+m	0.13016	0.03194	RBWH(D7)
Probability of death GN post AMS+m	0.081145	0.02433	RBWH(D7)
Probability of death GP post AMS+m+g	0.14385	0.05481	RBWH(D9)
Probability of death GN post AMS+m+g	0.08968	0.03299	RBWH(D9)
Gamma Distribution	**Point estimate**	**Standard Error**	**Source**
LOS for GP BSI and alive	38.608	4.309	RBWH(D2)
LOS for GP BSI that died	26.586	9.281	RBWH(D2)
LOS GN BSI and alive	31.598	2.487	RBWH(D2)
LOS GN BSI that died	28.729	7.562	RBWH(D2)
LOS GP BSI alive post AMS	32.820	3.924	RBWH(D7)
LOS GP BSI dead post AMS	19.303	10.352	RBWH(D7)
LOS GN BSI alive post AMS	26.302	3.274	RBWH(D7)
LOS GN BSI dead post AMS	39.553	13.381	RBWH(D7)
LOS GP BSI alive post AMS	34.102	6.389	RBWH(D9)
LOS GP BSI dead post AMS	30.119	17.115	RBWH(D9)
LOS GN BSI alive post AMS	20.443	4.226	RBWH(D9)
LOS GN BSI dead post AMS	14.802	15.854	RBWH(D9)
Uniform Distribution	**Point estimate**	**Min. $, Max $**	**Source**
Cost of a bed day in GW	$216	178.59, 253.41	Page et al,(193)
Cost of AMS	$153.24	126.70, 179.78	RBWH
Cost of CDSS	$28.22	23.330, 33.11	RBWH
Cost of pharmacy pre AMS	$99.00	81.85, 116.15	RBWH
Cost of pharmacy post AMS+M	$92.92	76.83, 109.01	RBWH
Cost of pharmacy post AMS+M+G	$81.68	67.53, 95.83	RBWH
Cost of lab pre AMS	$38.79	32.07, 45.51	RBWH
Cost of lab post AMS+M	$30.81	25.47, 36.15	RBWH
Cost of lab post AMS+M+G	$30.81	25.47, 36.15	RBWH
Abbreviations: AMS: Antimicrobial Stewardship; M: MALDI-TOF; G: Guidance MS; CDSS: Clinical Decision Support System; D2: dataset 2(Pre AMS); D7:Dataset 7 (AMS+M) and D9 (AMS+M+G); GP:Gram Positive; GN: Gram Negative; LOS Length of Stay; GW: General Ward			

These point estimates are now able to be inputted into the model and the cost-effectiveness analysis performed.

7.3 MODEL 2: MHS

The second model developed for the MHS is the same structure but compared different scenarios. At the MHS rapid diagnostics in the laboratory was well established prior to the implementation of the AMS intervention. The AMS intervention did not include a CDSS. The model was validated in the same way as for the RBWH as they are very similar in structure. In this model however the impact of rapid diagnostics (MALDI-TOF) can be evaluated prior to the AMS intervention being implemented.

The first arm of the model represents the situation prior to the AMS intervention as well as rapid diagnostics in the form of MALDI-TOF (Pre AMS/MALDI). The second arm uniquely represents the period where MALDI-TOF technology had been implemented (MALDI) and the final dataset is represented in the third arm of the model after the AMS intervention was implemented (AMS+M) (Figure 7.2). This decision tree represents Bloodstream infection datasets collected from October 2009 (Pre AMS/MALDI) to December 2014 (Post AMS+M).

7.3.1 STRUCTURE OF THE DECISION TREE

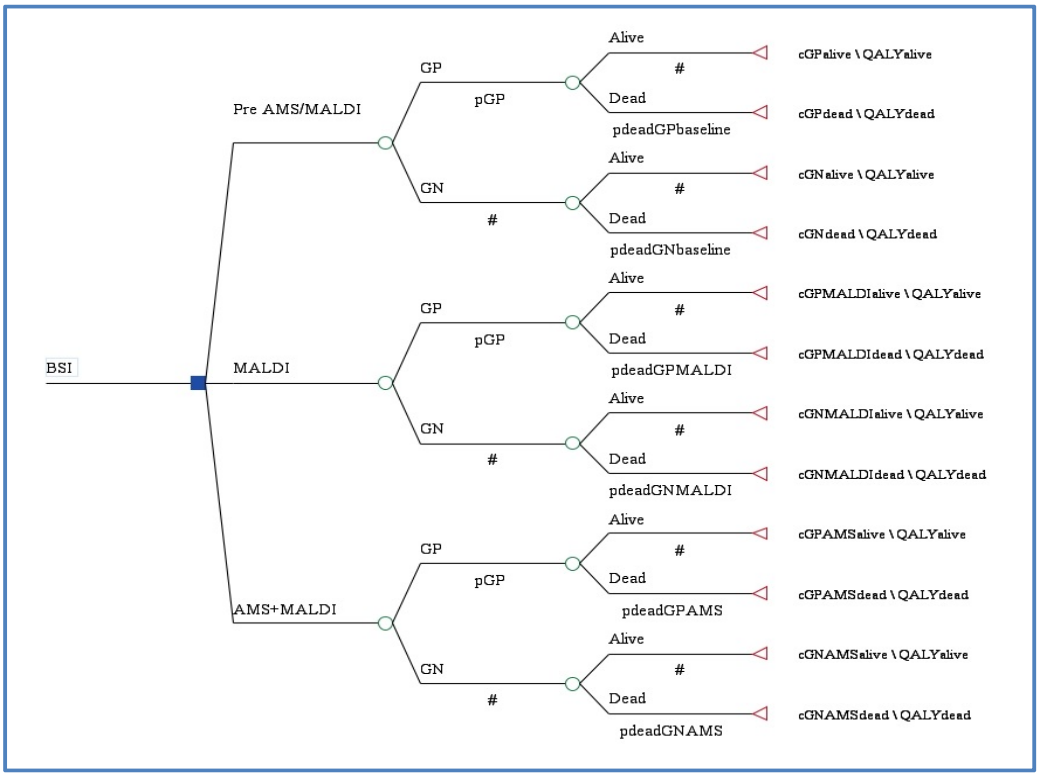

Figure 7.2 Schematic diagram of decision-analysis model

As for the RBWH an average for the proportion of GP BSIs in this patient cohort was derived for each of the interventions periods described below(Table 7.3).

Table 7.3 Proportion of GP for each intervention period

GP&GN	D1	D5	D8	Average	Low	High	SD
Not GP	170	185	126				
GP	49	79	44				
P(GP)	0.224	0.299	0.259	0.263	0.2300	0.2976	0.0172

Abbreviations: GP: Gram Positive; GN: Gram Negative; P(GP) proportion of GP Bloodstream Infections; SD: standard deviation; D1:Dataset 1(Pre AMS/MALDI); D5:Dataset 5 (MALDI-TOF); D8:Dataset 8 (AMS+M)

7.3.2 POINT ESTIMATES FOR THE MODEL AT THE MHS

Table 7.4 presents a combination of the point estimates for the cost of each of the components of the AMS intervention at the MHS calculated in Chapter 5 and the point estimates for effectiveness achieved in Chapter 6. A suitable distribution for each type of parameter was selected according to the guidelines provided in Briggs et al (189).

Table 7.4 Point estimates and distribution type and ranges used in Model at the MHS

Beta Distribution	Point estimate	Standard deviation	Data Source
Proportion of GP pre AMS	0.263	0.0172	Mater
Probability of death GP BSI Pre AMS	0.08052	0.03887	Mater(D1)
Probability of death GN BSI pre AMS	0.0765	0.02039	Mater(D1)
Probability of death GP post MALDI-TOF	0.06031	0.02678	Mater(D5)
Probability of death GP post AMS+M	0.10312	0.04585	Mater(D5)
Probability of death GP post MALDI-TOF	0.05730	0.01709	Mater(D8)
Probability of death GN post AMS+ M	0.09798	0.02648	Mater(D8)
Gamma Distribution	**Point estimate**	**Standard error**	**Source**
LOS for GP BSI and alive	25.122	3.652	Mater(D1)
LOS for GP BSI that died	14.720	9.801	Mater(D1)
LOS GN BSI and alive	16.403	1.543	Mater(D1)
LOS GN BSI that died	44.294	5.360	Mater(D1)
LOS GP BSI alive post AMS	27.932	3.999	Mater(D5)
LOS GP BSI dead post AMS	19.873	9.261	Mater(D5)
LOS GN BSI alive post AMS	14.935	1.803	Mater(D5)
LOS GN BSI dead post AMS	38.077	6.108	Mater(D5)
LOS GP BSI alive post AMS	26.074	2.845	Mater(D8)
LOS GP BSI dead post AMS	39.557	9.771	Mater(D8)
LOS GN BSI alive post AMS	16.240	1.459	Mater(D8)
LOS GN BSI dead post AMS	22.106	6.110	Mater(D8)
Uniform Distribution	**Point estimate**	**Min. $, Max. $**	**Source**
Cost of a bed day in GW	$216	178.59, 253.41	Page et al (193)
Cost of AMS	$411.79	340.47, 483.11	Mater
Cost of pharmacy pre AMS	$1383.82	1144.14, 1623.51	Mater
Cost of pharmacy post AMS+M	$721.54	596.57, 846.51	Mater
Cost of Pharmacy post MALDI-TOF	$646.67	534.66, 758.68	Mater
Cost of lab pre AMS	$53.14	43.94, 62.34	Mater
Cost of lab post AMS	$44.28	36.61, 51.95	Mater
Abbreviations: AMS: Antimicrobial Stewardship; M: MALDI-TOF; D1: dataset 2(Pre AMS/MALDI-TOF); D5:Dataset 5 (MALDI-TOF) and D8: Dataset 8(AMS+M); GP:Gram Positive; GN: Gram Negative; LOS Length of Stay;GW: General Ward			

7.4 VALUING HEALTH OUTCOMES IN NON ICU PATIENTS WTH BSIS

A study published by Hawthorne et al 2013(188) showed that most Australians enjoyed a high HRQoL (Health Related Quality of Life). The study provides a mean (AQoL) for age groups of males and females for the general Australian population. The mean AQoL for all patients in the general population represented in this study is a utility score of 0.81 (95%CI: 0.81-0.82) on a scale of 0-1. The assumption made in this research is that the patients at each of these hospitals have undergone a BSI and did not spend time in ICU and as such their long term quality of life has not changed from that of the general population. The HRQol gradually declines by age group as demonstrated in Figure 7.3.

Hawthorne, Korn and Richardson **Article**

Table 1: AQoL norms by age group and gender.

Age group (years)	Gender	n	AQoL utility scores					
			Mean	SD	95% CI	Statistics[a]	Median	IQR
16-19	Female	354	0.87	0.17	0.85-0.89		0.93	0.18
	Male	352	0.88	0.16	0.86-0.89		0.93	0.18
	All	705	0.87	0.17	0.86-0.88		0.93	0.18
20-29	Female	775	0.84	0.20	0.83-0.85		0.92	0.20
	Male	550	0.88	0.18	0.86-0.89	***	0.95	0.16
	All	1325	0.86	0.19	0.85-0.87		0.93	0.20
30-39	Female	916	0.84	0.21	0.83-0.85		0.91	0.20
	Male	702	0.84	0.21	0.82-0.86		0.92	0.22
	All	1681	0.84	0.21	0.83-0.85		0.91	0.23
40-49	Female	738	0.81	0.22	0.79-0.82		0.88	0.25
	Male	644	0.81	0.23	0.79-0.83		0.89	0.22
	All	1382	0.81	0.23	0.80-0.82		0.89	0.24
50-59	Female	736	0.80	0.23	0.78-0.81		0.89	0.27
	Male	559	0.79	0.25	0.77-0.82		0.89	0.26
	All	1295	0.80	0.24	0.78-0.81		0.89	0.27
60-69	Female	597	0.79	0.22	0.78-0.81		0.87	0.27
	Male	649	0.80	0.23	0.78-0.81		0.89	0.26
	All	1245	0.80	0.22	0.78-0.81		0.89	0.27
70-79	Female	473	0.76	0.24	0.74-0.78		0.84	0.28
	Male	439	0.79	0.22	0.77-0.81		0.86	0.22
	All	912	0.76	0.23	0.76-0.79		0.85	0.23
80-85	Female	225	0.68	0.26	0.65-0.72		0.73	0.37
	Male	132	0.73	0.27	0.68-0.78	*	0.81	0.37
	All	357	0.70	0.26	0.67-0.73		0.77	0.37
Total	Female	4814	0.81	0.22	0.80-0.81		0.89	0.25
	Male	4025	0.82	0.22	0.81-0.83		0.90	0.25
	All	8839	0.81	0.22	0.81-0.82		0.89	0.24

Notes:
N = number; SD = Standard deviation; 95%CI – Ninety-five percent confidence interval; IQR = interquartile range
*a = Independent t-test on transformed data. * p≤0.05; **p≤0.01; ***p≤0.001*

Figure 7.3 Table of values used in calculating the QALYs for each hospital adopted from Hawthorne et al (188)

7.4.1 THE RBWH

The average age of the patients at RBWH was 58.9 years (Table 7.5) and the average life expectancy in Australia for males and females combined is 82.2 years in 2015 (http://www.aihw.gov.au/deaths/life-expectancy/#trends). So, the remaining life years in this dataset is 23.3 years.

Using this number the QALYs remaining in patients that survived following a BSI at the RBWH were calculated. The mean per patient remaining lifetime QALYs for patients in this dataset was 18.02.

Table 7.5 Calculation of the QALYs for patients in this dataset

Age group	Time in age group	Utility score	Total utility
50-59	1.1	0.80	0.88
60-69	10	0.80	8.0
70-79	10	0.76	7.6
80-89	2.2	0.7	1.54
Total	23.3		18.02

7.4.2 THE MHS

The average age of the patients at the MHS was 66.2 (Table 6.3) and the average life expectancy in Australia for males and females combined is 82.2 years in 2015 (http://www.aihw.gov.au/deaths/life-expectancy/#trends). So the remaining life years in this dataset is 16 years.

Using this number the QALYs remaining in patients that survived following a BSI at MHS were calculated (Table 6.4). The mean per patient remaining lifetime QALYs for patients in this dataset was 12.18.

Table 7.6 Calculation of the QALYs for patients in this dataset

Age group	Time in age group	Utility score	Total utility
50-59	0	0.80	0
60-69	3.8	0.80	3.04
70-79	10	0.76	7.6
80-89	2.2	0.7	1.54
Total	16		12.18

7.5 MODEL EVALUATION

The process used to evaluate the models is the same for both hospitals and will be described in full in the following section. The initial evaluation consists of performing a fixed value analysis using the point estimates and then followed by a probabilistic analysis using a parameter range to estimate the impact of the uncertainty in the estimates used. Finally a one-way sensitivity analysis is performed to identify the estimates that contribute most to the uncertainty in the decision.

7.5.1 FIXED VALUE ANALYSIS

Described more fully in section 3.5.1 this fixed value analysis that does not account for uncertainty in the estimates is also known as the deterministic cost-effectiveness analysis (CEA). Results are presented as the change in costs and effectiveness and these results are plotted on a cost-effectiveness plane where the X axis represents the change in effectiveness and the Y axis the change in costs. To demonstrate the impact of uncertainty in the analysis probabilistic sensitivity analysis is performed using Treeage Pro software and a Monte Carlo simulation as detailed below. For each of the hospitals in this evaluation a deterministic analysis was performed using Treeage Pro software and is presented graphically and numerically in chapter 8.

7.5.2 PROBABILISTIC ANALYSIS

PSA described more fully in section 3.5.2 was used to determine the impact of the uncertainty in the parameter estimates used in the CEA using a Monte Carlo simulation where ICERS were generated 10,000 times using random combinations of the variables within a range. Types of distributions chosen for the parameters in this analysis are presented in Table 7.2 and 7.4 for each of the hospitals in this analysis. Beta distributions were chosen for the risk of mortality estimates, gamma distributions for the LOS estimates and uniform distributions for the cost estimates. The results from this analysis are presented graphically as a scatterplot where each point estimate for a random draw of parameters is plotted on a cost-effectiveness plane. The end result is 10,000 dots in the form of a cloud on a cost-effectiveness plane indicating possible outcomes for each of the combinations of variables.

This end result provides a visual representation of the overall position of the cost-effectiveness result and which quadrants have the majority of the dots. A cost-effectiveness plane has 4 quadrants as detailed in Chapter 3. If >50% of the dots are in the quadrants II and IV it would mean that the results indicate that the intervention was more effective than the baseline. If the majority of the dots are in quadrant III then the intervention was cost savings as well as more effective and this would be the most preferred position. However if the majority of estimates fall in quadrant II it would mean that while the intervention is more effective it is also more costly and the interpretation of these results would depend on what the willingness to pay for a unit of health gain is set at.

In this analysis the willingness to pay for a Quality adjusted life year (QALY) will be set at $64,000 as estimated by Shiroiwa et al in 2010 for Australia (192). There is much controversy regarding the appropriate value to use depending on the perspective of the analysis as well as the severity of the impact of the scenario under consideration. Since the impact of AMR in hospital environments and to a greater degree from a societal perspective can result in significant mortality and morbidity a QALY valued at this amount would stand to reason. However it is worth considering that this value may vary depending on the perspective of the decision maker in each healthcare environment. The priority given by a country's governing

body would also determine the willingness to pay for an additional unit of effectiveness in this intervention. To achieve the desired outcome set out by the WHO on AMR the WTP needs to reflect the priority placed on the reduction of resistance in the healthcare environment. However a fixed threshold for all interventions is less desirable as is the case in some countries such as the USA where the WTP is set at $50,000. Nimdet et al (190), in a systematic review concluded that policy makers need to initiate conversations among themselves and stakeholders regarding the criteria decisions are based on. The WTP is more likely to be a dynamic value that adapts to the healthcare priorities at the time of decision making.

7.5.3 ONE WAY SENSITIVITY ANALYSIS

To understand if the uncertainty in the parameters were evenly distributed among all the parameters used in the model or if some parameters had more impact on the end result one way sensitivity analysis on each of the individual parameters was performed. The low and high values for the parameters were estimated using the method of moments where the sample mean and variance were equated to the theoretical mean and variances to obtain two equations which could be simultaneously solved. Tornado diagrams of all the parameters in each of the analyses were evaluated.

7.5.4 NET MONETARY BENEFIT (NMB) AND TORNADO DIAGRAMS

The Net Monetary Benefit (NMB) of each of the interventions was calculated using the change in effectiveness multiplied by the willingness to pay for a measure of effectiveness minus the change in cost. This rearrangement of the cost-effectiveness rule overcomes the issues with negative ICERs generated when either the intervention is cost saving and more effective or when the intervention is more costly and less effective. Under these conditions a NMB framework can provides clearer information as to which intervention is the most cost-effective. For the high low estimates the parameters of the distributions were estimated using the method of moments using R. These estimates were used to calculate the mean NMB in this analysis as described by Drummond et al(181).

7.6 SCENARIO ANALYSIS

The effectiveness of the AMS interventions in both of the hospitals was measured using the estimates of the relative risk of death and LOS in each intervention period. To estimate the impact of these estimates on the final result a number of scenarios were tested. Firstly due to the small numbers of positive BSIs caused by ESKAPE organisms in our datasets, it was hoped that combining the GP&GN organism groups and recalculating the impact on the probability of death and LOS in hospital might strengthen the statistical significance of these estimates. Secondly while conservative estimates were used to value the cost of a bed day at $216, the impact of the cost of a bed day was also tested by reducing the value of the bed day to $0. This allows the financial value of the intervention to be assessed and not the opportunity cost. And finally, the impact of the estimates of the relative risk of death in each of the intervention periods was tested by using estimates from the literature instead of the ones derived from each dataset. These new parameters are used to run the model in each option evaluated.

7.6.1 COMBINED GP&GN ESTIMATES FOR THE RBWH

To possibly strengthen the statistical analysis the organism groups were combined and the estimates from this analysis used in a model that was designed for the scenario analysis depicted in Figure 7.4. This model groups GP&GN organisms and compares the two intervention arms as before to a time pre AMS.

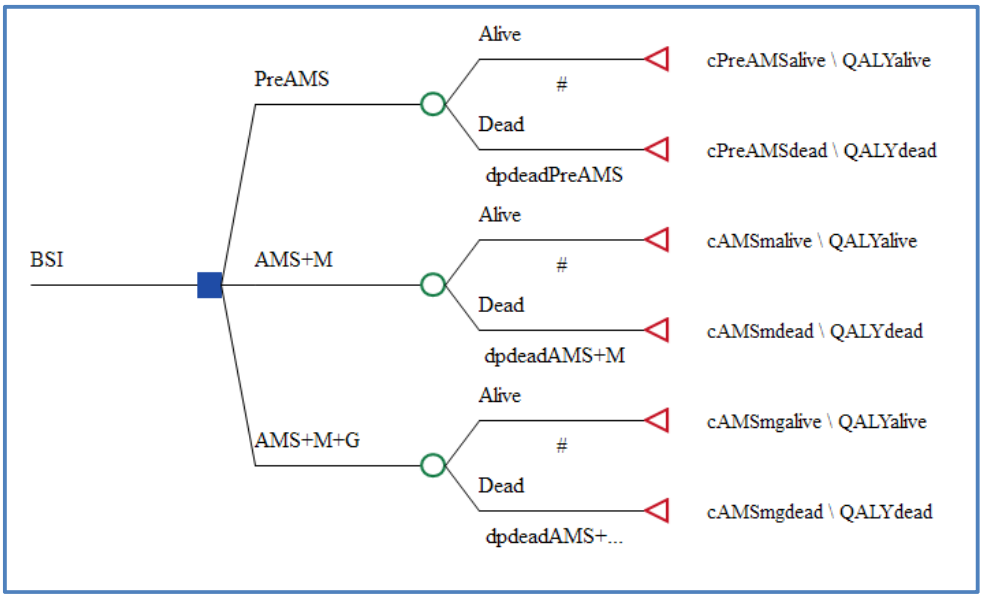

Figure 7.4 Model representing new estimate with combined GP&GN organism groups for the RBWH

Table 7.7 presents the new point estimates with suitable distributions to perform the scenario analyses. Note in each case only the parameters for the probability of death and LOS in hospital has changed.

Table 7.7 New estimates for the scenario analysis combining GP&GN organism groups for the RBWH

Beta Distribution	Point estimate	Standard deviation	Source
Probability of death Pre AMS	0.123077	0.018223	RBWH (D2)
Probability of death Post AMS+M	0.114462	0.02068	RBWH (D7)
Probability of death Post AMS+M+G	0.121846	0.030371	RBWH (D9)
Gamma Distribution		**Standard Error**	**Source**
LOS for PreAMS alive	33.466	2.176	RBWH (D2)
LOS for PreAMS that died	26.578	5.831	RBWH (D2)
LOS BSI alive post AMS+M	29.095	2.509	RBWH (D7)
LOS BSI dead post AMS+M	25.499	8.007	RBWH (D7)
LOS alive post AMS+M+G	24.802	3.545	RBWH (D9)
LOS dead post AMS+M+G	23.490	11.551	RBWH (D9)
Uniform Distribution	**Point estimate**	**Min.$, Max.$**	**Source**
Cost of a bed day in GW	$216	178.59, 253.41	Page et al, (193)
Cost of AMS	$153.24	126.70, 179.78	RBWH
Cost of CDSS	$28.22	23.330, 33.11	RBWH
Cost of pharmacy pre AMS	$99.99	81.85, 116.15	RBWH
Cost of pharmacy post AMS+M	$92.92	76.83, 109.01	RBWH
Cost of pharmacy post AMS+M+G	$81.68	67.53, 95.83	RBWH
Cost of lab pre AMS	$38.79	32.07, 45.51	RBWH
Cost of lab post AMS+M	$30.81	25.47, 36.15	RBWH
Cost of lab post AMS+M+G	$30.81	25.47, 36.15	RBWH

Abbreviations: AMS: Antimicrobial Stewardship; M: MALDI-TOF; G: Guidance MS; CDSS: Clinical Decision Support System; D2: dataset 2(Pre AMS); D7:Dataset 7 (AMS+M) and D9 (AMS+M+G); GP:Gram Positive; GN: Gram Negative; LOS Length of Stay; GW: General Ward

7.6.1.1 Point estimates for the scenario analysis 2 replaces the cost of a bed day of $216 with $0

The estimates from Table 7.7 were used in this analysis and the only change in this case is the cost of a bed day from$216 to $0. The model in Figure 7.4 is run with this new information to ascertain the impact of the value placed on a bed day.

7.6.1.2 Point estimates for the scenario analysis 3 replaces the probability of death post AMS+M and AMS+M+G as per table 7.9

In this analysis the model in Figure 7.4 is run with the literature based estimate of mortality as described in Table 7.8 for each of the intervention periods. All other parameters are the same as in Table 7.7. The results from this analysis are presented in Chapter 8.

Table 7.8 Point estimates for the literature based analysis

Description	Point estimate	Standard deviation	Distribution	Source
Probability of death Pre AMS	0.2105	0.02594	Beta	Literature(68)
Probability of death Post AMS+M	0.1202	0.02130	Beta	
Probability of death post AMS+M+G	0.1202	0.02130	Beta	

7.6.2 COMBINED GP&GN ESTIMATES FOR THE MHS

The same analysis as for the RBWH dataset was performed for the MHS dataset and GP&GN organism groups were combined and new estimates for the probability of death and LOS in each alternative was calculated. The new model for this analysis combining organism groups is presented in Figure 7.5.

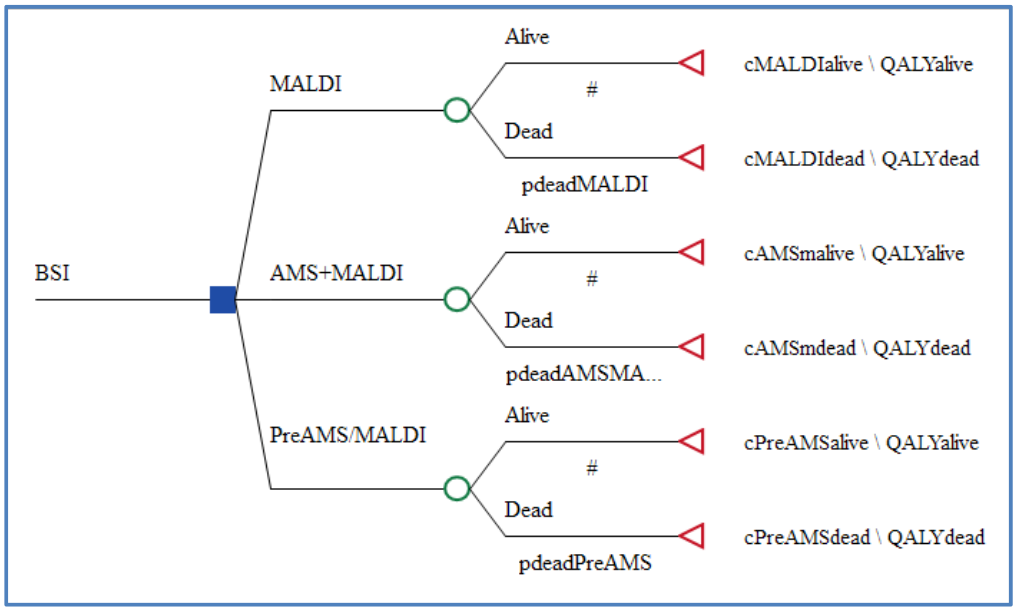

Figure 7.5 Model representing new estimate with combined GP&GN organism groups for the MHS

7.6.2.1 **Point estimate for the scenario analysis 1**

Table 7.9 presents the new estimates with suitable distributions for the scenario analysis. Note in each case only the parameters for the probability of death and LOS in hospital has changed. All cost parameters are the same as for the previous evaluation at MHS.

Table 7.9 New estimates for the scenario analysis combining GP&GN organism groups for the MHS

Beta Distribution	Point estimate	Standard deviation	Source
Probability of death Pre AMS	0.086758	0.019021	Mater
Probability of death Post MALDI-TOF	0.065068	0.01518	Mater
Probability of death post AMS+M	0.111918	0.02418	Mater
Gamma distribution	Point estimate	**Standard error**	**Source**
LOS for Pre AMS alive	18.211	1.498	Mater
LOS for GP BSI that died	35.141	4.862	Mater
LOS GP BSI alive post AMS	19.291	1.344	Mater
LOS GP BSI dead post AMS	28.569	5.295	Mater
LOS GN BSI alive post AMS	18.009	1.724	Mater
LOS GN BSI dead post AMS	30.774	5.151	Mater
Uniform distribution	Point estimate	**Min. $, Max. $**	**Source**
Cost of a bed day in GW	$216	178.59, 253.41	Page et al, (193)
Cost of AMS	$411.79	340.47, 483.11	Mater
Cost of pharmacy pre AMS	$1383.82	1144.14, 1623.51	Mater
Cost of pharmacy post AMS+M	$721.54	596.57, 846.51	Mater
Cost of Pharmacy post MALDI-TOF	$646.67	534.66, 758.68	Mater
Cost of lab pre AMS	$53.14	43.94, 62.34	Mater
Cost of lab post AMS	$44.28	36.61, 51.95	Mater
Abbreviations: AMS: Antimicrobial Stewardship; M: MALDI-TOF; D1: dataset 2(Pre AMS/MALDI-TOF); D5:Dataset 5 (MALDI-TOF) and D8: Dataset 8(AMS+M); GP:Gram Positive; GN: Gram Negative; LOS: Length of Stay;GW: General Ward			

7.6.2.2 Point estimates for scenario 2 replaces the cost of a bed day of $216 with $0

The estimates from Table 7.9 are used in this analysis and the only change in this case is the cost of a bed day from$216 to $0. The model in Figure 7.5 is run with this new information to ascertain the impact of the value placed on a bed day.

7.6.2.3 Point estimates for scenario 3

Table 7.10 presents the literature based estimates for the intervention related mortality used instead of the ones derived from the raw data at the MHS in the scenario analysis.

Table 7.10 Point estimated from the literature for the impact of mortality

Description	Point estimate	Standard deviation	Distribution	Source
Probability of death Pre AMS	0.2105	0.02594	Beta	Literature(68)
Probability of death Post MALDI-TOF	0.1202	0.02130	Beta	
Probability of death post AMS+M	0.1202	0.02130	Beta	

The results from this analysis are presented in Chapter 8

7.7 SUMMARY

The model design in this analysis is similar for the RBWH and the MHS, the only difference being the tools introduced in the two hospitals. The impact of rapid diagnostics in isolation without an AMS intervention can be evaluated at the MHS and the impact of AMS and rapid diagnostics combined can be evaluated for both hospitals. And finally the combined effect of AMS, rapid diagnostics and a clinical decision support system can be evaluated at the RBWH.

The next chapter presents the results for each of these options for the two hospitals evaluated. The analysis is performed as a deterministic model using point estimates for each parameter in the model and probabilistic and one way sensitivity analysis is performed to account for the uncertainty in the parameters.

Chapter 8: **RESULTS**

This chapter presents the results of the CEA of the AMS interventions at two Brisbane metropolitan hospitals. Section 8.1 presents a summary of the interventions and the preliminary findings with regard to the changes to the risk of mortality, hospital LOS and antimicrobial utilisation costs due to the intervention at the Royal Brisbane and Women's Hospital (RBWH) and the Mater Health Service (MHS). Section 8.2 presents the fixed value analysis of cost-effectiveness for each of the interventions followed by section 8.3 where the uncertainty due to the parameter estimates by the results are presented using probabilistic sensitivity analysis. Section 8.4 presents the results in terms of Net Monetary Benefits captured and section 8.5 presents the results from the one way sensitivity analysis. Section 8.6 presents the scenario analyses to explore the impact of a change to the estimates of mortality and the cost of a bed day from the original analysis. The final section 8.7 provides a summary of the results for the two hospitals.

8.1 THE ECONOMIC EVALUATION OF THE RBWH AND THE MHS AMS INTERVENTIONS

Table 8.1 includes a summary of the interventions included in this analysis. At the RBWH a scenario with AMS and MALDI-TOF technology and a second where the CDSS was included were compared to the baseline Pre AMS. At the MHS, AMS was implemented after MALDI-TOF technology had been in place for around two years. This makes it possible to model the impact of MALDI-TOF technology in isolation prior to the introduction of the AMS intervention compared to the baseline.

The interventions at each hospital with regard to the timeline of implementation and the types of strategies used have been described in detail in Chapter 4. The comparator which is the baseline has also been clearly defined in each setting in section 4.2.1 for the RBWH and Section 4.3.1 for the MHS.

The hospitals are different in the composition and the administration of the AMS intervention and the details are set out in Table 8.1. The risk of mortality expressed as a Hazard Ratio (HR), difference in hospital length of stay (LOS) (Table 8.2) and the cost of antimicrobials (Table 8.3) for the baseline prior to the intervention and for each of the intervention periods are summarised below.

Table 8.1 Summary of the interventions included in the CEA

Hospital	Interventions compared to baseline	Description
RBWH	AMS+MALDI-TOF(AMS+M)	AMS intervention with an aim of reducing antimicrobial use and MALDI-TOF technology in the laboratory
	AMS+MALDI-TOF+GMS(AMS+M+G)	AMS intervention with an aim of reducing antimicrobial use, MALDI-TOF technology in the laboratory and a CDSS (Guidance MS) to triage and educate prescribers
MHS	MALDI-TOF	MALDI-TOF technology in the laboratory
	AMS+MALDI-TOF(AMS+M)	AMS intervention with an aim of reducing antimicrobial use and MALDI-TOF technology in the laboratory

The incremental risk of mortality and the average LOS compared to the pre intervention period at each of the hospitals is tabulated in Table 8.2.

Table 8.2 Summary of incremental change to risk of mortality and average LOS

Intervention		Incremental change to Risk of Mortality (HR)		Incremental change to Average LOS (days)	
		GP	**GN**	**GP**	**GN**
RBWH	**AMS+M**	0.025↓	0.016↓	3.79↓	5.3↓
	AMS+M+G	0.011↓	0.007↓	2.51↓	11.16↓
MHS	**MALDI-TOF**	0.024↓	0.021↑	0.96↑	0.16↓
	AMS+M	0.021↓	0.026↑	2.82↑	1.46↓
GP: Gram Positive; GN: Gram Negative; HR: Hazard Ratio; LOS: Length of Stay;					

While there was no statistically significant difference in the risk of mortality or hospital LOS at either of the hospitals, at the RBWH there was an overall reduction in the risk of mortality and LOS following the implementation of the AMS intervention. At the MHS a reduction in the risk of mortality post intervention was seen in the GP BSIs but not in the GN BSIs and the average LOS reduced in GN BSIs but not in the GP BSIs.

There were some cost savings achieved by the reduction in total antimicrobial utilisation at both hospitals (Table 8.3). The AMS intervention at the RBWH was confined to the general wards at the time of data collection and therefore only the antimicrobial utilisation in those wards was included in the analysis. In the Non-ICU wards at the RBWH there was a gradual decline in antimicrobial use but the overall use when the ICU data were included showed a small increase straight after the AMS intervention was introduced. While the intervention had not been rolled out in the ICU at the time of data collection, whole institution wide education of prescribers on more appropriate prescribing had commenced. However it is important to note that an increase in cost does not necessarily indicate a less appropriate choice of antimicrobial.

The implementation of MALDI-TOF technology at the MHS, prior to the AMS intervention resulted in a large reduction in the consumption of antimicrobials and a consequent cost saving. The introduction of the AMS intervention also resulted in a further much smaller reduction in antimicrobial utilisation costs. The largest cost due to antimicrobial utilisation is generally seen in the ICU. However these savings achieved by the reduction in antimicrobial utilisation were smaller when the additional cost of the AMS interventions at both hospitals were included.

Table 8.3 Summary of the changes to the costs of antimicrobial utilisation at both the hospitals

Hospital	Intervention	Non ICU Antimicrobial Utilisation	Total Antimicrobial Utilisation
RBWH	**Pre AMS**	$92,266.45	$313,846.36
	AMS+M	$86,603.62 ($5,662.83↓)	$417,823.86
	AMS+M+G	$76,125.02 ($16,141.43↓)	$199,049.02
MHS	**Pre AMS**	n/a	$699,866.77
	MALDI-TOF	n/a	$358,636.07 ($341,230.70↓)
	AMS+M	n/a	$321,399.44 ($378,467.33↓)
Abbreviations: M: MALDI-TOF; G: Guidance MS			

Table 8.4 presents the cost of the AMS intervention at each hospital. At the RBWH the cost of the AMS intervention including MALDI-TOF technology (AMS+M) was $157,393.43 and the cost saved due to antimicrobial utilisation in the non-ICU wards was $5,662.83 resulting in an overall cost of $151,730.60. The cost of the AMS intervention with the addition of the CDSS guidance (AMS+M+G) was $182,613.48 and the cost saving due to antimicrobial utilisation was $16,141.43 making the cost of the AMS intervention with CDSS equal to $166,472.05.

However the intervention at the MHS was rolled out across all wards and the investment in MALDI-TOF technology in the microbiology laboratory cost a relatively small amount at $24,315.20 per annum. The costs saved from the reduced antimicrobial utilisation in that time period were 341,230.70 and the resulting net savings was quite large at $316,915.50. The AMS intervention and MALDI-TOF technology cost $227,375.05 and the savings due to antimicrobial utilisation $378,467.33, the net savings $151,092.28 was much less than prior to the AMS intervention was implemented but still achieved a large savings.

Table 8.4 Summary of the cost of the AMS intervention and the cost of the laboratory at both hospitals

Hospital	Intervention	Cost of AMS intervention	Cost of Laboratory	Total cost
RBWH	**Pre AMS**	0	$16,834.86	$16,834.86
	AMS+M	$142,820.30	$14,573.13	$157,393.43
	AMS+M+G	$169,118.70	$13,494.78	$182,613.48
MHS	**Pre AMS**	0	$24,315.20	$24,315.20
	MALDI-TOF	0	$23,114.16	$23,114.16
	AMS+M	$204,659.44	$22,715.64	$227,375.08
Abbreviations: M: MALDI-TOF; G: Guidance MS				

While it is important to reduce the cost of the unnecessary use of antimicrobials, the reduction of inappropriate prescribing may not always result in reduced costs. The addition of an AMS investment can also be quite costly depending on the strategies chosen. Cost-effectiveness analyses are required to quantitate the benefits in terms of improvements to patient outcomes as a result of better prescribing.

8.2 FIXED VALUE ANALYSIS OF THE INTERVENTIONS

The results for the CEA performed using fixed values for the cost and effect for each of the interventions is presented below. The individual variables and how they were derived are described in detail in chapters 5 and 6. Table 8.5 presents a summary of the incremental cost and incremental effectiveness as calculated using Treeage software, compared to the baseline (pre AMS) following the implementation of the AMS intervention including rapid diagnostics (MALDI-TOF) and a CDSS (Guidance MS) at the RBWH and rapid diagnostics (MALDI-TOF) followed by AMS at the MHS.

Table 8.5 Summary of the incremental costs and effectiveness for AMS strategies at RBWH and MHS per annum

Hospital	Strategy	Incremental Cost	Incremental QALY
RBWH	AMS + M	-$851	0.35
n=678	AMS+M+G	-$1,671	0.16
MHS	MALDI	-$910	0.23
n=653	AMS + M	-$250	-0.27
Abbreviations: M: MALDI-TOF; G: Guidance MS; QALY: Quality Adjusted Life Year			

When the cost-effectiveness analysis was performed there was a cost saving achieved in both hospitals for all of the interventions evaluated. At the RBWH there was a cost savings of $851 per BSI due to AMS+M and a larger savings of $1671 per BSI due to the AMS plus CDSS in the CEA. In terms of incremental effectiveness due to the interventions, the RBWH AMS+M achieved a gain of 0.35 QALYs and the addition of the CDSS achieved a gain of 0.16 QALY compared to the baseline.

At the MHS there was a cost saving of $910 per BSI after the MALDI-TOF technology was implemented and $250 per BSI after the implementation of AMS. However at the MHS while the introduction of MALDI-TOF technology resulted in a gain of 0.23 QALY the introduction of the AMS intervention resulted in a loss of 0.27 QALYs.

Figure 8.1 is a graphical representation of the change in costs and effectiveness resulting from each of the interventions at the RBWH plotted on a cost-effectiveness plane.

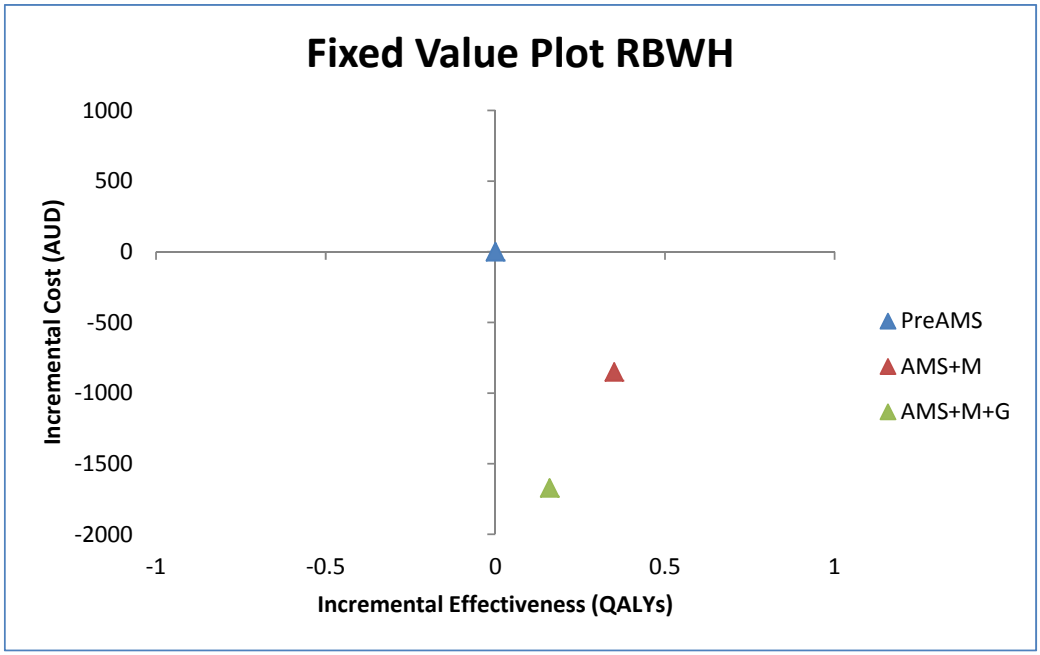

Figure 8.1 Fixed value CEA of the AMS interventions at the RBWH

At the RBWH, the interpretation for decision making is that AMS+M+G should definitely be adopted as compared to Pre AMS as costs reduced and health gains are positive. There remains a further decision of whether the extra gains to health are worth the extra cost from choosing AMS+M over AMS+M+CDSS. The additional cost is $820 and the additional QALYs are 0.19 revealing a cost per QALY gained of $4315.79. As this is well below the threshold for cost-effectiveness there is economic evidence to support the adoption of AMS+M.

The CEA of the AMS intervention at MHS following a fixed value analysis is summarised in Figure 8.2.

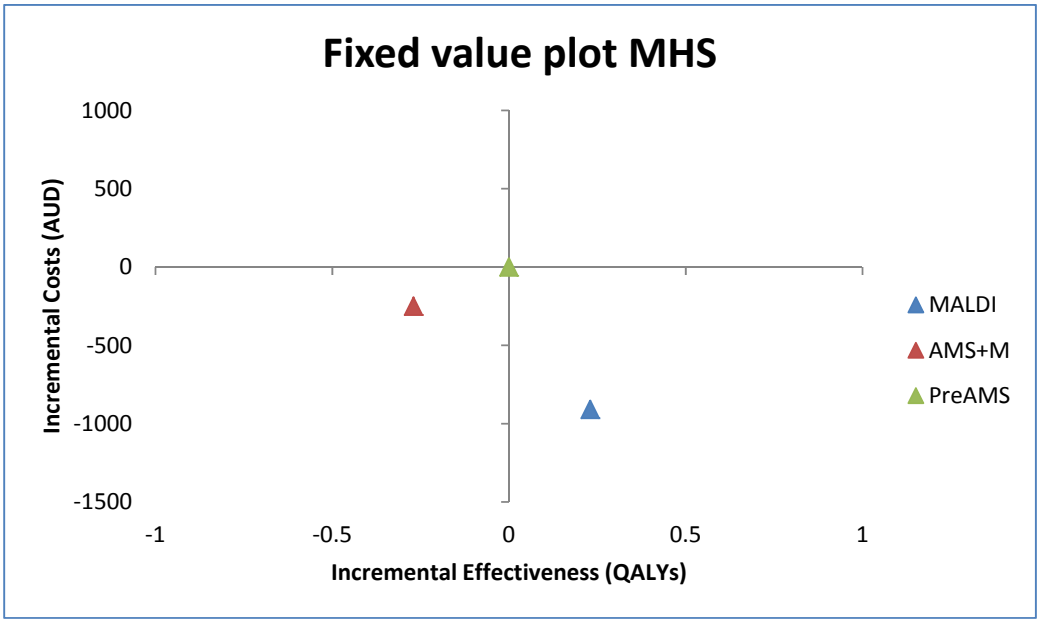

Figure 8.2 Fixed value CEA of the AMS intervention at the MHS

There is a cost savings overall with the introduction of MALDI-TOF and AMS at MHS, however while the implementation of MALDI-TOF resulted in improved health benefits there was a reduction in health benefits with the introduction of the AMS intervention at the MHS. However this adoption decision and a decision to remain with Pre AMS are both dominated by MALDI, which shows cost savings of $910 and gains to health of 0.23 QALYs compared to Pre AMS and cost savings of $660 and gains to health of 0.5 QALYs as compared to AMS+M. At the MHS there is economic evidence for the adoption of MALDI-TOF as the optimal choice. To understand the effect of parameter uncertainty on these conclusions a probabilistic sensitivity analysis (PSA) was performed and the results are presented in section 8.3.

8.3 PROBABILISITIC SENSITIVITY ANALYSIS OF THE INTERVENTIONS

To determine the uncertainty in the model's input parameters, PSA was undertaken for the AMS intervention at both hospitals. The results are presented graphically in Figures 8.3 for the RBWH.

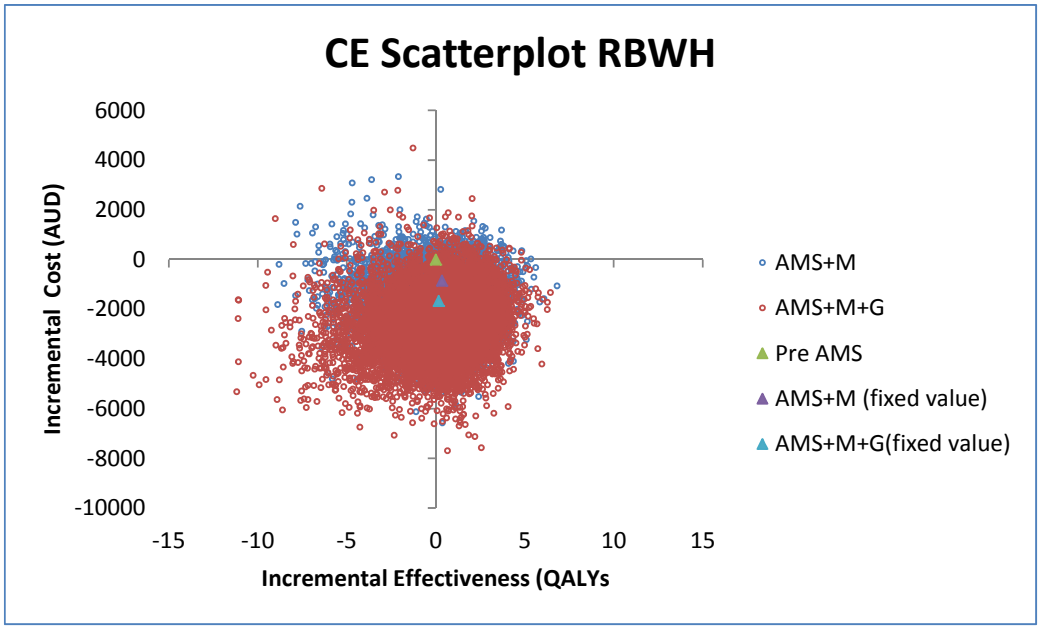

Figure 8.3 Cost-effectiveness scatterplot of the incremental cost vs incremental effectiveness for the AMS intervention at the RBWH

Probabilistic sensitivity analysis shows a scatterplot of 10,000 iterations selected randomly from the parameter distributions in the model (Figure 8.3). The incremental cost and the incremental effectiveness for each of the interventions are plotted on a cost-effectiveness plane, the red dots represent the AMS intervention with MALDI-TOF technology (AMS+M) and the blue dots AMS, MALDI-TOF technology with the addition of CDSS Guidance MS (AMS+M+G). As can be seen in the scatterplot there is an almost complete overlap in the distribution of blue and red dots. This indicates a high level of decision uncertainty and not much difference in either intervention.

The majority of simulations are in the cost savings part of the plane which indicates that the intervention is cost savings when compared to the pre-intervention period. This cost savings is mainly due to the reduction of antimicrobial usage which has been demonstrated in previous evaluations of the outcomes of AMS interventions. Over half of the simulations appear to be in the plane where there is a reduction in effectiveness.

Figure 8.4 represents the results from 10,000 simulations for the MHS model. The estimates confirm great uncertainty for change to costs and health benefits.

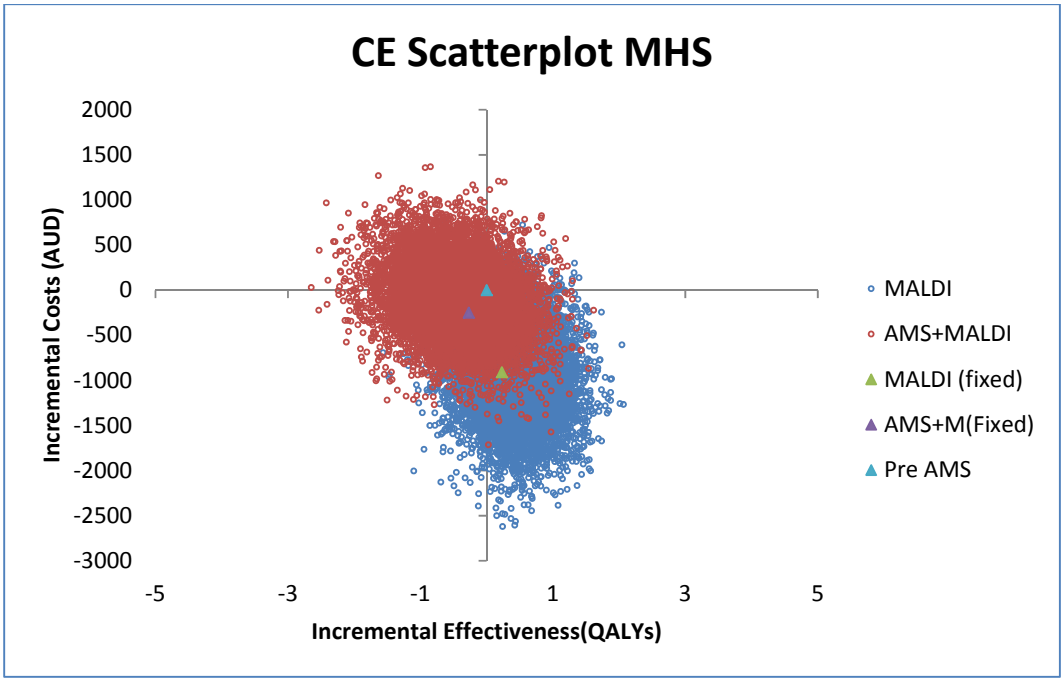

Figure 8.4 Cost-effectiveness scatterplot of the incremental cost vs incremental effectiveness for the AMS intervention at the MHS

The majority of dots are in the cost savings area. In this situation where there is such large parameter uncertainty the net monetary benefits framework is useful. The change to costs and effects are combined into a linear measure and shows the option most likely to return the best economic outcome(181). The net monetary benefit of an intervention can be assessed by evaluating the difference in effects between two options by rescaling to monetary value using the willingness to pay

unit of effect and the difference in cost between the options is subtracted from this value(181).

8.4 NMB ANALYSIS

The NMB that includes parameter uncertainty is an alternative measure for the value for money of health care interventions. Table 8.6 summarises the NMB for each of the alternatives assessed in this analysis with a willingness to pay of $64,000/QALY.

For the interventions at the RBWH the mean NMBs were greater for AMS+M at $24,877 than AMS+M+G with a NMB of $14,645, when a willingness to pay of $64,000 was used. This may indicate that the addition of the CDSS (Guidance MS) is not valuable by measure of costs saved of health benefit. So at the RBWH the intervention with AMS+MALDI-TOF is the optimal decision.

Table 8.6 Mean, Min & Max NMB calculations for the interventions at both hospitals

Scenario	Mean	95% credible interval
RBWH AMS+M	$24,877	(-$566,425 - $437,504)
RBWH AMS+M+G	$14,645	(-$710,016 - $413,931)
MHS MALDI-TOF	$25,673	(-$602,586 - $566,980)
MHS AMS+M	-$27,528	(-$631,227 - $491,907)
Abbreviations: M: MALDI-TOF; G: Guidance MS		

At the MHS the NMB are highest at $25,673 when the MALDI-TOF technology was in place and the NMB result was a negative $27,528 when the AMS intervention was added (AMS+MALDI) compared to Pre AMS. The minimum and maximum statistics show large uncertainty in these conclusions. Figure 8.5 represents a graph of the data summarised in Table 8.6 for the RBWH and for the MHS.

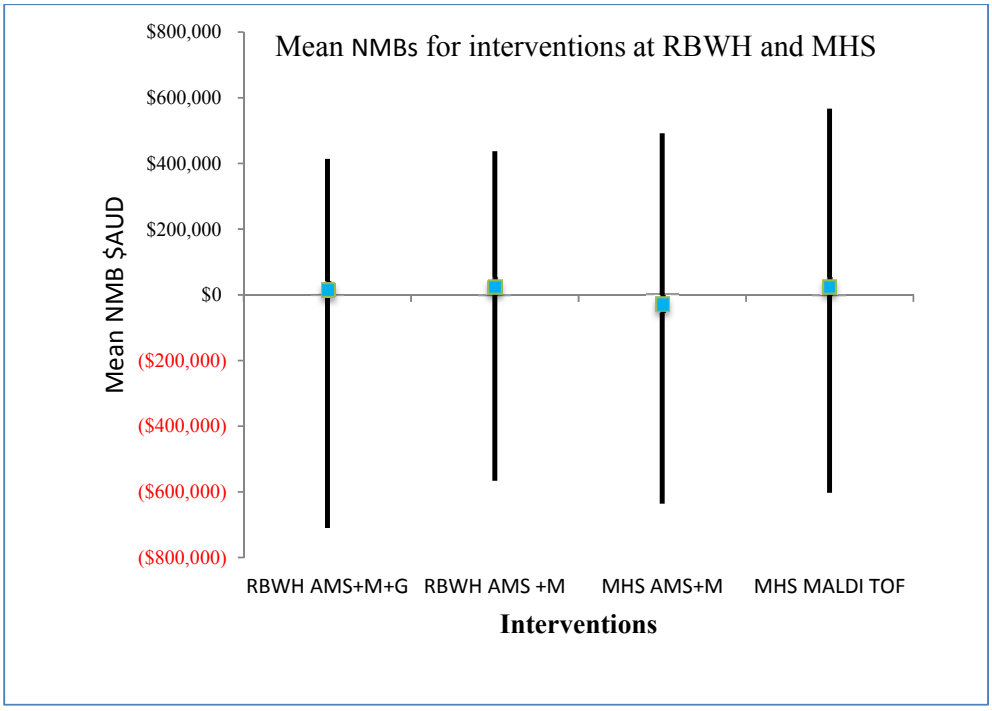

Figure 8.5 Mean NMB for AMS interventions at the RBWH & the Mater

As can be seen in Figure 8.5 the largest NMB was achieved at the RBWH for the intervention with AMS+MALDI-TOF the optimal decision. So the addition of the CDSS does not increase economic value for this health service. At the MHS the optimal decision is to use MALDI-TOF without AMS.

To determine the confidence in the decision to adopt either option at each of the hospitals the proportion of times that each option at each of the hospitals was most efficient, in other words returned the highest NMB across the simulations was calculated at a willingness to pay of $64,000.00. The results are presented in Table 8.7.

Table 8.7 The Percentage Probability in the CEA of each of the interventions at the RBWH and the MHS

RBWH			MHS		
Pre AMS (%)	**AMS+M** (%)	**AMS+M+G** (%)	**Pre AMS** (%)	**MALDI-TOF** (%)	**AMS+M** (%)
15.8	39.3	44.9	21.8	50	28.2
Abbreviations: M: MALDI-TOF; G: Guidance MS					

At the RBWH the option of AMS+M which is the most cost-effective option is associated with a 60.7% error rate. This means that a decision maker can expect it to be the correct decision 39.3% of the time. The second option at the RBWH is associated with a slightly lower error rate of 55.1% but the NMB is much higher for the AMS+M option. At the MHS the optimal option MALDI-TOF technology has an error rate of 50% and is the correct decision 50% of the time. While risk-averse decision makers would feel more confident with a 95% or above probability that their decision is cost-effective, a decision will still need to be made taking in to consideration the uncertainty. In all of the options doing nothing was not a good decision as each intervention at both hospitals was more cost-effective than a situation prior to AMS and MALDI-TOF technology.

To identify the parameters that have the greatest impact on the findings a one-way sensitivity analysis was performed.

8.5 ONE-WAY SENSITIVITY ANALYSIS

This analysis keeps all other parameters constant and isolates one parameter at a time to determine its sensitivity. A tornado analysis was used to show the effect of each parameter regarding the interventions evaluated (Figure 8.6 & 8.7 for the RBWH and Figures 8.8 & 8.9 for the MHS). A tornado diagram simply presents the parameter with the highest degree of uncertainty at the top of the diagram and continues to order the next parameters producing a graph resembling a tornado.

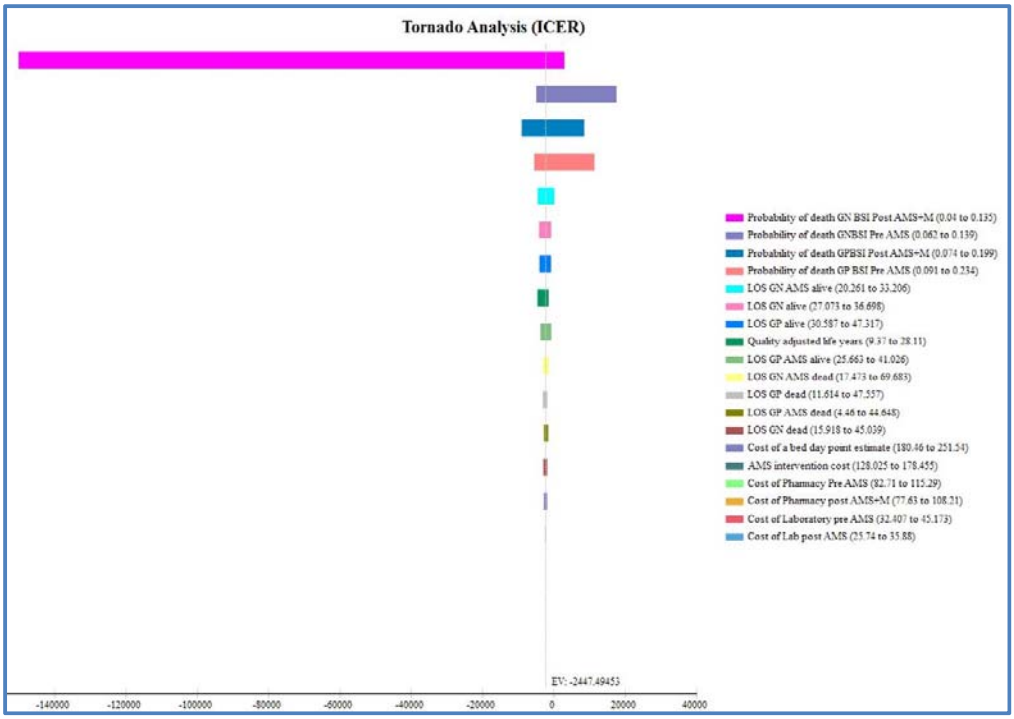

Figure 8.6 ICER Tornado analysis of parameters for AMS+M vs Pre AMS

At the RBWH when evaluating the first intervention which was AMS+M (Figure 8.6), the variables that had the highest impact on the decision were the probability of death following a GP&GN BSI Pre and Post AMS. This indicates that the estimates generated for the risk of dying from a BSI in the pre or post intervention periods has the highest degree of uncertainty.

Figure 8.7 represents the tornado diagram generated for the RBWH after the CDSS was implemented. The estimates for the probability of death pre and post intervention contributed most to decision uncertainty.

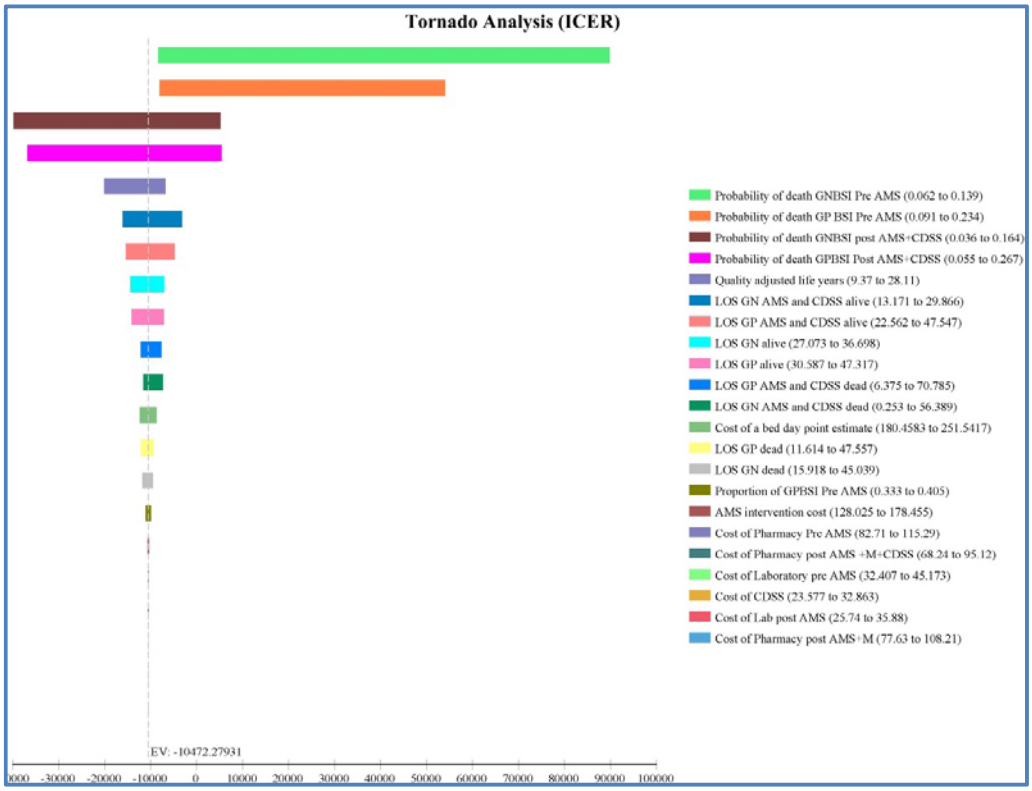

Figure 8.7 Tornado analysis of parameters for AMS+M+G vs Pre AMS

The probabilities of death parameters are particularly important ones as they also cause the conclusion to switch from offering incremental benefits to incremental losses which may be particularly off putting to risk-averse decision makers as opposed to say the LOS estimates which only vary from offering substantial to offering very limited benefits.

At the MHS similar results were generated to determine the parameters with the highest influence on the end result. The tornado diagram presented in Figure 8.8 for the first intervention which was the introduction of MALDI-TOF technology similar to the RBWH results identified the probability of death after a BSI pre and post MALDI-TOF were the most sensitive parameters.

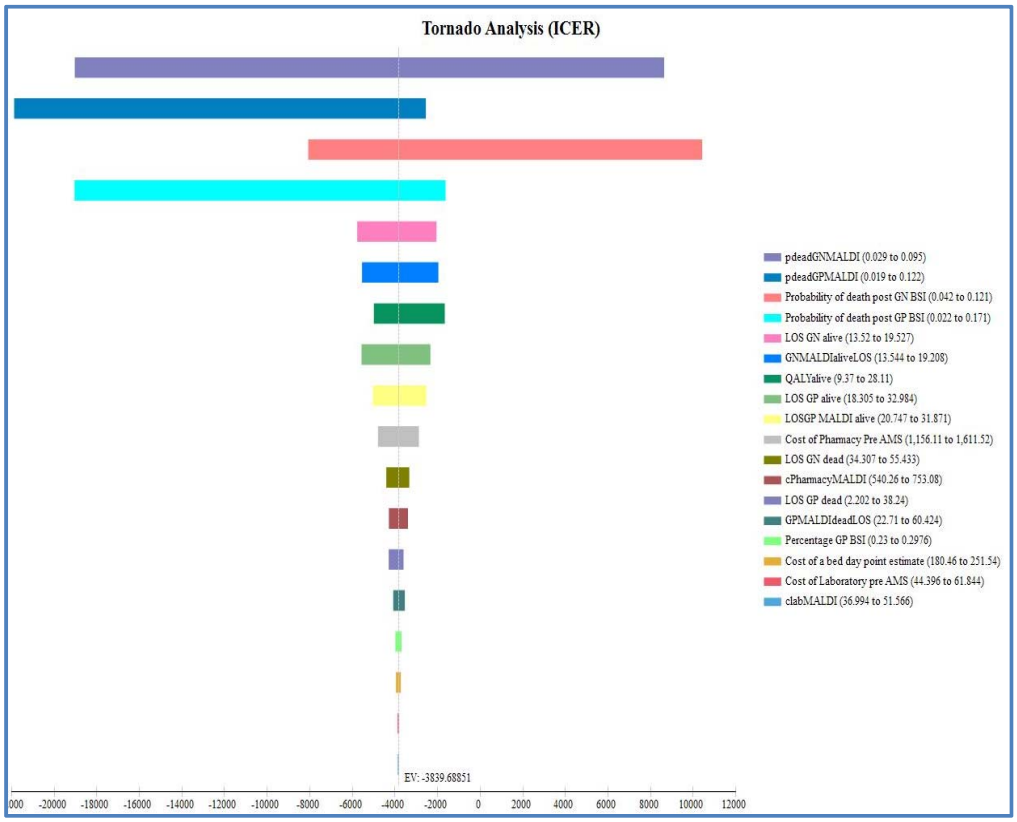

Figure 8.8 Tornado analysis of parameters for MALDI-TOF vs Pre AMS+MALDI

In Figure 8.9 the intervention where AMS was introduced the factors that have the greatest influence are also the probability of death in the pre AMS period.

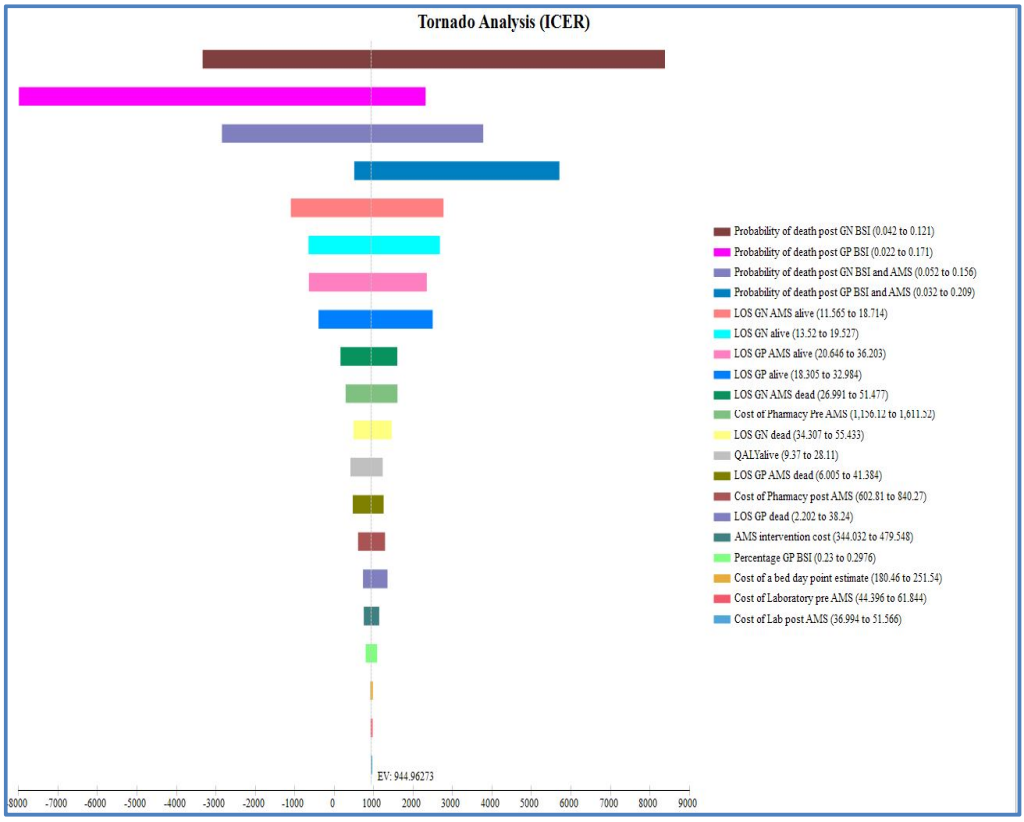

Figure 8.9 Tornado analysis of parameters for AMS+ MALDI-TOF vs Pre AMS+MALDI

In the scenario at MHS with AMS the probability of death post AMS had the highest impact on the outcome followed by the LOS for that patient population at the MHS. A larger data base may have provided estimates with less uncertainty. From the sensitivity analysis it was clear that the impact of the relative risk of death post intervention had the most impact on the outcome in this analysis. To mitigate this impact, better estimates from the literature were sourced and included in the scenario analysis that follows.

8.6 RESULTS FOR THE SCENARIO ANALYSIS

The scenarios for this analysis were described in Chapter 7 section 7.6. In order to achieve a more reliable estimate in the first scenario analysis the organism groups were combined and the impact on mortality and LOS in hospital for the pre and post intervention groups were recalculated to evaluate whether there was a more measurable impact on the clinical outcomes due to pooling the data.

8.6.1 RBWH

The cost-effectiveness analysis was repeated using the adapted model described in section 7.6 to produce incremental costs and health benefits in terms of QALYs for the RBWH. The same parameters were used to produce a new analysis with the cost of a bed day at $0 and new estimates from the literature for the impact on mortality. The summary results of the fixed value analysis using these estimates compared to the original analysis are presented in Table 8.8.

Table 8.8 Summary of results from the scenario analysis at the RBWH

Hospital	Strategy	Scenario	Δ Cost	Δ QALY	NMB
RBWH	AMS+M	Original Analysis	-$851	0.35	$23,251
		Combining GP&GN	-$711	0.16	$10,951
		$0 cost of a bed day	$138	0.16	$10,102
		Literature based estimates	-$595	1.62	$104,275
	AMS+M+ G	Original Analysis	-$1,671	0.16	$11,911
		Combining GP&GN	-$1,568	0.02	$2,847
		$0 cost of a bed day	$155	0.02	$1,125
		Literature based estimates	-$1,437	1.62	$105,117
Abbreviations: M: MALDI-TOF; G: Guidance MS; GP: Gram Positive; Gram Negative; NMB: Net Monetary Benefit					

When using estimates for GP&GN combined for the AMS+M intervention at the RBWH, the new estimates highlight less overall cost saving and a decrease in QALYs of 0.19. The AMS+M+G strategy also shows a small reduction in cost savings and a decrease in QALYs by 0.14. The NMB decreased from $23,251 to $10,951 for the AMS+M intervention and decreased from $11,911 to $2,847 for AMS+M+G. The new estimates still identify that the most cost-effective option for the RBWH was AMS+M.

The second scenario tested was to assign no value to a bed day for the analysis. Assigning no value to a bed day has little impact on the decision where the bed day was previously assigned a conservative cost of $216. However the intervention at the RBWH has changed from one that was cost saving to the AMS intervention needing an investment to gain health benefits. Despite requiring an investment, the investment is minor, with AMS+M costing $862/QALY and AMS+M+G $7,750/QALY. Given that the willingness to pay for health benefits in this analysis is $64,000 both of these options are cost-effective. However the conclusion would be that the intervention AMS+M was still optimal for this setting.

The final scenario analysed was one where the literature based estimates were substituted for the impact of the intervention on patient mortality. In this scenario the health benefits remain the same for both interventions. The option with a clinical decision support system AMS+M+G is more cost saving when compared to AMS+M. However the NMB for each of these interventions are much higher than the NMB achieved by using the effectiveness measure derived from the primary data from the RBWH and around the same at $104,275 and $105,117 for AMS+M and AMS+M+G respectively. In this case both interventions are cost saving and cost-effective with not much difference between the interventions.

The mean NMB and the maximum and minimum NMB for all simulations is shown in Table 8.9 and plotted in Figure 8.10 for each of the scenarios at the RBWH.

Table 8.9 NMBs for the scenario analysis at the RBWH

SCENARIO	MEAN	95% credible interval
AMS+M cbd $216	$11,305	(-$125,473 - $137,578)
AMS+M cbd $0	$10,609	(-$125,352 - $139,210)
AMS +M (lit based)	$112,869	(-$41,202 - $292,526)
AMS+M+G cbd $216	$4,152	(-$184,962 - $163,349)
AMS+M+G cbd $0	$928	(-$183,443 - $160,370)
AMS+M+G (lit based)	$114,801	(-$42,508 - $284,253)
Abbreviations: M: MALDI-TOF; G: Guidance MS; cbd: Cost of a bed day		

In figure 8.10, while there is still quite a large range for the NMB following 10,000 simulations all the interventions at the RBWH are cost-effective as they have a positive mean NMB. However compared to the original analysis when the organism groups are combined the 95% credibility interval for the AMS+M intervention is reduced. The cost of a bed day set at $0, made little impact on the final analysis in either intervention at the RBWH.

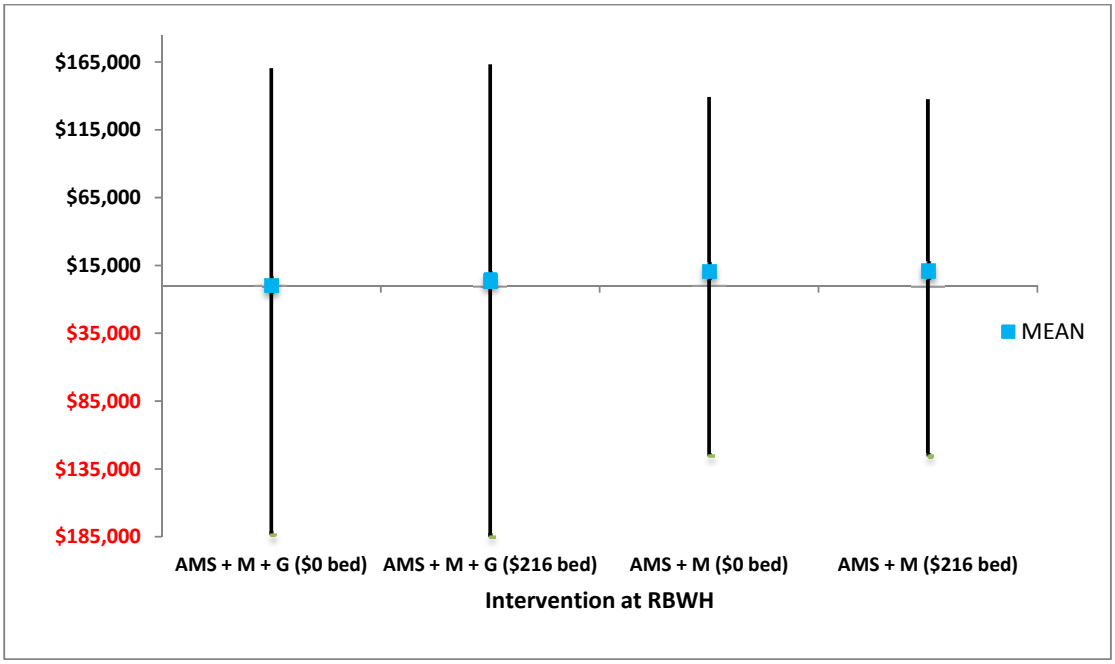

Figure 8.10 NMB at a threshold of $64,000/QALY for the scenario analysis at the RBWH

8.6.2 MHS

Similar scenario analysis was performed for the interventions at the MHS and the results are presented in Table 8.10.

Table 8.10 Summary of results from the fixed value analysis for each at the MHS

Hospital	Strategy	Scenario	Δ Cost	Δ QALY	NMB
MHS	MALDI-TOF	Original Analysis	-$910	0.23	$15,630
		Combining GP&GN	-$700	0.27	$17,980
		$0 cost of a bed day	-$746	0.27	$15,466
		Literature based estimates	-$1,040	1.1	$71,440
	AMS+M	Original Analysis	-$250	-0.27	$-17,030
		Combining GP&GN	-$315	-0.29	-$18,245
		$0 cost of a bed day	-$198	-0.29	-$17,082
		Literature based estimates	-$739	1.1	$71,139
Abbreviations: M: MALDI-TOF; GP: Gram Postive; GN: Gram Negative; NMB: Net Monetary Benefit, Δ: change in					

When using estimates for GP&GN combined for the MALDI-TOF intervention at the MHS, the new estimates highlight less overall cost saving, but an increase in QALYs by 0.04. However the AMS+M strategy shows a small increase in cost savings and a further reduction in QALYs by 0.02. The NMB increased from $15,630 to $17,980 for the MALDI-TOF intervention and decreased from $-17,030 to $-18,245 for the AMS+M intervention. The new estimates confirm that for the MHS the intervention prior to the introduction of AMS is still the optimal choice.

The second scenario tested was assigning no value to a bed day where the bed day was previously assigned a cost of $216. However for the intervention at the MHS there was little impact on the final outcome. For the intervention with only

MALDI-TOF there was a slight improvement in cost savings but the NMB remained around the same. The AMS+M intervention also demonstrated a cost saving but remained with a negative NMB making the optimal choice still conclusively the option prior to the introduction of AMS.

The final scenario in this analysis substituted an effectiveness estimate from the literature. Here the health benefits remain the same for both interventions and there is very little difference between the two interventions where the NMB for each are around the same at $71,440 and $71,139. In this scenario both interventions are cost saving and cost-effective but MALDI-TOF still remains the preferred option.

Table 8.11 presents the NMB analysis for the scenario analysis at the MHS at a cost-effectiveness threshold of $64,000/QALY. The 95% credibility interval still remains large even after combining the GP&GN organism groups. The cost of a bed day changing from $216 to $0 does not have an impact on the NMB at either hospital. The optimal choice still remains the implementation of rapid diagnostics at the MHS and the addition of the AMS intervention is not cost-effective at the MHS.

Table 8.11 NMBs for the scenario analysis at the MHS

Scenario	Mean	95% credible interval
MALDI-TOF cbd $216	$28,298.92	(-$532,580 - $516,537)
MALDI-TOF cbd $0	$28,451.01	(-$590,303 - $543,511)
MALDI-TOF(lit based)	$113,462	(-$29,742-$292,773)
AMS+M cbd $216	-$31,294.80	(-$603,091 - $627,244)
AMS+M cbd $0	-$31,548.03	(-$582,493 - $532,557)
AMS+M(lit based)	$112,220	(-$52,100-$322,128)
Abbreviations; cbd: cost of a bed day **M: MALDI-TOF**		

Figure 8.11 presents the NMB including the credibility intervals for each of these interventions.

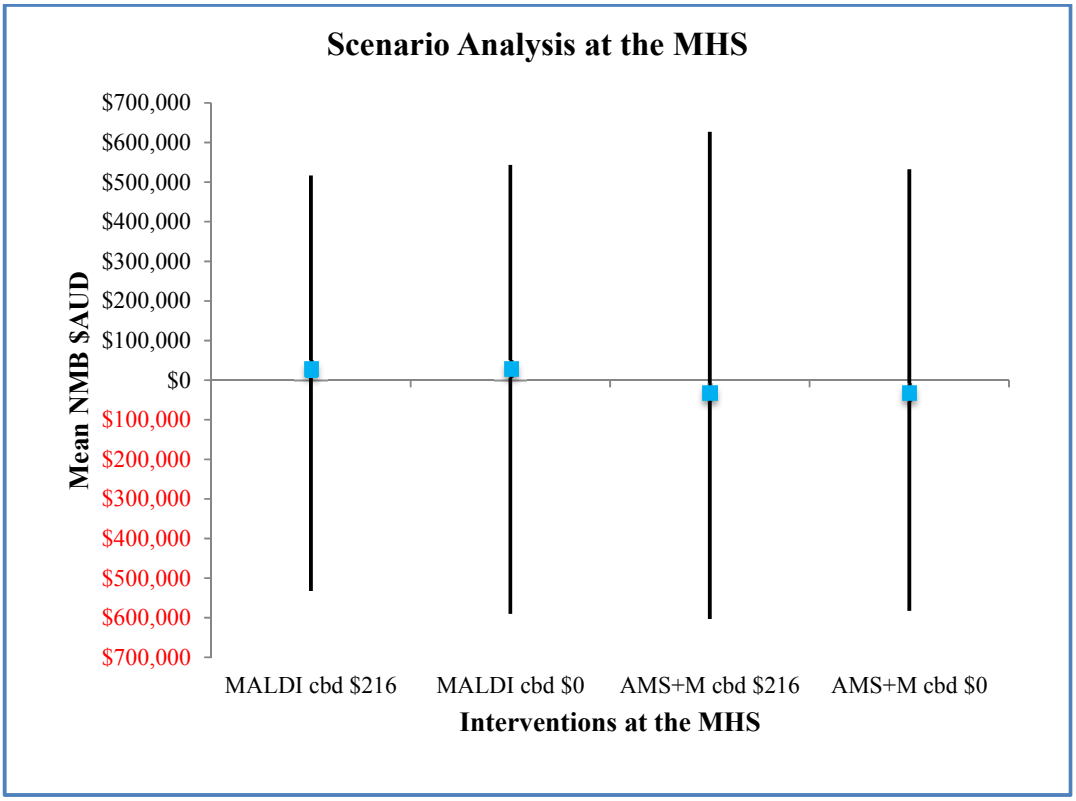

Figure 8.11 NMB at a threshold of $64,000/QALY for the scenario analysis at the MHS

The NMB analysis was performed to substitute the parameters with the highest degree of uncertainty with parameters derived from the literature. When the same estimate of mortality was substituted for the ones calculated using the raw data from RBWH and MHS the NMB at a threshold of $64,000/QALY results in both interventions at both hospitals being cost effective and are presented in Table 8.12.

Table 8.12 Mean NMBs for the literature based estimates for ($64,000/QALY) RBWH &MHS

SCENARIO	MEAN	95% credible interval
RBWH AMS+M+G	$114,801	(-$42,508 - $284,253)
RBWH AMS +M	$112,869	(-$41,202 - $292,526)
MATER AMS+M	$112,220	(-$52,100 - $322,128)
MATER MALDI-TOF	$113,462	(-$29,742- $292,773)
Abbreviations: AMS: Antimicrobial Stewardship; M: MALDI-TOF, G: Guidance MS		

As can be seen in Figure 8.12 the 95% credible interval is reduced in this analysis and all interventions have a positive NMB and are very close to each other.

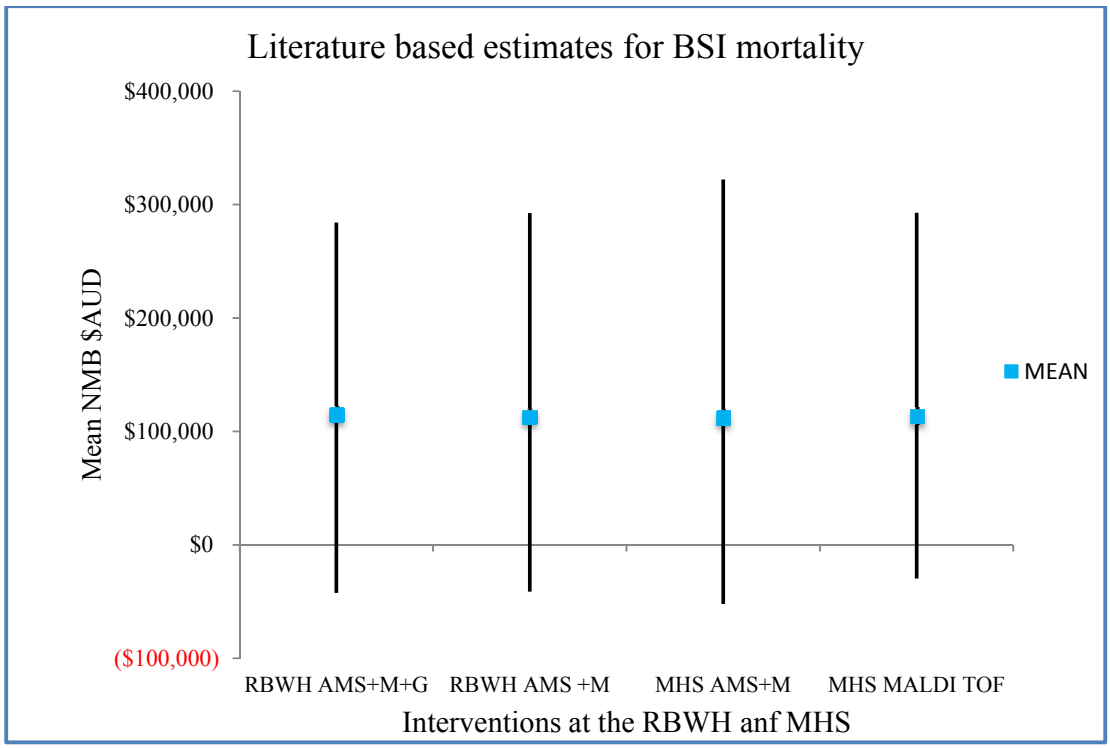

Figure 8.12 NMB analysis at a threshold of $64,000/QALY for the literature based estimates at both hospitals

The estimates with the highest impact on making the interventions cost-effective or not are the measures of effectiveness in this analysis. Greater certainty in these estimates will allow for a more conclusive decision on whether AMS is cost-effective in hospital environments.

Table 8.13 Summary of the probability of the cost effectiveness of each scenario at both hospitals at a willingness to pay of $64,000

Scenario	RBWH			MHS		
	Pre AMS	**AMS+M**	**AMS+M+G**	**Pre AMS**	**MALDI-TOF**	**AMS+M**
Original	**15.8**	**39.3**	**44.9**	**21.8**	**50**	**28.2**
GP&GN	14.2	46.7	39.1	22.4	51.4	26.2
CBD$0	14.5	45.7	39.8	22.6	50.8	26.6
Literature	0	48.5	51.5	0	51.1	48.9
Abbreviations: GP: Gram Positive, GN: Gram Negative; CBD: cost of a bed day; M: MALDI-TOF; G: Guidance MS						

At the RBWH while the original analysis concluded that AMS+M had the highest NMB there was a difference of about 5% between AMS+M and AMS+M+G supporting the option AMS+M+G being more cost-effective. However when the scenario analysis was performed the estimates used were derived from combining the GP&GN organism groups. The objective being in order to strengthen the statistical analysis when deriving the mortality and LOS estimates. The probability of AMS+M being cost effective increased from 39.3% to 46.7% supporting the conclusion that this is the optimal choice for the RBWH. All of the other scenarios also supported these findings for the RBWH. At the MHS MALDI-TOF technology continued to be the optimal choice. However all the scenarios confirmed that for both the hospitals a situation after the implementation of the interventions was better than a situation prior to implementation of all of the strategies that were part of the AMS intervention at both hospitals.

8.7 SUMMARY

At the RBWH both interventions were cost saving and also achieved gains in health benefits compared to the pre AMS scenario. The difference in health benefits derived from both interventions were comparable. However in this analysis the NMB was the highest at $23,251 in the original analysis and $10,951 when the GP & GN groups were combined for the strategy with AMS+MALDI-TOF at the RBWH. Therefore it is the option that is the best value for money at the RBWH in this analysis. While the addition of a CDSS (Guidance MS) also returned a NMB of $11,911 it did not result in additional health gains and it remains to be seen if this addition is of benefit longer term. However if we assume that the health outcomes from AMS for each intervention are the same as in the literature based analysis, then there is little difference in the options at either hospital. However, in the longer term the cost of CDSS might be justified by the improvement in health benefits by capturing the opportunity costs that are not quantified in this analysis.

At the MHS the option without an AMS intervention following the introduction of MALDI-TOF technology was found to be most cost-effective. When

an AMS intervention was introduced the incremental effectiveness was reduced and was also less than the effectiveness prior to AMS. The NMB in the option with MALDI-TOF was $15,630 in the original analysis and when GP&GN were combined at $17,980 is the strategy of choice in this analysis. The addition of the AMS intervention resulted in a NMB of -$17,030. In the case of the MHS the most value for money option was the introduction of MALDI-TOF technology in the laboratory.

If the assumption is made that there was no measurable change in the mortality post intervention at either hospital then the NMB achieved for all interventions was almost the same. So for the RBWH the addition of Guidance MS had no major advantage and at the MHS the addition of AMS made no difference to the NMB achieved. More complete estimates for the improvement in patient outcomes due to better prescribing is essential to convince decision makers that AMS interventions are good value for money in hospital settings.

Chapter 9 will draw on these findings and discuss the relevance of these results in the context of quality and safety in patient care in hospitals and address how this information is used in hospitals to achieve the best outcomes for patients with serious infections. It will also address whether the strategies used so far in metropolitan hospitals have been of value and how either of the strategies can be optimised.

Chapter 9: **DISCUSSION**

This chapter begins with the interpretation of the findings of this research in section 9.1 with reference to the aims of this research set out in Chapter 1. The following section 9.2 discusses the value for money of rapid diagnostics in the context of timely treatment of patients with BSIs. Section 9.3 discusses ways in which these findings can be used by Australian decision makers when allocating funding to AMS interventions, while section 9.4 discusses the limitations and highlights the strengths of this work. Section 9.5 & 9.6 examines future research directions and provides conclusions and recommendations.

9.1 INTERPRETATION OF FINDINGS ALIGNED WITH THE RESEARCH OBJECTIVES

The findings from this research are interpreted against the original research objectives identified in Chapter 2. Estimating the cost of the interventions at each of the hospitals, making best estimate of the change in health outcomes achieved as a direct consequence of introducing the AMS interventions, the cost-effectiveness of these strategies, and the impact of uncertainty in the estimates used in the model and what this means for decision making.

9.1.1 THE COST OF THE AMS INTERVENTIONS

At the RBWH the AMS intervention and rapid diagnostics in the microbiology laboratory (MALDI-TOF) were introduced within months of each other. The AMS intervention was evaluated including rapid diagnostics and resulted in a reduction of antimicrobial usage in the non-ICU group of around 6%. The CDSS was introduced almost two years after the initial AMS intervention was implemented and resulted in a further reduction in antimicrobial usage of 12%. At the MHS both non-ICU and ICU antimicrobial usage was included and the introduction of rapid diagnostics alone resulted in a 49% reduction in antimicrobial use when compared to a time prior to rapid diagnostics. The introduction of AMS resulted in a further 10% reduction in antimicrobial usage.

Consistent with the literature so far, at both hospitals the antimicrobial usage costs were reduced after each of the interventions were implemented. The cost savings achieved by the reduction of antimicrobial usage has been the main outcome reported in most studies evaluating the impact of AMS interventions so far (149). However these studies did not include the cost of the AMS intervention. At the RBWH the AMS intervention required an additional investment despite the savings achieved due to the reduction in antimicrobial usage due to the cost of the AMS intervention. While the impact of MALDI-TOF technology at the MHS, resulted in a large cost saving due to the reduction of antimicrobial usage, the additional cost of the AMS intervention reduced this cost saving by half.

The main driver of the cost of the AMS interventions at both hospitals was the human resource (HR) component allocated to the clinicians that were part of the AMS team. The cost of meetings to discuss the implementation of an intervention is often overlooked as the staff members are already employed by the hospital and their salaries accounted for. However this is a valuable resource and should be quantified when calculating the cost of any intervention. In Australia so far, a detailed analysis of the cost of the HR component of an AMS intervention has not been performed. If the cost of HR were to be excluded from the intervention then both interventions would appear much more cost saving but this would not represent the true cost of the intervention.

The cost of delivering an intervention will vary over time; they will likely fall as the programme matures. This research used a short time frame which may cause the interventions to appear less efficient than if a longer time frame were used. The initial outlay for all AMS interventions can be large but these costs are relative to the ongoing maintenance costs of AMS interventions, as once a reliable system has been implemented the maintenance may not require as costly a team as initially required to bring about change. However for hospitals to continue achieving sustainable improvements in patient care maintenance costs may not be insignificant, especially in programs that are heavily reliant on specialised equipment or large AMS teams.

It is important to recognise that the initial large cost savings due to reduced antimicrobial consumption may not be sustainable long term. The dramatic reduction and/or shift in antimicrobial prescribing patterns often seen when AMS programs are first implemented is often attributed to a focus on "picking off the low hanging fruit" and higher levels of clinical engagement during the initial phase. Once enthusiasm and interest wanes and the easiest changes in prescribing behaviour have been made, further changes to prescribing may be harder to achieve.

The narrow perspective used for this research is also likely to make the AMS interventions evaluated look more costly than if a broader perspective was adopted. For example there are a number of cost savings that are likely to occur over the longer term such as reduction of the costs of treating and managing unintended consequences of antimicrobial use. These additional costs include the costs to hospitals of HAIs such as *C. difficile* and multi-resistant organisms and of complications due to inadequate dosing of antimicrobials and inappropriate therapy resulting in more serious infections. The societal costs are much more difficult to quantify in terms of loss of productivity and the intangible cost of the development of antimicrobial resistance.

9.1.2 BSI AS A METRIC OF EFFECTIVENESS

At the RBWH the introduction of the AMS intervention including rapid diagnostics reduced the probability of death in the patients with GP BSIs by 2.6% and GN BSIs by 1.6%. The addition of CDSS reduced the probability of death slightly less in patients with GP BSIs by 1.2% and GN BSIs by 0.7% compared to the baseline mortality. When the GP&GN groups were combined to effectively strengthen the analysis, the introduction of AMS and rapid diagnostics, reduced the probability of death by 0.8% and the addition of CDSS by only 0.1%. In all scenarios the AMS intervention reduced the probability of death compared to the baseline but the addition of CDSS did not achieve any improvements compared to the initial AMS intervention.

At the MHS the introduction of rapid diagnostics reduced the probability of death in patients with GP BSIs by 2.4%, however in patients with GN BSIs the probability of death increased by 2.1%. The addition of the AMS intervention

reduced the probability of death in the GP BSIs by 2.1% but in the GN BSIs the probability of death increased by 2.6%. When the GP&GN groups were combined rapid diagnostics reduced the probability of death by 2.2% and the addition of the AMS intervention increased it to 2.5%.

The impact of seasonal mortality may have affected the estimates of mortality due to each of the interventions in this research. There is evidence that in Australia the overall deaths peak in August (winter months) and trough in February showing a 30% variation(206). The data collection was driven by the timeline of the implementation of each of the interventions at the two hospitals. This variation may have accounted for the increase in the relative risk of mortality in both the smaller datasets collected for each of the hospitals, specifically post CDSS for the RBWH (dataset August to December 2014) and post AMS for the MHS (May to December 2014).

The changes to LOS in hospital for each of the intervention periods were estimated using an ANCOVA. In all datasets the numbers of deaths were small, and as such, the LOS in these groups did not seem to have any detectable trends. However in the patients who survived, at the RBWH the GP BSIs stayed around the same but there was a trend to reduction in the LOS in GN BSIs from 31.60 days pre AMS, 26.30 and 20.44 with the addition of MALDI-TOF and CDSS respectively. When the GP&GN groups were combined a similar trend was observed. At the MHS however, there were no detectable trends to reduction or increase in either group or when the groups were combined.

While there is a growing body of evidence suggesting that there is a relationship between appropriate prescribing and the reduction of the risk of mortality in patients with BSIs (43, 99, 100) this research was unable to demonstrate this with sufficient confidence. The measure of effectiveness used in this research did not completely capture the impact of the interventions on patient outcomes. A broader range of benefits arising from AMS might have been captured in this research if both the time frame and information sources for mortality and morbidity were better. Particularly regarding the acquisition of HAIs such as *C*

difficile infections and other adverse events due to inappropriate prescribing not being included in this analysis.

The outcome of death due to BSI is a relatively rare event in most Australian health care institutions. So any changes to the probability of death are likely to be small. While it is important to describe the impact of improved prescribing practices on patients with severe infections such as BSIs, mortality alone is not a good metric to evaluate AMS interventions in our setting. An accurate estimate of the infection related mortality is difficult to make and the impacts of poor prescribing don't always result in death. Since there is a higher level of morbidity in patients with severe infections it would be valuable to track the health effects such as complicated infections in this patient group over a longer period of time.

The long-term unintended consequences of inadequate prescribing in either dosage or duration may not appear to have an impact on 30 day mortality but might only present later in the life of the patient in terms of complications. To capture the other adverse effects of inappropriate prescribing, longer than 30 day mortality in this subset of patients need to be collected. A recent systematic review by Winters 2010(207) also reported that the long term mortality and decrement of quality of life continue after patients have been discharged from hospital. Factors such as relapse, seeding from primary infections causing complications such as endocarditis and osteomyelitis from infections that have been treated with suboptimal doses cause significant hardship to individual patients. This information is difficult to capture in our dataset and it would have been more appropriate to look at 90 day mortality or longer, to capture a more accurate picture of the impact of mortality in this group of patients.

More complete data are difficult to access in routine databases and while at the outset the expert advisory committee suggested other metrics, they were not easily accessible. An adverse event register or documentation of adverse events such as nephrotoxicity, hepatotoxicity, *C difficile* infections and development of resistance in patients treated with antimicrobials need to be maintained in their permanent record. The adverse side effects of antimicrobial therapy needs to be

clearly detailed so prescribers are able to weigh up the benefits of treating patients with non-life threatening bacterial infections.

Tracking of patients who are admitted to a large referral hospital such as the RBWH and subsequently transferred to their local hospital can be difficult. Fully automated and validated data collection systems implemented with the guidance of biostatisticians would be of great value to ensure that the data collected will be useful in evaluating interventions in the future. The implementation of the electronic health record (EHR) would possibly enable better data collection and storage. An EHR that is able to track patient data regardless of which hospital they attend would enable better data collection on longer term patient outcomes.

A larger pool of patients with varying severity of illness might have also provided a better overall picture of the impact of improved prescribing as a result of an AMS intervention. Data collection at least 2 years after the implementation of an intervention would be a better representation of the changes brought about by the intervention.

9.1.3 THE COST EFFECTIVENESS OF THE AMS INTERVENTIONS

The deterministic analysis without considering uncertainty in the results indicated that at the RBWH that both the strategies used were cost saving and offered additional health benefits in terms of QALYS compared to a situation prior to the introduction of the AMS intervention.

The AMS intervention including rapid diagnostics resulted in a cost savings per patient of $851 and a gain in health benefits of 0.35 of a QALY and an overall NMB of $24,877 when a willingness to pay of $64,000 was used. The addition of the CDSS resulted in a savings of $1671 and additional health gains of 0.16 QALYs and a NMB of $14,645. Both interventions resulted in cost savings and gains in terms of health benefits when compared to a period prior to the intervention. However the optimal choice in this analysis would be the option of AMS with rapid diagnostics.

At the MHS the introduction of MALDI-TOF technology resulted in a cost savings of $910 and gain of 0.23 QALYs and a NMB of $25,673 compared to a period prior to the intervention. However when the AMS intervention was introduced the

NMB result was a loss of $27,528. The optimal choice in this analysis was the introduction of rapid diagnostics at the MHS.

The results from the PSA are a more useful reflection of the uncertainty in the decision with almost total overlap in the credible intervals for the NMB of all options. The error probability with both the optimal decisions is high at 60.7% for the option with AMS and rapid diagnostics at the RBWH and 50.0% for the option of implementation of rapid diagnostics at the MHS. At both hospitals one way sensitivity analysis revealed that the parameters that were most uncertain were the estimates of the probability of death after the intervention in both groups of patients with GP and GN BSIs. A more robust estimate (combining GP&GN organism groups) of the relative risk of mortality and changes to LOS due to the interventions at both hospitals resulted in no changes to the original conclusions at both hospitals. However this analysis reduced the error probability of the optimal choice at the RBWH to 53.3% improving the confidence that this option is cost effective in that setting. While the error probability is less than what a decision maker would prefer the decision to adopt rapid diagnostics at both hospitals appears cost effective.

The scenario analysis conducted in this research was to assess the impact of a willingness to pay of zero for a bed day and the impact of a more robust estimate of the change to mortality following an AMS intervention to patients with BSIs. The allocation of zero to the cost of a bed day is akin to only valuing changes in financial expenditure and not economic opportunity costs. When the cost of a bed day was allocated zero value, the intervention at the RBWH changed from being cost saving to needing a small monetary investment of $138 and $155 per patient for the AMS intervention including rapid diagnostics and following the addition of CDSS respectively. However at the MHS both interventions continued to be cost saving at $746 for the intervention with only rapid diagnostics and $198 per patient with the addition of the AMS intervention. If the cost of HR was not included in the cost of the interventions the cost savings would have been much greater.

The estimates of the change to mortality in this analysis were derived from the primary data collected from the hospital database. When literature based

estimates for mortality were substituted in each of the interventions in the scenario analysis, all the interventions at both hospitals were cost effective. The resulting CEA showed a large improvement in NMB for all the interventions. However this analysis didn't help differentiate between the different interventions as to which was the most efficient. This identifies a need to use a longer time frame and a broader range of health outcomes in order to differentiate between options.

At both hospitals the options including rapid diagnostics were the optimal choices. While the confidence in this decision is low due to the uncertainty in the estimates, it still supports the investment in MALDI-TOF technology at both hospital laboratories. The option including a CDSS in this analysis was also cost-effective at the RBWH. While there is mounting evidence that an individualised CDSS can assist in improving AMS activities (71) the need for CDSS may vary depending on the level of effective communication and workflow that exists in each individual health care institution.

The strategies used in each environment can make a difference to the success of the intervention. In a recent study two different approaches to AMS were evaluated in a CEA(10). The two strategies in this study were different as the first was more conventional and consisted of screening for anomalies in prescribing and having more telephone advice but the second was more detailed communication and face to face feedback and education. In this analysis the second bundled approach achieved better outcomes and was more cost-effective. This is a good example of where money spent on detailed feedback on a daily ward round may result in better outcomes for patients.

The use of a bundled approach with checklists to assist the team involved in AMS is an essential part of ensuring the sustainability of the AMS intervention. However these checklists need to be based on simplicity and be implemented with effective communication and good buy in. This approach involves the microbiology laboratory, pharmacy, nursing and clinical staff of a hospital.

9.2 THE VALUE OF RAPID DIAGNOSTICS

Fast accurate results can make a significant difference in providing optimal care to patients with severe infections in hospitals. There is evidence that AMS programs increase the streamlining of antimicrobial therapy in patients with BSIs leading to better outcomes (208). There are examples in the literature where the use of rapid diagnostics and in particular, MALDI-TOF technology has resulted in decreased LOS in hospitals (64, 67, 209). There is a growing body of evidence that rapid diagnostics in conjunction with AMS interventions is of significant benefit to patients (38, 57, 67, 68). A recent study by Patel et al in 2017(68), performed a cost analysis to study the impact of MALDI-TOF technology on a real time AMS intervention using BSIs as a metric to evaluate the implementation. In this study the total hospital costs decreased by $2,439 per BSI, for an approximate annual cost savings of $2.34 million.

The value of rapid diagnostics in the microbiology laboratory is evident in this research where, the optimal strategies at both hospitals included MALDI-TOF technology. At the RBWH it was not possible to decipher whether the optimal result was due to the AMS intervention or the MALDI-TOF technology as they were both implemented at the same time. At the MHS however the impact MALDI-TOF technology alone was found to be the optimal choice. At both hospitals the introduction of MALDI-TOF technology resulted in reducing the cost per test for the identification of pathogens in the microbiology laboratory due to the reduction in the cost of consumables and labour.

In the cost-effectiveness analysis incremental cost savings at the RBWH and the MHS were $851 and $910 per BSI after the implementation of rapid diagnostics. The additional health gains were 0.35 and 0.23 QALYs and the NMB $24,877 and $25,673 at the RBWH and the MHS respectively. In a recent review the need for more cost-effectiveness evidence to validate the importance of rapid diagnostics in conjunction with AMS initiatives was emphasised (38). The health benefits achieved with the introduction of rapid diagnostics (MALDI-TOF) and its important role in treating patients with BSIs has been identified in this research. This information is of value to decision makers in hospitals to emphasise the support needed for the

acquisition of essential laboratory resources to strengthen laboratory capacity to result in better outcomes for patients.

For a laboratory with a moderate to high throughput the cost of MALDI-TOF technology is minimal. Over the lifespan of the equipment the cost per test in our analysis was less than $5 at the RBWH. This cost pales into insignificance if compared to the cost of isolating a single patient with a HAI. Decision makers need to be made aware of the evidence that is available to support the fast and accurate detection of pathogens causing serious infection in hospitalised patients. This improved speed of detection will result in significant cost savings in terms of reduced morbidity and mortality and LOS in hospital. Rapid diagnostics in the microbiology laboratory has a vital role in containing the spread of resistant organisms and for the prevention of hospital outbreaks.

Good communication between the laboratory and pharmacy needs to be supported as this information from the laboratory can be utilised in the first instance by the pharmacists to advise treating clinicians in collaboration with the clinical microbiologist and the infectious diseases physician. Particularly if pharmacists are infectious disease trained there will be a greater understanding of the “drug-bug” combinations.

Dik et al(210) suggests a system where there is a financial incentive for the appropriate use of diagnostics where diagnostics and therapy are rolled into one single product. This would ensure that the value of diagnostics is not lost due to budgeting issues. In Australia for example it would be part of the diagnosis related group (DRG) where it is easy for governments to invest in and subsidize more costly rapid diagnostics as part of AMS interventions. This would raise the profile of laboratories and provide support for the role of rapid diagnosis in the treatment of infectious diseases.

In some settings, an investment in rapid diagnostics in the laboratory maybe sufficient if this information is reaching the treating clinician in a timely manner. It may be better to spend scarce resources establishing a good network between pharmacy and the microbiology laboratory in collaboration with the clinical microbiologist and infectious diseases physicians and ensuring that pharmacists are

trained in infectious diseases than investing in a more costly formalised AMS intervention.

9.3 USING THIS EVIDENCE FOR DECISION MAKING IN AUSTRALIA

To quantify the impact of any hospital intervention in isolation will always be challenging. Hospital environments by their very nature are a hub of activity with many teams working together to achieve optimal patient care. However, more often than not these teams work in silos, lacking collaboration which results in many individual initiatives being implemented simultaneously but in isolation. Evaluation of these interventions to determine the impact of an individual strategy on patient outcomes becomes difficult(211). A clear plan of data collection and evaluation of the strategies prior to the implementation of a new initiative would be ideal. However this scenario is a rare occurrence in clinical practice.

The long term benefits of AMS interventions lie in better prescribing and not merely reducing the amount of antimicrobials used. These decisions can only be made by clinicians trained in infectious diseases and microbiology. A recent meta-analysis on the impact of infectious diseases consultations in patients with *S aureus* bacteraemia reported significant improvements in 30 day and 90 day mortality(43). Also the patients that had an infectious disease consult were less likely to relapse and have endocarditis and other complications. This strengthens the case for an AMS intervention to be led by infectious disease physicians. This improvement in treating serious infections could result in even more substantial cost savings and improvements in the quality of care provided to patients due to the reduction in the unintended negative consequences of antimicrobial use.

While there is a high level of uncertainty in the conclusions in the CEA of AMS interventions in our study, there is no doubt that strategies to improve patient safety through more responsible use of antimicrobials should be implemented in hospital environments. In all situations the probability of each intervention being cost effective was greater than the situation prior to the implementation of any of the strategies. However each hospital will have varying requirements in terms of AMS and the strategies need to be tailored to suit that need. If there is nothing new

that needs to be introduced then the decision to do nothing but continue with the status quo should also be acceptable and considered meeting the national requirement for AMS.

The question arises whether the mandatory nature of AMS interventions in Australian hospitals has created an obligatory situation where it has become more important to "tick the box "that an AMS intervention was implemented, rather than consider the ways in which the strategies need to be implemented to achieve optimal results in each setting. Especially in a country with the vast geographical expanse as Australia, many factors need to be considered when designing a suitable AMS intervention.

To date there have been no CEAs performed on AMS interventions in Australia and only a few globally. Due to the complex nature of AMS interventions CEAs may not be the best method for the evaluation of these interventions. Many outcomes due to AMS interventions are not measurable especially if you expand the analysis to include a societal perspective. The impact of inappropriate prescribing can have dire consequences to society due to the emergence of antimicrobial resistance. As suggested by Richard Smith and Joanna Coast the current worst case scenario is still an underestimate of the economic burden of antimicrobial resistance(183). A world without effective antimicrobials has the potential to disable our healthcare system. The responsible use of antimicrobials should definitely be mandatory in all areas of healthcare.

A wider range of costs of inappropriate use of antimicrobials may have been captured better in a Cost Benefit Analysis where a monetary value is placed on the cost to society through AMR and the loss of productivity from the lack of options to treat resistant infections. But collecting this information will be difficult. This analysis was conducted from a hospital perspective and as such only partially captures the true impact of inappropriate prescribing. It is difficult to quantify the true cost of inappropriate prescribing using a model with a short term healthcare perspective. To see the true effect of the intervention, data needs to be collected at a time period at least 3 years or greater after the implementation is established (75).

The amount of resources invested in an AMS intervention may need to be moderated depending on the issues identified at each health care environment. AMS interventions are complex and often the strategies used are tailored to suit a specific healthcare environment or budget. Therefore comparing one AMS intervention with another is difficult and not always appropriate. A good example of the valuable and appropriate use of resources was presented by Dik and colleagues(5) in a cost minimisation study performed in a urology ward in a hospital in the Netherlands. In this study the costs of implementing an intervention as part of a larger AMS program was evaluated. This involved using the time of a clinical microbiologist, an infectious diseases doctor and a pharmacist to evaluate a subset of patients in the urology ward 48 hours after commencing antimicrobials. All costs involved (personnel, medical, overheads etc.) were carefully taken into account and the costs saved (LOS and nursing time) also accounted. For example changing therapy from IV to PO reduced nursing time on average 64.83 minutes per patient per day. The reduction in LOS and nursing time made this intervention at this hospital value for money. While the intangible benefits to patients from avoiding unnecessary antimicrobial therapy were not captured in this research the study was able to prove that the intervention was in-fact worthwhile.

In an environment where antimicrobial use is generally well managed the mandatory implementation of a formal AMS intervention may not lead to quantifiable changes to the outcomes to patients. Both hospitals in this evaluation met the criteria set out by the IDSA for the recommended components of an AMS team. AMS programs at both hospitals differed from each other in the tools used and the general approach to AMS. Since it is mandatory that all hospitals implement an AMS intervention the decision is not whether an AMS intervention is a good idea or whether it should be adopted but what strategies provide the best outcomes in differing healthcare environments. Nevertheless, all AMS intervention would require some investment in personnel regardless of the size of the hospital to decide on how the intervention would be implemented. An AMS intervention is always a good idea as it focuses on patient safety and educating healthcare professionals on best practice in the area of antimicrobial prescribing.

9.4 STRENGTHS AND LIMITATIONS OF THE RESEARCH

This is the first time an economic evaluation of AMS interventions has been performed in Australia. This study uses primary data from the individual hospitals evaluated rather than relying on estimates from the literature. It is also the first time the full cost of an AMS intervention has been estimated. This allows for the analysis to be specifically relevant to the individual hospitals. This information may be used to design AMS interventions in other hospitals and to flag the opportunity cost investment required for these mandatory programs. Unless careful consideration is given to the design of AMS programs this large investment can quickly become a burden for small facilities. Small changes to the way things are done in these environments are likely to achieve better patient outcomes. This may be achieved by tapping into larger facilities that are better resourced.

It must also be acknowledged that however effective the AMS intervention is, it will be undermined if infection control is absent or deficient. It is not possible to assess AMS in total isolation in a hospital environment as there is a strong relationship between infection prevention and AMS. While there are some limitations in the choice of metric selected for the measure of effectiveness, this research has indicated how improvements to the effectiveness measure may be achieved. It is important to bear in mind that the primary goal of an AMS program is to address patient safety and to reduce adverse events associated with antimicrobial use. Collecting accurate data on clinical outcomes to capture the improvements to patient care resulting from more appropriate therapy should be valued.

While at the initial stages of an AMS intervention there could be large economic gains in terms of reduction of antimicrobial utilisation this may not be sustainable long term. However, improved prescribing practice for serious infections in hospitalised patients will result in the reduction of unintended consequences of antimicrobial therapy leading to significant savings due to shorter hospital stays and reduced morbidity and mortality. This is where cost-

effectiveness analyses in healthcare are far superior to cost analyses as they aim to capture the health benefits achieved by the intervention as well as the cost savings.

This research aims to raise interest and awareness among infectious disease physicians, clinical microbiologists, pharmacists and AMS committees about the value of cost-effectiveness analysis. Future evaluations of interventions need to be able to capture longer term patient outcome data. The EHR may have the functionality to be able to track patients with BSIs and other serious infections beyond hospital discharge to inform researchers on long term outcomes. Collaborative research with universities allowing easy access to low risk, de-identified data with a streamlined process to timely linkage of patient admission and discharge data, will make this type of analysis easier to perform. This will provide decision makers access to more timely information on the cost-effectiveness of interventions.

A limitation of this research is the short time frame and relatively narrow perspective adopted. The interventions at both hospitals had not been in place for sufficient time prior to data collection. While a societal perspective would have been preferred, this was outside the scope of this research. The societal impact of inappropriate or unnecessary antimicrobial prescribing needs to be emphasised. Infections that are treated sub-optimally can recur and become more serious infections. The cost to the hospital from a complicated infection can be quite significant and more than justify the investment in AMS to improve patient outcomes.

The data on BSIs in this research was limited to patients that were in general wards at the RBWH as the intervention was introduced in the non-ICU setting only. The illness severity in patients in ICU is much greater and the impact of inappropriate therapy would in turn be expected to be greater in this group, particularly in patients with resistant infections. This probably reduced the severity of the illnesses encountered in this analysis. This would have led to an underestimation of the impact of mortality in patients with BSIs. The assumption made in this research was that the QALYs for this group of patients were not different to the QALYs for the general population of this age group. No adjustments

were made to the QALYs based on the impact of BSIs due to the patients not being in ICU.

Finally an additional limitation of this work was the reliance on retrospective survey data to cost the programs in this research. Future research needs to collect real-time cost data alongside effectiveness data at the time of implementation of the intervention with the purpose being to perform a more reliable cost-effectiveness analysis.

9.5 FUTURE RESEARCH

The model used in this analysis may be adapted to perform cost-effectiveness analyses in a number of related areas. However access to the morbidity information such as adverse events due to inappropriate antimicrobial therapy need to be included in the model. This may be achieved by adding a Markov state to the decision tree that tracks the adverse outcomes due to inappropriate therapy.

In Australia there is a significant amount of work currently performed in Victoria as part of a national AMS program where regional hospitals and long term care facilities (LTCF) are being evaluated in terms of effectiveness of the strategies that are currently being used to prevent AMR. While cost-effectiveness analyses in this area are required, there will need to be some clarity as to the available data to estimate the impact of AMS interventions. LTCF have been recognised to have high levels of resistance(47-70%) as a number of residents in LTCF are on systemic antimicrobials (212). These facilities are known as reservoirs of resistance in the community. There is no current evidence on AMS in these settings and there is a gap in the evidence that needs to be addressed in future research (97).

Regional healthcare facilities are not covered in the current research but certainly need to be better resourced to ensure good prescribing practices are adopted in these hospitals. Once again the value of CDSSs, telehealth and rapid diagnostics in this setting will need to be investigated due to the remoteness of some of these regional hospitals in Australia. In Queensland a state-wide AMS program has been established with this in mind. In due course CEA may be required

to justify investments in these areas. It is possible to perform this CEA in regional hospitals; however the quality of the results will be limited only by the quality and quantity of the data that is available in each setting for analysis. Smaller hospitals would require a longer period of time to collect sufficient data, or the pooling of data from several like-sized hospitals using similar strategies to provide more accurate estimates of the impact of the intervention.

The model used in this analysis can also be used in resource limited settings where AMR rates are much higher. It is envisaged that there would be significant cost savings and improvements in patient outcomes to be achieved in this setting. In areas of the world that have higher levels of resistance an AMS intervention has the capacity to achieve greater health benefits and be more cost-effective. The baseline resistance in most Australian healthcare institutions is low for example the resistance of *E coli* to third generation cephalosporins is about 9% and as such the rate of resistance is low. Whereas in some resource limited settings this figure can be as high as 60%. The greatest impact on the cost-effectiveness of interventions will be seen in environments where the relative risk of death due to inappropriate therapy is high. In these settings an appropriate starting place may be a cost minimisation model to convince decision makers of the immediate benefits of the investment in rapid diagnostics in the first instance and then as resources are made available in AMS interventions.

Since responsible use of antimicrobials and the development of resistance is a global issue, resource limited countries need to be supported to also achieve reduction in their rates of inappropriate prescribing. The impact of rapid diagnostics in this setting has been recognised in other areas such as in tuberculosis (TB) control. The implementation of the GenXpert instrument by Cepheid across Africa to detect multidrug drug resistant TB was proven to be cost-effective and resulted in saving many lives (213, 214). The technology is simple and does not require special laboratories and can be performed in low technology environments. The MALDI-TOF instrument may require a bit more space and the operation of the instrument is not technically demanding and as such can be installed in a setting with limited technical expertise.

The interpretation of the results and the communication of the result to enable clinicians to choose the most appropriate choice of antimicrobials may prove more challenging. However, the evaluation of current practices in laboratories in this setting may be appropriate. An economic evaluation to demonstrate to decision makers that the investment in rapid diagnostics in these areas especially in areas where there is a high burden of resistance could result in considerable cost savings not only in terms of reduced antimicrobial consumption but in prevention of significant morbidity and mortality in hospitalised patients.

Both the RBWH and the MHS included in this analysis have improved their practices in the laboratory and have started performing direct detection from blood cultures using MALDI-TOF technology. This additional step has further improved the turnaround times for the identifications of the pathogens from BSIs to be delivered to the treating clinician. An evaluation assessing the cost-effectiveness of this intervention may also be a valuable exercise.

9.6 CONCLUSIONS AND RECOMMENDATIONS

This is the first evaluation of cost-effectiveness of AMS interventions in Australia and the message for policy makers is that AMS interventions are cost-saving from a hospital perspective. This research also indicates that the interventions are cost-effective particularly if teamed with rapid diagnostics in the laboratory. However the uncertainty in the mortality estimates does not allow for a high level of confidence in the decision as the intervention is at best only cost effective 50% of the time. This is due to the inability to quantify the unintended consequences of inappropriate prescribing in monetary terms. When a less uncertain estimate of mortality due to inappropriate prescribing was substituted from the literature the analysis concluded that all interventions at both hospitals were cost-effective.

The research found that rapid diagnostics such as MALDI-TOF technology is cost saving and provides good value for money for the small monetary investment per patient. The benefit to patients of rapid diagnostics in the laboratory is often

undervalued and not seen as core business in the hospital. Decision makers need to be made aware of the value of providing rapid results to treating clinicians in the most efficient and streamlined manner. This information on the causative agent of the infection if used with the input of infectious disease physicians, microbiologists and pharmacists on an AMS round can achieve significant improvements in the way in which serious infections are managed in hospital environments. Getting the right antibiotic, in the correct route of administration at the appropriate dose would provide optimal results. The time spent educating prescribers one to one on an AMS ward round is supported by a recent cost-effectiveness analysis by Okumura et al(10) where a bundled approach to AMS achieved a better outcome to the traditional approach.

The AMS strategies used in each healthcare environment needs to be selected with care to ensure that the needs of that particular health care environment are met. The HR component dedicated to the AMS intervention needs to be carefully considered as this is the tipping point as to whether an intervention is cost-effective or not. The continuous monitoring of these interventions to ensure that heath care resources are being utilised in the best possible way in each individual setting is essential for the sustainability of these interventions. Long term outcomes for patients with BSIs could provide significant insight as to the outcomes of antimicrobial therapy in terms of LOS, mortality, readmission and adverse events. An AMS intervention can only be of benefit to patients and as such there are no qualms about the value of such programs. However it is possible to over invest in terms of staff and strategies that may not work for all environments.

Until better data collection is possible it is difficult to truly estimate the benefits of AMS interventions from the perspective of prevention of unintended consequences of inappropriate use of antimicrobials. Russo et al(215), when reviewing the framework in Australia for HAI surveillance reported a high level of fragmentation of the systems used in the different states in Australia limiting the collation of data at a national level. There were also concerns about the level of training of those involved in HAI surveillance. Often data entry is left to individuals that have clerical expertise and limited if any clinical knowledge. A large percentage

of the data that is currently collected is not necessarily used for decision making. It may be better use of scarce resources to discontinue historical data collection practices and develop electronic databases in consultation with biostatisticians for the collection of better quality data. This could be a vital resource for monitoring outcomes of healthcare interventions. Material collected must be subject to strict definitions and standardised to enable comparison not only between hospitals and health care systems but between countries as well.

While BSI mortality is a useful metric, the morbidity associated with these serious infections due to inappropriate prescribing should be collected in hospital databases over a longer period of time to capture the true benefits of AMS interventions. As discussed earlier there are distinct advantages of an EHR to track patient outcomes over time, in order to capture the adverse events related to antimicrobial therapy and quantify the unintended consequences of antimicrobial use. Published studies thus far have followed patients over 5 years with severe sepsis and patients discharged from an ICU (187, 216). This data has been utilised to provide information on the impact to quality of life after sepsis. More research needs to be performed in areas to follow up all patients that encounter a serious illness such as a BSI and the long term impacts on not only the infection but also the outcomes related to appropriate and inappropriate therapy over time.

In conclusion the rate limiting step in economic evaluations as identified by Joanna Coast more than 30 years ago is that we need better information to decipher the true societal impact of AMR (217, 218). There is still work to be done to improve data collection in hospitals. To evaluate the true impact of AMR and the effect of AMS better, longitudinal laboratory data needs to be collected and the process to link this information to patient admission and discharge data needs to be more streamlined. The accuracy of data collection and interpretation should also be taken into account in these estimates. A recent review of studies that have evaluated the economic burden attributed to AMR by Gandra et al(219), states that the true economic burden of AMR needs to take into account the broader consequences of resistance to society such as increasing resistance and the loss of effectiveness of antimicrobials. The studies so far have not accurately allowed for

co-morbidities due to other factors other than AMR contributing to morbidity and mortality in their estimates.

The gathering of this information would allow for more sound and useful cost-effectiveness analyses in the future, capturing a more accurate estimate of the impact of new interventions in healthcare. AMS interventions are essential to ensure that the patients in hospitals get the optimal quality of care but the investment in the strategies at each individual hospital must be chosen wisely. If the structure that is in place is sufficient then no further investment is required.

The value of investing in the formal training of our doctors in laboratory medicine and infectious diseases cannot be underestimated. It may be worth reviewing the curriculum and ensuring that the current system includes training and examination for competence in antimicrobial prescribing. Antimicrobial stewardship should be made part of the job plan for every consultant clinical microbiologist and medical director. Each speciality college could include a mandatory component on AMS that is relevant to their speciality area.

The sum of the global health initiatives to prevent AMR mandated by the WHO, are only as strong as the individual components of the member states. This research has highlighted that there is value for money in investing in strategies to improve AMS in the Australian context.

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APPENDICES

Appendix A: Ethics and gatekeeper approval letters

Approval was obtained from the following Ethics Committees and Gatekeepers to access hospital data (letters attached).

1. **Queensland Government Department of Health**, Health and Medical Human Research Ethics Committee, HREC reference number: HREC/13/QHC/33, approved **3 September 2013**.

2. **Queensland University of Technology**, University Human Research Ethics Committee, UHREC reference number: 1300000719, approved **12 November 2013**.

3. **Queensland Government Department of Health,** Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Research Governance HREC/13/QHC/33 approved **25 November 2013.**

4. **Queensland Government Department of Health,** Release of Confidential Information for the Purposes of Research under the provision of Section 280 of the Public Health Act 2005, reference RD004843, approved **12 December 2013**.

5. **Mater Health Service & Mater Medical Research Institute,** Site Specific Assessment Authorisation, Mater Research Governance reference: RG-80A, approved **20 February 2014.**

6. **Queensland Government Department of Health,** Release of Confidential Information for the Purposes of Research under the provision of Section 280 of the Public Health Act 2005, reference RD004844, amendment approved by data custodian **6 July 2015**.

Queensland Government

Department of Health

03 September 2013

Enquiries to: Health & Medical Research
Human Research Ethics Committee
Phone: 07 3328 9866
HREC Ref: HREC/13/QHC/33
E-mail: HMR_REG@health.qld.gov.au

Ms Sonali Coulter
Institute of Health and Biomedical Innovation
Queensland University of Technology (QUT)
60 Musk Avenue
Kelvin Grove QLD 4059

Dear Ms Coulter,

HREC Reference number: HREC/13/QHC/33
Project Title: An Economic Evaluation of Antimicrobial Stewardship Programs in Metropolitan Hospitals in Australia

Thank you for submitting the above research protocol to the Queensland Health Central Office Human Research Ethics Committee for ethical and scientific review. This protocol was first considered by the Human Research Ethics Committee (HREC) at the meeting held on 19 August 2013.

I am pleased to advise that the HREC has granted approval of this research protocol.

You are reminded that this letter constitutes ethical approval only. You must not commence this research protocol at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the District Research Governance Office(r)/Delegate of the relevant institution with a completed Site Specific Assessment (SSA) Form for authorisation from the CEO or Delegate to conduct this research at the Royal Brisbane Women's Hospital and Mater Adult Hospital, Brisbane.

The documents reviewed and approved include:

Document	Version	Date
Application		
Protocol	1	05 August
Response to request for further information		16 July 2013
Letters of support : Confirmation Panel Report Sonali Coulter		05 August 2013
CV for Professor Nicholas Graves		05 August 2013
CV for Dr Kate Halton		05 August 2013
CV for Dr Jason Roberts		05 August 2013
CV Sonali Coulter		05 August 2013
Letters of support: Data Custodian (RBWH)		

Please note the following conditions of approval:

1. In accordance with the requirements of the *NHMRC National Statement on Ethical Conduct in Human Research 2007*, sections 2.3.6 - 2.3.8, the HREC waived the requirement for consent for the collection, use and/or disclosure of personal information in medical research or personal health information for the research project listed.

   However Queensland law requires that where potentially identifiable confidential information is disclosed for the purposes of research without the written consent of the person to whom the data applies, a Public Health Act application must be made.
   http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp

2. The Coordinating Principal Investigator will immediately report anything which might warrant review of ethical approval of the protocol in the specified format, including unforeseen events that might affect continued ethical acceptability of the protocol. Serious Adverse Events must be notified to the HREC as soon as possible. In addition the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Coordinating Principal Investigator, including duration of treatment and outcome of the event.

3. Amendments to the research protocol which may affect the ongoing ethical acceptability of a protocol must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a cover letter from the principal investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents, with *tracked changes*, must also be submitted to the HREC office as per standard HREC SOP. (Further advice on submitting amendments is available at
   http://www.health.qld.gov.au/ohmr/documents/researcher_userguide.pdf

4. Amendments to the research protocol which only affect the ongoing site acceptability of the protocol are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office/r.

5. Proposed amendments to the research protocol which may affect both the ethical acceptability and site suitability of the protocol must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submitted to the Research Governance Office/r.

6. Amendments which do not affect either the ethical acceptability or site acceptability of the protocol (e.g. typographical errors) should be submitted electronically (track changes) and in hard copy (final clean copy) to the Research Ethics Manager. These should include a cover letter from the Coordinating Principal Investigator or Study Co-ordinator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.

7. The HREC will be notified, giving reasons, if the protocol is discontinued at a site before the expected date of completion.

8. The Coordinating Principal Investigator will provide an annual report to the HREC and at completion of the study in the specified format.

This HREC approval is valid for 3 years from the date of this letter.

9. If you require an extension for your study, please submit a request for an extension in writing outlining the reasons. Note: One of the criteria for granting an extension is the compliance with the approval's conditions including submission of progress reports.

10. Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes (WHO / ICMJE 2008 definition) should be registered, including early phase and late phase clinical trials

Office	Postal	Phone	Fax
Department of Health Level 2 15 Butterfield Street Herston QLD 4006	HMR – Level 2 PO Box 2368 Fortitude Valley BC QLD 4006	61 7 3328 9866	61 7 3328 9115

(phases I-III) in patients or healthy volunteers (WHO Recommendation / ICMJE policy). If in doubt, registration is recommended. All studies must be registered prior to the study's inception, i.e. prospectively. http://www.anzctr.org.au/

Should you have any queries about the HREC's consideration of your protocol please contact the Ethics Secretariat on 07 3288 9866

Please note that the Queensland Health Central Office HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Attached is the HREC Composition with specialty and affiliation with the Hospital (Attachment I).

The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the following website:
http://www.health.qld.gov.au/ohmr/html/regu/hrec_contacts.asp

*Once authorisation to conduct the research has been granted, please complete the Commencement Form (*Attachment II*) and return to the Queensland Health Central Office Human Research Ethics Committee or email to HMR_REG@health.qld.gov.au .*

The Queensland Health Central Office HREC wishes you every success in your research.

Yours sincerely,

Professor Mervyn Eadie
Chair
Queensland Health Central Office
Human Research Ethics Committee (EC00334)

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From:	QUT Research Ethics Unit
To:	Sonali Coulter
Cc:	QUT Research Ethics Unit
Subject:	Ethics Application Approval - 1300000719
Date:	Tuesday, 12 November 2013 3:31:01 PM

Dear Mrs Sonali Coulter

Project Title: An Economic Evaluation of Antimicrobial Stewardship Programs in Metropolitan Hospitals in Australia

Ethics category: Human - Administrative Review
QUT approval number: 1300000719 (As per Queensland Health Central Office Human Research Ethics Committee, Approval number: HREC/13/QHC/33)
QUT clearance until: 13/09/2016

We are pleased to advise that your administrative review application has been reviewed by the Chair, University Human Research Ethics Committee (UHREC), and confirmed as meeting the requirements of the National Statement on Ethical Conduct in Human Research (2007).

I can therefore confirm that your application has received QUT administrative review approval based on the approval gained from the responsible Human Research Ethics Committee (HREC). We note this HREC has awarded the project ethical clearance until 13/09/2016.

CONDITIONS OF APPROVAL
Please ensure you and all other team members read through and understand all UHREC conditions of approval prior to commencing any data collection:
- Standard: Please see attached or www.research.qut.edu.au/ethics/humans/stdconditions.jsp
- Specific:

Projects approved through an external organisation may be subject to that organisation's review arrangements. Researchers must immediately notify the QUT Research Ethics Unit if their project is selected for investigation / review by an external organisation.

VARIATIONS
All variations must first be approved by the responsible HREC before submission to QUT for ratification. Once approval has been obtained please submit this to QUT using our online variation form:
www.research.qut.edu.au/ethics/humans/var/

MONITORING
Please ensure you also provide QUT with a copy of each adverse event report and progress report submitted to the responsible HREC.

Administrative review decisions are subject to ratification at the next available UHREC meeting. You will only be contacted again in relation to this matter if UHREC raises additional questions or concerns.

Please don't hesitate to contact us if you have any queries.

We wish you all the best with your research.

Kind regards

Janette Lamb on behalf of the Chair UHREC
Research Ethics Unit | Office of Research | Level 4 88 Musk Avenue
Kelvin Grove | Queensland University of Technology
p: +61 7 3138 5123 | e: ethicscontact@qut.edu.au | w: www.research.qut.edu.au/ethics/

Royal Brisbane and Women's Hospital
Metro North Hospital and Health Service

Queensland Government

Enquiries to: Adj Assoc Prof Lesley Fleming
A/Executive Director, RBWH
Phone: 07 3646 1585
Fax: 07 3646 4481
Ref:

Dr Krispin Hajkowicz
Department of Infections Diseases
Level 6 Joyce Tweddell Building
RBWH, Herston QLD 4029

Dear Dr Hajkowicz

Re: HREC/13/QHC/33 An Economic Evaluation of Antimicrobial Stewardship Programs in Metropolitan Hospitals in Australia

Thank you for submitting an application for authorisation of the above research project. I am pleased to inform you that authorisation has been granted for this study to be conducted at the Metro North Hospital and Health Service, Royal Brisbane and Women's Hospital.

In addition to the conditions of approval imposed by the Human Research Ethics Committee, when submitting an amendment to the HREC, please also submit (electronically) to the RGO a copy of the covering letter for the amendment as well as a description and the rationale for it. This is to allow the RGO to determine whether or not there are research governance implications connected with the amendment. Amendments may include changes to the protocol, budget, information sheets, consent forms, clinical trial agreements and any other research-related documentation. The RGO will then advise you whether or not further documentation is required.

When the study commences, please complete the Commencement Form and send it to the Research Governance Office.

If you have any questions relating to this authorisation please contact the Research Governance Officer on 3646 8579.

I wish you every success with your research.

Thank you for conducting this important research.

Yours sincerely

Adj Assoc Prof Lesley Fleming
A/Executive Director
25/11/13

c.c. Sonali Coulter, 11 Hooker St, Windsor QLD 4030, QUT PhD student

Queensland Government

Department of Health

Enquiries to: Vanessa Druett
Health and Medical Research
Preventive Health Unit
Telephone: (07) 3328 9866
Ref QCOS13635/**RD004843**

Ms Sonali Coulter
Institute of Health and Biomedical Innovation
Queensland University of Technology (QUT)
60 Musk Avenue
KELVIN GROVE QLD 4059

Dear Ms Coulter

Research Title: An Economic Evaluation of Antimicrobial Stewardship Programs in Metropolitan Hospitals in Australia.
HREC Number: HREC/13/QHC/33

I am writing to inform you that your request for access to confidential health information for the above project has been approved under the delegation of the Director-General. In accordance with Section 284 of the *Public Health Act 2005* the researchers listed in your application, dated 26 November 2013 can access and use the specified confidential information, providing they act within the limits detailed in your submission.

This approval (RD004844) commences on the date of this letter and is valid to 03 September 2016.

This approval relates to data for the period from 01 October 2009 to 31 December 2014 from the Royal Brisbane and Women's Hospital and Queensland Hospital Admitted Patient Data Collection.

This approval means that you must undertake the responsibilities and obligations of confidentiality of the information under the provisions of the *Public Health Act 2005.* You must take all reasonable steps necessary to ensure that the confidential information is kept confidential, including storing or disposing of all data, information, documents and associated correspondence in a secure manner. Unauthorised use or disclosure of confidential information may incur a penalty under the laws of the Queensland Government. These obligations include providing notification of any change in the names of persons who will be given the information for the research.

When conducting research within the Queensland public health system, a copy of this Approval Letter must be provided to the relevant Research Governance Officer as part of your research governance application.

Please display this letter and a copy of your application when requesting the confidential information from the relevant data custodian.

You are required to provide an annual progress report and a final report at the completion of your project, to Health and Medical Research, Preventive Health Unit. Templates can be found on the web page http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp

Should you wish to extend your research project beyond this time or amend the study protocol, you will need to seek approval of these amendments from the approving HREC and re-apply for approval of the release of confidential data. This includes disclosing this information to and recruiting additional people to this project. Please provide a copy of your HREC approval of the amendments when re-applying.

Please feel free to contact Health and Medical Research, Preventive Health Unit on email HMR@health.qld.gov.au or phone 07 3328 9866 if you have any queries on this matter.

Yours sincerely

Kaye Pulsford
Senior Director, Preventive Health Unit
Chief Health Officer Branch
Health Services and Clinical Innovation Division

12 / 12 /2013

MHS & MMRI Human Research Governance - SSA Authorisation

20th February, 2014

Ms Sonali Coulter
Institute of Health & Biomedical Innovation
Queensland University of Technology
60 Musk Avenue
Kelvin Grove Qld 4059

Dear Ms Coulter

Re: HREC/13/QHC/33; Mater Research Governance Ref. RG-80A. An Economic Evaluation of Antimicrobial Stewardship Programs in Metropolitan Hospitals in Australia

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following site(s):

Mater Adults' Hospital, South Brisbane

Documents reviewed and Authorised by Mater Research Governance are as per HREC Approval Letter dated 3rd September 2013 and include:

- *Research Protocol; Ver 1 dated 5Aug2013*

The following conditions apply to this research proposal. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval.

1. The Research Governance Officer must be informed of any problems that arise during the course of the study which may affect conduct of the study at the site.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the HREC for review, are copied to the research governance officer;

3. Proposed amendments to the research protocol or conduct of the research which only affects the ongoing site acceptability of the project, are to be submitted to the research governance officer;
4. Proposed amendments to the research protocol or conduct of the research which may affect both the ongoing ethical acceptability of the project and the site acceptability of the project are to be submitted to the research governance officer after a HREC decision is made.

We wish you every success in undertaking this research.

Yours sincerely

Dr Louise Hutley, PhD
Senior Research Governance Officer
Room 294, Lvl 2, Aubigny Place
Mater Research Office
Raymond Terrace
South Brisbane Qld 4101

Ph: (07) 3163 8336
Fax: (07) 3163 1588
Email address: research.governance@mmri.mater.org.au

PHA Title: An economic evaluation of Antimicrobial Stewardship Program in Metropolitan Australian Hospitals

Researchers: Ms Sonali Coulter, Prof. Nicholas Graves, Dr Kate Halton, Dr Jason Roberts, Dr Katharina Merollini

Signed by QHAPDC Data Custodian: 26 November 2013
Signed by the Delegate: 12 December 2013
Delegate letter provided to HSB: 18 December 2013

PHA Amendment Request

The Amendment requests the following change.

Dates	Original	PHA Amendment
1 January 2010 to 31 January 2016	QHAPDC Data Items: - Length of Stay (capped at 30+ days) - Admission ward - Admission date (mm-yyyy) - Separation date (mm-yyyy) - Discharge status - DRG - ICD-10-AM (Principal and Other diagnosis) - Sex - D.O.B (mm-yyyy) - Hospital in the home care (flag yes/no)	QHAPDC Data Items: - **Length of Stay (not capped)**

Amendment Extract

The original PHA application requested the above QHAPDC data be linked to the AUSLAB and Kestrel cohort. The researcher is now requesting all Length of Stay (LOS) counts, removing the 30+ day cap. The researcher has explained that the evaluation being used needs the LOS information to model different scenarios in BSIs. This uses the mean LOS for these groups of patients, which cannot be determined if LOS is capped at 30+ days. All extraction dates remain the same.

With Data Custodian approval, a complete extract from 1 January 2010 to 31 January 2016, of the existing QHAPDC variables, including LOS counts now without a 30+ day cap, will be provided.

All other requested data items remain the same as the original PHA.

Authorisation from Data Custodian:

I have considered this proposal and consulted the appropriate personnel and I confirm that I have seen all relevant documents that are required. The Department is: *(tick whichever applies):*

☒ able to confirm that the data services indicated will be provided, within the present resources;

☐ unable to provide data services indicated, on the following grounds:

The custodian has supplied these data for an approved research request, but makes no warranty as to the fitness of the data, nor of the proposed methods, for the purpose for which the data has been provided and do not necessarily represent those of Queensland Health.

Name NEIL GARDINER Date 6/7/15

Position DIR HSB

Signature .....

Department

Appendix B: Wage rates at Queensland Health

Health professional	Wage rates per annum
Infectious Diseases Physicians and Clinical Microbiologists MO1 1.4-1.6	L21 MO1-4 $159,343 L22 MO1-5 $163,293 L23 MO1-6 $167,245
Hospital Administrators and Eminent status Physicians	L28 MO3-1 $194,897 L29 MO4-1 $205,435
AMS Pharmacist:	HP4 L1$96,786 L2$98,803 L3$101,383 L4$104,146 HP5 L1$109,492 L2$114,245
Nurse Grade7(NUMs and Nurse educators) Nursing (ICP)	L1$102,609 L2$107,250 L3$109,917 L4$111,399
IT specialists on AO scale	AO7 L 1 $102,724 L 2 $105,229 L3 $107,741 L4 $110,243 AO8 L1 $113,958 L2 $116,176 L3 $118,380 L4 $120,582

Source: https://www.health.qld.gov.au/hrpolicies/wage_rates

Calculation of costings using wage rates at Queensland Health

Intervention	Components	Costings
AMS Team	0.3FTE ID physician	0.3FTE ID physician($163,293.66) x0.3 =$49,988.10
	0.6FTE Pharmacists	0.6FTE Pharmacist ($111,868.50) x 0.6 =$67,121.10
	Clinical Microbiologist estimate 0.1FTE	0.1FTE Clinical Microbiologist ($163,293.66) x 0.1 =$16,329.40 Total = $133,438.60
AMS committee **Meets 1.5hrs every second month commitment per annum = 6X1.5hrs each(9hrs)** **Based on a 40 hour week total hours =2080** **FTE per year = 9/2080= 0.0043FTE**	ID Physician 1x MO1 1xMO4	ID Physician MO1 1.4-1.6 Av: $163,293.66x 0.0043=$702.16 ID physician MO4 205,435x0.0043=$883.37
	AMS Pharmacist	Clinical pharmacist HP5 111,865.50x 0.0043=$481.02
	Clinical Microbiologist	Clinical microbiologist MO4 $205,435x0.0043=$883.37
	IT specialist	IT specialist AO7/AO8 $111,879.125=$481.08
	Hospital Administrator	Hospital Administrator MO4 $205,435=$883.37
	ICP	ICP Grade 7 $107,793.75=$463.50
	Other Surgeon	4X senior medical officers MO3 $194,897x0.0043x4=$3403.83
	Other ED Physician	Total costs =$8181.70
	Other Clinical	

	pharmacologist Other Cancer care pharmacist	
Training resources		$1200
Additional Equipment	Cost of instrumentation	$33,744.91/10years=$3374.40
Guidance MS	Guidance	
	Guidance MS: licence and set up fee	$69200 +GST once =$76120/10=$7612(assuming updated after 10 years)
	Annual support fee	$13920 per annum plus GST=$15312
		Total cost= $26298.40 per annum
AMS intervention RBWH total cost	AMS Team + AMS committee, Training resources and Guidance MS	$169,118.70

Appendix C: Survey from hospitals for costings and context

The data collection document (questionnaire) to obtain information required for the economic evaluation of the AMS intervention is included in the following pages.

Information required for the economic evaluation of the AMS intervention

Institute of Health and Biomedical Innovation
QUT

Sonali Coulter PhD Candidate

Table 1 Organisms included in the Analysis

Organisms included in the Analysis:
Staphylococcus aureus
Methicillin Resistant Staphylococcus aureus (MRSA)
Enterococcus faecalis
Enterococcus faecium
Vancomycin resistant *Enterococcus faecium and Enterococcus faecalis (VRE)*
Escherichia coli
Escherichia coli with Extended Spectrum Beta Lactamases (ESBL)
Klebsiella pneumonia
Klebsiella pneumoniae with ESBL
Pseudomonas aeruginosa
Candida albicans
Candida species
Anaerobic organisms

Table 2 Empirical Therapy for common Bloodstream Infections

Empirical Therapy			
Category	**Preferred**	**Alternative Penicillin allergy intolerance or Syndrome based**	**Suspected Drug resistant variant**
GPC (pairs and chains) ?Strep or Enterococcus	Benzyl Penicillin Ampicillin	Vancomycin Pip/Tazo	Teicoplanin Linezolid Daptomycin
GPC (Clusters) ?Staph	Flucloxacillin	Vancomycin Cefazolin/ Cephalothin Clindamycin	Vancomycin Linezolid Daptomycin
GNB ?Enterobacteriaceae ?Pseudomonas ?anaerobe	Ampicillin +Gentamicin Pip/Tazo	Ceftriaxone Meropenem (if in critical care) Tobramycin Amikacin Ceftazidime Cefepime Ciprofloxacin	Meropenem Ciprofloxacin Colistin
Mixed infections GPC (Strep)and GNB	Amp and Gent	Pip/Tazo Vacomycin + Ceftriaxone Vancomycin +Gentamicin	Daptomycin+ Amikacin or Meropenem
Mixed infections GPC(Staph) and GNB	Fluclox and Gent	Vancomycin + Gentamicin Vancomycin + Ceftriaxone	Vancomycin + Meropenem
Yeast ? C albicans C species	Fluconazole	Caspofungin Lipid Amphotericin	

Table 3 Targeted therapy for common Bloodstream Infections

Targeted Therapy		
Organism	**Preferred**	**Alternative**
Staphylococcus aureus	Flucloxacillin	Cephazolin Cepahlothin
Staphylococcus aureus (MRSA)	Vancomycin	Daptomycin Teicoplanin Clindamycin
Enterococcus faecalis/faecium	Ampicillin	Vancomycin
VRE	Teicoplanin Daptomycin Linezolid	
Escherichia coli **Klebsiella pneumoniae**	Cephalothin Cephalzolin Pip/tazo(or Timentin) Ampicillin	Ceftriaxone Gentamicin
E coli or K pneumonia ESBL	Meropenem Ertapenem	
Enterobacter cloacae/aerogenes	Meropenem Ertapenem	
Acinetobacter baumanii	Meropenem	
Carbapenem resistant Acinetobacter baumanii	Colistin	

Pseudomonas aeruginosa	Pip/Tazo(or Timentin) Ceftazidime Gentamicin	Meropenem Ciprofloxacin Tobramicin
Anaerobes	Metronidazole	Pip/Tazo Timentin
Candida albicans	Fluconazole	
Candida species non albicans	Caspofungin	Lipid Amphotericin B

List of Antimicrobials that antimicrobial utilisation results are required for as DDD per 1000PD

Table 4 List of commonly used antimicrobials

Benzyl Penicillin	Ampicillin	Vancomycin	Pip/Tazo
Timentin	Teicoplanin	Linezolid	Daptomycin
Flucloxacillin	Cefazolin	Cephalothin	Clindamycin
Gentamicin	Ceftriaxone	Meropenem	Tobramycin
Amikacin	Ceftazidime	Cefepime	Ciprofloxacin
Colistin	Fluconazole	Metronidazole	Caspofungin
Lipid Amphotericin			

Please comment here if there are differences to antimicrobials administered in your institution

Do the scenarios in Table 2 and Table 3 represent the antimicrobials used in your institution?

☐ Yes

☐ No

If No then please list specific antimicrobials used in your institution that are not included in Table 4:

_____

_____

_____

_____

Could you please provide the antimicrobial utilisation data for your institution for the antimicrobials listed above?

Data required from each hospital for analysis

Hospital : _____

Bed numbers for your institution: _____

ICU

Surgical

Medical

Did you have an existing restricted formulary prior to AMS intervention?

☐ Yes

☐ No

What antimicrobials were on your restricted formulary

_____

_____

_____

_____

_____

_____

Whilst there is no consensus in Staffing recommendations in Australia the general suggestion is that for every 100 acute beds, at least 10 hours (0.3FTE) of a senior pharmacists and at least 3.5hours of a lead clinician (0.1FTE) per week should be dedicated to AMS activities[1].

Who is included in your AMS team and at what proportion of FTE?

☐ID Physician ☐FTE
☐AMS Pharmacist ☐FTE
☐Clinical Microbiologist ☐FTE
☐IT specialist ☐FTE
☐ICP ☐FTE
☐Other ☐FTE
☐Other ☐FTE

Do you have an AMS Committee?

☐No
☐Yes

If yes how often does this committee meet?

☐Monthly
☐Quarterly
☐Other _____
How long are the meeting in duration in hours?

_____

What categories and how many FTEs constitute your AMS committee?
☐ID Physician ☐FTE
☐AMS Pharmacist ☐FTE
☐Clinical Microbiologist ☐FTE
☐IT specialist ☐FTE
☐Hospital Administrator ☐FTE
☐ICP ☐FTE
☐Other _____ ☐FTE
☐Other _____ ☐FTE

Antibiotic management program in place Pre AMS intervention:

Please tick which AMS strategies were present prior to the AMS intervention being implemented at your institution (Extracted from the list of core activities recommended for effective AMS in Australia)

☐Implementation of clinical guidelines that are consistent with the latest version of Therapeutic Guidelines: Antibiotic (taking into account local microbiology and antimicrobial susceptibility patterns)

☐Establishing formulary restriction and approval systems

☐Reviewing antimicrobial prescribing with intervention and direct feedback to the prescriber

- ☐ICU
- ☐General Ward

Comments:

☐Monitoring performance and antimicrobial prescribing by collecting and reporting ward specific use data

- ☐Regularly
- ☐Infrequently

Comments:

☐Selective reporting by the Microbiology laboratory

☐Education of prescribers

- ☐Seminars
  - Frequency
- ☐Individual Detailing
  - Frequency

☐ De-escalation

☐ Dose optimisation

☐ Parenteral to Oral conversion

☐ Hospital in the home intervention

☐ Use of a clinical decision support system

☐ Use of rapid technology to improve turnaround times

☐ Annually publishing facility specific antibiogram

☐ Other

Please record the date when the AMS intervention Commenced at your institution:_____

Please tick the relevant strategies that were introduced as part of the AMS intervention at your institution (Extracted from the core activities recommended for effective AMS in Australia)

☐ Implementation of clinical guidelines that are consistent with the latest version of Therapeutic Guidelines: Antibiotic(taking into account local microbiology and antimicrobial susceptibility patterns)

☐ Establishing formulary restriction and approval systems

☐ Reviewing antimicrobial prescribing with intervention and direct feedback to the prescriber

- ☐ ICU
- ☐ General Ward

Comments:

☐ Monitoring performance and antimicrobial prescribing by collecting and reporting ward specific use data

☐ Regularly
☐ Infrequently
Comments:

☐ Selective reporting by the Microbiology laboratory

☐ Education of prescribers

☐ Seminars
Frequency

☐ Individual Detailing
Frequency

☐ De-escalation

☐ Dose optimisation

☐ Parenteral to Oral conversion

☐ Hospital in the home intervention

☐ Use of a clinical decision support system

☐ Use of rapid technology to improve turnaround times

☐ Annually publishing facility specific antibiogram

☐ Other

If AMS intervention at your institution was implemented in several stages please list AMS Strategies implemented in chronological order below:

_____

_____

_____

_____

_____

_____

_____

Time line of educational activities as part of the AMS intervention

_____

_____

_____

_____

Frequency of AMS ward rounds

_____

_____

Frequency of Point Prevalence Surveys(PPS)

_____

_____

_____

Information gathered during PPS

Date	Result
---/---	
---/---	
---/---	
---/---	
---/---	
---/---	
---/---	

Pharmacy:

Any periods of “stock outs” of antimicrobials during the AMS intervention period

Were there any antimicrobials taken off patent during the AMS intervention period?

General

Other hospital interventions that may have affected antimicrobial prescribing since the AMS intervention

☐ Infection control initiatives	---/---	to	---/---
☐ Hospital cleaning initiatives	---/---	to	---/---
☐ Sepsis bundle introduction	---/---	to	---/---
☐ Central line bundle initiatives	---/---	to	---/---
☐ Outbreaks of HAIs	---/---	to	---/---
	---/---	to	---/---

AMS Intervention

Pay Stream and level of contributors to AMS Team or Committee

ID Physician

Clinical Microbiologist

Clinical Pharmacists

IT specialist

Hospital Administration

Senior Clinician

Other

Equipment

Type ☐Cost

IT resources

Type ☐Cost

Stationary

Type ☐Cost

Meeting resources

Type ☐Cost

Other

Type ☐Cost

Additional Support Systems for AMS

☐Clinical Decision Support System

☐Electronic Medical Record

☐Other
Please estimate cost of the additional Support Systems for AMS used in your institution: (If exact amount is not available please estimate minimum, maximum and best guess for expenditure)
What were the barriers to implementation of AMS at your institution? ☐Financial considerations/cost ☐Opposition from prescribers ☐Resistance from administration ☐Other clinical initiatives are higher priority ☐Personnel shortages ☐None of the above ☐Other

Laboratory Pre AMS
Instrument or equipment used to analyse blood cultures
Cost of processing a blood culture set
Please indicate what the reporting protocol is to treating clinician when a blood culture is positive What are the operational hours of the laboratory
Stages of reporting results Gram stain Direct susceptibilities Same day tests (please list test and turnaround time)

Instrument or system for Bacterial pathogen identification: Instrument or system used for Candida species identification:
Cost of per test including cost of instrument, consumables and labour
Method used to perform susceptibility testing and turnaround time **Bacterial pathogens** Gram positive (Staphylococcus species and Enterococcus species) Gram Negatives (E coli, K pnemoniae, P aeruginosa, Acinetobacter baumanii) **Candida species**

Cost of per test including cost of instrument, consumables and labour for **Bacterial pathogens** Gram Positive Gram Negative **Candida species**
Laboratory Post AMS
Equipment used to analyse blood cultures
Cost of processing a blood culture set
Please indicate what the reporting protocol is to treating clinician when a blood culture is positive What are the operational hours of the laboratory
Stages of reporting results Gram stain Direct susceptibilities

Same day tests (please list test and turnaround time)
Instrument or system for **Bacterial pathogen identifica**tion: Instrument or system used for Candida species identification:
Cost of per test including cost of instrument, consumables and labour
Method used to perform susceptibility testing and turnaround time **Bacterial pathogens** Gram positive (Staphylococcus species and Enterococcus species) Gram Negatives (E coli, K pneumoniae, P aeruginosa, Acinetobacter baumanii)

Candida species
Cost of per test including cost of instrument, consumables and labour for Bacterial pathogens Gram Positive Gram Negative Candida species

Thank you for providing me with valuable information that will enable me to evaluate the cost effectiveness of your AMS intervention

Sonali Coulter

Appendix D: Peer-Reviewed Publications from this Thesis

D1. ARTICLE 2 (100)

S Coulter, JA Roberts, K Hajkowicz, Kate Halton. The use of bloodstream infection (BSI) mortality to measure the impact of antimicrobial stewardship (AMS) interventions: assessing the evidence. *Infectious Disease Reports* 2017; 9: 6849. PMID: 28458799.

D2. ARTICLE 1 (148)

S Coulter, K Merollini, JA Roberts, N Graves, K Halton. The need for cost-effectiveness analyses of antimicrobial stewardship programmes: a structured review. *International Journal of Antimicrobial Agents*, 2015; 46(2): 140-9. PMID: 26058776.

The use of bloodstream infection mortality to measure the impact of antimicrobial stewardship interventions: assessing the evidence

Sonali Coulter,[1] Jason A. Roberts,[2,3] Krispin Hajkowicz,[3] Kate Halton[4]

[1]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane; [2]Burns Trauma and Critical Care Research Centre, UQ Centre for Clinical Research, The University of Queensland, Brisbane; [3]Royal Brisbane and Women's Hospital, Brisbane; [4]Faculty of Health, School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia

Abstract

This review sets out to evaluate the current evidence on the impact of inappropriate therapy on bloodstream infections (BSI) and associated mortality. Based on the premise that better prescribing practices should result in better patient outcomes, BSI mortality may be a useful metric to evaluate antimicrobial stewardship (AMS) interventions. A systematic search was performed in key medical databases to identify papers published in English between 2005 and 2015 that examined the association between inappropriate prescribing and BSI mortality in adult patients. Only studies that included BSIs caused by ESKAPE (*Enterococcus faecium/faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*) organisms were included. Study quality was assessed using the GRADE criteria and results combined using a narrative synthesis. We included 46 studies. Inappropriate prescribing was associated with an overall increase in mortality in BSI. In BSI caused by resistant gram positive organisms, such as methicillin resistant *S. aureus*, inappropriate therapy resulted in up to a 3-fold increase in mortality. In BSI caused by gram negative (GN) resistant organisms a much greater impact ranging from 3 to 25 fold increase in the risk of mortality was observed. While the overall quality of the studies is limited by design and the variation in the definition of appropriate prescribing, there appears to be some evidence to suggest that inappropriate prescribing leads to increased mortality in patients due to GN BSI. The highest impact of inappropriate prescribing was seen in patients with GN BSI, which may be a useful metric to monitor the impact of AMS interventions.

Introduction

One of the main goals of an antimicrobial stewardship (AMS) intervention is to ensure patients with infections receive the most appropriate antimicrobial agent at the optimal dose at the earliest time.[1] As AMS programs can take many forms there is a need to ensure that the intervention(s) selected can maximize the outcomes of the program. However, there is a lack of clarity around the outcome measures that provide the best indicators of a successful AMS program with most studies focusing on changes in antimicrobial utilization rates.[2] An update by Akpan *et al.* (2016) on current metrics to measure the impact of AMS programs in a recent review reported that only a handful of studies included patient outcomes.[3] The authors reported that only 13 of the 63 studies that met their inclusion criteria reported on mortality, length of stay and unplanned admissions related to post-AMS infection as an outcome measure. Okumura *et al.* (2015) focused on six studies that examined mortality and the non-significant impact was highlighted with only one study reporting an absolute risk reduction in 30-day mortality.[4]

A recent study by Cairns (2016) found that active review of patients with bloodstream infections (BSI) by their AMS team improved the timeliness of appropriate therapy.[5] BSI mortality has been proposed as a useful indicator to evaluate AMS programs,[6,7] based on the premise that better prescribing practices should improve patient outcomes. While this premise may make sense, the evidence to support this link is not clear.

Bloodstream infections are serious infections and factors such as the choice of antimicrobial, duration of therapy, dosage, and route of administration can impact patient outcomes. While there are many infectious agents causing serious infections in a hospital environment, a group of organisms referred to as the ESKAPE bacteria (*Enterococcus faecium/faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*) are particularly problematic.[8] Patients with BSI due to ESKAPE organisms who are not receiving appropriate therapy, and patients with infections caused by resistant organisms, have worse outcomes than those caused by susceptible organisms.[9] It follows that if BSI are managed more effectively, morbidity, mortality and length of stay in this subset of patients can be reduced.[10]

This systematic review aims to synthesize findings from epidemiological studies to determine whether there is an association between inappropriate (*i.e.*, inadequate, incorrect or delayed) prescribing and an increased risk of mortality in adult hospitalized patients with BSI caused by ESKAPE organisms. In addition, the impact of factors such as organism group (gram positive, GP, or gram negative, GN) and resistance status will be assessed.

Search strategy

A systematic literature search was performed in November 2015 in key medical databases (PubMed, Embase and Cochrane) to identify all papers published in English between January 2005 and November 2015 that assessed the association between inappropriate prescribing and BSI mortality. The review protocol was not registered but was aligned with the PRISMA Statement.[11]

The search strategy used is given in

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E-mail: sonali.coulter@qut.edu.au

Key words: Antimicrobial stewardship; bloodstream infection; mortality; antibiotic resistance; ESKAPE organism.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

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*doi:10.4081/idr.2017.*6849

Supplementary Figure S1. All retrieved studies were scanned using title and abstract to determine whether the inclusion and exclusion criteria were met for the review. Where a decision could not be made based on the title or abstract, the paper was subject to full review.

Only primary studies in English that met the following inclusion criteria were analyzed: adult inpatients in hospital settings; studies performed in member countries of the Organization for Economic Co-operation and Development (OECD); the sample size was greater than 99; the risk of mortality related to BSI was expressed as a relative risk (odds ratio, relative risk or hazard ratio); and, included only organisms belonging to the ESKAPE group. Exclusions included: immunocompromized populations (transplant and oncology patients); neonatal and pediatric populations; and non-hospital inpatients.

Data on the study design, context, organisms, definition of inappropriate prescribing, main study objective and main outcome measure was extracted from all included studies using specifically designed data extraction forms that were piloted prior to use. The overall quality of the evidence to support an association between inappropriate prescribing and BSI mortality was assessed using the GRADE criteria.[12] The main summary measure was the relative risk of mortality. Results were combined using a narrative synthesis due to anticipated heterogeneity between studies. Subgroup analyses were conducted to look at differences in outcomes by organism group (GP or GN) and resistance status (sensitive or resistant) of BSIs.

Results

Of 9046 studies screened for inclusion, forty-six met the inclusion and exclusion criteria. Reasons for exclusion are shown in Figure 1. Of the 46 studies two were large multi-center studies: one including data from USA, Canada and Saudi Arabia;[13] and the second including data from nine European countries.[14] Thirteen studies were from the USA,[12,15-26] eight from Spain,[27-34] five from Italy,[35-39] four from Korea,[40-43] three each from Turkey[44-46] and Israel,[47-49] two each from the Netherlands[50,51] and the UK,[52,53] and single studies from Denmark,[54] Germany,[55] Norway,[56] and Australia.[57] Of the 46 studies 34 were retrospective in design and only three of these studies were case controlled.[16,36,49] Whilst a few studies focused on specific patient groups, most included all adult patients.

The majority of studies reviewed used a retrospective study design but used different analytical methods and adjusted for different confounders, making results difficult to directly compare. The definition for inappropriate prescribing varied significantly between countries although most studies defined appropriate prescribing as the correct antimicrobial for the pathogen according to local guidelines. The definition for inadequate therapy was no different from the one used for inappropriate therapy, in most cases. The definition of inappropriate, inadequate and delayed therapy used in each of the studies is described in Supplementary Tables S1 and S2. The time to antimicrobial therapy varied with a range from 6 hrs in septic shock and severe sepsis to up to 72 hrs being deemed acceptable. This variation of sickness severity in some patient cohorts explains the range in time to therapy, as a shorter time would be more appropriate for more severely unwell patients.

Impact of delayed therapy

The impact of timing of antimicrobial therapy on the risk of mortality in patients with BSI was reported in 12 of the 46 studies (Supplementary Table S3). The definition of delayed therapy varied from ≥1hr to >72hrs in the studies making it difficult to compare the impact on mortality in these patients. The impact of delayed therapy on BSI-associated mortality combined with the analysis of GP and GN organisms were reported in five of the 12 studies and reported a two-fold increase.[15,50,52,56,57] Only two of the twelve studies were case controlled and reported on the impact of Methicillin Resistant *Staphylococcus aureus* (MRSA) with a delay in therapy of two days, resulting in an odds of mortality of 1.85 (95%CI: 0.094-3.64, P=0.074)[16] and patients with BSI due to ESBL organisms with a delay in therapy of 48 hours resulting in an OR of 25.1 (95%CI: 10.5-60.2, P≤0.001).[49]

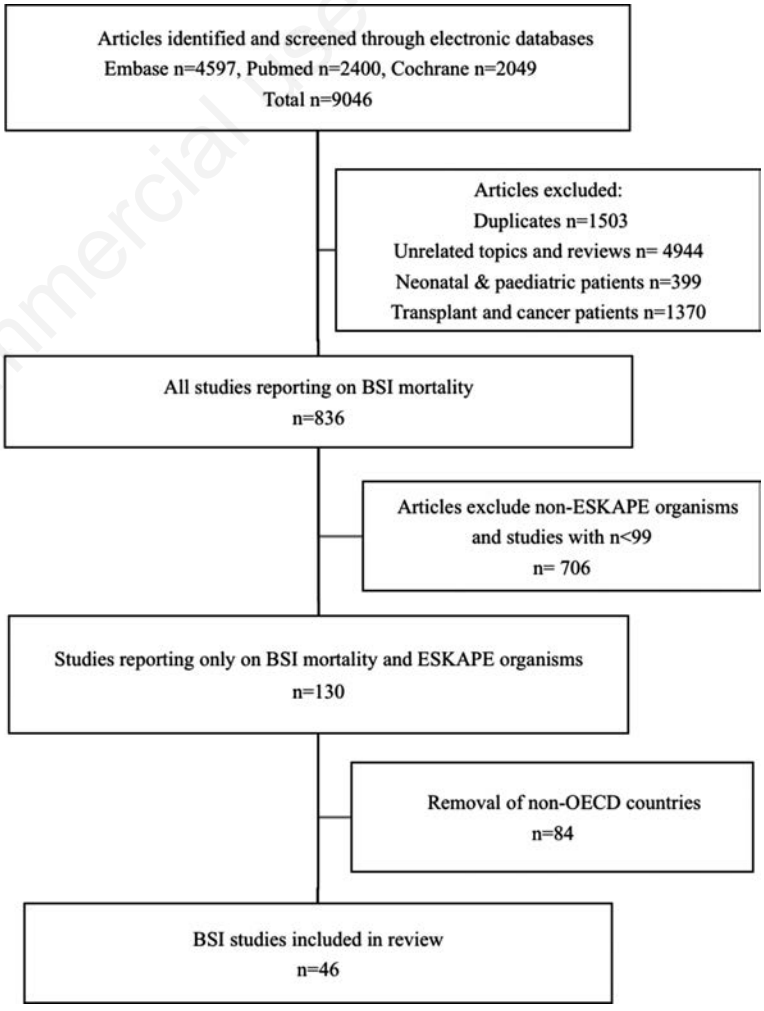

Figure 1 Search strategy to identify studies of bloodstream infections (BSI) and mortality or quality of life measures, from the Organization for Economic Cooperation and Development (OECD) countries.

Overall a greater impact was seen in GN resistant infections ranging from 3 to 25-fold increases in the risk of BSI-associated mortality.

Impact of inappropriate or inadequate therapy

The definitions for inadequate and inappropriate therapy used in the studies overlap and as such these studies will be presented collectively. Six of 34 studies that described the impact of inappropriate therapy on BSI-associated mortality combined the analysis of GP and GN organisms, seven only reported GP BSI and 21 reported GN BSI. In the six studies that pooled GP and GN BSI data, the odds of mortality ranged from no significant impact to a nine-fold increase in death; however, this higher estimate was observed in a subset of patients with severe sepsis. The risks associated with inappropriate prescribing were higher for studies looking at MRSA than studies reporting on Methicillin Susceptible *Staphylococcus aureus* (MSSA) infections.

The highest reported risks were due to infections with resistant GN infections. Studies that looked at the impact of mortality in all GN BSI, including *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter species*, reported an increase in the odds of mortality from two to five-fold due to inappropriate therapy. The impact increased significantly when inappropriate prescribing involved BSI due to resistant GN gram negative organisms ranging from two to nine-fold increases in the risk of death. The only case controlled study in this group reported data from multi drug resistant *P mirabilis* BSI and observed a nine-fold (9.85, 95%CI: 2.67-36.25, P<0.001) increase in mortality due to inappropriate prescribing.[36]

The overall quality of the papers included in this study were of medium to low quality only reaching an average score of Grade C according to the GRADE criteria. The evidence on GN as well as GP BSIs were of the same quality.

Discussion

Inappropriate (*i.e.,* inadequate, incorrect or delayed) therapy is associated with a higher risk of mortality in BSI caused by resistant GP organisms (*e.g*., MRSA) than MSSA organisms. However, the impact of inappropriate prescribing on mortality is greatest in BSI caused by GN organisms, with the risk of death ranging from 3 to 25-fold depending on the resistance status of the pathogen.

While the quality of studies is tempered due to study design, and the variation in the definition of appropriate prescribing, there is some evidence to suggest that inappropriate prescribing leads to unfavorable outcomes in patients with BSI, particularly in those BSI caused by resistant organisms. Only two studies investigating outcomes of BSI mortality in GN organisms reported no impact;[22,23] all other studies reported a higher risk of death if therapy was inappropriate. However, the exact magnitude of this association is somewhat unclear. While most studies adjusted for co-morbidities using multivariate logistic regression there was variety in the confounders considered and no studies used methods that accounted for time-dependent bias. Earlier work has demonstrated that adjustment for time-dependent bias can lead to a dramatic reduction in estimates of the attributable mortality and length of stay associated with infection in hospitalized patients.[58]

While short term outcomes such as 30-day mortality in susceptible GP infections, *e.g.,* those caused by *S. aureus,* does not seem to be associated with inadequate prescribing these infections can cause significant complications such as osteomyelitis and endocarditis in the longer term if not treated effectively.[59] The long term effects of poor prescribing are more difficult to capture and there is a need for prospective studies assessing longer term mortality outcomes and an assessment of morbidity impact in this area of research.

While it is perhaps intuitive that the dose as well as the timely delivery of antimicrobials to a patient with a BSI would be considered important, it remains not well studied in the current published evidence. To be considered appropriate therapy, the correct dose according to the local guidelines needs to be delivered. Roberts *et al.* (2008) advocated the delivery of the highest tolerable dose to achieve the best clearance of infection.[60] However in this review, most studies focused solely on timely delivery of the correct antibiotic, with no information as to what percentage of patients with BSI received an inadequate dose of the correct antimicrobial. The dose of the antimicrobial is important for a number of reasons. If therapeutic exposures of antimicrobials are not achieved at the site of infection, then the infection will not be controlled. Additionally, sub-optimal doses have been associated with the emergence of resistance.

To achieve improved prescribing practices in hospitals, the most informative data on the causative pathogen needs to be made available to the treating clinician in the most efficient manner. The delivery of rapid and accurate information on the identification and susceptibility of the pathogen causing the infection could lead to better prescribing and improved outcomes for patients. There has been published evidence to support the claim that rapid technology in conjunction with an AMS intervention improved survival in resistant GN BSI.[61] More data needs to be collected on the long term effects to measure the impact of AMS interventions and the use of rapid technology over longer periods of time. This data may indicate whether the improvements in prescribing achieved by AMS programs translate into improved patient outcomes and provide some insight as to the sustainability of the outcomes of these interventions.

Our review has a number of limitations due to the quality and the heterogeneity of the studies included therefore a meta-analysis of the data was not able to be performed. The various study designs, definitions and variation in the way the risk of death was quantified in these studies made it difficult to compare outcomes. A standardized metric of measuring the risk of mortality would be of benefit when measuring these outcomes so that it would be easier to compare studies in the future. Some studies may have been missed as the strict inclusion criteria meant other potentially important groups, such as the immunocompromized, were excluded due to their higher risks of mortality and morbidity. Studies that had a sample size of less than 99 were also excluded to minimize the influence of chance findings on our summary; this exclusion may have excluded small but potentially important studies.

The nature of the subject matter is not suitable for RCT methodology as it would be unethical to randomize any patient or patient group to inappropriate therapy. Hence it is unlikely that GRADE A evidence will be available in this space. The Cochrane handbook for systematic reviews endorses the use of high quality observational evidence where the quality of studies is of a high to moderate quality.[62] In our case what is thought of as lower level evidence in the absence of RCT studies might be the best available evidence on this topic.

The ESKAPE organisms are the main pathogens in hospital settings. BSI-associated mortality in patients caused by these organisms resulted in an increased risk of mortality; this finding suggests a link between inappropriate prescribing and an increased risk of death in these BSI. Since the largest impact of inappropriate prescribing was seen in resistant GN BSI, these may be a suitable metric to describe the impact of an AMS intervention on patient out-

comes. However, little is known on the longer term impacts of BSI that are treated with inappropriate antimicrobials and future longitudinal studies would provide better information on morbidity and quality of life impacts on patients receiving inappropriate therapy for BSI.

Conclusions

More effort into better study design and more consistent definitions of appropriate versus inappropriate therapy would be advantageous. The current review of evidence suggests that BSI mortality in GN may be associated with the adequacy of prescribing and thus may be a useful metric for evaluating the impact of AMS programs that focus on improving prescribing practices. Further evidence is needed to make a more conclusive recommendation.

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Supplementary Figure S1. Search strategy.

The search strategy included the terms: ((("anti-infective agents"[Pharmacological Action] OR "anti-infective agents" [MeSH Terms] OR ("anti-infective"[All Fields] AND "agents"[All Fields]) OR "anti-infective agents"[All Fields]) OR ("anti"[All Fields] AND "infective"[All Fields]) OR "antiinfective" [All Fields]) OR ("anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR ("anti-infective"[All Fields] AND "agents"[All Fields]) OR "anti-infective agents"[All Fields] OR "antimicrobial"[All Fields]) OR ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields])) OR "Anti-Infective Agents"[Mesh]) AND (((((("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) OR "Mortality"[Mesh]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields])) OR "Quality of Life"[Mesh]) AND ("Sepsis"[Mesh] OR (("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR (("blood"[Subheading] OR "blood"[All Fields] OR "blood"[MeSH Terms]) AND ("rivers"[MeSH Terms] OR "rivers"[All Fields] OR "stream"[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields])))))) AND ("2005/11/21"[PDat] : "2015/11/18"[PDat] AND "adult"[MeSH Terms]).

Supplementary Table S1. Aim of study and definitions.

First Author Year [Ref]	Aim of study and definitions
Kumar 2009 [13]	**Impact of inappropriate therapy in patients with septic shock within 6 h** of the administration of the first new antimicrobial agent.
Vazquez-Guillamet 2014 [10]	**Impact of appropriate therapy in patients with severe sepsis and septic shock Definition:** Antimicrobial treatment was classified as appropriate if the initial regimen was active against all identified pathogen(s) based on in vitro susceptibility testing and administered within **24 hours** of blood culture collection.
Gaieski 2010 [15]	**Impact of time to antibiotics Definition**: The time the antibiotic covering the causative organism was started, up to **36 hrs.** after triage or qualification; Appropriate antibiotics were defined as: 1) antibiotics for which the causative pathogens were sensitive *in vitro*; 2) in cases of polymicrobial infection, all pathogens felt to be contributing to severe sepsis or septic shock had to be covered by antibiotics for which the organisms were sensitive *in vitro*
Garnacho-Montero 2015 [27]	**Impact of adequate therapy in patients with severe sepsis and septic shock Definitions:** Antimicrobial therapy was considered adequate when the antibiotics prescribed covered all of the isolated pathogens (in blood and/or in the infection focus) and the dose and pattern of administration were in accordance with current standards.
Retamar 2012 [28]	**Impact of inadequate therapy Definition:** (i) at least one antimicrobial was administered as recommended following Spanish guidelines (5), including drug, route, and dosage; (ii) all organisms isolated from blood were susceptible *in vitro*; and (iii) the first dose was administered within the **first 24 h** after the blood culture had been drawn.
Son 2010 [40]	**Impact of inappropriate therapy Definition: T**he initial antibiotics, which were administered within **24 hr.** after acquisition of blood culture samples, included at least one antibiotic that was active in vitro and when the dosage and route of administration confirmed with current medical standards.
De Groot 2015 [50]	**Timing of antibiotic therapy Definition**: Time to antibiotics was measured by subtraction of registration time at the ED desk from the registered time of antibiotic administration by the nurse. In culture-positive patients, initial antibiotics were considered to be appropriate if the cultured microorganism could be a causative pathogen in relation to the clinical findings, and showed in-vitro sensitivity for the initial dose of the antimicrobial agent
Hounsom 2011 [52]	**Delay in appropriate therapy Definition:** Appropriate treatment was defined as any component of an antibiotic regimen, empiric or definitive, used to treat an infection to which the organism was susceptible in vitro. For calculating delay in treatment, the first day was defined as the day a significant blood culture was taken from the patient
Turan 2008 [44]	**Impact of inappropriate therapy Definition**: The antibiotic therapy was accepted as appropriate if the isolated bacteria was susceptible to at least one antibiotic in vitro, beginning time of the antibiotic was in **24 hours** after bacteria isolation**;** appropriate duration and dose
Wisdom 2015 [57]	**Impact of timing of antimicrobial therapy in patients in ED Definition:** Prescribed empirical antibiotics were considered adherent if they were consistent with current Australian Therapeutic Guidelines: Antibiotic, version 14.17 Non-adherent antibiotic regimens were categorized as adequate, insufficient or broader than required through consensus by a hospital panel comprised of an infectious disease physician and two senior pharmacists
Nygard 2014 [56]	**Timing of appropriate therapy Definition:** Timing and adequacy of antimicrobial agents was evaluated together with their appropriateness according to local recommendations.

Ammerlaan 2009 [14]	**Impact of inadequate therapy Definition:** intravenous administration of at least 1 antibiotic to which the isolate expressed in vitro susceptibility that started **within 2 days** after the positive index blood culture had been obtained or **within 1 day** if the patient had severe sepsis or septic shock.
Marchaim 2010 [16]	**Impact of delayed appropriate therapy Definition:** Delay in appropriate antimicrobial therapy DAAT was calculated according to the number of calendar days between the time blood cultures were obtained and **appropriate treatme**nt was given, based on in vitro susceptibilities.
Schweizer 2010 [17]	**Impact of appropriate therapy Definition**: Antibiotic therapy was defined as appropriate if the S. aureus isolate from the blood culture was susceptible to that antibiotic in vitro. Empiric antibiotic therapy was defined as receipt of any antibiotic during the period 24 hours before to 24 hours after the culture collection. And, time to appropriate therapy was measured as the time from culture collection to the time appropriate therapy was first received no matter if the appropriate therapy was given empirically or definitively.
Rodrıguez-Bano 2009 [34]	**Impact of inappropriate therapy Definition:** Empirical therapy was considered appropriate whenever an active antimicrobial agent (according to in vitro data) had been administered at standard doses and by the recommended route for at least 24 h during the **first 48 h** after the culture had been obtained; Therapy administered once the susceptibility results were known was considered definitive.
Gasch 2013 [29]	**Impact of inappropriate therapy Definition**: Antibiotic treatment was considered appropriate if the strain was susceptible to at least one of the administered antibiotics, with the exception of aminoglycosides, which were considered inappropriate, regardless of the sensitivity tests.
Kaasch 2013 [55]	**Impact of delayed appropriate therapy Definition:** The appropriateness of antimicrobial therapy was judged by the study physician based on in vitro susceptibility testing, dosage, mode of administration, and duration of therapy.
Paul 2010 [47]	**Impact of inappropriate therapy Definition:** Empirical therapy was defined as appropriate if the infecting pathogen was shown by in vitro susceptibility testing to be susceptible to the antibiotic used and therapy was started **within 48 h** of blood-culture taking**,** except for single aminoglycoside or rifampicin treatment
Kim 2006 [41]	**Impact of inappropriate therapy Definition**: The empirical antibiotic treatment was considered appropriate if the therapy given intravenously **within 48 h** of the onset of bacteremia included at least one antibiotic to which the isolate was susceptible.
Suppli 2011 [54]	**Impact of inappropriate therapy Definition:** Appropriate antimicrobial therapy was defined when: (i) the antimicrobial therapy was instituted **no later than the day when the blood culture sample was positive for growth** (median 1 day; IQR, 1–2); (ii) the spectrum of the administered antibiotics covered the susceptibility of the Enterococcus spp. and was an accepted treatment for enterococcal infection (iii) the dosage was adequate according to national recommendations (Danish national guidelines published in the relevant years by a committee of peers from the Danish Medical Association)
Shorr 2014 [18]	**Impact of initially inappropriate therapy Definition:** if the patient did not receive an anti-infective active *in vitro* against the culprit Gram-negative bacteria recovered. Additionally, **an active antimicrobial had to be administered within 24 hrs.** of the eventually positive culture being drawn.
Zilberberg 2014 [19]	**Impact of initially inappropriate therapy Definition:** if the initially prescribed antibiotic regimen was active against the identified pathogen based on in vitro susceptibility testing and was administered within **24 hours following blood culture** collection. Combination therapy was not required to be considered IAAT.
Micek 2011 [20]	**Impact of resistance and initial inappropriate therapy Definition**: Empiric antimicrobial treatment was classified as being appropriate if the initially prescribed antibiotic regimen was active against the identified pathogen(s) based on in vitro susceptibility testing and **administered within 12 hours following blood culture collection.**

Micek 2010 [21]	**Impact of initial inappropriate antibiotic therapy Definition**: Antimicrobial treatment was classified as being appropriate if the initially prescribed antibiotic regimen was active against the identified pathogen based on *in vitro* susceptibility testing and **administered within 24 h of blood culture collection.** For patients with polymicrobial infection the initial antimicrobial regimen had to be active against all identified pathogens in order to be classified as appropriate.
Thom 2008 [22]	**Impact of appropriate antimicrobial therapy Definition**: Empiric antimicrobial therapy was defined as the receipt of an antimicrobial agent by the patient between **8 hours before and 24 hours after the index blood culture was drawn.** Empiric therapy was considered appropriate if it included intravenous and/or oral antimicrobials to which the specific isolate (or isolates, if polymicrobial displayed *in vitro* susceptibility.
Osih 2007 [23]	**Impact of appropriate antimicrobial therapy Definition**: assessed adequate therapy in three distinct windows: **between 8 h before the time the culture was obtained and 24 h afterward,** between 24 and 48 h after the culture was obtained, and from 48 h after the culture was obtained to 4 h after the time the antibiotic susceptibility testing results were available
Lodise 2007 [24]	**Impact of delayed appropriate therapy>52 Definition**: Classification and regression tree analysis(CART) was used to analyze the duration of time that elapsed between the collection of index *P. aeruginosa* blood culture and the administration of appropriate antibiotic treatment and to identify the temporal breakpoint that maximized the difference in 30-day mortality
Anderson 2006 [25]	**Impact of delayed effective therapy>72h Definition**: Definitive therapy is antimicrobial therapy initiated after in vitro antimicrobial susceptibility test results were released by the clinical microbiology laboratory. Typically, the period for definitive therapy began 48 h after the day of infection and spanned until 5 days after the date of the initial positive culture. Effective therapy is antimicrobial therapy active in vitro against the BSI isolate.
Micek 2005 [26]	**Impact of appropriate initial therapy Definition:** the microbiological documentation of infection (i.e., a positive blood culture result) that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known. Inappropriate antimicrobial treatment included the absence of gram-negative antimicrobial agents with in vitro activity against *P. aeruginosa* and the administration of gram-negative antimicrobial agents to which the *P. aeruginosa* isolates were resistant based on susceptibility testing.
Peralta 2012 [30]	**Impact of adequate therapy Definition:** Empirical antimicrobial therapy was defined as adequate in terms of in vitro susceptibility of an organism isolated, and if antibiotic treatment was started **within 24 hours** after drawing blood cultures. The **dosage of the antibiotic was not taken into account when assessing adequacy.**
Morata 2012 [31]	**Impact of inappropriate therapy Definition:** Appropriate empirical therapy was considered when the patient received at least one *in vitro* active antimicrobial agent **within 24 h** after blood cultures were obtained and before susceptibility results were available and if the dosage and route of administration were in accordance with the current medical standards. Specific dosages of antibiotics were not recorded
Ortega 2009 [32]	**Impact of inappropriate empirical therapy Definition**: Antibiotic treatment, either empirical or definitive (before or after the microbiological results and susceptibilities were known, respectively), was considered appropriate if at least one of the antibiotics involved had in vitro activity against the bacteria and the dose and route of administration were adequate
Peralta 2007 [33]	**Impact of inadequate empirical therapy Definition:** Empirical antimicrobial therapy was judged to be either adequate or inadequate on the basis of the in vitro susceptibility of an isolated organism, and/or the initiation of antibiotic treatment **within 24 h** of blood culture extraction.
Tumbarello 2012 [36]	**Impact of inadequate initial antimicrobial therapy Definition:** (i) no antibiotics with potential activity against *P. mirabilis* were prescribed **during the first 24 h after BSI onset**, (ii) the infecting pathogen was non susceptible *in vitro* (as defined below) to the drug(s) being administered, and/or (iii) the regimen used was not consistent with the current recommendations in *The Sanford Guide to Antimicrobial Therapy* .

Tumbarello 2012 [35]	**Impact of inadequate antimicrobial therapy Definition**: An antimicrobial treatment regimen was defined as **adequate when it included at least 1 drug displaying in vitro activity against the KPC-producing isolate.** Depending on the number of in vitro–active drugs they included (1 or >1), treatment regimens were classified as monotherapy or combination therapy.
Tumbarello 2011 [37]	**Impact of inappropriate therapy and multidrug Definition**: Antibiotic treatment empirically prescribed before in vitro susceptibility test results were available was defined as initial antibiotic treatment and considered inadequate when treatment with an antibiotic possessing in vitro activity against the isolated pathogen was absent
Tumbarello 2008 [38]	**Impact of initial Inadequate antimicrobial therapy Definition** The initial treatment was classified as inadequate if the infecting pathogen displayed in vitro resistance to the drug being administered.
Tumbarello 2007 [39]	**Impact of initial Inadequate antimicrobial therapy Definition**: as the initiation of treatment with active antimicrobial agents (identified as such based on in vitro susceptibility testing) **>72 h after BSI onset.**
Song 2010 [42]	**Impact of inappropriate therapy Definition:** Appropriate antimicrobial therapy, which was defined as receipt of antimicrobial agent(s) to which the organism is susceptible in vitro for ≥48 h **within 5 days after positive blood culture is obtained**
Kang 2005 [43]	**Impact of inappropriate initial antimicrobial therapy Definition:** The initial empirical antimicrobial therapy was considered appropriate if the initial antibiotics, which were administered **within 24 h after acquisition of a blood culture samples**, included at least one antibiotic that was active in vitro against the causative microorganisms and when the dosage and route of administration conformed with current medical standards.
Marchaim 2010 [48]	**Impact of delay in adequate therapy Definition:** Antimicrobial therapy was defined as appropriate or adequate if an agent with an *in vitro* activity for a specific isolate was administered to the patient, not including penicillins, cephalosporins, or monobactams, or aminoglycosides if given alone for a non-urinary-tract infection
Schwaber 2006 [49]	**Impact of delay in adequate therapy Definition**: the absence of treatment with an antibiotic possessing in vitro activity against the isolated **pathogen within 48 h of the blood culture draw**), Per CLSI guidelines, treatment with penicillins and cephalosporins was considered inappropriate for all ESBL producers, while all other treatments (including inhibitor combinations) were evaluated individually based on the in vitro susceptibility test results for each isolate.
Gozel 2012 [45]	**Impact of inappropriate therapy Definition**: If a patient received at least one antimicrobial agent at **the day of blood culture collection** to which the causative microorganisms were susceptible, empirical antimicrobial therapy was considered to have been appropriate.
Erbay 2009 [46]	**Impact of early appropriate therapy Definition:** Initial empirical antimicrobial therapy was considered to be 'appropriate' if the initial antibiotics, **which were administered within 48 h after the acquisition of a blood culture sample**, included at least one antibiotic that was active in vitro and when the dosage and route of administration were in accordance with current medical standards.
Frakking 2013 [51]	**Impact of appropriate empirical therapy Definition:** Initial therapy was defined as therapy given **in the first 24 h after blood culture drawing**. Appropriateness was based on CLSI interpretive criteria. Appropriate therapy also required administration of appropriate agents on =>7 consecutive days, except if interrupted by the death of a patient..
Melzer 2007 [53]	**Impact of delay in appropriate therapy Definition**: appropriate treatment defined as an antimicrobial agent to which E. coli was susceptible by BSAC disc diffusion methods. **Delay in appropriate treatment was defined as time from bacteraemia to administration of an appropriate antibiotic and dichotomized as more or less than 24 h**

Supplementary Table S2. Impact of inappropriate therapy on bloodstream infections: study design of included studies and the definitions of delayed, inadequate and inappropriate therapy.

First Author Year [Ref]	Study Design & Sample Size	Reported Risk & Methodology of Analysis	Patient Group	Country	Organism group
Kumar 2009 [13]	Retrospective large multi-center study n=5715	Odds ratio (OR) Multivariate logistic regression model	Adult patients >18 year of age with septic shock	22 medical institutions Canada (17 sites USA (4 sites) Saudi Arabia (1 site)	GP&GN
Vazquez-Guillamet 2014 [10]	Retrospective single center cohort study n=2594	OR Multivariate logistic regression model	Adults patients with severe sepsis or septic shock	1250 academic hospitals USA	GP&GN
Gaieski 2010 [15]	Retrospective single center cohort study n=261	OR Multivariable logistic regression	Patients with severe sepsis and septic shock	Emergency Dept., Academic Hospital USA	GP&GN
Garnacho-Montero 2015 [27]	Prospective observational n=638	OR Multivariate regression analysis	ICU Adult patients with severe sepsis or septic shock	40 Bed ICU Spain	GP&GN
Retamar 2012 [28]	Retrospective multicenter propensity score based matched cohort study n=801	OR Multivariate regression analysis	All consecutive episodes of clinically significant BSI in adult patients >14 years	15 hospitals Spain	GP&GN
Son 2010 [40]	Retrospective review of Hospital Acquired (HA) BSI n=1144	OR Multivariate logistic regression model	Adult patients	9 hospitals Korea	GP&GN
De Groot 2015 [50]	Prospective multicenter study n=1168	Hazard Ratio (HR) of 28 day survival	ED Pients >17 years	3 Emergency Department Netherlands	GP&GN
Hounsom 2011 [52]	Retrospective cohort study n=681	OR Multivariate logistic regression analysis	Adult (elderly patients)	2 large hospitals of 900 and 600 beds UK	GP&GN
Turan 2008 [44]	Prospective single center study n=109	OR Univariate logistic regression analysis	Adult patients	Turkey	GP&GN
Wisdom 2015 [57]	Retrospective observational study	HR Survival analysis	Adult ED patients	ED 550 bed tertiary care hospital Australia	GP&GN

	n=220				
Nygard 2014 [56]	Retrospective observational study n=220	OR Multivariate stepwise backward logistic regression model	Adult patients >15 years	Large university hospital Western Norway	GP&GN
Ammerlaan 2009 [14]	Retrospective cohort study n=334	OR Multivariate logistic regression	Adult patients	9 European countries	GP SAB
Marchaim 2010 [16]	Retrospective multi center case controlled study n=388	OR Multivariable logistic regression analysis	Adult patients	3 large tertiary teaching hospitals USA	GP MRSA
Schweizer 2010 [17]	Retrospective cohort study n=814	HR Multivariable analysis	Adult patients	Tertiary care Hospital USA	GP SAB
Rodrıguez-Bano 2009 [34]	Prospective cohort study n=209	OR Multivariate logistic regression model	All adult (>14 years) patients	59 hospitals Spain	GP MRSA
Gasch 2013 [29]	Multicenter prospective cohort study n=579	OR Multivariate logistic regression model	Adult patients >16 years	21 hospitals Spain	GP MRSA
Kaasch 2013 [55]	Prospective multi center observational study n=168	OR Multiple regression analysis	Adult patients	10 tertiary care university hospitals Germany	GP *SAB*
Paul 2010 [47]	15 year Retrospective cohort study n=510	OR Multivariate logistic regression model	Adult patients	1 hospital Israel	GP MRSA
Kim 2006 [41]	Retrospective cohort propensity score matched controls n=238	OR Multivariate logistic regression model	Adult patients >15 years	1500 bed hospital Korea	GP *SAB*
Suppli 2011 [54]	Retrospective analysis n=196	OR Multivariate logistic regression model	Adult patients >16 years old	1120 bed referral hospital Denmark	GP *Enterococcus species*
Shorr 2014 [18]	Retrospective cohort study n=131	HR Cox proportional hazards model	Adult patients with severe sepsis	1200 bed teaching hospital USA	GN
Zilberberg 2014 [19]	4 year Retrospective cohort study n=1076	OR Multivariate logistic regression model	Adult ICU patients with severe sepsis/septic shock	1200 bed urban academic medical center USA	GN including *P aeruginosa* and *Acinetobacter*
Micek 2011 [20]	Retrospective cohort	OR	Adult patients with severe sepsis	1200 bed hospital	GN

	study n=535	Multiple logistic regression		USA	*P. aeruginosa*
Micek 2010 [21]	Retrospective cohort study n=760	OR Univariate logistic regression	Adult patients with severe sepsis or septic shock	1200 bed teaching hospital ICU USA	GN including *P aeruginosa* and *Acinetobacter*
Thom 2008 [22]	Retrospective cohort study n=416	HR Multivariable survival analysis	Adult patients >18 years	656 bed tertiary care hospital USA	GN *E. coli* and *Klebsiella species*
Osih 2007 [23]	Retrospective cohort analysis n=167	OR Multivariate logistic regression	Adult patients	Large teaching hospital USA	GN *P. aeruginosa*
Lodise 2007 [24]	Retrospective cohort study n=100	Adjusted OR Multivariable logistic regression	Adults >18years	651 bed teaching hospital USA	GN *P aeruginosa*
Anderson 2006 [25]	Retrospective cohort study n=779	OR Multivariable logistic regression	Adult patients	750 Tertiary care Hospital USA	GN ceftazidime-resistant *Klebsiella pneumoniae*
Micek 2005 [26]	6 year Retrospective cohort study n=305	OR Multivariate logistic regression model	Adult patients	1200 bed teaching hospital USA	GN *P. aeruginosa*
Peralta 2012 [30]	4 year Retrospective study n=387	OR Multivariate analysis	Adult patients	19 hospitals Spain	GN ESBL
Morata 2012 [31]	Prospective cohort study n=709	OR Multivariate logistic regression	Adult patients	850 bed university hospital Spain	GN *P. aeruginosa*
Ortega 2009 [32]	Prospective cohort study n=4758	OR Multivariate logistic regression	Adult patients	700 bed university teaching hospital Spain	GN *E coli*
Peralta 2007 [33]	Retrospective cohort study design n=663	OR Multivariate analysis	Adult patients	250 bed community teaching hospital Spain	GN *E. coli*
Tumbarello 2012 [36]	Retrospective case controlled study over 11 year period n=99	OR Multivariable logistic regression	Adult patients > 18 years	1500 bed hospital Italy	GN
Tumbarello 2012 [35]	Multi-center retrospective cohort study n=125	OR Multivariate analysis	Adult patients >18years	3 large teaching hospitals Italy	GN KPC
Tumbarello 2011 [37]	Retrospective cohort study of n=109	21 day mortality Multivariate logistic regression	Adult patients	Two university hospitals, 1500 & 1600 beds Italy	GN *P. aeruginosa*

Tumbarello 2008 [38]	7 year retrospective cohort study n=129	OR Multivariate analysis	Adult patients	1,700 bed hospital Italy	GN *E coli* ESBL
Tumbarello 2007 [39]	6 year Retrospective cohort analysis n=186	OR Multivariate analysis (21 Day mortality)	Adult patients	1700 bed teaching hospital Italy	GN ESBL
Song 2010 [42]	Prospective observational study n=239	OR Multivariate logistic regression	Adult patients	2200 bed tertiary care hospital Korea	GN *Enterobacter cloacae and Enterobacter aerogenes*
Kang 2005 [43]	4 year Retrospective observational cohort study n=286	OR Multivariate logistic regression	Adult patients >16 years with antibiotic resistant bacteremia	1500 bed tertiary care referral center Korea	GN including *P aeruginosa*
Marchaim 2010 [48]	Prospective multi center study n=447	OR Multivariable logistic regression	Adult patients	10 hospitals with >500 bed capacity Israel	GN
Schwaber 2006 [49]	Retrospective case controlled study n=99	OR Multivariable logistic regression	Adult patients	1200 bed tertiary care hospital Israel	GN
Gozel 2012 [45]	2 year Prospective observational study n=253	Univariate analysis	Adult patients >16 years	1196 bed teaching hospital Turkey	GN nosocomial
Erbay 2009 [46]	Retrospective cohort study n=103	HR Multivariate logistic regression	Adult patients >16 years	1196 Bed teaching hospital Turkey	GN *Acinetobacter baumannii*
Frakking 2013 [51]	Retrospective multicenter cohort study n=232	OR Multivariate logistic regression	Adult patients	8 Hospitals The Netherlands	GN ESBL
Melzer 2007 [53]	Prospective cohort study n=354	OR Multivariable logistic regression	Adult patients >16 years	Large hospital England, UK	GN

Supplementary Table S3. Impact of inappropriate therapy on bloodstream infections (BSI) and associated risk of mortality: main estimates and 95% confidence intervals.

First Author Year [Ref]	Organism group	Objective	Reported Risk	Main estimate	95% CI (p value)	Association
Kumar 2009 [13]	GP&GN	Impact of inappropriate therapy in patients with septic shock	OR	**8.99**	6.60-12.23 (p ≤0.0001)	+ve
Vazquez-Guillamet 2014 [10]	GP&GN	Impact of inappropriate therapy in patients with severe sepsis and septic shock	OR	**3.4**	2.8–4.1 (p<0.001)	+ve +ve
Gaieski 2010 [15]	GP&GN	Impact of time to appropriate antibiotics ≤1hr	OR	**0.5**	0.27– 0.92 (p<0.03)	+ve
Garnacho-Montero 2015 [27]	GP&GN	Impact of adequate therapy in patients with severe sepsis and septic shock	OR	**0.37**	0.24-0.56 (p<0.001)	+ve
Retamar 2012 [28]	GP&GN	Impact of inadequate therapy	OR 14 days 30 days	 **3.03** **1.7**	 1.60-5.74 0.98 - 2.98	 +ve +ve
Son 2010 [40]	GP&GN	Impact of inappropriate therapy	OR	**6.04**	2.16-16.87 (p≤0.00)	+ve
De Groot 2015 [50]	GP&GN	Timing of antibiotic therapy	HR delayed therapy >3hrs	**1.46**	1.05 - 2.02	+ve
Hounsom 2011 [52]	GP&GN	Delay in appropriate therapy	OR	**1.35**	1.05 - 1.75	+ve
Turan 2008 [44]	GP&GN	Impact of inappropriate therapy	OR	**8.62**	2.55-29.1 (p≤0.05)	+ve
Wisdom 2015 [57]	GP&GN	Impact of timing of antimicrobial therapy in patients in ED	HR >6hrs to ABS compared to <1h	**2.25**	0.91–5.59 (p = 0.08)	+ve
Nygard 2014 [56]	GP&GN	Timing of appropriate therapy	OR >6hr delay	**2.48**	1.02-6.02 (p= 0.046)	+ve
Ammerlaan 2009 [14]	GP *SAB*	Impact of inadequate therapy	OR	**0.69**	0.36–1.32 (p=0.57)	None
Marchaim 2010 [16]	GP MRSA	Impact of delayed appropriate therapy	OR 2 day delay	**1.85**	0.94-3.64 (p=0.074)	+ve
Schweizer 2010 [17]	GP *SAB*	Impact of inappropriate therapy	HR	**1.52**	0.99- 2.34	+ve
Rodrıguez-Bano 2009 [34]	GP MRSA	Impact of inappropriate therapy	OR	**3.0**	1.01-9.0 (p<0.04)	+ve

Gasch 2013 [29]	GP MRSA	Impact of inappropriate therapy	OR	**1.39**	1.04–1.86	+ve (None)
Kaasch 2013 [55]	GP *SAB*	Impact of delayed appropriate therapy	OR	**0.79**	0.26–2.45 (p= 0.69)	None
Paul 2010 [47]	GP MRSA	Impact of inappropriate therapy	OR	**1.98**	1.62-2.44	+ve
Kim 2006 [41]	GP *SAB*	Impact of inappropriate therapy	OR	**1.39**	0.62–3.15	+ve
Suppli 2011 [54]	GP *Enterococcus species*	Impact of inappropriate therapy	OR	**0.33**	0.14–0.79	*+ve*
Shorr 2014 [18]	GN Acinetobacter species	Impact of inappropriate therapy	RR	**1.42**	1.10-1.58	+ve +ve
Zilberberg 2014 [19]	GN *Entreobacteriaceae* including *P aeruginosa* and *Acinetobacter*	Impact of initially inappropriate therapy and multidrug resistance	OR OR MDR	**3.87** **13.05**	2.77-5.41 7.00-24.31	+ve +ve
Micek 2011 [20]	GN *P. aeruginosa*	Impact of resistance and initial inappropriate therapy	OR	**2.28**	1.69-3.08 (p< 0.006)	+ve
Micek 2010 [21]	GN including *P aeruginosa* and *Acinetobacter*	Impact of initial inappropriate antibiotic therapy	OR	**2.30**	1.89-2.80	+ve
Thom 2008 [22]	GN *E. coli* and *Klebsiella species*	Impact of appropriate antimicrobial therapy	HR	**1.03**	0.60 to 1.78	None
Osih 2007 [23]	GN *P. aeruginosa*	Impact of appropriate antimicrobial therapy	OR	**0.96**	0.31- 2.93	None
Lodise 2007 [24]	GN *P aeruginosa*	Impact of delayed appropriate therapy>52h	OR	**4.1**	1.2-13.9 (p=0.03)	*+ve*
Anderson 2006 [25]	GN ceftazidime-resistant *Klebsiella pneumoniae*	Impact of delayed effective therapy>72h	OR	**3.32**	1.07-10.3	+ve
Micek 2005 [26]	GN *P. aeruginosa*	Impact of appropriate initial therapy	OR	**2.04**	1.42-2.92 (p=0.048)	+ve

Peralta 2012 [30]	GN ESBL *Enterobacteriaceae*	Impact of adequate therapy	OR	**0.39**	0.31-0.97 (p = 0.04)	+ve
Morata 2012 [31]	GN *P. aeruginosa*	Impact of inappropriate therapy and multidrug resistance	OR OR MDR	**2.1** **2.2**	1.3-3.5; 0.9-5.4	*+ve* *+ve*
Ortega 2009 [32]	GN *E coli*	Impact of inappropriate empirical therapy	OR	**4.83**	3.48-6.71 (p<0.001)	+ve
Peralta 2007 [33]	GN *E. coli*	Impact of antibiotic resistance and inadequate empirical therapy	RR OR MDR	**2.98** **.11**	1.25-7.11 (P= 0.006). 3.11 1.3-7.44	+ve +ve
Tumbarello 2012 [36]	GN *P mirabilis*	Impact of inadequate initial antimicrobial therapy and multidrug resistance	OR OR MDR	**9.85** **6.62**	2.67-36.25 (p= 0.001) 1.64-26.68 (p=0.008)	+ve +ve
Tumbarello 2012 [35]	GN KPC	Impact of inadequate therapy	OR	**4.17**	1.61–10.76 (p=0.003)	+ve
Tumbarello 2011 [37]	GN *P. aeruginosa*	Impact of inappropriate therapy and multidrug resistance (21 day mortality)	OR OR MDR	**2.73** **3.3**	1.08-6.85 (p=0.03) 1.27-8.59 (p= 0.01)	+ve +ve
Tumbarello 2008 [38]	GN *E coli* ESBL	Impact of initial Inadequate antimicrobial therapy	OR	**6.22**	2.33–6.61 (p<0.001)	+ve
Tumbarello 2007 [39]	GN ESBL *K pneumoniae, E coli* and *P mirabilis* ESBLs	Impact of initial Inadequate antimicrobial therapy	OR	**2.38**	1.76 to 3.22 (p<0.001)	+ve
Song 2010 [42]	GN *Enterobacter cloacae and Enterobacter aerogenes*	Impact of inappropriate therapy and multidrug resistance	OR *E cloacae OR E aerogenes*	**10.27** **7.74**	4.28–2463 (p=0.004) 1.0–57.4 (p<0.045)	+ve +ve
Kang 2005 [43]	GN including *P aeruginosa*	Impact of inappropriate initial antimicrobial therapy	OR	**3.64**	1.13-11.72 (p< 0.030)	+ve
Marchaim 2010 [48]	GN ESBL *Enterobacteriaceae.*	Impact of delay in adequate therapy or ESBL	OR >48hrs OR ESBL	**9.1** **2.3**	2.44-33.3 (p=0.001) 1.07-4.8 (p= 0.048)	+ve +ve
Schwaber 2006 [49]	GN *ESBL Enterobacteriaceae.*	Impact of delay in adequate therapy or ESBL	OR ESBL OR delay + ESBL	**3.6** **25.1**	1.4–9.5 (p= 0.008) 10.5–60.2 (p= 0.001)	+ve +ve
Gozel 2012 [45]	GN nosocomial	Impact of inappropriate therapy	OR	**4.5**	2.8-7.3, p<0.001	+ve

	Entreobacteriaceae including *P aeruginosa* and *Acinetobacter*					
Erbay 2009 [46]	GN *Acinetobacter baumannii*	Impact of early appropriate therapy	HR	**2.4**	1.3–4.2 (p=0.004)	+ve
Frakking 2013 [51]	GN ESBL *Enterobacteriaceae*.	Impact of appropriate empirical therapy	OR	**1.53**	0.68 to 3.45	+ve
Melzer 2007 [53]	GN *E coli* ESBL	Impact of delay in appropriate therapy	OR ESBL OR Delay in app	**1.81** **3.36**	0.69-3.52, p=0.23 1.59-7.09, p=0.001	+ve +ve

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Review

The need for cost-effectiveness analyses of antimicrobial stewardship programmes: A structured review

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ABSTRACT

The cost effectiveness of antimicrobial stewardship (AMS) programmes was reviewed in hospital settings of Organisation for Economic Co-operation and Development (OECD) countries, and limited to adult patient populations. In each of the 36 studies, the type of AMS strategy and the clinical and cost outcomes were evaluated. The main AMS strategy implemented was prospective audit with intervention and feedback (PAIF), followed by the use of rapid technology, including rapid polymerase chain reaction (PCR)-based methods and matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) technology, for the treatment of bloodstream infections. All but one of the 36 studies reported that AMS resulted in a reduction in pharmacy expenditure. Among 27 studies measuring changes to health outcomes, either no change was reported post-AMS, or the additional benefits achieved from these outcomes were not quantified. Only two studies performed a full economic evaluation: one on a PAIF-based AMS intervention; and the other on use of rapid technology for the selection of appropriate treatment for serious *Staphylococcus aureus* infections. Both studies found the interventions to be cost effective. AMS programmes achieved a reduction in pharmacy expenditure, but there was a lack of consistency in the reported cost outcomes making it difficult to compare between interventions. A failure to capture complete costs in terms of resource use makes it difficult to determine the true cost of these interventions. There is an urgent need for full economic evaluations that compare relative changes both in clinical and cost outcomes to enable identification of the most cost-effective AMS strategies in hospitals.

1. Introduction

Use of antimicrobial agents to both treat and prevent infections is an essential component of medical care. Indeed, many advances in critical care medicine, surgery and transplantation would not be possible without the use of effective antimicrobials. Whilst antimicrobials benefit the individual patient, the emergence of resistance has consequences to all of society. In 2014, the World Health Organization (WHO) urged all countries to work together to improve surveillance and to address the issue of antimicrobial resistance (http://www.who.int/drugresistance/documents/surveillancereport/en).

An effective approach to improving antimicrobial use in hospitals may be achieved by an organised antimicrobial management programme known as antimicrobial stewardship (AMS). The overarching goals of an AMS programme are to optimise clinical outcomes while minimising unintended consequences of antimicrobial use, including toxicity, the selection of opportunistic pathogens (such as *Clostridium difficile*) and the emergence of antimicrobial resistance [1]. AMS interventions have been reported to reduce antimicrobial consumption by 22–36% and lead to a cost reduction of US$200 000–900 000 per annum in some hospitals in the USA [2]. Despite this, it has been reported that it is difficult to attract adequate support for these activities as AMS is competing for resources against many other healthcare initiatives.

Whilst there are many combinations of strategies available for the development of an AMS programme, it is unclear which are optimal. In evaluating the cost effectiveness of AMS interventions, all relevant changes to costs as well as health benefits achieved must be quantified and compared in order to understand whether the intervention offers value for money. Whilst there have been some studies that have reported AMS results in cost savings in

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terms of reducing drug acquisition costs, these do not include costs of AMS staff and other implementation activities, thus they may underestimate the cost of the intervention [3–10]. It is not clear whether the cost effectiveness of these programmes has been assessed fully. Such information is essential for making credible arguments to decision-makers about the value of funding these programmes.

The aim of this structured review was to synthesise the existing literature on the cost effectiveness of AMS programmes. We report the costs and health outcomes assessed, the economic evaluation methods used and the overall findings of this body of research, including important knowledge gaps in this area.

2. Methods

2.1. Literature search

A search for economic evaluations of AMS interventions was undertaken in the databases Embase, PubMed, Scopus, Web of Science, ProQuest, CINAHL and EconLit up to June 2014. Search terms used included the Mesh term 'Anti Infective' in conjunction with Stewardship, and search terms 'Antimicrobial Stewardship' AND 'cost*'; 'Antimicrobial Stewardship' AND 'cost effectiveness'; and 'Antimicrobial Stewardship' AND 'economic*'.

2.2. Inclusion and exclusion criteria

The inclusion criteria for critical assessment of studies on AMS cost effectiveness were: AMS intervention; cost-effectiveness analyses (CEAs) and cost analyses; based on adult inpatient population; AMS strategy clearly defined; and language restricted to English (Fig. 1). The exclusion criteria were: reviews; editorials; letters; commentaries; conference reports; and an AMS programme performed in a country that did not belong to the Organisation for Economic Co-operation and Development (OECD).

Duplicates, reviews, editorials, conference reports, commentaries and studies from non-OECD countries were removed (Fig. 1). This was done so that only countries with similar economic capacities would be compared. The following information was extracted from the remaining studies: a clear definition of AMS strategies; costs; outcomes; and the perspective of the economic analysis. Only studies that included cost data relating to AMS initiatives were reviewed in further detail. For studies that reported a full CEA or a cost-utility analysis, a specifically designed data extraction tool was used based on the Drummond [11] checklist for CEAs. Studies were evaluated by one author (SC) under the guidance of KH.

3. Results

The final review included 36 studies [3–6,8–10,12–40] conducted in the USA (22), UK (2), Canada (2), France (2), Spain (2) Japan (2), Israel (1), Slovenia (1), Belgium (1) and Germany (1). The most common AMS strategy implemented was prospective audit with intervention and feedback (PAIF), followed by rapid technology such as rapid PCR-based methods, matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) technology, peptide nucleic acid probes for fluorescence in situ hybridisation (PNA FISH) and Etest strips, for the detection of minimum inhibitory concentrations of various antimicrobials for the treatment of bloodstream infections (BSIs). Specifically, the types of AMS strategies evaluated were: PAIF (18), rapid technology (6), antifungal stewardship (4), intravenous-to-oral (i.v.-to-p.o.) conversion (4), formulary restriction plus PAIF (2), rapid technology plus antifungal stewardship (1), and PAIF plus i.v.-to-p.o. conversion (1).

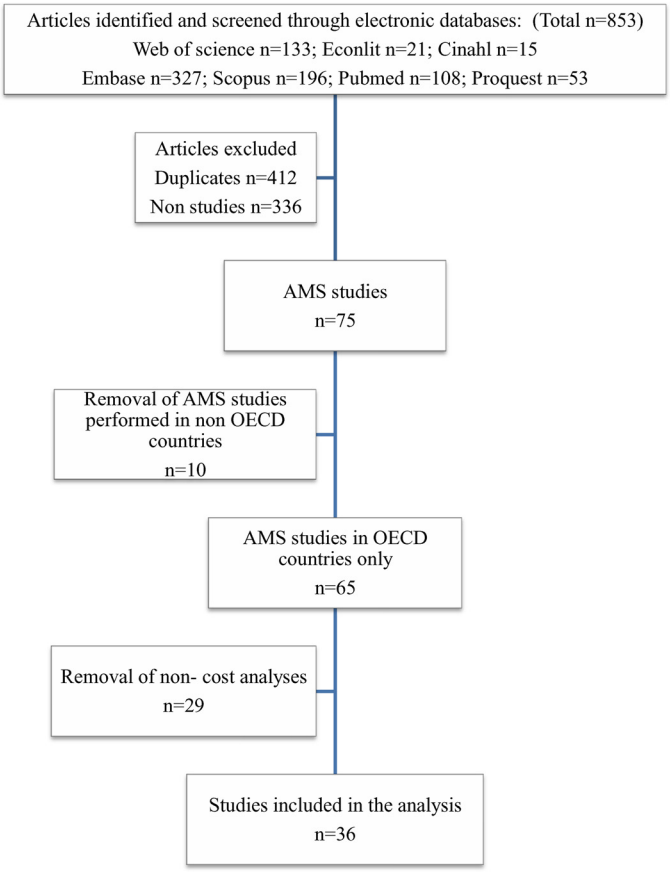

Fig. 1. Flowchart of selection of studies on cost-effectiveness of antimicrobial stewardship (AMS) based on the inclusion and exclusion criteria. OECD, Organisation for Economic Co-operation and Development.

Of the 36 included studies, 2 were full CEAs [13,14]; 27 studies reported changes to costs and health outcomes separately [3,5,8–10,12–14,22–40] and 9 reported only changes to costs [4,6,15–21]. Table 1 presents the methods and results for studies that measured only cost outcomes and Table 2 presents the methods and findings of those studies that measured both a clinical as well as a cost outcome.

3.1. Costing studies that did not measure clinical outcomes

Table 1 groups 9 of the 36 included studies that measured only the cost impact of AMS strategies [4,6,15–21]. PAIF was the most commonly evaluated strategy in this group (5/9; 56%) [4,6,15–17]; 2 studies focused on i.v.-to-p.o. conversion as a strategy [18,19] and 2 studies evaluated antifungal stewardship [20,21]. All nine studies reported a reduction in costs related to antimicrobial use as a result of implementing the AMS strategy.

Five of the nine studies assessed reduction in total antibiotic expenditure (TAE) as a measure of success of the AMS strategy [4,15,16,18,20]. One of the remaining four studies expressed the cost savings as TAE per patient-day (PD) [17], the second as TAE per 1000 PDs [6], the third as TAE per patient [21] and the final study as mean additional cost per patient [19].

3.2. Cost consequence studies that measured clinical outcomes

Table 2 groups the 27 studies that evaluated a change in cost as well as clinical outcome as a result of implementing an AMS strategy [3,5,8–10,12–14,22–40]. Thirteen (48.1%) of the studies measured cost savings as only TAE [3,5,8,10,22,23,25,26,28–32], 1

Table 1
Antimicrobial stewardship (AMS) evaluations measuring cost outcomes only ($n = 9$).

AMS strategy	Author, year (country)	Reference	Comparison/research question	Study design	Data sources	Cost outcomes	Results/ conclusions
PAIF	Vettese et al. (2013) (USA)	[15]	To decrease antimicrobial use and tailor duration of therapy	Quasi-experimental	Pharmacy records	DOT/1000 PD, 6.4%↓ TAE, 37%↓	Net saving, $206 948 (**$215,367.06**)
PAIF	Michaels et al. (2012) (USA)	[16]	Impact of AMS intervention on antimicrobial utilisation	Quasi-experimental	Pharmacy records	DDD/1000 PD, 5.2%↓ TAE, 22.4%↓	Savings of $290 000 (**$340,615.15**) in 2 years
FR and PAIF	Beardsley et al. (2012) (USA)	[4]	Long-term impact of an AMS programme (11 years)	Quasi-experimental	Electronic medical records	TAE, ↓	Savings of $920 070 (**$992,448.23**) to $2,064,441 (**$2,226,842.32**) per year
PAIF	Katsios et al. (2012) (Canada)	[17]	Impact of AMS on appropriate treatment of infections using microbiology culture results	Quasi-experimental uncontrolled study	Hospital pharmacy records	DDD/1000 PD, 13.7%↓ TAE, 27%↓ TAE/PD, 24%↓	ICU antimicrobial cost savings, US$13,319.92 (**$14,367.74**)
PAIF	Bevilacqua et al., 2011 (France)	[6]	To measure the impact on hospital antibiotic prescription rates and costs	Quasi-experimental, cluster controlled	Hospital pharmacy records	DDD/1000 PD, 33.6%↓ TAE/1000 PD, 43.1%↓	Savings of (€603,900) US$683,562.36 Adjusted (**$768,957.07**)
i.v.-to-p.o.	Jones et al. (2012) (USA)	[18]	To estimate avoidable i.v. fluoroquinolone use	Retrospective, quasi-experimental	Hospital records	TAE, ↓	Saving of $4,000,000 (**$4,314,664**)
i.v.-to-p.o.	Buyle et al. (2010) (Belgium)	[19]	To measure the impact of interventions: G1, newsletter G2, educational sessions G3, proactive interaction on ward rounds	Interrupted time-series analysis, quasi-experimental, prospective	Hospital records	Mean additional cost per patient	G1, ↓$231.39 G2, ↓ $126.77 G3, ↓ $54.16
AFS	Mondain et al. (2013) (France)	[20]	To assess the impact of AMS on antifungal prescribing and cost	Prospective observational	Hospital records	Total antifungal use, 38%↓	Savings of (€682,409) US$772,244 Adjusted to 2014 (**$832,993.35**)
AFS	Guarascio et al. (2013) (USA)	[21]	To assess the caspofungin DOT, drug costs and adherence to bundle criteria	Matched control analysis	Hospital records	TAE per patient, ↓	Cost savings of $1013 (**$1092.69**) per patient

PAIF, prospective audit with intervention and feedback; DOT, days of therapy PD, patient-days; TAE, total antibiotic expenditure DDD, defined daily doses; FR, formulary restriction; ICU, intensive care unit; i.v.-to-p.o., intravenous-to-oral conversion; AFS, antifungal stewardship.
All costs converted to US$ for ease of comparison (using conversion rate as of 9 December 2014, http://www.ozforex.com.au/currency-converter). All US$ figures were adjusted to 2014 prices using the Bureau of Labor Statistics Consumer Price Index specific to Medical Care (SEMF01, http://www.bls.gov/data/).
Where the cost year used for analysis was not stated, it was assumed to be 1 year prior to publication.

(4%) as TAE per admission [24], 1 (4%) as TAE per 1000 PDs [27] and finally 1 (4%) as TAE per PD [9] as a measure of success of the AMS strategy. One study [25] reported a loss of $215.99 due to implementation of the AMS strategy assessed. No pre-intervention data were included in this study and the loss recorded was due to the difference between prescribed and pharmacy-recommended antimicrobials. Of the studies that reported cost savings due to total antimicrobial expenditure, the range of savings was from $22 433.99 [31] to $4 314 664 [18] (adjusted to 2014 US$). Two further studies reported significant cost savings due to only antifungal stewardship interventions of $257 507.94 [9] and $399 841.83 [32], respectively.

Five studies included cost savings in terms of length of stay (LOS) [5,10,35,36,39]; these cost savings ranged from $20 365.45 to $4 228 370.72 (adjusted to 2014 US$). Four studies recorded cost savings in terms of reduced healthcare costs owing to more appropriate treatment of infections. Two studies compared different approaches of AMS: one study found no difference in costs [33]; whilst the second study recorded cost savings when a more active approach was used [34]. One study performed an economic analysis and found rapid technology to be cost effective in monetary terms only [40], and two further studies performed CEAs including a measure for health benefits gained by two different approaches [13,14].

PAIF was the most commonly evaluated strategy (12/27; 44%) [3,8,10,13,22–28,30]. In these 12 studies, the clinical outcomes measured ranged from LOS (6/12), mortality (6/12), presence of multiresistant organisms (3/12), *C. difficile* infection (CDI) rates (5/12) and 30-day re-admission rates (1/12). Of the 12 studies, 8 were from the USA, 2 from Japan and 1 each were from Israel and Canada. Eleven of the twelve studies reported a reduction in TAE and cost savings [3,8,10,13,22–24,26–28,30], but one reported a loss of $215.99 [25]. One study also noted cost savings associated with the reduction in LOS [10]. Ten of the twelve studies reported the TAE [3,8,10,22,23,25,26,28–30], whilst one study reported TAE per admission [24] and one reported findings as TAE per 1000 PDs

Table 2
Antimicrobial stewardship (AMS) evaluations measuring clinical and cost outcomes ($n = 27$).

AMS strategy	Author, year (country)	Reference	Comparison/research question	Study design	Data sources	Clinical outcomes	Cost outcomes	Results/conclusions
PAIF	Rimawi et al. (2013) (USA)	[22]	To assess impact of ID fellow input on antimicrobial and healthcare expenditure	Quasi-experimental	Hospital records	LOS, ↓ Mortality, ↓ Not costed	TAE, ↓	Savings due to reduction of antimicrobial utilisation US$89,944 (**$93,710.05**) per year
PAIF	Hagert et al. (2012) (USA)	[23]	To compare antimicrobial usage before and after AMS	Retrospective, quasi-experimental	Hospital records	LOS (no change)	TAE, 25%↓	Savings of US$48 044 (**$54,045.94**)
PAIF	Standiford et al. (2012) (USA)	[3]	To estimate the cost savings as a result of an AMS programme	Quasi-experimental cost analysis	Pharmacy records	LOS, re-admissions and mortality (no significant changes)	DDD/1000 PD, 29%↓ TAE, 37%↓	Savings of US$20 248 (**$21,840.83**) per 1000 PD and US$3,000,000 (**$3,235,998**) in the first 3 years of the programme i.v.-to-p.o. switch therapy alone saved US$180,000 (**$194,160**) in the first year
PAIF	Storey et al. (2012) (USA)	[24]	To assess the impact of an AMS programme on the medical-surgical service of a 100-bed community hospital	Quasi-experimental	Hospital records	CDI (not useful as the testing method changed)	DDD/1000 PD, 16%↓ DDD/100 PD, 22%↓ TAE per admission, 32%↓	Reduction in expenditure on all antimicrobial agents US$27.6 (**$31.05**) per admission and US$5.6 (**$6.30**) per PD
PAIF and i.v.-to-p.o.	Ijo and Feyerharm (2011) (USA)	[25]	To assess the impact of prospective pharmacy-driven AMS intervention in the ICU on clinical and financial outcomes	Interventional prospective	Hospital records	LOS and mortality No data collected prior to AMS intervention (no comparator)	TAE (difference between prescribed and pharmacy-recommended antimicrobials)	Overall loss of US$192 (**$215.99**) was associated with the intervention in the ICU
PAIF	Nowak et al. (2012) (USA)	[26]	To assess the impact of an AMS programme using data mining software	Quasi-experimental	Hospital records	Rates of CDI, ↓ MRSA, ↓ VRE, ↓ Mortality (no significant difference)	TAE, ↓	Projected cost savings of US$1.7 million (**$1,833,732.20**)
PAIF via telemedicine in a rural hospital	Yam et al. (2012) (USA)	[27]	To determine the impact of an AMS programme using telemedicine on patient outcomes and cost	Observational study	Hospital records	Decrease in *C. difficile* cases from 5.5 to 1.6 cases per 10 000 PD	TAE/1000 PD (2010), 28%↓ TAE/1000 PD (2011 first two quarters), 51%↓	Savings in 2010 US$3764.44 (**$4234.72**) Savings in 2011 first two quarters US$6583 (**$7100.86**)
PAIF	Carling et al. (2003) (USA)	[28]	To evaluate the impact of a multidisciplinary team on antibiotic usage in terms of cost and clinical outcomes	Prospective, quasi-experimental	Hospital records	CDI, ↓ Resistant Enterobacteriaceae, ↓	DDD/1000 PD TAE, 22%↓	Savings US$200–250 000 (**$397,260.20–$496,575.25**) per year Programme cost US$43 000 (**$85,410.94**) per year
PAIF	Leung et al. (2011) (Canada)	[8]	To determine the impact of AMS on antibiotic utilisation, expenditure and *C. difficile* rates	Observational, quasi-experimental	Hospital records	*C. difficile* and mortality rates (no significant decrease)	DDD/100 PD TAE, 38.9%↓	Savings of US$27 917 (**$31,404.56**)

Table 2 (*Continued*)

AMS strategy	Author, year (country)	Reference	Comparison/research question	Study design	Data sources	Clinical outcomes	Cost outcomes	Results/conclusions
PAIF	Miyawaki et al. (2010) (Japan)	[29]	To investigate the effect of the AMS team on appropriate antimicrobial use	Retrospective, observational	Hospital records	MRSA rate, ↓ (0.92% to 0.68%) LOS, ↓ (31.4 to 19.9 days) Mortality (no change)	DDD/1000 PD, 26.3%↓ TAE, ↓	Savings of US$ 827 609.04 (**$1,036,436.32**)
PAIF Period 2, initial intervention Period 3, active intervention	Niwa et al. (2012) (Japan)	[10]	To evaluate the impact of different approaches to PAIF and the resulting cost and clinical outcomes	Quasi-experimental, cost analysis	Hospital records	LOS (reduced by 2.9 days)	TAE LOS	Savings due to TAE: Period 2, US$58 000 (**$62,562.63**) Period 3, US$247 000 (**$266,430.50**) Savings due to reduction in LOS: Period 2, US$1.95 million (**$2,103,398.70**) Period 3, US$3.92 million (**$4,228,370.72**)
PAIF	Potasman et al. (2012) (Israel)	[30]	To evaluate the impact of computerised antibiotic control by ID physicians	Quasi-experimental	Pharmacy records	Mortality rate reduced from 4.0 to 3.8 (not statistically significant)	TAE, 17%↓	Savings US$181,000 (**$195,238.55**) per year
i.v.-to-p.o.	Dunn et al. (2011) (UK)	[31]	Impact of switching from i.v. to p.o. antimicrobials	Prospective quasi-experimental	Daily collection of patient details by pharmacist	LOS (no change)	TAE, 5.9%↓	Savings US$19,942.64 (**$22,433.99**) per year
i.v.-to-p.o.	Gray et al. (2012) (UK)	[5]	To assess the impact of antimicrobial management and early discharge on hospital costs	Economic analysis	Hospital financial records, British National Formulary, literature	LOS in hospital	LOS, ↓ TAE, ↓	Savings due to reduction in LOS US$ 292,045.54 (**$343,017.71**) Savings due to reduction in TAE US$31,616.07 (**$37,134.18**)
AFS	López-Medrano et al. (2013) (Spain)	[32]	To assess the outcomes of a voluntary antifungal AMS programme	Non-randomised, uncontrolled, quasi-experimental	Hospital records	LOS and in-hospital mortality (no significant difference)	TAE antifungals, 11.8%↓	US$370 681.78 (**$399,841.83**)
AFS	Malani et al. (2013) (USA)	[9]	To describe clinical and economic outcomes from the first year of an AMS programme	Retrospective, observational, quasi-experimental	Hospital records	30-day mortality and 30-day re-admission rates (no change) CDI, 50%↓	TAE/PD, 13.3%↓ TAE, 15.2%↓ DDD of target antimicrobials, 25.4%↓	Savings of US$228 911 (**$257,507.94**)
Comparison of PAIF strategies	Gross et al. (2001) (USA)	[33]	To compare the impact of ID fellows versus AMS team on cure rates	Comparative study	Hospital records	Appropriateness (87% vs. 47%); cure rate (64% vs. 42%); treatment failures (15% vs. 28%)	AMS team performed better than ID fellows	No statistically significant difference in cost outcomes

Comparison of PAIF and FR strategies	Beovic et al. (2009) (Slovenia)	[34]	To evaluate the impact of: (A) antimicrobials prescribed without ID physician (B) Restricted drugs prescribed by ID physician (C) All antimicrobial prescribed by ID physician with daily rounds	Observational study	Hospital records	Mortality remained the same, LOS decreased in B and C	Cost savings in B and C	Antibiotic cost was less in B and C
RT	Bauer et al. (2010) (USA)	[35]	To evaluate the clinical and economic outcomes of rPCR for differentiation of MRSA and MSSA from blood cultures in conjunction with an AMS intervention	Cost analysis	Costs obtained from hospital cost centres Cost of treatment of *S. aureus* bacteraemia Estimated	Mean LOS 6.2 days shorter	Significant cost savings in LOS	US$21 387 ↓ (**$25,119.78**)
RT	Perez et al. (2013) (USA)	[36]	To evaluate the impact of MALDI-TOF technology on the treatment of Gram-negative BSIs	Clinical trial and cost analysis	Hospital records	ICU LOS Hospital LOS	Net savings	US$19 547 (**$20,365.45**)
RT	Heil et al. (2012) (USA)	[37]	To assess the impact of (PNA FISH *Candida* spp. ID) rapid testing to identify *Candida* spp. to select most appropriate treatment strategy for BSI with *Candida* spp.	Clinical trial and cost analysis	Average wholesale price of antifungal agents Commercial cost of test	LOS, mortality, outcome of BSI (no significant change in LOS or mortality)	Cost savings	US$415 (**$447.65**) per patient
RT	García-Vázquez et al. (2013) (Spain)	[12]	To evaluate the outcome of BSI as a result of using RT in the form of Etest in the treatment of Gram-negative BSIs	Prospective randomised study and cost analysis	Pharmacy records Commercial cost of Etest	Outcome of BSI	Cost of RT-guided treatment Cost of ideal treatment Cost savings	US$2720.07 (**$2833.96**) US$512.04 (**$533.48**) US$2085.08 (**$2172.38**)
RT and AFS	Aitken et al. (2014) (USA)	[38]	To assess the utility of (PNA FISH, MALDI-TOF and T2 *Candida*) in the identification of *Candida* spp. in BSI	Prospective study and cost analysis	Average wholesale price from pharmacy and cost of commercial test kits	Outcome of BSI Time to initiation of therapy: T2 0.6 ± 0.2 days PNA FISH 2.6 ± 1.3 days MALDI-TOF 2.5 ± 1.4 days	Time to initiation of therapy	US$70,000 (**$72,847.74**) to US$140,000 (**$145,695.48**) per year
RT	Wong et al. (2012) (USA)	[39]	To evaluate the impact of RT in the form of rPCR to differentiate *S. aureus* from CoNS in the treatment of BSIs	Quasi-experimental, cost analysis	Hospital records	LOS (decreased 4.5 days)	Decrease in total hospital costs	US$8338 (**$8993.92**)

Table 2 (*Continued*)

AMS strategy	Author, year (country)	Reference	Comparison/research question	Study design	Data sources	Clinical outcomes	Cost outcomes	Results/conclusions
RT	Hubner et al. (2012) (Germany)	[40]	To examine whether rPCR testing to identify MRSA and MSSA infections is helpful in treatment	Economic analysis using a decision analytic model	Peer-reviewed literature	MRSA and MSSA treatment outcome	Cost savings achieved in the treatment of MRSA and MSSA infections when rPCR was used	MRSA treatment cost savings US$1838.90 (**$1983.56**) MSSA treatment costs savings US$1324.41 (**$1428.60**)
PAIF	Scheetz et al. (2009) (USA)	[13]	To determine the cost effectiveness of AMS teams on the reduction of morbidity and mortality associated with nosocomial bacteraemia	CEA	Hospital records	Cost per QALY gained	AMS intervention cost per QALY US$2367 Clinical decision support system	Intervention found to be cost effective
PAIF	Brown and Paladino (2010) (USA)	[14]	To compare the cost effectiveness of the rPCR assay compared with traditional empirical therapy	CEA	All data obtained from literature for the EU and the USA	Cost per LY gained	EU: without rPCR, cost per LY US$855.45 and US$845.69; with rPCR, cost per LY US$782.91 USA: without rPCR, cost per LY US$898; with rPCR, cost per LY US$820	Use of RT was found to be cost effective both in the EU and the USA

PAIF, prospective audit with intervention and feedback; ID, infectious diseases; LOS, length of stay; TAE, total antibiotic expenditure; DDD, defined daily doses; PD, patient-days; i.v.-to-p.o., intravenous-to-oral conversion; CDI, *Clostridium difficile* infection; ICU, intensive care unit; MRSA, meticillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; AFS, antifungal stewardship; FR, formulary restriction; RT, rapid technology; rPCR, rapid polymerase chain reaction; MSSA, meticillin-susceptible *S. aureus*; MALDI-TOF, matrix-assisted laser desorption/ionisation time-of-flight; BSI, bloodstream infection; PNA FISH, peptide nucleic acid probes for fluorescence in situ hybridisation; CoNS, coagulase-negative staphylococci; CEA, cost-effectiveness analysis; QALY, quality-adjusted life-year; LY, life-year.
All costs converted to US$ for ease of comparison (using conversion rate as of 9 December 2014; http://www.ozforex.com.au/currency-converter). All US$ figures were adjusted to 2014 prices using the Bureau of Labor Statistics Consumer Price Index specific to Medical Care (SEMF01, http://www.bls.gov/data/).
Where the cost year used for analysis was not stated, it was assumed to be 1 year prior to publication.

[27]. One study also specifically mentioned that a saving of $194 160 [3] was achieved by i.v.-to-p.o. conversion as one of the strategies included as well as PAIF in just 1 year of the programme.

The second most common strategy evaluated in these 27 studies was rapid technology (7; 26%) [12,35–40]. All studies evaluated the impact of rapid technology in terms of rapid PCR [35,39,40], MALDI-TOF technology [36,38], PNA FISH [37,38] and Etest strips [12] for rapid results for the change to more appropriate antimicrobials for the treatment of BSIs. These studies took into account the cost to the hospital of the treatment of specific infections such as meticillin-resistant *Staphylococcus aureus* (MRSA), *Candida* spp. and infections due to Gram-negative organisms in BSIs. Six of these seven studies were performed in the USA and one in Spain. Four of the seven studies included LOS as a clinical outcome [35–37,39] and three reported a reduction and associated savings due to this [35,36,39]. One found no significant change in LOS [37]. Two studies evaluated the impact on the management of BSI and the outcomes of these clinical conditions [12,38], and one other evaluated the outcome of MRSA and meticillin-susceptible *S. aureus* (MSSA) infections with the use of rapid technology [40].

Of the remaining eight studies, two evaluated the impact of antifungal stewardship [9,32] and looked at LOS, mortality, re-admission rates and CDI, and one of them found a significant reduction in CDI rates and no change in the other parameters, but significant cost savings due to reduced antimicrobial utilisation [9]. Two further studies evaluated the impact of i.v.-to-p.o. conversion [5,31]; both studies were performed in the UK and measured LOS as a clinical outcome. Both studies reported a reduction in TAE and significant associated cost savings due to this reduction. One of the two studies reported a reduction in LOS and included the cost savings due to this. The second study [31] noted no change to the LOS in their setting. Two studies compared different AMS strategies with one another [33,34] and found that a more interactive approach resulted in better outcomes and that pharmacist-driven AMS was more effective than strategies involving infectious diseases fellows.

3.3. Cost-effectiveness analyses

Only two studies performed a full CEA [13,14] and quantified the relative changes in costs and health gains due to AMS strategies, allowing an estimate of whether the strategy is value for money. Both evaluations used a US hospital context, although Brown and Paladino [14] also undertook an analysis for a European Union (EU) hospital context. Both CEAs used a hospital perspective and did not evaluate changes in societal costs as a result of the AMS programmes. Both of these interventions were found to be cost effective.

The CEA by Scheetz et al. [13] used a decision analytic model with a decision tree depicting the clinical pathways followed by patients with BSIs. The aim of the study was to determine the cost effectiveness of AMS teams on the reduction of morbidity and mortality associated with nosocomial bacteraemia.

The model is based on the assumption that an AMS programme can improve the clinical outcomes in patients with BSIs. The structure described was based on the outcomes of BSIs in the adult patient cohort at a large academic medical centre in the USA. The study used data from the literature as well as local cost information from the relevant healthcare environment to inform the model. This study found that an AMS team informing the most appropriate antibiotics to treat BSIs provided improved clinical outcomes in terms of reduced hospital stay and mortality. They also found that in their setting a clinical decision support system used to triage cases for specific attention was also found to be cost effective. The AMS programme was cost effective at US$2367 per quality-adjusted life-year (QALY) gained and the addition of a clinical decision support system was cost effective at US$481–36 319 per QALY.

A second US study also used a decision analytic model with a decision tree to assess the cost effectiveness of novel technology based on rapid PCR testing in the microbiology laboratory compared with traditional empirical therapy [14]. The study found the implementation of rapid testing to inform the most appropriate selection of antibiotic for the treatment of infections with MRSA and MSSA resulted in improved outcomes for patients [14]. This study used data derived from the literature both from the EU and the USA to inform the model. Results showed that rapid PCR testing for MRSA reduced mortality rates while being less costly than empirical therapy in the EU and the USA across a wide range of MRSA prevalence rates and PCR test costs. In the EU, the cost-effectiveness ratios for empirical vancomycin and penicillin for the treatment of patients were €695 and €687 per life-year saved, respectively, compared with €636 per life-year saved for rapid PCR testing. In the USA, the cost-effectiveness ratio was US$898 per life-year saved for empirical vancomycin and US$820 per life-year saved for rapid PCR testing

Both studies were well designed and aligned with the recommendations by Drummond et al. [11] for the structure of CEAs. They provide useful information on the value for money of strategies to improve the quality of prescribing in hospitals. Also, one in particular [14] provided information on the cost effectiveness of rapid technology to assist in the timely selection of appropriate antimicrobials in the more effective treatment of BSI. However, both studies used published estimates rather than local primary data, a narrow economic perspective (i.e. hospitals), and a short time horizon for the evaluation.

4. Discussion

The majority of existing work evaluating AMS programmes has focused on clinical effectiveness. However, in the current economic climate, governments need to identify the optimal allocation of health resources to maximise health outcomes. A well performed CEA can provide valuable information on the gains in health relative to the cost of different health interventions. This will enable comparisons to be made to assess the value for money of strategies that are implemented. CEAs are currently being used in many countries for decision-making in health resource allocation [41]. The lack of cost-effectiveness studies for AMS programmes has been highlighted in a recent update to a Cochrane review on interventions to improve antibiotic prescribing practices for hospital inpatients [42].

AMS programmes are greatly varied in content owing to healthcare institutions having a range of patient demographics, resource availability, size and access to specialist services. This is demonstrated by the wide variety of AMS strategies evaluated by the studies included in this review. It may be that AMS is not a 'one-size-fits-all' approach and programmes need to be tailored to the local context. A standardised approach to the collection of clinical and cost outcome data will allow for the efficient comparison of the different interventions.

The lack of consistency in cost outcomes reported, evaluation perspectives taken, and availability of full economic evaluations that compare relative changes both in costs and health outcomes currently inhibits these comparisons and identification of efficient AMS strategies. More economic evaluations undertaken using a standardised approach to the evaluation and collection of relevant information to inform it are required to assess these interventions.

The 36 studies included in this review all reported on the cost outcomes of the AMS strategies implemented in their specific institution. They all reported a decrease in cost after the introduction of AMS strategies, except for one study by Ijo and Feyerharm [25] that reported an overall loss of $215.99 (adjusted to 2014 US$).

In all studies the costs were reported in multiple formats, including TAE as well as TAE per admission, per PD and per 1000 PDs. Antibiotic consumption was also reported in a few different formats, as days of therapy as well as defined daily doses (DDD) per 100 PDs and per 1000 PDs. Consistency in these parameters using WHO-recommended reporting of DDD/1000 occupied bed days (OBD) would be useful when comparing the success of different strategies.

Of the 36 studies, 24 studies reported on cost savings associated with reduced antimicrobial utilisation. The others included a broader range of cost savings, including hospital and rapid technology costs.

In the studies evaluated in this review, 27 studies measured some clinical outcome as well as the cost savings associated with the intervention. The problem with only reporting cost savings, particularly when the focus is solely on reduced antimicrobial utilisation, is that this can be a misleading parameter to use to assess the success of AMS programmes, as this may not necessarily translate to improved clinical outcomes for patients. Even where studies have measured both clinical and cost outcomes, they are often reported separately and do not look at the relative change in both these outcomes, which would be important to assess the true value for money of the programme.

Only 2 of the 36 studies evaluated the cost effectiveness of two AMS strategies. Both CEAs found that the strategies were cost effective using commonly used willingness-to-pay thresholds. However, both used a narrow hospital perspective and short timeframe for evaluations and as such may not have captured all costs and benefits to AMS programmes. If a societal perspective was adopted, the benefits of the intervention would have been far greater as the costs of antimicrobial resistance need to be assessed over a longer period of time. They were also both undertaken in a US context, which may limit generalisability, although one study also evaluated the AMS strategy in an EU context and reached the same conclusions, providing support that the findings are likely to be broadly generalisable. Both studies also used data from the literature to populate their models and did not use raw data to generate the situation at each individual healthcare setting. This might be a design issue as the data collected may not be maximally accurate for the purposes of the new analysis and therefore may not be a true reflection of what is occurring at that specific healthcare setting. The more accurate the parameters that can be used to analyse a strategy in an economic model, the less uncertainty will be associated with the final result.

Other forms and variants of AMS programmes have not been subject to a full economic evaluation and have not been compared with one another, but compared only with a situation of no AMS. This means that although AMS programmes appear cost effective, it is not possible to compare between strategies to identify the most efficient strategy for a given setting. This is particularly problematic in the case of rapid technology. Rapid technology as a strategy in AMS has featured in many studies and they have concluded that the overall cost savings achieved were greater than the cost of the technology utilised. However, some of these technologies, such as MALDI-TOF, require significant monetary investment in set up and maintenance costs and no economic analyses have been performed to conclude whether these technologies are indeed cost effective. Further research is required to assess whether investment in these rapid technologies, in addition to less resource intensive AMS programmes, is justified.

It is clear from the evidence presented in this review that AMS strategies can reduce antimicrobial costs and a broader range of hospital costs. Existing evidence also shows that rapid technology in conjunction with AMS programmes can improve patient outcomes by reducing the length of time patients are in hospital [36]. However, to identify the AMS programmes that offer the best value for money in a healthcare system that is facing ever-increasing resource constraints, there is an urgent need for more evidence on the cost effectiveness of these programmes. It is also important to note that the studies so far have not included the costs related to the reduction or delayed emergence of resistance, as recommended by Coast et al. [43]. Future economic evaluations need to accommodate these costs where possible.

AMS programmes achieved a reduction in pharmacy expenditure, but a lack of consistency in cost outcomes was reported. A failure to capture other shifts in resource use that result from their introduction makes it difficult to determine the true cost of these interventions. There is an urgent need for full economic evaluations that compare relative changes both in clinical and cost outcomes to enable identification of the most cost-effective AMS strategies in hospitals.

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Competing interests

None declared.

Ethical approval

Not required.

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