The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antibiotic Management

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By

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Thesis Declaration

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Abstract

Background

Inappropriate antibiotic prescribing is a key contributor to increasing antibiotic resistance. Despite the standard practices promoted through clinical practice guidelines (CPGs), treatment regimens are not always in accordance with these guidelines. In Australia, a significant proportion of inappropriate antibiotic prescriptions in hospitals and primary care is due to noncompliance with CPGs. This is further exacerbated by the difficulty faced by clinicians in integrating and managing multiple information streams at the point of care to inform evidence-based decision- making.

There is increasing recognition that digital health interventions such as clinical decision support systems (CDSS) may assist in optimising antimicrobial management. CDSS provide treatment recommendations based on patient-specific risk factors and research evidence, allowing clinicians to provide personalised care. Many studies provide evidence of the potential of CDSS for promoting optimal antibiotic management; however, adoption of these systems in clinical practice remains low. In addition to this lack of effective system adoption, there is a high rate of clinicians' ignoring or overriding the systems' recommendations or only engaging with partial use of the systems' features. These factors limit the efficacy of CDSS in improving antibiotic prescribing.

Objective

The objective of this thesis was to evaluate individual, organisational, and system-level factors that impact CDSS implementation for evidence-based antibiotic management. An understanding of the different aspects of CDSS implementation in Australia has been sought by bringing together the perceptions and experiences of different stakeholders. The project aimed to achieve this objective by i) synthesising the evidence on the efficacy of CDSS for antibiotic management; ii) understanding clinicians' perceptions regarding CDSS use for optimal antibiotic prescribing; and iii) evaluating the challenges of integrating CDSS into the healthcare system.

Methods

To achieve the objectives outlined above, the thesis was divided into four studies:

In study I, a systematic review and meta-analyses were conducted to evaluate the impact of CDSS implementation on various clinical and economic outcomes associated with antibiotic management. The study protocol was developed using the PRISMA-P checklist. Studies were selected using specific pre-defined study eligibility criteria. Studies providing sufficient data on the outcomes were included in the

meta-analyses to calculate pooled effect estimates of the impact of CDSS implementation on antibiotic management.

In studies II & III, a cross-sectional online survey was conducted in Australia. Clinicians directly involved in prescribing, administering, and managing antibiotics in hospital and primary care settings were invited to participate. We adopted the Unified Theory of Acceptance and Use of Technology (UTAUT) model to understand factors contributing to clinicians' inappropriate antibiotic prescribing behaviour and their behavioural intent to adopt CDSS. Using this framework, we also examined the role of moderating factors such as gender, age, clinical experience, and care settings in shaping users' behaviour in adopting CDSS. We used multivariate logistic regression models to investigate the association between these moderating factors and users' perceptions regarding CDSS adoption.

Finally, in study IV, we used a qualitative approach to conduct in-depth interviews with policymakers involved in the implementation and evaluation of CDSS in Australia. The focus of this study was to understand what is required to effectively scale-up CDSS implementation from pilot studies to a system-wide innovation. Participants shared their experiences and perceptions concerning the gaps and challenges in the Australian healthcare system for integration of CDSS into healthcare processes. The interview transcripts were thematically analysed to establish a contextual understanding of the system-wide challenges for CDSS implementation.

Results

Results from this research highlight that CDSS can help reduce the risk of inappropriate antibiotic prescribing by increasing compliance with prescribing guidelines. The findings further indicate that CDSS can improve antibiotic prescribing by reducing the volume of overall antibiotic use, duration of therapy, length of hospital stay and thereby decreasing the overall cost of therapy. However, most of the evidence included in our systematic review was from studies having moderate to low methodological quality. Non-randomised studies tended to overestimate the effect of CDSS on appropriate antibiotic management, compared to randomised studies. However, the direction of the effect was largely consistent across both study types and favoured the positive impact of CDSS for antibiotic management. There was also substantial statistical heterogeneity in the results across the included studies which can be explained by the large variability in CDSS adoption across studies.

Findings from the survey with clinicians indicated that different individual and setting specific characteristics are important factors that influence clinicians' perceptions regarding CDSS adoption and lead to variability in uptake across different clinicians. Experienced clinicians were more sceptical of using CDSS for clinical decision-making, potentially due to limited digital health literacy, mistrust in the

information provided by CDSS and fear of compromising their professional autonomy. Similarly, in comparison to users, CDSS non-users were more likely to lack trust in CDSS recommendations and fear compromising their professional autonomy due to CDSS adoption. A lack of transparency and explainability in CDSS design, in which end-users are not aware of how systems have computed recommendations can reduce their trust in CDSS. Consistent with the context of primary care, primary care clinicians believed that time constraints and patient expectations were important drivers of CDSS adoption. These findings highlight that the efficacy of CDSS implementation may be limited by a lack of consideration of contextual factors such as clinical experience, setting of use, and users' skills which impact the users' behaviour to adopt CDSS. Targeted clinician engagement, digital health literacy and better communication of the reliability of information provided may assist with more successful implementation of CDSS at point of care.

Interviews with Australian policymakers further explored system-level challenges and gaps that may impede successful CDSS implementation. The results show that the lack of shared vision between different stakeholders, and the fragmented infrastructure within the healthcare system are major barriers to the integration of CDSS within existing processes in the healthcare system. CDSS implementation needs to be supported by an effective governance structure that can establish clear roles, prioritise investment in health system capacity building and incorporate cross-discipline and inter-organisational collaboration for quality data sharing. The ability of CDSS to ensure coordinated and interoperable care by exchanging information across organisations requires mutually agreed data standards at a national level. There is a need to establish standards not only for generating data in a standardised format, but for semantic interoperability that allows data communication and interpretation across different systems. Notwithstanding the significance of standardisation to ensure interoperability in CDSS, our findings also highlight that this standardisation must be balanced with adequate flexibility in the CDSS design and implementation process, so that user and setting specific requirements can be incorporated to improve adoption.

Conclusion

In conclusion, our findings illustrate that CDSS reflects best practice for antibiotic management through evidence-based clinical decision making, integrating the knowledge base, and flagging medication errors. The integration of these systems in healthcare settings is, however, challenging due to the complex interaction between the system, organisational and human factors. The findings from our research suggests that individual and setting characteristics such as clinical experience, use of CDSS and the type of setting, influence the clinicians' perception of CDSS role in antibiotic management. These characteristics provide a better understanding of why CDSS adoption varies across different

clinicians and care settings. We also found that the lack of synergy evident between multiple stakeholders and organisations - who seem to have varying interests and objectives regarding CDSS implementation - is limiting the ability to develop a shared vision and collaborative action.

These findings provide evidence firm foundation for policymakers for developing a holistic CDSS implementation framework that considers the interaction of the system within the context of organisational and human behavioural characteristics. Implementation processes need to be tailored to specific user and setting requirements for improved adoption and use of CDSS by clinicians. A better understanding of the clinical culture would support successful CDSS implementation, along with effective strategies to develop broader digital literacy, methods for sustaining clinicians' engagement with the technology, and approaches to facilitating cross-discipline collaboration.

Publications arising from this thesis

- Laka M, Milazzo A, Merlin T. Can evidence-based decision support tools transform antibiotic management? A systematic review and meta-analyses. J Antimicrob Chemother. 2020;75(5):1099-111. DOI: 10.1093/jac/dkz543.
- Laka M, Milazzo A, Merlin T. Factors That Impact the Adoption of Clinical Decision Support Systems (CDSS) for Antibiotic Management. Int J Environ Res Public Health. 2021;18(4):1901.
- Laka M, Milazzo A, Merlin T. Inappropriate antibiotic prescribing: understanding clinicians' perceptions to enable changes in prescribing practices. Australian Health Review. 2021 Oct 5.

Under-review:

- Laka M, Carter D, Milazzo A, Merlin T. Challenges and opportunities in implementing clinical decision support systems (CDSS) at scale: interviews with Australian policymakers. Health Policy and Technology

Conference proceedings

- Laka M, Milazzo A, Merlin T. Sustainable Implementation of Electronic Decision Support Tools for the Evidence-based Management of Antibiotics. In: Proceedings of the 9th International Conference on Digital Public Health. 2019 p. 7-8.
- Laka M, Milazzo A, Merlin T. Why provision of clinical decision support (CDS) is not enough? Factors influencing the CDS adoption. Eur J Public Health. 2020;30(Supplement_5):ckaa165. 223.
- Laka M, Carter D, Milazzo A, Merlin T. Clinical Decision Support System for Antibiotic Management: Factors Limiting Sustainable Digital Transformation. HTAi 2021 Annual Meeting; 2021; Virtual: Health Technology Assessment International
- Laka M, Carter D, Milazzo A, Merlin T. From Pilot Studies to System-Wide Innovation: Challenges and Opportunities for Clinical Decision Support Systems (CDSS) Implementation in Australia. HTAi 2021 Annual Meeting; 2021; Virtual: Health Technology Assessment International.

Conference presentations arising from this thesis

International Conferences

- Laka M, Milazzo A, Merlin T. (2021). Clinical Decision Support Systems (CDSS) For Antibiotic Management: Factors Limiting Sustainable Digital Transformation. [*Oral Presentation*]. Health Technology Assessment International 2021 Annual Meeting [virtual conference].
    - **Award**: Winner for best student presentation

- Laka M, Milazzo A, Merlin T. (2021). From Pilot Studies to System-Wide Innovation: Challenges and Opportunities for Clinical Decision Support Systems (CDSS) Implementation in Australia. [*Oral Presentation*]. Health Technology Assessment International 2021 Annual Meeting [virtual conference].

- Laka M, Milazzo A, Merlin T. (2021). Challenges and opportunities to appropriate antibiotic prescribing: a survey of clinicians' perceptions in Australia. [*Oral Presentation*]. World Congress of Epidemiology 2020 [virtual conference].

- Laka M, Milazzo A, Merlin T. (2020). Why provision of clinical decision support Systems (CDSS) is not enough? Factors influencing the CDSS adoption. [*Oral Presentation*]. 16th World Congress of Public Health 2020 [virtual conference].

- Laka M, Milazzo A, Merlin T. (2019). Sustainable Implementation of Electronic Decision Support Tools for the Evidence-based Management of Antibiotics. [*Oral Presentation*]. 9th International Conference on Digital Public Health. Marseille. France.
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National Conferences

- Laka M, Milazzo A, Merlin T. (2020). Inappropriate Antibiotic Prescribing: Understanding Clinicians' Perceptions for Sustainable Change in Prescribing Practices. *[Oral Presentation]*. Australian Public Health Conference 2020 [virtual conference].

State Conferences

- Laka M, Milazzo A, Merlin T, Computer-Based Clinical Decision Support Systems (CDSS) for Antibiotic Management *(Oral presentation)*. The Public Health Association of Australia (PHAA) SA State Population Health Conference, Adelaide, Australia, 2019.

- Laka M, Milazzo A, Merlin T. (2018). Computer-based Clinical Decision Support Systems for optimizing antimicrobial use: A systematic review. [*Poster Presentation*]. The Public Health Association of Australia (PHAA) SA State Population Health Conference. Adelaide. Australia.

- Laka M, Milazzo A, Merlin T. (2019). Promoting Evidence-Based Antibiotic Management through Electronic Decision Support Systems. [*Poster Presentation*]. The University of Adelaide Florey Postgraduate Research Conference. Adelaide. Australia.
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        - School of Public Health Poster Prize, Florey Conference, the University of Adelaide
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-Isaac Newton

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List of Abbreviations

ABR	Antibiotic Resistance
ACSHQC	Australian Commission on Safety and Quality in Health Care
ADHA	Australian Digital Health Agency
AMS	Antimicrobial Stewardship
ASPs	Antimicrobial stewardship programs
CPGs	Clinical practice guidelines
CDSS	Clinical decision support systems
CPOE	Computerised physician order systems
CI	Confidence interval
DDD	Defined daily dosage
EE	Effort expectancy
EHR	Electronic health records
EMRAM	Electronic Medical Record Adoption Model
FE	Facilitating environment
FDA	Food and Drug Administration
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HAI	Hospital acquired infections
HCI	Human-computer interface
HIMSS	Healthcare Information and Management Systems Society
HIT	Health information technology
HL7	Health Level Seven International
ICD	International Classification of Diseases
ICU	Intensive care units
IT	Information Technology
MeSH	Medical Subject Headings
MRSA	*Methicillin-resistant Staphylococcus aureus*
NRS	Non-randomised studies
OR	Odds ratios
PE	Performance expectance
PRISMA	Preferred Reporting of Items in Systematic Reviews and Meta-analyses

RCTs	Randomised controlled trials
RR	Relative risk
ROBINS-I	Risk of Bias in Non-randomised Studies - of Interventions
SI	Social influence
SoF	Summary of findings
SNOMED	Systematized Nomenclature of Medicine
UK	United Kingdom
US	United States
UTAUT	Unified Theory of Acceptance and Use of Technology
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Background

Antibiotic resistance is a significant global public health challenge with considerable economic burden and increasing challenges for health care systems. Antibiotic resistance negatively impacts the quality and safety of patient care. It is becoming increasingly difficult to treat infections or perform simple surgical procedures due to the risk of drug-resistant hospital-acquired infections (1). Inappropriate and unnecessary antibiotic prescribing has been identified as one of the main drivers of increasing antibiotic resistance (2-4). Therefore, antimicrobial stewardship (AMS) efforts have been directed at reducing inappropriate and unnecessary prescribing of antibiotics through the restriction of broad-spectrum antibiotics, promotion of compliance with antibiotic prescribing guidelines, addition of feedback and audit mechanisms for antimicrobial prescribing and through rapid diagnostic testing (5, 6).

AMS success depends on timely access to information that will optimise health care delivery and ensure evidence-based decision making (7). This information may come from multiple sources and cover identification of the pathogen and strain, pathogen susceptibility, diagnostic criteria, guideline recommendations, selection of the appropriate antibiotics with the optimal dose and frequency, possible adverse drug events and drug-drug interactions. Managing multiple streams of information about prescribing at the point-of-care contributes to the complexity of evidence-based decision making. It appears that passive dissemination of clinical knowledge through clinical practice guidelines (CPGs) adds little value to the prescribing process (8, 9). Studies conducted in Australia estimated that approximately 18% of errors related to medications are caused by a lack of timely access to patient information. In addition, the rate of prescribing errors related to documentation in paper based systems was five errors per patient (10, 11).

Many studies have established digital health systems such as clinical decision support systems (CDSS) as a solution to address these shortcomings in the care process (12-16). CDSS are an emerging technology that has the capability to address the prevalence of medication errors and to improve healthcare quality (17). Traditionally, these systems match patient-specific data to computerised knowledge bases and so can provide diagnosis or treatment recommendations that are based on patient-specific risk factors, enabling personalised care (18). In many cases, CDSS are integrated into existing systems such as Electronic Health Records (EHRs) or Computerised Provider Order Entry (CPOE), but CDSS are also being developed as standalone applications. In literature, CDSS are classified into different types depending on a range of factors such as system functionality, decision-making model and nature of advice provided. For instance, some CDSS are limited to providing diagnostic or treatment recommendations while most systems provide both.

Another important factor in classifying CDSS is whether the system provides advice passively – where users do not need to acknowledge the alerts or notifications to continue with clinical workflow - or actively, requiring users' active engagement to overcome or accept the alerts. In this regard, the type of decision-making models is also an important factor in the characterisation of CDSS. The knowledge-based CDSS decision-making model utilises conditional models to provide recommendations eg if the patient has a particular risk factor then a particular treatment is appropriate. Non-knowledge-based models provide recommendations on mathematical models, artificial intelligence, and machine learning (further details provided in section 2.3.1) to identify the likelihood that a patient is at risk. The clinical implications of CDSS may, therefore, vary across the different designs and models; however, the purpose of this thesis was not to focus on a specific type or category of CDSS.

CDSS are becoming more important for healthcare because of the increasing volume of clinical data. It is estimated that only 14% of the research data gets translated into clinical practice with a time lag of 17 years (19). Despite the promising potential of CDSS for antibiotic management which has been identified in many proof-of-concept and limited-scale studies, adoption in healthcare systems remain low (20-22). Several technology adoption models, such as the Healthcare Information and Management Systems Society (HIMSS) Analytics Electronic Medical Record Adoption Model (EMRAM) are employed to measure and guide the digital maturity of healthcare organisations. The highest levels of this model (stage 6 and stage 7) are achieved when healthcare organisations are digitally mature enough to fully implement CDSS. In Australia only two hospitals - the Royal Children's Hospital in Melbourne, Victoria and St Stephen's in Hervey Bay, Queensland - have been accredited at stage 6 and stage 7 of HIMSS Analytics EMRAM for digital transformation and effective implementation of CDSS. Despite increasing recognition of the value of CDSS for evidence-based care, there are very few success stories of long-term implementation of these systems in Australia. The benefits of CDSS reported in research studies cannot currently be up scaled to system-wide digital transformation (23).

Even in organisations where CDSS has been successfully implemented, low adoption by healthcare practitioners adds an additional layer of complexity. Researchers have found that 33 -96% of recommendations or alerts provided by CDSS are ignored or overridden (24, 25). An evaluation of CDSS use in primary care in Australia found that 20-40% of the features provided by the systems were not adopted by clinicians, and 20-26% of the features were only partially adopted (26). Clinicians' fatigue from excessive CDSS alerts has been extensively discussed in the literature as a contributing factor to the low adoption of CDSS more generally. However, there is not enough

evidence available to indicate how this might impact CDSS effectiveness specifically for antibiotic prescribing, in Australia. However, overall variability in CDSS adoption across different studies suggests that CDSS use is not entirely about system design but a result of the interaction of technology, users, and the clinical environment. CDSS are essentially a socio-technical system. This means that there needs to be recognition of individual users' digital literacy, willingness to adopt the innovation, and clinical culture, along with technical feasibility. Peek *et al*. (27) have argued that the demand for digital transformation of healthcare systems indicates that many of these digital systems have existed for several years but lack infrastructure and policies to facilitate their penetration into clinical workflows.

Changing dynamics of care in the wake of COVID-19 has forced healthcare organisations and governments to realise the significance of coordinated care, which can be supported through systematic healthcare digitalisation (27, 28). During the pandemic, healthcare systems faced innumerable challenges in the delivery of care, triggering the need to introduce innovative solutions such as telehealth, Internet of Things (IoT) and artificially intelligent decision support. This unprecedented interest in digitally enabled models of care has revealed that there are still many missed opportunities and gaps in creating a strong ecosystem for sustainable digitalisation of healthcare systems.

The Australian Digital Health Agency (ADHA) has introduced a number of initiatives to promote CDSS implementation including projects related to eReferrals, standard-based CDSS for primary care, clinical documentation architecture (CDA), My Health Records and HL7 standards for medical records (29). Currently little is known about the gap between the potential value of CDSS for antibiotic management and the actual utilisation of such systems in healthcare settings. Few studies have examined the challenges faced by health organisations to effectively integrate CDSS into established clinical workflows (30-33). Addressing these gaps may help inform targeted strategies to effectively implement CDSS in Australia and similar health systems.

1.2 Thesis Aims

This research had two aims. The first aim was to assess whether CDSS utilisation can improve the clinical and economic outcomes of antibiotic stewardship in different healthcare settings. The second aim was to identify the challenges and opportunities for sustainable CDSS implementation at the individual, organisational, and system-level. Digital systems such as CDSS have the potential to improve the safety and quality of care. However, lack of an effective implementation process may limit the benefits of the system and lead to errors that can cause harm to patients (34-36). Therefore,

it is important to identify different factors in the digital health landscape that can hinder or restrict the effective use of CDSS.

1.3 Research Program

The format of this thesis is by publication and is divided in eight chapters.

Following this brief introduction and aims of the research, Chapter 2 provides a comprehensive literature review on the role of CDSS for antibiotic management and the different behavioural and technical factors that influence the uptake of CDSS in healthcare settings. A summary of the knowledge gaps identified in the literature that this research aims to address concludes chapter 2.

Chapter 3 (Study Design and Methodology) provides the rationale, objectives, and research questions along with the methods used to address each objective and research question.

Chapters 4, 5, 6 and 7 discuss the findings of research studies conducted to answer the research questions. Chapter 4 investigates the effect of CDSS on the clinical and economic outcomes of antibiotic stewardship. Chapter 5 examines the perceptions of different clinicians regarding CDSS adoption and approaches for addressing these barriers, whereas Chapter 6 explores the barriers to appropriate antibiotic prescribing in hospitals and primary care. Chapter 7 assesses the challenges and opportunities for implementing CDSS at a system-level.

Finally, Chapter 8 provides an overview of the evidence arising from the different studies presented in Chapter 4-7. This chapter also presents a synthesis of the key findings from the four studies with a discussion on the significance and limitations of this research. This chapter also concludes the thesis by providing recommendations and suggestions for further areas of research for effective CDSS implementation.

The published articles and manuscripts included in Chapters 4-7 are re-formatted for consistency with other sections of the thesis. This included consecutive numbering of headings, figures and tables and unifying lists of references at the end of the thesis.

Chapter 2: Literature Review

2.1 Antibiotic Resistance (ABR)

Since the discovery of penicillin in 1928, the commercialisation of antibiotics has helped in shaping the therapeutic options that target an increasing number of bacterial infections. Antibiotics have been successfully used in many medical procedures such as pre- and post-surgical care, organ transplantation, palliative care, and cancer-patient management. However, the significant increase in antibacterial resistance over the last few decades has compromised the efficacy of treatment (37). Increasing lack of susceptibility of drug-resistant bacteria to therapeutic agents has resulted in increased mortality and morbidity and prolonged illness, particularly in the immuno-compromised population (38, 39).

Clinical practices resulting in unnecessary antibiotic prescriptions, increased use of broad-spectrum antibiotics, 'drug-bug' mismatch, suboptimal dosage and length of antibiotic use have created a selection pressure (40). Because of this pressure, bacteria acquire drug-resistance which allows them to survive and multiply. Epidemiological studies have established a direct correlation between the distribution of antibiotic-resistant strains and the inappropriate use of antibiotics (2-4). In community settings, diagnostic ambiguity is a significant underlying factor for the over-prescription of antibiotics. Because viral and bacterial infections have similar symptoms, the majority of prescriptions are for conditions that do not warrant antibiotics (2, 41). Survey studies highlight that approximately 50% of patients in community settings were prescribed antibiotics for colds or viral sore throats that usually do not require antibiotics (42-44). In many cases, antibiotics are prescribed as a precautionary measure even when there is no evidence of bacterial infection. On the other hand, the duration and type of antibiotics prescribed in hospital settings significantly contribute to the emergence of drug-resistant strains (42, 45).Other factors such as the presence of an immuno-comprised or highly susceptible populations, duration of antibiotic therapy, length of hospital stay and influx of bacterial infections further increase the risk of drug-resistant infections (37, 46).

The economic burden associated with antibiotic resistance is also of great concern for healthcare systems and governments. Economic models have demonstrated that excess expenditure in hospitals is associated with hospital acquired infections (HAI). For instance, a study conducted in United States (US) estimated an average increase of 9.58 days in length of hospital stay, and an increase of USD $38,656 in therapy costs due to HAI (47, 48). Similarly, a simulation economic model estimated that in Australia, managing drug-resistant *E.coli* and *Methicillin-resistant Staphylococcus aureus* (MRSA) infections contributed to an additional annual cost of AUD$5.8 million and AUD$5.5 million respectively (49). Because of this clinical and economic burden, there is

an increasing interest in developing strategies for the prevention and management of antimicrobial resistance.

2.2 Strategies to Control ABR

Development of new potent antibiotics has significantly declined over the past few decades. For example, Boucher *et al*. indicated that there is a significant decline in new antibiotics annually approved in the US by Food and Drug Administration (FDA). As indicated in the Table 2.1, 16 new antibiotics were approved from 1983 to 1987, but only two new antibiotics were approved during 2008 – 2012 (50).

Table 2.1 Decline in new antibiotics approved in US from 1983-2012.

Year	Number of new antibiotics approved by FDA
1983-1987	16
1988-1992	14
1993-1997	10
1998-2002	7
2003-2007	5
2008-2012	2

Declining interest in research and investment in antibiotic development by the pharmaceutical industry is due to the rapid increase in antibiotic resistance against new drugs and the fact that reimbursement mechanisms are linked to sales (whereas drugs that address ABR must be conserved) (50).

The lack of antibiotic development and reduced efficacy of current antibiotics have led to antibiotic resistance being declared a significant public health challenge. In response to the increasing threat of drug-resistance, antimicrobial stewardship programs (ASPs) have been introduced in different countries following the initiative of the World Health Organisation (WHO) (51). The purpose of these programs is to establish a holistic approach to control and prevent ABR through collaboration,

surveillance, rational drug use policy, standard treatment guidelines and drug research and development (5, 52).

2.2.1 Antimicrobial Stewardship Programs (ASP)

Antimicrobial stewardship encompasses multi-dimensional and coordinated efforts including surveillance, policies, practice evaluation, guidelines, and training for optimal antibiotic prescribing in healthcare (53, 54). Programs include interventions and activities that evaluate antimicrobial use and promote evidence-based and standardised prescription regimens (5). Antimicrobial stewardship is an approach that systematically promotes effective antimicrobial control through guidelines for prescription and usage, with efforts aimed at reducing rate of prescription errors and adverse drug effects.

There is no standardised framework for ASPs as there are diverse requirements in different care settings (5, 6). Usually multiple interventions and activities are simultaneously introduced to address the specific requirement of the care setting. Different studies indicate that effective ASPs tend to adopt a holistic approach to foster optimal antimicrobial management, and active surveillance to reduce the risk of increasing drug-resistance in pathogens (55). Davey *et al.* (56) proposed that enablement and restriction should be underlying principles for optimal antibiotic use. Enablement promotes appropriate and evidence-based antimicrobial use through interventions such as an audit and feedback mechanism, educational outreach, and the use of decision support tools. Restriction, on the other hand, aims to reduce unnecessary and inappropriate antibiotic prescribing (56). Formulary restrictions are an example of interventions to restrict unnecessary prescriptions (5). The goal of these measures is to optimise antimicrobial use and to reduce the risk of toxicity, development of resistance and drug-bug mismatch (57).

2.2.1.1 Antimicrobial Stewardship in Australia

In 2011, an ASP was made a compulsory component for the hospital accreditation in Australia (58). The aim was to standardise antimicrobial prescribing and dispensing, establish audit systems, enact formulary restrictions, and promote decision tools for the better implementation of prescribing standards. The strategic framework underpinning the stewardship program focuses on restricting the use of antibiotics for specific clinical conditions approved by infection specialists, as well as review of antimicrobial recommendations to limit inappropriate prescribing (59, 60). Quality improvement initiatives introduced in the ASP rely on clinician behavioural change through the provision of appropriate best evidence and prospective audit and feedback. As a result of these initiatives, there

was an 18% improvement in the appropriateness of antimicrobial prescribing in hospitals, with inappropriate prescribing decreasing by almost 8% between 2013 - 2016 (42). Education strategies and effective governance also improved outcomes with an overall decrease in antimicrobial use, resulting in cost savings. These findings are highly encouraging but there is still some way to go to reduce inappropriate antimicrobial prescribing in Australia.

A study conducted by Dik *et al*. (61) argued that an integrated approach is required for ASPs as no single intervention is sufficient to address the antimicrobial resistance. This study suggested an approach called "theragnostic model" that combines effective prevention, optimal prescribing, and diagnostic activities to positively impact antibiotic prescribing. Multidisciplinary collaboration for surveillance of resistance, and the provision of evidence-based information and training can help to establish an optimal environment for effective stewardship activities. ASP initiatives and strategies can be supported by incorporating information technology tools. One of the national standards developed by the Australian Commission on Safety and Quality in Health Care (ACSHQC) (Standard 4) recommends that antimicrobial management should be supported by the provision of up-to-date and relevant information through digital technology tools (62). This will improve the availability of information required for evidence-based and personalised decision-making at-the-point of care.

2.3 Information Technology (IT) for Healthcare

The integration of information technology in healthcare has improved the quality of care by reducing medication prescription errors and providing real-time data for improved decision-making (63, 64). Healthcare management involves complex decision-making utilising several data sources within a dynamic and fast-paced clinical environment. It includes identifying the pathogen, susceptibility results, diagnostic measures followed by selecting the optimal antimicrobial agent with the appropriate dose and frequency conforming to best-practice evidence. In this context, digital systems provide the capability to draw these data from relevant sources and process it at the point-of-care for evidence-based decision-making. These systems can provide innovative solutions for managing large volumes of data and integrating different sources of information and current evidence into practice across different healthcare settings. For example, a study conducted in the US identified that approximately 85% of those aged above 65 are prescribed an average of four medications per day and visit seven different care providers in a year (65). Integrated digital systems can work to safeguard the patient from a lack of continuity of care. Without digital systems, it is becoming increasingly difficult to coordinate and optimise medical records.

With changing healthcare system dynamics, digital systems provide opportunities for improved quality and safety of care. However, without an effective implementation, the digitalisation of healthcare may result in unintended consequences related to data entry errors and retrieval, communication gaps, and workflow issues (66-69). Campbell *et al*. used the term "e-iatrogenesis" which refers to patient harm caused by new unintended errors through application of digital health systems (70, 71). It highlights that complex socio-technical interactions between digital systems and clinical workflows need to be understood to reduce the risk of patient harm. Without the consideration of this complex interaction, the implemented system may lead to increased harm than benefit (67, 72). This socio-technical approach emphasises that digital health systems are dependent on the context in which they are implemented involving technology, processes, and people. Many unintended consequences are the result of this complex interaction as errors rarely arise due to the failure of single factor. For instance, a study conducted by Coiera, Ash and Berg (67) classified unintended consequences of digital health systems into two broad categories: i) errors in information entry and retrieval due to an incompatible human-computer interface, and ii) lack of flexibility in digital systems leading to errors in coordination and communication. This suggests that source of these errors is poor fit between technology, human and clinical processes. Although some of these errors exist in standard clinical practices (without the use of digital systems), they were more likely to occur if socio-technical aspects of digital systems were not effectively considered in the implementation process. Recent studies in the implementation science also highlight that there is a need to shift the focus from the mere installation of new technology to establishing implementation as an adaptive process (67, 73).

Despite these challenges surrounding digital health systems, on balance there is a greater potential to improve health outcomes by enabling coordinated care and providing appropriate information at the point-of-care (74-76). There is, therefore, a need to understand and mitigate the risks of poor digital systems implementation. The success of digital systems, services and applications is not limited to technical design but requires the evaluation of socio-technical factors, as well as safety and usability of these systems.

2.3.1 Clinical Decision Support Systems (CDSS)

As discussed in the previous section (2.3), the need for an optimal prescribing process has paved the way for increased use of information technology systems such as clinical decision support systems (CDSS). These systems can improve the quality of health care by providing treatment recommendations based on clinical practice guidelines (CPGs) and evidence-based medicine at the

point-of -care. CDSS assist in health care decisions by integrating a general knowledge base as well as patient-specific information (77). A CDSS comprises of three basic components: knowledge base, inference mechanisms and communication (Figure 2.1). The knowledgebase is the clinical evidence, usually in the form of a probabilistic association or an 'if-then' rule of different symptoms linked with drug interactions or diagnoses. The inference mechanism is also known as the reasoning engine and is usually based on logic functions, decision-theory or probabilistic methods to combine patient-specific data with the knowledgebase. This provides customised recommendations or assessment. The communication component provides the mechanism to input patient data into the system and export the findings to end users (78, 79).

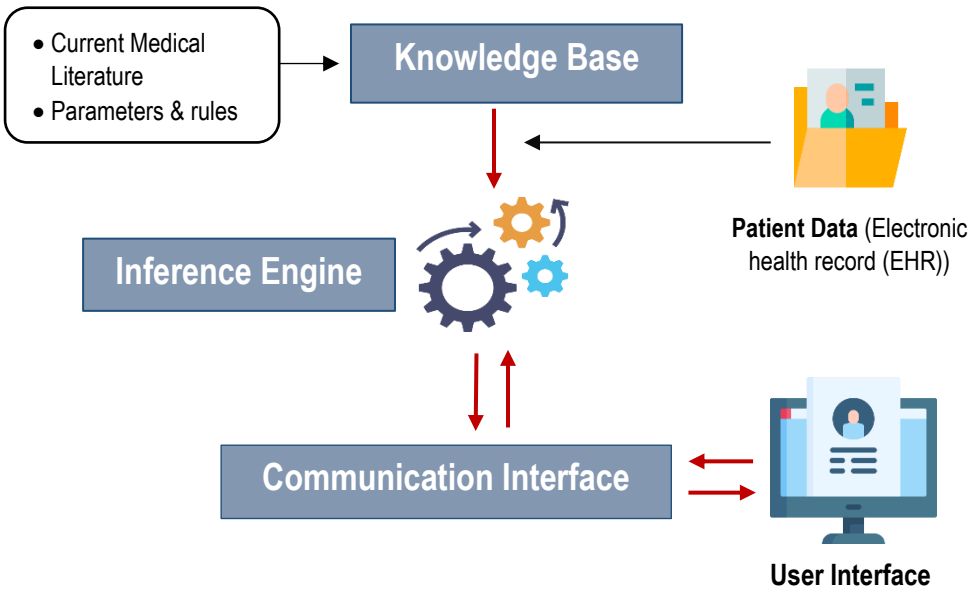


Figure 2.1 Components of Knowledgebase Clinical Decision Support Systems (CDSS)

Different CDSS have features such as drug-dosage calculators, reminders, alerts, and order sets allowing the retrieval of relevant and context-specific information required for decision making. They also provide automated reminders about important actions at different stages of the care process (80). These systems vary depending on different dimensions such as system type (knowledge and non-knowledge base), and type of support provided (active and passive alerts). The active alerts usually referred as pop-ups are usually interruptive in the clinical workflow and require certain action by the user such as clicking a button or closing the pop-up window to continue. The passive alerts, on the other hand, do not need active engagement by the end user and thus considered non-

interruptive alerts. Newer systems employ machine learning and pattern recognition techniques to provide support for decision-making (81). Several CDSS provide suggestions or information on possible disease aetiologies while many other systems present the patient-related data in a way which is more relevant to the clinical context.

The increasing use of CDSS has been driven by the different challenges faced by healthcare systems. These include the growing complexity of managing high volume data in care settings, the meaningful utilisation of electronic health records in decision-making and the need to deliver personalised care (79). A systematic review by Kawamoto *et al*. (82) identified moderate to significant improvements in different patient and system-specific outcomes after the implementation of CDSS in 68% of the included 70 randomised controlled trials. There was an overall 4.4% improvement in the prescribing behaviour with a 7.1% increase in adherence to standard documentation. Moreover, a 16 – 35% improvement in compliance with clinical practice guidelines (CPGs) has been reported in different studies (83, 84). However, studies also identified that the CDSS effectiveness was dependent on the automatic provision of decision support at point of care, with significantly lower success rates in passive CDSS where end-users need to seek out recommendations or advice. As mentioned above, passive alerts have been recognised in many studies as non-interruptive and beneficial for maintaining the continuity of clinical workflow as clinicians choose to assess alerts provided by the system. However, clinicians have also acknowledged that passive alerts are less likely to be seen and may not be effective in impacting the prescribing behaviour (82, 85, 86).

CDSS use also positively impacts the quality of decision-making by improving communication and information sharing between different individuals, units, and organisations. However, many studies on CDSS efficacy have been undertaken in controlled or simulated environments, therefore, unknown factors that may affect the system efficacy in clinical practice have not been considered. A systematic review by Varghese *et al*. (87) identified that uncertainty and dynamics of the clinical environment contribute to significant differences in the clinical impact of CDSS reported in different studies. Almost 73% of the studies included in this review were single-site studies with CDSS implemented at a single practice or hospital. As highlighted, little consideration is given to system-level factors that account for organisational dynamics and diversity inherent in different care settings.

2.3.1.1 Clinical Decision Support Tools for Antimicrobial Stewardship

Clinical practice guidelines (CPGs) are a standard support for promoting best clinical practice and improved the quality of care. Despite efforts targeted at the development and dissemination of CPGs

in different healthcare settings, the adoption and use of CPGs has varied (88). Different factors such as the volume of information, inconvenient presentation and constraints of time and effort have limited the usability of CPGSs (89). Increased compliance with prescription guidelines is a basic strategy of ASPs to reduce unnecessary and sub-optimal antibiotic prescribing (90). CDSS can provide easy access to CPGs at the point-of-care and facilitate evidence-based decision making. Studies have indicated that CDSS use can improve the selection of antimicrobial agents, reducing medication errors and adverse drug events (14, 91, 92).

There is a role for CDSS for antimicrobial stewardship at three different phases of antibiotic treatment: pre-prescription; peri-prescription and post-prescription support (93, 94). In the pre-prescription stage, the CDSS interacts with clinicians to recommend different possible care protocols, provide diagnostic support, evaluate differential diagnosis and assess the severity of infection (95). In the peri-prescription process, the CDSS integrates the knowledge-base and CPGs with patient specific data to provide recommendations for antimicrobial therapy for that specific patient. At this stage, the system considers clinical evidence including local antibiogram, resistance patterns, pharmacokinetics, microbiology test results and formulary restrictions to provide therapy recommendations. The post-prescription phase is also the evaluation phase, where the empirical therapy is re-evaluated by the CDSS following susceptibility test results and de-escalation or treatment adjustment is recommended as required (94). At this stage, system feedback and audit functionality enable the identification of any sub-optimal selection of antibiotics by the clinicians and reduces the risk of treatment inefficacy by flagging inappropriate frequency and dosage regimens, identifying local resistance patterns, drug adverse effects or secondary infection (93, 96).

There are a range of studies that have reported on the impact of CDSS on different outcomes related to antibiotic management ranging. Many of the core ASP activities (formulary restrictions, audit and feedback, therapy de-escalation and increased compliance with prescription guidelines) were found to be supported by CDSS (14, 92, 93, 95). By incorporating CPGs as clinical rules, CDSS has improved the use of best-practice evidence in the decision-making process regarding antibiotic prescribing. Positive impacts from CDSS use have been reported in a number of studies on the key quality ASP metrics, such as overall volume of antimicrobial use, length of hospital stay, duration of therapy, resistance pattern, mortality and cost-effectiveness of the treatment (97). A study conducted by Cook *et al*. (98) showed that by providing decision support functionality in electronic health record (EHR) systems the audit and review of patient charts improved by 36.6%, and antimicrobial prescriptions reduced by 29%. Similarly, in one of the recent review studies, 90.9% of the included studies reported a reduction in antibiotic consumption rate for bronchitis, sinusitis, and urinary tract

infections. Many studies relate this reduction in antibiotic consumption after CDSS use to increased compliance with prescribing guidelines and more appropriate antibiotic prescribing. The studies further indicated that because of CDSS implementation, antibiotic prescriptions were four times more likely to comply with the guidelines as compared to prescriptions made without using CDSS. The increased compliance with guidelines also resulted in an overall 50% reduction in inappropriate antibiotic prescriptions in the included studies (99, 100). The positive impact of CDSS is not limited to improvement in compliance with guidelines and reduction in overall consumption of CDSS. One of the main factors in reducing the risk of antibiotic resistance and improving ASP activities is the optimal duration of antibiotic treatment. A study conducted in 3 emergency departments in France indicated that due to the significant improvement in compliance with the guidelines after the implementation of CDSS, there was an increase in the selection of the approved antibiotic for an optimal duration (measured as days of therapy). Therefore, by providing functionalities such as alerts for a sub-optimal duration of therapy, treatment de-escalation if required after susceptibility test results, recommending antimicrobial dosage adjustment based on renal function, alerts about possible conversion from intravenous to oral treatment and potential drug-drug interactions, CDSS improved the compliance with guidelines and ensured optimal antibiotic treatment (101, 102). However, systems which provide excessive, irrelevant, and disruptive alerts have also given rise to clinicians' ignoring or overriding system alerts.

An important feature of CDSS requires clinicians to provide justification for the selection and duration of specific antimicrobial agents thus allowing them to reconsider and improve therapeutic decisions where required. Electronic approval functionality in CDSS augments ASPs by improving the collaboration of, and communication between, healthcare units, microbiology services and infectious disease specialists. A CDSS system deployed in an Australian study required approved indications before restricted antimicrobials could be prescribed (96). The system also established an effective feedback and audit process by involving infectious disease specialists in decision-making processes and provided feedback at the point-of-care. The study indicated that in the CDSS post-implementation period, there were reduced numbers of late-generation antimicrobial agents (fluoroquinolones, aminoglycosides, cephalosporins and carbapenems) prescribed (96). Similarly, another web based CDSS system with electronic approval functionality implemented at multiple sites (public and private hospitals) reported a decrease in inappropriate antimicrobial prescriptions, with a subsequent improvement in local resistance patterns and increased compliance with prescribing guidelines (103).

While many studies identified the positive impact of CDSS on overall antibiotic use and compliance with clinical guidelines, there are some conflicting results as well. For instance, in a recent cluster randomised controlled trial conducted across 33 primary care practices, no significant support was found for a CDSS impact on antibiotic prescribing. The authors argued that a less than optimal adoption rate (<10%) across different study sites might be a contributing factor in observing no effect (104). Similarly, the majority of evidence on CDSS impact is focused on improvement in clinical practices, such as increased compliance with guidelines and reduced consumption of antibiotics, but it is still unclear how these changes impact patient outcomes such as infection and resistance rate and mortality. Carracedo-Martinez et al. indicated that lack of evidence on CDSS impact on overall patient health is due to the dilution of effect by other factors such as CDSS adoption rate (99). Therefore, the positive impact identified in studies might be difficult to translate into 'real world' clinical practice due to limited adoption by clinicians. This suggests that although evidence of CDSS impact on quality and quantity of antibiotic prescription is encouraging, there is still a need for large clinical trials to assess the long-term CDSS impact on patient health and clinical outcomes such as morbidity and mortality.

The collaboration and communication functionality of CDSS can also help in surveillance and prevention of infection. Communication and data exchange between healthcare services, pharmacies and diagnostic laboratories enable all relevant information to be collated in one platform prescribing in a manner that accounts for diagnostic and susceptibility test results and optimal dosage and frequency selection (95, 105). However, functionalities and benefits of CDSS are, as always, dependent on the successful adoption of these systems in a clinical workforce. CDSS can only improve healthcare decisions when clinicians are willing to monitor and consider different recommendations and alerts provided by the system. Several studies have established that complex decision-making using recommendations and information provided by CDSS requires effective integration of the system into the clinical workflow (8, 106-108). Despite increasing innovation and capabilities of systems such as CDSS, these successes are often isolated due to poor clinical adoption and adherence to system recommendations (18). There is also a lack of understanding whether CDSS are unable to provide long-term benefits as the research to date has been limited to understanding system performance in a controlled environment. Therefore, the focus of this thesis is to understand the challenges and opportunities for sustainable implementation of CDSS in real world settings and to identify factors that can improve their use as a tool for effective antimicrobial stewardship.

2.3.1.1.1 In Australia

The implementation of CDSS specifically for antibiotic management in Australia is still in its early stages. There are only a few Australian studies that assess the efficacy of CDSS in reducing excessive and inappropriate antibiotic prescribing. The results from these studies are quite varied making it difficult to determine the value of CDSS for improving antibiotic management. One of the studies deployed a CDSS in 12 Australian hospitals as an ASP intervention (96). The CDSS showed promising results in reducing the overall use of restricted antimicrobials including third-generation cephalosporins, fluoroquinolones, carbapenems and macrolides whereas antimicrobials such as benzylpenicillin and aminopenicillins showed improved levels of use. Implementation of CDSS also resulted in reduced rates of healthcare-associated *Clostridium difficile* infection (HCA-CDI) (96). Similarly, Thursky and Mahemoff also observed that CDSS implementation can reduce the use of broad-spectrum antibiotics. There was a significant reduction in the prescribed courses of third-generation cephalosporins, vancomycin and carbapenems after the implementation of CDSS without any increase in antibiotic susceptibility mismatches (109). Along with the optimal selection of antimicrobial agents, many CDSS provide post-prescription review function for antimicrobial therapies. Through prospective feedback and audit, systems provide alerts for de-escalation or discontinuation of treatment specifically for empirical antimicrobial therapy (101, 110).

There were, however, conflicting results reported regarding CDSS impact on antibiotic prescribing. A study conducted to assess the CDSS efficacy for community-acquired pneumonia (CAP) identified no significant impact of CDSS on antibiotic therapy. The study observed that CDSS implementation did not reduce the use of broad-spectrum antibiotics specifically for CAP. However, this might be related to the fact that the rate of broad-spectrum antibiotic use for CAP was already lower in the pre-CDSS period (12.7%), therefore, no significant effect was observed in the post-implementation period (111). Similarly, Baysari et al identified no significant difference in the appropriateness of antimicrobial prescribing and compliance to the antibiotic prescription policy during pre and post periods of CDSS implementation. Researchers identified that one of the contributing factors for the lack of effect was limited CDSS uptake due to misalignment of the system with the clinical workflow. In this study, clinicians reported intentionally recording incorrect indications in the system to avoid or bypass the approval pathway of the CDSS. The system provided excessive alerts which clinicians overrode or ignored without validation or verification in order to save time (112).

Trevena *et al.* further argued that the use of different forms of CDSS available to clinicians both in hospitals and primary care in Australia is mostly ad hoc and not well studied (113). Different systems with varied functionalities and quality make it difficult to understand the underlying factors that

determine the success and failure of CDSS as well as their impact on workflow and overall quality of care.

2.3.2 CDSS Uptake in Healthcare

Despite the potential benefits of CDSS for evidence-based decision making and ASPs (section 2.3.1.1), studies indicate that provision of the system is not sufficient for successful and effective adoption (114-116). There are inconsistencies in the literature regarding the practical merit of CDSS in care settings likely due to limitations in uptake and utilisation (18, 115). For instance, a study conducted by Simon *et al.* (117) indicated that despite significant financial incentives provided by the US Government's Health and Medicare Act, only 40% of healthcare institutions in the US had implemented CDSS by 2017. Similarly, a national survey conducted in Dutch hospitals identified the implementation rate of CDSS to be as low as 48%, whereas in Canada, 63% of healthcare practitioners indicated using some form of CDSS (18, 118).

The CDSS effectiveness appears partly dependent on users' perceptions regarding the time and effort required to interact with the systems (119). System alerts regarding guideline recommendations or adverse events can improve the decision-making process, but excessive alerts increase the risk of cognitive overload and workflow disruption (86, 120). Payne *et al.* (121) identified that 69% of alerts related to adverse drug reactions and drug allergies were usually ignored by physicians, while 88% of drug-interaction reminders and alerts were ignored or overridden. Similarly, the rate of over-riding CDSS alerts in primary care was identified to be 91% for drug allergy and 89% for drug interaction alerts (86, 122). Specifically, for antibiotic management, studies indicate that only 25 – 36% of the provided alerts are actionable and have any impact on antibiotic prescribing. Hermsen *et al*. estimated that clinicians spent significant time (approximately 2 -3 hours each day) on non-actionable alerts related to antibiotic management majority of which were redundant and dismissed previously (123-125). In another study, it was identified that on average clinicians encounter 56 alerts per day with approximately 11 alerts for each patient, thus requiring a significant clinicians' time and effort during their clinical workflow (126). As a result, clinicians ignore or disable the alerts due to clinical irrelevance and time required to find actionable information in these excessive alerts. This suggests that despite the availability of clinically significant information at point of care, adoption can be limited in healthcare settings and that this undermines the potential value of CDSS (127).

Lack of fit between context and information leads to reduced relevance of CDSS recommendations contributing to limited adoption and usability (128). A study conducted by Shah *et al.* (129) indicated

that after reducing the disruption in the workflow, the acceptance rate of CDSS alerts improved with 67% of alerts accepted without any modifications by clinicians whereas only 33% were overridden. In this study, disruptive alerts were defined as those which required a certain action before the prescription was approved. The authors argued that reducing the workflow disruptiveness and limiting the information presented according to context and relevance can improve the specificity and acceptance of CDSS alerts (129). Each healthcare setting differs considerably, for example, intensive care units (ICU) have different requirements than other in-patient or out-patient settings. Therefore, recommendations provided by CDSS for in-patient or out-patients may not be relevant for critical and vulnerable patients in ICU. Failure to consider contextual differences may negatively impact CDSS uptake across different healthcare settings (86, 130).

Inadequacies concerning the incorporation of a comprehensive knowledge-base which is actionable and interoperable in different clinical environments, also presents challenges to successful CDSS adoption (131). In many cases, different organisations have developed their own respective clinical libraries for clinical data and patients health records which can be difficult to maintain and update (132). Despite the sophisticated algorithm and architecture of CDSS, transfer and maintenance of these libraries from one system to another is complex and, in many cases, impossible (133). Therefore, implementing CDSS is usually dealt at the site-level making interoperability with other digital systems quite difficult (134). However, considerable progress has been made recently as standards have been developed for documentation and information transfer between systems. Common terminologies and definition have been created such as the Systematized Nomenclature of Medicine (SNOMED), International Classification of Diseases (ICD-9-CM/10), drug names (RxNorm) and Current Procedural Terminology (CPT). These standards support the effective translation of CPGs into a computer-interpretable format that allows interoperability across diverse clinical information systems (135, 136).

The quality of the human-computer interface (HCI) has also been also a critical factor in determining the adoption and uptake of CDSS. Prior studies established that the quality and quantity of human interaction with the CDSS is governed by the "5 right rule" which emphasises the provision of "right information to the right person in the right format through the right channel at the right time" (134, 137). It is the availability of context-specific information in a concise format that enables clinically valuable interpretations. Miller *et al.* (138) further identified that the provision, presentation and placement of information is important when determining the quality of HCI. When the presentation and display of the information is ineffective, the potential benefits of alerts provided by the system remain untapped. A meta-synthesis conducted to assess the CDSS use highlighted that despite

evidence acknowledging the important role of human factors in determining the acceptance of alerts or recommendations provided by the CDSS, there is limited understanding of how to present information in a way that positively impacts the clinical utility of the system (134). The basic purpose of CDSS alerts is to ensure that the decision-making is criterion based and well rooted in the current evidence, but workflow disruptions and cognitive overload may undermine the efficacy of alerts. (18, 139, 140).

Healthcare settings comprise complex networks of interconnected technical, cultural, and clinical factors placed within a broader societal environment (133, 141). Therefore, implementation of health information technology (HIT) systems, like CDSS, is not just a technical process but involves a multi-dimensional and complex change process. Evidence shows that even high-quality and technically very sound systems fail to perform to their anticipated potential when implemented in the 'real world' (18, 116, 141). The barriers to uptake and utilisation of CDSS are not limited to system design but extend within a sociotechnical paradigm (Figure 2.2) characterised by the complex interaction of people, process, and technology. In this way, all the following factors come into play: governance, infrastructure, resource availability, clinical culture, clinicians' attitudes and acceptance, and workflow considerations (86, 142, 143).

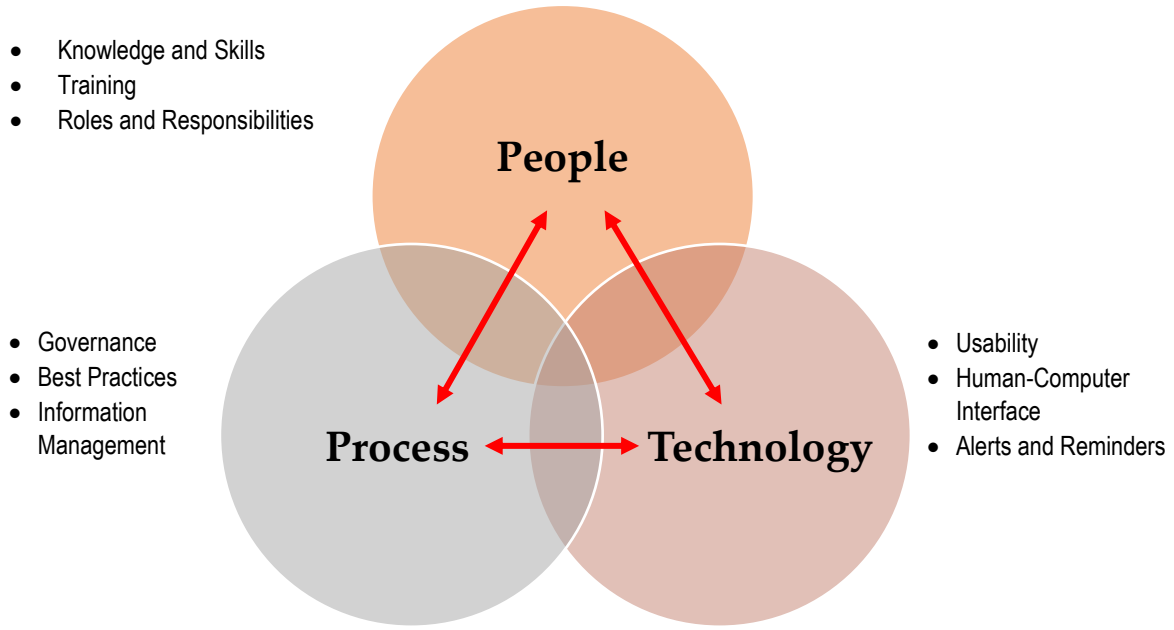


Figure 2.2 Sociotechnical paradigm in CDSS context (86).

Different studies have proposed and utilised a range of theoretical models and frameworks to understand the underlying sociotechnical factors impacting the adoption and use of HIT including CDSS in healthcare settings (114, 116, 133, 144). These theoretical frameworks aim to explain the

users' technology acceptance and uptake behaviour based on different contextual, social, and technology factors. The Unified Theory of Acceptance and Use of Technology (UTAUT) model has been extensively used due to its ability to integrate the key elements of other technology acceptance models (TAMs) in a single framework to explain behavioural variation in the adoption of technology (145, 146). To understand the barriers and opportunities for sustainable CDSS implementation, UTAUT (discussed further in subsequent section 3.7.1) has been adopted as the basic theoretical framework in this thesis to identify the different sociotechnical drivers of CDSS adoption and use. It provides a comprehensive framework to understand the interaction between different individual, organisational and technical factors in determining the feasibility of CDSS for evidence-based decision making in healthcare.

2.3.3 CDSS Uptake in Australia

The Australian Commission on Safety and Quality in Health Care (ACSHQC) highlighted that one of the basic strategies for ensuring medication safety lies in the provision of up-to-date and relevant information to healthcare professionals through electronic medication management (EMM) and decision support tools for healthcare professionals (62). This can be achieved by maintaining a current and relevant evidence-base that is consistent with the organisations' work practices and integrating it into the organisational electronic system.

Under the umbrella of ACSHQC and the Australian Digital Health Agency (ADHA), state governments and healthcare organisations in Australia have initiated different projects to implement CDSS for improved safety and quality of care. In recent years, there has been a significant increase in implementation of electronic health records (EHR) across public and private healthcare organisations to electronically record patient test results, medication history, drug allergies, and medications, and to create order sets and discharge summaries (113). Many of these systems also provide, to varying levels, data analytic capabilities to analyse patient data and help professionals make informed decisions about antibiotic prescribing. ADHA and Standards Australia have worked together to introduce projects with the objective of improving the digital capabilities of healthcare organisations and increase the availability of CDSS for evidence-based decision making. An initiative introduced at the national level was Rapid Integration Projects (RIP). These emphasised the need of standardised documentation, particularly discharge summaries, which can be integrated and shared across EHRs (147, 148). Similarly, the use of unique patient and individual healthcare identifiers to improve communication and data sharing between different EHRs was promoted to ensure interoperability across systems. A standards-based CDSS was promoted nationally in primary care

to ensure coordinated care across practices and jurisdictions (113). Along with these initiatives, several proprietary CDSS in numerous formats and versions, are also available for healthcare organisations, making data standardisation and communication between different systems challenging. For addressing this challenge, Standards Australia established a HL7 Version 3 Standard: Clinical Decision Support; Virtual Medical Record (vMR) to specify the data representation relevant to clinical practice in CDSS. This standard ensures easy and simple data representation for CDSS to ensure interoperability across different systems.

Despite these efforts, the CDSS available in Australia vary in terms of their quality, design, and the way they are implemented or utilised in healthcare organisations. A study conducted by Robertson *et al*. (149) evaluated seven different CDSS implemented in primary care and identified limited compliance with standards in many of the systems, further increasing the risk of medication errors due to limited linkage with the current and relevant evidence-base. In those systems evaluated, 25% of the CDSS features were partially implemented, whereas 15-40% of the system functionalities were not implemented at all. In the absence of a broader policy on CDSS, the majority of systems are developed, acquired, and implemented on an ad hoc basis and their overall impact on clinical decision making is not well understood (113, 150). There is a lack of comprehensive information on what kind of CDSS are being used or how frequently these systems are being consulted by healthcare practitioners in Australia. Moreover, third-party products or add-ons to the existing systems pose a serious risk for their applicability and interoperability across systems.

There are several digital maturity models utilised in Australia to assess the capacity of health organisational structures and systems to implement and sustain digital systems. One of the most common and internationally accredited models is the HIMSS EMR adoption model. This model comprises of seven phases to evaluate organisational progress from converting paper charts to EHRs and establishing data analytics to provide decision support. As discussed in the previous chapter (section 1.1), only two hospitals in Australia have achieved the higher stages of digital maturity (stage 6 and 7) in this model through establishing an advanced EMR and a digital environment. A report published by Trevena *et al.* (113) indicated that the progress of digitalisation in Australia is lagging in comparison to many similar countries such as the United Kingdom (UK) due to a lack of a framework for the dissemination of high-quality evidence-based decision support systems.

2.4 Research Gap

In summary, this chapter provided an overview of the literature concerned with the CDSS implementation for antibiotic management and the impact of technical, individual, and organisational factors on uptake of the system in healthcare settings. Most of the evidence on this topic comes from

studies conducted in the USA and UK and provides insight into the CDSS implementation from the perspective of their healthcare systems. However, in Australia there is very little evidence on how systems such as CDSS can effectively be implemented for evidence-based antibiotic management across technological, health and social boundaries. As indicated in section 2.3.3, a variety of strategies have been introduced by different jurisdictions and healthcare organisations in Australia to facilitate successful CDSS adoption. Despite this, only a minority of healthcare practitioners access recommendations and alerts provided by CDSS for appropriate antibiotic management (113, 149). It is not clear what explains this limited adoption of CDSS in Australia. For instance, it could reflect poor integration of these systems within the clinical workflow, a limited professional demand for the systems, perceptions of the CDSS recommendation being of unclear benefits, or a lack of understanding of how to effectively implement the system.

The increasing interest in implementing and utilising tools such as CDSS is reflected in Australian Government initiatives to introduce these systems. It is acknowledged that CDSS have the capability to address economic and clinical challenges presented by excessive and inappropriate antibiotic prescribing. However, ad hoc implementation of CDSS and lack of a broader strategy for standardisation has limited the ability of Australian health care jurisdictions and organisations to deploy these systems effectively to enable collaborative and coordinated care. Many systems that have provided proof of concept at a limited scale are unable to provide anticipated benefits at a larger scale due to the lack of an effective implementation plan. Greenhalgh *et al*. (22) argued that the inability to translate pilot programs to a system-wide service is usually the result of lack of guidance on the potential sociotechnical drivers of change. Therefore, there is a need to develop a system-wide implementation policy like that seen in countries similar to Australia (151), which considers the organisational structure, workflows and end-user behaviours and aligns these with the objective of ensuring evidence-based decision making.

In this context, the research presented in this thesis (Chapter 4-7) addresses these research gaps and focuses on two basic aspects. Firstly, the existing evidence from studies on the impact of CDSS on antibiotic management has been synthesised in a novel way, contributing to the growing body of evidence. Secondly, through new empirical research, a comprehensive picture is painted of the different individual, organisational and system-level challenges facing the effective implementation of CDSS for antibiotic management in Australia.

Chapter 3: Study Design and Methods

3.1 Rationale

Previous studies have shown that CDSS can improve the quality of care, reduced medication errors and increased adherence to prescribing guidelines (14, 18, 152, 153). Despite this, CDSS implementation in different care settings and adoption by the clinical workforce is limited (21, 115). Even with the increasing trend of embedding health information technology (HIT) tools into clinical workflows, it is not clear how CDSS can be optimally developed and deployed to ensure maximum end-user adoption and uptake. Existing literature on the effectiveness of CDSS in Australia is limited with the contextual feasibility of these systems yet to be determined. There is also a lack of research evidence concerning challenges faced at different levels of implementation including at the macro (policymakers), meso (organisational) and micro levels (clinical practices). There exists a gap between available evidence on the efficacy of these systems and actual use in healthcare settings. Thus, it is timely to assess the practicality of CDSS within the Australian healthcare context, and to investigate the role of CDSS in translating evidence-based knowledge into best-practice antibiotic management. Moreover, an understanding of the different factors that influence the adoption and sustainable use of CDSS in healthcare is required. Ad hoc development and dissemination of CDSS in Australia highlights the need for system-wide guidance and implementation policy. Thus, it is necessary to identify gaps in implementation practices to help inform the national e-health implementation strategy (154, 155). The specific aims and objectives of this research are discussed below.

3.2 Aim

The aim of this research is to determine the feasibility of CDSS for evidence-based antibiotic management, and to identify the challenges and opportunities for sustainable implementation of CDSS in different healthcare settings.

3.3 Objectives

The objectives of this research are to:

a. Evaluate the effectiveness of CDSS for optimal antibiotic management

    - Assess the impact of CDSS on clinical and economic outcomes that are markers for the effectiveness of antimicrobial stewardship programs.

b. Determine factors that influence CDSS uptake for antibiotic prescribing in different care settings

- Identify the perceptions and attitudes of Australian healthcare practitioners concerning the utilisation of CDSS for antibiotic management
- Identify different factors that moderate clinicians' perceptions regarding CDSS adoption in healthcare in Australia.

c. Identify barriers to appropriate antibiotic prescribing in different healthcare settings.

d. Investigate the challenges and opportunities for implementing CDSS at scale in Australia

3.4 Research Questions

i. Can CDSS enable evidence-based antibiotic management to reduce the risk of inappropriate prescribing?

ii. What factors need to be considered to ensure successful CDSS adoption in different care settings?

- What factors moderate clinicians' perceptions about CDSS adoption?
- Is there an association between individual characteristics and care settings factors and CDSS adoption?

iii. How do individual and setting-specific characteristics impact appropriate antibiotic prescribing?

iv. What are the different challenges and opportunities for system-wide implementation of CDSS?

3.5 Study Framework

This section provides the framework anchoring the studies conducted for this research. Different data sources were used to address the proposed research questions and objectives. This approach enabled a detailed and comprehensive investigation of the research problem from individual, organisational and system perspectives. Figure 3.1 illustrates the framework and individual studies that were conducted as a part of this research and the respective methodologies that were used to address the corresponding research questions.

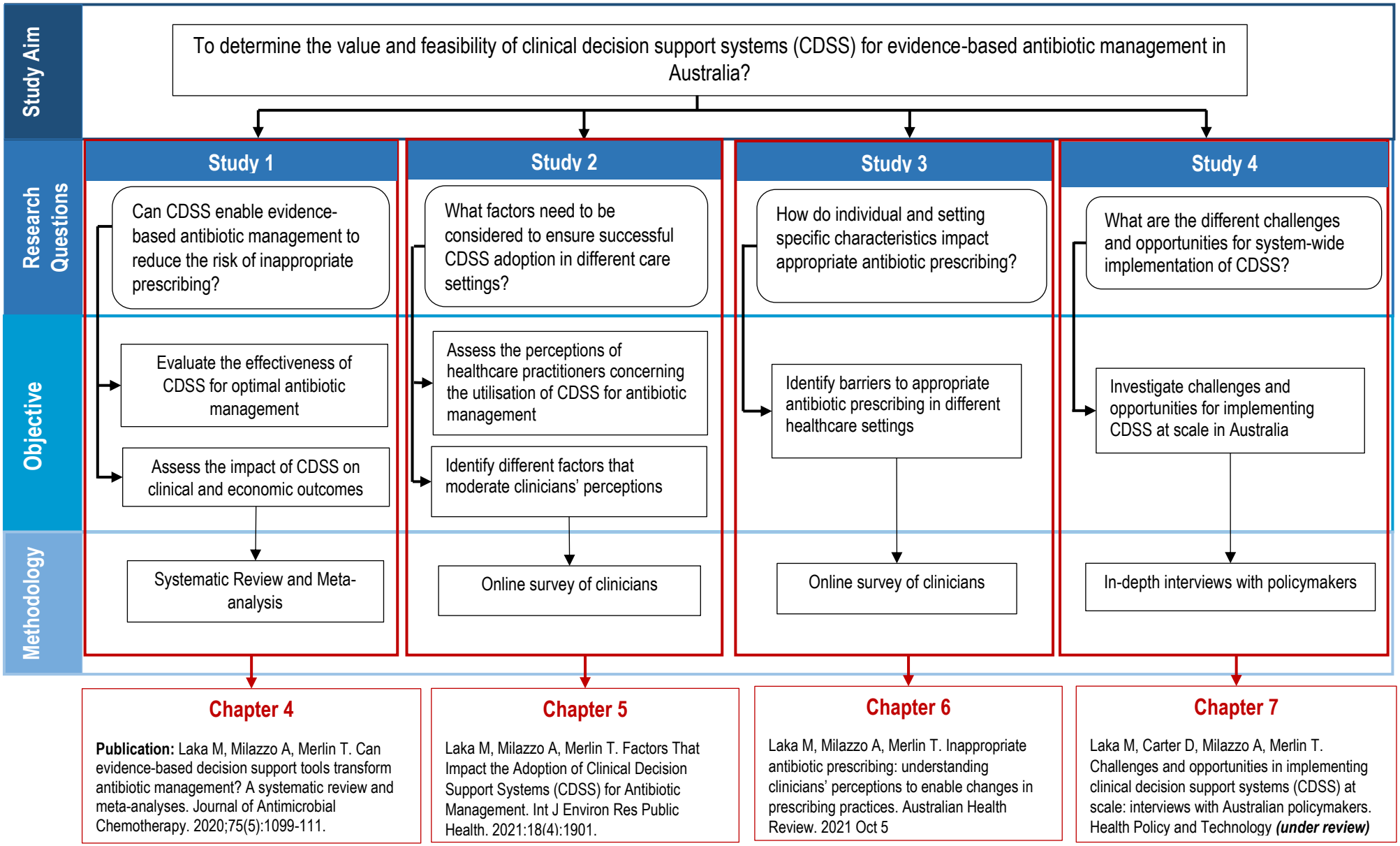


Figure 3.1 Framework of the thesis aim, research questions and objectives.

As indicated in Figure 3.1, study 1 (section 3.6) was an evaluation of CDSS effectiveness for increasing compliance with guidelines and promoting optimal antibiotic management. This involved identifying the impact of CDSS on clinical and economic outcomes defined as quality measures of antibiotic stewardship interventions. The results of this study suggested that there was a need to assess the underlying factors that limits the uptake and use of CDSS in healthcare settings. Study 2 and 3 (section 3.7) comprised a cross-sectional online survey with clinicians to identify the factors that influence antibiotic prescribing patterns and CDSS adoption and use across different care settings in Australia. The findings suggested that that there is a lack of comprehensive policy to govern the broader implementation of CDSS in the Australian healthcare system, specifically as it relates to communication from individual-to-individual, individual-to-machine, and machine-to-machine. This encompasses variation in how different individual and organisations relate to the CDSS as well as how different systems interact with each other for successful CDSS implementation at a broader scale. Thus, study 4 (section 3.8) of this research investigated the significant gaps and opportunities for system-wide implementation of CDSS through in-depth interviews with key policymakers. Overall, all the studies (study 1-4) were conducted sequentially where outcomes of one study informed the research design of the subsequent studies. Finally, the findings of all studies were considered together (Chapter 8) to indicate different challenges facing CDSS use for the evidence-based antibiotic management.

Previous studies have established CDSS as a sociotechnical system, thus, it required understanding the implementation from different viewpoints to consider the interaction of technology with people, clinical processes, and health systems. The CDSS implementation is a dynamic process as clinical workflows, technology, and perceptions and skills of end-users continue to evolve. For this purpose, mixed-method has been adopted as a research approach in this project to provide a panoramic view of challenges and gaps in CDSS implementation (156, 157). This approach enabled synergistic use of both quantitative and qualitative data to understand varied perspectives and relationships between different aspects of CDSS implementation. The quantitative data collection and analysis methods allowed to evaluate the magnitude and the direction of the CDSS effect on antibiotic management and assess the association of different individual and organisational factors on CDSS adoption. The qualitative data were collected to have an in-depth understanding of stakeholders' experiences and challenges in implementing CDSS. This provided the opportunity to understand the implementation as a multi-dimensional process and answer research questions more deeply.

3.6 Impact of CDSS on Antibiotic Management

To investigate the effectiveness of CDSS as a tool to optimise antibiotic management in different care settings, a systematic review and meta-analysis was conducted in the study 1 of this research. The focus of this study was to evaluate the existing evidence on the ability of CDSS to reduce inappropriate antibiotic prescribing by increasing adherence with antibiotic prescription guidelines. Systematic review was the preferred research design for this study as it minimises the risk of selection bias due to a detailed and specific search strategy to include and synthesise all the relevant evidence on the research topic (158). Quality assessment enabled analysis of the validity and methodological certainty of the included evidence. A meta-analysis was also conducted to quantitatively synthesise and pool the findings from individual studies into a single measure to determine CDSS effectiveness. This included estimating the overall effect of the CDSS on the study outcomes (section 3.6.1.1) and exploring the heterogeneity in the results.

Few previous systematic review studies (14, 91, 159) focus on the effect of digital interventions on antibiotic management. However, due to the limitations in the scope, design, and definitions of CDSS used, these studies did not provide a focused evaluation of CDSS for antibiotic management. Also, these studies failed to adequately consider different prescribing patterns in different care settings such as hospital and primary care. It is not clear whether evidence established in specific care settings such as hospitals can be translated into primary care settings (160). Therefore, this review focused on a comparative analysis of CDSS efficacy in hospital and primary care settings. The overview of the methodology used in this study is provided in the section below without repeating the information already provided in the study manuscript (161) (Chapter 4).

3.6.1 Systematic Review

A detailed review protocol was developed for the systematic review using the Preferred Reporting of Items in Systematic Reviews and Meta-analyses (PRISMA) – Protocol (PRISMA-P) checklist (162).

3.6.1.1 Study Eligibility Criteria

The studies were selected based on pre-selected inclusion criteria aligned with the study's PICO question. These detailed criteria are provided in the paper by Laka, Milazzo, Merlin (161) which is included in chapter 4. The outcomes selected for the review are mentioned below.

3.6.1.2 Study Outcomes

The outcomes of this study were based on the standard quality metrics of antimicrobial stewardship that have been reported in previous studies (163-166).

The primary outcome concerned the overall appropriateness of the antibiotic therapy prescribed. This definition generally encompasses selection of the right agent, dosage, and route for an appropriate duration after considering all the potential allergies, toxicities and local resistance patterns (164, 167). Although it has been identified as an ideal outcome to measure the quality of antimicrobial treatment, due to its subjective nature, there is a lack of standard and a widely accepted measuring unit to quantify the appropriateness of therapy. Therefore, in this study, it was defined as the extent to which the prescribed treatment was evidence-based by complying with antibiotic prescription guidelines or in vitro susceptibility test results.

Secondary outcomes of this study comprised different clinical and economic measures to identify the impact of the intervention on the overall quality of antibiotic treatment. These include:

- **Volume of use:** An underlying objective of ASPs is to minimise excessive and unnecessary antibiotic use; therefore, average consumption of antibiotics is one of the widely recognised measures to evaluate the quality of antibiotic therapy. This is usually measured as a ratio of defined daily dosage (DDD) to 1000 days present, or patient days where the numerator specifies the antibiotic consumption and the denominator represents time factor of patients at risk (163). According to the WHO definition DDD is the "average maintenance dose per day for a drug used for its main indication in adults"(164). Patient days refers to the total number of patients measured at a specific location at a given day, whereas days present are the number of days when any specific patient is present in a specific practice or unit on the basis of admission-transfer-discharge data (163, 166).
- **Length of hospital stay**: This is the overall length of a patient's stay in hospital measured in days. The data on this outcome was specifically reported for inpatients only.
- **Duration of antibiotic therapy**: Overall duration of antibiotic therapy measured in days assists in identifying the impact of CDSS in promoting the optimal duration of therapy recommended by guidelines. Some research highlights the need to focus on reducing the therapy period to a short but sufficient effective duration through use of an audit and feedback process (168, 169).
- **Mortality**: Includes 30-days all-cause and in-hospital mortality. It is one of the objective outcomes reported in different studies in hospital settings. It is usually reported not only as a

quality improvement measure but also as a safety measure to ensure that reduction in antibiotic prescriptions will not lead to elevated health risks.

- **Cost of therapy**: Different studies measured the cost of therapy to evaluate the economic impact of CDSS. It is measured and reported in different units such as cost of therapy per patient, annual cost of therapy, and total cost of hospitalisation.

3.6.1.3 Search Strategy

Different electronic bibliographic databases were searched for peer-reviewed literature. The search was conducted from database inception to August 2018 using a detailed search strategy. An updated search was also conducted in PubMed (including MEDLINE) from September 2018 to November 2018 to avoid the risk of missing any recent publications.

The search terms included both indexed (MeSH) terms and text words for CDSS and antibiotics. The list of search terms was established from keywords in the relevant literature. A variety of synonyms and relevant terms for CDSS such as 'expert system', 'management system' and 'approval system' were also included in the text word search as this is an emerging research area and it was anticipated that nomenclature might have varied over the period of time as well as from one country to another. The detailed search strategy is provided in Appendix A.1.

3.6.1.4 Study Selection

The study selection process follows the PRISMA flow diagram (170) which comprises the following stages:

Stage I: The abstracts of search hits from different bibliographic databases were exported into Endnote X8.

Stage II: Extraneous duplicate citations were removed from the endnote library.

Stage III: The studies were selected based on whether the study title and abstract potentially meets the pre-defined eligibility criteria (further information provided in Chapter 4). To validate the screening process, a double screening approach was employed in which a second reviewer (Tracy Merlin (TM)) reviewed 10% of the abstracts against the study selection criteria to avoid any systematic errors in study selection.

Stage IV: The full-text of all studies selected in the previous stage were again screened against the study inclusion/exclusion criteria to determine eligibility. The full-text was reviewed by a second reviewer

(TM) if the eligibility of any particular study was unclear. In case of any uncertainty regarding selection of a study, a decision was taken after discussion with TM and Adriana Milazzo (AM).

Stage V: Reference lists of the included studies were pearled to identify any potentially relevant study that might have been missed in the initial search. Studies identified through this process were again screened through Stages III & IV.

The PRISMA diagram illustrating the study selection process is available in Laka, Milazzo and Merlin (161) (Chapter 4).

3.6.1.5 Quality Assessment

The methodological certainty and quality in individual studies were assessed by two individual reviewers (ML and TM) using risk-of-bias tools. Any discordance regarding quality assessment was resolved by discussion with the third reviewer (AM). The scientific reliability of individual study findings is greatly dependent on the quality of study design, therefore, tools developed for specific study designs were used. For non-randomised studies, ROBINS-I (Risk of Bias in Non-randomised Studies - of Interventions) (171) was used for critical appraisal whereas randomised studies were assessed using the Cochrane Risk of Bias tool (158). Included studies were classified as having a low, medium, or high risk of bias.

The ROBINS-I tool consists of seven domains assessing non-randomised studies at different stages of the intervention. The first two domains, focusing on confounding and the selection of participants, address potential sources of bias in the study before the start of the intervention, whereas the third domain focuses on the classification of participants receiving the intervention. The last four domains identify different issues that can cause bias in the study after the start of the intervention such as deviation of method from the designed intervention, the measurement and selection of reporting results and missing values (171). The ROBINS-I risk of bias assessment of the non-randomised studies included in the systematic review is provided in Appendix A.2

The Cochrane Risk of bias tool is used for randomised controlled studies and assesses the quality of the study design. This includes participants' selection (including randomisation and allocation concealment), blinding of study participants and assessors, missing data and selective reporting. Besides these domains, studies were also assessed for other biases such as loss of clusters or different recruitment processes in different clusters in the cluster randomised trials, carry over effect in cross-over design and potential contamination of the intervention in the control groups.

Risk of bias across studies for different outcomes was recorded using the GRADEpro Guideline Development Tool. The tool uses GRADE (Grades of Recommendation, Assessment, Development and Evaluation) methodology to evaluate the certainty of the evidence on the basis of the precision and consistency of the findings and the risk of bias (172). Different domains considered by GRADE include risk of bias, inconsistency across studies, indirectness of the evidence, imprecision of results and publication bias.

3.6.1.6 Data Collection and Synthesis

For the data extraction from the included studies, a standardised extraction form (Microsoft Excel Spreadsheet) was created. This form was informed by Cochrane Collaboration guidelines for data collection in intervention reviews (173) and by the Joanna Briggs Institute reviewer's manual 2015 (174). Information relating to the following attributes was extracted for each of the included studies: author and year of publication, study design, setting of use, study methodology, type of intervention, comparator, outcome measured, sample size and main findings. Where required, additional comments were also included in the variable's fields, such as different units of measure for estimating outcomes in included studies. To pilot and validate the form, data were extracted from the sample of 20% of included studies. After verification from other reviewers (TM and AM), required modifications were made such as including unit of measure as a separate variable. The results of the systematic review were reported using the PRISMA checklist for systematic reviews (APPENDIX A.3). The full summary of findings (SoF) table is available in the supplementary data of the paper by Laka, Milazzo and Merlin (161) (Chapter 4).

To estimate the intervention's effect on the pre-selected outcomes, data from the included studies were extracted. For the dichotomous variables, such as appropriateness of therapy and mortality, pooled odds ratios (OR) [and 95% confidence interval (CI)] were computed, whereas for other continuous variables such as volume of use, length of hospital stay, duration of therapy and cost of therapy standardised mean differences (SMD) were calculated. The approximation method proposed by Luo *et al*. (175) was utilised to estimate sample mean and variance when these data were not available, but rather the data was in the form of a sample median, range or interquartile range and sample size. This method provides improved estimators as compared to the previously proposed methods by Hozo *et al*. (176) and Wan *et al*. (177) by incorporating study weightage as a sample size function. The study weight in estimation method not only addresses the limitation of using insufficient information provided by sample size but also provides optimal approximation of the sample mean and error measures.

The SMD was calculated as Cohen's *d:*

$$d = \frac{\bar{X}_1 - \bar{X}_2}{S_{within}}$$

where $\bar{X}_1$ and $\bar{X}_2$ are the sample means of CDSS and non-CDSS groups and S_{within} is the pooled standard-deviation (within groups) of the outcome. However, for smaller samples the measure *d* is associated with overestimation of the absolute effect, leading to a biased estimate. Therefore, Hedges (1981) introduced a correction factor J for calculation of an unbiased estimate of the SMD.

3.6.2 Meta-analysis

CDSS efficacy was estimated by pooling the data on the pre-specified outcomes from the included studies. To account for different sources of sampling variability including both within-study and between-study variance, random effect models following the methods of DerSimonian and Laird were used to calculate pooled effect estimates (odds ratios OR) and 95% confidence intervals. The within-study variance represents variability in studies due to the internal sampling procedure, whereas between-study variance reflects differential effect size in the included studies due to different factors such as different patient populations, their characteristics, nature and implementation of interventions and other study characteristics. Further details are available in the paper by Laka, Milazzo and Merlin (161) (Chapter 4).

Underreporting of relevant trials with either positive or negative results greatly undermines the validity of a meta-analysis. Similarly, studies with statistically significant results are more likely to get published, thus resulting in publication bias which leads to subjective and biased conclusions in systematic reviews and meta-analyses (178, 179). The funnel-plot graphical method was utilised to assess the impact of potential publication bias on the study effect estimates (180). The funnel-plot represents a scatter plot with study effect estimates (log OR) plotted on the horizontal axis against the precision of log OR on the vertical axis for the included studies. An asymmetry or skewness in the funnel-plot indicates that publication bias has the potential to affect the pooled results. As there is a certain degree of subjectivity in interpretation of graphical results, Egger's regression test was also carried out (181). It performs a linear regression of the effect estimate against the measure of study precision (standard error). However, to ensure that pooled estimates are not affected by small sample size, this test performs a weighted regression where the weights taken are the inverse of the variance of the effect estimates. The intercept of zero in this test represents the absence of any publication bias. To compensate for the low power of this test when there are a limited number of studies (180), the significance level of 10% (p value <0.1) was used.

3.6.2.1 Sub-group Analysis

In the first stage of the meta-analysis, the main effect of CDSS on study outcomes was estimated, however, in the second phase, pre-specified sub-group analysis was completed to determine whether the summary estimates differed by the type of CDSS systems and by type of study design. As the search strategy did not specify particular types of CDSS (diagnostic, approval or alerting systems), all types of CDSS which fulfil the definition used in this study were included (available from Laka, Milazzo and Merlin (161) - Chapter 4). As the CDSS impact may differ depending on the feature and functional design of different types of systems, included studies were grouped based on the functional scope of the system and characteristics of platforms providing the decision support. This study used the classification of CDSS specified in a previous study (110).

Similarly, the observed effect can also vary depending on the type of study designs used and resulting biases. Therefore, through sub-group analysis, variation in the summary estimates due to different study designs was also investigated. The details of different sub-groups are provided in Table 3.1.

Table 3.1 Categories of Sub-group Analysis

Criteria	**Sub-groups**
	Types of CDSS
Functional Domains	• Prescribing • Dosage optimisation • Alerts and physician feedback
Platforms	• Web-based • Stand-alone application/software • CDSS integrated into existing electronic medical record (EMR) system or computerised physician order entry
	Study Design
Randomisation	• Randomised controlled trials (RCTs) • Non-randomised studies (NRS)
Interventional and Non-Interventional Studies	• Interventional studies were defined as: *Studies in which CDSS was implemented as an intervention ie guiding prescribing practice, and its performance was compared with standard care in the clinical setting.*
	• Non-interventional studies were defined as:

	CDSS was not implemented but patients' data were entered into the system prospectively or retrospectively in a simulation exercise. No changes were made in prescriptions based on the CDSS recommendations.

3.7 Perceived Barriers and Facilitators to CDSS Adoption

To address the second and third objectives of this project, a cross-sectional online survey was conducted. The overall aim of this survey was to determine the individual, and organisational factors that influence the adoption and use of CDSS for optimal antibiotic management. The first step was to gain clinicians' insight into different factors that limit appropriate antibiotic prescribing in different care settings. The second step was to assess clinicians' perception about the benefits of CDSS, in addressing these barriers to appropriate prescribing as well as to identify different factors that influence CDSS adoption in different care settings. The aim was to collate this information and identify the underlying factors that limit the acceptance of CDSS by healthcare practitioners.

3.7.1 Conceptual Framework

Due to the complex nature of the healthcare systems which can involve multiple autonomous units which might not interrelate easily, it is often difficult to introduce automation in the care process (182, 183). Over the last few decades, theoretical frameworks for understanding the uptake of digital health interventions have tended to shift away from viewing technology as a driver of social change to viewing uptake as shaped by dynamic and complex associations between the environment, individuals, and technology. The intention to adopt and use technology is dependent on a range of organisational, personal, social, and technical factors. Over the years, several models have used different social and behavioural approaches to explain users' behaviour relating to the adoption of technology. These models provide some conflicting and some overlapping elements in explaining the factors underlying technology adoption. Venkatesh *et al*. (146) established a comprehensive model called the 'Unified Theory of Acceptance and Use of Technology (UTAUT)' by integrating eight models, namely the Theory of Reasoned Action (TRA), the Technology Acceptance Model (TAM), the Theory of Planned Behaviour (TPB), combined TAM-TPB, the Social Cognitive Theory, the Motivational Model, the Innovation Diffusion Theory and the personal computer (PC) utilisation model. The unification of these models in UTAUT provided a flexible theoretical framework to investigate multi-dimensional determinants of technology adoption.

As the second objective of my research was to understand the different factors (individual and organisational) that influence CDSS adoption, therefore, UTAUT was adopted to provide the comprehensive understanding of the potential modifying factors. The UTAUT model is based on four basic constructs, namely effort expectancy (EE), performance expectance (PE), social influence (SI) and facilitating environment (FE). The first three constructs shape behavioural intention which in the presence of a facilitating environment leads to use of the technology. The UTAUT model is provided in Figure 3.2.

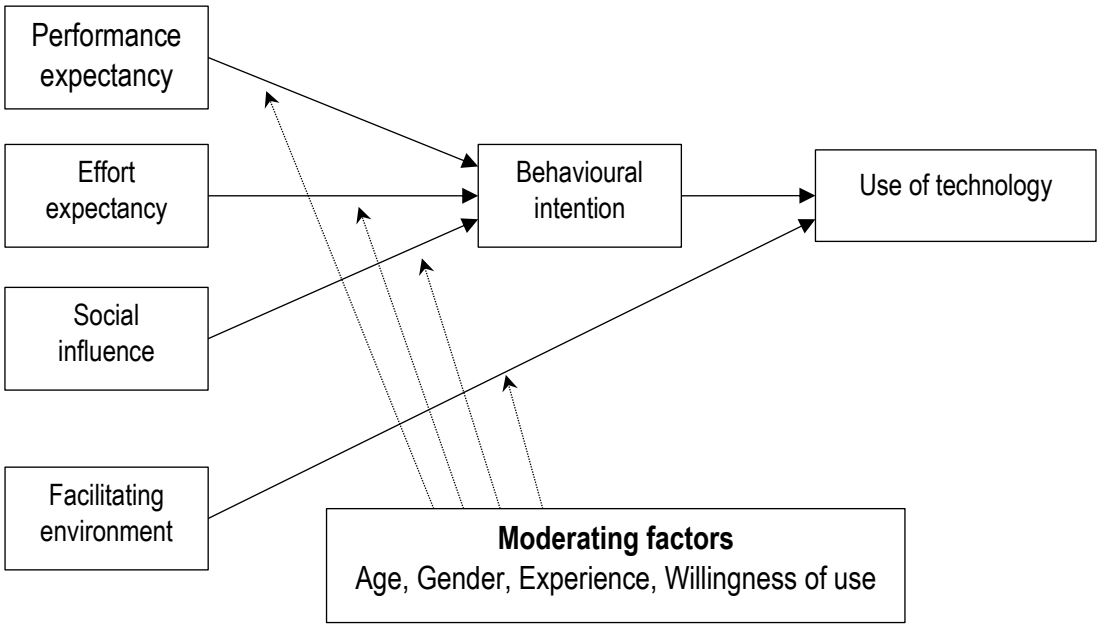


Figure 3.2 Unified Theory of Acceptance and Use of Technology (146)

The UTAUT model considers the characteristics of end-users, including age, gender, experience, and willingness to use technology in predicting the behavioural intention of users. These factors moderate the association between the outcome variable (behavioural intention) and constructs of this model (EE, PE, SI, and FE). For example, Venkatesh *et al*. (146) emphasised that the key associations of the model constructs and their impact on user's behaviour to adopt technology are shaped by these moderating factors. This was articulated as differences in beliefs, values and adaptation to a change in different individuals depending upon their gender, age or experience (184). For instance, some studies have identified that the impact of EE for use of technology was more significant in women (185, 186) whereas other studies suggested that younger users and those having experience of using the system might perceive technology differently from their older peers (187-189).

The main UTAUT conceptual framework used in this study is available from Laka, Milazzo, & Merlin (190) in Chapter 5. Using this framework, different determinants of CDSS adoption such as overall performance expectancy, effort expectancy, social influence and the facilitating environment were explored. Effort expectancy refers to the end-users perceptions regarding the degree of effort associated with the adoption and use of CDSS at the point-of-care (145, 146). It is related to overall ease of use which can positively impact the users' intentions to adopt the system. Performance expectancy is the perception of users regarding the systems' benefits for evidence-based antibiotic management (145, 191). It encompasses improvement in the quality of care as well as the job performance of users. The belief that CDSS can positively impact users' productivity and efficiency increases the likelihood of adoption. Social influence is based on a notion that an individual behaviour to adopt CDSS is a result of compliance or defiance to the social pressure regarding technology adoption. This construct represents individual's perceptions of how their peers will view their technology adoption behaviour (192). Finally, facilitating environment focus on the availability of organisational support and infrastructure for CDSS adoption and use (145, 146). It represents users' perceptions that organisations have appropriate structures and measures to support CDSS adoption and use in daily practice. The availability of technical support, end-users' training and a supportive organisational culture along with the behavioural intent of users can result in CDSS adoption (188).

The purpose of this study was to identify the clinicians' perception regarding different barriers to CDSS use in different care settings. To investigate the role of different individual and setting-specific characteristics in shaping these perceptions, we considered gender, age, clinical experience, care settings and CDSS use to assess if these factors moderate the effect of the key constructs discussed above. This can help understand if there is any variability in perceptions regarding CDSS use in different clinicians and to what extent these factors contribute to that variability.

3.7.2 Clinicians' Survey

The data collection and analysis method adopted for study II is provided in published article (190) (Chapter 5). To avoid any repetition of information, the subsequent section will provide a broad overview of the study design used to address the objective of identifying factors that influence the adoption of CDSS for antibiotic management in different care settings.

The objective of this study was to gain insight into individual perspectives and beliefs of a cohort of healthcare professionals regarding CDSS adoption, therefore, cross-sectional survey design was used. The online survey allowed to collect information in a short time from a representative sample to draw inference about this cohort. The survey questions were based on UTAUT framework to understand

clinicians' perception regarding different factors that can impact the CDSS adoption. The survey design is further discussed in the published article (190) (Chapter 5).

3.7.2.1 Sample size

As discussed above, the targeted population for this study was clinicians in Australia directly involved in antibiotic management in healthcare. This included general practitioners, physicians, and surgeons in primary care and hospital settings in order to compare their perceptions of CDSS adoption for antibiotic management. The sampling framework was established using information from the "Australian National Health Workforce Data Set: medical practitioners 2018" to ensure that the sample was representative of the Australian health workforce. This dataset comprises records of medical practitioners registered with the Australian Health Practitioner Regulation Agency (AHPRA). A sample of 350 clinicians from primary care and hospitals was estimated assuming a 5% margin of error, 95% confidence interval and power of 0.80, assuming the independent variable is distributed following a standard Normal distribution.

3.7.2.2 Participants and Recruitment

Engaging with healthcare practitioners in different care settings was important to address the second and third objectives of this study. Recruitment was assisted by relevant organisations – the Royal Australasian Colleges of General Practitioners (RACGP), Physicians (RACP) and Surgeons (RACS), the Rural Doctors Association of Australia (RDAA) and health networks in all states and territories. To streamline the recruitment process, we developed a project summary document (Appendix B.1) outlining the scope, objectives, and study design. The research governance offices for each organisation and network were then approached and asked to disseminate the study information and provide access to the online survey to clinicians in their respective networks. To maximise participation, different sub-committees and affiliated societies of these organisations were also approached. For example, we contacted regional committees, the Australian Faculty of Public Health Medicine (AFPHM) and Adult Medicine Division (AMD) in RACP, General Surgeons Australia, Australian Orthopaedic Association and RACGP Expert Committee – Quality Care (REC– QC), among many others. The notice (provided in appendix B.2) inviting potential participants and providing the online links to complete the survey was published in the relevant organizations' newsletters, social media accounts mailing lists, online portals, and websites.

All potential participants accessed the survey and related study information through an online survey engine link (designed in SurveyMonkey). For each specific care setting (primary care and hospitals), two separate anonymous and voluntary surveys were conducted from June to October 2019. The survey preamble outlined that completion and submission of survey results indicated the consent of

participants in the study. Moreover, participant information sheets providing details of the project and what was expected of the participants was also included in the preamble to the online survey (Appendix B.3).

The survey (Appendix B.4) consisted of four major sections with section I on participants' demographic characteristics. This section comprised five main questions with one additional question for hospital clinicians about their specialisation. Section II comprised four questions centred on challenges of appropriate antibiotic prescribing, and in section III three questions were centred around the availability of CDSS and the perceived impact of these systems on antibiotic management. The last section comprised three questions, including one open-ended question, and identified factors that influence the implementation of CDSS in different care settings.

3.7.2.3 Data Analysis

To analyse the relationship between factors influencing the adoption of CDSS by different individuals and type of setting, multivariate logistic regression analyses were used. Different outcome variables were derived from the responses to the questions in section II, III and IV of this survey.

The question regarding the barriers to appropriate antibiotic prescribing (section II) was provided in a multiple-response format. Therefore, dichotomous dependent variables were generated for each valid response to this question and coded as 1 if the response was selected and 0 if not selected.

Responses to questions concerning the perceived benefits, barriers, and facilitators for CDSS adoption in the survey (section III and section IV) were categorised using a 5-point Likert scale (strongly disagree – through to strongly agree). These responses were combined to generate dichotomous dependent variables ("Yes" and "No"). Strongly agree and agree responses were collapsed into "Yes" and coded as 1, and strongly disagree and disagree were combined into a "No" category and coded as 0. To identify only those participants who agreed with the provided statements, the neutral response of "Neither agree nor disagree" was collapsed into the "No" category which was then renamed as "No/unsure".

The survey included an open-ended question to obtain respondents' detailed comments on their concerns regarding CDSS adoption for antibiotic management. This qualitative data was analysed using content analysis. As the responses were brief, therefore, manifest content analysis was identified to be an appropriate analytical approach to gain a contextual understanding of the data. Manifest content analysis involves describing content that is explicit and easily observable in the data. Kondricki *et al*. (193) described manifest content analysis as "staying close to the text". It involves analysing and organising text into different categories that provide structure to the data and reflect a shared meaning. For the analysis of free-text comments using manifest content analysis, preliminary codes were

generated to focus on specific data characteristics. The preliminary or first-order codes provided overview of the data which were later collated into second order codes that provided better distinctions between and within cases (details provided in Appendix B6 and B7) (194). For instance, free-text comments related to lack of transparency regarding sources of information on which CDSS recommendations are based, and how often that information is updated, were separately coded as "Source of Information" and "Information Upgrade". Further analysis suggested that both of these codes relate to the overarching concept of reliability of the information, therefore, both codes were later collated into "information accuracy" code. It was ensured that all codes generated are not redundant and have clear boundaries. We also utilised data triangulation to compare the data themes with the results from the quantitative analysis to gain additional understanding of the responses.

3.7.2.4 Ethics Approval

The survey was approved by The University of Adelaide Human Research Ethics Committee (HREC) (H-2019-094) (Appendix B.5). Participation in this study was voluntary and no identifiable data were collected.

3.8 Opportunities and Challenges to CDSS Implementation

As discussed above, the survey study investigated individual and organisational factors that impact the CDSS adoption in health care settings. But to understand the CDSS implementation in totality, it is also important to consider system-level factors that influence the integration of these system in clinical practices. Implementation of any new health technology is expected to transform clinical processes, work structures, and individual and organisational practices. In the absence of appropriate planning, implementation and an evaluation framework, poorly implemented systems can cause more harm than benefit (195, 196). Along with the technical design of the system, there is a need to understand interactions of the CDSS with clinical practices and the broader healthcare system to ensure long-term, safe, and sustainable implementation for improved quality of care. The overall focus of this study (Chapter 7) was to assess the different challenges and opportunities for implementing CDSS into the healthcare system. Therefore, semi-structured in-depth interviews were conducted with policymakers to gain insights into what is required for successful CDSS implementation in the Australian healthcare system.

3.8.1 Interviews with Policymakers

A qualitative methodological framework using in-depth interviews was adopted to understand the processes, perspectives, and experiences of policymakers in implementing CDSS. The CDSS

implementation and use has been studied majorly from an intra-organisational perspective. However, the value of CDSS to improve the coordination of care in a healthcare system is dependent on how effectively it is integrated across different organisations. The complexity of a health system-wide rollout of CDSS which encompass and cross technological, social and organisational boundaries, is not well understood. Due to lack of this formalised knowledge and theoretical framework, we adopted an inductive approach, whereby data analysis was directed by the concepts and language of the study participants. The existing literature and previous studies in this thesis (Chapter 4-6) informed the content of initial interview schedule.

We adopted a naturalistic approach to establish an understanding of the research problem by considering the meaning and context of study participants (197). This means that a subjective analysis and interpretation can help in understanding the reality of the research problem. This approach is increasingly adopted in healthcare research as it considers context and perceptions and provides a rich description of the research problem (198, 199).

The method adopted for the in-depth interviews is given in manuscript in Chapter 7. For clarity, the following sections provides a detailed outline of the methods that are not provided in the manuscript compromising Chapter 7.

3.8.1.1 Sampling

Interview participants included different policymakers from national and state-based agencies and committees focusing on digital health in Australia. Participants were recruited purposively to include professionals who were directly involved in policy development, implementation, evaluation, or governance of CDSS in Australia. Considering the broad aim of the study, specificity of the study sample and the recruitment process was guided by the information power approach (200). Using this approach, we recruited participants who had shared experience and characteristics that were relevant to the area of research. Participation in the study did not involve remuneration and participants could withdraw from the study within 4 weeks of completion of the interview. Further details on the recruitment process are provided in Chapter 7.

3.8.1.2 Data Collection

Interviews consisted of open-ended questions with probes where necessary to explore areas of interest. The interview schedule (Appendix C.1) was informed by the findings of Laka, Milazzo, & Merlin (161, 190) in chapters 4, 5 & 6. Furthermore, information from relevant literature and guidelines on the safe implementation of digital systems was used in developing the interview guide (59, 151, 201, 202). The

interview schedule began with general questions about participants' knowledge and experiences of CDSS implementation. This was followed by specific questions concerning standardisation versus localisation of system design, workflow requirements, available infrastructure and resources, and system governance. The last section focused on challenges regarding coordination of implementation efforts across different organisations and states and the interoperability of CDSS implementation.

A participant's information sheet (Appendix C.2) outlining the objectives and scope of the study and consent form (Appendix C.3) were provided to participants prior to interviews. Interviews were conducted by video or teleconference according to participants' preferences.

3.8.1.3 Epistemology

The data collected through the semi-structured interviews represented participants' perceptions and experiences related to their specific context. We adopted pragmatism as a research paradigm in this study because it acknowledges that there can be a single or multiple truths depending upon perspectives or interpretations (203, 204). It acknowledges that reality is socially constructed but selection of one version of truth over another is determined by how well that version meets individuals' needs and experiences. Pragmatism has been widely used in research related to health systems. Biesta (2010) indicated that pragmatism must not be taken as a position, but rather as a tool to produce knowledge that can be applied to address the research problem (205). It orients itself toward generating knowledge that is socially beneficial and focusing on solving real world problems (206).

The objective of our research was to generate knowledge regarding challenges and opportunities for CDSS implementation that can influence the sustainable and effective adoption of a system. As this research falls within the category of health systems, we therefore tool the pragmatic approach to analysis with an intention to establish empirical knowledge that is grounded in contextual experiences and perspectives.

3.8.1.4 Data Analysis

The interviews were recorded, and data were transcribed verbatim by an independent transcriber. Interview transcripts were imported into QSR NVivo 11.0 (QSR International Pty Ltd) for reflexive thematic analysis.

Interview transcripts were first read in full to establish a broad understanding of the data. In the next phase, codes were generated from the interview transcripts using Braun and Clarke's (2006) thematic analysis process. The coding process was iterative with each transcript and code reconsidered repeatedly as understanding of the overall data and themes developed. During the analysis process,

text adjacent to the text highlighted as belonging to a particular code was also kept in view in order to aid interpretation and develop a clear context of each code. Similar codes were then grouped into themes, and these were also reviewed iteratively to ensure adequate data for each theme, and to determine if related themes needed to be further collapsed.

Reflexive thematic analysis highlights that researchers' prior knowledge and experience play an active part in knowledge production. This approach was defined by Braun and Clark as "the researcher's reflective and thoughtful engagement with their data" (207). They argued that the coding process reflects the researcher's analysis of the data conducted by converging the dataset and the researcher's knowledge and analytical skills. The data analysis in this study was not directed by existing theoretical frameworks but by the explicit content of the data. However, the researcher's previous knowledge of the literature and findings from previous studies (Chapter 4-6) may have informed the process of coding and theme development. This prior knowledge helped in understanding the meanings of participants in the context of what has already been reported in the literature and what was found in previous studies regarding CDSS adoption.

3.8.1.5 Ethical Consideration

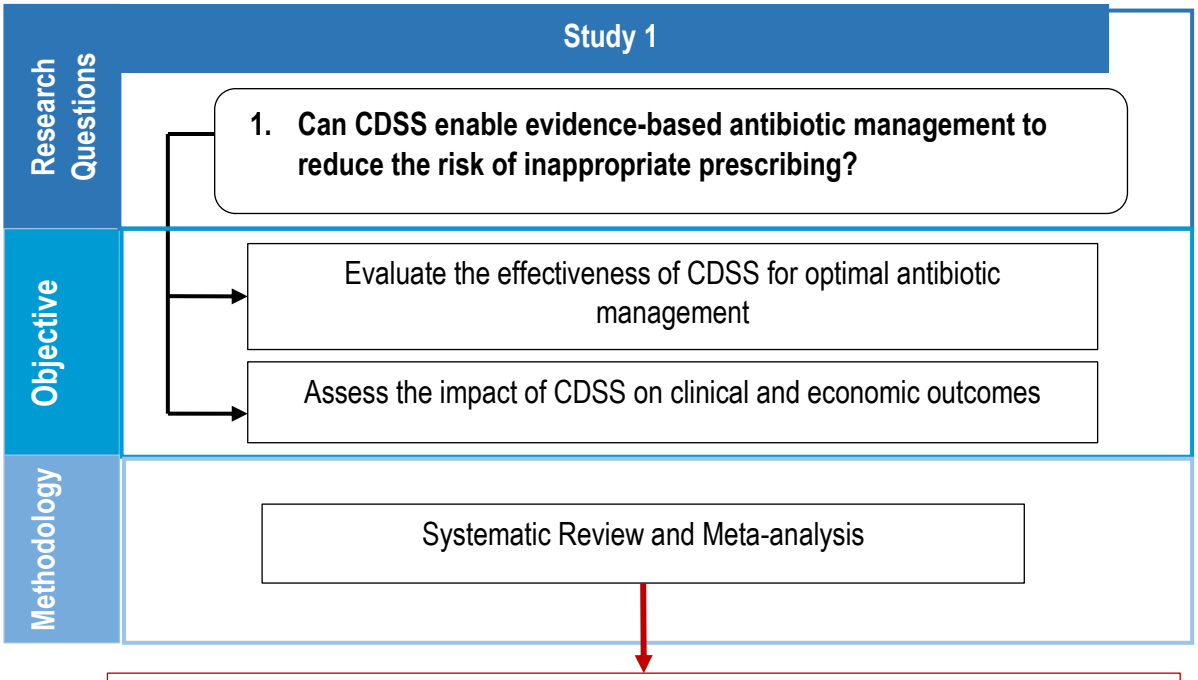
Ethics approval for in-depth interviews was provided by The University of Adelaide Human Research Ethics Committee as an extension to the previously mentioned ethics approval (HREC) (H-2019-094). A copy of the ethics approval is provided in Appendix C.4.

Chapter 4: Impact of CDSS on Antibiotic Management

4.1 Preface

This chapter assesses the impact of CDSS on antibiotic management by investigating if CDSS implementation can reduce unnecessary and inappropriate antibiotic prescribing by health professionals. A systematic review and meta-analyses were carried out to synthesise the evidence on the efficacy of CDSS based on clinical and economic outcomes. Previous studies have evaluated the potential of CDSS to improve antibiotic management, but the observed effect was inconsistent across the body of evidence with many studies reporting conflicting results. Despite the growing peer-reviewed literature in this field, the underlying factors that may contribute to the varying effect of CDSS on antibiotic management are still unclear. Previous systematic review studies have focused on specific healthcare settings or included certain types of study design, and thus were limited in their scope to explain why there have been variable findings concerning the impact of CDSS on antibiotic management. The systematic review conducted for this thesis addressed this gap in literature by mapping the different outcomes and features of CDSS, and assessing whether outcomes varied by study design or health care setting, to characterise and explain the observed heterogeneity in study findings. The aim was to contribute to this growing body of literature by comparatively analysing the evidence across different care settings, study designs and CDSS features.

This study was published in the *Journal of Antimicrobial Chemotherapy* and addresses the first research question and its corresponding objective highlighted in Figure 4.1 below:



Publication: Laka M, Milazzo A, Merlin T. Can evidence-based decision support tools transform antibiotic management? A systematic review and meta-analyses. Journal of Antimicrobial Chemotherapy. 2020;75(5):1099-111. DOI: 10.1093/jac/dkz543.

4.2 Statement of Authorship

Statement of Authorship

Title of Paper	Can Evidence-Based Decision Support Tools Transform Antibiotic Management? A Systematic Review and Meta-analyses
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Laka M, Milazzo A, Merlin T. Can evidence-based decision support tools transform antibiotic management? A systematic review and meta-analyses. Journal of Antimicrobial Chemotherapy. 2020;75(5):1099-111. DOI: 10.1093/jac/dkz543.

Principal Author

Name of Principal Author (Candidate)	Mah Laka
Contribution to the Paper	I contributed to the concept of the study, study design, performed the systematic review and meta-analyses, interpreted the results, and drafted the mansucript. I also acted as the corresponding author and was responsbile for all major and minor revisions.
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 24/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Adriana Milazzo
Contribution to the Paper	A. Milazzo contributed to the conception of the study as well as study design. She also assisted in the critical appraisal of studies and the interpretation of results. She provided feedback on the manuscript and evaluated the revised manuscript against reviewers' comments.
Signature	Date 24/8/21

Name of Co-Author	Professor Tracy Merlin
Contribution to the Paper	T. Merlin contributed to the conception of the study as well as study design. She assisted in the critical appraisal of studies and the interpretation of results. She provided feedback on the manuscript and evaluated the revised manuscript against reviewers' comments.
Signature	Date 24/8/21

Please cut and paste additional co-author panels here as required.

4.3 Publication

Title:

Can Evidence-Based Decision Support Tools Transform Antibiotic Management? A Systematic Review and Meta-analyses

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4.3.1 Abstract

Objective: To assess the effectiveness of clinical decision support systems (CDSS) at reducing unnecessary and suboptimal antibiotic prescribing within different healthcare settings.

Methods: A systematic review of published studies was undertaken with seven databases from database inception to November 2018. A protocol was developed using the PRISMA-P checklist and study selection criteria were determined prior to performing the search. Critical appraisal of studies was undertaken using relevant tools. Meta-analyses were performed using a random effects model to determine whether CDSS use affected optimal antibiotic management.

Results: Fifty-seven studies were identified that reported on CDSS effectiveness. Most were non-random studies with low methodological quality. However, randomised controlled trials of moderate methodological quality were available and assessed separately. The meta-analysis indicated that appropriate antibiotic therapy was twice as likely to occur following the implementation of CDSS (OR 2.28, 95% CI: 1.82, 2.86, k=20). The use of CDSS was also associated with a relative decrease (18%) in mortality (OR: 0.82, 95% CI: 0.73, 0.91, k=18). CDSS implementation also decreased the overall volume of antibiotic use, length of hospital stay, duration and cost of therapy. The magnitude of the effect did vary by study design, but the direction of the effect was consistent in favouring CDSS.

Conclusion: Decision support tools can be effective to improve antibiotic prescribing, although there is a limited evidence available on use in primary care. Our findings suggest that a focus on system requirements and implementation processes would improve CDSS uptake and provide more definitive benefits for antibiotic stewardship.

Keywords: antibiotics; decision support systems; clinical decision support systems; evidence-based practice; prescribing behaviour

4.3.2 Introduction

Increasing antibiotic resistance poses a significant threat to the effectiveness of current antibiotic therapies. Due to the increasing drug-resistance of pathogens, the range of effective antibiotic agents has greatly reduced, resulting in an escalation of morbidity, mortality and hospital-related costs (208, 209). Clinical malpractices such as inappropriate prescribing of antibiotics has become one of the major drivers for the selection pressure in bacterial species that has facilitated the emergence of drug-resistant strains (4). It is estimated that 50% of antibiotics are dispensed inappropriately in outpatient settings, mainly due to unnecessary prescriptions, and suboptimal selection of antibiotic agents or duration of therapy (38, 210).

In response to this challenge of drug-resistance, antimicrobial stewardship programs (ASP) have been introduced in different countries following the initiative of the WHO (211). To optimise antibiotic usage, clinical practice guidelines (CPG) have been developed to promote a reduction in inappropriate prescribing, thereby minimising the risk of resistance (212). Despite increasing emphasis on appropriate antibiotic prescription in stewardship programs, clinician non-compliance with CPGs has been widely reported, largely due to the high volume of information in CPGs, and the consequent time and clinical workflow constraints (129, 213).

One way of reducing the time and workflow impacts of CPGs is to integrate them into the information technology tools available in health care settings (75, 214). Electronic clinical decision support systems (CDSS) have been developed to connect clinical observations with this knowledge base to ensure improved and informed decision making (105, 110, 215).CDSS are electronic tools or software that support clinical decision-making at the point of care by combining patient-specific data with a clinical knowledge base (77, 216).

Although previous studies have reported on the potential of CDSS to improve antibiotic management in health care settings, there have been conflicting findings regarding the success of these systems in practice (14). System uptake and improvement in physicians' performance is variable, with only 60% of randomised controlled trials reporting an improvement in clinical practice (217). A number of reviews have investigated the potential of decision support systems to reduce inappropriate antibiotic use (14, 91, 110, 120). However, these reviews predominantly focused on particular care settings (hospital in-patient or out-patient) (14, 120) or study designs (randomised controlled trials or non-randomised studies) (91, 110). Other systematic reviews examined a range of health information technology interventions including surveillance systems, computerised physician order systems (CPOE), electronic health record systems (EHR) and CDSS, thus, were quite diverse in focus (14, 91). The scope of these

reviews is very broad and specific aspects such as the efficacy of CDSS across different settings of use, study types and system features has not been considered.

The aim of this systematic review is to assess the impact of CDSS use on inappropriate antibiotic prescriptions, volume of antibiotic use, duration of therapy, hospital stay, mortality and cost of therapy. Moreover, effect of CDSS on these study outcomes was also quantified by pooling the data into a single measure and heterogeneity was explored. We have attempted to identify those factors that modify the effectiveness of CDSS as an antibiotic stewardship tool. Despite the fact that the majority of antibiotics are prescribed in primary care, there has been limited research regarding the implementation of CDSS in this sector. Therefore, the focus of this review is on the efficacy of CDSS in diverse care settings including hospital and primary care.

4.3.3 Methodology

A review protocol and study selection criteria were developed prior to performing the systematic review.

4.3.3.1 Study Eligibility Criteria

Studies were selected in the systematic review on the basis of specific inclusion and exclusion criteria provided in Table 4.1.

Table 4.1 Inclusion and exclusion criteria for selecting studies for the systematic review

Item	Criteria	Definition
Population	Health care professionals in hospitals and in primary care settings	
Intervention	Clinical decision support systems (specifically for antibiotic management).	For study selection, we applied a pre-existing definition for CDSS by Hunt *et al. (77)*: "*Software that is designed to be a direct aid to clinical decision-making in which the characteristics of an individual patient are matched to a computerised clinical knowledge base (KB), and patient-specific assessments or recommendations are then presented to the clinician and/or the patient for a decision.*"
Comparator	Standard patient care	Antibiotics were prescribed without using any electronic decision support tools
Outcomes	Primary Outcome i. Appropriateness of antibiotic therapy (AoT)	Treatment that is compliant with clinical practice guidelines or *in vitro* susceptibility test results (laboratory-based sensitivity analysis of the microorganism to the chosen therapeutic agents)
	Secondary Outcomes: i. Volume of antibiotic use (VoU) ii. Length of hospital stay (LoS) iii. Duration of antibiotic therapy (DoT) iv. Mortality v. Cost of therapy (CoT)	<u>Volume of antibiotic use</u>: Average consumption of antibiotics at the patient level. It is usually measured as defined daily dose (DDD) which is defined by WHO as "*The assumed average maintenance dose per day for a drug used for its main indication in adults*" (164, 218). <u>Length of hospital stay:</u> Total duration of hospitalisation in days (164) <u>Duration of antibiotic therapy:</u> Total days of antibiotic therapy (166). <u>Mortality</u> (hospital studies only): In-hospital or 30 day all-cause mortality. <u>Cost of therapy:</u> Overall cost associated with antibiotic therapy including cost of therapy per patient, annual cost of therapy, and total cost of hospitalisation (164).

Study Design	Randomised controlled trials (RCTs),	RCTs: both individual and cluster-controlled trials
	Non-randomised studies (NRS)	NRS: controlled before-and-after study, uncontrolled before-and-after study, interrupted time series study, case series, historically controlled and cohort study.
Language	Only studies in English were included	

Moreover, CDSS systems that were included in our review must have applied algorithms or rule-based software for the evidence-based guidance and decision making of end users. Systems providing guidance in any form were eligible, including those with alerts, recommendations, feedback, and reminders or prompts. Systems providing expertise in diagnosis, treatment planning, and patients' follow-up were also eligible for inclusion. If studies did not report original or primary data, they were excluded from further analysis. Literature such as conference abstracts or editorials were also excluded from the review.

4.3.3.2 Search Strategy

We searched seven databases: PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Embase.com, Scopus, CINAHL, PsychINFO and Web of Science utilising broad and detailed criteria to maximise the results against the search query. Peer-reviewed articles were searched from database inception to August 2018. An updated electronic database search was also conducted using the same search query in PubMed (including MEDLINE) from September to November 2018 to include any recent publications. The search strategy encompassed indexing (MeSH) terms and text words for antibacterial agents and CDSS (including synonyms). The reference lists of the included studies were also pearled to identify any relevant study that might have been missed in the database search. The full strategy is provided in Appendix A.1.

4.3.3.3 Study Selection

Two reviewers (M.L. and T.M.) independently reviewed included studies against study eligibility and inclusion/exclusion criteria. M.L. screened the full text of all studies against the eligibility criteria while T.M. reviewed 10 percent of the eligible articles to validate the screening process; no discordance was identified between the reviewers (219). Any uncertainty regarding the inclusion of a study was resolved by discussion with T.M. and A.M. A standardised data extraction form (Microsoft Excel Spreadsheet) was created by the research team following the Cochrane Collaboration guidelines for data collection in intervention reviews and the Joanna Briggs Institute reviewer's manual 2015 (173, 220). The data extraction form was piloted using a sample of 20% of included studies resulting in modifications as necessary. The data were only reported if they could be accurately extracted from the included papers. The NHMRC Evidence Hierarchy for Interventional Evidence was used to determine the level of evidence of each study (221).

4.3.3.4 Reporting of the Literature Search

The protocol was developing using the Preferred Reporting of Items in Systematic Reviews and Meta-analyses (PRISMA) – Protocol (PRISMA-P) checklist and the systematic review was reported according to conventions from the PRISMA checklist (162, 170) (Appendix A.2).

4.3.3.5 Quality Assessment

Individual studies were critically appraised for methodological certainty and quality by two reviewers (M.L. and T. M.) utilising risk of bias assessment tools. Uncertainty regarding the study quality was resolved by discussion with T.M. and A.M. For non-randomised studies, evidence was appraised using ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions). Through ROBINS-I, confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes and reported results were assessed (171).

Similarly, for the critical appraisal of randomised controlled trials, the Cochrane Risk of Bias tool was used. The Cochrane Risk of Bias tool focuses on five possible domains of bias based on participants' selection process, difference of performance between groups, detection of outcomes, withdrawal or attrition, and reporting of study outcomes. The judgment of bias was based on empirical evidence from studies and assessment of the relative significance of each domain (158).

For diagnostic accuracy studies, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was applied which determines the risk of bias in domains such as selection of patients, conduction and interpretation, reference standard and flow and timing (222).

4.3.3.6 Data Collection and Synthesis

Data were extracted from the included studies and key findings on the pre-specified outcomes of interest were presented using the GRADEpro (Grades of Recommendation, Assessment, Development and Evaluation) Guideline Development Tool (223). Authors were contacted for additional information that was not provided in the published studies. For outcomes in which the effect estimate could not be meta-analysed because of differences in unit of analysis, the findings are discussed separately.

Results from statistical analyses of individual studies were extracted and standardised mean differences (SMD) and pooled odds ratios (OR) [95% confidence interval (CI)] were computed for continuous and dichotomous variables, respectively. Numerator and denominator information was extracted and error measures were calculated (eg. standard deviations (SD), confidence intervals (CI)).

The sample mean and variance were estimated from sample median, range or interquartile range and sample size (175). This estimation method provides improved estimators by incorporating study weight as a sample size function.

SMD was computed as the mean difference between the intervention arm and the comparator arm divided by the pooled SD (within groups) of the outcome. Due to the reported bias of overestimating the absolute effect in small samples, the Hedges' correction factor (J) was introduced using the following approximation:

$$J(df) = 1 - \frac{3}{4df - 1}$$

In this formula, df is the degree of freedom for estimating the within-groups pooled SD (224).

4.3.3.7 Meta-Analysis

Studies reporting sufficient data on study outcomes were meta-analysed. Meta-analysis was done using the metan user-written command in Stata version 15. Eligible studies included in the meta-analyses focused on the primary and secondary outcomes (as discussed in the study eligibility criteria) for improving antibiotic therapies and quality of care (164).

Outcome data were extracted from studies to calculate pooled effect estimates and 95% confidence intervals. Only studies with complete data were included. The random-effects model developed by DerSimonian and Laird method was used given there was considerable between-study heterogeneity (225). The estimate of between-study heterogeneity was computed from the Mantel-Haenszel model (226). The use of subgroup analysis in the random-effects model enabled evaluation of whether the statistical heterogeneity in the meta-analysis could be explained by study characteristics (227). We also used funnel plots and Egger's weighted regression statistic to determine whether publication bias had influenced the results of the meta-analyses (with a p value of <0.1 to compensate for the low power of Egger's test) (181).

4.3.3.8 Subgroup Analysis

To explore the impact of different types of decision support systems and study types on the pooled results, subgroup analysis was conducted. The types of CDSS considered in this meta-analysis were based on one of the previously conducted systematic reviews (110). The systems are classified into different types according to functional scope and characteristics of platforms providing decision support. We considered the functional domains of prescribing, dosage optimisation, alerts, and physician feedback for the subgroup analysis. Additional subgroup analysis concerning CDSS platforms involved

categorisation into web-based, stand-alone software and CDSS integrated into existing EMR or CPOE systems (110). Similarly, clinical heterogeneity was also explored according to the different study designs used, such as RCTs or NRS and interventional or non-interventional studies. In non-interventional studies, the CDSS was not implemented in the clinical practice, but patients' data were entered into the system prospectively or retrospectively. Treatment recommendations generated by the CDSS were then compared with the actual antibiotics prescribed by the physician. No changes were made in prescriptions based on the CDSS recommendations. In the interventional studies, CDSS was implemented as an intervention ie guiding prescribing practice, and its performance was compared with standard care in the clinical setting.

Statistical heterogeneity was assessed using the I^2 statistic. Consistent with the Cochrane Handbook, an I^2 value above 50% was taken as considerable heterogeneity, whereas less than 40% was considered to be modest heterogeneity (228).

4.3.4 Results

4.3.4.1 Database Search Results

Figure 4.2 describes the process undertaken to select eligible studies for the systematic review. An initial 6410 studies were identified, of which 57 studies were eventually included, comprising of 48 (84%) studies conducted in a hospital setting and 9 (16%) in primary care. Most of the studies (n=37, 65%) were carried out in the United States, while 21% (n=12) were from Europe and the remaining 14% (n=8) from the Asia-Pacific region. With regards to outcomes, 26 studies evaluated the impact of CDSS on the appropriateness of antibiotic therapy, 20 on the overall volume of antibiotic usage, 17 on length of hospital stay, 5 on duration of therapy, 19 on all-cause mortality, and 9 on the cost of therapy. The complete summary of finding table providing information on the magnitude of effect and quality of evidence for all the included studies is provided in Table S1 (provided in Appendix A.4).

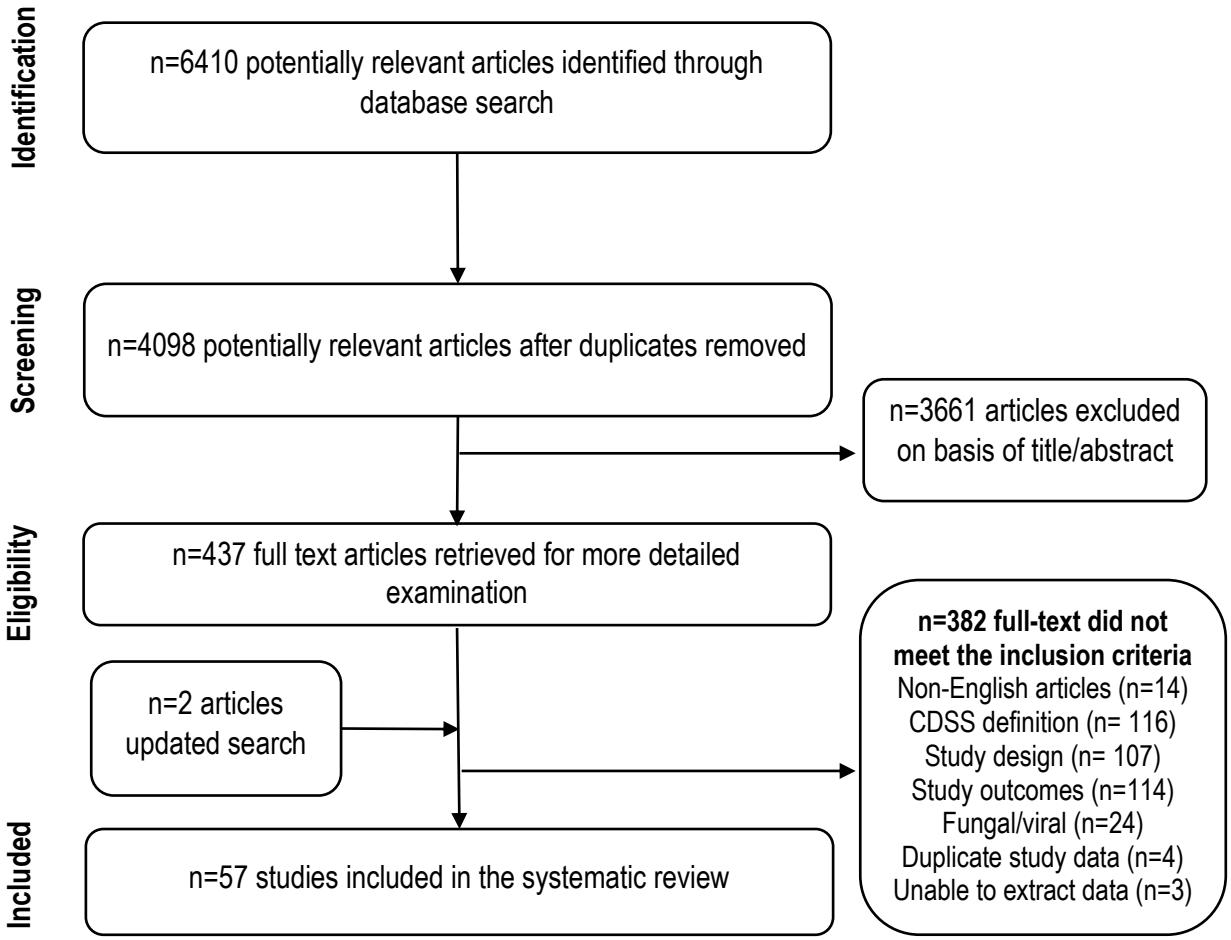

Figure 4.2 Study selection according to PRISMA flowchart

4.3.4.2 Methodological Quality Assessment

The risk of bias and methodological quality varied among the included studies. Of the 57 studies, 13 (23%) were RCTs. As shown in Figure 4.3, in many of these trials the risk of bias was found to be unclear due to insufficient information on the blinding of study personnel, allocation concealment, and incomplete outcome data. Incomplete outcome data were mostly observed in cluster randomised trials due to the loss of participating clusters (eg practices). In one trial, a number of prescribers were removed from the analysis as fewer cases were received than required by the study threshold (229). Whereas in another cluster randomised trial, 4 practices (3 from the intervention arm and 1 from the control arm) were excluded from the analysis because the contributed data did not match with intervention timeline (230). Additionally, only six of the included trials (12, 230-234) provided details of the methods used to conceal the allocation sequence, whereas one trial (235) lacked a sufficient method to reduce the risk of selection bias in the study design. For the six remaining trials (229, 235-240) there was an unclear risk of selection bias affecting their findings. Loss to follow-up was also reported in 4 studies contributing to the risk of attrition bias in these trials. Thus, due to incomplete information, the magnitude and direction of the bias in the trials remains unclear. Due to the nature of the intervention, the blinding of healthcare professionals was not possible, however, lack of blinding could affect the study outcomes in either direction. Knowledge of the intervention received in a trial may affect the behaviour of trial participants - leading to a reporting of enhanced or reduced effect for subjectively determined outcomes, based on whether the participant believed in the efficacy of the intervention.

Of the included trials, six were cluster RCTs (12, 229-231, 233, 238) with randomisation carried out at an institutional level; however in one trial adjustment for clustering was not performed and so there were artificially precise results due to the unit-of-analysis error.39 To correct for this, each individual cluster was considered as a unit of analysis thereby reducing the overall statistical power of the study.

A total of 44 NRS were included in the review with 36 pre-post (21 uncontrolled and 15 controlled pre-post studies), 5 cohort, 2 interrupted time series and 1 cross-sectional study (supplementary Table S1- provided in Appendix A.4). These were appraised using ROBINS-I and were found to be generally of low quality. Of the included NRS, seven studies (16%) indicated a moderate risk of bias due to confounding and missing data, whereas a high risk of bias was identified in 35 studies (79.5%) due to confounding, biased selection of participants, selective reporting and missing data. Two studies (4%) had an unclear risk of bias due to incomplete study design information (241, 242). Most of the NRS had compromised internal validity as the non-randomised study design makes it difficult to account for all the possible confounding variables. There was also a lack of blinding of study participants and assessors in

most studies which may have overestimated the effect size for the subjectively assessed outcomes. Many of the studies allocated the same healthcare practitioners to the control and intervention study arms, potentially contaminating the CDSS effect (243-246). In a few NRS, applicability of the results was compromised by the short follow-up period (247-251). To address the potential for effect modification due to type of study design, the meta-analyses were stratified into subgroups (RCTs and NRS) to check whether the observed effects were robust, even despite the high risk of bias associated with most of the NRS findings (see subgroup analysis section below).

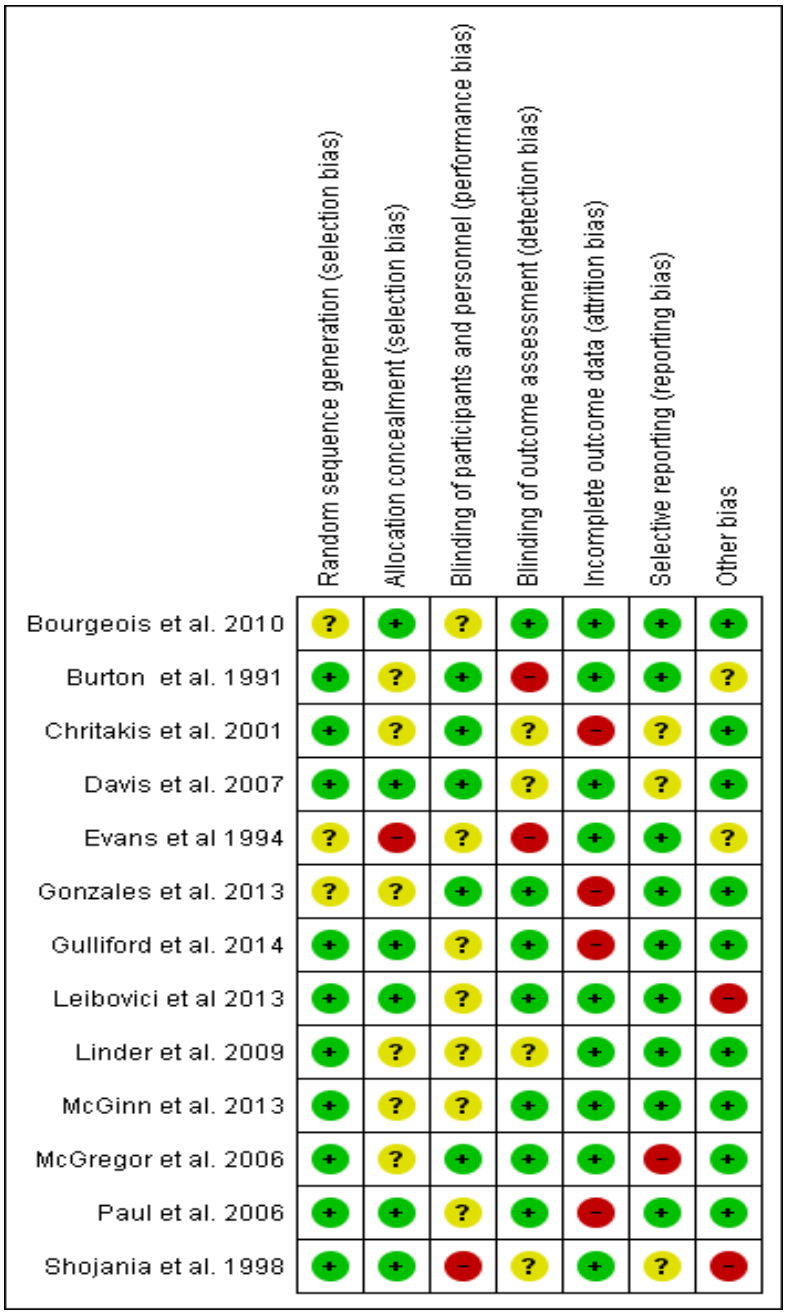

Figure 4.3 Summary of risk of bias assessments for randomised controlled trials

4.3.4.3 Meta-analyses

Meta-analyses were conducted where data were available and so results were pooled for two study outcomes: the appropriateness of antibiotic therapy and mortality. The GRADEPro Summary of Findings table for these two outcomes is depicted in Table 4.2.

Table 4.2 Summary of findings table for meta-analyses of CDSS compared to standard care for antibiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard care	Risk with CDSS			
Appropriateness of antibiotic therapy	643 per 1,000	**698 per 1,000** (639, 750)	**OR 1.24** (0.95, 1.62)	1161 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]
	507 per 1,000	**729 per 1,000** (673, 778)	**OR 2.45** (1.95, 3.08)	8197 (18 NRS)	⨁⨁◯◯ LOW [b,c]
Mortality	109 per 1,000	**104 per 1,000** (90, 121)	**OR 0.95** (0.81, 1.12)	8369 (3 RCTs)	⨁⨁⨁◯ MODERATE [d]
	49 per 1,000	**35 per 1,000** (31, 40)	**OR 0.72** (0.63, 0.82)	42364 (9 NRS)	⨁⨁◯◯ LOW [b]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio; RCT: Randomised controlled trials; NRS: Non-randomised studies

a. Imprecision in point estimates due to small sample size and a small number of events.

b. Serious concerns encountered across the body of evidence in domains such as selection bias, performance bias, and attrition bias. The study quality ranges from moderate to low. On the basis of study weights, sample size and number of outcome events, the overall quality of evidence is identified to be low.

c. The overall I-squared value is 84.7% which indicates a serious variance in the point estimate. The results are statistically heterogeneous due to the different types of CDSS used in different studies as well as conflicting results in uptake of the system.

d. Unclear risk of bias for allocation concealment encountered throughout the body of evidence. There was also a lack of blinding of participants and outcome assessors in included studies.

4.3.4.3.1 Appropriateness of Antibiotic Therapy

Overall 26 studies reported data on the appropriateness of antibiotic therapy, with 23 conducted in hospital settings and two in primary care. Of the hospital-based studies, 20 (2 RCTs and 18 NRS) reported sufficient data for a meta-analysis. The total sample size of studies was 9,358 participants with 4,300 participants in the intervention arm and 5,058 in the control arm.

To evaluate the impact of covariate and clustering adjustment on the overall pooled estimate, both adjusted and unadjusted data were taken into consideration in the meta-analyses as shown in the supplementary figure S1 (provided in Appendix A.4). Only five studies presented both adjusted and unadjusted estimates (231, 247, 248, 252, 253). For the final analysis, the adjusted estimates for these studies were taken into consideration. Overall, no substantial effect of clustering and covariate adjustment was identified in the pooled OR as shown in Figure S1.

CDSS was positively associated with the appropriateness of antibiotic therapy, with an overall pooled OR of 2.28 (95% CI 1.82, 2.86) (Figure 4.4). On the basis of the random effects model, this pooled estimate indicated that on average CDSS-assisted prescriptions were twice as likely to be appropriate compared to standard care. According to individual effect estimates, five studies indicated no effect of the intervention on the outcome, whereas 15 studies reported a statistically significant and positive impact on the outcome. No study reported a negative impact of CDSS on appropriate antibiotic prescribing behaviour. As shown in Figure 4.4 substantial between-study heterogeneity was observed ($I2 = 80.8\%$, $p<0.001$).

Individual studies showing a comparatively higher magnitude of effect in the forest plot (Figure 4.4) were further analysed to determine the plausibility of the observed results. One common theme among these studies was the development or deployment of CDSS to target a specific class of antibiotics (e.g. aminoglycosides) or infections (e.g. acute respiratory infections) for dosage management, monitoring, and administration (247, 254-257).

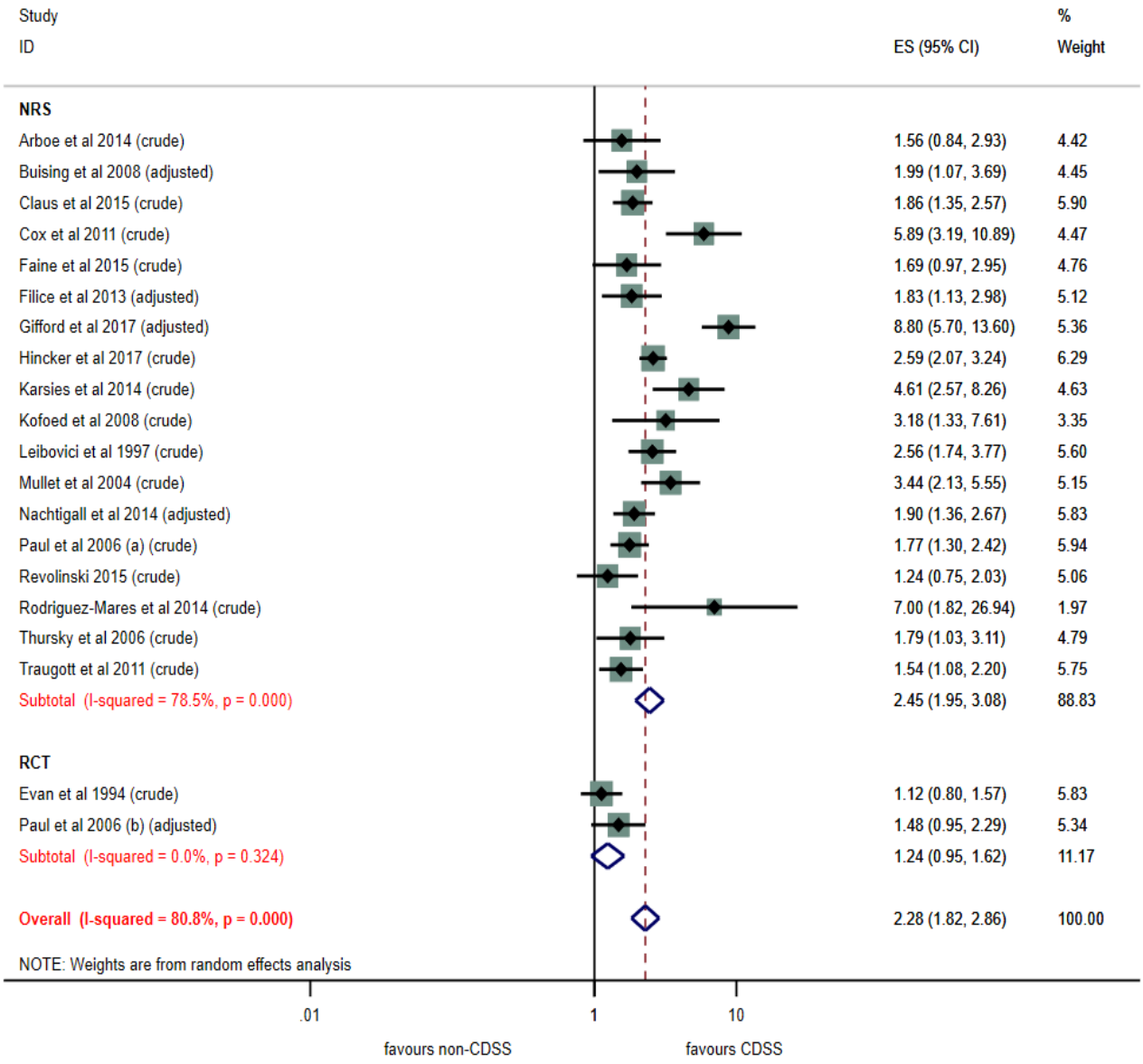

Figure 4.4 Effect of CDSS on appropriateness of antibiotic therapy, by study design (RCTs and NRS)

a. Publication Bias

Figure S2 (provided in Appendix A.4) shows a funnel plot for the impact of CDSS on the appropriateness of therapy across 20 studies. The log OR was plotted on the x-axis against the precision of log OR for the evaluated studies. Asymmetry of the funnel plot indicates that most of the results on appropriateness of therapy were reported from studies with a larger sample size or smaller standard error. This also suggests that small studies with less precise results remain unpublished. However, the Egger statistic (p= 0.259) indicates that the results of the meta-analyses were likely to be unaffected by any small study effect for appropriateness of therapy. As Egger's test, when using log OR, can produce artificially small p values, this result is likely conservative (181).

b. Subgroup Analysis

To further investigate the observed statistical heterogeneity, subgroup analysis was completed for different types of CDSS (functional and platforms) and study types. CDSS was found to be positively associated with an increase in the appropriateness of antibiotic therapy irrespective of CDSS type. As shown in supplementary figures S3 and S4 (provided in Appendix A.4), prescribing (pooled OR: 2.40 (95% CI 1.76, 3.28)) and dose optimisation systems (pooled OR: 2.52 (95% CI 1.69, 3.76)) appeared to be slightly more effective than alerts/prompts (pooled OR: 1.43 (95% CI 1.07, 1.91)). Albeit all pooled analyses were affected by statistically significant heterogeneity. The I-squared values of sub-groups in supplementary figures S3 and S4 (provided in Appendix A.4) indicated that stratifying the findings by different functional domains or platforms (stand-alone, web-based, and integrated into EMR/CPOE) had no effect on between-study heterogeneity. This suggests that the differences in the magnitude of the impact of CDSS on the appropriateness of antibiotic therapy could not be explained on the basis of CDSS characteristics or the types of systems implemented. Subgroup analysis on the basis of study type (RCTs versus NRS) found that NRS over-estimated the impact of CDSS on the appropriateness of antibiotic therapy (pooled OR: 2.45 (95%CI 1.95, 3.08)) when compared with RCTs (pooled OR: 1.24 (95%CI 0.95, 1.62). However, the direction of effect was essentially the same (Figure 4.4).

A comparison between interventional and non-interventional studies, also showed that results were similar (supplementary figure S5 (provided in Appendix A.4)). The pooled effect estimate in five non-interventional studies was 2.28 (95% CI 1.77, 2.95) with I^2 of 46.9% (p=0.110) whereas in interventional studies it was 2.27 (95% CI 1.68, 3.05) with I^2 of 84.7% (p=0.000). Supplementary figure S6 (provided in Appendix A.5) shows that the pooled OR was comparatively similar in both groups, but the between-study heterogeneity was less in the non-interventional study subgroup.

4.3.4.3.2 Mortality

A total of 19 hospital-based studies investigated the impact of CDSS on mortality. This outcome was used as a surrogate measure for improvement in the quality of care as the purpose for implementing CDSS is to improve antibiotic treatment and reduce mortality due to sepsis. Moreover, mortality is also taken as a balancing factor to ensure that the intervention did not result in an elevated health risk (164). Of these studies, 18 (2 RCTs and 16 NRS) provided sufficient data to be included in the meta-analysis. The total sample size of the included studies is 58,715 with 29,875 in control arm, and 28,840 in the interventional arm.

Overall, the meta-analysis on the basis of the random effects model showed that CDSS resulted in an 18% relative reduction in mortality (pooled OR: 0.82, 95% CI 0.73, 0.91). As highlighted in Figure 4.5, the between-study heterogeneity was low to moderate with I^2 of 39.2% (p=0.045).

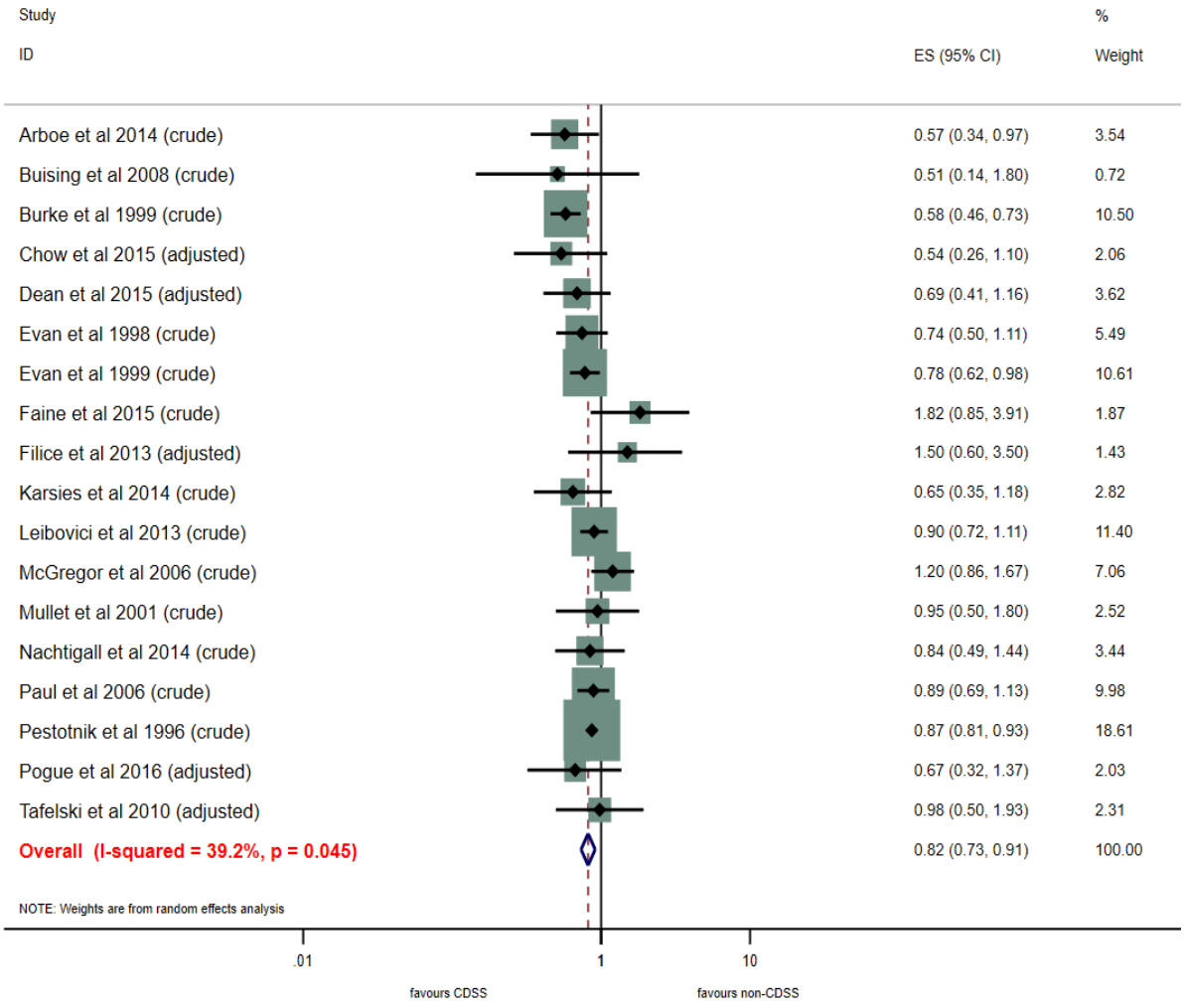

Figure 4.5 Forest plot of individual studies and meta-analysis for mortality

a. Publication Bias:

Figure S6 (provided in Appendix A.4) shows a funnel plot for the impact of CDSS on mortality across 18 studies. The funnel plot indicated an asymmetric pattern with possible publication bias due to non-publication of small trials. However, the Egger statistic (p= 0.539) failed to reject the null hypothesis, indicating that it was unlikely that a small-study effect had influenced the results of the meta-analysis.

4.3.4.4 Narrative Synthesis

4.3.4.4.1 Volume of Antibiotic Use

In different health care settings, 20 studies (6 RCTs and 14 NRS) assessed the overall use of antibiotics. Of these, five studies (25%) were carried out in primary care and 15 (75%) in hospitals. In these studies, results were presented as the number of antibiotic prescriptions before and after CDSS implementation, antibacterial agents administered per day and DDD (per 1000 or per 100 bed days) making it difficult to pool the results.

The total number of participants in the RCTs was 25,397 with 11,445 in the control arm and 13,952 in the intervention arm. Four of the included RCTs involved cluster randomisation of clinics, practices or wards (230). The total sample size could not be determined for the NRS due to limited information on participants in the pre and post-intervention population in five of the NRS studies.

As depicted in Table 4.3, overall antibiotic use decreased after implementation of CDSS in 16 studies, with three studies reporting no effect of the intervention on the volume of antibiotic use. One study reported a +32% increase in antibiotic use in the post-intervention group (258). This unexpected outcome may be the result of a decrease in the intensive care unit length of stay. It may also be due to the age of the study as it is one of the oldest studies in the evidence base, hence clinical practice may have changed in the ensuing 20 years.

Table 4.3 Impact of CDSS intervention on the overall volume of antibiotic use

Study	Study Setting	Unit	Non-CDSS	CDSS	Percentage Change	P-value
Agwu *et al.* 2008	Hospital	Doses/day (restricted antibiotics)	125.8	111.8	▼ -11.13%	NR
Bourgeois *et al.* 2010	Primary care	Proportion of total visits	46%	39.7%	▼ -6.30%	0.84
Burke & Pestotnik 1999	Hospital	DDD/1000 PDs [a]	226	299	▲ +32%	NR
Evan *et al.* 1999	Hospital	DDD/1000 PDs [a]	2009	1956	▼ -2.64%	NR
Evan *et al.* 1998	Hospital	DDD/1000 BDs [b]	1852	1619	▼ -12.58%	NR
Nault *et al.* 2018	Hospital	% difference in DDD/1000 PDs[a]	NA	NA	▼ -12.2%	0.02
Okumura *et al.* 2016	Hospital	DDD/1000 BDs	63.1	21.5	▼ -65.93%	NR
Pestotnik *et al.* 1996	Hospital	DDD/1000 OBDs [a]	359	277	▼ -22.84%	NR
Rattinger *et al.* 2012	Primary care	Proportion of unwarranted antibiotic prescriptions	22%	3.3%	▼ -18.7%	<0.0001
Tafelski *et al.* 2010	Hospital	Antibacterial Agents administered/ day	1.5	1.3	▼ -13.33%	<0.05
Thursky *et al.* 2006	Hospital	DDD/1000 ICU BDs [c]	1670	1490	▼ -10.78%	NA
Relative Difference						
Study	**Study Setting**	**Unit**	**Relative difference**			**P-value**
Bond *et al.* 2017	Hospital	Change in level (95% CI) (DDDs/1000 OBDs [a])	▼ -58 (-87, -29)			<0.01
Gonzales *et al.* 2013	Hospital	OR (95% CI)	▼ 0.64 (0.45, 0.91)			0.003
Gulliford *et al.* 2014	Hospital	Antibiotic rate prescriptions per 1000 years	Mean Difference (95% CI): ▼ -9.69 (-18.63, -0.75)			0.034
Huh *et al.* 2016	Hospital	Change in slope (95% CI) (DDD/1000 PDs) [b]	▲ -1.95 (-2.93, -0.96)			<0.01
Linder *et al.* 2009	Primary care	OR (95% CI)	▬ 0.80 (0.6, 1.2)			0.30
McCullough *et al.* 2014	Primary care	RR (95% CI)	▼ 0.81 (0.66, 0.96)			NR
McGinn *et al.* 2013	Primary care	RR (95% CI)	▼ 0.74 (0.6, 0.92)			0.008

Mullet *et al*. 2001	Hospital	Mean (SD) [d]	▲ 2.2 (-1.53 5.53)	NS
Shojania *et al*. 1998	Hospital	Mean (SD)[d]	▼ -5.4 (-10.7 -0.09)	0.04

▼ Decrease ▲ Increase ▬ No effect

a: Defined daily dosage/1000 occupied bed days **b**: Defined daily dosage/1000 patients days **c:** Defined daily dosage/1000 Bed days **d:** Computed as Hedges' g

CI: Confidence interval **ICU**: Intensive care unit **NS**: Not significant **NR**: Not reported

OR: Odds ratio **RR**: Relative risk **SD**: Standard deviation

4.3.4.4.2 Length of Stay

17 studies (3 RCTs and 14 NRS) evaluated the impact of CDSS on the length of hospital stay. Results are given in Table 4.4. In 12 of the studies, effect estimates indicate a reduction in length of stay, whereas no effect was observed in five studies, presumably due to the small sample sizes. One study provided contrary results. This study by Nachtigall *et al.* (252) found that hospital stays increased after the implementation of CDSS. No specific reason could be identified, although this study also reported an increase in antibiotic free-days from 30% to 44% (p-value <0.01). Therefore, despite the increase in hospital stay, aggregate antibiotic consumption was reduced.

Table 4.4 Impact of CDSS intervention on length of hospital stay (days)

Study	Non-CDSS Mean (SD)	CDSS Mean (SD)	Percentage Change	P-value
Agwu *et al.* 2008	6.78 (14.3)	6.67 (14.1)	▼ -1.63%	0.65
Bond *et al.* 2017	2.1 (0.6-5.6)	1.9 (0.5-5.0)	▼ -10%	NR
Burke & Pestotnik 1999	10.28	8.84	▼ -14%	NR
Pestotnik *et al.* 1996	7.5	7.3	▼ -2.70%	NR
Rodriguez-Maresca *et al.* 2014	20.1	19.7	▼ -2.01%	0.94
Sintchenko *et al.* 2005	7.15 (0.29)	6.22 (0.99)	▼ -13.01%	0.02
Vermeulen *et al.* 2014	14.6 (12.5)	12.1 (11.6)	▼ -17.12%	<0.001
Relative Difference				
Study	**Non-CDSS Mean (SD)**	**CDSS Mean (SD)**	**SMD [95%CI]**	**P-value**
Arboe *et al.* 2014	6.5 (10)	5 (17.16 [a])	▬ -0.11 [-0.42, 0.02]	NR
Buising *et al.* 2008	15 (29[a])	13 (27.75 [a])	▬ -0.07 [-0.46, 0.32]	NR
Burton *et al.* 1991	17.6 (1.6)	13 6.9)	▼ -0.93 [-1.26, -0.58]	0.013
Evan *et al.* 1998	12.9 (20.47)	10 (16.72)	▼ -0.15 [-0.25, -0.05]	0.001
Evan *et al.* 1999	7 (8.6)	6.6 (7.4)	▼ -0.05 [-0.08, -0.01]	0.001
Giuliano *et al.* 2011	15.7 (24.7)	17.8 (18.5)	▬ 0.097 [-0.24 , 0.43]	0.58
McGregor *et al.* 2006	3.99 (4.61[a])	3.84 (4.54 [a])	▬ -0.03 [-0.09, 0.02]	0.38
Nachtigall *et al.* 2014	9.2 (10.7)	11.3 (12.2)	▲ 0.18 [0.03, 0.34]	0.01
Paul *et al.* 2006	9.45 (11.5)	8.83 (11.3)	▼ -0.05 [-0.14, -0.03]	0.05
Pogue *et al.* 2016	8 (5.97) [a]	10.3 (8.59) [a]	▬ -0.14 [-0.34, 0.06]	<0.001

▼ Decrease ▲ Increase ▬ No effect
a: Estimation of mean and SD using estimation method (175).
NR: Not reported SD: Standard deviation SMD: Standardised mean difference

4.3.4.4.3 Duration of Antibiotic Therapy

Five studies (three RCTs and two NRS studies) reported on the duration of antibiotic therapy. As shown in Table 4.5, there was a significant reduction in the duration of antibiotic therapy after the implementation of CDSS in all studies. This decrease was evident in both hospital (n=3) and primary care settings (n=2).

Table 4.5 Impact of CDSS intervention on duration of antibiotic therapy

Study ID	Study Settings	Unit of Measure	Non-CDSS	CDSS	Percentage change	P value
Chritakis *et al*. 2001	Primary care	Change in mean outcome	10.48%	44.43%	▼ -323.95%	p<.01
Davis *et al.* 2007	Primary care	Change in mean outcome	13%	7%	▼ -6%	NR
Shojania *et al*. 1998	Hospital	Mean (SD) days	2.0 (SD 1.1)	1.8 (SD 1.1)	▼ -10.50%	0.05
Nault *et al*. 2018	Hospital	Level change (SE) days	NR	NR	▼ -0.92 (0.3)	p<0.01
Evans *et al.* 1998	Hospital	Mean (SD) hours	263 (441)	128 (169)	▼ -51.33%	NR

▼ Decrease NR: Not reported SD: Standard deviation SE: Standard error

4.3.4.4.4 Cost of Therapy

To evaluate the economic implications of CDSS implementation, nine studies (three RCTs and six NRS) provided information on the effect of CDSS on overall cost of antibiotic therapy. The direct cost of therapy per patient, annual cost of therapy, and total cost of hospitalisation in pre and post-intervention populations were recorded in the included studies. In two studies (231, 257) the total cost of therapy also took into consideration factors such as cost relating to expected adverse effects and the ecological impact of antibiotic inefficacy (future resistance) along with direct cost of therapy. The ecological component summed three basic factors: individual cost, eco-system cost due to the emergence of resistance against current therapeutics and penalty for using last-resort drugs.

Despite differences in the measurement unit of the cost-analysis, a reduction in the overall cost of antibiotic therapy was reported in seven studies (Table 4.6). The cost of therapy is depicted in different currencies such as US Dollar, Australian Dollar and Euro depending on the origin of the study. In one Australian study (248), the mean cost of therapy per patient for pneumonia increased by 16.60% after CDSS implementation. This study was carried out over three time periods beginning with baseline, academic detailing, and CDSS. The academic detailing period comprised of two days of face-to-face training on antibiotic prescriptions. The cost was observed to increase from baseline to the second time point (academic detailing portion), but decreased from second to third time point (CDSS) during the study. This would appear to be consistent with results reported in the other studies.

Table 4.6 Impact of CDSS Intervention on the cost of antibiotic therapy

Study ID	Study Settings	Study location	Unit of Measure	Non-CDSS	CDSS	Percentage change	P-value
Buising *et al.* 2008	Hospital	Australia	Mean cost per patient for pneumonia (AUD)	72.07	84.04	▲ 16.60%	NR
Evans *et al.* 1998	Hospital	United States	Mean cost per patient (USD)	340	102	▼ -70%	<0.001
Evans *et al.* 1999	Hospital	United States	Mean cost per patient (USD)	92.96	80.62	▼ -13.27%	<0.02
Evans *et al.* 1994	Hospital	United States	Mean cost per patient (USD)	51.93	41.08	▼ -20.89%	<0.001
Kofoed *et al.* 2008	Hospital	Denmark	Mean cost per treatment (Euro)	624	528	▼ -15.38	0.06
McGregor *et al.* 2006	Hospital	United States	Total cost of antibiotics for study period (USD)	370,006	285,812	▼ -22.75%	NR
Mullet *et al.* 2001	Hospital	United States	Total cost per patient (USD)	274.79	289.60	▼ -5.39%	NS
Paul *et al.* 2006	Hospital	Israel, Germany and Italy	Mean cost per patient (Euro)	623.2	565.4	▼ -9.27%	0.473
Pestotnik *et al.* 1996	Hospital	United States	Mean cost per treated patients (USD)	122.66	51.90	▼ -57.69%	NR

▼ Decrease ▲ Increase **NS**: Not Significant **NR**: Not reported
AUD: Australian Dollar USD: United States Dollar

4.3.5 Discussion

The aim of this systematic review was to assess the potential of CDSS in promoting appropriate antibiotic treatment in hospitals and primary care settings. Our study examined how operational and functional differences in these systems influence the study outcomes and decision-making processes in healthcare settings. Due to the scope and breadth of this review, the analysis was based on many studies which were not included in previous reviews. The positive outcomes reported in this study are consistent with the findings of previous systematic reviews (14, 91, 110, 120, 159). However, these reviews differed in their scope, study settings, study inclusion criteria and definition of CDSS. Our study contributes to the existing body of evidence by providing a specific evaluation of CDSS across different healthcare settings and a broad range of health outcomes, and it explores whether different types of systems produce different health benefits.

The included studies assessed the performance of CDSS by measuring health-related outcomes of antibiotic appropriateness, the volume of prescribed antibiotics, length of hospital stay, duration of antibiotic therapy, mortality, and costs of therapy. A total of 57 studies were included in this systematic review, comprising of 13 RCTs and 44 NRS. Studies varied in how they reported the performance of CDSS for antibiotic stewardship. There was also large variability in the types of CDSS and outcome measures in these studies. The review outcomes were based on studies that were mostly of moderate to low methodological quality.

We found evidence in favour of CDSS for promoting appropriate antibiotic therapy. The meta-analysis showed that CDSS has the potential to improve appropriateness of therapy and reduce mortality by providing evidence-based recommendations using local or national prescription guidelines and in vitro organism susceptibility results. Moreover, studies also reported a reduction in the overall volume of antibiotic use, duration and cost of therapy. The majority of the evidence came from studies with moderate to low methodological quality because of inherent biases in non-randomised study designs. Due to the nature of digital health interventions, it is usually difficult to adopt a randomised study design. Factors such as administrative feasibility and contamination makes randomisation difficult for these types of studies. The pooled results of the non-randomised studies did over-estimate the impact of CDSS on appropriate antibiotic prescribing in comparison to the pooled RCT evidence (only two studies). However, the RCT studies showed results in the same direction.

Certain health risks may result from a reduction in antibiotic usage, particularly for immunocompromised or aged patients. Therefore, studies reporting on markers of safety, such as duration of hospital stay, and mortality were included. We found that mortality and length of stay remained unchanged or reduced

in some studies following CDSS implementation. However, a smaller sample size and shorter follow-up period in many studies limit the generalisability of intervention effects over an extended time period (248-252, 259-261).

Despite considerable between-study heterogeneity, improvement in the quality of antibiotic management was reported in the majority of studies. The meta-analysis highlighted that antibiotics prescribed using CDSS may be up to twice as likely to be compliant with guidelines or in vitro susceptibility test results. This suggests that CDSS can be an effective intervention to optimise antibiotic prescription processes. The observed heterogeneity was expected due to the variability in decision support systems, implementation processes, and settings of use, type of infections, clinician compliance with systems, and the study designs. What is important, however, is that although the magnitude of the effect of CDSS varied across studies, the direction of the effect was largely consistent – favouring CDSS.

Subgroup analysis exploring the impact of different types of CDSS and study designs indicated that CDSS improves the appropriateness of antibiotic therapy irrespective of platform, CDSS characteristics or study type. It was evident that variability in the implementation process and system uptake in different settings were the likely explanations for statistical heterogeneity across studies. In non-interventional studies, patients' data were used to evaluate the appropriateness of therapy recommended by CDSS. Due to the nature of these studies, systems were not actually implemented in health care settings. Therefore, factors associated with adoption of CDSS such as clinicians' willingness, system uptake, organizational limitations, and implementation constraints may not have been considered (114, 262). Clinician compliance and uptake is a major concern for the adoption of health-related technologies which can cause interventions to fail to provide benefits in the long-term (217). Our findings further indicated that studies adopting a need-based and focused approach for the development and deployment of CDSS showed a higher magnitude of effect for promoting appropriateness of antibiotic therapy (247, 254-256). However, due to limited evidence it was difficult to clearly identify the factors separating a higher magnitude of effect from less favourable results in other studies.

We found that interventions resulted in promoting evidence-based prescriptions in reducing the risk of unwarranted and unnecessary prescriptions. However, many studies had a short follow-up period. It is unclear whether the positive impact of CDSS would reduce over a longer period of time. The common theme arising from previous reviews suggest that the lack of effective implementation and end-user acceptance could greatly limit the clinical benefits of CDSS in diverse health care settings (110, 120). The end-users and stakeholder inclinations and decision mapping need to be considered to promote end-user-oriented system design (110). The consideration of the dynamics of the decision-making

process in clinical settings and environment-specific system requirements may improve system integration and uptake in clinical settings.

Despite the fact that primary care is the major setting of antibiotic misuse, there were comparatively few studies on effect of CDSS in this setting. Only 3 of the included studies reported data on appropriateness of therapy, 4 on volume of antibiotic use and 2 on duration of antibiotic therapy in primary care. Given the small number of studies in primary care, we had limited evidence available on the beneficial effect of CDSS on patient and economic outcomes within the community.

4.3.5.1 Study Limitations

Several studies included in this review were uncontrolled pre-post intervention studies with inherent methodological limitations due to the lack of a control arm. Even the controlled NRS were likely affected by confounding and blinding of study personnel. The short follow-up period in many studies may have provided a biased effect estimate. In the comparison of RCTs with NRS the pooled results indicated that the NRS are more likely to over-estimate the benefits of CDSS. Nevertheless, even though the magnitude of the effect differed by study design (and possible biases), the direction of the effect was consistent. The statistical heterogeneity observed could not be explained completely by the diverse range of system types, study settings, and contextual features in the included studies. We investigated the possible impact of publication bias and did find asymmetry in the funnel plots, indicating that small or medium sized trials reporting either a positive or negative effect of CDSS remain unpublished. However, the statistical test for publication bias suggests that it is unlikely that the omission of these studies has influenced the pooled effect estimates.

There was limited published research evidence on the effectiveness of CDSS specifically in primary care settings so the findings of this review must only be cautiously applied to the broader context of primary care.

4.3.6 Conclusion

Our study demonstrates that CDSS has great potential to optimise antibiotic management by increasing adherence to evidence-based care. After the CDSS intervention, improvements in clinical and economic outcomes and appropriate antibiotic therapy were identified across different healthcare settings and different types of CDSS. Successful implementation of CDSS appears to optimise antibiotic management by increasing compliance with the guidelines or in vitro susceptibility test results, but the magnitude of benefit is likely to vary. Future studies need to focus on study quality and follow-up period to provide evidence on long term efficacy of CDSS with higher certainty. In order to achieve the

anticipated benefit, it will also be necessary to focus on the specific functional requirements of the system as well as an implementation process that will facilitate CDSS uptake in different settings.

Funding

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Transparency declarations

None to declare.

4.4 Chapter Synopsis

This chapter addresses the first research question of this thesis and assesses whether implementation of CDSS can improve the clinical and economic outcomes of antibiotic management. This was achieved through systematic review and meta-analyses of articles published on the topic. This study systematically compares and analyses the features and aspects of CDSS to help understand why CDSS has a variable impact on antibiotic management across different studies. With this aim, we differentiated from previous reviews by broadly investigating whether the role of CDSS in reducing inappropriate and unnecessary antibiotic prescribing is impacted by different contextual factors such as study designs, care settings and system features. This was specifically relevant as previous studies have highlighted that there is a need to investigate the underlying factors that determine whether CDSS will be effective for the clinical practice and translate benefits into clinical practice. Our study has shown that CDSS improves the clinical and economic outcomes of antibiotic management and reduces the risk of inappropriate antibiotic prescribing. However, the magnitude of the impact relies on the level of adoption by health professionals in different clinical settings.

The principal findings of the meta-analysis highlighted that CDSS implementation can improve the appropriateness of antibiotic prescribing and reduce in-hospital mortality by increasing compliance with the prescribing guidelines and *in vitro* susceptibility test results. The antibiotic prescriptions made using CDSS were twice as likely to be appropriate in comparison to standard care or prescriptions made without use of CDSS. Although the magnitude of effect varied across the studies in the meta-analysis, the direction of effect was largely consistent in supporting the positive impact of CDSS in improving appropriateness of antibiotic therapy, whether the evidence involved randomised or non-randomised studies.

For other outcomes such as volume of antibiotic use, length of hospital stays and cost of therapy, the studies estimated the effect of CDSS using different units making it difficult to pool results. These were therefore synthesised narratively. The results of the narrative review identified that CDSS implementation results in a reduction of the overall volume of antibiotic use and duration of therapy, thus, leading to optimal antibiotic treatment. The reduction in unnecessary and inappropriate prescribing was also reflected in a decreased cost of therapy which was reported in many of the included studies.

In conclusion, we also identified a substantial between-study heterogeneity in the meta-analysis. This was investigated through stratification by sub-group. The sub-group analysis indicated that variability in CDSS adoption and use by clinicians may be a contributing factor to the considerable heterogeneity in the estimated effect. However, due to limited evidence it was not possible to clearly determine specific

factors contributing to more favourable results in the evidence base. This variability in system uptake and its contribution to the varying magnitude of effect in different studies warranted further investigation Therefore, the next study (chapter 5) address this gap and investigate different factors and drivers of CDSS adoption across healthcare settings.

4.5 Update to Systematic Review

In June 2021, an updated database search was conducted in PubMed using the same search strategy mentioned in section 3.6.1.3 to identify recent studies addressing the impact of CDSS for antibiotic management as our systematic review and meta-analyses was published in December 2019. The updated search identified four additional studies. The findings of these studies are discussed briefly below, with further details provided in the Summary of Findings table (Table S1, provided in Appendix A.4).

Three (93, 263, 264) studies utilised a retrospective before-and-after study design, and the fourth was a single-blinded randomised controlled trial (265). These studies were conducted in hospitals with only one carried out across multiple sites. Two studies were conducted in the UK, one in the US and one in Germany.

The study by Heard *et al*. (93) compared the clinical impact of CDSS during three month corresponding periods in both before and after CDSS implementation. Results found an improvement in the antibiotic optimisation based on sensitivities and culture results in the post-CDSS period. Following CDSS implementation, 13.5% of antibiotic prescriptions were optimised in terms of dose and drug selection in comparison to only 2.9% in the pre-CDSS period. Similarly, a reduction in the overall use of antibiotics was reported with the volume of antibiotic use decreasing from 283 DDD/1000 occupied bed days (OBD) in the pre-CDSS period to 231 DDD/1000 OBD in the post-CDSS period. Another recent study conducted by Al Bahar *et al*. (263) also found a positive impact of CDSS on the overall use of antibiotics. This study collected data on antibiotic use during the two-year intervention period when CDSS was implemented followed by two years without intervention when CDSS was withdrawn. There was an increase of +110 DDD/1000 bed-days in overall use of antibiotics from the CDSS period to non-CDSS period resulting in a 17% increase in mean volume of antibiotic use. During the complete intervention period, the use of antibiotic was identified to be at a lower level compared to the period when CDSS was not used. These results support our findings of our systematic review and meta-analysis that CDSS implementation can decrease volume of antibiotic use leading to an optimal antibiotic regimen.

Moreover, two studies (264, 265) assessed the impact of CDSS on antibiotic use in urinary tract infections (UTIs). A study conducted by Watson *et al.* (264) determined a decrease of 15.2% in the duration of therapy in patients with a UTI indication in the post-CDSS period. CDSS implementation resulted in optimal duration of therapy, but also decreased the number of misdiagnosis of UTIs as more cases in the post-CDSS period correctly fulfilled the diagnostic criteria specified in national guidelines

(264, 265). The impact of an optimal duration of therapy and reduction in misdiagnosis was also observed on the overall cost of antibiotic therapy leading to an annual cost saving of US$535,181 (264).

Overall, the findings of the four studies are consistent with previous studies included in our systematic review and meta-analyses. These studies also support our conclusion that implementation of CDSS can result in optimal antibiotic management by improving appropriateness of therapy, decreasing overall volume of use, and reducing the duration and cost of antibiotic therapy.

Chapter 5: Barriers and Enablers of CDSS Adoption for Antibiotic Management

5.1 Preface

The study presented in this chapter is the first of two studies that investigated the perceptions and experiences of clinicians as CDSS end-users regarding appropriate antibiotic prescribing and CDSS adoption.

The aim of this study was to understand the different factors that influence clinicians' perceptions regarding CDSS that might lead to variability in adoption in different care settings. This survey was conducted with clinicians from both hospitals and primary care and evaluated predictors of clinicians' behavioural intent to adopt CDSS.

The chapter addresses the second research question of this thesis and respective objective identified in Figure 5.1. The online survey questionnaire is provided in the Appendix B.4. This study was published in a special issue "Digital Healthcare Innovation" of the International Journal of Environmental research and Public Health.

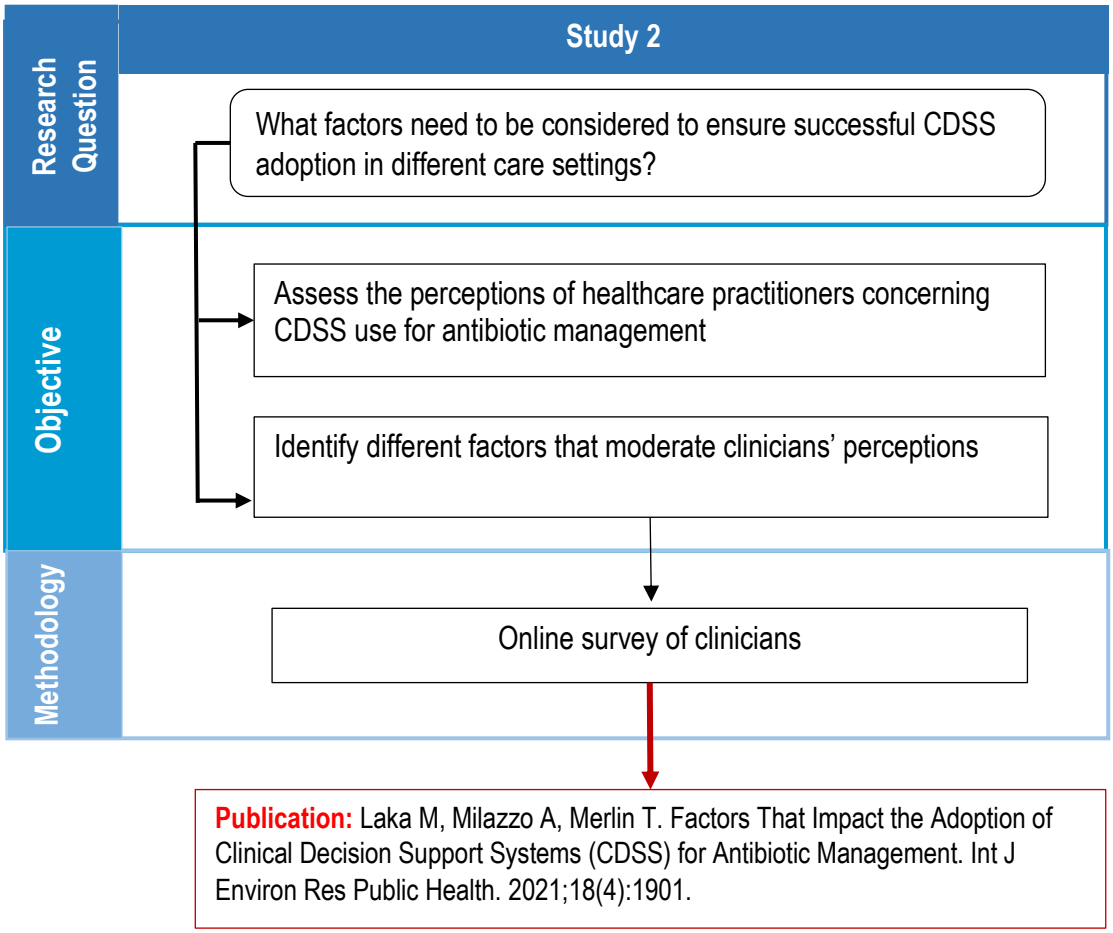

Figure 5.1 Structure of chapter's research question and objectives

5.2 Statement of Authorship

Statement of Authorship

Title of Paper	Factors That Impact the Adoption of Clinical Decision Support Systems (CDSS) for Antibiotic Management.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Laka M, Milazzo A, Merlin T. Factors That Impact the Adoption of Clinical Decision Support Systems (CDSS) for Antibiotic Management. Int J Environ Res Public Health. 2021;18(4):1901.

Principal Author

Name of Principal Author (Candidate)	Mah Laka
Contribution to the Paper	I contributed to the study concept, study design and statistical framework. I recruited the study participants, collected the data, performed the analyses and prepared the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 24/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	T. Merlin contributed to the study concept as well as study design. She assisted in the interpretation of the results. She provided feedback on the manuscript and evaluated the revised manuscript against reviewers' comments.
Signature	Date 24/8/21

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5.3 Publication

Title

Factors That Impact the Adoption of Clinical Decision Support Systems (CDSS) for Antibiotic Management.

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5.3.1 Abstract

The study evaluated individual and setting-specific factors that moderate clinicians' perception regarding use of clinical decision support systems (CDSS) for antibiotic management. A cross-sectional online survey examined clinicians' perceptions about CDSS implementation for antibiotic management in Australia. Multivariable logistic regression determined the association between drivers of CDSS adoption and different moderators. Clinical experience, CDSS use, and care setting were important predictors of clinicians' perception concerning CDSS adoption. Compared to nonusers, CDSS users were less likely to lack confidence in CDSS (OR = 0.63, 95%, CI = 0.32, 0.94) and consider it a threat to professional autonomy (OR = 0.47, 95%, CI = 0.08, 0.83). Conversely, there was higher likelihood in experienced clinicians (>20 years) to distrust CDSS (OR = 1.58, 95%, CI = 1.08, 2.23) due to fear of comprising their clinical judgement (OR = 1.68, 95%, CI = 1.27, 2.85). In primary care, clinicians were more likely to perceive time constraints (OR = 1.96, 95%, CI = 1.04, 3.70) and patient preference (OR = 1.84, 95%, CI = 1.19, 2.78) as barriers to CDSS adoption for antibiotic prescribing. Our findings provide differentiated understanding of the CDSS implementation landscape by identifying different individual, organisational and system-level factors that influence system adoption. The individual and setting characteristics can help understand the variability in CDSS adoption for antibiotic management in different clinicians.

Keywords: clinical decision support tools; barriers; facilitators; UTAUT

5.3.2 Introduction

Antibiotic resistance has been recognised as a top-five major global health threat, and, by 2050, drug-resistant infections could lead to 10 million deaths worldwide (266). Standardising clinical practice, improving the quality and safety of care and reducing inappropriate prescribing have become priorities for antimicrobial stewardship (7, 105).

Clinical decision support systems (CDSS) are a digital health technology that provide clinicians with information at the point-of-care. By connecting evidence-based information on appropriate antibiotic prescribing with patient information, these systems filter and present accurate, real-time information to assist clinical decision making (267, 268). Benefits of CDSS for antibiotic stewardship include optimising the prescribing process by auditing decisions and providing real-time feedback, as well as increasing compliance with antibiotic prescribing guidelines and reducing the risk of unnecessary and inappropriate prescribing of specific antibiotics (14, 269). There is varying evidence available on the efficacy of CDSS for antibiotic management, but some studies have suggested that there can be reductions in the duration of antibiotic therapy, length of hospital stays, cost of antibiotic therapy and in-hospital mortality after the implementation of CDSS (14, 91, 161).

Studies have also shown that the availability of CDSS does not guarantee optimal adoption of the system by end-users. As a consequence, despite increasing evidence regarding CDSS benefits, CDSS adoption by end-users remains limited (270). In healthcare organisations with CDSS in place, adoption is less than anticipated with 96% of CDSS alerts or recommendations usually overridden or ignored (114, 115, 271) for reasons attributed to end-users' negative attitudes, evasion or scepticism regarding the system, as well as the unanticipated consequences of CDSS on clinical workflows (21, 272).

The healthcare environment is characterized by an array of interdependent factors including clinical culture, processes, workflows and professional norms which can impact the successful introduction of systems such as CDSS (262). A study conducted by Yusof *et al*. (273) established that implementation of CDSS can be challenging due to the complex interaction of system, organisational and human factors. Due to this complexity, it is difficult to ensure that improvement in one particular domain does not result in unanticipated consequences in another aspect of the care process.

CDSS implementation is also complicated because its scope extends far beyond a traditional information technology tool and integrates an evidence-based paradigm into every day clinical practice (18). Liberati *et al*. (114) report that scientific evidence provided by the system can sometimes challenge deep-rooted beliefs concerning professional autonomy and hierarchies of authority in the clinical setting, resulting in

scepticism regarding the use of CDSS. Many studies have focused on technical appropriateness and users' experience to understand factors related to CDSS adoption (8, 144, 274), but there is limited information on how end-users' individual characteristics influence perceptions about adopting CDSS for antibiotic management.

Our aim was to identify the different individual, organisational and system level factors that influence the adoption and use of CDSS for antibiotic management. This included identifying different individual- and setting-specific factors that moderate the perceptions of end-users. In doing so, we aim to establish a more differentiated understanding of the CDSS implementation landscape for antibiotic management in different settings. This information will be key to understanding the dynamics of CDSS implementation and identify underlying reasons for variation in CDSS adoption by clinicians.

5.3.3 Materials and Methods

5.3.3.1 Theoretical Framework

We used the unified theory of acceptance and use of technology (UTAUT) model to understand the interplay between different organisational, individual and technical factors influencing adoption and use of CDSS for antibiotic management (145, 146). Denktash *et al*. identified that the majority of information technology adoption models offer similar constructs to explain technology acceptance behaviour. Researchers tended to choose feasible elements from these models thereby reducing the overall breadth and depth of the favoured framework. To overcome this, eight of the most commonly used models were integrated into the UTAUT to provide a comprehensive framework for the behavioural intent to adopt and use technology (146). The UTAUT model comprises of four main constructs that impact technology adoption: effort expectancy, performance expectancy, social influence, and facilitating environment. Effort and performance expectancy are related to the quality of system design in terms of ease of use, integration into a normal workflow and perceived benefits for improving the performance. Social influence reflects the effect of social networks in an organisation to shape users' behaviour to adopt and use any technology. The last construct of this framework, the facilitating environment, captures the users' belief that any setting or organisation has an appropriate structure in place to sustain use of the technology. The environment may not impact the users' intentions, but it directly influences the actual technology adoption and use. One of the key aspects of UTAUT is integration of user-specific factors that moderate the impact of model constructs. These moderating variables, including age, gender, and experience, influence the direction and magnitude of the effect of model constructs on the behavioural intent and actual use of technology.

5.3.3.2 Study Design

This study employed a cross-sectional descriptive design. An online survey of physicians, surgeons and general practitioners across Australia was administered through Survey Monkey TM (www. surveymonkey.com, San Mateo, California, US) from June–October 2019. Recruitment was assisted by the Royal Australasian Colleges of Physicians, General Practitioners and Surgeons and local health networks. The survey was promoted via their newsletters, websites, and social media accounts. We utilised the checklist by Kelley *et al*. (275) as a standard guide for the development, analysis and reporting of the survey.

5.3.3.3 Study Participants

Our survey population was hospital and primary care clinicians in Australia who are directly involved in antibiotic prescribing. The sampling framework used information from the National Health Workforce Data Set comprising medical practitioner data (2015–2018). With a 5% margin of error and a 95% confidence interval, we estimated we would need a sample size of 350 clinicians from primary care, and hospitals to generalise the results to all Australian clinicians. However, we also knew that this would be difficult to achieve, with low response rates common for clinician surveys (276-278).

5.3.3.4 Questionnaire Instrument

The survey questionnaire provided in the Supplementary S1 was designed following an extensive literature review of similar studies (8, 20, 83, 108, 279-285). Supplementary S2 (supplementary table) (provided in Appendix B.8) outlines the studies from which the questionnaire constructs were derived. Questions regarding perceived benefit, barriers and facilitators of CDSS adoption could be answered using five-point Likert-type scales, where 1 represented “Strongly Disagree” and 5 = “Strongly Agree”. Most survey questions were closed, except for one open-ended question and comments section.

5.3.3.5 Piloting

The online survey was pilot tested with known clinical contacts (n = 10) to identify any potential problems in the survey questionnaire before it was widely distributed. After reviewing the results in the pilot phase, modifications were made to the survey’s text.

5.3.3.6 Measures

As it was not mandatory for participants to provide a response to all questions, the number of responses to each question was calculated separately.

Responses to the questions tended to cluster at the ends of each Likert five-point scale, so dichotomous dependent variables were generated by collapsing the responses of “Agree” and “Strongly Agree” into “Yes” and “Disagree” and “Strongly Disagree” into “No/Unsure”. The neutral response of “Neither Agree nor Disagree” was included in the “No/Unsure” category as the low responses meant it could not be included as a separate category. The rationale of combining neutral with negative responses was that the focus of the analysis was in identifying participants who positively or negatively responded to the survey questions.

5.3.3.7 Statistical Analysis

For analysis, the moderating factors (gender, age, clinical experience, care settings) and use of CDSS were considered as independent or predictor variables whereas perceived benefits, barriers and facilitators to use of CDSS were analysed as dependent variables. To evaluate the association between these dependent and predictor variables, we used multivariable logistic regression. The results were provided as an odds ratio (OR) with 95% confidence interval (CI). Statistical analysis was performed using Stata 15 (College Station, TX: StataCorp LLC).

5.3.3.8 Qualitative Analysis

An open-ended question was used to obtain information on any specific concern(s) participants had about CDSS. The responses were categorised using a thematic analysis approach described by Braun and Clarke (286) using NVivo12 (QSR International Pty Ltd., Doncaster, Victoria, Australia). Preliminary codes were generated through open coding of the qualitative data (287). Using recursive comparison, these codes were then refined and merged into conceptual themes (details provided in Appendix B.6).

5.3.3.9 Ethics Approval

Ethical approval was obtained from the University of Adelaide Human Research Ethics Committee (approval number: H-2019-094). Participation was voluntary and the data collected was non-identifiable. To offset the expected low participation, the respondents were given the opportunity to participate in a draw either to win an iPad or equivalent donation made to the Hospital Research Foundation in recognition of their participation.

5.3.4 Results

5.3.4.1 Characteristics of Study Participants

A total of 180 clinicians participated in the survey with 74 from primary care and 106 from hospitals. Missing values for questions ranged from 5.1% to 13.3%. Participant demographic characteristics are described in Table 5.1.

Table 5.1 Characteristics of study participants.

Characteristics		*n* = 180 (%)
Gender		
Male		118 (66)
Female		62 (34)
Age-Group		
18–34 years		61 (34)
35–54 years		84 (47)
55 years and over		35 (19)
Years of Experience		
1–10 years		57 (32)
11–20 years		75 (42)
More than 20 years		48 (27)
Care setting and Type of Practice*		
Hospital(s)	Public	44 (24)
	Private	14 (8)
	Mixed	35 (19)
	Total	93 (51)
Primary care	Private	15 (8)
	Community clinic	11 (6)
	Hospital-based clinic	12 (7)
	Mixed	25 (14)
	Total	63 (35)
State and Territory, Australia (*n* = 139)*		
Eastern (ACT/NSW/Qld/Tas/Vic)		101 (73)
Central (SA/NT)		21 (15)
Western (WA)		17 (12)

* Non-mandatory question in the survey, thus, number not equal to total sample size (n=180) due to missing value.

5.3.4.2 Perceived Benefit of CDSS

Respondents had access to a variety of electronic systems/modules in their respective practices, with 52% having some form of CDSS available. Access to CDSS was higher in hospitals (58%) than in primary care (42%). Predefined order sets (57%) and alerts (49%) for antibiotic management were common features available to CDSS users. Conversely, CDSS did not provide specific functionality for antibiotic stewardship for 31% of respondents in our study.

In terms of perceived benefits, respondents (79%) agreed that CDSS implementation can increase accessibility to information for antibiotic management (Figure 5.2). CDSS users were 61% more likely than nonusers to believe that it can improve access to guidelines and care-related protocols (Figure 5.3). Clinicians in primary care were 69% less likely to recognise this benefit which may be related to the higher proportion of CDSS users in hospitals in our data.

Approximately half (52%) of the participants agreed that CDSS use is associated with improvements in the quality of care and would decrease unnecessary antibiotic prescriptions (46%), although this view was held mostly by clinicians with limited clinical experience. Respondents with 11–20, and >20 years of clinical experience were 42% and 56% less likely to believe that CDSS can positively impact the quality and safety of care. Experienced clinicians were also 58% (experience 11–20 years) and 66% (experience >20 years) less likely to believe that CDSS use is associated with a decrease in unnecessary antibiotic prescribing (Figure 5.3).

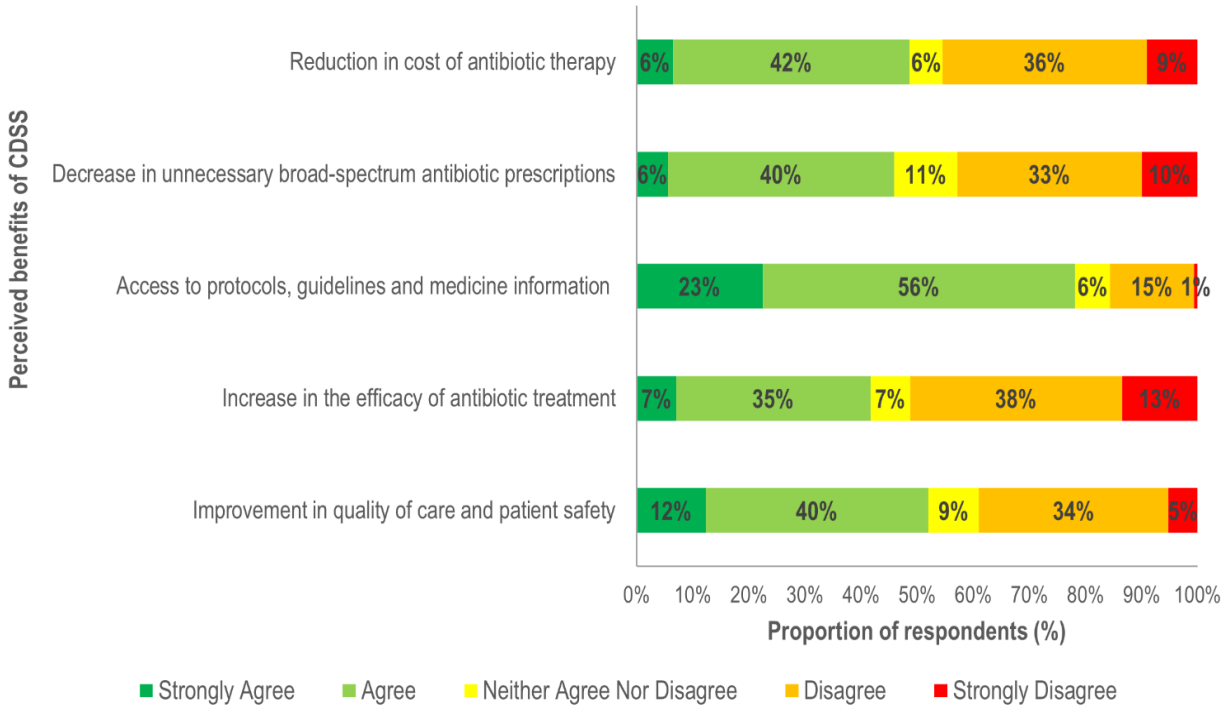
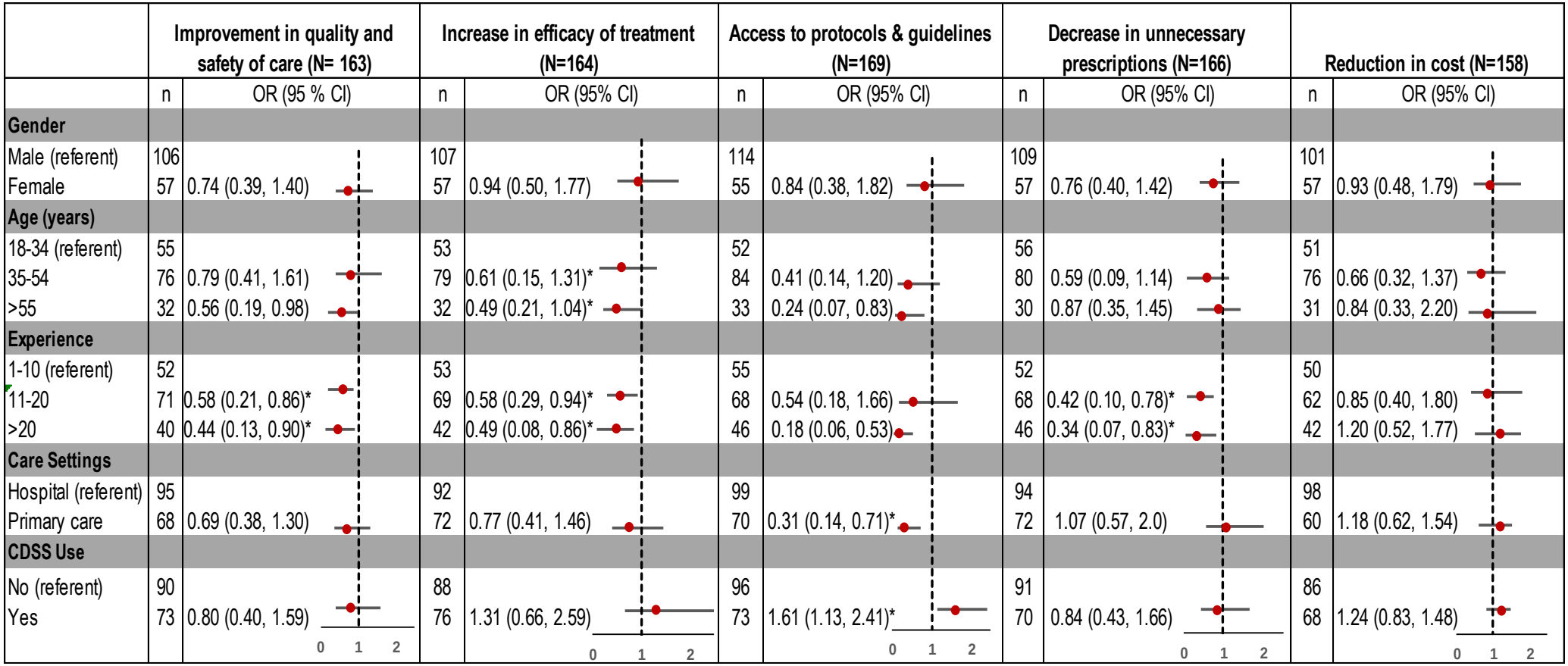


Figure 5.2 Overall perceived benefits of clinical decision support systems (CDSS).

	Improvement in quality and safety of care (N= 163)		Increase in efficacy of treatment (N=164)		Access to protocols & guidelines (N=169)		Decrease in unnecessary prescriptions (N=166)		Reduction in cost (N=158)	
	n	OR (95 % CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Gender										
Male (referent)	106		107		114		109		101	
Female	57	0.74 (0.39, 1.40)	57	0.94 (0.50, 1.77)	55	0.84 (0.38, 1.82)	57	0.76 (0.40, 1.42)	57	0.93 (0.48, 1.79)
Age (years)										
18-34 (referent)	55		53		52		56		51	
35-54	76	0.79 (0.41, 1.61)	79	0.61 (0.15, 1.31)*	84	0.41 (0.14, 1.20)	80	0.59 (0.09, 1.14)	76	0.66 (0.32, 1.37)
>55	32	0.56 (0.19, 0.98)	32	0.49 (0.21, 1.04)*	33	0.24 (0.07, 0.83)	30	0.87 (0.35, 1.45)	31	0.84 (0.33, 2.20)
Experience										
1-10 (referent)	52		53		55		52		50	
11-20	71	0.58 (0.21, 0.86)*	69	0.58 (0.29, 0.94)*	68	0.54 (0.18, 1.66)	68	0.42 (0.10, 0.78)*	62	0.85 (0.40, 1.80)
>20	40	0.44 (0.13, 0.90)*	42	0.49 (0.08, 0.86)*	46	0.18 (0.06, 0.53)	46	0.34 (0.07, 0.83)*	42	1.20 (0.52, 1.77)
Care Settings										
Hospital (referent)	95		92		99		94		98	
Primary care	68	0.69 (0.38, 1.30)	72	0.77 (0.41, 1.46)	70	0.31 (0.14, 0.71)*	72	1.07 (0.57, 2.0)	60	1.18 (0.62, 1.54)
CDSS Use										
No (referent)	90		88		96		91		86	
Yes	73	0.80 (0.40, 1.59)	76	1.31 (0.66, 2.59)	73	1.61 (1.13, 2.41)*	70	0.84 (0.43, 1.66)	68	1.24 (0.83, 1.48)



OR: odds ratio; CI: confidence interval. *Significant predictors, as confidence interval does not include 1.0

Figure 5.3 Association of perceived benefits to implementation of CDSS, by demographic characteristics.

5.3.4.3 Perceived Barriers

A lack of technical knowledge and training (69%) is an important barrier for CDSS adoption. Respondents (63%) also believed that end users' lack of trust and confidence in the system's content limits the usability (Figure 5.4).

As shown in Figure 5.5, the type of healthcare setting was associated with clinician's perceptions regarding barriers of time constraints, limits on professional autonomy, and patients' expectations. Clinicians in primary care were more likely than those in hospitals to believe that factors such as time limitation (34%), threats to professional autonomy (27%) and patients' preferences (84%) restrict the use of CDSS. Moreover, the likelihood of perceiving limited professional autonomy as a barrier was also found to increase with clinical experience (11–20 years: OR = 1.36, 95%, CI = 1.10, 1.97; >20 years: OR = 1.68, 95%, CI = 1.27, 2.85). Respondents in primary care (71%) were more likely to have >11 years clinical experience compared to those in hospitals (54%). Therefore, the association of settings with a threat to professional autonomy as a barrier may be related to a higher proportion of experienced respondents in the primary care group. Overall, clinicians with >20 years of clinical experience were more likely to believe that a lack of confidence in the CDSS content (58%) and risk of medico-legal liability (41%) would inhibit its use.

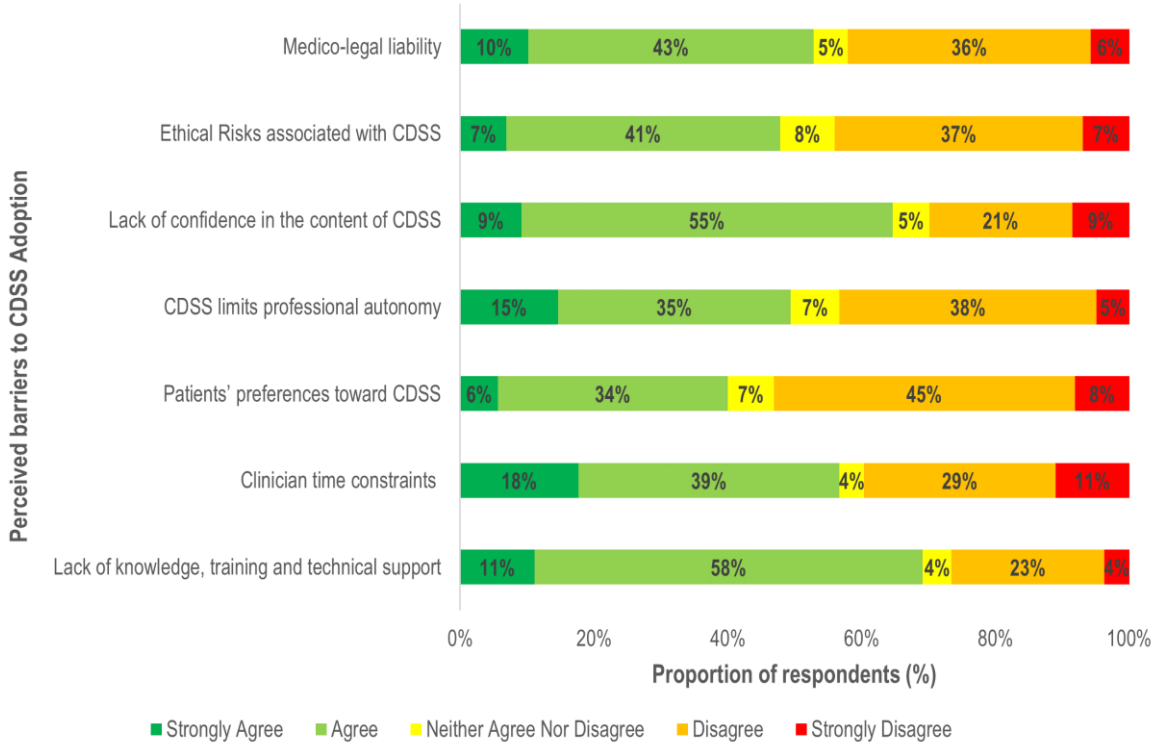
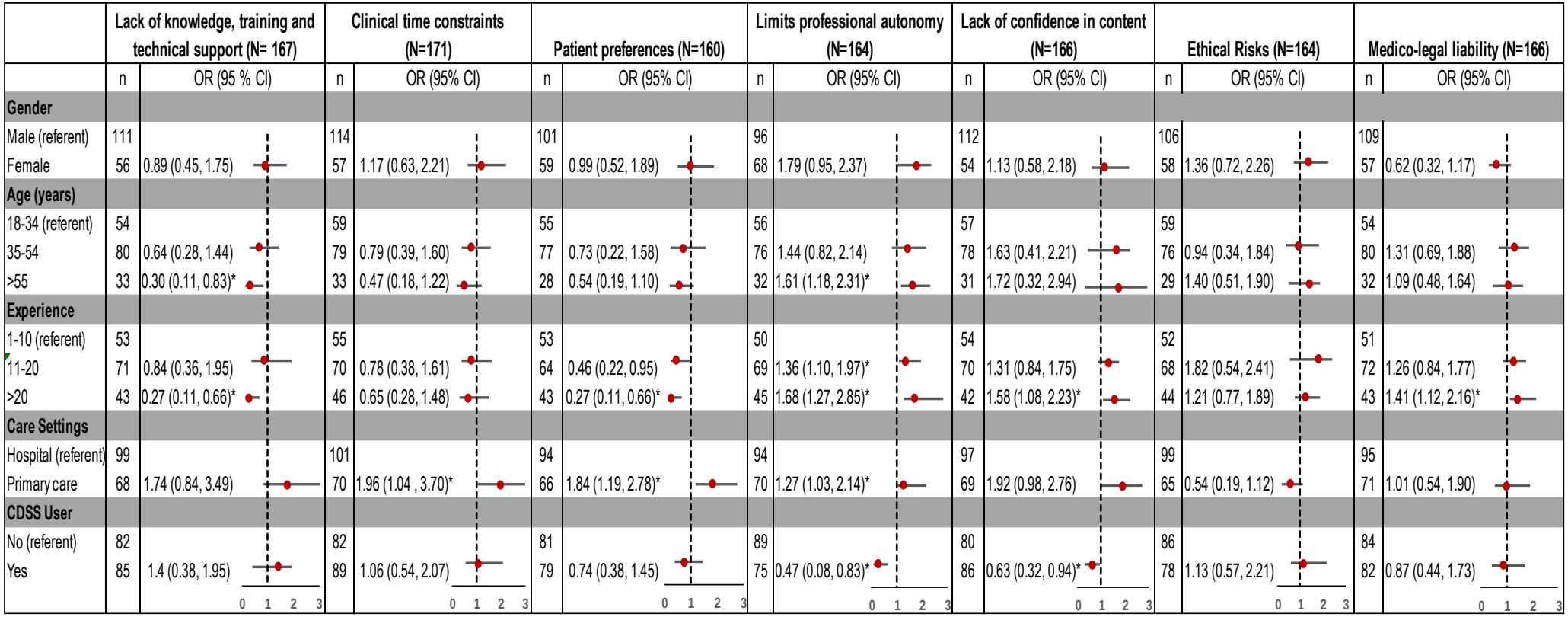


Figure 5.4 Reported barriers to CDSS adoption



OR: odds ratio; CI: confidence interval. *Significant predictors as confidence interval does not include 1.0

Figure 5.5 Association of perceived barriers to implementation of CDSS, by demographic characteristics

5.3.4.4 Perceived Facilitators

Figure 5.6 highlights strong agreement (75%) of CDSS adoption if systems are easy to use, whereas 64% believed that organisational support is required for successful implementation. Along with organisational support, 61% also agreed that effective training and technical support ensures clinicians receive adequate support and skills to use it effectively.

Healthcare setting, years of experience and CDSS use were associated with clinicians' perception of different factors as enablers to CDSS adoption. Compared to hospitals, clinicians in primary care settings were 29% more likely to believe that ease of use will facilitate CDSS adoption (Figure 5.7).

Clinical experience (years) was also a significant predictor, with experienced clinicians more likely to believe that end-user consultation in the design and development of the system and the availability of technical support as important facilitators for use of CDSS. In comparison to non-users, there was higher likelihood in CDSS users to consider ease of use (OR = 1.37, 95%, CI = 1.09, 1.94) and users' participation in the design and implementation phases (OR = 1.41 95%, CI = 1.17, 1.53) as factors that enable adoption (Figure 5.7).

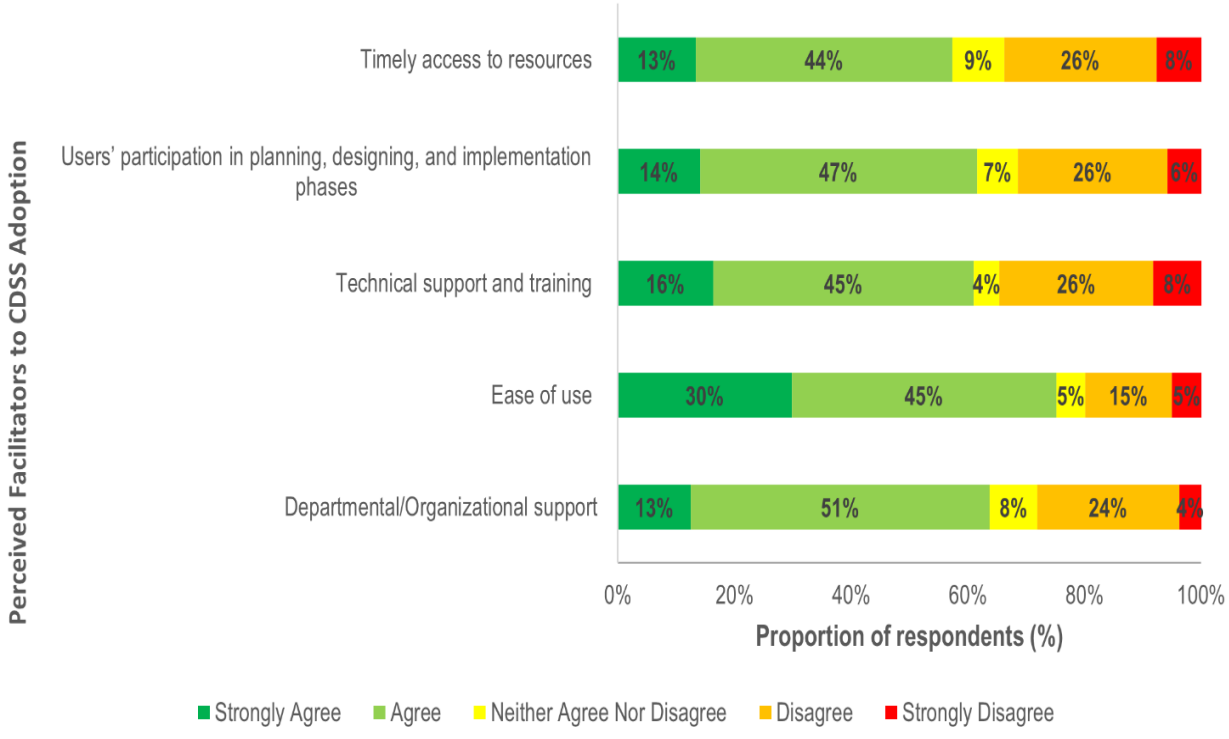
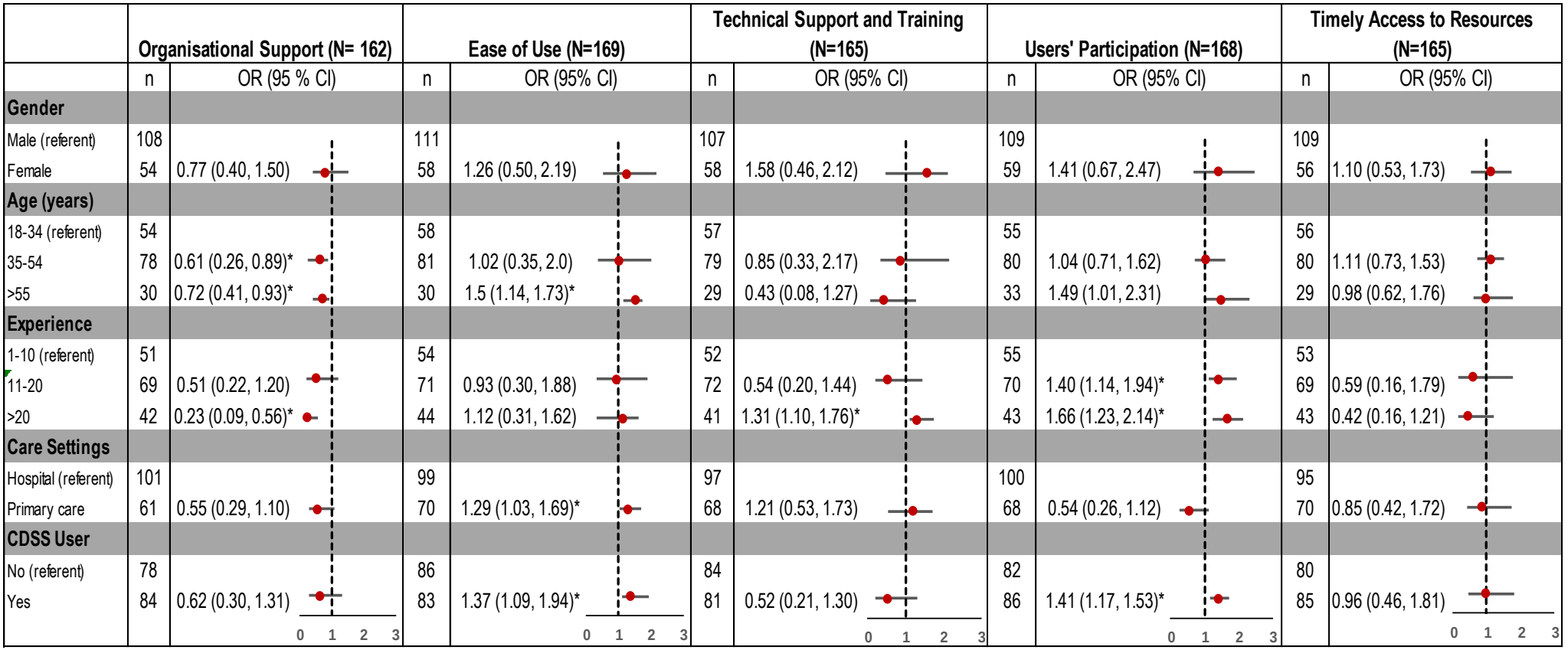


Figure 5.6 Facilitators to CDSS adoption

	Organisational Support (N= 162)		Ease of Use (N=169)		Technical Support and Training (N=165)		Users' Participation (N=168)		Timely Access to Resources (N=165)	
	n	OR (95 % CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Gender										
Male (referent)	108		111		107		109		109	
Female	54	0.77 (0.40, 1.50)	58	1.26 (0.50, 2.19)	58	1.58 (0.46, 2.12)	59	1.41 (0.67, 2.47)	56	1.10 (0.53, 1.73)
Age (years)										
18-34 (referent)	54		58		57		55		56	
35-54	78	0.61 (0.26, 0.89)*	81	1.02 (0.35, 2.0)	79	0.85 (0.33, 2.17)	80	1.04 (0.71, 1.62)	80	1.11 (0.73, 1.53)
>55	30	0.72 (0.41, 0.93)*	30	1.5 (1.14, 1.73)*	29	0.43 (0.08, 1.27)	33	1.49 (1.01, 2.31)	29	0.98 (0.62, 1.76)
Experience										
1-10 (referent)	51		54		52		55		53	
11-20	69	0.51 (0.22, 1.20)	71	0.93 (0.30, 1.88)	72	0.54 (0.20, 1.44)	70	1.40 (1.14, 1.94)*	69	0.59 (0.16, 1.79)
>20	42	0.23 (0.09, 0.56)*	44	1.12 (0.31, 1.62)	41	1.31 (1.10, 1.76)*	43	1.66 (1.23, 2.14)*	43	0.42 (0.16, 1.21)
Care Settings										
Hospital (referent)	101		99		97		100		95	
Primary care	61	0.55 (0.29, 1.10)	70	1.29 (1.03, 1.69)*	68	1.21 (0.53, 1.73)	68	0.54 (0.26, 1.12)	70	0.85 (0.42, 1.72)
CDSS User										
No (referent)	78		86		84		82		80	
Yes	84	0.62 (0.30, 1.31)	83	1.37 (1.09, 1.94)*	81	0.52 (0.21, 1.30)	86	1.41 (1.17, 1.53)*	85	0.96 (0.46, 1.81)



OR: odds ratio; CI: confidence interval. *Significant predictors as confidence interval does not include 1.0

Figure 5.7 Association of perceived facilitators to CDSS implementation, by demographic characteristics

5.3.4.5 Qualitative Analysis

Analysis of free-text comments provided three major themes concerning factors that influence CDSS implementation:

5.3.4.5.1 Lack of Flexibility

Respondents expressed concerns regarding CDSS inflexibility to change as a barrier to adoption. System usefulness is significantly limited if it lacks the ability to reflect the complex clinical context by:

"*Systems I have experienced are comically bad in design mainly because they are inflexible in their ability to change*." (Hospital)

Clinicians require flexibility and adaptability in systems instead of "constant rule-making" to tailor recommendations to a specific context.

"There is never a 'one size fits all'. So there must always be room to make exceptions." (Primary care)

5.3.4.5.2 Information Overload

"*My major frustration with it [CDSS] in terms of antibiotic therapy is the presence of excessive alerts, which do nothing to protect patients and simply lead to alert fatigue*." (Hospital)

Information relevance and precision emerged as important factors influencing CDSS adoption. Excessive information with low specificity and relevancy leads to alert fatigue and the decision to override, thereby reducing the overall use of CDSS. Furthermore, it was highlighted that time and workload pressures make it difficult for clinicians to distinguish important information from irrelevant data.

5.3.4.5.3 Information Accuracy

"*I, as a user, need to know on what basis any recommendation is provided, what is the source of this knowledge and how often it is updated.*" (Primary care)

The accuracy of the content was also identified as an important theme for clinicians to trust the CDSS. Respondents expressed doubts concerning the currency and reliability of the content which then determines their overall trust in the system.

"[W]ithout knowing how often guidelines are updated in the system, we cannot rely on system alerts." (Hospital)

The uncertainty felt by clinicians about the quality and accuracy of evidence negatively impacts their perception of CDSS.

5.3.5 Discussion

Our study contributes to the existing body of evidence by highlighting clinicians' perceptions regarding CDSS implementation for antibiotic management. We focused on internal and external factors influencing users' intent to adopt CDSS by incorporating the UTAUT framework. Internal related factors were specific to personal perceptions, whereas external factors represented organisational, technical or patient related factors. While previous studies have illustrated different factors determining users' acceptance of CDSS related to antibiotic use, there is limited understanding of underlying factors that contribute to variations in acceptance of CDSS by different end-users. We addressed this gap in knowledge by evaluating the impact of age, gender, clinical experience, care setting and CDSS availability on users' intention to adopt CDSS for antibiotic management.

5.3.5.1 Barriers and Facilitators

5.3.5.1.1 External Factors

Lack of organisational capacity to provide appropriate technical support and training was a significant barrier and has been shown to limit users' confidence in a system and the ability to resolve any technical issues that may arise, thus discouraging CDSS adoption (288, 289). Organisational theories also identify culture as an enabling factor for promoting the adoption of any new technology (290). We found that young clinicians were more likely to require organisational support in order to adopt CDSS for antibiotic management, perhaps because clinical hierarchy and seniors' preferences greatly influence the practices of young clinicians (291) and seniors' in our study were less likely to adopt CDSS.

One of the basic system quality constructs of UTAUT is the ease of use. In our survey, ease of use was a key factor that facilitates the adoption and adherence of clinicians to CDSS use for antibiotic management. This is consistent with measures in the information system (IS) success model proposed by DeLone and Mclean (1992) that relates user satisfaction and adoption to ease of use (273, 292). We found that primary care clinicians and those with experience of using CDSS perceived ease of use to be one of the most important features for CDSS adoption. Limited consultation time, workload, and the potential for compromise of direct communication with patients due to the time required to navigate the system, make ease of use a highly relevant requirement for the successful implementation of CDSS in primary care (281, 293, 294).

System effort expectancy and perceived benefit is related to users' trust that the system is a fit for their specific requirements (146). Our results highlighted that clinicians with longer working experience tended to rate end-user consultation as an important facilitator for CDSS implementation. Similarly, our results also indicated that clinicians with longer clinical experience (>11 years) were more likely to see CDSS as a threat to their clinical autonomy. Therefore, inclusion of experienced clinicians in the CDSS development and implementation process would likely foster increased acceptance, trust and compliance with the system.

5.3.5.1.2 Internal Factors

In our study, internal factors were frequently reported as barriers to CDSS adoption for antibiotic management, with lack of confidence in the content of the system most frequently reported. This was a common concern of CDSS nonusers in our study, which suggests that it could be a result of limited understanding of how the system sources information to guide recommendations, along with a lack of trust in personnel involved in system development, and lack of agreement with the content (295, 296). The apprehension that adoption of CDSS would compromise individual clinical judgements increases the reluctance of clinicians to engage with the technology (213, 297). Clinicians in our study with experience of using CDSS were less likely to believe that use of CDSS would compromise their professional autonomy, suggesting that end-user reluctance to adopt CDSS for these reasons might be the result of a perception about the system rather than actual experience with the system. Experienced clinicians were also less likely to use CDSS due to fear of compromising established work practices and reducing autonomous control over these processes and the content of clinical decisions. Studies indicate that younger clinicians tend to have better technological literacy and are more confident in using systems such as CDSS (270, 298). Our results are consistent with this literature, as a higher proportion of younger clinicians amongst our respondents were CDSS users as compared to senior clinicians. To overcome barriers to CDSS adoption, an effective clinical engagement process with experienced clinicians is required. The aim would be to empower early adopters amongst this cohort to drive the change process and advocate use of CDSS among their peers.

We found that clinicians' time constraints and risk of workflow disruptions may also contribute to end-user resistance to CDSS adoption for antibiotic management. This is consistent with previous studies suggesting that failure to provide a fit between relevance, format and timeliness of recommendations negatively impact the uptake and utilisation of CDSS more generally (115, 137). Moreover, our findings also highlight that there is a greater likelihood in primary care of perceiving time and workflow constraints as barriers to CDSS adoption. Despite the fact that workflow disruptions and time sensitivities (high

workloads) are relevant across all healthcare settings, the need to assess clinical data within a short consult might contribute to limited CDSS adoption in primary care (299).

Our findings highlight the impact of moderating factors, such as age, clinical experience and digital health literacy, shape clinicians' behaviour in adopting digital health systems. These findings are consistent with the wider literature on the influence of these factors on the perceived usefulness and users' intention to adopt other digital health systems (300-302). For example, Jacob *et al*. (303) recommended that understanding users' inclination based on these moderating factors can help reduce the heterogeneity in system adoption and enable a cultural shift across all clinicians. Future work should be directed toward establishing guidelines and a policy framework to address the barriers to CDSS adoption for antibiotic management. Our findings identified a range of individual and setting characteristics that influence the adoption and use of these types of CDSS. Further work in addressing organisational barriers and identifying optimal structures in terms of planning, management, leadership and communication to support CDSS implementation should be considered. Our study has several limitations. Because of low participation, the results may not be representative of the knowledge and perceptions of all Australian clinicians. Although the participation rate was not as high as planned, it is not dissimilar to other surveys conducted with clinicians (278, 304, 305). Participants may have self-selected as a consequence of polarised views on the topic, introducing selection bias. Another limitation is the cross-sectional design of this survey limiting the ability to draw any causal inference. Also, respondents' perceptions of factors related to CDSS for antibiotic management may not correlate with their actual practice. We allowed open responses to some questions which may have mitigated this to some extent.

5.3.6 Conclusion

This study advances the current knowledge of how different factors influence clinicians' perceptions about CDSS adoption for antibiotic management. Comparisons between CDSS users and nonusers indicate that certain negative perceptions about CDSS for antibiotic management were related to a lack of clinical engagement and understanding of CDSS. Experienced clinicians were more likely to trust their own knowledge and approaches to prescribing antibiotics and were more sceptical of adopting CDSS. Similarly, time constraints and patient preferences in primary care were important factors in understanding clinicians' reluctance to adopt CDSS for this purpose. Easy-to-use, flexible systems are more likely to be adopted, particularly if experienced clinicians are involved in their development, have confidence in the information and currency of the content in the CDSS and are trained in how to use the systems. These findings may help health service delivery organisations to successfully implement CDSS for antibiotic stewardship.

Author Contributions: M.L., A.M. and T.M. developed the conceptual framework and research protocol for the study. M.L. performed the analysis and drafted the manuscript. All authors contributed to interpretation of the analyses, critical revision of the manuscript and gave final approval of the version to be published.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The survey data is not publicly available due to restricted data consent provided by participants concerning sharing of information. A limited dataset is available from the corresponding author on request.

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Conflicts of Interest: The authors declare no conflict of interest.

5.4 Chapter Synopsis

Chapter 5 presented the findings of a survey conducted with clinicians regarding the drivers of CDSS adoption in different care settings. The focus was to identify underlying factors that shape clinicians' perceptions concerning CDSS adoption for antibiotic management. For this purpose, the theoretical framework of Unified Theory of Acceptance and Use of Technology (UTAUT) model was adopted to understand how different moderating factors such as age, gender, clinical experience, and care settings influence the users' behavioural intent to adopt CDSS.

The findings suggested that CDSS adoption is influenced by the organisational environment as well as individual perceptions regarding how adaptable the system is to specific requirements and needs. Not surprisingly, users are more inclined to adopt the systems when they are easy-to-use and flexible. These findings reinforce the UTAUT theory by indicating that effort expectancy and facilitating environment are important drivers of users' behavioural intention to adopt CDSS.

The results also suggested that different care settings and years of clinical experience were important moderators of users' perceptions regarding the efficacy of these systems. The experienced clinicians were more likely to express concerns about CDSS adoption due to the risk of compromising their professional autonomy in clinical decision-making. Moreover, negative perceptions about CDSS use such as fear of limited professional autonomy and lack of trust in systems' recommendations were more prevalent in non-users.

In conclusion, this study highlights the importance of contextual factors such as clinicians' years of experience and the care setting within which they work when understanding the users' behavioural intent to adopt CDSS. The setting dynamics and user-specific requirements should be considered when implementing CDS systems, with the implementation process tailored to address these moderating factors.

Chapter 6: Barriers to Appropriate Antibiotic Prescribing

6.1 Preface

The study presented in this chapter is the second part of the survey conducted with clinicians in Australia to identify barriers and enablers for the uptake of CDSS to support evidence-based antibiotic management.

This chapter aims to provide a better understanding of the circumstances that surround antibiotic prescribing in different care settings. The study focused on gaining insight into factors that influence the antibiotic prescribing behaviour among different clinicians. Clinicians across primary care and hospitals were surveyed to determine factors that drive the prescribing behaviour in these different settings.

The chapter addresses the third research question and respective objective indicated in Figure 6.1.The online survey questionnaire is provided in the supplementary information. This study was published in the *Australian Health Reviews.*

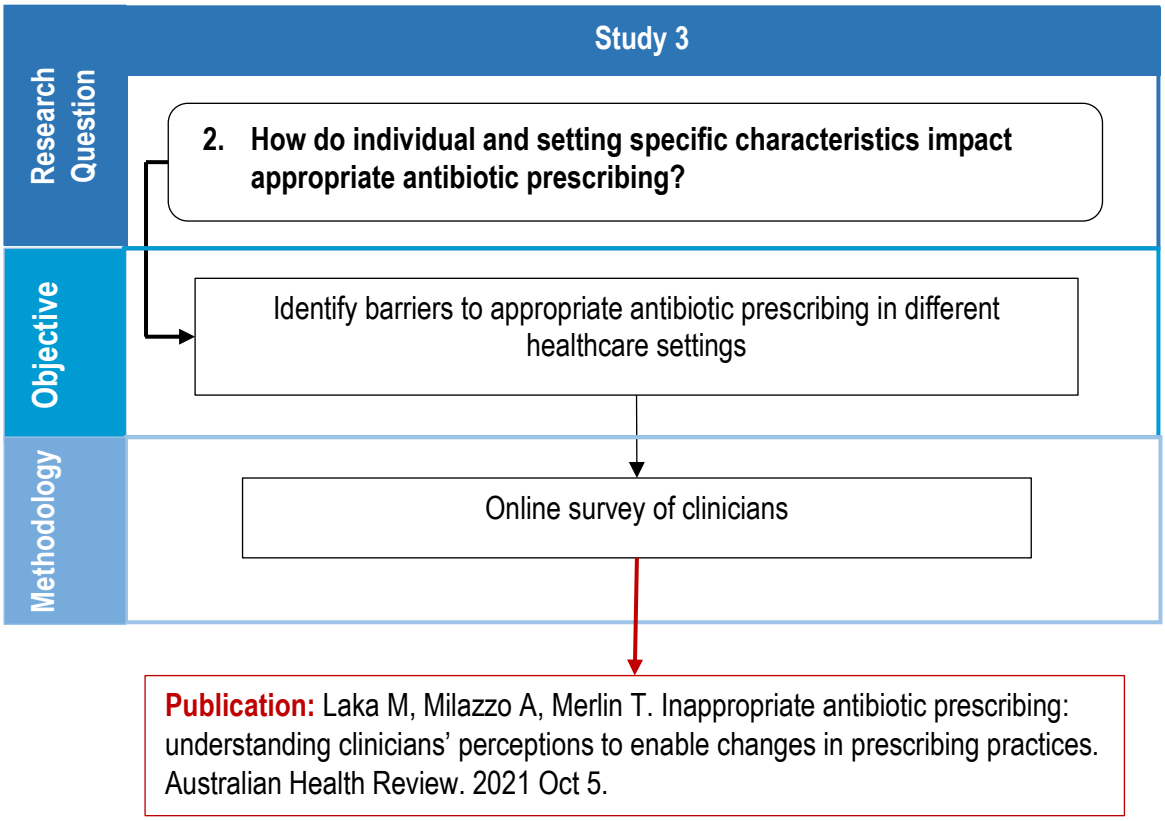

Figure 6.1 Structure of chapter's research question and objectives

6.2 Statement of Authorship

Statement of Authorship

Title of Paper	Inappropriate antibiotic prescribing: Understanding clinicians' perceptions to enable change in prescribing practices
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Laka M, Milazzo A, Merlin T. Inappropriate antibiotic prescribing: Understanding clinicians' perceptions to enable change in prescribing practices. Australian Health Review.

Principal Author

Name of Principal Author (Candidate)	Mah Laka
Contribution to the Paper	I contributed to the study concept, study design and statistical framework. I recruited the study participants, collected the data, performed the analyses and prepared the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 24/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Adriana Milazzo
Contribution to the Paper	A. Milazzo contributed to the study concept as well as study design. She also assisted in the interpretation of the results. She provided feedback on the manuscript and evaluated the revised manuscript against reviewers' comments.
Signature	Date 24/8/21

Name of Co-Author	Professor Tracy Merlin
Contribution to the Paper	T. Merlin contributed to the study concept as well as study design. She assisted in the interpretation of the results. She provided feedback on the manuscript and evaluated the revised manuscript against reviewers' comments.
Signature	Date 24/8/21

Please cut and paste additional co-author panels here as required.

6.3 Manuscript

Title

Inappropriate antibiotic prescribing: Understanding clinicians' perceptions to enable change in prescribing practices

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6.3.1 Abstract

Objective: To identify perceived barriers to appropriate antibiotic prescribing across different healthcare settings.

Methods: A cross-sectional survey of clinicians in Australian hospitals and primary care was undertaken between June–October 2019. The perceived barriers to appropriate antibiotic prescribing were considered as dependent variables whereas factors including age, gender, clinical experience, healthcare setting and use of guidelines were independent variables in our study. We applied multivariate logistic regression to identify predictive factors of inappropriate antibiotic prescribing. Content analysis of free-text responses provided additional insight into the impediments to appropriate prescribing.

Results: A total of 180 clinicians completed the survey. Overall, diagnostic uncertainty and limited access to guidelines and prescribing information were significant barriers to appropriate antibiotic prescribing. Factors associated with these barriers were clinical experience, care setting (hospitals vs. primary care) and use of guidelines. Experienced clinicians (>11years) were less likely to consider that limited access to information negatively impacted prescribing practices (experience: 11-20years: OR 0.66, 95%CI 0.31, 0.84; >20years: OR 0.51, 95%CI 0.24, 0.91). On the other hand, general practitioners considered diagnostic uncertainty (OR: 1.31, 95%CI 1.09, 1.63) and patient expectations (OR: 1.41, 95%CI 1.12, 1.84) were more likely to be perceived barriers to appropriate prescribing. Use of guidelines and clinical experience may counteract this.

Conclusion: Clinicians' years of experience, use of guidelines and type of setting were predictors of clinicians' perceptions regarding antibiotic prescribing. Our data highlights the importance of individual and setting characteristics in understanding variations in prescribing practices and designing targeted interventions for appropriate antibiotic prescribing.

6.3.2 Introduction

Antibiotic resistance has emerged as a significant public health issue due to increasing health and economic burden. Many studies have attributed this increasing resistance to excessive and inappropriate antibiotic use (2, 306). Worldwide antibiotic consumption has increased by 65% from year 2000 - 2015 with inappropriate antibiotic use established as one of the main factors contributing to this (46).

In Australia, antibiotic consumption is high compared to other high income countries (307). It is estimated that 22 million antibiotics are prescribed yearly equating to one antibiotic per person each year (42). Overall, 46% of the Australian population in 2014 was dispensed antibiotics for which it is estimated that half were unnecessary (42). The majority of patients over 18 years who were seen in primary healthcare in Australia were prescribed antibiotics for conditions such as acute bronchitis (92.4%), pneumonia (92.9%), sinusitis (90.2%) and acute upper respiratory tract infections (URTIs) (62.3%) for which antibiotics are not generally recommended by prescription guidelines (42).

Antimicrobial stewardship (AMS) initiatives have been introduced to improve prescribing behaviour by increasing access to evidence-based antibiotic prescribing guidelines. However, adherence to these guidelines remains problematic. Studies have highlighted limited compliance, ranging from 30–70% (308, 309). Behavioural and contextual determinants may influence the prescribing behaviour of healthcare practitioners, hence it is important to consider these factors when designing interventions to promote rational antibiotic prescribing. This includes identifying the opportunities and challenges at an individual or organisational level for promoting sustainable antimicrobial stewardship.

Previous studies have reported on a number of factors influencing inappropriate antibiotic prescribing (306, 307, 310, 311), however, there is little information on how different individual and setting-specific characteristics contribute to variability in prescribing patterns. We aimed to identify perceived barriers to appropriate antibiotic prescribing as well as assess the impact of individual and setting characteristics on clinicians' perceptions around antibiotic prescribing. This knowledge may inform the design of stewardship interventions that encourage greater levels of compliance with appropriate prescribing.

6.3.3 Methods

6.3.3.1 Study design

An online survey of primary care and hospital clinicians was conducted across Australia. The questionnaire was developed following a detailed review of existing literature (310, 312-315) (Appendix B.4). Its design was described in a previous study (190). In the survey preamble, inappropriate antibiotic

prescribing was defined as when antibiotics are not required, are prescribed for a non-optimal duration and dose, or when the wrong type of antibiotic has been selected. The current sub-study specifically examined factors related to inappropriate antibiotic prescribing, while the broader study (190) was concerned with barriers and facilitators for computer decision support system adoption for antibiotic management. The survey question concerning barriers to appropriate antibiotic prescribing was presented in a multiple-response format; however, if participants did not agree with the provided options, the 'others (please specify)' option was provided with a free-text box to write additional comments. Prior to its release, the survey was piloted on 10 clinicians, amended and then distributed.

6.3.3.2 Study participants

On behalf of the study investigators, information about the study and the survey link was distributed to clinicians by Royal Australasian Colleges of Physicians, General Practitioners and Surgeons, and local health networks across Australia through their newsletters, websites and social media accounts. The National Health Workforce Data Set on medical practitioners (2015–2018) was used to establish the sampling framework. We estimated a sample size of 350 clinicians from hospitals and primary healthcare based on a 5% margin of error, 95% confidence interval and power of 0.80.

6.3.3.3 Data collection

The survey questionnaire included a section on demographic characteristics (gender, age, clinical experience (years) and practice in hospital or primary care) and questions about antibiotic prescribing. This included availability and frequency of use of antibiotic prescribing guidelines and perceived barriers to appropriate antibiotic prescribing. The online survey was administered using SurveyMonkey (www.surveymonkey.com, San Mateo, California, US).

6.3.3.4 Data Analysis

6.3.3.4.1 Quantitative

Initially, data were descriptively analysed to identify the characteristics of the survey participants and the perceived barriers to appropriate antibiotic prescribing. As it was not mandatory to respond to all questions, the total number of participants varied depending on the number of responses for that question. For the multiple-response question, a separate dichotomous variable was created for each valid response. Each variable was assigned two possible values i.e. 1 if the response was selected and 0 if not selected. We considered demographic characteristics and use of guidelines as independent variables whereas perceived barriers to appropriate prescribing were analysed as the dependent variable. We applied multivariate logistic regression to estimate associations between the dependent

and independent variables. Results were reported as odds ratios (OR) with 95%CI relative to a referent category. The data was statistically analysed using Stata15 (StataCorp LP, College Station, TX).

6.3.3.4.2 Content Analysis

The questionnaire allowed for one free-text comment box for respondents to include additional information on their perceptions of barriers to appropriate antibiotic prescribing. These comments were analysed for contextual content in NVivo12 (QSR International Pty Ltd, Doncaster, Victoria, Australia). Most responses were brief, thus, manifest content analysis was an appropriate approach to understand the context of the data (316). The manifest content analysis aided interpretation through examining the obvious elements in the data. Open coding identified preliminary categories which were then organised into relevant first and second order codes through multiple iterations (details provided in Appendix B.7). Themes were compared with results from the quantitative analysis to triangulate the data for an additional understanding of responses.

6.3.3.5 Ethical Approval

The University of Adelaide Human Research Ethics Committee provided approval for this study (approval number: H-2019-094). Participation was voluntary and data collected were non-identifiable. To offset expected low participation rates from clinicians, the respondents were provided the opportunity to take part in a draw to win either an iPad or have an equivalent value donation made in their name to a Hospital Research Foundation.

6.3.4 Results

6.3.4.1 Characteristics of respondents

A total of 180 clinicians completed the survey, and of these 74 (41%) were from primary healthcare and 106 (59%) from hospitals. Participants' demographic characteristics are provided in Table 6.1

Table 6.1 Characteristics of study participants

Gender	**n(%)**
Male	118 (66)
Female	62 (34)
Age-group	
18-34 years	61 (34)
35-54 years	84 (47)
55 years and over	35 (19)

Years of experience		
1-10 years		57 (32)
11-20 years		75 (42)
More than 20 years		48 (27)
Healthcare setting and type of practice*		
Hospital(s)	Public	44 (24)
	Private	14 (8)
	Mixed	35 (19)
Primary care	Private	15 (8)
	Community clinic	11 (6)
	Hospital-based clinic	12 (7)
	Mixed	25 (14)
Specialisation (hospital settings, n=84)*		
General Medicine		23 (27)
Infectious Disease		10 (12)
Emergency Medicine & Critical Care		8 (10)
Orthopaedics		8 (10)
Surgery		8 (10)
Paediatrics		6 (7)
Urology		6 (7)
Clinical Pharmacy		5 (6)
Gynaecology and Obstetrics		4 (5)
Anaesthesia		3 (4)
Gastroenterology		2 (2)
Dermatology		1 (1)
State and territory, Australia (n=139)*		
Eastern (ACT/NSW/Qld/Tas/Vic)		101 (73)
Central (SA/NT)		21 (15)
Western (WA)		17 (12)

6.3.4.2 Use of guidelines and antibiotic prescribing

Most respondents (68%) used specific guidelines when prescribing antibiotics. Clinicians in hospitals used guidelines more frequently with 48% using them daily compared to 33% in primary care. Of respondents who used specific guidelines for antibiotic prescribing, 78% reported using national guidelines (Therapeutic Guidelines: Antibiotics) whereas 22% used local/intranet guidelines.

The majority of respondents (75%) stated that delays in receiving diagnostic tests/cultures was a contributing factor to inappropriate antibiotic prescribing, particularly in primary care (OR=1.31, 95%CI 1.09, 1.63). Similarly, participants who use guidelines less frequently (monthly or longer) were 70% less likely to believe that delays in diagnostic tests can negatively impact their prescribing behaviour (Figure 6.2 and Figure 6.3).

More than half of the respondents believed that limited information such as local resistance patterns, formulary restrictions etc. (55%), and the absence of antibiotic prescribing guidelines (53%) limits clinicians' ability to appropriately prescribe antibiotics (Figure 6.2). General practitioners (GPs) were more likely to perceive that the lack of guidance was a barrier to appropriate antibiotic prescribing (OR=1.24, 95%CI 1.05, 1.64). Participants who use guidelines for antibiotic prescribing were nearly a third more likely to believe that access to guidelines can improve prescribing practices (OR=1.31, 95%CI 1.1, 1.73). This was consistent with the observation that clinicians accessing guidelines less frequently (monthly) compared to daily were more likely to believe that their personal perceptions can be a contributing factor to inappropriate prescribing (OR=1.24, 95%CI 1.04, 1.77). On the other hand, clinicians with more than 20 years of clinical experience were 34% less likely to believe that they require guidance on appropriate antibiotic prescribing (OR=0.66, 95%CI 0.45, 0.94). Presumably, this was because they felt more comfortable relying on their own experience. Likewise, older clinicians were less likely to believe that their knowledge and perceptions contribute to inappropriate prescribing (age 35-54 years: OR=0.44, 95%CI 0.16, 0.80; >55 years: OR=0.27, 95%CI 0.09, 0.42) (Figure 6.3).

The impact of patient expectations on inappropriate prescribing was considered important by 42% of respondents. Those working in primary care were 41% more likely than those in hospitals to report that patient expectations influence inappropriate antibiotic prescribing (OR=1.41, 95%CI 1.12, 1.84). Clinicians with longer clinical experience (11- 20 years: OR=0.54, 95% CI 0.21, 0.73; >20 years: OR=0.39, 95% CI 0.19, 0.56) and those using guidelines for prescribing antibiotics (OR=0.68, 95% CI 0.45, 0.97) were less likely to be influenced by this pressure.

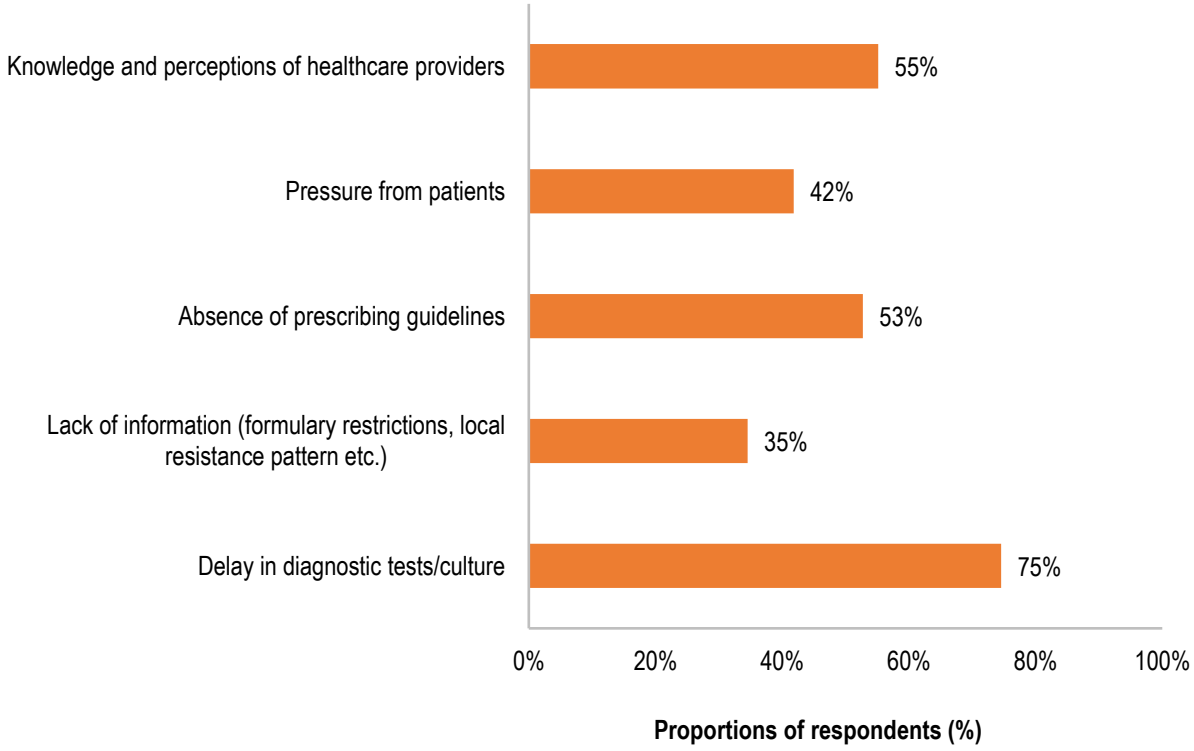
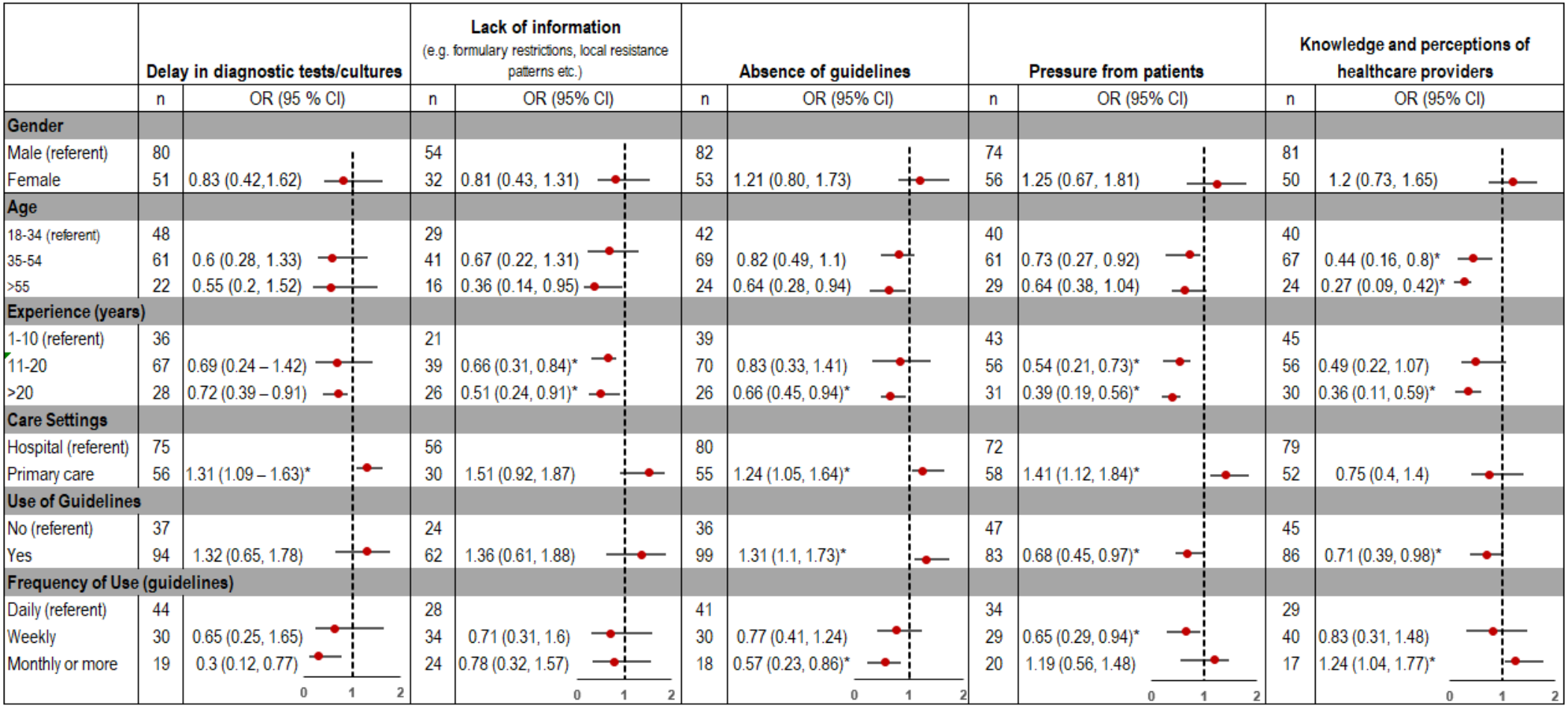


Figure 6.2 Overall perceived barriers to appropriate antibiotic prescribing

	Delay in diagnostic tests/cultures		Lack of information (e.g. formulary restrictions, local resistance patterns etc.)		Absence of guidelines		Pressure from patients		Knowledge and perceptions of healthcare providers	
	n	OR (95 % CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Gender										
Male (referent)	80		54		82		74		81	
Female	51	0.83 (0.42,1.62)	32	0.81 (0.43, 1.31)	53	1.21 (0.80, 1.73)	56	1.25 (0.67, 1.81)	50	1.2 (0.73, 1.65)
Age										
18-34 (referent)	48		29		42		40		40	
35-54	61	0.6 (0.28, 1.33)	41	0.67 (0.22, 1.31)	69	0.82 (0.49, 1.1)	61	0.73 (0.27, 0.92)	67	0.44 (0.16, 0.8)*
>55	22	0.55 (0.2, 1.52)	16	0.36 (0.14, 0.95)	24	0.64 (0.28, 0.94)	29	0.64 (0.38, 1.04)	24	0.27 (0.09, 0.42)*
Experience (years)										
1-10 (referent)	36		21		39		43		45	
11-20	67	0.69 (0.24 – 1.42)	39	0.66 (0.31, 0.84)*	70	0.83 (0.33, 1.41)	56	0.54 (0.21, 0.73)*	56	0.49 (0.22, 1.07)
>20	28	0.72 (0.39 – 0.91)	26	0.51 (0.24, 0.91)*	26	0.66 (0.45, 0.94)*	31	0.39 (0.19, 0.56)*	30	0.36 (0.11, 0.59)*
Care Settings										
Hospital (referent)	75		56		80		72		79	
Primary care	56	1.31 (1.09 – 1.63)*	30	1.51 (0.92, 1.87)	55	1.24 (1.05, 1.64)*	58	1.41 (1.12, 1.84)*	52	0.75 (0.4, 1.4)
Use of Guidelines										
No (referent)	37		24		36		47		45	
Yes	94	1.32 (0.65, 1.78)	62	1.36 (0.61, 1.88)	99	1.31 (1.1, 1.73)*	83	0.68 (0.45, 0.97)*	86	0.71 (0.39, 0.98)*
Frequency of Use (guidelines)										
Daily (referent)	44		28		41		34		29	
Weekly	30	0.65 (0.25, 1.65)	34	0.71 (0.31, 1.6)	30	0.77 (0.41, 1.24)	29	0.65 (0.29, 0.94)*	40	0.83 (0.31, 1.48)
Monthly or more	19	0.3 (0.12, 0.77)	24	0.78 (0.32, 1.57)	18	0.57 (0.23, 0.86)*	20	1.19 (0.56, 1.48)	17	1.24 (1.04, 1.77)*



OR: Odds ratio; CI: Confidence Interval

*Significant values of predictors; OR >1 means more likely a barrier to appropriate antibiotic prescribing and OR<1 means less likely a barrier

Figure 6.3 Effect Estimates of perceived barriers to appropriate antibiotic prescribing, by demographic characteristics and use of guidelines

6.3.4.3 Content Analysis

Free-text comments on perceived barriers to appropriate antibiotic prescribing was reported from primary care (n=11) and hospital clinicians (n=16). Major themes included limited diagnostic certainty, inter-professional practices and adaptability of guidelines. Some of these themes provided elaboration on data measures included in the quantitative analysis whereas others, such as inter-professional practices, emerged as an additional theme as highlighted through triangulation of the data.

6.3.4.3.1 Limited diagnostic certainty

Respondents indicated that to avoid missing potential infection, antibiotics are sometimes prescribed as a precautionary measure.

"At times, it is difficult to identify the exact source of infection for whatever reason, but as a professional you know the symptoms are definitely there, then surely, antibiotics are given more as a safety blanket." (P05, Primary Care).

Antibiotics are prescribed even when there is "*uncertainty about infection being bacterial or viral*" (P117, Primary Care). Participants identified that the main driver of antibiotic prescribing decisions is to reduce the potential risk of any future complication.

6.3.4.3.2 Inter-professional practices

Different inter-professional factors such as clinical hierarchy and collaboration between different departments are important issues influencing antibiotic prescribing.

"…inpatient teams that escalate to broad-spectrum antibiotics for any patient that is remotely unwell. This does have a trickle-down effect on ED doctors prescribing patterns." (P77, Hospital)

Junior clinicians indicated that there is a significant influence of clinical hierarchy on prescribing patterns as they expressed reluctance to challenge seniors' prescriptions even when they feel antibiotics are not required.

6.3.4.3.3 Adaptability of guidelines

Clinicians expressed scepticism regarding the utility of guidelines because of their poor specificity and adaptability for context-specific decision making. Lack of trust in guidelines was a perceived barrier because participants believed that guidelines do not capture the complexity of the clinical environment.

"Guidelines not covering the context of the particular patient and their problems eg poorly controlled diabetes or immune suppression and major surgery, where a prolonged course of antibiotics is prescribed." (P09, Hospital)

6.3.5 Discussion

This study provides insight into the behavioural drivers of inappropriate antibiotic prescribing and the impact of individual and setting specific characteristics on prescribing behaviour. Antibiotic prescribing practices are dependent on individuals' perceptions and knowledge but are also influenced by the type of care setting, clinical experience, and availability of data for decision-making and patient expectations. We identified several differences and similarities between clinicians regarding factors that influence antibiotic prescribing practices. Previous studies (306, 310, 311) have investigated different drivers of inappropriate prescribing, but there is not enough information on how different individual and setting specific characteristics influence the prescribing behaviour. Our findings have significant implications for understanding variations in antibiotic prescribing behaviour. We believe our results can help guide the design of appropriate antimicrobial stewardship interventions as well as to identify whom should be the target of these interventions.

We found that type of care setting, use of guidelines and clinical experience are important predictors of self-described antibiotic prescribing behaviour. Primary care clinicians were more likely to perceive factors such as delays in diagnostic test/culture results, lack of antibiotic prescribing guidelines and patient expectations as perceived barriers to appropriate antibiotic prescribing. Multiple factors may contribute to diagnostic ambiguity including the overlap between clinical features of different viral and bacterial infections, and the time constraints in a clinical consult to carry out a detailed assessment (314, 317). Diagnostic uncertainty has been consistently identified by other studies conducted in primary care settings as a barrier to appropriate antibiotic use (318, 319). In primary care limited follow-up of patients and limited time to assess patients presenting with co-morbid conditions, may impact on clinicians' capacity to identify the most likely pathogen, thus contributing to unnecessary antibiotic prescribing (315).

Primary care clinicians were also more likely to perceive that lack of timely access to prescription guidelines can negatively impact on the appropriateness of antibiotic prescribing. This suggests that primary care clinicians may consider these guidelines to be beneficial for managing patients. Clinicians who accessed guidelines frequently agreed that easy access to guidelines at the point of care is important for reducing the risk of inappropriate prescribing. In the context of current clinical practice in

Australia, in primary care approximately 33 – 73% of prescriptions assessed did not comply with antibiotic prescribing guidelines as compared to 23% in hospitals (320).

In primary care, clinicians may be more inclined to prescribe antibiotics because of patients' expectations which in many cases may differ from guidelines (321). It has been reported that explicit requests for antibiotics were made in only 1% of total visits, but in 34% of cases, clinicians perceived that patients expected to be prescribed antibiotics (322). Our findings are confirmed by many studies conducted in primary care frequently report 'demand' and 'expectations' as drivers of prescriptions with 10-30% of patients expecting antibiotics for acute respiratory infections, a common presentation (323, 324).

Our results further indicate that level of clinical experience and use of guidelines counteracts the impact of patient expectations on prescribing practices. Given the uncertainty integral to antibiotic prescribing, research has suggested that less experienced clinicians may passively comply with patient demands due to fear of criticism, to garner the approval of patients, and to manage their own reputation (325). On the other hand, experienced clinicians in our study were less likely to be concerned about the absence of guidelines and lack of information such as formulary restrictions, local resistance patterns etc. during clinical decision-making. They tend to trust their own clinical reasoning and judgement when their opinion differs from the information presented in guidelines. A study conducted by Charani *et al*. (311) found that decision making autonomy in a healthcare setting is directly related to the experience and knowledge of clinicians, with senior clinicians considering themselves exempted from following guidelines or policy. On the other hand, less experienced clinicians, specifically those in training, are more likely to follow guidelines to ensure standard practice and avoid the risk of malpractice (311). Our findings also suggest that frequent consultation of guidelines can help in reducing the negative influence of patient pressure on prescribing decisions, although this is less likely to be needed by experienced clinicians. The majority of experienced clinicians in our study engaged with guidelines less frequently than their younger or less experienced peers. This is consistent with other studies conducted in other countries showing that clinical experience impacts clinicians' adoption and adherence to clinical guidelines (326, 327). AMS interventions targeted at more experienced clinicians to enable them to engage with guidelines would not only affect their own prescribing behaviour but also potentially that of their junior colleagues.

Due to the complexity of the clinical environment, interventions for rational antibiotic prescribing need to consider the requirements of specific setting (primary care or hospitals) with an explicit focus on inter-professional networks and prescribing practices to ensure there is a cultural shift across all individuals involved in prescribing decisions. This study contributes to the field by evaluating different predictors

that might help in explaining variability in appropriate antibiotic prescribing in Australia. Consideration of these individual and setting specific factors that determine prescribing behaviour is vital for designing targeted interventions to promote appropriate antibiotic prescribing. Table 6.2 outlines the key findings in this study and provides recommendations to address the barriers identified.

Table 6.2 Summary of findings and recommendations to address the barriers to appropriate antibiotic prescribing

No	Findings	Recommendations
1.	Diagnostic uncertainty has been identified as a bigger issue in primary care, than in hospitals, as a contributor to inappropriate antibiotic prescribing.	Acknowledging the inevitability of a certain level of diagnostic uncertainty in primary care is required in order to establish effective strategies to promote appropriate antibiotic prescribing (328). Developing consultation strategies that increase the use of decision tools, and involve discussing diagnostic risks with patients, understanding their expectations and participating in shared decision making can help mitigate the risk of inappropriate antibiotic prescribing in primary care.
2.	For experienced/senior clinicians, lack of access to guidelines and other relevant prescribing information is less likely to be a barrier to appropriate antibiotic prescribing.	Strategies for implementing antibiotic prescribing guidelines must be supported by a better understanding of the professional hierarchy in clinical settings. Through effective clinical engagement, use of guidelines must be encouraged in senior clinicians. This can not only improve their own prescribing behaviour but will have a trickledown effect on the prescribing practices of their junior colleagues.

3.	As compared to junior clinicians, experienced clinicians are also less likely to consider patients' expectations while prescribing antibiotics.	Shared decision making between clinicians and patients can help establish better understanding of antibiotic resistance and the need to promote appropriate antibiotic use. Better communication between patients and clinicians, specifically those who have less clinical experience, will also help to build confidence and trust (329).
4.	General practitioners are more likely than hospital clinicians to perceive patients' expectations as an important contributing factor to inappropriate antibiotic use.	AMS strategies must be tailored to the setting of use. Practices such as delayed prescribing and shared-decision making are particularly relevant for primary care.
5.	Effective use of guidelines can help counteract the negative impact of patient expectations and clinicians' perceptions on antibiotic use.	Timely, accurate, evidence-based clinical practice guidelines concerning the appropriate prescribing of antibiotics should be easily accessible in both primary care and the hospital sector.

6.3.5.1 Study Limitations

One of the limitations of our study was that we did not achieve the target sample size, although this might have been an ambitious target. We did achieve participation from 180 clinicians but this may not be sufficient to generalise the findings to all Australian clinicians. We were unable to determine the true survey response rate because the denominator, or number from the targeted population who viewed the survey notices published across different platforms, could not be identified. It is recognised that the response rate among physicians and general practitioners is comparatively lower than the general public (304). For example, an Australian longitudinal survey reported a response rate of 17.6% in GPs and 22.3% in specialists (305). The findings in this study are also based on respondents' perceptions and opinions and these might not reflect their actual clinical practice. To mitigate this issue, we allowed open-ended responses regarding potential perceived barriers for appropriate antibiotic prescribing. The free-text responses were brief and provided limited contextual data. However, triangulation of quantitative and qualitative data established a better understanding of participants' perceptions concerning the different barriers.

6.3.6 Conclusion

Our results provide a robust assessment of the range of factors associated with inappropriate antibiotic prescribing in Australia. The comparison of perceptions by different clinicians indicates that variation in antibiotic prescribing patterns can be partly attributed to clinical experience, care setting dynamics in hospitals and primary care and disparate use of guidelines. Efforts should be directed at improving accessibility to information through evidence-based guidelines, understanding clinical culture and actively engaging clinicians across different age groups, as well as explicitly identifying strategies to address clinician concerns about patient expectations for antibiotic prescribing. AMS strategies should be tailored to specific users' requirements and the nature of the setting in which these are implemented to ensure compliance with appropriate prescribing. These strategies can provide limited benefits if these contextual factors remain unacknowledged.

Ethics approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Human Research Ethics Committee of University of Adelaide (approval number: H-2019-094). Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no competing interests.

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6.4 Chapter Synopsis

Chapter 6 presented the findings of a survey with clinicians regarding factors that influence inappropriate antibiotic prescribing. The findings suggest that limited access to relevant information and diagnostic uncertainty at the point of care are likely to contribute to inappropriate antibiotic prescribing. Time constraints and patients' preferences were found to have a higher influence on the prescribing behaviour of general practitioners in our study. Our findings also indicated that clinicians' experience, their familiarity and use of guidelines and the care settings that they work within were important moderators of their perceptions regarding inappropriate prescribing. The comparison between different clinicians groups indicated that these moderating factors can be a contributing factor in varying antibiotic prescribing patterns. Therefore, interventions to improve antibiotic prescribing behaviour needs to be tailored to consider the setting of use and clinicians' individual circumstances in order to promote behavioural change.

While chapters 5 and 6 focused on an intra-organisational perspective to investigate the individual and organisational level factors that influence CDSS adoption and antibiotic prescribing, the next chapter (Chapter 7) has a broader scope and focuses on challenges for integrating CDSS at a health system level. This helped in establishing a pragmatic understanding of challenges facing CDSS implementation by bringing together different perspectives in this thesis.

Chapter 7: Challenges and Opportunities for CDSS Implementation at Scale

7.1 Preface

Despite the increasing evidence on the efficacy of CDSS for evidence-based care, the adoption of this technology in healthcare systems is inconsistent. Many systems which have shown a positive effect in limited scale research studies or pilot studies could not be up-scaled to an effective system-wide innovation. The study presented in this chapter evaluated the CDSS implementation process from a system level perspective to understand those factors that face the wider integration of CDSS in the healthcare systems.

To understand different aspects of CDSS implementation in Australia, we adopted a qualitative approach and carried out in-depth interviews with policymakers involved in CDSS implementation projects.

This chapter addressed the fourth and last research question of this thesis and respective objective highlighted in Figure 7.1. This study is currently in manuscript format and has been submitted to a peer-reviewed journal for publication.

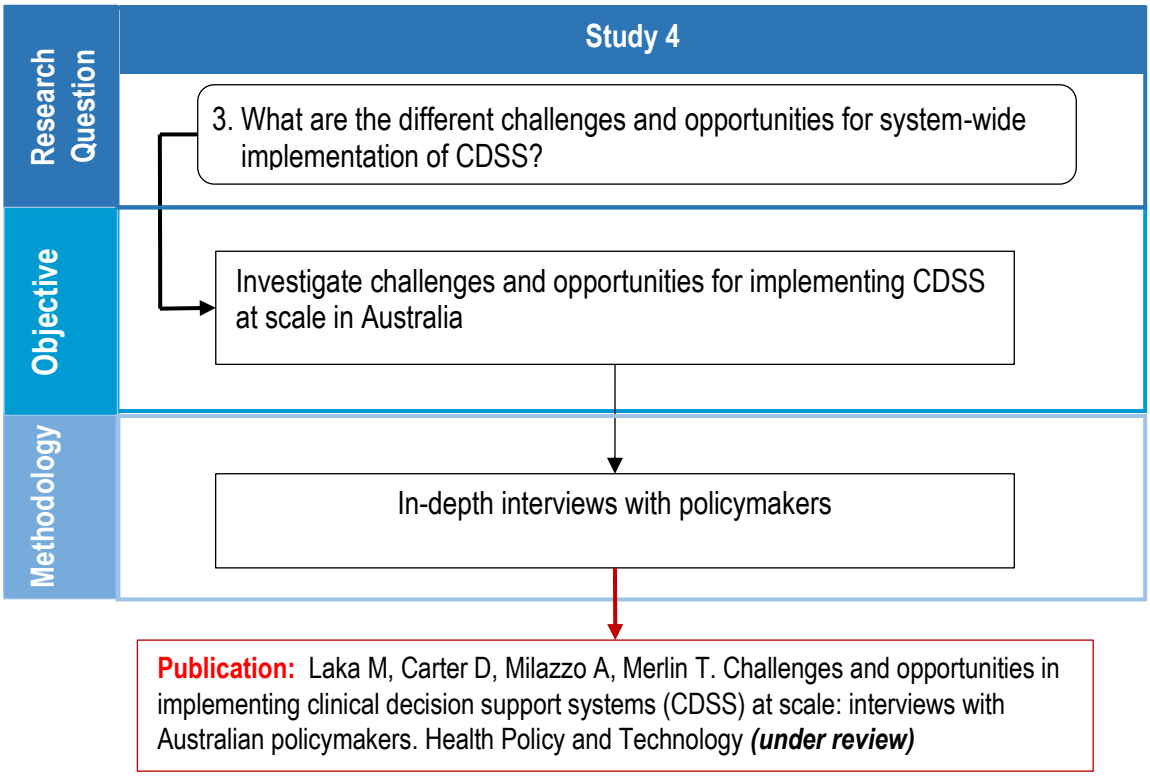

Figure 7.1 Structure of chapter's question and objectives

7.2 Statement of Authorship

Statement of Authorship

Title of Paper	Challenges and opportunities in implementing clinical decision support systems (CDSS) at scale: interviews with Australian policymakers.
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Principal Author

Name of Principal Author (Candidate)	Mah Laka
Contribution to the Paper	I contributed to the study concept and study design.I recruited study participants, conducted the in-depth interviews, performed the analyses and prepared the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 24/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Drew Carter
Contribution to the Paper	D. Carter contributed to the study concept as well as study design. He also assisted in the interpretation of the results and provided feedback on the manuscript.
Signature	Date 26/08/2021

Name of Co-Author	Dr Adriana Milazzo
Contribution to the Paper	A. Milazzo contributed to the study concept as well as study design. She also assisted in the interpretation of the results and provided feedback on the manuscript.
Signature	Date 24/8/21

Please cut and paste additional co-author

Name of Co-Author	Professor Tracy Merlin
Contribution to the Paper	T. Merlin contributed to the study concept as well as study design. She also assisted in the interpretation of the results and provided feedback on the manuscript.
Signature	Date 24/8/21

7.3 Manuscript Submitted for Publication

Title

Challenges and opportunities in implementing clinical decision support systems (CDSS) at scale: interviews with Australian policymakers.

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7.3.1 Abstract

Objectives: While many pilot projects have provided proof-of-concept information on CDSS efficacy, they encompass disparate systems unable to fully realize digital transformation. A lack of system-wide guidance on CDSS integration limits the efficacy of even technically well-positioned systems. The objective of this study was to identify challenges and opportunities relating to CDSS implementation in Australia.

Methods: Opting for a qualitative approach, we purposefully sampled at national and state levels policymakers involved in CDSS implementation in Australia. We completed 11 semi-structured interviews from March to June 2020. The data were analyzed using reflexive thematic analysis.

Results: The Australian digital health landscape for CDSS implementation appears to be fragmented, characterised by a lack of integration between clinical and technological elements. This fragmentation is exacerbated by the lack of a shared understanding and collaboration between key stakeholders, increasing the risk of conflicting interests. CDSS are usually designed for a particular clinical workflow, and a lack of interoperability reduces the information flow between systems. Most efforts to achieve data standardisation are limited to organisational or state-level programs, thus increasing the risk of uncoordinated care across organisations. Considering different stakeholder perspectives on the value of CDSS could help to foster sustainable partnerships between governments, organisations, and consumers.

Conclusion: Our findings emphasise the importance of three things, each underpinned by stakeholder engagement: developing a clear and shared vision for innovation, building clinicians' skills and organisational capacity for change, and establishing a national consensus on data standards for interoperable CDSS.

Keywords: clinical decision support; CDSS; system-level transformation; implementation; health policy

7.3.2 Introduction

The scale and speed at which digital systems have been integrated into healthcare have generally been meagre due to a multitude of factors, such as a lack of incentives, limited digital health literacy, and reimbursement and regulation issues (330, 331). COVID-19 has significantly changed this and catalysed the digital transformation process across healthcare systems (28, 332). There is an increasing realisation that digital health systems are capable of improving the quality and safety of patient care.

The volume of clinical data is also growing at a considerably faster rate than the capacity of clinicians to utilise it (333). Studies have shown that digital systems such as clinical decision support systems (CDSS) can effectively manage vast amounts of clinical knowledge by filtering and intelligently presenting patient-specific information to healthcare providers (14, 334). CDSS are medical software applications that perform a wide range of functions to support and facilitate clinical decision making. For example, they provide reminders and alerts about care processes; easy access to clinical practice guidelines, patient summaries and related reports; treatment-specific order sets; templates for standard documentation; and reference information that helps with optimal clinical decision making. There is increasing recognition of the value of CDSS in facilitating evidence-based decision making (18), realising the benefits in clinical practice over an extended period of time has proven difficult due to limited adoption (335). Although there is some information of proof-of-concept at a limited scale, in practice CDSS adoption has been short lived (21, 336).

The Australian healthcare system reflects that Australia is a Federation of six States and two Territories. The healthcare system is essentially two-tiered, with public hospitals being managed by the States and Territories, private operators running private hospitals and the federal government overseeing primary care and aged care (12)., Although not widespread yet, healthcare delivery models are increasingly shifting to value-based care, where reimbursements for care services are based on patient outcomes rather than the number of services provided (13, 14). Planners recognise that this shift is not possible without credible data being collected on process efficiency and patient outcomes (13). In this regard, the integration of CDSS is seen as important for achieving continuity of care and the interoperability it requires. This is also reflected in the National Digital Health Strategy, which aims to establish a connected healthcare system characterised by the safe and uninterrupted sharing of quality data at the right time with the right person (15). Even though there is an interest in digital health solutions such as CDSS, these systems will continue to require an understanding of the Australian context, service delivery models, workflow requirements and local regulations (13). Major projects implemented to roll out electronic medical records, integrated clinical information systems and CDSS are managed by state

governments. However, each jurisdiction having its own industry partners and investment cycle means that there is an increased risk of limited coordination of care when precisely the opposite is sought (16).

Decision-making processes in healthcare are complicated, CDSS themselves are technically intricate, and there are underlying social dimensions to introducing change in the clinical environment. This all makes CDSS implementation a complex intervention (114). Limited adoption rarely owes to technical issues alone but is usually the result of institutional, cultural, political or legal challenges (337). But studies often focus on single factors such as the quality of the system, users' adoption and organisational flexibility. Greenhalgh *et al.* (22) proposed a pragmatic framework for theorising the non-adoption of digital systems. They suggested that the implementation of digital health tools involves multiple dynamic factors at both the micro and macro level. This interplay between technological, behavioural and organisational factors is usually non-linear and not fully understood. It is also likely to be context-dependent (151). Shaw *et al*. (21) argued that to understand how digital innovations can be up-scaled and sustained in a healthcare system, one needs to understand interactions between the tool (digital system), the team (healthcare providers and relevant stakeholders) and associated changes in the care delivery process. Many studies in the implementation science field emphasise that the implementation of digital health systems is not necessarily about the technology, but about reconfiguration of the service process (10, 21-23). However, the precise scope and nature of changes required in service delivery are not sufficiently examined in the literature.

To date, there has not been a comprehensive understanding of the policy implications of CDSS implementation, namely the challenges and opportunities relating to CDSS implementation at scale, across organisations and jurisdictions in tiered healthcare systems such as in Australia (22, 114). This is important because, as Andargoli argued, discrepancies in implementation policies in Australia for systems such as CDSS have contributed to increased complexities at the political, financial and medico-legal levels (337, 338).

Most studies within the digital health literature merely adopt an intra-organisational perspective to understand the changes required to integrate CDSS (339). But there is a real need to consider the inter-organisational perspective, particularly since CDSS may be most valuable when aligned across organisations. Therefore, this study aimed to contribute knowledge toward the development of a framework for CDSS implementation at scale, namely from a healthcare system perspective. We investigated the impact of technical, organisational and system level factors on the broader implementation of CDSS. This included understanding the preferred system design to make it practicable for healthcare organisations, but also the capacity of the healthcare system to implement and sustain this innovation. We focused on Australian policymakers' experiences and perceptions to

generate this knowledge. The objective of our study was to answer the following research question: *What are the challenges and opportunities facing effective system-wide implementation of CDSS?*

7.3.3 Methods

7.3.3.1 Study Design

We conducted in-depth interviews with policymakers to understand the challenges and opportunities for CDSS implementation in the Australian healthcare system. We adopted qualitative approach in this study informed by the epistemology of pragmatism (340). As there are many unknown in this area due to the lack of formalised evidence in the literature, therefore qualitative approach was identified to be appropriate for this study. We also utilised reflexive thematic analysis to arrive at a contextualised understanding of the research problem (207, 286). In this study, we focused on a system-level rather than an organisational-level perspective because the value of CDSS relates to its ability to coordinate care (341, 342).

7.3.3.2 Recruitment and Data Collection

Using a purposive sampling strategy, we invited to participate - from different national and state agencies engaged in digital health activities in Australia – to participate in an interview. Participants needed to be involved in the development and implementation of digital health policies nationally and within their states to ensure they were able to discuss the challenges associated with CDSS implementation at scale. Snowballing was employed to identify further potential participants for the interviews. A total sample size of 12 semi-structured interviews was planned, as studies indicate that 10-12 interviews can suffice to provide 90% of themes during analysis (343). However, data saturation was reached after 11 interviews. No additional insights were being made into the data and constructs were becoming redundant, therefore recruitment was terminated.

The interviews were conducted by the first author (ML) via audio or video conference. Written and verbal consent were sought before the interview, and the interviews were recorded with participant consent. The interview guide (Supplementary data) included questions based on the Australian government report on the safe implementation of digital health systems as well as other relevant literature concerning CDSS implementation (21, 59, 202, 336, 344). The questions were open-ended in order to explore participants' views and experiences concerning different aspects of CDSS implementation. The first part of the interviews focused on generic questions about the participants' role, their experiences of CDSS implementation and its relevance to national and state digital health policies. This helped in comparing and contrasting different implementation approaches used in various organisations and jurisdictions and their impact on overall adoption of the CDS system. The second part

of the interviews featured more focused questions relating to the capacity of healthcare organisations to implement and sustain CDSS. This included understanding the factors that make technologies such as CDSS practicable for clinical practice. These factors included infrastructure, system design, workflow requirements, change management, financial incentives, and digital health literacy. This led to a final set of questions focusing on data sharing and care coordination across different CDSS implemented in a range of organisations and jurisdictions in Australia.

7.3.3.3 Data Analysis

Audio recordings were transcribed verbatim by a professional transcriber and checked by the first author (ML) for accuracy. The first interview was independently analysed using the reflexive thematic analysis approach described by Braun and Clarke (286) by two researchers (ML and DC) using NVivo 12. The analysis was informed by the critical realist and inductive approaches in which the coding is directed by explicit content of the data. These approaches identify experiences and meanings of participants and reflect the reality apparent in the data. In the first phase, the transcripts were read to develop familiarity with the content. Data were then analysed iteratively to generate codes that represented patterns of meaning relevant to the research question. The first two transcripts were independently coded by ML and DC and initial coding schemes was then discussed, and differences were resolved. The researcher's post-interview notes also helped in the reflexive coding process. As further interviews were conducted, codes were added to and refined and later abstracted into broader overarching themes. For instance, interviewees identified customisation in the CDSS design both as a facilitator for addressing user-specific requirements and as a barrier for achieving standardisation across clinical practices. These themes were separately coded as "localised design" and "digital standards". As interviews progressed, it became apparent that these themes related to the overarching concept of "the right balance between customisation and standardisation".

7.3.4 Results

A total of 9 males and 2 females participated in this study. The average duration of the interviews was 46 minutes (ranging from 35 to 69 minutes). There was a diversity of age and years of experience in the participants.

Most participants indicated that CDSS implementation is not as easy as introducing digital innovations into healthcare systems and hoping there is uptake. Participants unanimously believed that an important aspect to CDSS development and implementation is understanding how these systems can be made practicable in a specific clinical context. The CDSS implementation process was seen as a "balance between clinical autonomy and innovation", thus, requiring multidisciplinary investigations of how

technical, organisational, system and social factors interact. This involved understanding the local context to enable customised and user-centred design but also balancing it with a level of standardisation in information generation and sharing to ensure coordinated care across different organisations. We have sorted these factors into a range of themes as described by participants, and these represent the challenges and opportunities, reported by the participants, for promoting the successful implementation of CDSS across the Australian health system.

7.3.4.1 User-centred design

All participants viewed user-centred design as closely collaborating with end-users to understand the individual and organisational practices that affect clinical workflows in terms of information generation, consumption and transformation. For instance, one interviewee encouraged:

"[…] putting clinicians and patients first and designing technology in a way that suits them and trying not to be seduced by just shiny stuff out there. The bottom line is the design should be for the users, not something which is imposed on them." [Policymaker, 01]

While all interviewees identified user-centred design as relevant to increasing effective CDSS use, they differed on where and how they saw the concept as applying. Most participants said that user-centred design applies in a local context at a single site or network of sites, but that there is a lack of understanding in how the concept can apply at a system level, involving multiple stakeholder groups, sites, resources, infrastructure types, and policies. Participants who had worked in different CDSS implementation projects as clinical leaders or champions specifically identified usability and end-user satisfaction as outcomes of user-centred design. By contrast, participants who had roles in developing business cases and governance structures for CDSS implementation saw user-centred design as a way to understand how users can be involved in the design and implementation process to achieve the business goals.

Interviewee responses indicated that many CDSS implemented in Australia are either based on architecture from legacy systems or US-based products retrofitted for the Australian health setting, even when there are many elements that do not align. This has translated into workflow disruptions, leading to increased time required to perform a task and promoting users' misperceptions of CDSS being ineffective.

"We've still got very asynchronous systems/processes that are disruptive for workflow because you continuously have to deal with a third person in the room and that third person is a machine and they need attention too." [Policymaker, 06]

7.3.4.2 The right balance between customisation and standardisation

Interviewees talked about how CDSS implementation is dependent on a complex interaction of technical, organisational and individual factors. They indicated that implementation requires a better understanding of the local context to integrate customisation into the CDSS intervention:

"You are not implementing in a vacuum, these [clinical settings] *are complex environments. So, the real challenge is to keep the goal of standard benchmarking in sight while allowing local variations in design and approach where required."* [Policymaker, 04]

Respondents identified standards for documentation as critical for achieving the anticipated benefits of CDSS, but noted that usually clinicians record important patient information and observations in the form of free text. The standard coding system embedded in CDSS allows the system to assign a standard vocabulary to un-coded data like free text to trigger notifications for decision making. Interviewees asserted that without a standard vocabulary and some uniformity in knowledge representation, the basic functioning of CDSS, requiring the integration of the knowledge base with patient information, cannot be realised:

However, there were contrasting views on the level of standardisation required in CDSS, as many interviewees suggested that applying a 'one size fits all' approach in implementation may overlook the impact of the clinical culture on system adoption. Excessive standardisation and inflexibility in the design and implementation processes were seen to conflict with the workflow dynamics in clinical settings, giving rise to clinician pushback and poor system adoption. While customisation was seen to facilitate successful CDSS adoption, there were also concerns regarding the interoperability of overly-customised systems across organisations.

"[The] whole point of the integrated system is that we can benchmark, compare cohorts, measure by the same stick, use same evidence base. So, with customisation especially when you are overdoing it, these benefits go out of the window." [Policymaker, 05]

The lack of a formal process to ensure conformance with e-health standards and the continuous maintenance of locally developed or customised systems was also identified as a risk factor for the safety and quality of care:

"Locally developed systems usually run into issues where there is nobody to make sure these are fit. Nobody is making sure this product conforms to digital health standards and cybersecurity." [Policymaker, 07]

7.3.4.3 Interoperability

Information sharing between systems for coordinated care is not possible without adherence to data standards, which relates to achieving the right balance between standardisation and customisation (Theme 2). Interviewees observed that, at national and state levels, there is an increasing awareness of the need to develop a standard framework for interoperability and data sharing, but current technology is limited in its ability to combine and share data between different systems.

"For the last 10 to 15 years, there has been a lot of discussion around standard Australian processes for standard messaging, data security and terminologies but to establish a healthcare system where data flows securely, safely, without being corrupted, with maintaining it's meaning, is still a long way to go." [Policymaker, 06]

Interviewees frequently discussed how standard terminologies and standard clinical libraries were needed to integrate disparate systems. A significant barrier to achieving interoperability is the current lack of a standardised framework for knowledge representation and varied terminologies used in different CDSS. Several interviewees recognised that, to ensure the cross-setting utility of CDSS, CDSS architecture is based on technical standards such as Health Level 7 (HL7) for the exchange of clinical information and SNOMED-CT for standard terminologies. However, excessive local customisation in vendor-based or locally developed systems was seen as a barrier to data sharing between organisations even when the same system architecture is used. Moreover, interviewees recognised that in certain cases the permissible variants of these standards also add a layer of complexity for interoperability.

"[…] different sites implementing systems with apparently similar architecture may face semantic interoperability issues due to using variations within standards to represent the same concept." [Policymaker, 09]

7.3.4.4 Governance

Interviewees argued that governance in digital health requires a multi-stakeholder structure to deal with the complexity of managing the parallel processes of information technology (IT) governance and clinical governance:

"[…] it is quite challenging because you've got that interplay of governance that causes some challenges around ICT governance and medication governance, and how that segues together has been quite a painful experience." [Policymaker, 08]

Reflecting on their experiences, interviewees stated that most governance structures and data management processes for CDSS are fragmented and lack the scope to ensure that CDSS are well-integrated and valued in the organisation. A lack of consensus on responsibilities to manage governance issues among IT, clinical and administrative teams contributes to this fragmentation.

"Healthcare, it is not quite a system rather a large network of loosely collaborated teams welded together by professional pride and priorities. So, the net result is there is a very poor coherence in investing around making sure that all stakeholders are on same page and there is an agreement between behaviour and governance rules" [Policymaker, 02].

Interviewees recommended a pragmatic approach to designing CDSS governance structures and aimed at minimising disruption when integrating CDSS into existing clinical infrastructure. For instance, risk monitoring was seen as a pre-eminent governance technique to identify critical incidents involving the use of CDSS in clinical practices, alongside establishing protocols to minimise the risk of critical incidents. According to interviewees, risk monitoring processes must include indicators that focus on the cost-effectiveness and safety of care and can identify potential errors or incidents in the system. Some interviewees argued that risk monitoring can also drive wider discussions on governance policy that must not be limited to achieving benefits but also consider the burden and risk associated with intervention.

7.3.4.5 Organisational Readiness for Change

A major reason for limited adoption of CDSS in healthcare organisations was thought to be the lack of reliable and valid measures to assess an organisation's capability to manage change:

"[…] these are big projects and they can be controversial and difficult, we still don't know how to assess whether you have a favourable organisational environment for the change, it's not as simple as plugging in, switching on and you are good to go." [Policymaker, 05]

The intended digital transformation in clinical practice was recognised as an outcome reliant on organisational capabilities to foster change. Many interviewees argued that the needed change management is not limited to the assessment of financial resources and infrastructure available for CDSS implementation, but extends to understanding how change can become a part of the organisational vision and culture in the long term:

"As a part of the change process, organisations are required to invest financially and administratively in the transformation process as much as they usually do in systems [CDSS] *because most of this shell shocker is the culture, not the technology."* [Policymaker, 01]

Interviewees suggested that rushing into technological solutions such as CDSS without assessing the organisational capability to support and sustain the intervention may give rise to a mismatch between expectations and reality. The majority of interviewees described the implementation of CDSS as an "adaptive process" rather than a purely technical process. Therefore, engaging staff in the change process was seen as a potential way to reduce the risk of abandonment and non-adoption of CDSS.

"[…] it's a transition, if you don't set up an accessible and real-time support service within your hospital to help troubleshoot issues, you won't be able to alleviate the fear of a new system." [Policymaker, 09]

7.3.4.6 Digital Health Literacy

Interviewees identified that organisational capacity to sustainably implement CDSS is related to end-users' digital literacy. The users' knowledge of, and ability to interact with, the digital systems could be seen as a defining factor in shaping individuals' ability and willingness to adopt CDSS. Interviewees indicated that among clinicians there is a general sense of antipathy and wariness when it comes to digital systems:

"The transformation of healthcare we expect from a digital system is so big and overwhelming that, for many clinicians, it is quite scary and out of their comfort zone." [Policymaker, 08]

Many interviewees talked about how CDSS implementation requires a shift in deep-rooted perceptions and attitudes. They suggested that, as automation creeps into the clinical workflow through the introduction of digital systems, a healthcare worker's personal motivation to embrace these systems seems to depend on their existing digital knowledge and skills, with knowledgeable and adept staff also being the more motivated.

"No matter how much sophistication your digital system offers, if our workforce is not equipped with the right skills and competencies, they will be intimidated by these systems because they have no control or they don't fully understand the system." [Policymaker, 12]

Interviewees were particularly concerned about variations in the level of digital health literacy in the clinical workforce. Younger clinicians were seen as more knowledgeable and confident about using digital health systems than older clinicians. Thus, interviewees highlighted the irony of propagating disparities in accessing information through CDSS due to the varying levels of digital literacy in the clinical workforce.

Several participants believed that Australia lacks a framework to develop digital health literacy as a legitimate skillset for clinicians. Interviewees argued that as digital technologies are integrated into the

clinical workflow, the skills required in medicine are shifting tremendously, but there is not enough investment in equipping the clinical workforce with this dual skillset (clinical and digital).

"We have seen other countries like the US and UK, they have developed pathways to invest in digital literacy and digital skill is rewarded as a legitimate career path. Here, we usually took a single person out from their clinical work for 6-12 months for the project and then sent them back. We don't continue to develop them, not provide them money or resources to develop this as a skillset." [Policymaker, 07]

7.3.4.7 Stakeholder Engagement

Interviewees described CDSS implementation as a system-wide transformation involving a range of stakeholders in different capacities. For instance, many interviewees argued that product development and project management teams are more focused on cost, timelines, and the impact of CDSS on clinical performance, whereas users are more focused on reliability and an easy or simple user interface. Interviewees saw asymmetrical access to information (when some stakeholders have more information available to them than others) as a significant barrier to aligning the interests of various stakeholders with the project goals and to ensuring buy-in from clinical and management staff.

"it's absolutely necessary not to do the implementation in isolation. It should not be the orchestrated vision of people like us who might not be developers or frontline workers. Rather, have two-way communication, understand what their expectations are, discuss your objectives and align this with the national or state digital strategy." [Policymaker, 04]

One of the major problems identified by interviewees is the dogmatic approach taken in implementation, with minimal understanding of the clinical environment owing to a lack of stakeholder engagement. Several interviewees argued that, without establishing open communication with the local healthcare organisations to understand their individual needs and dynamics, it is extremely difficult to motivate care providers to engage in the CDSS implementation and adoption process.

"unless you've got leaders or the champions who are going to promote the system to other clinicians – it's the only way to get that foot and overcome this resistance and ensure that change is implemented successfully" [Policymaker, 07]

Furthermore, many interviewees pointed to a lack of long-term collaborative relationships between the medical software industry and clinical organisations in Australia. Relationships that extend beyond just rolling out a particular system were seen as having the potential both to manage clinicians' expectations about product optimisation and to reduce the risk of a never-ending cycle of customisation for the vendors.

"Having contractual models which are spread out in time with 50% front-end payment and 50% remaining when users are satisfied with the product 2-3 years after going in. But what we have is 90% money upfront and see ya later, good luck to everybody who has to suffer with this system."
[Policymaker, 10]

7.3.5 Discussion

Our findings reinforce the existing body of evidence by illustrating that a lack of guidance at an inter-organisational level limits the ability of organisations to translate the success of CDSS pilot projects to a system-level transformation. Despite increasing evidence on the potential of CDSS to improve the safety and quality of care (14, 161, 334), the system-side frameworks for implementation are still lagging. Stakeholders lack a shared understanding of the strategic significance of implementing systems such as CDSS, and there is a lack of clarity about responsibilities in managing the change associated with CDSS implementation. Against the backdrop of the Australian National E-health Strategy (345), strategies for the effective CDSS implementation must follow an evolutionary approach which allows developing and evaluating infrastructure and processes at a smaller scale before implementing at a system level (337).

Given the complexity of the health care process, integrating CDSS unobtrusively into the clinical workflow is a challenge. Our findings resonate with those of other studies, which suggest that understanding user priorities and the clinical context is essential to ensure a good fit of CDSS in the clinical workflow (21, 346). However, we have also uncovered that stakeholders often fail to share the same concept of user-centred design. For instance, our interviewees expressed diverse views on what are the important features of user-centred design for CDSS. This diversity was underpinned by different individual experiences and past roles in CDSS implementation. An overarching, shared understanding of user-centred design is required at a system level to align stakeholder priorities across a wide range of healthcare organisations. This finding is consistent with the framework provided by the International Standards Organisation (ISO) for user-centred design, which emphasises establishing a multidisciplinary design team to include different perspectives and skills in the design phase (347).

While the idea of designing a customised CDSS that fulfils users' requirements and fits well in a specific organisational workflow seems like an appropriate goal, such a unique system poses serious questions regarding sustainability and interoperability with other systems within and beyond the organisation. Each organisation faces the dilemma of whether it should build customised CDSS or acquire a proprietary product (348). Interviewees identified that locally developed systems might provide benefits of customisation, but continuous maintenance and a lack of interoperability with other systems make

such systems a less favourable option. A significant barrier to information exchange between systems is semantic interoperability (18, 349). There is still a lack of interoperable CDSS, as most systems are standalone applications developed for a specific clinical workflow or health condition, which can limit the clinician's ability to access the ever-expanding information related to clinical decisions. For instance, different data models such as free text in existing information systems make the transfer of information between different organisations really challenging. Many approaches have been discussed in the literature, such as HL7 standards for semantic interoperability (350-352). However, our findings indicate that there is a lack of strategy and close collaboration across sectors in Australia to implement standards required for semantic and structural interoperability. Most efforts to support interoperability are limited to a discrete set of organisations or to state-level programs. Mutually agreed standards and a conformance strategy could allow CDSS to exchange clinical data between different healthcare organisations at local, state, and national levels. The strategy must be rooted in data safety and privacy laws in different states and territories to ensure data flows unobtrusively between different systems without compromising data privacy. An effective governance structure would be required to specify timelines and activities to allow governments, developers and healthcare organisations across jurisdictions to align with the data standards.

Interviewees identified that the Australian healthcare system is characterised by a disparate and fragmented space for digital health systems, perhaps as a consequence of a two-tiered health system. Studies have shown that even well-designed CDSS can become irrelevant if not supported by collaboration and engagement at organisational and individual levels (353, 354). We can use the example of digital health test bed framework recommended by Australia's National Digital Health Strategy to understand how collaboration between key stakeholders can help in achieving sustainable CDSS implementation. The enhanced models of care suggested in this framework highlight that information sharing and collaborative activities between governments, the health sector, industry, and the research community can reduce the risk of conflicting interests and improve the cross-sector coordination for successful implementation.

Our findings suggest that applying a standard policy approach to CDSS implementation can sometimes unduly take the form of 'one size fits all'. This can reduce flexibility in the implementation process which might have served to adapt activities to varied organisational structures (21). The top-down, forced implementation observed in many digital health projects exhibits a lack of understanding of clinical culture and an inability to recognise whether the organisation has the right infrastructure and incentive models to support change (151).

These findings are important considering the Australian National Digital Health Strategy, which includes building clinicians' digital health skills as one of the basic objectives. However, interviewees indicated that there is a lack of appropriate incentive models for clinicians to get involved in digital skills development, as most medical guidelines do not include digital literacy as a requisite skill. This is also consistent with our previous findings, which suggested that experienced clinicians are less likely to adopt CDSS due to limited digital skills (190). The demand for technologically literate healthcare professionals is expected to increase over the next few years, which means that there is a need to bridge the gap between the medical technology and healthcare industries through cross-sector collaborations and by incentivising digital literacy as a legitimate skillset.

CDSS implementation is a multifaceted and iterative process (202). Our findings include pragmatic recommendations provided by interviewees (Table 7.1) for achieving an effective and successful system-level CDSS implementation.

Table 7.1 Recommendations for system-wide CDSS implementation

No.	Theme	Recommendations
1	User-centred design	• Establish among stakeholders a shared understanding of user-centred design that can align user requirements with the business goals of implementing the CDSS.
2	Balance between customisation and standardisation	• Ensure there is some flexibility in the CDSS implementation process to adapt to varied organisational structures, clinical culture and user requirements. • Balance the customised system design with the information standardisation required for data generation and representation to ensure interoperability across different organisations.
3	Interoperability	• Develop among state, territory and federal governments agreed data standards for data generation and exchange between different CDSS. • Support data standards with an effective conformance strategy that allows transition to these standards in a staged manner.
4	Governance	• Establish effective governance rules to remove uncertainty regarding responsibilities in the CDSS lifecycle, the regulation of privacy and data ownership. • Consider using collaborative care models to reduce the risk of conflicting interests and establish a shared governance framework.
5	Organisational Readiness for Change	• Develop valid measures and evaluation models to assess an organisation's capability to go through the digital transformation required for CDSS implementation. This assessment requires understanding the existing clinical practices, organisational processes, infrastructure, skills, and resources.
6	Digital Health Literacy	• Develop digital health literacy as an essential skillset for healthcare professionals. Do this partly by including digital health literacy in medical and nursing education and continuous professional development.

7	Stakeholder Engagement	• Engage key stakeholders by establishing multi-disciplinary teams in each phase of the CDSS design and implementation to understand different perspectives and expectations. • Undertake extensive clinical engagement and debate on the risks and benefits of CDSS to address concerns around safety and usability.

7.3.5.1 Study limitations

This study was conducted in the Australian healthcare system, therefore the findings are somewhat limited in their applicability to other countries. However, issues such as a lack of standards and the fragmentation of care processes are relevant in a global context. A number of stakeholders such as system developers, vendors and patients were not included in our sample due to the scope of the study, so some aspects (such as CDSS development, vending and post-market regulation) could not be examined. Future research could invite the views of multiple stakeholders to validate our research findings and extend the research questions into related domains.

7.3.6 Conclusion

Debate about the limited adoption of digital health technologies such as CDSS in healthcare settings is ongoing. Our study found that CDSS implementation in Australia lacks system-wide guidance to integrate CDSS into a complex and multi-stakeholder healthcare system in a way that ensures digital systems are interoperable and aligned with the national digital health strategy. The CDSS implementation process is not limited to introducing a new technological solution but rather extends to an effective reconfiguration of organisational activities to support the innovation. This requires a collaborative care model facilitating stakeholder involvement in all phases of CDSS implementation to understand how the existing organisational structure can be improved or revised. Establishing agreed interoperability standards and a conformance strategy between different healthcare organisations and systems would allow CDSS to communicate and exchange clinical data between different systems. The customisation of CDSS to incorporate users' requirements can facilitate the adoption of CDSS, but it can also pose a serious problem for interoperability. Our interviewees identified that getting the right balance between some levels of customisation in CDSS design and ensuring standardisation in information representation is integral for the interoperability of CDSS.

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7.4 Chapter Synopsis

Chapter 7 presented the findings of in-depth interviews conducted with different policymakers in Australia to understand the different challenges and opportunities for CDSS implementation at scale. Previous studies (Chapter 5 & 6) investigating the factors influencing CDSS implementation have focused on intra-organisational factors related to CDSS implementation. However, there is limited evidence available on how these systems can be integrated into the wider healthcare system comprising of different organisations and stakeholders. Our study contributes to this growing body of evidence by adopting a system-level perspective and focusing on different factors impacting CDSS implementation across different healthcare organisations.

Our findings showed that despite an increasing number of pilot projects providing proof-of-concept information on CDSS efficacy, CDSS adoption and use has been limited. A lack of system-wide guidance on CDSS integration limits the effectiveness and sustainability of even technically well-positioned systems. We found that there is a lack of shared vision for implementing CDSS among different stakeholders and poor integration between clinical and technological elements during the CDSS implementation process. Fragmentation of the digital health landscape, including a lack of mutually agreed data standards between organisations, has contributed to a lack of interoperability between different CDSS implemented in Australia.

In conclusion, our findings emphasised the importance of developing organisational capacity for change and establishing a national consensus on data standards for interoperable CDSS. Collaborative care models are required to establish a clear vision for implementing CDSS which is shared between all stakeholders. This sort of vision can help to align organisational structures and processes to take advantage of this system-level innovation.

Chapter 8: Synthesis and Conclusion

8.1 Introduction

This thesis has examined the effectiveness of CDSS for optimal antibiotic management by identifying how these systems can be developed and deployed to enable evidence-based decision making for antibiotic prescribing. Individual, organisational, and system-level challenges in CDSS implementation have been evaluated through engaging with various stakeholders. The overall aim of the research was to generate evidence to inform policies on CDSS implementation, as well as to contribute knowledge on the sustainable implementation of these systems for optimal antibiotic management. The goal of the sustainable and effective implementation of these systems is to improve the safety and quality of patient care by reducing antibiotic resistance.

This chapter summarises the key findings from the four studies (Chapters 4-7) conducted to address the overall aim of this thesis, as well as to consider the implication of these findings. Further, this chapter provides key recommendations for policy and future research regarding the implementation of CDSS for antibiotic management.

8.2 Key Findings and Contributions

8.2.1 What is the Impact of CDSS on Evidence-Based Antibiotic Management?

Key messages

- CDSS implementation is associated with improved and appropriate antibiotic prescribing characterised by increased compliance with antibiotic prescribing guidelines or in vitro susceptibility test results.
- Overall, CDSS reduces unnecessary antibiotic prescribing and improve the clinical and economic outcomes associated with antibiotic management.
- Considerable between-study heterogeneity on the extent of CDSS impact on antibiotic management appears to relate to the variability in CDSS uptake by healthcare professionals.

The first aim was to investigate the potential of CDSS in enabling evidence-based antibiotic management to reduce the risk of inappropriate prescribing in hospital and primary care settings. While several studies had reported the positive impact of CDSS on antibiotic management, results appeared to be inconsistent across the body of literature (14, 15, 91, 159). Therefore, a systematic review and meta-analysis (Chapter 4) was conducted to synthesise the evidence on the impact of CDSS and determine, overall, whether CDSS was effective. Results from the systematic review and meta-analysis have been discussed in detail in Chapter 4; key findings are discussed below.

There was large variability in the outcomes measured to identify the impact of CDSS on antibiotic management. Most studies measured process or clinical outcomes. A common outcome measured was improvement in the appropriateness of antibiotic therapy after CDSS was implemented. Studies defined antibiotic therapy to be appropriate if it adhered to the advice provided by the antibiotic prescribing guidelines or complied with *in vitro* susceptibility test results. The principal findings from the meta-analysis showed that antibiotic prescriptions using CDSS were twice as likely to be categorised as appropriate. However, studies reported that the extent to which clinicians adhered to a system's recommendations depended on the specificity of the information. For example, a high volume of non-essential and non-specific recommendations leads to clinicians ignoring or overriding alerts provided by the CDSS (18, 355, 356). Despite a system's ability to improve prescribing outcomes, the quality and quantity of system alerts are directly linked with clinicians' adherence to CDSS recommendations. Alert

fatigue and a high override rate are significant problems, since it is difficult to achieve a balance between providing necessary alerts to ensure patient safety, and reducing information overload for clinicians (357). Taking this into account, recent studies have highlighted the role of machine learning methods such as pattern recognition and predictive models to stratify and reduce the number of alerts in CDSS. These methods allow a system to learn and identify user patterns, using training datasets and past cognitive decisions of the users, so that recommendations can be filtered and adapted for each user (358-360). Approaches like this can mitigate the risk of non-adoption or alert over-ride and help to ensure the benefits of CDSS are translated into clinical practice (18).

Along with the impact of CDSS on the appropriateness of therapy, we also found that CDSS can reduce unnecessary antibiotic prescribing. Following CDSS implementation, studies reported a decrease in the overall volume of antibiotic use and duration of therapy leading to an optimal antibiotic regimen. This decrease in the volume of antibiotic use was related to different restrictive measures recommended by CDSS, such as delayed prescriptions, limiting antibiotic prophylaxis before surgery in the absence of an appropriate clinical without indication, providing information on the optimal dose and duration, and notifications to adjust empirical therapy to reduce unnecessary antibiotic use. Morris (164) argued that reductions or changes in antibiotic therapy should not lead to any elevated health risks. Therefore, we were particularly interested in whether reduction in antibiotic therapy led to changes in outcomes such as mortality and length of hospital stay. These outcomes were identified as markers of safety of care in quality metrics for antimicrobial stewardship programs (163, 164). We observed a relative reduction, and in some cases no change, in these outcomes after implementation of CDSS. There is, however, a caveat as many of the included studies had a shorter follow-up period, so the impact of CDSS on these outcomes over a longer period could not be established.

Few studies considered the economic outcomes of the cost of therapy and hospitalisation to assess the impact of CDSS on the cost-effectiveness of antibiotic therapy. Following CDSS implementation, we identified a reduction in the overall cost of therapy in our systematic review. Analysis of the included studies revealed that this reduction could be linked to an overall decrease in the volume of antibiotic use and length of hospital stay as well as an increase in the optimal duration of therapy. Moreover, a study conducted by Kofoed *et al.* (257) indicated that CDSS systems tend to recommend antibiotic therapies with an overall lower cost, not only because direct dispensing costs are reduced but also because the costs associated with future resistance are mitigated. In Kofoed *et al.* study, the economic implications of future antibiotic resistance included factors such as treatment failure due to resistance, reduced antibiotic efficacy within a specific department, and penalties associated with using last resort antibiotics.

Our findings demonstrate the capability of CDSS to optimise antibiotic management by reducing unnecessary prescriptions and increasing compliance with prescribing guidelines. Although the direction of effect was largely consistent in favouring CDSS, the magnitude of benefits varied considerably across studies. Our analysis suggested that variation in the outcomes was likely to be related to inconsistency in system adoption and uptake by users. Based on a sub-group analysis, we identified that between-study statistical heterogeneity was reduced in the non-interventional studies (5 studies) included in our meta-analysis. In these studies, CDSS had not been implemented in clinical settings but, rather, patient data were retrospectively or prospectively entered into the CDSS system to compare the treatment recommended by the system with that of standard care. Low statistical heterogeneity may be related to factors related to system implementation in non-interventional studies such as users' willingness to use the systems and clinical integration of the systems into workflow. Similarly, even for those studies that were 'interventional', the majority were single-site studies conducted in a particular practice or hospital, therefore organisational diversity and setting-specific factors for CDSS implementation were not considered.

8.2.2 What Factors Need to be Considered to Ensure Successful CDSS Adoption in Different Care Settings?

Key messages

- Individual and setting characteristics are important in understanding the variability in CDSS adoption for antibiotic management.
- CDSS non-users are more likely than users to lack confidence in the systems' recommendations and consider that the use of these systems can compromise professional autonomy.
- Experienced clinicians are less likely to adopt CDSS due to a mistrust of the systems' data, and fear of losing their autonomy in clinical decision-making.
- Increasing workloads and limited consultation time are important barriers to the adoption of CDSS in primary care.

As found in Chapter 4, the extent to which CDSS can impact on antibiotic management is largely dependent on uptake and use of these systems by clinicians. Variability in the benefit of CDSS across different studies warrants an understanding of the factors that might influence system adoption by healthcare professionals. The integration of CDSS into clinical practices is more complicated than that for traditional information technology tools because CDSS also incorporates an evidence-based paradigm into decision-making. This can challenge conservatism present within the clinical culture. It is important to understand the individual perceptions and experiences that may explain variability in CDSS uptake. For this purpose, we conducted an online survey (Chapters 5 and 6) with clinicians in Australia to understand their perceptions regarding the adoption and use of CDSS for antibiotic management.

In line with the UTAUT model, we found that perceived ease-of-use and improvement in clinical performance directly influence clinicians' behavioural intent to adopt CDSS. This suggests that if clinicians believe that CDSS can advance their knowledge and easily integrate current evidence into their practice, they will probably be more willing to adopt CDSS. This is consistent with previous research indicating that those systems that provide evidence-based patient-specific information in a way that is non-disruptive to clinical workflow are more likely to be adopted by end-users (108, 361, 362).

We found that clinicians' perceptions regarding the adoption of CDSS are moderated by individual and setting-specific factors. We observed the significant impact of clinical experience, familiarity with these systems and type of care settings on clinicians' intent to adopt CDSS. For instance, senior clinicians

frequently perceived CDSS as a threat to their professional autonomy and preferred to rely on their own clinical experience and judgement rather than recommendations provided by CDSS.

Some studies have related clinicians' mistrust in CDSS to how these systems communicate the reliability and currency of the information presented (363, 364). The explainability and transparency of recommendations is a significant criterion with which to establish end-users' trust in the system. The use of 'black box' models in many CDSS - whereby users are unaware of how the CDSS has computed recommendations or decisions on treatment - limits clinicians' trust in the credibility of the presented information (365). Opaque decision-making in these systems raises serious questions about litigation risks when clinicians are relying on system information without understanding how the specific recommendations have been derived (366). Clinicians have been reported as being concerned about excessive dependence on these systems when they believe that the knowledge base may be rooted in experts' professional opinion rather than objective medical evidence (367).

A crucial aspect of successfully implementing CDSS is, therefore, to establish an understanding by clinicians of how and why the system computes certain recommendations or decisions. A better understanding of system functioning is not only important to increase trust, but it can also mitigate the risk of certain biases such as automation bias where clinicians blindly accept the system information without reflecting on the process (368). Zihni *et al*. (365) reported that there is an increasing need for regulation bodies to recognise the importance of system explainability in the regulatory requirements for CDSS. It can foster increased transparency and trust in CDSS, especially for experienced clinicians who have established practices and preferences, and who sometimes consider CDSS as a threat to their own clinical expertise (295).

Clinicians' perceptions regarding the use of CDSS for antibiotic management are also moderated by their experience in using these systems. Unsurprisingly, we found that a lack of confidence in system' recommendations and fear of compromising clinical autonomy were more prevalent in non-users compared to CDSS users. This suggests that as clinicians gain experience with the system, they are less likely to have negative perceptions. The comparison of CDSS users and non-users further showed that there was a higher proportion of younger clinicians using CDSS in our survey which suggests that younger clinicians are more likely to interact with CDSS compared to older clinicians. This could in part be explained by young clinicians having better computer literacy (270). The assumption that clinicians' digital knowledge and proficiency are significant determinants of CDSS usage is also supported by previous studies. Trivedi *et al*. (369) identified that clinicians who routinely use computers show better motivation to adopt CDSS in their clinical practices due to a higher confidence in interacting with the system. Therefore, establishing a suitable fit between the system and the users' skills is pivotal for

integrating CDSS in clinical practice. Digital health literacy is continuously evolving, where the pace is determined by personal, environmental and social contexts (370). This type of literacy empowers healthcare professionals and patients to effectively engage with technologies to improve care processes, but our survey results show that varying levels of digital knowledge, or skills in different clinician groups (e.g. by age), can propagate practice gaps in the workforce. These differences in knowledge and skills can lead to inconsistent adoption of CDSS across different groups.

Finally, we identified differences in clinicians' perceptions regarding CDSS adoption depending on the setting of use. Constraints in primary care such as increasing workloads and limited time for consultation were reported as important barriers to CDSS integration in daily practice. Primary care clinicians' consultation times are typically constrained in Australia, therefore becoming familiar with different dimensions of patient care in limited consultation time makes it difficult to engage with CDSS. In our study, clinicians working in primary care were more likely to perceive that the time and effort required to retrieve relevant information from CDSS directly impacted the use of the system during their daily practice. These findings are consistent with key insights provided by Medlock *et al*. (348) who found that timing, format, content, and interaction functionality are determining factors in the adoption of CDSS.

Our results were consistent with the UTAUT model in that it suggests that individual and setting characteristics are important moderators of users' intentions to adopt CDSS. Clinical experience, digital health literacy and the clinical settings in which these systems are used are important to consider so that clinicians' willingness to use CDSS can be optimised. Our findings acknowledge the complex nature of CDSS implementation and contribute to establishing a comprehensive understanding of how multiple factors shape users' behavioural intent to adopt CDSS.

8.2.3 What are the Policy Challenges and Opportunities for Sustainable Implementation?

Key messages

- Lack of collaboration between different stakeholders (i.e. governments, industry, vendors, users, and patients) has limited the capacity in Australia to develop a shared vision for CDSS implementation.
- The lack of centralised governance policies for has created operational fragmentation for the system-wide rollout of CDSS.
- Customisation in CDSS design for user-centred innovation must be balanced with the standardisation, particularly in how information is generated and presented, to facilitate interoperable CDSS implementation.

Notwithstanding increasing evidence of the potential of CDSS to impact efficacy and quality of care when it comes to antibiotic management, the application of these systems remains limited to pilot studies in Australia. Failure to integrate CDSS into daily clinical practice has been linked to an inability to scale up these technologies within the broader healthcare system. A guiding principle from the Australian National Digital Health Strategy is to reconsider existing and new practices to achieve a digitally enabled healthcare system. This Strategy highlights the lack of guidance on CDSS system-wide integration, and how it critically depends on understanding barriers to CDSS implementation. We conducted a qualitative study (Chapter 7) to investigate system-level challenges to integrate CDSS into the healthcare systems. The key findings from these policymaker interviews are discussed below.

Our results show that the CDSS implementation process is not simply an on-off function but requires significant co-ordination between different stakeholders to understand how existing care structures can be aligned with CDSS as an innovation process. However, the goal of implementing CDSS within the healthcare environment is often not shared by all the stakeholders. Different stakeholders might have different objectives and expectations from CDSS implementation. Without acknowledging these varying expectations and priorities, it is extremely difficult to establish collaborative actions and mutual ownership of the implementation process by all key stakeholders. The failure to embed digital systems such as CDSS extends beyond technical or financial issues and can be attributed to the competing interests of different stakeholders. In recognising problems with collaboration in a multi-stakeholder environment, policymakers have suggested cross-disciplinary solutions involving all relevant

stakeholders in the planning, design, implementation, and evaluation phases of CDSS. Cresswell *et al*. (143) argued that the implementation process – which assumes benefits including improved efficiency of care - might translate differently in practice for different stakeholders. Without a mutually shared vision for implementing CDSS, it is difficult to build a consensus on specific objectives and resulting outcomes that can help conceptualise the transformation process for all stakeholders.

Stakeholders in our study believed that poor governance structure is the main contributor limiting sustainable and wide-scale CDSS rollouts. Effective governance helps to create an enabling environment to empower the transformation process and coordinate implementation efforts at local, state, and national levels for better alignment with national digital goals. However, stakeholders conveyed concerns that the decentralised policies observed in many digital health programs, in which local institutions are responsible for establishing incentives and willingness are only effective for facilitating *intra*-organisational adoption. At a system-level, these policies have caused problems for the coordination of care and digital interoperability. For example, if CDSS across different organisations cannot access, share and exchange health information when a patient transfers from one healthcare practice or setting (e.g. hospital) to another (e.g. community or aged care), it can lead to delays in treatment, limited understanding of individual' needs, poorer health outcomes and increase in treatment cost. A lack of holistic policies has resulted in fragmentation of digital health implementation, contributing to duplication of efforts, lack of transparency and an unclear definition of roles and responsibilities. This fragmentation has further propagated due to the difficulties of blending the parallel processes of clinical and information technology governance. Interviewees acknowledged that input from different organisations and stakeholders can ensure that the implementation process is well adapted to specific needs and requirements of the health system. However, governments have a significant role to play in aligning these local policies with overall health system goals to promote interoperability.

Understanding the local context and specific requirements of users is important to ensure a better integration and adoption of CDSS in the healthcare environment. However, we identified that the value of CDSS for coordinated care is not limited to its technical sophistication and ability to address specific clinical needs. It requires establishing methods and pipelines to generate information in a standard format and incorporate different data streams into the decision-making process. In this regard, the interoperability of data generated across different CDSS is a key element to ensure continuity of care across organisations and jurisdictions. Stakeholders identified that the current digital health landscape in Australia is characterised by loosely connected organisations and datasets because of a lack of mutually agreed standards for information representation and sharing. Recent efforts to increase

interoperability have focused on establishing data format standards for structural interoperability such as HL7 standards, which mainly focus on data exchange between different systems. These efforts also need to extend to incorporate other important interoperability dimensions such as semantics, which not only allows exchange of data in a standardised format, but a shared interpretation of data that is exchanged between systems. The National Digital Health Strategy recognises that interoperable digital space is a pre-requisite for achieving the benefits of evidence-based and coordinated care through systems such as CDSS. Achieving interoperability is a significant undertaking for the Australian healthcare system, given it is a two-tiered health system consisting of a federation of independent locally governed jurisdictions that are each responsible for the delivery of health care in public hospitals in their own jurisdiction, while the federal government is responsible for primary care and private operators manage private hospitals and allied health care (371). To achieve interoperability would require close collaboration across organisations to leverage different CDSS for an uninterrupted data flow. Ensuring mutually agreed interoperability standards at a national level will allow better conformance with these standards as systems are updated or new systems are introduced.

Therefore, a balance must be maintained between, on the one hand, customisation of the CDSS system design and implementation strategy for ease of use in the local environment and, on the other, standardisation in the knowledge representation. As discussed in the above section (section 8.2.2), customisation of the implementation process by understanding users and setting requirements is important to improve CDSS adoption. However, supporting this customisation with multi-stakeholder consensus and data standardisation is required before there can be interoperability and wide-scale CDSS implementation.

8.3 Synthesis

This research shows that the potential of CDSS in reducing excessive and inappropriate antibiotic prescribing is considerable if attention is paid to improving the alignment of CDSS with clinical workflow and the expectations of clinicians at the point of care. With the changing dynamics of healthcare and increasing volume of clinical data, CDSS enable the generation, analysis, and dissemination of clinical data to facilitate evidence-based and coordinated decision making at the point of care (25, 74). It provides diagnosis and treatment recommendations based on patient-specific risk factors and can help increase compliance with prescription guidelines and/or enable consideration of bacterial resistance patterns when prescribing. This can reduce the risk of inappropriate prescribing, reduce the length of hospital stay and reduce the cost of antibiotic treatment. By providing knowledge-translation functionality, CDSS integrate evidence into clinical practice. Our analysis suggested that although many studies have provided evidence of the positive impact of CDSS on the quantity and quality of antibiotic prescribing, many of the systems were unable to provide sustainable and long-term practical benefits in influencing health professionals' prescribing practices. Moreover, the magnitude of the CDSS effect in improving antibiotic management was quite variable in the literature. While some studies identified a significant impact of CDSS on different clinical and economic outcomes of antibiotic use, other studies were unable to observe any significant impact.

Research has indicated that the inability to translate CDSS benefits into clinical practice might be related to less-than-optimal adoption and uptake of CDSS (59, 82, 85). We identified that CDSS is a complex intervention that is challenging to integrate into clinical practices for antibiotic management due to factors such as lack of fit with existing clinical workflows and poor implementation strategies. The lack of understanding of the underlying factors that determine the appropriateness of CDSS for a clinical environment and workflow has negatively impacted the CDSS adoption. Our findings indicated that the design and implementation of CDSS as a mere technical system has overlooked the complex interaction between technology, clinical processes, and individuals that drives the adoption of new technologies. CDSS are characterised as interventions to overcome barriers to evidence-based antibiotic management. However, there has been very little attention paid to understand clinicians' resistance to adoption of the technology and other factors that may limit its uptake in clinical practice.

Our research identified varying perceptions of CDSS in different healthcare settings and these perceptions varied by certain characteristics of the prescribing clinicians. We noted that clinicians CDSS adoption decisions extend beyond the technical proficiency of the system and depends on how the implementation process addresses their specific needs and requirements. For instance, clinicians in primary care believed that increasing workload and limited time in the standard consultation can limit

their use of CDSS if they need to invest effort and time to retrieve relevant information from the system. Therefore, the CDSS implementation can only provide limited benefit if the contextual factors such as settings of use, workflow requirements and clinicians skills are not taken into consideration. In our interviews with policymakers, a 'one size fits all' policy in CDSS implementation was recognised as a barrier and a source of conflict with the dynamic and complex clinical environment. Healthcare practitioners, like most expert groups, are likely to resist change in the way they work, unless there are obvious benefits in terms of efficiency and ease of use. Therefore, it is particularly important to recognise the varying organisational and behavioural components that determine the CDSS users' adoption behaviour in different clinical settings. This involves understanding how implementation strategies can be customised to accommodate the unique requirements of different settings and clinicians and the varying digital skillset in the healthcare workforce.

We identified that the ability of any healthcare organisation to successfully integrate CDSS into clinical practices and optimise its use for antibiotic management is strongly correlated to clinicians' digital health literacy. As established above, CDSS can improve access to clinical knowledge, antibiotic prescribing guidelines, resistance patterns and patient-specific risk factors for evidence-based care. Conversely, implementation of CDSS can also exacerbate inequalities in accessing this information due to varying levels of digital health skills and knowledge in the healthcare workforce. Therefore, in CDSS implementation strategies, there is a need to consider this digital health literacy divide among the healthcare workforce to avoid creating any practice inequalities.

Our findings suggested that younger clinicians and ones with better digital skills are more prepared and inclined to adopt CDSS whereas limited digital skills in experienced clinicians may be a contributing factor to their resistance to CDSS. As an increasing number of digital health interventions are being introduced in the Australian healthcare system, the requirement of the workforce skillset is also shifting. Several initiatives were introduced by relevant agencies such as ADHA and the Australasian Institute of Digital Health (AIDH) to develop digital capabilities as a part of the medical curriculum and continuing professional development. Stakeholders identified that there are not enough incentives for healthcare organisations specifically for smaller and medium enterprises to invest in digital health education and training of existing and new healthcare workforce. Previous studies have also argued that this limited investment capacity for digital health literacy has led to resistance in adopting these interventions as they reshape the clinical practices and may not align with existing funding models (372, 373). Therefore, along with the consideration of different settings and contexts across the healthcare sector, the implementation strategies need to focus on developing appropriate incentives for promoting digital health literacy in the healthcare workforce. It will enable them to effectively navigate the system and

understand different challenges associated with the use of CDSS (20, 374). Our findings also suggested that if senior clinicians and consultants engage with CDSS and change their antibiotic prescribing behaviour, that this behaviour will likely filter down to the more junior health professionals in the healthcare setting.

These findings suggested that CDSS implementation must not be limited to introducing new technology but rather understanding how existing elements, actors and processes can be adapted to support the innovation. This is especially important when the objective for implementing CDSS varies across different organisations and stakeholders. Our findings indicated that without acknowledging these varying expectations and perceptions across different stakeholders, it is difficult to establish trust and mutual ownership of the implemented system. Based on these findings, the subsequent section provides pragmatic recommendations for effective and sustainable CDSS implementation.

8.4 Recommendations

Findings from this research provides future directions in two major areas related to CDSS implementation. These include translating the findings into practice and policy, and highlighting areas which require subsequent research.

8.4.1 Implications for Policy and Practice

8.4.1.1 Understanding End-users' Specific Needs and Requirements

Despite access to CDSS, adoption and use by healthcare practitioners is not always optimal. There is a gap in the available evidence of the benefits of CDSS and actual use of the system in healthcare settings. Findings from Chapter 5 and 6 highlights the variability in CDSS adoption among different groups of clinicians. We identified that clinicians' perceptions regarding CDSS are moderated by clinical experience, setting of use and experience with using CDSS.

Based on the above findings, it is recommended that CDSS implementation strategies should be tailored to users' and setting requirements to improve positive perceptions and address users' lack of trust in the system. Understanding users' behaviour based on their clinical experience, use of CDSS and care settings can help to address specific concerns and establish an implementation policy promoting behavioural change in clinicians. For instance, while we found that there is a general sense of distrust in clinicians regarding CDSS use, experienced clinicians were more likely to resist adoption due to a perceived risk of compromising their professional autonomy. This suggests that CDSS design needs to communicate the reliability and transparency of the information presented, to establish the

trust of clinicians. This include minimising 'black box' models and ensuring clear referencing so clinicians can see the source of the data informing the system recommendations (363, 364).

There is also the need for an effective clinical engagement process in which a wide range of clinicians are actively involved in problem identification, planning, design, implementation, and evaluation of the proposed CDSS. Senior or experienced clinicians usually have established practices and find it more difficult to adopt technological change. Therefore, active engagement of these clinicians in iterative co-design of the system will help ensure that CDSS are designed and implemented in a way that suits their workflow and minimises disruptions (31, 375). This can also help reduce the clinicians' resistance by establishing a mutual ownership of the intervention. It is likely that this would have to occur through 'buying out' clinicians' time to participate (or the use of some other incentive), as they are usually time-poor.

We also identified that negative perceptions regarding CDSS were more prevalent in non-users. Therefore, communication of CDSS benefits is an important aspect to change the narrative and generate confidence in healthcare providers for CDSS adoption. In this regard, the clinical peer networks including clinical leaders and champions can play an important role in communicating the benefits of CDSS as clinicians are more likely to trust their own peers (376). Although senior clinicians are more likely to resist use of CDSS, if they can be persuaded to adopt these systems then, given the hierarchical nature of medicine, they are more likely to generate cultural change amongst their peers and facilitate CDSS adoption. Targeted clinical engagement and communication can ensure that CDSS implementation is planned in a way that can help clinicians to feel comfortable with this change.

In primary care, the time and effort required to extract information from a CDSS was identified as a major barrier to CDSS adoption because of limited patient consultation time. Therefore, it is important to consider the visibility of the information and workflow interruptions while implementing CDSS. The CDSS Five Rights Rule (discussed in section 2.3.2) highlights the significance of clinicians' role as well as the format and timing of the system's recommendations so as to provide a better fit between CDSS and clinical workflow (377). The amount and timing of CDSS alerts should be proportional to the criticality of the information presented to healthcare providers, with the aim of reducing the risk of workflow interruptions and alert fatigue.

8.4.1.2 Developing Training and Digital Health Literacy

Organisational capability to implement and sustain CDSS is dependent on the users' skills and knowledge (Section 8.2.2). However, participants (Chapter 7) expressed their concerns that there is a lack of incentives and training to develop digital literacy as a skillset alongside clinical training. Although,

digital health education and training has been emerging in Australia, the health workforce census reports that 71.8% of clinicians do not have any credentials for digital health (378). Given this finding it is recommended that digital literacy modules be incorporated into clinical and nursing education as well as continuous medical education upskilling. Our findings are consistent with the Australian National Digital Health Workforce and Education roadmap which established digital health literacy as a pillar for building health workforce competency (378). This requires a national strategy to embed key learnings into the clinical curriculum to promote the behaviour and skills required for digital transformation of the future healthcare workforce. Opportunities and incentives for digital health training for the existing workforce should also be considered and implemented to avoid perpetuating gaps in skills and technological disparities in the workforce. With this in mind, clinical champions and leaders with better computer literacy and prior experience with digital systems must be supported to effectively advocate and drive the change process (376, 379). The aim of CDSS implementation should be to provide adequate digital health training for the healthcare workforce and to empower early adopters, who may be digitally literate clinicians in the role of engaging peers and advocating for change.

8.4.1.3 Mutually Agreed Interoperability Standards and Conformance Strategy

The ability of CDSS to enable evidence-based and coordinated care between different organisations requires standardised data generation and exchange between different systems. However, as described in Chapter 7, the fragmented infrastructure and lack of mutually agreed data standards at a national level in Australia has compromised the interoperability of different systems.

There is a need to establish consensus between federal and state governments on standards for data representation and interpretation. These standards are required not only for sematic interoperability to generate standard medical terminologies that represent concepts unambiguously across different systems, but to guide the processes that will leverage this knowledge to generate CDSS recommendations. Without mutually agreed standards, it is difficult to implement knowledge and processes developed for a particular information system or clinical context across systems.

Therefore, we recommend a national framework for data standardisation be developed with explicit and clear documentation on the usability of standards. Healthcare stakeholders and governments also need to form partnerships to develop a deployment and conformance strategy to ensure and harmonise the use of interoperability standards across different healthcare organisations. This can only be achieved through a mutually agreed vision, strategy and timelines between governments, the health sector and industry.

8.4.1.4 Establishing a Collaborative Care Strategy through Multi-stakeholder Engagement

Findings from Chapter 7 show that the lack of a robust strategy, that brings together different stakeholders to establish a shared vision and mutual ownership of CDSS implementation, has increased the risk of conflicting interests and lack of collaboration.

A robust strategy that aligns the interests of different stakeholders with a strategic vision should guide a scaled-up implementation process. This requires strategic partnership and dialogues between governments, industry, healthcare sectors and patients to ensure that the implementation process addresses the broader agenda of digital transformation within healthcare systems, while promoting shared ownership. The aim would be to facilitate cross-discipline coordination and minimise perpetuating conflicting interests across different professional hierarchies.

8.4.2 Future Direction for Research

The findings from my thesis have highlighted several key areas for future research. Although primary care has been established as a sector with a significant burden of inappropriate antibiotic prescriptions, we identified that there is limited evidence on the impact of CDSS on antibiotic management in this setting (42). Therefore, further research should be conducted in community settings to confirm the findings we observed on a very limited primary care dataset.

Moreover, studies tended to evaluate the impact of CDSS on antibiotic management as measured by clinical outcomes and did not consider how different organisational and behavioural aspects interact to generate the value of CDSS for antibiotic prescribing, as well as the overall care process. There is a lack of multi-dimensional outcomes in studies which extend beyond the technical and clinical dimension of CDSS impact. Therefore, future studies need to consider holistic outcome measures to enable the evaluation of process improvements, behavioural change and system uptake, organisational impact, and technical reliability along with the ultimate measurement of health outcomes. Further research is required to establish such holistic outcomes that are appropriately powered to measure CDSS benefits for clinicians, patients, and healthcare organisations. There is also a need for more collaborative multi-site studies to investigate the impact of specific individual, organisational, and setting factors. We also observed a lack of follow up in studies implementing CDSS, such that the long-term impact of CDSS on the care process was often unknown. Future studies should assess the impact of CDSS longitudinally to provide insight on the long-term impact of the challenges identified in this thesis.

Overall, CDSS implementation is complex with underlying technical, clinical, social, and behavioural dimensions. We have investigated clinician and policymakers' perspectives to understand the challenges of implementing and adopting CDSS for antibiotic management. However, as CDSS

implementation is a multi-dimensional process, future research can extend our research findings by including the viewpoints of other relevant stakeholders to understand the synergy of different actors and elements in CDSS implementation (for example, nurses, registrars, consultants, social workers, infectious disease physicians, pharmacists). In this regard, the socio-technical models can provide a robust framework to evaluate CDSS implementation from multidimensional perspectives.

With improving sophistication in this field, various CDSS with newer technologies such as artificial intelligence and machine learning are emerging. Along with the challenges and opportunities discussed in this thesis, these newer systems will need formal evaluation of other aspects such as the role of data quality, and bias in the training data used to provide personalised care recommendations.

8.5 Significance of This Thesis

Healthcare is one of the key industries to realise benefits from digitalisation through easy and increased access to information, timely coordination, and communication (154, 380). Studies conducted in Australia estimate that hospitalisation costs due to medication adverse events, in which antibiotics were a prominent class, are approximately $1.2 billion (10, 381). Moreover, the increasing volume of clinical data and the changing healthcare landscape has increased investment and interest in digital health services such as CDSS. However, due to the complexity of healthcare settings and clinicians' resistance to change, it is not clear how these systems can be optimally implemented to ensure long-term and successful adoption.

This research has addressed this issue by assessing the challenges and opportunities relating to CDSS implementation from individual, organisational, and system-level perspectives. The findings have provided a holistic picture concerning CDSS implementation with recommended policies and strategies to improve the healthcare system's capacity to adopt and sustain technologies like CDSS for antibiotic management.

Evidence on the efficacy of CDSS for antibiotic management is increasing but the effect observed in these studies is varied. This can result in ambiguity in knowledge translation by making it difficult for healthcare professionals to understand the value of CDSS for evidence-based antibiotic management. This is further compounded by different review studies focusing on specific care settings or study design, meaning that healthcare professionals only see part of the picture. Given this uncertainty, our study has contributed evidence by providing a comprehensive assessment of CDSS impact on antibiotic management through incorporation of different care settings and study designs. Our study is the first to explore different factors that may be contributing to the large variability in CDSS effectiveness by investigating the impact of study design, system features, and care settings on CDSS performance for

antibiotic management. In addition, our research shows that differences in system uptake could be an underlying reason for the significant between-study heterogeneity.

An important contribution of our research which adds to the overall significance of this thesis is understanding why CDSS are not effectively adopted by users even when they are widely developed and deployed. We have utilised a theoretical framework of UTAUT to understand the underlying factors that shape a user' inclination to adopt CDSS. The UTAUT provided the foundation to assess not only the users' behavioural intent to adopt CDSS but also allowed us to evaluate different moderating factors that can impact the user's behaviour. This facilitated an understanding of how different individual and setting specific characteristics contribute to the variation in CDSS adoption identified in the literature. Our results point towards the variability in the perceived benefits and utility of CDSS in clinicians and provide a better understanding of the factors that determine clinician's behavioural intent to adopt CDSS. These findings will contribute to the development of targeted policies and interventions (as suggested in the previous section) for CDSS implementation which will address specific users' concerns and requirements for optimal adoption.

This research has identified that CDSS implementation is complex involving different elements and stakeholders such as healthcare professionals, the public, government, and the medical technology industry with the potential for conflicting agendas and interests. To understand multiple perspectives on CDSS implementation, we have integrated the insights from clinicians and policymakers. This not only helped in assessing end users' views on CDSS adoption but also in identifying gaps in the health system's capacity to successfully introduce innovative technologies such as CDSS. This insight is particularly useful in illustrating that successful implementation of digital innovations is not determined by individual factors, but by the dynamic and complex interaction between individual, organisational and system-level factors.

Overall, the findings presented in the previous chapters (chapter 4 -7) have wide applicability for the development of effective implementation strategies for CDSS at local and national levels.

8.6 Thesis Limitations

Limitations related to each study (Chapter 4, 5, 6, & 7) have been discussed in each respective chapter. In this section, I present the limitations of the research overall.

A main limitation is that the barriers to CDSS implementation are reported from the Australian healthcare context. Although many issues discussed in this thesis may be applicable to a global context, there may be limitations with transferring the findings to other countries. With different healthcare

systems and implementation strategies, the challenges faced by stakeholders may differ according to the local context. Thus, our findings are not proposed to be generalizable to all healthcare systems.

To identify barriers, clinicians from different healthcare organisations and relevant agencies were recruited through self-selection of an online survey. Lack of random sampling in online surveys can introduce selection bias impacting on the applicability of the results. It was not possible to evaluate the effect of selection bias on our results because data on non-participants was not available. As clinicians responded to participation notices published on relevant websites, social media accounts and newsletters for the study, willingness to participate in the study could be related to their experience and interest in the field. This could have impacted the representativeness of a self-selected sample of clinicians. The data from the free-text comments was concise, and therefore provided limited contextual understanding of the responses. The qualitative comments were triangulated with the quantitative data to provide additional understanding of the responses.

Moreover, the clinicians' perceptions investigated in Chapter 5 may not correlate to their actual use of CDSS. Therefore, our findings may be limited in establishing whether clinicians' intentions regarding CDSS influence their use of the system. This phenomenon is referred to as the 'intention-behaviour gap' and is not unique to information technology research. Studies have argued that positive perceptions regarding information technology may not necessarily translate into usage (382). Many critics of technology acceptance models such as UTAUT and TAM have also highlighted that these models attempt to predict behaviour based on users' intentions (383, 384). There is empirical evidence that suggests perceptions inconsistently or in many cases may not influence behaviour. Therefore, future research that assesses intention and behaviour before and after the implementation of a CDSS is needed to understand which perceptions regarding CDSS may or may not influence the subsequent behaviour.

Following the online survey with clinicians, identifying challenges and opportunities in upscaling CDSS from pilot studies to system-wide implementation in Australia was undertaken. The interviews with policymakers were conducted from March – June 2019 during the COVID-19 lockdown in Australia. Many potential participants for this study were working in the healthcare and policy sector but in different capacities. Although it was challenging to arrange interviews during this period, the sample was selected for maximum diversity by recruiting participants from different jurisdictions and professional backgrounds while ensuring data saturation. We used the definition of data saturation provided by Guest, Bunce, & Johnson (385) as the point where no new theme or concept emerged from the data. Due to the scope of the study, we limited the sample to professionals involved in policy development, implementation and governance related to CDSS projects. Therefore, future studies could extend our

findings by investigating the perspectives of other important stakeholders including patients, developers, vendors and regulators.

It is also important to remember that our study was carried out over a relatively short time frame. The digital health landscape and systems are quite dynamic in nature, therefore, CDSS implementation activities relate to the evolving technology and policies. There could have been significant changes in the design, implementation, and regulation of CDSS during the study which we were unable to capture. Perspectives may also have shifted because of the requirement to use telehealth and engage more with digital health systems during the COVID-19 pandemic.

This study highlights important gaps in knowledge and provides important recommendations. However, given that implementation challenges are time variant, the context and relevance of the findings could change over time.

8.7 Conclusions

In conclusion, there is an increasing need to effectively integrate CDSS in the Australian healthcare system for optimal antibiotic management. However, a range of key areas must be addressed within the existing processes and policy to achieve the real potential of CDSS for evidence-based and coordinated care.

This thesis set out to assess the feasibility of CDSS for optimal antibiotic management by identifying different challenges for CDSS implementation. The findings indicated that CDSS has the potential to promote appropriate antibiotic prescribing by increasing compliance with prescribing guidelines and reducing unnecessary prescribing. However, there is considerable variability in system uptake by end-users leading to conflicting results on CDSS efficacy. This variability appears to be related to clinicians' perceptions regarding CDSS benefits and efficacy and these perceptions determine their behavioural willingness to adopt CDSS. Questionnaire responses suggested that effective and widespread CDSS adoption requires a better alignment of the system with specific requirements of users and the care setting. CDSS implementation can provide only limited benefit if the contextual factors such as users' skills, their requirements and setting of use are not acknowledged in the implementation process.

The success of integrating CDSS into a healthcare system is dependent on how the implementation process is understood and planned. The process presents multifaceted challenges characterised by the involvement of multiple stakeholders with varying interests. To ensure CDSS are integrated unobtrusively, there is a need to consider collaborative care models to create a mutual understanding between different stakeholders and reduce the risk of conflicting interests. The capacity of CDSS to promote coordinated care is limited by the lack of interoperability standards between CDSS in different organisations. The CDSS implementation needs to be supported by a framework for generating and communicating information in a standard format to enable evidence-based decision making.

Based on the above findings and recommendations, it is important to understand that CDSS are complex systems that require interdisciplinary implementation frameworks that consider the interaction of the CDSS with clinical workforce, organisational processes, and health systems. The implementation must be considered as a transformation process shifting the focus from volume-based models to value-based models. This paradigm shift in healthcare is a result of increasing interest in defining success in terms of quality of care that a patient receives, rather than the number of services provided or patients attended. CDSS can play a significant role in achieving this transformation as they have the potential to improve quality and safety of care if effectively implemented and sustained.

Appendices

Appendix A

Chapter 4: Systematic review and meta-analyses to evaluate the effectiveness of CDSS for optimal antibiotic management: Supporting documentation

- Appendix A.1: Search Strategy for Systematic Review
- Appendix A.2: Risk of Bias Assessment of Non-randomised Studies
- Appendix A.3: PRISMA Checklist for systematic Reviews
- Appendix A.4: Supplementary data of the published article

Appendix A.1: Search Strategy for Systematic Review

Text Word Search

1. Electronic OR computer* OR automat* OR digital OR “web-based”
2. “Order entry” OR “approval system*” OR “surveillance system*” OR “decision support*” OR “reminder system*” OR prescribing OR “expert system*” OR feedback OR alert OR reminder OR “management system*” OR CDSS OR DSS OR HIS
3. Antimicrobial* OR antibacterial* OR antibiotic*
4. 1 AND 2 AND 3

Mesh Terms Search

1. "Decision Support Systems, Clinical"[Mesh] OR "Medical Order Entry Systems/utilization" [Mesh] OR "Electronic Health Records"[Mesh] OR "Drug Therapy, Computer-Assisted"[Mesh] OR "Prescription Drug Monitoring Programs"[Mesh] OR "Medical Audit"[Mesh] OR "Medication Errors/prevention and control"[Mesh] OR "Electronic Prescribing"[Mesh]
2. "Anti-Bacterial Agents/pharmacology"[Mesh] OR "Anti-Bacterial Agents/therapeutic use"[Mesh] OR "Bacterial Infections/drug therapy"[Mesh] OR "Drug Resistance, Bacterial"[Mesh] OR "Drug Resistance, Multiple, Bacterial"[Mesh] OR "Antimicrobial Stewardship/methods"[Mesh] OR "Antimicrobial Stewardship/utilization"[Mesh]
3. 1 AND 2

Appendix A.2: Risk of Bias Assessment of Non-randomised Studies

Risk of Bias: Critical Serious Moderate Low

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall risk
Agwu *et al*. 2008								Serious
Arboe *et al*. 2014								Critical
Bond *et al*.2017								Moderate
Buising *et al*. 2008 (a)								Serious
Buising *et al*. 2008 (b)								Serious
Chow *et al*. 2015								Moderate
Cox *et al*. 2011								Serious
Dean *et al*. 2015								Moderate
Demonchy *et al*. 2014								Moderate
Evan *et al*. 1998								Moderate
Evan *et al*. 1999								Serious
Faine *et al*. 2015								Serious
Filice *et al*. 2013								Serious
Gifford *et al*. 2017								Serious
Giuliano *et al*. 2011								Serious
Hincker *et al*. 2017								Serious
Huh *et al*. 2016								Critical
Karsies *et al*. 2014								Serious
Kim *et al*. 2008								Critical
Kofoed *et al*. 2008								Serious
Leibovici *et al*. 1997								Serious

Litvin *et al*. 2012								Serious
Mainous *et al*. 2012								Moderate
McCullough *et al*. 2014								Moderate
Mullet *et al*. 2001								Serious
Mullet *et al*. 2004								Serious
Nachtigall *et al*. 2014								Moderate
Nault *et al*. 2017								Serious
Okumura *et al*. 2016								Serious
Pogue *et al*. 2016								Moderate
Rattinger *et al*. 2012								Serious
Revolinski 2015								Serious
Rodriguez-Maresca *et al*. 2014								Serious
Sintchenko *et al*. 2005								Critical
Tafelski *et al*. 2010								Moderate
Thursky *et al*. 2006								Moderate
Traugot *et al*. 2011								Serious

Appendix A.3: PRISMA Checklist for systematic Reviews

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	45
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	46
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	47
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	49
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	49
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	51
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	51 & Appendix A.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	51

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	52
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	50
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	52
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	53
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	54

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	53
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	53
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	55
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	166 (Table S1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	56, 161 (Appendix A.2), 166 (Table S1)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	58 (Table 4.2), 58-62
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	58-62

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	58 (Table 4.2)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	61 & 63
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	70-72
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	72
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	72
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	73

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix A.4: Supplementary data of the published article

Table S1. Characteristics of all the included studies

Study (author, year)	Study Setting	Study Design	Intervention (type)	Sample Size	Study Outcomes	Study Quality	Findings
Agwu *et al*. 2008	Inpatient	Uncontrolled pre - post treatment study	Web based CDSS	NI	LoS Vol	Moderate ⊕⊕⊕◯	The volume of unrestricted antibiotics decreased by 11.78% after the implementation of CDSS. Non-significant (p-value 0.65) decrease in length of hospital stay by 1.63% was also reported.
Arboe *et al*. 2014	Inpatient	Cohort study	TREAT (CDSS)	511	AoT LoS Mortality	Very low ⊕◯◯◯	No effect was observed on AoT (OR: 1.56 [0.54 2.93]) and LoS (SMD: -0.106 [-0.41 0.020]) after the implementation of CDSS. However, reduction in hospital mortality was reported (OR: 0.57 (0.34 0.97))
Bond *et al*. 2017	Inpatient	Interrupted time series study	Guidance MSVR (CDSS)	NI	VoU LoS	Moderate ⊕⊕⊕◯	No difference was identified in volume of use between pre and post intervention groups. However, the LoS decreased by 10% after implementation of CDSS
Bourgeois *et al*. 2010	Outpatient	Randomized controlled trial	Acute respiratory illness interactive template (ARI-IT) (CDSS)	12316	VoU	High ⊕⊕⊕⊕	Non-significant reduction was observed in volume of use by 6.30% (p value 0.84). The intervention did not show any significant difference in overall antibiotic prescription rates.
Buising *et al*. 2008	Inpatient	Uncontrolled pre - post treatment study	Web based CDSS	NI	AoT CoT	Low ⊕⊕◯◯	The concordance of therapy was significantly higher in CDSS period (period 3) in comparison to academic detailing period (period 2) (OR: 1.99 [1.07 3.69]) and baseline period (OR: 2.79 [1.88 4.14]) There was an increase in the average cost/patient from baseline to period 2 by 27% whereas it decline in period 3 by -11.6%.

Buising *et al*. 2008	Inpatient	Uncontrolled pre - post treatment study	Computerized antimicrobial approval system (CDSS)	740	VoU LoS Mortality	Low ⊕⊕◯◯	There was a decline in the consumption of cephalosporin, glycopeptides, carbapenems and aminoglycosides. No significant changes were observed in LoS and 30-day mortality rate.
Burke, & Pestotnik, 1999	Inpatient	Uncontrolled pre - post treatment study	HELP (CDSS)	11,634	VoU(DDD/1000 PDs) LoS Mortality	Low ⊕⊕◯◯	The DDD/1000 PDs increased from 226 (baseline period) to 299(post-intervention period. However, reduction in ICU length-of-stay by 15.06% and in mortality by 43% was observed
Burton *et al*. 1991	Inpatient	Randomized controlled trial	Bayesian pharmacokinetic dosing program (CDSS)	147	LoS	Moderate ⊕⊕⊕◯	The significant reduction in the ICU length of stay was observed (SMD -0.93 [-1.26 -0.58]) (p-value 0.013)
Calloway *et al*. 2013	Inpatient	Uncontrolled pre - post treatment study	TheraDoc (CDSS)	NI	CoT	Low ⊕⊕◯◯	The intervention resulted in almost 96% decrease in monthly cost of antibiotic therapy.
Chow *et al*. 2015	Inpatient	Uncontrolled pre - post treatment study	Antimicrobial Resistance Utilization and Surveillance Control (ARUSC)	1,886	Mortality	Moderate ⊕⊕⊕◯	Receiving antibiotics according to CDSS recommendations resulted in non-significant reduction in mortality rate (OR 0.45 [0.26 1.10]
Christakis *et al*. 2001	Outpatient	Randomized controlled trial	CDSS	NI	DoT	Low ⊕⊕◯◯	Total 10.48% prescriptions for otitis media were written for a duration <10 days in pre-intervention group. In the post-intervention period, this proportion increased to 44.43%
Clause *et al*. 2015	Inpatient	Prospective pre-post treatment study	Antimicrobial Dose alert based upon Creatinine clearance (ADC-alert)	309	AoT	Low ⊕⊕◯◯	The increase in treatment accuracy of intervention was observed (OR: 1.86 [1.35 2.57]). In the standard care, total 435/554 prescription fulfil the guidelines whereas after the CDSS implementation 483/554 prescriptions were identified to be appropriate.

Cox *et al*. 2011	Inpatient	Historically controlled pre-post treatment study	CDSS advisor integrated into existing computerized provider order entry (CPOE)	216	AoT	Low ⊕⊕◯◯	The CDSS resulted in significant improvement in prescriptions that were compliant with reference guideline (OR 5.89 [3.19 10.89], p-value <0.001)
Davis *et al*. 2007	Outpatient	Cluster randomized controlled trial	CDSS	12,195	DoT	Moderate ⊕⊕⊕◯	Prescribing behaviour was observed to be more in compliance with the evidence in the intervention group. The adjusted effect size was reported to be 8% [1%, 15%)
Dean *et al*. 2015	Outpatient	Controlled pre-post treatment study	electronic CDSS tool	4,758	Mortality	Moderate ⊕⊕⊕◯	Overall no effect of intervention was reported on severity-adjusted mortality with OR: 0.69 [0.41 1.16]
Demonchy *et al*. 2014	Inpatient	Controlled pre-post treatment study	CDSS	912	AoT	Low ⊕⊕◯◯	The antibiotic choices were improved after the implementation of CDSS with greater number of prescriptions complying with guidelines (OR: 1.94 [1.13 3.32])
Evans *et al* 1994	Inpatient	Randomized controlled trial	Computerized anti-infective-management program (CDSS)	602	AoT CoT	Low ⊕⊕◯◯	The appropriateness of therapy was significantly improved from 77% to 94% (p-value <0.001). The cost of therapy was also reduced by -16.18% (p-value<0.001)
Evans *et al*. 1998	Inpatient	Uncontrolled pre - post treatment study	HELP (CDSS)	545	VoU LoS DoT Mortality CoT	Low ⊕⊕◯◯	Significant reduction in volume of usage (-13.45%), length of stay (SMD: -0.15 [-0.25 -0.05]), duration of therapy (-69%) and cost of therapy (-107.49%) was reported.
Evans *et al*. 1999	Inpatient	Uncontrolled pre - post treatment study	Antibiotic dose monitor	4,483	VoU (DDD/1000 BDs) LoS Mortality CoT	Moderate ⊕⊕⊕◯	Significant reduction in LoS (SMD: -0.049 [-0.084 -0.012]), mortality [0.78 (0.62 0.98]) and cost (-14.22%) was reported. There was also slight reduction in the volume of use (-2.67%).
Faine *et al*. 2015	Inpatient	Retrospective pre-post treatment study	Weight-based vancomycin dosing guidance (CDSS)	278	AoT Mortality	Moderate ⊕⊕⊕◯	No effect was observed on AoT (OR: 1.69 [0.97 2.95]) and mortality (OR: 1.09 [0.94 1.65]) after the implementation of CDSS.

Filice *et al*. 2013	Inpatient	Retrospective pre-post treatment study	CDSS	500	AoT Mortality	Low ⊕⊕◯◯	The appropriateness of therapy was significantly improved (OR: 1.58 [1.10 2.27]) but no effect was identified on mortality (1.50 [0.60 3.50]).
Gifford *et al*. 2017	Inpatient	Uncontrolled pre - post treatment study	CDSS	876	AoT	Low ⊕⊕◯◯	There was a significant improvement in the appropriateness of therapy after the implementation of CDSS (OR: 9.98 [6.62 15.04])
Giuliano *et al*. 2011	Inpatient	Uncontrolled pre - post treatment study	Protocol Watch (CDSS)	135	AoT LoS	Very low ⊕◯◯◯	No significant improvement was observed in the study outcomes.
Gonzales *et al*. 2013	Outpatient	Cluster randomized controlled trial	CDSS	12,776	VoU (prescription rates)	Low ⊕⊕◯◯	The overall volume of use was significantly reduced with OR of 0.64 [0.45 0.91] (p-value 0.003)
Grayson *et al*. 2004	Inpatient	Uncontrolled pre - post treatment study	Antibiotic advice and approval system (IDEA3S)	NI	VoU	Very low ⊕◯◯◯	
Gulliford *et al*. 2014	Outpatient	Cluster randomized controlled trial	VISION (CDSS)	603,409	VoI	Moderate ⊕⊕⊕◯	The volume of use was significantly reduce by the mean difference of -9.69 [-18.63 -0.75] (p-value 0.034)
Hincker *et al*. 2017	Inpatient	Historically controlled pre-post treatment study	MetaVision (CDSS)	1348	AoT	Low ⊕⊕◯◯	The antibiotic therapy was significantly improved with increased compliance with the guidelines (OR: 2.59[2.07 3.24].
Huh *et al*. 2016	Inpatient	Interrupted time series study	Samsung Antibiotic Prescription System (SAPS)	NI	VoU	Very low ⊕◯◯◯	The change in slope of antimicrobial use was -1.95 (DDD/1000 PDs) with significant reduction in cephalosporin and aminoglycosides.
Karsies *et al*. 2014	Inpatient	Uncontrolled pre - post treatment study	Antibiotic Protocol (CDSS)	324	AoT Mortality	Low ⊕⊕◯◯	The intervention resulted in increase in culture-appropriate by 32.67% and risk-appropriate prescriptions by 134.06%. No effect was identified on overall mortality with OR: 0.92 [0.72 1.11]

Kim *et al*. 2008	Inpatient	Uncontrolled pre - post treatment study	CDSS	NI	VoU	Very low ⊕○○○	The use of cephalosporin decreased significantly from pre-intervention (103.2 DDD/1000 PDs) to immediate post-intervention period (84.9 DDD/1000 PDS) but this effect could not be maintained for extended period of time as increase was observed from phase II to Phase III (maintenance phase).
Kofoed *et al*. 2009	Inpatient	Retrospective pre-post treatment study	TREAT (CDSS)	171	AoT CoT	Low ⊕⊕○○	There was significant improvement in appropriateness of therapy by 26.3% (p-value 0.007). The total cost of therapy per patients increased after intervention by 2.73% it was not statistically significant (p-value 0.77)
Leibovici *et al*. 1997	Inpatient	Prospective pre-post treatment study	CDSS	496	AoT	Low ⊕⊕○○	The proportion of inappropriate prescription was significantly reduced. Total 42% inappropriate prescriptions were made by physicians as compared to only 23% by CDSS (p-value <0.05)
Leibovici *et al*. 2013	Inpatient	Cluster randomized controlled trial	CDSS	1683	180 days survival rate	Moderate ⊕⊕⊕○	Insignificant increase in survival rate was observed after intervention (71% vs 74%) with p-value of 0.2.
Linder *et al*. 2009	Outpatient	Cluster randomized controlled trial	ARI Smart form (CDSS)	111,820	VoU (prescription rates)	Moderate ⊕⊕⊕○	No effect of intervention was identified on overall volume of use with OR: 0.8 [0.5 1.3]
Litvin *et al*. 2013	Outpatient	Uncontrolled pre - post treatment study	ABX-TRIP (CDSS)	NI	AoT	Low ⊕⊕○○	The estimated change in appropriateness of therapy was insignificant (1.57% [-5.35% 8.49%])
Mainous *et al*. 2013	Outpatient	Uncontrolled pre - post treatment study	CDSS	NI	AoT	Low ⊕⊕○○	There was increase in inappropriate prescription in control group by 4.2% but decrease was observed in intervention group by -0.6% (p-value 0.03).
McCullough *et al*. 2014	Inpatient	Uncontrolled pre - post treatment study	CDSS		VoU (number of prescriptions	Moderate ⊕⊕⊕○	There was a 19% decrease in receiving antibiotic in post-intervention group (RR: 0.81 [0.66 0.96])

McGinn *et al*. 2013	Outpatient	Randomized controlled trial	Integrated clinical prediction rules (CPRs)	1,382	VoU (number of orders)	Moderate ⊕⊕⊕◯	Only the number of order for quinolones was significantly reduced with RR: 0.50 [0.29 0.88]. No effect was identified on overall volume of use for other classes of antibiotics.
McGregor *et al*. 2006	Inpatient	Randomized controlled trial	web-based system (PharmWatchTM)	4,507	LoS Mortality CoT	Moderate ⊕⊕⊕◯	No significant difference was identified for length of stay and mortality. The total cost of therapy was reduced by -25.67% as a result of intervention.
Mullett *et al*. 2001	Inpatient	Controlled pre-post treatment study	HELP (CDSS)	1,758	VoU (number of doses) Mortality CoT	Very low ⊕◯◯◯	There was significant reduction of 11.5% in number of antibiotic doses (p-value<0.01). However, mortality rate remain unchanged during the pre and post-intervention periods. The cost of therapy was decreased by 5.25% as a result of reduced overall antibiotic use.
Mullett *et al*. 2004	Inpatient	Retrospective pre-post treatment study	HELP (CDSS)	226	AoT	Low ⊕⊕◯◯	The intervention provided 86% appropriate prescriptions as compared to 66% in control group. The overall appropriateness of therapy was increased with OR: 3.44 [2.13 5.55]
Nachtigall *et al*. 2014	Inpatient	Prospective pre-post treatment study	CDSS	593	AoT LoS Mortality	Low ⊕⊕◯◯	Approximately 10% increase in compliance with prescription guidelines was identified during the study period with OR: 1.905 [1.39 2.669]. No effect was identified on overall mortality but length of hospital stay increased by 20% as a result of intervention.
Nault *et al*. 2017	Inpatient	Retrospective pre-post treatment study	Antimicrobial Prescription Surveillance System (APSS)	35,778	VoU (DDD/1000 PDs) AoT LoS DoT	Low ⊕⊕◯◯	Significant level change was identified for length of stay (-0.92 days) and appropriateness of therapy (+2.3) as a result of intervention. The overall volume of use also reduced by 12.2%.
Okumura *et al*. 2016	Inpatient	Cross Sectional study	CDSS	NI	VoU (DDD/100 BDs)	Very low ⊕◯◯◯	Almost three times reduction in volume of usage was identified from 6.31 DDD/100BDs in pre-intervention period to 2.15 DDD/100BDs in post-intervention period.

Paul *et al*. 2006 (cRCT)	Inpatient	Cluster randomized controlled trial	TREAT (CDSS)	2,326	AoT LoS Mortality CoT	Moderate ⊕⊕⊕◯	There was an improvement in appropriate prescription in intervention arm (73%) as compared to control arm (64%). No significant impact was identified on length of stay, mortality and cost.
Paul *et al*. 2006 (NRS)	Inpatient	Uncontrolled pre - post treatment study	TREAT (CDSS)	1,203	AoT	Moderate ⊕⊕⊕◯	In the multi-site cohort study, the appropriate empirical treatment increased by 20.47% (p-value 0.001).
Pestotnik *et al*. 1996	Inpatient	Uncontrolled pre - post treatment study	CDSS	162,196	VoU (DDD/100 BDs) LoS Mortality CoT	Low ⊕⊕◯◯	Decrease in volume of use by 25.8%, length of stay by 2.7% and cost of therapy by 81% was observed. The overall mortality rate was significantly reduced with OR: 0.87 [0.73 0.93].
Pogue *et al*. 2016	Inpatient	Retrospective pre-post treatment study	TheraDoc (CDSS)	388	LoS Mortality	Moderate ⊕⊕⊕◯	No significant difference was identified for the length of stay and mortality. The intervention resulted in slight but insignificant reduction in the study outcomes
Rattinger *et al*. 2012	Outpatient	Retrospective pre-post treatment study	CDSS	3831	VoU AoT	Low ⊕⊕◯◯	The intervention resulted in decrease of prescriptions from 22% in pre-intervention period to 3.3% in post-intervention period (p-value 0.0001) The congruence of prescription with guidelines significantly increased as a result of intervention (RR: 2.57 [1.86 3.54]).
Revolinski 2015	Inpatient	Uncontrolled pre - post treatment study	C. difficile best practice alert (BPA)	333	AoT	Low ⊕⊕◯◯	There was no effect of intervention on appropriateness of therapy as compliance with guidelines remained unchanged during pre and post-intervention period.
Rodriguez-Maresca *et al*. 2014	Inpatient	Prospective pre-post treatment study	GERB (CDSS)	218	AoT LoS	Low ⊕⊕◯◯	The appropriateness of therapy was significantly reduced after the implementation of interventions however the reduction in length of stay by 2% was non-significant.

Shojania *et al*. 1998	Inpatient	Randomized controlled trial	CDSS	1798	VoU (number of orders) DoT	Moderate ⊕⊕⊕◯	The number of order in the intervention group was reduced by 32% with significant reduction of 10.5% in duration of therapy (p-value 0.05).
Sintchenko *et al*. 2005	Inpatient	Uncontrolled pre - post treatment study	CDSS	NI	LoS	Low ⊕⊕◯◯	The length of stay was significantly reduced by 13.9% (p-value 0.02) as a result of intervention
Traugott *et al*. 2011	Inpatient	Uncontrolled pre - post treatment study	Therapeutic drug monitoring system (CDSS)	200	AoT	Low ⊕⊕◯◯	The CDSS resulted in significant improvement in prescriptions that were compliant with reference guideline (OR 1.54 [1.08 2.20]
Tafelski *et al*. 2010	Inpatient	Uncontrolled pre - post treatment study	CDSS	186	VoU (daily use) AoT Mortality	Very low ⊕◯◯◯	The adherence to guidelines was increased from mean of 52.3% (SD 35.7%) in pre-intervention period to 87.2% (SD 20.5%) in post-intervention period. There was also a decrease in consumption of total antibiotic/day by 14.28% (p-value<0.05).
Thursky *et al*. 2006	Inpatient	Prospective pre-post treatment study	ADVISE (CDSS)	1060	VoU (total use) AoT	Low ⊕⊕◯◯	There was significant reduction in susceptibility mismatches in the prescriptions in the post-intervention treatment (OR 0.63 [0.39 0.98], p-value 0.02). The proportion of cephalosporin, carbapenems and vancomycin prescriptions was also significantly reduced.
Vermeulen *et al*. 2014	Inpatient	Interrupted time series study	Medicator® (CDSS)	NI	LoS	Low ⊕⊕◯◯	The length of stay was significantly reduced by 18.72% (p-value<0.001) as a result of intervention.
Heard *et al*. 2019	Inpatient	Uncontrolled pre - post treatment study	ICNet® (CDSS)	2664	VoU (total use) AoT	Moderate ⊕⊕⊕◯	The drug/dose optimisation increased from 2.9% in pre-CDSS period to 13.5% in post-CDSS period. Reduction in overall antimicrobial use from 283 DDDs/1000 occupied bed days (OBD) to 231 DDDs/1000 OBD.

Bahar *et al*. 2020	Inpatient	Retrospective pre-post treatment study	Patient Information Communication System (PICS) with CDSS	NI	VoU (rate of overall antibiotic consumption)	Very low ⊕○○○	The antibiotic usage increased by 13% from intervention period to without intervention period with a mean difference of + 110 DDD/1000 bed-days.
Watson *et al*. 2020	Inpatient & outpatient Emergency Department	Uncontrolled pre - post treatment study	CDSS	200	DoT AoT	Low ⊕⊕○○	Overall, 42% randomly selected patients met the criteria (IDSA) for antibiotic therapy in pre-intervention period in comparison to 57% in post-intervention period. The DoT decreased by 15.2% with 102.5 per 1000 patients in pre-intervention period to 86.9 after the implementation of CDSS.

Figure S1: Forest plots from individual studies, and meta-analysis for appropriateness of antibiotic therapy

(a) Crude estimates (b) Adjusted and crude estimates*

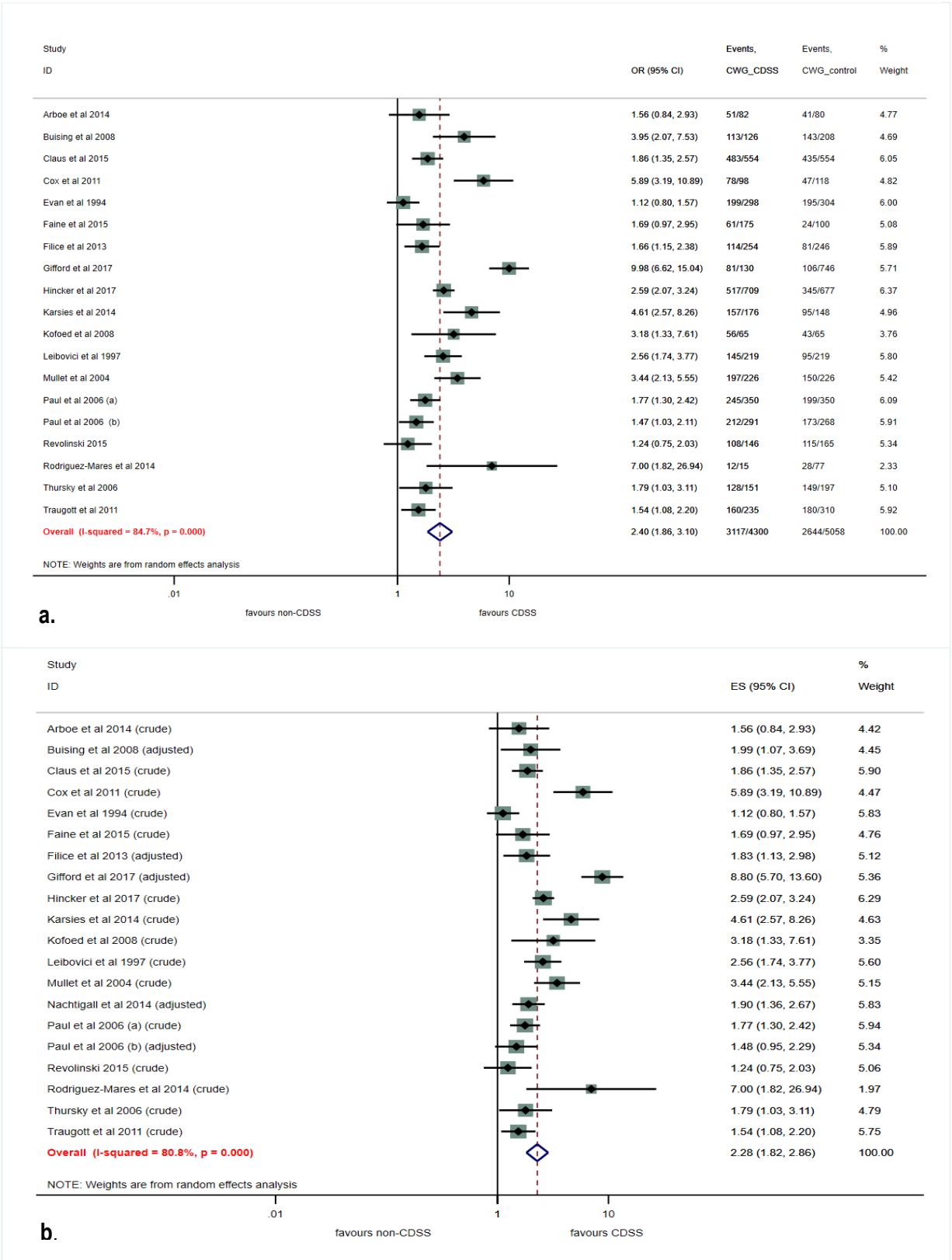


Figure S2: Funnel plot of effect of CDSS on appropriateness of therapy. Log(OR) of individual studies (x-axis) plotted against selog(OR)(y-axis)

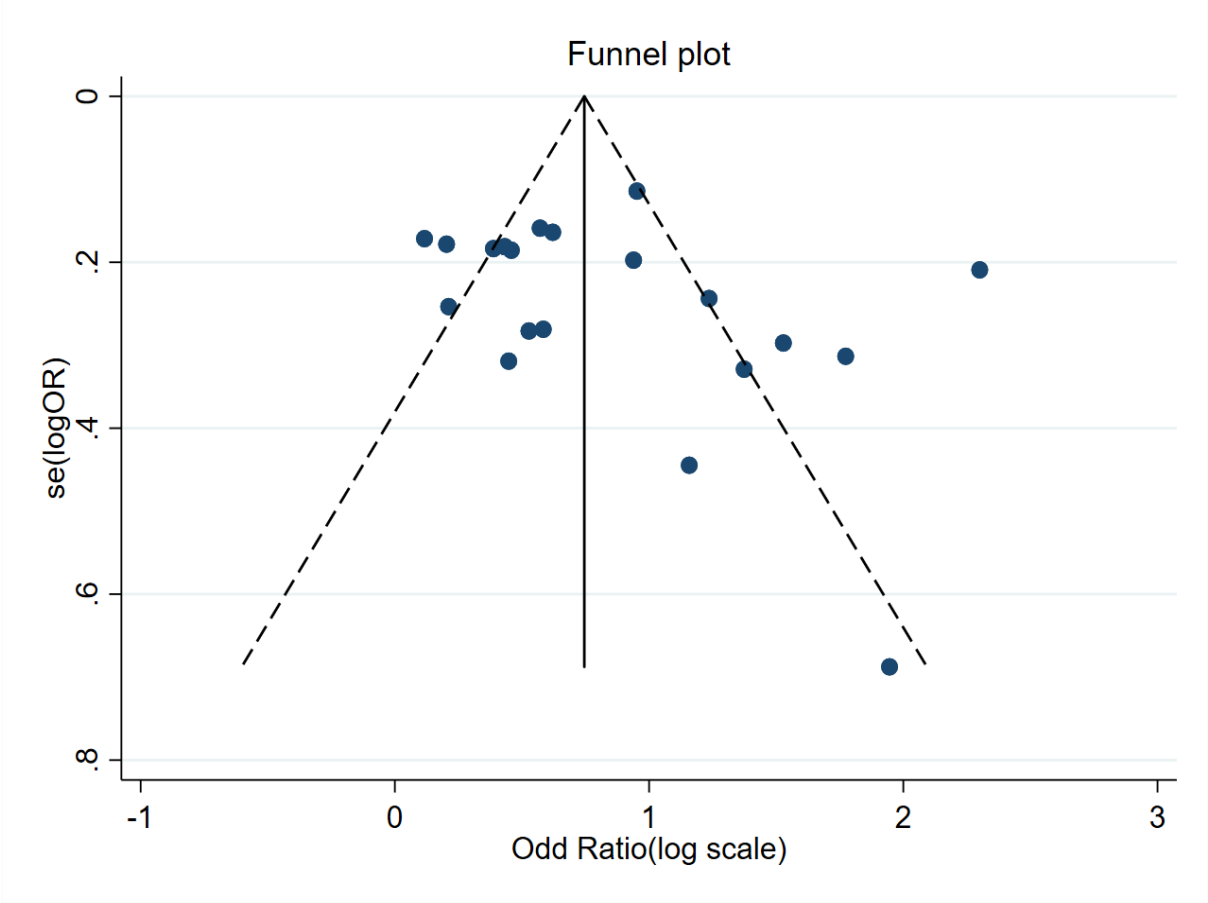
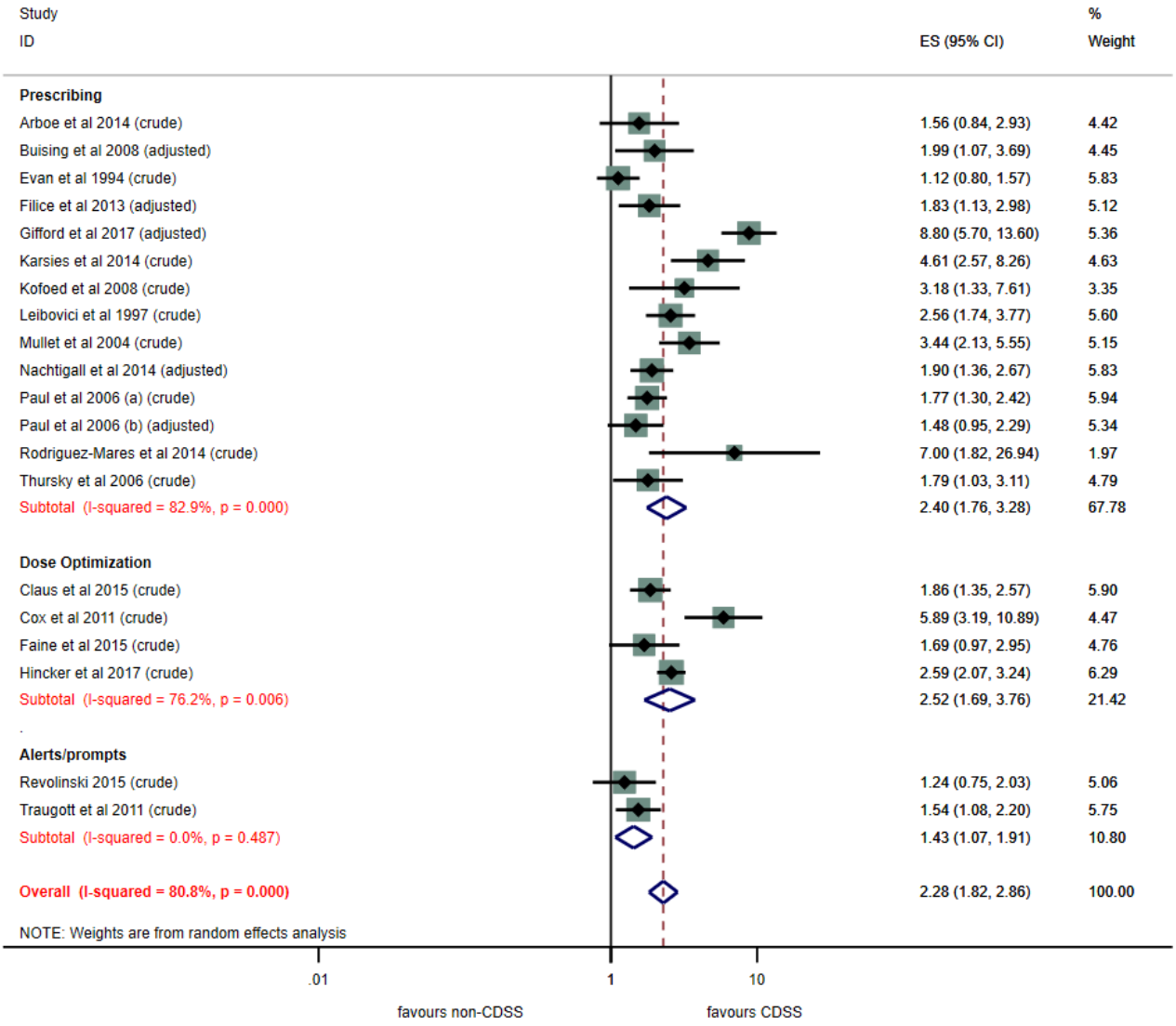
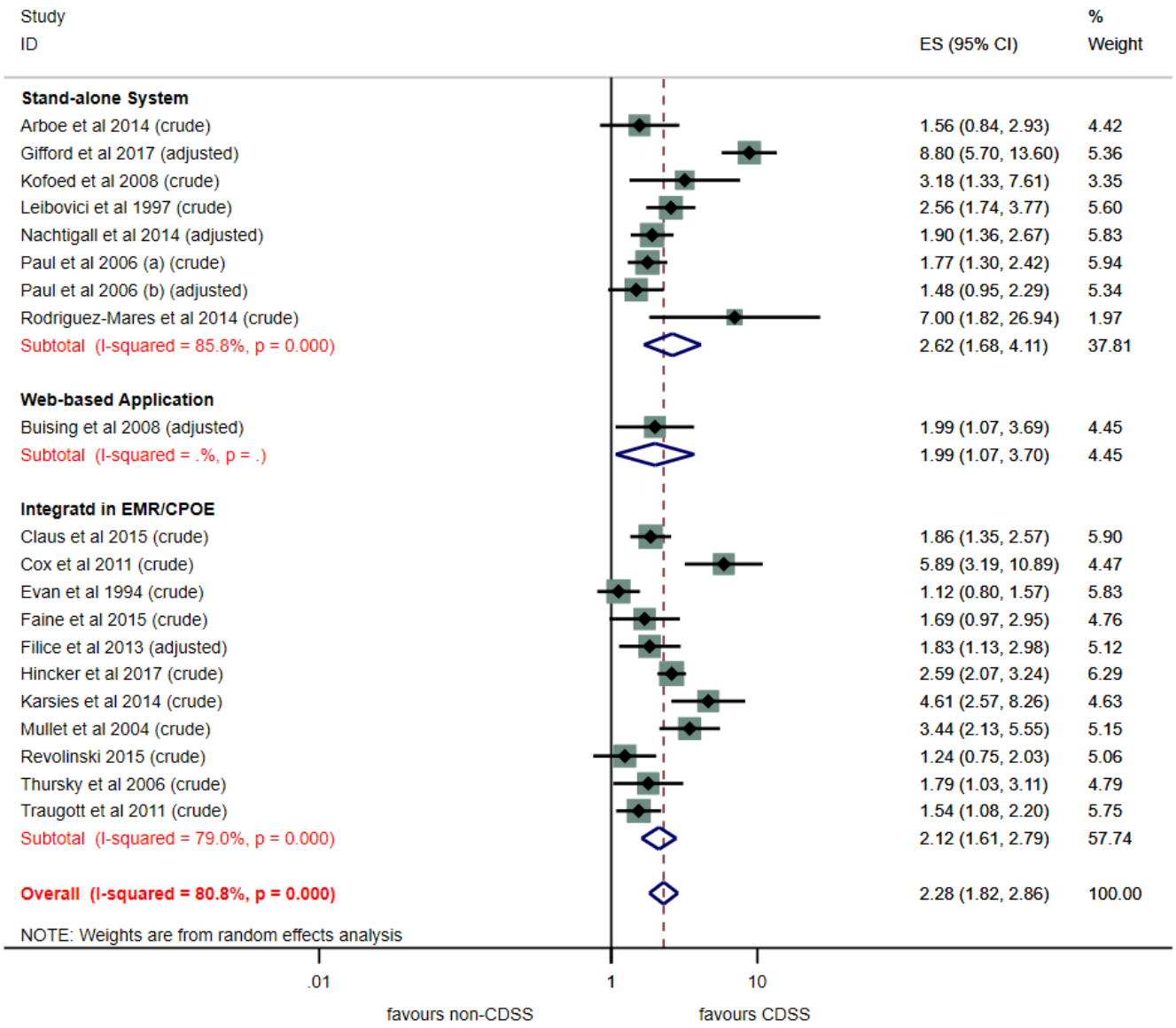


Figure S3: Subgroup analysis of effect of functional types of CDSS, by appropriateness of therapy, and by crude or adjusted effect estimates*



*Individual studies are depicted as crude or adjusted depending upon the availability of adjusted or unadjusted effect estimates.

Figure S4: Subgroup analysis of effect of different types of CDSS platforms, by appropriateness of therapy, and by crude or adjusted effect estimates*.



*Individual studies are depicted as crude or adjusted on the basis of availability of adjusted or unadjusted effect estimates.

Figure S5: Subgroup analysis of effect of study design, by appropriateness of therapy, and by crude or adjusted effect estimates*

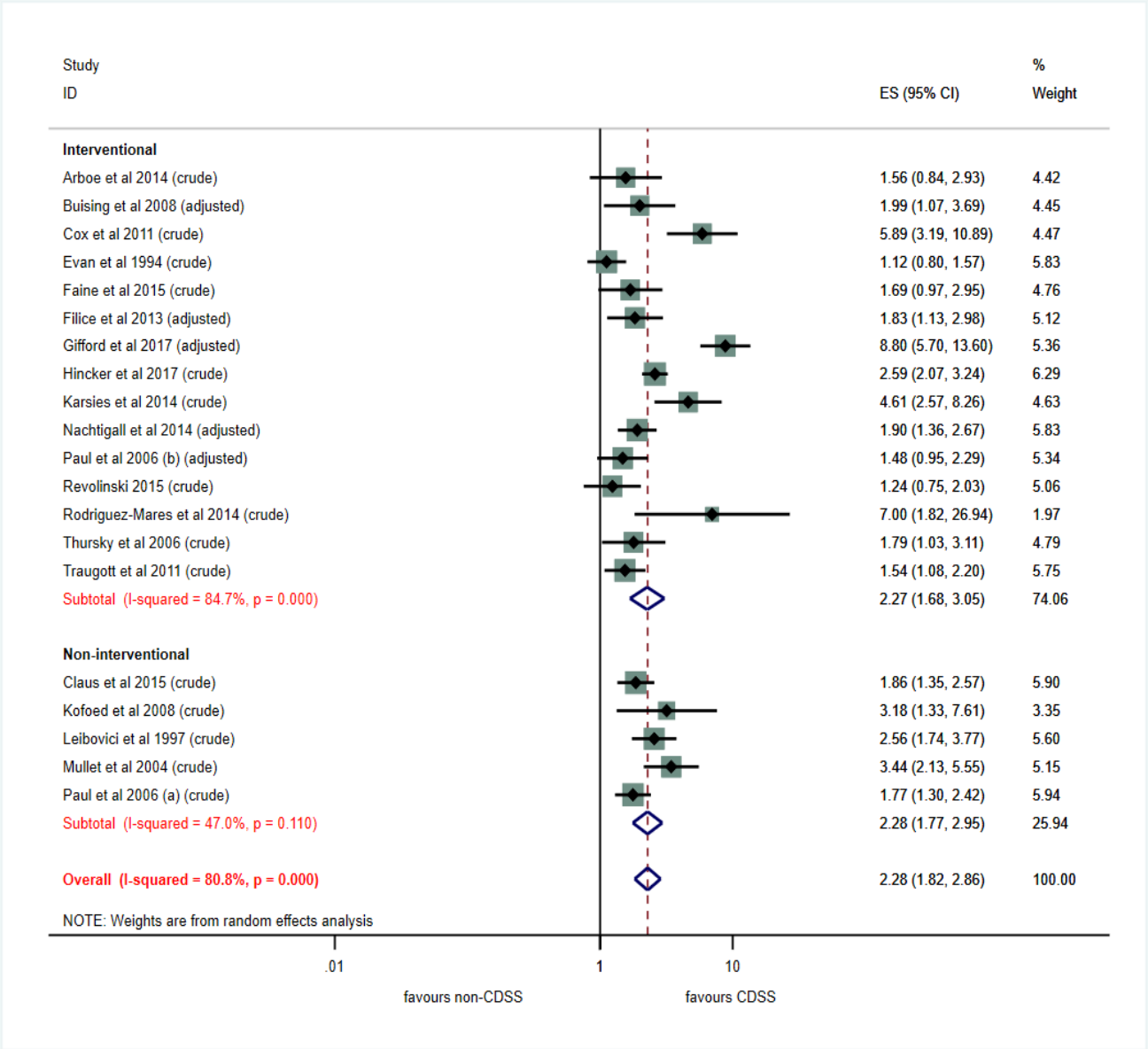
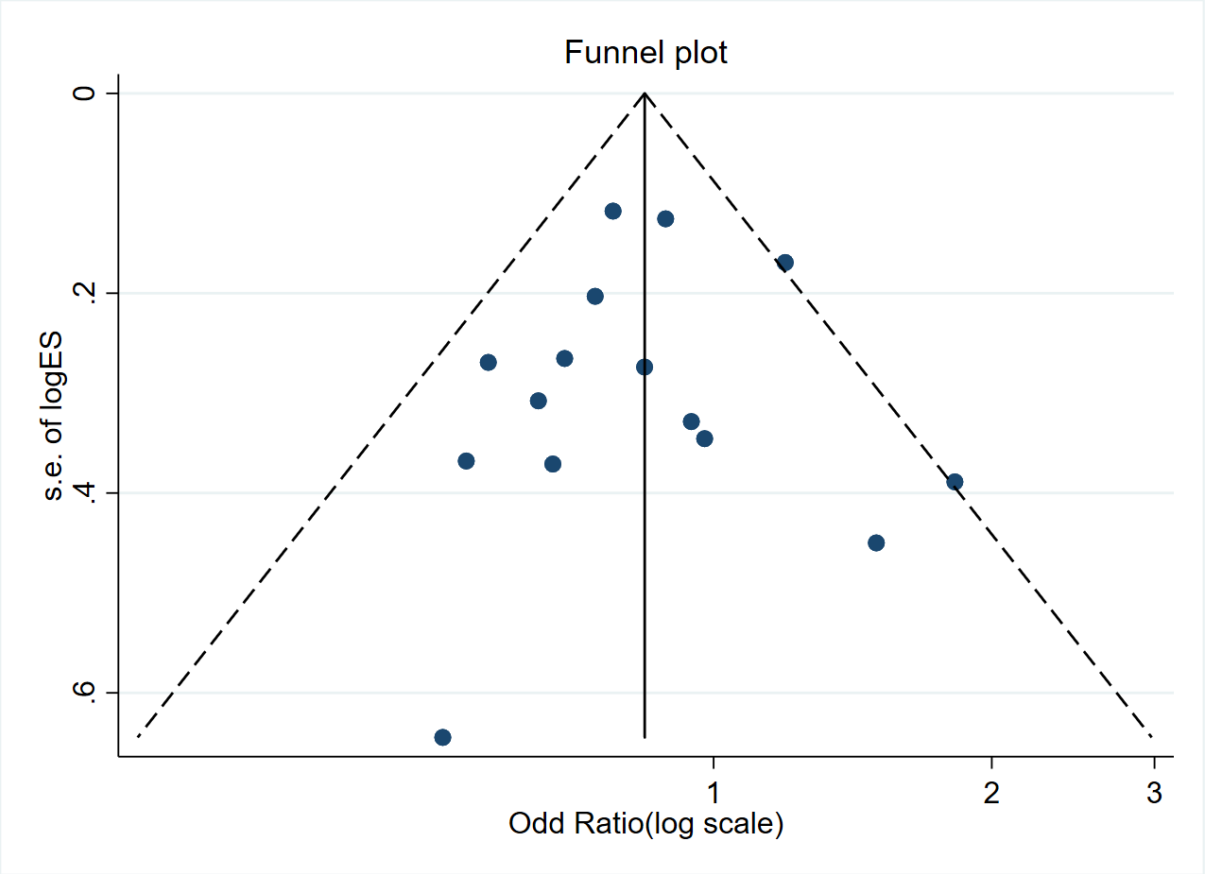


Figure S6: Funnel plot of effect of CDSS on mortality. Log(OR) of individual studies (x-axis) plotted against selog(OR)(y-axis)



Appendix B

Online survey to assess the factors influencing the CDSS adoption in healthcare setting: Supporting documentation.

- Appendix B.1: Project summary provided to the survey participants' in the recruitment phase
- Appendix B.2: Survey notice (invitation to participate) published on different platforms.
- Appendix B.3: Participant Information Sheet
- Appendix B.4: Online Survey Questionnaire
- Appendix B.5: Ethics Approval
- Appendix B.6 Qualitative Analysis of the Free-text Comments Regarding Barriers to CDSS Adoption
- Appendix B.7 Qualitative Analysis of the Free-text Comments Regarding Barriers to Appropriate Antibiotic Prescribing
- Appendix B.8: Supplementary data of the published articles

Appendix B.1: Project summary provided to the relevant organisations and health networks in the recruitment phase

1. Title

The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management.

2. Synopsis

Clinical malpractices such as over-prescribing and inappropriate prescribing of antibiotics have contributed significantly to the development of resistant pathogenic strains. Excessive antimicrobial usage is a significant public health issue in Australia as 22.4% antimicrobial prescriptions were reported to be inappropriate with 30.5% surgical prophylaxis given for more 24 hours.

The need for an optimal prescribing process has paved the way for increased use of digital tools such as CDSS. These systems have shown great ability to improve the quality and safety of care by reducing the medication errors and enabling evidence-based decision making. Although there are benefits from using CDSS, its implementation in different care settings and adoption by the clinical workforce is limited. The purpose of the current study is to investigate the applicability of CDSS for antibiotic management in Australia. We will highlight the perceptions and attitudes of the clinical workforce in integrating these systems into their daily practices. This study will contribute knowledge on the barriers and challenges to the implementation of CDSS into hospitals and primary care settings in Australia.

A voluntary and anonymous online survey distributed to clinicians in hospital and primary care settings is being conducted. General practitioners, physicians, pharmacists and surgeons will be invited to participate in the survey and to share their perception and opinions from a stakeholder perspective.

3. Objectives

The aim of this research is to assess opportunities and barriers for sustainable implementation of CDSS for antibiotic management in Australia. The research will help in:

- Evaluating the perceptions and attitudes of healthcare professionals for utilising CDSS for antibiotic management;
- Identifying barriers and enablers that may influence the implementation and uptake of CDSS in healthcare settings.

4. Study Design

4.1. Study Type:

A voluntary and anonymous online survey distributed to clinicians in hospital and primary care settings will be conducted. General practitioners, physicians and surgeons will be invited to participate in the survey and to share their perception and opinions from a stakeholder perspective. The questions will be centred on the availability of CDSS and use of these systems, implementation barriers, and opportunities for CDSS to be used in antimicrobial management. The survey will elicit information and identify factors influencing implementation and uptake of these systems by end users.

4.2. Subjects

4.2.1. Potential Participants:

The targeted population for the survey is clinicians who have experience of medication management specifically antibiotic in healthcare settings.

4.2.2. Inclusion/exclusion criteria:

Participants are health care professionals aged above 18 years working in either hospital or primary care settings.

Healthcare professionals who are not directly involved in antibiotic management will not be included in the study.

5. Data Collection

The invitation notices will be published in newsletters, websites, and online portals of local health networks and state-based and national committees of colleges such as The Royal Australian Colleges of General Practitioners (RACGP), Physicians (RACP) and Surgeons (RACS). These committees will be contacted through email to request their assistance in recruiting participants for the study. The participant information sheets will be incorporated into the online survey preamble.

As a token of recognition and appreciation for their time, all participants will be given the opportunity to take part in a draw to win an iPad or an equivalent amount of donation made to the hospital research foundation (https://www.hospitalresearch.com.au/).

Participants will not be required to provide any identifiable information to complete the survey. However, identifiable information such as contact details (name and email address/phone number) will only be requested if participants are willing to take part in the draw for an iPad or a charitable contribution. This identifiable information for the lucky draw will be collected through a separate contact details form with the link available at the end of the main survey. Contact details of participants will be collected in a separate document with no links to the main survey data. It will solely be used to contact the winner of the prize draw. This identifiable information will also be saved separately and securely and will not be linked to the survey results at any stage of the study

6. Data management

The study will be designed in accordance with privacy legislation. The identifiable data from participants contact form will be kept confidential and stored securely in the University of Adelaide online digital repository Figshare as a confidential file. This data will only be accessible to student researcher (ML) and supervisors (TM and AM).

Electronic survey data will be stored in a password protected folder which will only be accessible to the student researcher (ML) and supervisors (TM and AM).

According to the Code and State Records Act 1997, research data will be stored securely in The University of Adelaide online digital repository Figshare 5 years post publication date or public interest. After this period, electronic files will be permanently deleted, and any paper records will be shredded and disposed of in a secure university bin.

The participants' contact details collected solely for the prize draw will contain personal identifiers such as names and email address/phone number thus making it liable to participant identification. Due to this,

any participant identifiable information will be stored securely and will not be linked in any form with the survey results.

7. Statistical consideration

The National Health Workforce (NHW) Dataset (2015) was utilized to establish a sample frame of the healthcare workforce in primary and hospital care settings. The number of participants for the survey was determined using as the denominator the number of healthcare practitioners registered in the NHW dataset.

However, survey response rates of healthcare practitioners are reported to be very much lower than the general population (Cho, Johnson & VanGeest 2013). A response rate of 30-70% in healthcare professionals is reported in different studies, however, lower than 20% is also not unusual (Taylor & Scott 2019). A national longitudinal survey of medical professionals in Australia named 'MABEL' (Medicine in Australia: Balancing Employment and Life) undertaken in 2008 reported an overall response rate of 19.36%, with 17.6% in GPs and 22.3% in specialists (Joyce *et al*. 2010).

On the basis of the sample frame discussed above, evidence in the literature and sample size calculation using Cochran's Sample Size Formula, the sample size is estimated to be 350 clinicians from primary care settings and for hospital care.

Appendix B.2: Survey notice (invitation to participate) published on different platforms

Clinical Decision Support Systems (CDSS) and Antibiotic Management

Research Participants Invited

A quarter of antibiotic prescriptions in Australia have been deemed to be inappropriately prescribed. CDSS may help reduce this inappropriate prescribing.

As a part of a research project, an online voluntary survey is being conducted by Mah-laka (student researcher, PhD) and Prof. Tracy Merlin (principal investigator) (HREC approval number: H-2019-094). Take part in this survey and share your opinion with us on the feasibility of CDSS to manage antibiotic prescribing in healthcare settings. Your participation may enable us to develop recommendations for the integration and implementation of CDSS into clinical workflow.

Criteria for participation

- A clinical professional
- Working in either primary or hospital care
- Involved in prescription or administration of antibiotics

What are you required to do

- Complete an online survey
- It will takes 8-10 minutes
- Participation will be anonymous

How to participate

If you are interested in participating, please follow the link for more information and the survey:

- If you are working in **primary care**, please click on this link: https://www.surveymonkey.com/r/FD83XK8
- If you are working in **hospital care**, please click on this link: https://www.surveymonkey.com/r/N5VH8HV

As an appreciation of your time and participation in the study, you will be given a chance to take part in a draw to **win an iPad or help us donate an equivalent monetary amount to the hospital research foundation** (https://www.hospitalresearch.com.au/).

THE UNIVERSITY of ADELAIDE

Win an iPad or donate equivalent amount to a charity

Appendix B.3: Participant Information Sheet

PROJECT TITLE: The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management.

HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2019-094

PRINCIPAL INVESTIGATOR: Professor Tracy Merlin

STUDENT RESEARCHER: Ms. Mah-Laka

STUDENT's DEGREE: Doctor of Philosophy (Ph.D.)

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?

The purpose of this study is to identify opportunities and barriers for sustainable implementation of e-prescribing systems in different healthcare settings in Australia. This study will evaluate different barriers and enablers that influence integration and uptake of e-prescribing in normal clinical workflow. Moreover, this study will also investigate the feasibility of implementing e-prescribing for evidence-based antibiotic management in Australia.

Clinical malpractices such as over-prescribing and inappropriate prescribing of antibiotics in clinical settings have contributed significantly to the development of resistant pathogenic strains. Integration of information technology tools in health care has the ability to improve the quality of patient care. Electronic prescribing tools (e-prescribing) including electronic medication management and decision support systems have the capability to improve health care quality through access to medical records, computer-assisted and dynamic decision making, and electronic drug ordering at the point of care. E-prescribing assists in reducing medication errors by providing functionalities of drug-drug interactions, formulary restrictions, allergy alerts, evidence-based order sets, inventory solutions, and decision support.

Who is undertaking the project?

This project is being conducted by Mah-Laka, a postgraduate researcher in the School of Public Health, The University of Adelaide under the supervision of Professor Tracy Merlin and Dr. Adriana Milazzo.

Why am I being invited to participate?

You have been invited to participate in this study because as a healthcare professional we are interested in your opinion on the feasibility of implementing e-prescribing for antibiotic management in Australia. As you are directly involved in the prescription/management of antibiotics, your views on this topic will be highly relevant.

What am I invited to do?

You are invited to participate in an online survey that will focus on the identification of opportunities and barriers for improving antibiotic management. The survey will elicit information on the status of e-prescribing in Australia, and identify implementation challenges in different healthcare settings. Your participation in this online survey is completely voluntary and no additional follow-up is required.

As a token of appreciation and recognition of your participation in the study, we would like to thank you by giving you a chance to take part in a draw to win an iPad, or we can make the equivalent amount of donation in your name to the Hospital Research Foundation (https://www.hospitalresearch.com.au).

How much time will my involvement in the project take?

The survey will take approximately 10-15 minutes to complete. Follow-up will not be required.

Are there any risks associated with participating in this project?

There are no foreseeable risks associated with this project related to your physical or psychological health. We do not expect any harm, potential risk or cost involved with your participation in the study, other than the time it will take for you to complete the survey. Stringent data security and confidentiality measures are in place to limit any risk associated with participating in the research project.

What are the potential benefits of the research project?

The project is not associated with any direct personal benefits, but your participation will help us identify opportunities and challenges for the implementation of e-prescribing systems, with the potential for improving evidence-based antibiotic management in Australia.

In the recognition of your participation in the study, you have the opportunity to enter a draw to win an iPad or equivalent donation that will be made in your name to the Hospital Research Foundation (https://www.hospitalresearch.com.au). If you agree to participate in the prize draw, you will be asked to provide your contact information such as name and email address/phone number. This information will only be used for the prize draw and will not be linked to the survey results.

Can I withdraw from the project?

Participation in this project is completely voluntary. If you agree to participate, you can withdraw from participating until the submission of your responses.

What will happen to my information?

Responses you provide through completing the survey will contribute information for the outcomes of this study. No identifiable information will be captured in the survey. Any information you provide for the prize draw will be collected through a separate contact details form and will not be linked with survey results at any stage. Moreover, to ensure data security, your personal information will be stored separately and securely.

The results from the survey will be completely aggregated and non-identifiable before publication and presentation in peer-reviewed journals, presentations, and the student researcher's (ML) thesis. If you are interested in receiving the outcomes or summary of the results, please inform the student researcher (ML) by email (address is below).

Your information will only be used as described in the participant information sheet, and it will only be disclosed according to the consent provided, except as required by law. At the completion of the study, all the information will be stored and subsequently destroyed following University procedures.

Digital copies of the personal information and survey questionnaire will be retained securely and separately in The University of Adelaide online digital repository 'Figshare'. Your consent will be sought for future use of the non-identifiable data from this project. If you agree to your non-identifiable information being used for future research purposes, the data will be published in the University of Adelaide online research repository 'Figshare'. However, if you don't agree, the data will not be re-used for any future research. As per requirement of the University of Adelaide, the record of the lucky draw will be retained for 3 months following the prize draw. After this period, all the personal information will be destroyed completely. According to the Code and State Records Act 1997, research data will be stored securely in the Figshare for 5 years post publication or public interest. After this period, electronic files will be permanently deleted and any paper records will be shredded and disposed of in a secure university bin.

None of the researchers have a conflict of interest with regard to e-prescribing tools. The researchers are not involved in the development or commercialisation of any particular product and are not involved with the marketing of these tools. They do not have any links with industry.

Who do I contact if I have questions about the project?

If you have any further questions regarding the project you can contact any of the following research team members:

Principal Supervisor
Professor Tracy Merlin
(08) 8313 3575
tracy.merlin@adelaide.edu.au

Student Researcher
Mah-laka
(08) 8313 3538

mah.laka@adelaide.edu.au

Co-supervisor
Dr Adriana Milazzo
(08) 8313 0199
adriana.milazzo@adelaide.edu.au

What if I have a complaint or any concerns?

The study has been approved by the University of Adelaide Human Research Ethics Committee (approval number H-2019-094). This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research 2007 (Updated 2018). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat on:

Phone: +61 8 8313 6028

Email: hrec@adelaide.edu.au

Post: Level 4, Rundle Mall Plaza, 50 Rundle Mall, ADELAIDE SA 5000

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

If I want to participate, what do I do?

If you wish to participate in this study, please proceed to the survey by pressing the "Next" button. Completion of the survey indicates your consent to being involved in this study.

Yours sincerely,

Prof. Tracy Merlin
Principal Investigator

Ms. Mah-laka
Student Researcher

Dr. Adriana Milazzo
Co-supervisor

Appendix B.4: Online Survey Questionnaire

Electronic Consent

Please note that completion of the survey indicates your consent to being involved in the study.

i. **What is your age, please select the appropriate age category**

☐ Below 18 ☐ 18-24 ☐ 25-34 ☐ 35-44 ☐ 45-54 ☐ 55-64
☐ Above 65

ii. **What is your gender?**

☐ Male ☐ Female ☐ Other

iii. **You have been practicing medicine for**

☐ 1-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☐ > 20 years

iv. **Select the area of specialization**

☐ Medicine ☐ Surgery ☐ Paediatrics ☐ Gynaecology and Obstetrics ☐ Orthopaedics

☐ Urology ☐ Dermatology ☐ Ophthalmology ☐ Cardiology ☐ Others

v. **Select the type of your practice(s)**

☐ Public practice ☐ Private practice ☐ Mixed practice

vi. **Please enter the postcode of your workplace(s)**

_____

vii. **Do you follow any specific antibiotic prescription guidelines in your practice?**

a. Yes
b. No
c. No information about antibiotic prescription guidelines

If yes, please specify whether these guidelines are:

a. Intranet/local guidelines
b. National guidelines (e.g. Therapeutic Guidelines: Antibiotics)

viii. **How often do you use the above specified guidelines for prescribing antibiotics?**

a. Multiple times in a day

b. Once a day
c. Once a week
d. Once a month
e. Never

ix. **In your opinion, which of the following factors can be barriers to appropriate antibiotic prescribing (please select all that apply):**

a. Delay in diagnostic tests/cultures
b. Lack of information (formulary restrictions, local resistance pattern etc.)
c. Absence of prescription guidelines
d. Pressure from patients
e. Knowledge and perceptions of healthcare providers
f. Others (please specify):

x. **Does your hospital have any electronic system/module for the following purposes?**

	No system	Basic system	Fully functional advanced system
a. Patient information management (i.e. electronic medical records)			
b. Medication management (i.e. electronic ordering)			
c. Decision support (i.e. alerts and reminders)			

xi. **If there is an clinical decision support system in your hospital(s), which of the following functionalities it provides specifically for antibiotic stewardship (please select all that apply):**

a. Optimal selection of treatment
b. Formulary information on antibiotic treatments
c. Protocols and antibiotic prescription guidelines
d. Knowledge-base (central repository of information)

e. Allergy/mismatch alerts
f. Prescription based-reminders
g. Dosing calculators
h. No functionality is specific to antibiotic stewardship
i. Any other: (please specify) _____

xii. **In your opinion, what can be the likely impact of electronic decision support systems on antibiotic management in your hospital?**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
a. Improvement in quality of care and patient safety					
b. Increase in efficacy of antibiotic treatment					
c. Access to protocols, guidelines and medicine information					
d. Decrease in unnecessary broad-spectrum antibiotic prescriptions					
e. Reduction in cost of antibiotic therapy					

xiii. **Do you think that the following factors can be considered as barriers for clinical decision support system?**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
a. Lack of knowledge, training and technical support on					
b. Clinical time constraints					
c. Patients' preferences					
d. Limits professional autonomy					

e. Lack of confidence in the content of the system	
f. Ethical Risks associated with clinical decision support systems	
g. Medico-legal liability	

xiv. **Which of the following factors can facilitate the use of clinical decision support system in your daily practice?**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
a. Departmental/Organizational support					
b. Ease of use					
c. Technical support and training					
d. Users' participation in planning, designing and implementation phases					
e. Timely access to resources					

xv. **Do you want to share any specific recommendation(s)/concern(s) for implementation of clinical decision support systems for antibiotic management?**

Appendix B.5: Ethics Approval

Our reference 33631

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
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EMAIL hrec@adelaide.edu.au

CRICOS Provider Number 00123M

30 May 2019

Professor Tracy Merlin
Public Health

Dear Professor Merlin

ETHICS APPROVAL No: H-2019-094
PROJECT TITLE: The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management

The ethics application for the above project has been reviewed by the Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences) and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)* involving no more than low risk for research participants.

You are authorised to commence your research on: 30/05/2019
The ethics expiry date for this project is: 31/05/2022

NAMED INVESTIGATORS:

Chief Investigator: Professor Tracy Merlin

Student - Postgraduate Masters by Research: Ms Mah Laka

Associate Investigator: Dr Adriana Milazzo

CONDITIONS OF APPROVAL: Thank you for your responses to the matters raised. The revised ethics application provided on the 27th of May, 2019 has been approved.

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Ms Michelle White
Secretary

The University of Adelaide

Appendix B.6 Qualitative Analysis of the Free-text Comments Regarding Barriers to CDSS Adoption

Themes	Sub-themes	Illustrative Quotes
Lack of Flexibility	System flexibility	"*There is never a "one size fits all". So, there must always be room to make exceptions*" (P31 – Hospital) "*Adaptability and flexibility need to be ensured to make it easy for clinical staff to use it in their practices*" (P15 – Hospital) "*The power chart eMeds system that most hospitals in NSW use is comically bad in design and that it is inflexible in its ability to change*" (P87 – Hospital). "*We should be able to initiate prescribing without having to use the fixed doses*" (P54 – Primary care) "*Constant 'rule making' is a problem for prescribers in the community. It's also seen as patronising quite often"* (P132 – Hospital). "*PBS Authority Lines are clumsy and poor support to very busy clinicians*" (P72 – Hospital). "*Systems should be flexible and easy to use, if it requires lot of efforts and time to understand and the system and then use it, then automatically that system will not be successful*" (P26 – Primary care).
	Inability to change	
	Fixed doses	
	Rule making	

Information Accuracy	Source of Knowledge	"*I, as a user, need to know on what basis any recommendation is provided, what is the source of this knowledge and how often it is updated.*" (P11 - Primary care) "*The eMEDS system used here requires an approval through the linked EASY system for many commonly used antibiotics. The EASY system is not easy to navigate and is slow. Turns out you can put anything into the approval space and the prescription will go through so a quick and dirty work around completely undermines any stewardship the eASY is trying to engender*" (P133 – Hospital). "*Our ability to access and analyse eprescribing data, knowing if the information presented is recent and up-to-date and link it to eMR data and streamline decision support for the individual prescriber is what will help with antibiotic*" (P42 – Hospital). "*Over the years, we have seen multiple such systems were implemented but after few months not only the usage decreased tremendously because no attention was paid to maintenance and updating the information*" (P106 – Hospital).
	Up-to-date information	
Information Overload	Excessive interaction and allergy alerts	"*My major frustration with it in terms of antibiotic therapy is the presence of trigger-happy interaction and allergy alerts, which do nothing to protect patients and simply lead to alarm fatigue in clinicians*" (P71 – Hospital). "*Policies to reduce alert fatigue*" (P08 – Hospital) *"Excessive alert and prompts which disturb workflow thus eventually leading to prompt over ride without even seeing the recommendation"* (P48 – Hospital). "*Need to reduce unnecessary and redundant alerts."* (P16 – Hospital)
	Alert fatigue	
	Disruptive alerts	
	Unnecessary alerts	

		"*This can be great resource but without proper planning and consultation it has turned into a mess interrupting workflows and giving excessive alerts. Need to reduce unnecessary and redundant alerts.* (P151 – Primary) *"What I have seen is problems due to bad design, e.g. excessive and unnecessary alerts which are usually ignored and cause frustration*." (P68 – Hospital)

Appendix B.7 Qualitative Analysis of the Free-text Comments Regarding Barriers to Appropriate Antibiotic Prescribing

Themes	Sub-themes	Illustrative Quotes
Adaptability of guidelines	Competency of guidelines	"*Guidelines not covering the context of the particular patient and their problems eg poorly controlled diabetes or immune suppression and major surgery, where a prolonged course of antibiotics is prescribed*." (P82 - Hospital) "*Guidelines do not always reflect the subtleties of clinical practice*" (P54 - Primary) "[…] *guideline ever made that can address every patient's unique circumstances*." (P06 – Primary Care) "*We don't know how often guidelines are updated in the system*." (P39 - Hospital) "*There are no guidelines that can encompass the complexity of clinical decision-making*" (P163 - Hospital). "*allows not just routine prescription, but specific dosages and indications to be available indication should be entered then prescribers should be directed to guideline or esp for 3-4th generation cephalosporins, aminoglycosides, quinolones, antifungals."* (P13 - Hospital) *"Experiential feeling that clinician 'knows better' than the guidelines from past experiences"* (P162 - Hospital)
	Updating guidelines/content	
	Improve clinical knowledge	
	Increased access to guidelines	
	Improve visibility	
Limited diagnostic certainty	Delayed Diagnosis	*"At times, it is difficult to identify the exact source of infection for whatever reason, but as a professional you know the symptoms are definitely there, then surely, antibiotics are given more as a safety blanket*." (P05, Primary Care) "*Vague history of antibiotic allergy*" (P36, Hospital). *"Sometime patients are sick and need treatment but I am unable to 'prove' exact source of infection"* (P112, Primary Care).
	Antibiotic prescribing as a precaution	

		"*Frequently misdiagnosis or delayed diagnosis*" (P81, Hospital) *"Due to shared symptoms between different viral and bacterial infections, antibiotics are usually prescribed as a precaution"* (P33, Hospital) "*Community overprescribing is often from bulk billed practices who do not spend enough time reviewing patients and antibiotics are prescribed without certain diagnosis*." (P127, Primary Care)
Inter-professional practices	Supervisors' approval Pressure from in-patients Time pressure	"*Prescribing practices of young clinicians are always influenced by their senior registrars/consultants. They will not change prescriptions if they think that their supervisors don't approve of it. They don't want to be seen as someone who needs assistance for decision making*." (P36 - Hospital) "*Inpatient teams that escalate to broad-spectrum antibiotics for any patient that is remotely unwell. This does have a trickle-down effect on ED doctors prescribing patterns*." (P77 - Hospital) "*[…] pressure from inpatient teams*" (P103 - Hospital) "*[…] 'preferred practice' of senior team members*" (P93 - Hospital) "*Beliefs and general practices of registrars/consultants*" (P21 - Hospital) "*Time pressures to have dispositions sorted in ED*" (P111 - Hospital)

Appendix B.8: Supplementary data of the published articles

Supplementary S1 Selection of questionnaire constructs from the literature

	Factors	Sources
Performance Expectancy	Improvement in quality and safety of care	(8, 283, 285)
	Increase in efficacy of treatment	(280, 285, 386)
	Access to protocol & guidelines	(8, 283)
	Decrease in unnecessary prescriptions	(285, 386)
	Reduction in cost	(280)
Effort Expectancy	Lack of digital skills/knowledge	(8, 20, 108, 282, 387)
	Clinical time constraint	(8, 20, 279, 387)
	Limit professional autonomy	(20, 108, 279, 280)
	Lack of confidence in content	(8, 20, 284)
	Ease of use	(8, 20, 108, 274, 279, 282, 283)
	Ethical risks	(8, 108)
	Medico-legal liability	(8, 387)
Facilitating Conditions	Organisational support	(8, 20, 274, 284)
	Technical support & training	(8, 20, 282, 387)
	Users' participation	(20, 108, 279, 284)
	Timely access to resources	(108, 274, 279, 284)

Appendix C

In-depth interviews with policymakers to evaluate the challenges and opportunities for CDSS implementation: Supporting documentation

- Appendix C.1: Interview schedule
- Appendix C.2: Participants Information Sheet
- Appendix C.3: Consent Form
- Appendix C.4: Ethics Approval

Appendix C.1: Interview schedule

Question 1:

Can you talk a bit about your role and how your role relate to CDSS implementation?

Question 2:

Tell us about your experience of clinical decision support systems (CDSS) implementation?

Follow-up

- *Key goals of implementing CDSS*
- *How does implementation process differ across different care settings?*
- *Are there any setting-specific factors that are important for implementation?*
- *What are the current gaps in policies to enable CDSS implementation at scale?*

Question 3:

Reflecting on your experiences, what do you see as major challenges in implementation of CDSS systems in Australia?

Follow-up:

- *Changes in organizational structure and processes*
- *Workflow changes*
- *Incentives and system readiness*
- *Infrastructure*

Question 4:

When thinking about CDSS implementation, what are the important components at a system level?

Follow-up

- *How can it be ensured that right infrastructure is in place? Internal capacity?*
- *Considerations for implementation such as rushed timelines or financially driven milestones*
- *Gap between demand for innovative health services such as CDSS and available resources?*

Question 5:

Why are the majority of hospitals unable to achieve international standards for adoption and implementation?

Question 6:

Do you think that the implementation process can influence the use of the system?

Follow -up:

- *Expectation and beliefs of users*

- *Do knowledge and expertise of end-users play any role? If yes, how can we ensure users have right sets of skills*
- *Issues like alert-fatigue*
- *How important it is to engage stakeholder for successful implementation*

Question 7:
Organisations might have their own CDSS requirements. But policymakers might want standardised systems across different settings and organisations, to ensure interoperability. What do we do about this?

Follow-up:

- *Should there be a trade-off between localisation (tailoring to organisation specific context) and standardisation for implementation of CDSS?*
- *What are main challenges for data standardisation in Australia?*
- *For decision making, how can the quality of data be ensured?*

Question 8:

Is there a broader-level coordination between organisations and jurisdictions for CDSS implementation? If not what can we do about this?

Follow-up:

- *How can it impact the interoperability and standardisation?*
- *Impact on national level policy*
- *What can be done to promote system-level innovation?*

Appendix C.2: Participants Information Sheet

PROJECT TITLE: The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management.

HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2019-094

PRINCIPAL INVESTIGATOR: Professor Tracy Merlin

STUDENT RESEARCHER: Ms. Mah-Laka

STUDENT's DEGREE: Doctor of Philosophy (Ph.D.)

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
The purpose of this research project is to investigate the policy and regulation challenges that accompany the development and deployment of decision support tools aimed at optimal antibiotic management. Information elicited will not only help in adding depth to our understanding of legal and administrative barriers to implementing decision support tools, but will also assist in developing recommendations to improve the integration and deployment of decision support tools in hospital and primary healthcare settings.

One of the basic strategies for antimicrobial stewardship reported by the Australian Commission on Safety and Quality in Health Care (ACSHQC) is the provision of up-to-date and relevant information through electronic medication management systems for healthcare professionals (Action 4.13). However, there is limited evidence concerning the challenges faced at the different levels of implementation, including at the macro (policymaker), meso (organizational) and micro levels (clinical practice).

Despite the potential advantages of increased quality and safety of care with the use of CDSS, the adoption and sustainable implementation of different CDSS is greatly hindered by policy gaps.

Who is undertaking the project?
This project is being conducted by Mah-Laka, a postgraduate researcher in the School of Public Health, The University of Adelaide under the supervision of Professor Tracy Merlin, Dr Adriana Milazzo and Dr Drew Carter.

Why am I being invited to participate?
You have been invited to participate in this study because as a professional related to policy development of digital health technologies we are interested in your opinion on different policy challenges that need to be considered for the successful implementation of decision support tools.

What am I invited to do?
You are invited to participate in an interview with the student researcher (Mah-Laka) that will take place via videoconferencing, teleconferencing, or in-person. Your participation in this interview is voluntary and no additional follow-up will be required.

How much time will my involvement in the project take?
The duration of the interview is approximately 30-60 minutes.

Are there any risks associated with participating in this project?
There are no foreseeable risks associated with this project related to your physical or psychological health. We do not expect any harm, potential risk or cost involved with your participation in the study. However, there may be potential for reputational and/or professional risk if information provided in this interview was disclosed. Therefore, to limit any risk and ensure confidentiality, all identifying information will be omitted and replaced by pseudonyms in all publications, the thesis and presentations. Stringent data security and confidentiality measures will be adopted to avoid identification of any individual or organization from data extracts.

What are the potential benefits of the research project?
The project is not associated with any direct personal benefits, but your participation will contribute in determining the outcomes of this study. These outcomes may have considerable policy significance as it will contribute to effective use of decision support tools in healthcare settings in Australia. The findings from this study may help in the development of recommendations for a sustainable development and implementation framework for the use of decision support systems in healthcare settings.

Can I withdraw from the project?
Participation in this project is completely voluntary. If you agree to participate, you can withdraw your involvement within 4 weeks of completion of the interview by submitting a withdrawal of consent form.

What will happen to my information?
The information you provide during the interview will be de-identified, stored securely and published in different academic journal(s) and the student researcher's thesis. All identifiable information will be omitted and replaced by pseudonyms in all publications and presentations.

Digital copies of the interview recording, accompanying transcripts and consent forms will be stored securely in The University of Adelaide online digital repository 'Figshare'. According to the Code and State Records Act 1997, research data will be stored securely in Figshare for 5 years post publication or released in the public interest. After this period, electronic files will be permanently deleted and any paper records will be shredded and disposed of in a secure university bin. All the paper records related to this project will be kept in a locked drawer in a secure area within the School of Public Health, The University of Adelaide. Your consent will be sought for future use of non-identifiable data collected from this project. If you agree to your non-identifiable information being used for future research purposes, the data will be retained indefinitely and made publicly available via in The University of Adelaide online research repository 'Figshare'. Your information will only be disclosed according to the consent provided, except as required by law.

None of the researchers have a conflict of interest with regard to decision support/medication management systems. The researchers are not involved in the development or commercialisation of any particular product and are not involved with the marketing of these tools.

Who do I contact if I have questions about the project?
If you have any further questions regarding the project you can contact any of the following research team members:

Principal Supervisor
Professor Tracy Merlin
(08) 8313 3575 | tracy.merlin@adelaide.edu.au

Student Researcher
Mah-laka

(08) 8313 3538 | mah.laka@adelaide.edu.au

Co-supervisor
Dr Drew Carter
(08) 8313 0620 | drew.carter@adelaide.edu.au

Co-supervisor
Dr Adriana Milazzo
(08) 8313 0199 | adriana.milazzo@adelaide.edu.au

What if I have a complaint or any concerns?

The study has been approved by the University of Adelaide Human Research Ethics Committee (approval number H-2019-094). This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research 2007 (Updated 2018). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat on:

Phone: +61 8 8313 6028

Email: hrec@adelaide.edu.au

Post: Level 4, Rundle Mall Plaza, 50 Rundle Mall, ADELAIDE SA 5000

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

If I want to participate, what do I do?
If you wish to participate in this study, please contact the student researcher Mah-laka (08) 8313 3538 or mah.laka@adelaide.edu.au to book an appointment for an interview.

Yours sincerely,

Prof. Tracy Merlin
Principal Investigator

Ms. Mah-laka
Student Researcher

Dr Drew Carter
Co-supervisor

Dr. Adriana Milazzo
Co-supervisor

Appendix C.3: Consent Form

Human Research Ethics Committee (HREC)

1. I have read the attached participant information sheet and agree to take part in the following research project:

Title:	The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management.
Ethics Approval Number:	**H-2019-094**

2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research worker. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.
3. Although I understand the purpose of the research project is to improve the quality of health care, it has also been explained that my involvement may not be of any benefit to me.
4. I agree to participate in the activities as outlined in the participant information sheet.
5. I agree to be:

   Audio/video recorded ☐ Yes ☐ No
6. I understand that I am free to withdraw from the project within 4 weeks of completion of the interview
7. I have been informed that the information gained in the project may be published in a journal article(s), thesis and conference presentations.
8. I have been informed that in the published materials I will not be identified and my personal results will not be divulged.
9. I agree to my information being used for future research purposes as follows:
   - Research undertaken by these same researcher(s) Yes ☐ No ☐
   - Related research undertaken by any researcher(s) Yes ☐ No ☐
10. I understand my information will only be disclosed according to the consent provided, except where disclosure is required by law.
11. I am aware that I should keep a copy of this consent form, when completed, and the attached participant information sheet.

Participant to complete:

Name: _____ Signature: _____

Date: _____

Appendix C.4: Ethics Approval

THE UNIVERSITY of ADELAIDE

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
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CRICOS Provider Number 00123M

Our reference 33631

03 October 2019

Professor Tracy Merlin
Public Health

Dear Professor Merlin

ETHICS APPROVAL No: H-2019-094
PROJECT TITLE: The Role of Computer-based Clinical Decision Support Systems (CDSS) in Improving Antimicrobial Management

Thank you for the amendment request submit on the 9th of September 2019, to add a second phase to the project involving conducting interviews with policy makers, add Dr Carter and change the student status. This amendment is approved.

The ethics amendment for the above project has been reviewed by the Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences) and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)* involving no more than low risk for research participants.

You are authorised to commence your research on: 30/05/2019
The ethics expiry date for this project is: 31/05/2022

NAMED INVESTIGATORS:

Chief Investigator:	Professor Tracy Merlin
Student - Postgraduate Doctorate by Research (PhD):	Ms Mah Laka
Associate Investigator:	Dr Adriana Milazzo
Associate Investigator:	Dr Drew Allen Carter

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Miss Sarah Harman
Secretary

The University of Adelaide

Reference List

1. Lushniak BD. Antibiotic resistance: a public health crisis. Public Health Rep. 2014;129(4):314-6.
2. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016;4(2):10.1128/microbiolspec.VMBF-0016-2015. DOI: 10.1128/microbiolspec.VMBF-0016-2015.
3. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet. 2016 2016/01/09/;387(10014):176-87. DOI: https://doi.org/10.1016/S0140-6736(15)00473-0.
4. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. [journal article]. 2014 January 09;14(1):13. DOI: 10.1186/1471-2334-14-13.
5. Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? Clin Microbiol Infect. 2017 2017/11/01/;23(11):793-8. DOI: https://doi.org/10.1016/j.cmi.2017.08.026.
6. Emberger J, Tassone D, Stevens MP, Markley JD. The Current State of Antimicrobial Stewardship: Challenges, Successes, and Future Directions. Curr Infect Dis Rep. 2018 2018/06/29;20(9):31. DOI: 10.1007/s11908-018-0637-6.
7. Flynn HW, Batra NR, Schwartz SG, Grzybowski A. Antibiotic Stewardship. Endophthalmitis in Clinical Practice. Cham: Springer International Publishing; 2018. p. 171-3.
8. Catho G, Centemero NS, Catho H, Ranzani A, Balmelli C, Landelle C, et al. Factors determining the adherence to antimicrobial guidelines and the adoption of computerised decision support systems by physicians: A qualitative study in three European hospitals. Int J Med Inform. 2020 2020/09/01/;141:104233. DOI: https://doi.org/10.1016/j.ijmedinf.2020.104233.
9. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. BMJ. 1998 Aug 15;317(7156):465-8. DOI: 10.1136/bmj.317.7156.465.
10. Roughead L, Semple S, Rosenfeld E. Literature review: medication safety in Australia: Australian Commission on Safety and Quality in Health Care, Sydney; 2013.
11. Xu J, Gao X, Sorwar G, Croll P. Current status, challenges, and outlook of e-health record systems in Australia. Know Eng Manag: Springer; 2014. p. 683-92.

12. Bourgeois FC, Linder J, Johnson SA, Co JPT, Fiskio J, Ferris TG. Impact of a computerized template on antibiotic prescribing for acute respiratory infections in children and adolescents. Clin Pediatr. [Article]. 2010;49(10):976-83. DOI: 10.1177/0009922810373649.
13. Buising, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, et al. Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. J Antimicrob Chemother. 2008;62(3):608-16. DOI: 10.1093/jac/dkn218.
14. Curtis CE, Al Bahar F, Marriott JF. The effectiveness of computerised decision support on antibiotic use in hospitals: A systematic review. PLoS One. 2017;12(8):e0183062. DOI: 10.1371/journal.pone.0183062.
15. Feldstein DA, Hess R, McGinn T, Mishuris RG, McCullagh L, Smith PD, et al. Design and implementation of electronic health record integrated clinical prediction rules (iCPR): a randomized trial in diverse primary care settings. Implement Sci. 2017 Mar 14;12. DOI: 10.1186/s13012-017-0567-y.
16. Nomura Y, Garcia M, Child J, Hurst AL, Hyman D, Poppy A, et al. Effect of provider-selected order indications on appropriateness of antimicrobial orders in a pediatric hospital. Am J Health Syst Pharm. 2018 Feb;75(4):214-22. DOI: 10.2146/ajhp160557.
17. Donaldson MS, Corrigan JM, Kohn LT. To err is human: building a safer health system: National Academies Press; 2000.
18. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med. 2020 2020/02/06;3(1):17. DOI: 10.1038/s41746-020-0221-y.
19. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011 Dec;104(12):510-20. DOI: 10.1258/jrsm.2011.110180.
20. Devaraj S, Sharma SK, Fausto DJ, Viernes S, Kharrazi H. Barriers and facilitators to clinical decision support systems adoption: A systematic review. J Bus Adm Res. 2014;3(2):p36.
21. Kortteisto T, Komulainen J, Mäkelä M, Kunnamo I, Kaila M. Clinical decision support must be useful, functional is not enough: A qualitative study of computer-based clinical decision support in primary care. BMC Health Serv Res. 2012 10/08;12:349. DOI: 10.1186/1472-6963-12-349.
22. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. J Med Internet Res. 2017 2017/11/01;19(11):e367. DOI: 10.2196/jmir.8775.

23. Healthcare IT Australia. Two Australian hospitals break through digital barriers to reach EMRAM Stage 7 status. 2018. Available from: https://www.healthcareit.com.au/article/two-australian-hospitals-break-through-digital-barriers-reach-emram-stage-7-status
24. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc. 2006 Mar-Apr;13(2):138-47. DOI: 10.1197/jamia.M1809.
25. Wasylewicz A, Scheepers-Hoeks A. Clinical Decision Support Systems. In: Kubben P, Dumontier M, Dekker A, editors. Fundamentals of Clinical Data Science: Cham (CH): Springer; 2019.
26. Sweidan M, Williamson M, Reeve JF, Harvey K, O'Neill JA, Schattner P, et al. Evaluation of features to support safety and quality in general practice clinical software. BMC Med Inform Decis Mak. 2011;11:27-. DOI: 10.1186/1472-6947-11-27.
27. Peek N, Sujan M, Scott P. Digital health and care in pandemic times: impact of COVID-19. BMJ Health Care Inform. 2020;27(1):e100166.
28. Petracca F, Ciani O, Cucciniello M, Tarricone R. Harnessing digital health technologies during and after the COVID-19 pandemic: context matters. J Med Internet Res. 2020;22(12):e21815.
29. Hambleton SJ, Aloizos AM J. Australia's digital health journey. Med J Aust. 2019;210(6):S5-S6.
30. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. BMC Med Inform Decis Mak. 2016;16(1):1-15.
31. Lennon MR, Bouamrane M-M, Devlin AM, O'connor S, O'donnell C, Chetty U, et al. Readiness for delivering digital health at scale: lessons from a longitudinal qualitative evaluation of a national digital health innovation program in the United Kingdom. J Med Internet Res. 2017;19(2):e42.
32. Sligo J, Gauld R, Roberts V, Villa L. A literature review for large-scale health information system project planning, implementation and evaluation. Int J Med Inform. 2017;97:86-97.
33. Keasberry J, Scott IA, Sullivan C, Staib A, Ashby R. Going digital: a narrative overview of the clinical and organisational impacts of eHealth technologies in hospital practice. Aust Health Rev. 2018;41(6):646-64.
34. Alotaibi YK, Federico F. The impact of health information technology on patient safety. Saudi Med J. 2017;38(12):1173.
35. Kim MO, Coiera E, Magrabi F. Problems with health information technology and their effects on care delivery and patient outcomes: a systematic review. J Am Med Inform Assoc. 2017;24(2):246-50.

36. Sujan M, Scott P, Cresswell K. Digital health and patient safety: Technology is not a magic wand. SAGE Publications Sage UK: London, England; 2020.
37. Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect. 2015;6:22-9. DOI: 10.1016/j.nmni.2015.02.007.
38. Carl L, Lars B. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014 2014/12/01;5(6):229-41. DOI: 10.1177/2042098614554919.
39. French G. Clinical impact and relevance of antibiotic resistance. Adv Drug Deliv Rev. 2005;57(10):1514-27.
40. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014;5(6):229-41. DOI: 10.1177/2042098614554919.
41. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015 2015/10/03;109(7):309-18. DOI: 10.1179/2047773215Y.0000000030.
42. Australian Commission on Safety and Quality in Health Care. AURA 2019: Third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2019.
43. Van der Velden A, Duerden MG, Bell J, Oxford JS, Altiner A, Kozlov R, et al. Prescriber and patient responsibilities in treatment of acute respiratory tract infections—essential for conservation of antibiotics. Antibiotics. 2013;2(2):316-27.
44. Hawker JI, Smith S, Smith GE, Morbey R, Johnson AP, Fleming DM, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. J Antimicrob Chemother. 2014 Dec;69(12):3423-30. DOI: 10.1093/jac/dku291.
45. Hulscher ME, Grol RP, Van Der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. Lancet Infect Dis. 2010;10(3):167-75.
46. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci USA. 2018;115(15):E3463-E70. DOI: 10.1073/pnas.1717295115.
47. Zhan C, Miller MR. Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. Jama. 2003;290(14):1868-74.

48. Roberts RR, Scott RD, Hota B, Kampe LM, Abbasi F, Schabowski S, et al. Costs attributable to healthcare-acquired infection in hospitalized adults and a comparison of economic methods. Medical care. 2010:1026-35.
49. Wozniak TM, Bailey EJ, Graves N. Health and economic burden of antimicrobial-resistant infections in Australian hospitals: a population-based model. Infect Control Hosp Epidemiol. 2019;40(3):320-7. DOI: 10.1017/ice.2019.2.
50. Boucher HW, Talbot GH, Benjamin Jr DK, Bradley J, Guidos RJ, Jones RN, et al. 10×'20 progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(12):1685-94.
51. WHO. ANTIMICROBIAL RESI STANCE: Global Report on Surveillance. WHO Library Cataloguing-in-Publication Data. 2014.
52. Karam G, Chastre J, Wilcox MH, Vincent J-L. Antibiotic strategies in the era of multidrug resistance. Critical Care. 2016 2016/06/22;20(1):136. DOI: 10.1186/s13054-016-1320-7.
53. File TM, Jr., Srinivasan A, Bartlett JG. Antimicrobial stewardship: importance for patient and public health. Clin Infect Dis. 2014 Oct 15;59 Suppl 3:S93-6. DOI: 10.1093/cid/ciu543.
54. Doron S, Davidson LE. Antimicrobial stewardship. In: Mayo Clinic Proceedings. 2011: Elsevier; p. 1113-23.
55. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis. 2007;44(2):159-77. DOI: 10.1086/510393.
56. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. The Cochrane database of systematic reviews. 2017;2(2):CD003543-CD. DOI: 10.1002/14651858.CD003543.pub4.
57. Nagel JL, Stevenson JG, Eiland EH, 3rd, Kaye KS. Demonstrating the value of antimicrobial stewardship programs to hospital administrators. Clin Infect Dis. 2014 Oct 15;59 Suppl 3:S146-53. DOI: 10.1093/cid/ciu566.
58. ACSQHC. Second Australian report on antimicrobial use and resistance in human health: Australian Commission on Safety and Quality in Health Care; 2017.
59. Australian Commission on Safety Quality in Health Care. Electronic Medication Management Systems—A Guide to Safe Implementation. Sydney: Australian Commission on Safety Quality in Health Care; 2019.

60. Chung GW, Wu JE, Yeo CL, Chan D, Hsu LY. Antimicrobial stewardship: A review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence. 2013;4(2):151-7. DOI: 10.4161/viru.21626.
61. Dik J-WH, Poelman R, Friedrich AW, Panday PN, Lo-Ten-Foe JR, Assen Sv, et al. An integrated stewardship model: antimicrobial, infection prevention and diagnostic (AID). Future Microbiol. 2016;11(1):93-102.
62. ACSQHC. Safety and Quality Improvement Guide Standard 4: Medication Safety. Sydney; 2012.
63. Meskó B, Drobni Z, Bényei É, Gergely B, Győrffy Z. Digital health is a cultural transformation of traditional healthcare. Mhealth. 2017;3.
64. Mathews SC, McShea MJ, Hanley CL, Ravitz A, Labrique AB, Cohen AB. Digital health: a path to validation. NPJ Digit Med. 2019;2(1):1-9.
65. Barrett LL. Prescription drug use among midlife and older Americans: AARP, Knowledge Management; 2005.
66. Colicchio TK, Cimino JJ, Del Fiol G. Unintended Consequences of Nationwide Electronic Health Record Adoption: Challenges and Opportunities in the Post-Meaningful Use Era. J Med Internet Res. [Viewpoint]. 2019;21(6):e13313. DOI: 10.2196/13313.
67. Coiera E, Ash J, Berg M. The Unintended Consequences of Health Information Technology Revisited. Yearb Med Inform. 2016(1):163-9. DOI: 10.15265/IY-2016-014.
68. Magrabi F, Ong M-s, Runciman W, Coiera E. Patient safety problems associated with heathcare information technology: an analysis of adverse events reported to the US Food and Drug Administration. In: AMIA Annu Symp Proc. 2011: American Medical Informatics Association; p. 853.
69. Magrabi F, Ong M-S, Runciman W, Coiera E. An analysis of computer-related patient safety incidents to inform the development of a classification. J Am Med Inform Assoc. 2010;17(6):663-70.
70. Weiner JP, Kfuri T, Chan K, Fowles JB. "e-Iatrogenesis": the most critical unintended consequence of CPOE and other HIT. J Am Med Inform Assoc. 2007 May-Jun;14(3):387-9. DOI: 10.1197/jamia.M2338.
71. Bernstam EV, Hersh WR, Sim I, Eichmann D, Silverstein JC, Smith JW, et al. Unintended consequences of health information technology: a need for biomedical informatics. J Biomed Inform. 2010;43(5):828.

72. Smith B, Magnani JW. New technologies, new disparities: The intersection of electronic health and digital health literacy. Int J Cardiol. 2019 2019/10/01/;292:280-2. DOI: https://doi.org/10.1016/j.ijcard.2019.05.066.
73. Ogundaini O, de la Harpe R, McLean N. Unintended consequences of technology-enabled work activities experienced by healthcare professionals in tertiary hospitals of sub-Saharan Africa. African J Sci Technol Innov Dev. 2021:1-10. DOI: 10.1080/20421338.2021.1899556.
74. Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of clinical decision-support systems: a systematic review. Ann Intern Med. 2012;157(1):29-43.
75. Castaneda C, Nalley K, Mannion C, Bhattacharyya P, Blake P, Pecora A, et al. Clinical decision support systems for improving diagnostic accuracy and achieving precision medicine. J Clin Bioinform. 2015;5(1):1-16.
76. Sharma A, Harrington RA, McClellan MB, Turakhia MP, Eapen ZJ, Steinhubl S, et al. Using Digital Health Technology to Better Generate Evidence and Deliver Evidence-Based Care. J Am Coll Cardiol. 2018 2018/06/12/;71(23):2680-90. DOI: https://doi.org/10.1016/j.jacc.2018.03.523.
77. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA. 1998 Oct 21;280(15):1339-46.
78. Musen MA, Middleton B, Greenes RA. Clinical decision-support systems. Biomedical informatics: Springer; 2014. p. 643-74.
79. Lobach D, Sanders GD, Bright TJ, Wong A, Dhurjati R, Bristow E, et al. Enabling health care decisionmaking through clinical decision support and knowledge management. 2012.
80. Cheerkoot-Jalim S, Khedo KK, Jodheea-Jutton A. An exploratory study of evidence-based clinical decision support systems. Information Systems Design and Intelligent Applications: Springer; 2019. p. 207-18.
81. Roshanov PS, Fernandes N, Wilczynski JM, Hemens BJ, You JJ, Handler SM, et al. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. BMJ. 2013;346.
82. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ. 2005;330(7494):765. DOI: 10.1136/bmj.38398.500764.8F.
83. Kwan JL, Lo L, Ferguson J, Goldberg H, Diaz-Martinez JP, Tomlinson G, et al. Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. BMJ. 2020;370:m3216. DOI: 10.1136/bmj.m3216.

84. Tygesen H, Eriksson H, Herlitz J. Clinical decision support system (CDSS)–effects on care quality. Int J Health Care Qual Assur. 2014.
85. Trinkley KE, Blakeslee WW, Matlock DD, Kao DP, Van Matre AG, Harrison R, et al. Clinician preferences for computerised clinical decision support for medications in primary care: a focus group study. BMJ Health Care Inform. 2019;26(1):e000015.
86. Olakotan OO, Yusof MM. Evaluating the alert appropriateness of clinical decision support systems in supporting clinical workflow. J Biomed Inform. 2020:103453.
87. Varghese J, Kleine M, Gessner SI, Sandmann S, Dugas M. Effects of computerized decision support system implementations on patient outcomes in inpatient care: a systematic review. J Am Med Inform Assoc. 2017;25(5):593-602. DOI: 10.1093/jamia/ocx100.
88. Dizon JM, Machingaidze S, Grimmer K. To adopt, to adapt, or to contextualise? The big question in clinical practice guideline development. BMC Res Notes. 2016;9(1):1-8.
89. Durkin MJ, Keller M, Butler AM, Kwon JH, Dubberke ER, Miller AC, et al. An assessment of inappropriate antibiotic use and guideline adherence for uncomplicated urinary tract infections. In: Open Forum Infect Dis. 2018: Oxford University Press US; p. ofy198.
90. Goff DA, Reeve W, Naumovski S, Epson E, Zenilman J, Kaye KS, et al. Approaches to modifying the behavior of clinicians who are noncompliant with antimicrobial stewardship program guidelines. Rev Infect Dis. 2016;63(4):532-8.
91. Holstiege J, Mathes T, Pieper D. Effects of computer-aided clinical decision support systems in improving antibiotic prescribing by primary care providers: A systematic review. J Am Med Inform Assoc. [Review]. 2015;22(1):236-42. DOI: 10.1136/amiajnl-2014-002886.
92. Albarillo FS, Labuszewski L, Lopez J, Santarossa M, Bhatia NK. Use of a Clinical Decision Support System (CDSS) to improve antimicrobial stewardship efforts at a single academic medical center. Germs. 2019;9(2):106.
93. Heard KL, Hughes S, Mughal N, Azadian BS, Moore LS. Evaluating the impact of the ICNET® clinical decision support system for antimicrobial stewardship. Antimicrob Resist Infect Control. 2019;8(1):1-6.
94. Hermsen ED, VanSchooneveld TC, Sayles H, Rupp ME. Implementation of a clinical decision support system for antimicrobial stewardship. Infect Control Hosp Epidemiol. 2012;33(4):412.
95. Segura BC, Morales A, Juarez JM, Campos M, Palacios F. WASPSS: A Clinical Decision Support System for Antimicrobial Stewardship. Advances in Intelligent and Personalized Clinical Decision Support Systems: IntechOpen; 2020.

96. Bond SE, Chubaty AJ, Adhikari S, Miyakis S, Boutlis CS, Yeo WW, et al. Outcomes of multisite antimicrobial stewardship programme implementation with a shared clinical decision support system. J Antimicrob Chemother. 2017;72(7):2110-8.
97. Heng ST, Wong J, Young B, Tay HL, Tan SH, Yap MY, et al. Effective Antimicrobial StewaRdship StrategIES (ARIES): Cluster Randomized Trial of Computerized Decision Support System and Prospective Review and Feedback. In: Open Forum Infect Dis. 2020: Oxford University Press US; p. ofaa254.
98. Cook PP, Rizzo S, Gooch M, Jordan M, Fang X, Hudson S. Sustained reduction in antimicrobial use and decrease in methicillin-resistant Staphylococcus aureus and Clostridium difficile infections following implementation of an electronic medical record at a tertiary-care teaching hospital. J Antimicrob Chemother. 2011;66(1):205-9. DOI: 10.1093/jac/dkq404.
99. Carracedo-Martinez E, Gonzalez-Gonzalez C, Teixeira-Rodrigues A, Prego-Dominguez J, Takkouche B, Herdeiro MT, et al. Computerized clinical decision support systems and antibiotic prescribing: a systematic review and meta-analysis. Clinical therapeutics. 2019;41(3):552-81.
100. Rittmann B, Stevens MP. Clinical decision support systems and their role in antibiotic stewardship: a systematic review. Current infectious disease reports. 2019;21(8):1-12.
101. Akhloufi H, Verhaegh S, Jaspers M, Melles D, van der Sijs H, Verbon A. A usability study to improve a clinical decision support system for the prescription of antibiotic drugs. PloS one. 2019;14(9):e0223073.
102. Kuper KM, Nagel JL, Kile JW, May LS, Lee FM. The role of electronic health record and “add-on” clinical decision support systems to enhance antimicrobial stewardship programs. Infect Control Hosp Epidemiol. 2019;40(5):501-11.
103. Yong MK, Buising KL, Cheng AC, Thursky KA. Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. J Antimicrob Chemother. 2010 May;65(5):1062-9. DOI: 10.1093/jac/dkq058.
104. Mann D, Hess R, McGinn T, Richardson S, Jones S, Palmisano J, et al. Impact of Clinical Decision Support on Antibiotic Prescribing for Acute Respiratory Infections: a Cluster Randomized Implementation Trial. J Gen Intern Med. 2020 Nov;35(Suppl 2):788-95. DOI: 10.1007/s11606-020-06096-3.
105. Forrest GN, Van Schooneveld TC, Kullar R, Schulz LT, Duong P, Postelnick M. Use of electronic health records and clinical decision support systems for antimicrobial stewardship. Clin Infect Dis. 2014 Oct 15;59 Suppl 3:S122-33. DOI: 10.1093/cid/ciu565.

106. Zaidi ST, Thursky KA. Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship. J Clin Pharm Ther. 2013 Dec;38(6):490-7. DOI: 10.1111/jcpt.12093.
107. Zaidi STR, Marriott JL. Barriers and Facilitators to Adoption of a Web-based Antibiotic Decision Support System. Southern med review. 2012;5(2):42-50.
108. Esmaeilzadeh P, Sambasivan M, Kumar N, Nezakati H. Adoption of clinical decision support systems in a developing country: Antecedents and outcomes of physician's threat to perceived professional autonomy. Int J Med Inform. 2015 Aug;84(8):548-60. DOI: 10.1016/j.ijmedinf.2015.03.007.
109. Thursky KA, Mahemoff M. User-centered design techniques for a computerised antibiotic decision support system in an intensive care unit. International journal of medical informatics. 2007;76(10):760-8.
110. Rawson TM, Moore LSP, Hernandez B, Charani E, Castro-Sanchez E, Herrero P, et al. A systematic review of clinical decision support systems for antimicrobial management: are we failing to investigate these interventions appropriately? Clin Microbiol Infect. 2017 Aug;23(8):524-32. DOI: 10.1016/j.cmi.2017.02.028.
111. Mostaghim M, Snelling T, McMullan B, Ewe YH, Bajorek B. Impact of clinical decision support on empirical antibiotic prescribing for children with community-acquired pneumonia. Journal of Paediatrics and Child Health. 2019;55(3):305-11. DOI: https://doi.org/10.1111/jpc.14191.
112. Baysari MT, Del Gigante J, Moran M, Sandaradura I, Li L, Richardson KL, et al. Redesign of computerized decision support to improve antimicrobial prescribing. A controlled before-and-after study. Applied clinical informatics. 2017;8(3):949-63. DOI: 10.4338/ACI2017040069.
113. Trevena L, McCaffery K, Salkeld G, Glasziou P, Del Mar C, Doust J, et al. Clinical decision-making tools: how effective are they in improving the quality of health care. Deeble Institute for Health Policy Research, Australian Healthcare and Hospitals Association. 2014.
114. Liberati EG, Ruggiero F, Galuppo L, Gorli M, González-Lorenzo M, Maraldi M, et al. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. Implement Sci. 2017 2017/09/15;12(1):113. DOI: 10.1186/s13012-017-0644-2.
115. Moxey A, Robertson J, Newby D, Hains I, Williamson M, Pearson S-A. Computerized clinical decision support for prescribing: provision does not guarantee uptake. J Am Med Inform Assoc. 2010;17(1):25-33.
116. Kux BR, Majeed RW, Ahlbrandt J, Röhrig R. Factors Influencing the Implementation and Distribution of Clinical Decision Support Systems (CDSS). GMDS. 2017:127-31.

117. Simon SR, McCarthy ML, Kaushal R, Jenter CA, Volk LA, Poon EG, et al. Electronic health records: which practices have them, and how are clinicians using them? J Eval Clin Pract. 2008 Feb;14(1):43-7. DOI: 10.1111/j.1365-2753.2007.00787.x.
118. Chang F, Gupta N. Progress in electronic medical record adoption in Canada. Can Fam Physician. 2015 Dec;61(12):1076-84.
119. Smithburger PL, Buckley MS, Bejian S, Burenheide K, Kane-Gill SL. A critical evaluation of clinical decision support for the detection of drug–drug interactions. Expert Opin Drug Saf. 2011;10(6):871-82.
120. Baysari MT, Lehnbom EC, Li L, Hargreaves A, Day RO, Westbrook JI. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: A systematic review and meta-analysis. Int J Med Inform. [Review]. 2016;92:15-34. DOI: 10.1016/j.ijmedinf.2016.04.008.
121. Payne TH, Nichol WP, Hoey P, Savarino J. Characteristics and override rates of order checks in a practitioner order entry system. In: AMIA Annu Symp Proc. 2002: American Medical Informatics Association; p. 602.
122. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med. 2003;163(21):2625-31.
123. Ghamrawi RJ, Kantorovich A, Bauer SR, Pallotta AM, Sekeres JK, Gordon SM, et al. Evaluation of Antimicrobial Stewardship-Related Alerts Using a Clinical Decision Support System. Hospital pharmacy. 2017;52(10):679-84. DOI: 10.1177/0018578717726869.
124. Patel J, Esterly JS, Scheetz MH, Bolon MK, Postelnick MJ. Effective use of a clinical decision-support system to advance antimicrobial stewardship. American Journal of Health-System Pharmacy. 2012;69(18):1543-4. DOI: 10.2146/ajhp110729.
125. Hermsen ED, VanSchooneveld TC, Sayles H, Rupp ME. Implementation of a clinical decision support system for antimicrobial stewardship. Infect Control Hosp Epidemiol. 2012 Apr;33(4):412-5. DOI: 10.1086/664762.
126. McCoy AB, Thomas EJ, Krousel-Wood M, Sittig DF. Clinical decision support alert appropriateness: a review and proposal for improvement. Ochsner J. 2014 Summer;14(2):195-202.
127. Seidling HM, Phansalkar S, Seger DL, Paterno MD, Shaykevich S, Haefeli WE, et al. Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. Journal of the American Medical Informatics Association. 2011;18(4):479-84.

128. Jani YH, Barber N, Wong ICK. Characteristics of clinical decision support alert overrides in an electronic prescribing system at a tertiary care paediatric hospital. Int J Pharm Pract. 2011;19(5):363-6.
129. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform Assoc. 2006;13(1):5-11.
130. Bakker T, Klopotowska J, Eslami S, De Lange D, van Marum R, van der Sijs H, et al. The effect of ICU-tailored drug-drug interaction alerts on medication prescribing and monitoring: protocol for a cluster randomized stepped-wedge trial. BMC Med Inform Decis Mak. 2019;19(1):1-10.
131. Wright A, Sittig DF. A framework and model for evaluating clinical decision support architectures. J Biomed Inform. 2008;41(6):982-90.
132. Lehne M, Sass J, Essenwanger A, Schepers J, Thun S. Why digital medicine depends on interoperability. NPJ digital medicine. 2019;2:79-. DOI: 10.1038/s41746-019-0158-1.
133. Greenes RA, Bates DW, Kawamoto K, Middleton B, Osheroff J, Shahar Y. Clinical decision support models and frameworks: Seeking to address research issues underlying implementation successes and failures. J Biomed Inform. 2018 2018/02/01/;78:134-43. DOI: https://doi.org/10.1016/j.jbi.2017.12.005.
134. Miller A, Moon B, Anders S, Walden R, Brown S, Montella D. Integrating computerized clinical decision support systems into clinical work: A meta-synthesis of qualitative research. Int J Med Inform. 2015 Dec;84(12):1009-18. DOI: 10.1016/j.ijmedinf.2015.09.005.
135. González-Ferrer A, Peleg M. Understanding requirements of clinical data standards for developing interoperable knowledge-based DSS: A case study. Comput Stand Interfaces. 2015;42:125-36.
136. Middleton B, Bloomrosen M, Dente MA, Hashmat B, Koppel R, Overhage JM, et al. Enhancing patient safety and quality of care by improving the usability of electronic health record systems: recommendations from AMIA. J Am Med Inform Assoc. 2013;20(e1):e2-e8.
137. Belard A, Buchman T, Forsberg J, Potter BK, Dente CJ, Kirk A, et al. Precision diagnosis: a view of the clinical decision support systems (CDSS) landscape through the lens of critical care. J Clin Monit Comput. 2017;31(2):261-71.
138. Miller K, Mosby D, Capan M, Kowalski R, Ratwani R, Noaiseh Y, et al. Interface, information, interaction: a narrative review of design and functional requirements for clinical decision support. J Am Med Inform Assoc. 2018;25(5):585-92.

139. Kanstrup AM, Christiansen MB, Nøhr C. Four principles for user interface design of computerised clinical decision support systems. Stud Health Technol Inform. 2011 2011;166:65-73.
140. Phansalkar S, Zachariah M, Seidling HM, Mendes C, Volk L, Bates DW. Evaluation of medication alerts in electronic health records for compliance with human factors principles. J Am Med Inform Assoc. 2014;21(e2):e332-e40. DOI: 10.1136/amiajnl-2013-002279.
141. Wijnhoven F, Koerkamp RK. Barriers for Adoption of Analytical CDSS in Healthcare: Insights from Case Stakeholders. In: 5th International Conference on Information and Communication Technologies in Organizations and Society, ICTO 2019: The Impact of Artificial Intelligence on Business and Society. 2019
142. Cresswell K, Mozaffar H, Shah S, Sheikh A. Approaches to promoting the appropriate use of antibiotics through hospital electronic prescribing systems: a scoping review. Int J Pharm Pract. [Review]. 2017;25(1):5-17. DOI: 10.1111/ijpp.12274.
143. Cresswell K, Callaghan M, Mozaffar H, Sheikh A. NHS Scotland's Decision Support Platform: a formative qualitative evaluation. BMJ Health Care Inform. 2019;26(1):e100022. DOI: 10.1136/bmjhci-2019-100022.
144. Camacho J, Zanoletti-Mannello M, Landis-Lewis Z, Kane-Gill SL, Boyce RD. A Conceptual Framework to Study the Implementation of Clinical Decision Support Systems (BEAR): Literature Review and Concept Mapping. J Med Internet Res. 2020;22(8):e18388-e. DOI: 10.2196/18388.
145. Venkatesh V, Thong JY, Xu X. Unified theory of acceptance and use of technology: A synthesis and the road ahead. J Assoc Inf Syst. 2016;17(5):328-76.
146. Venkatesh V, Morris MG, Davis GB, Davis FD. User Acceptance of Information Technology: Toward a Unified View. MIS Quarterly. 2003;27(3):425-78. DOI: 10.2307/30036540.
147. Authority OHD. Victorian Health Design Forum Report – Clinical Decision Support; 2013.
148. Eden R, Burton-Jones A, Scott I, Staib A, Sullivan C. Effects of eHealth on hospital practice: synthesis of the current literature. Aust Health Rev. 2018;42(5):568-78.
149. Robertson J, Moxey AJ, Newby DA, Gillies MB, Williamson M, Pearson S-A. Electronic information and clinical decision support for prescribing: state of play in Australian general practice. J Fam Pract. 2011;28(1):93-101. DOI: 10.1093/fampra/cmq031.
150. Shaw T, Hines M, Kielly-Carroll C. Impact of Digital Health on the Safety and Quality of Health Care. Sydney: ACSQHC; 2017.

151. Ross J, Stevenson F, Dack C, Pal K, May C, Michie S, et al. Developing an implementation strategy for a digital health intervention: an example in routine healthcare. BMC Health Serv Res. 2018;18(1):794-. DOI: 10.1186/s12913-018-3615-7.
152. Souza-Pereira L, Pombo N, Ouhbi S, Felizardo V, Garcia N. Clinical decision support systems for chronic diseases: A Systematic literature review. Comput Methods Programs Biomed. 2020 Oct;195:105565. DOI: 10.1016/j.cmpb.2020.105565.
153. Osheroff J, Teich J, Levick D, Saldana L, Velasco F, Sittig D, et al. Improving outcomes with clinical decision support: an implementer's guide: HIMSS Publishing; 2012.
154. Australian Digital Health Agency. Safe, Seamless and Secure: Evolving Health and Care to Meet the Needs of Modern Australia. 2018.
155. Australian Digital Health Agency. Framework For Action; 2018.
156. Östlund U, Kidd L, Wengström Y, Rowa-Dewar N. Combining qualitative and quantitative research within mixed method research designs: a methodological review. Int J Nurs Stud. 2011;48(3):369-83.
157. Shorten A, Smith J. Mixed methods research: expanding the evidence base. Royal College of Nursing; 2017.
158. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928. DOI: 10.1136/bmj.d5928.
159. Shebl NA, Franklin BD, Barber N. Clinical decision support systems and antibiotic use. Pharm World Sci. [Review]. 2007;29(4):342-9. DOI: 10.1007/s11096-007-9113-3.
160. Zanichelli V, Monnier AA, Gyssens IC, Adriaenssens N, Versporten A, Pulcini C, et al. Variation in antibiotic use among and within different settings: a systematic review. J Antimicrob Chemother. 2018;73(suppl_6):vi17-vi29.
161. Laka M, Milazzo A, Merlin T. Can evidence-based decision support tools transform antibiotic management? A systematic review and meta-analyses. J Antimicrob Chemother. 2020;75(5):1099-111. DOI: 10.1093/jac/dkz543.
162. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015 2015/01/01;4(1):1. DOI: 10.1186/2046-4053-4-1.
163. Science M, Timberlake K, Morris A, Read S, Le Saux N. Quality Metrics for Antimicrobial Stewardship Programs. Pediatrics. 2019;143(4).

164. Morris AM. Antimicrobial Stewardship Programs: Appropriate Measures and Metrics to Study their Impact. Curr Treat Options Infect Dis. 2014;6(2):101-12. DOI: 10.1007/s40506-014-0015-3.
165. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis. 2017 Feb 1;64(3):377-83. DOI: 10.1093/cid/ciw787.
166. Brotherton AL. Metrics of Antimicrobial Stewardship Programs. Med Clin North Am. 2018 Sep;102(5):965-76. DOI: 10.1016/j.mcna.2018.05.008.
167. van Santen KL, Edwards JR, Webb AK, Pollack LA, O'Leary E, Neuhauser MM, et al. The Standardized Antimicrobial Administration Ratio: A New Metric for Measuring and Comparing Antibiotic Use. Clin Infect Dis. 2018 Jul 15;67(2):179-85. DOI: 10.1093/cid/ciy075.
168. Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med. 2012;172(12):922-8. DOI: 10.1001/archinternmed.2012.1690.
169. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62(10):e51-e77. DOI: 10.1093/cid/ciw118.
170. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339: e1000100. DOI: 10.1136/bmj.b2700.
171. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. DOI: 10.1136/bmj.i4919.
172. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. [journal article]. 2004 December 22;4(1):38. DOI: 10.1186/1472-6963-4-38.
173. Li T, Higgins J, Deeks Je. Chapter 5: Collecting data. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions (updated September 2020): Cochrane; 2020.

174. Peters M, Christina G, Patricia M, Cassia S, Hanan K, Deborah P. The Joanna Briggs Institute Reviewers' Manual 2015: Methodology for JBI Scoping Reviews. Adelaide, SA Australia: The Joanna Briggs Institute; 2015.
175. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018 Jun;27(6):1785-805. DOI: 10.1177/0962280216669183.
176. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. [journal article]. 2005 April 20;5(1):13. DOI: 10.1186/1471-2288-5-13.
177. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. [journal article]. 2014 December 19;14(1):135. DOI: 10.1186/1471-2288-14-135.
178. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74(3):785-94.
179. Schmid CH. Outcome reporting bias: a pervasive problem in published meta-analyses. Am J Kidney Dis. 2017;69(2):172-4.
180. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001;20(4):641-54. DOI: 10.1002/sim.698.
181. Sterne JA, Egger M, Moher D. Addressing reporting biases. Cochrane handbook for systematic reviews of interventions: Cochrane book series. 2008:297-333.
182. Chiasson MW, Davidson E. Pushing the contextual envelope: developing and diffusing IS theory for health information systems research. J Inf Organ. 2004;14(3):155-88.
183. Chambers D, Wilson P, Thompson C, Harden M. Social network analysis in healthcare settings: a systematic scoping review. PloS one. 2012;7(8).
184. Venkatesh V, Sykes TA, Zhang X. 'Just what the doctor ordered': a revised UTAUT for EMR system adoption and use by doctors. In: 2011 44th Hawaii International Conference on System Sciences. 2011: IEEE; p. 1-10.
185. Lee J-M, Lee B, Rha J-Y. Determinants of mobile payment usage and the moderating effect of gender: Extending the UTAUT model with privacy risk. Int J Electron Commer Stud. 2019;10(1):43-64.
186. Venkatesh V, Morris MG. Why don't men ever stop to ask for directions? Gender, social influence, and their role in technology acceptance and usage behavior. MIS quarterly. 2000:115-39.
187. Morris MG, Venkatesh V. Age differences in technology adoption decisions: Implications for a changing work force. Pers Psychol. 2000;53(2):375-403.

188. Wills MJ, El-Gayar OF, Bennett D. Examining healthcare professionals' acceptance of electronic medical records using UTAUT. 2008.
189. Khechine H, Lakhal S, Pascot D, Bytha A. UTAUT model for blended learning: The role of gender and age in the intention to use webinars. Interdisciplinary Journal of E-Learning and Learning Objects. 2014;10(1):33-52.
190. Laka M, Milazzo A, Merlin T. Factors That Impact the Adoption of Clinical Decision Support Systems (CDSS) for Antibiotic Management. Int J Environ Res Public Health. 2021;18(4):1901.
191. Maillet É, Mathieu L, Sicotte C. Modeling factors explaining the acceptance, actual use and satisfaction of nurses using an Electronic Patient Record in acute care settings: An extension of the UTAUT. Int J Med Inform. 2015;84(1):36-47.
192. Attuquayefio S, Addo H. Review of studies with UTAUT as conceptual framework. Eur Sci J. 2014;10(8).
193. Kondracki NL, Wellman NS, Amundson DR. Content analysis: review of methods and their applications in nutrition education. J Nutr Educ Behav. 2002 Jul-Aug;34(4):224-30. DOI: 10.1016/s1499-4046(06)60097-3.
194. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis: Striving to meet the trustworthiness criteria. Int J Qual Methods. 2017;16(1):1609406917733847.
195. Agboola SO, Bates DW, Kvedar JC. Digital health and patient safety. Jama. 2016;315(16):1697-8.
196. Huang F, Blaschke S, Lucas H. Beyond pilotitis: taking digital health interventions to the national level in China and Uganda. Glob Health. 2017;13(1):1-11.
197. Kim H, Sefcik JS, Bradway C. Characteristics of Qualitative Descriptive Studies: A Systematic Review. Res Nurs Health. 2017;40(1):23-42. DOI: 10.1002/nur.21768.
198. Colorafi KJ, Evans B. Qualitative Descriptive Methods in Health Science Research. HERD. 2016;9(4):16-25. DOI: 10.1177/1937586715614171.
199. Bradshaw C, Atkinson S, Doody O. Employing a Qualitative Description Approach in Health Care Research. Glob Qual Nurs Res. 2017;4:2333393617742282-. DOI: 10.1177/2333393617742282.
200. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies:Guided by Information Power. Qual Health Res. 2016;26(13):1753-60. DOI: 10.1177/1049732315617444.
201. Kawamoto K, Del Fiol G, Lobach DF, Jenders RA. Standards for scalable clinical decision support: need, current and emerging standards, gaps, and proposal for progress. Open Med Inform J. 2010;4:235-44. DOI: 10.2174/1874431101004010235.

202. Scheepers-Hoeks A-M, Grouls R, Neef C, Ackerman E, Korsten E. Success Factors and Barriers for Implementation of Advanced Clinical Decision Support Systems. In: Jao C, editor. Efficient Decision Support Systems - Practice and Challenges in Biomedical Related Domain 2011.
203. Kankam PK. The use of paradigms in information research. Libr Inf Sci Res. 2019.
204. Kaushik V, Walsh CA. Pragmatism as a Research Paradigm and Its Implications for Social Work Research. Soc Sci. 2019;8(9):255.
205. Biesta G. Pragmatism and the philosophical foundations of mixed methods research. Sage handbook of mixed methods in social and behavioral research. 2010;2:95-118.
206. Smith J, Bekker H, Cheater F. Theoretical versus pragmatic design in qualitative research. Nurse Res. 2011;18(2):39-51.
207. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health. 2019 2019/08/08;11(4):589-97. DOI: 10.1080/2159676X.2019.1628806.
208. Davies SC, Fowler T, Watson J, Livermore DM, Walker D. Annual Report of the Chief Medical Officer: infection and the rise of antimicrobial resistance. The Lancet. 2013 2013/05/11/;381(9878):1606-9. DOI: https://doi.org/10.1016/S0140-6736(13)60604-2.
209. Nikaido H. Multidrug Resistance in Bacteria. Annu Rev Biochem. 2009;78:119-46. DOI: 10.1146/annurev.biochem.78.082907.145923.
210. Centres for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013.
211. While A. 'No action today means no cure tomorrow': the threat of antimicrobial resistance. Br J Community Nurs. 2016;21(7):344-7.
212. Owens RC, Jr., Bulik CC, Andes DR. Pharmacokinetics-pharmacodynamics, computer decision support technologies, and antimicrobial stewardship: the compass and rudder. Diagn Microbiol Infect Dis. 2018 Aug;91(4):371-82. DOI: 10.1016/j.diagmicrobio.2018.03.015.
213. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999 Oct 20;282(15):1458-65.
214. Ranji SR, Rennke S, Wachter RM. Computerised provider order entry combined with clinical decision support systems to improve medication safety: a narrative review. BMJ Qual Saf. 2014;23(9):773-80. DOI: 10.1136/bmjqs-2013-002165.
215. Holstiege J, Mathes T, Pieper D. Effects of computer-aided clinical decision support systems in improving antibiotic prescribing by primary care providers: A systematic review. Journal of the

American Medical Informatics Association. [Review]. 2014;22(1):236-42. DOI: 10.1136/amiajnl-2014-002886.

216. Berner ES. Clinical decision support systems: Springer; 2007.

217. Granja C, Janssen W, Johansen MA. Factors determining the success and failure of eHealth interventions: systematic review of the literature. J Med Internet Res. 2018;20(5):e10235.

218. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology: ATC classification index with DDDs and Guidelines for ATC classification and DDD assignment. Oslo, Norway: Norwegian Institute of Public Health. 2006.

219. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. DOI: 10.1136/bmj.j4008.

220. Peters M, Godfrey C, McInerney P, Baldini SC, Khalil H, Parker D. Methodology for JBI scoping reviews. In: E A, Z M, editors. Joanna Briggs Institute Reviewer's Manual: The Joanna Briggs Institute; 2015. p. 1-24.

221. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC Med Res Methodol. [journal article]. 2009 June 11;9(1):34. DOI: 10.1186/1471-2288-9-34.

222. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Arch Intern Med. 2011;155(8):529-36.

223. Conway A, Clarke MJ, Treweek SP, Schunemann H, Santesso N, Morgan RL, et al. Summary of findings tables for communicating key findings of systematic reviews. Cochrane Database of Systematic Reviews. 2017.

224. Hedges LV, Olkin I. CHAPTER 9 - Random Effects Models for Effect Sizes. In: Hedges LV, Olkin I, editors. Statistical Methods for Meta-Analysis. San Diego: Academic Press; 1985. p. 189-203.

225. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 1986/09/01/;7(3):177-88. DOI: https://doi.org/10.1016/0197-2456(86)90046-2.

226. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemp Clin Trials. 2007 2007/02/01/;28(2):105-14. DOI: https://doi.org/10.1016/j.cct.2006.04.004.

227. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med. 1999 Oct 30;18(20):2693-708.

228. Deeks J, Higgins J, Altman De. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook of Systematic reviews of Interventions (updated September 2020): The Cochrane Collaboration; 2020.
229. Gonzales R, Anderer T, McCulloch CE, Maselli JH, Bloom FJ, Jr., Graf TR, et al. A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. JAMA Intern Med. 2013 Feb 25;173(4):267-73. DOI: 10.1001/jamainternmed.2013.1589.
230. Gulliford MC, van Staa T, Dregan A, McDermott L, McCann G, Ashworth M, et al. Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT study). Ann Fam Med. 2014 Jul;12(4):344-51. DOI: 10.1370/afm.1659.
231. Paul M, Andreassen S, Tacconelli E, Nielsen AD, Almanasreh N, Frank U, et al. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. J Antimicrob Chemother. 2006 Dec;58(6):1238-45. DOI: 10.1093/jac/dkl372.
232. Shojania KG, Yokoe D, Platt R, Fiskio J, Ma'luf N, Bates DW. Reducing Vancomycin Use Utilizing a Computer GuidelineResults of a Randomized Controlled Trial. J Am Med Inform Assoc. 1998;5(6):554-62. DOI: 10.1136/jamia.1998.0050554.
233. Davis RL, Wright J, Chalmers F, Levenson L, Brown JC, Lozano P, et al. A cluster randomized clinical trial to improve prescribing patterns in ambulatory pediatrics. PLoS Clin Trials. [Article]. 2007;2(5):e25. DOI: 10.1371/journal.pctr.0020025.
234. Leibovici L, Kariv G, Paul M. Long-term survival in patients included in a randomized controlled trial of TREAT, a decision support system for antibiotic treatment. J Antimicrob Chemother. 2013 Nov;68(11):2664-6. DOI: 10.1093/jac/dkt222.
235. Evans RS, Classen DC, Pestotnik SL, Lundsgaarde HP, Burke JP. Improving empiric antibiotic selection using computer decision support. Arch Intern Med. 1994 Apr 25;154(8):878-84.
236. Burton Michael E, Ash Cynthia L, Hill Donald P, Handy T, Shepherd Marvin D, Vasko Michael R. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. Clin Pharmacol Ther. 1991;49(6):685-94. DOI: 10.1038/clpt.1991.86.
237. Christakis DA, Zimmerman FJ, Wright JA, Garrison MM, Rivara FP, Davis RL. A randomized controlled trial of point-of-care evidence to improve the antibiotic prescribing practices for otitis media in children. Pediatr. [Article]. 2001;107(2):e15.
238. Linder JA, Schnipper JL, Tsurikova R, Yu T, Volk LA, Melnikas AJ, et al. Documentation-based clinical decision support to improve antibiotic prescribing for acute respiratory infections in primary care: a cluster randomised controlled trial. Inform Prim Care. 2009;17(4):231-40.

239. McGinn TG, McCullagh L, Kannry J, Knaus M, Sofianou A, Wisnivesky JP, et al. Efficacy of an evidence-based clinical decision support in primary care practices: A randomized clinical trial. JAMA Intern Med. [Article]. 2013;173(17):1584-91. DOI: 10.1001/jamainternmed.2013.8980.
240. McGregor JC, Weekes E, Forrest GN, Standiford HC, Perencevich EN, Furuno JP, et al. Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: a randomized controlled trial. J Am Med Inform Assoc. 2006 Jul-Aug;13(4):378-84. DOI: 10.1197/jamia.M2049.
241. Pestotnik SL, Classen DC, Evans R, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: Clinical and financial outcomes. Ann Intern Med. 1996;124(10):884-90. DOI: 10.7326/0003-4819-124-10-199605150-00004.
242. Okumura LM, Veroneze I, Burgardt CI, Fragoso MF. Effects of a computerized provider order entry and a clinical decision support system to improve cefazolin use in surgical prophylaxis: A cost saving analysis. Pharm Pract. [Article]. 2016;14(3):717. DOI: 10.18549/PharmPract.2016.03.717.
243. Litvin CB, Ornstein SM, Wessell AM, Nemeth LS, Nietert PJ. Use of an electronic health record clinical decision support tool to improve antibiotic prescribing for acute respiratory infections: the ABX-TRIP study. J Gen Intern Med. 2013 Jun;28(6):810-6. DOI: 10.1007/s11606-012-2267-2.
244. Mainous AG, 3rd, Lambourne CA, Nietert PJ. Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial. J Am Med Inform Assoc. 2013 Mar-Apr;20(2):317-24. DOI: 10.1136/amiajnl-2011-000701.
245. Nault V, Pepin J, Beaudoin M, Perron J, Moutquin JM, Valiquette L. Sustained impact of a computer-assisted antimicrobial stewardship intervention on antimicrobial use and length of stay. J Antimicrob Chemother. 2017 Mar 1;72(3):933-40. DOI: 10.1093/jac/dkw468.
246. Sintchenko V, Coiera E, Gilbert GL. Decision support systems for antibiotic prescribing. Curr Opin Infect Dis. 2008 Dec;21(6):573-9.
247. Gifford J, Vaeth E, Richards K, Siddiqui T, Gill C, Wilson L, et al. Decision support during electronic prescription to stem antibiotic overuse for acute respiratory infections: a long-term, quasi-experimental study. BMC Infect Dis. 2017 Jul 31;17. DOI: 10.1186/s12879-017-2602-7.
248. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, et al. Improving antibiotic prescribing for adults with community acquired pneumonia: Does a computerised decision support system achieve more than academic detailing alone? – a time series analysis. BMC Med Inform Decis Mak. 2008;8:35. DOI: 10.1186/1472-6947-8-35.
249. Dean NC, Jones BE, Jones JP, Ferraro JP, Post HB, Aronsky D, et al. Impact of an Electronic Clinical Decision Support Tool for Emergency Department Patients With Pneumonia. Ann

Emerg Med. 2015 2015/11/01/;66(5):511-20. DOI: https://doi.org/10.1016/j.annemergmed.2015.02.003.

250. Huh K, Chung DR, Park HJ, Kim MJ, Lee NY, Ha YE, et al. Impact of monitoring surgical prophylactic antibiotics and a computerized decision support system on antimicrobial use and antimicrobial resistance. Am J Infect Control. 2016 Sep 1;44(9):e145-52. DOI: 10.1016/j.ajic.2016.01.025.

251. Sintchenko V, Iredell JR, Gilbert GL, Coiera E. Handheld computer-based decision support reduces patient length of stay and antibiotic prescribing in critical care. J Am Med Inform Assoc. 2005 Jul-Aug;12(4):398-402. DOI: 10.1197/jamia.M1798.

252. Nachtigall I, Tafelski S, Deja M, Halle E, Grebe MC, Tamarkin A, et al. Long-term effect of computer-assisted decision support for antibiotic treatment in critically ill patients: a prospective 'before/after' cohort study. BMJ Open. 2014;4(12):e005370. DOI: 10.1136/bmjopen-2014-005370.

253. Filice GA, Drekonja DM, Thurn JR, Rector TS, Hamann GM, Masoud BT, et al. Use of a Computer Decision Support System and Antimicrobial Therapy Appropriateness. Infect Control Hosp Epidemiol. 2015;34(6):558-65. DOI: 10.1086/670627.

254. Cox ZL, Nelsen CL, Waitman LR, McCoy JA, Peterson JF. Effects of clinical decision support on initial dosing and monitoring of tobramycin and amikacin. Am J Health Syst Pharm. 2011;68(7):624-32. DOI: 10.2146/ajhp100155.

255. Karsies TJ, Sargel CL, Marquardt DJ, Khan N, Hall MW. An empiric antibiotic protocol using risk stratification improves antibiotic selection and timing in critically ill children. Ann Am Thorac Soc. [Article]. 2014;11(10):1569-75. DOI: 10.1513/AnnalsATS.201408-389OC.

256. Mullett CJ, Thomas JG, Smith CL, Sarwari AR, Khakoo RA. Computerized antimicrobial decision support for hospitalized patients with a bloodstream infection. AMIA Annu Symp Proc. [Article]. 2003:946.

257. Kofoed K, Zalounina A, Andersen O, Lisby G, Paul M, Leibovici L, et al. Performance of the TREAT decision support system in an environment with a low prevalence of resistant pathogens. J Antimicrob Chemother. 2009;63(2):400-4. DOI: 10.1093/jac/dkn504.

258. Burke JP, Pestotnik SL. Antibiotic use and microbial resistance in intensive care units: impact of computer-assisted decision support. J Chemother. 1999 Dec;11(6):530-5. DOI: 10.1179/joc.1999.11.6.530.

259. Demonchy E, Dufour JC, Gaudart J, Cervetti E, Michelet P, Poussard N, et al. Impact of a computerized decision support system on compliance with guidelines on antibiotics prescribed for urinary tract infections in emergency departments: a multicentre prospective before-and-

after controlled interventional study. J Antimicrob Chemother. 2014 Oct;69(10):2857-63. DOI: 10.1093/jac/dku191.

260. Rodriguez-Maresca M, Sorlozano A, Grau M, Rodriguez-Castaño R, Ruiz-Valverde A, Gutierrez-Fernandez J. Implementation of a computerized decision support system to improve the appropriateness of antibiotic therapy using local microbiologic data. Biomed Res Int. [Article]. 2014;2014. DOI: 10.1155/2014/395434.

261. Tafelski S, Nachtigall I, Deja M, Tamarkin A, Trefzer T, Halle E, et al. Computer-Assisted Decision Support for Changing Practice in Severe Sepsis and Septic Shock. Int J Med Res. 2010;38(5):1605-16. DOI: 10.1177/147323001003800505.

262. Kilsdonk E, Peute LW, Jaspers MWM. Factors influencing implementation success of guideline-based clinical decision support systems: A systematic review and gaps analysis. Int J Med Inform. 2017 2017/02/01/;98:56-64. DOI: https://doi.org/10.1016/j.ijmedinf.2016.12.001.

263. Al Bahar F, Curtis C, Alhamad H, Marriott J. The impact of a computerised decision support system on antibiotic usage in an English hospital. Int J Clin Pharm. 2020;42(2):765-71.

264. Watson KJ, Trautner B, Russo H, Phe K, Lasco T, Pipkins T, et al. Using clinical decision support to improve urine culture diagnostic stewardship, antimicrobial stewardship, and financial cost: A multicenter experience. Infect Control Hosp Epidemiol. 2020;41(5):564-70.

265. Neugebauer M, Ebert M, Vogelmann R. A clinical decision support system improves antibiotic therapy for upper urinary tract infection in a randomized single-blinded study. BMC Health Serv Res. 2020;20(1):1-10.

266. Sugden R, Kelly R, Davies S. Combatting antimicrobial resistance globally. Nature Microbiology. [Comment]. 2016 09/27/online;1:16187. DOI: 10.1038/nmicrobiol.2016.187.

267. Freundlich RE, Wanderer JP, Ehrenfeld JM. Clinical Decision Support Tools Need to Improve More Than Just Process Outcomes. Anesthesiology. 2018;129(3):614-.

268. Jaspers MW, Smeulers M, Vermeulen H, Peute LW. Effects of clinical decision-support systems on practitioner performance and patient outcomes: a synthesis of high-quality systematic review findings. J Am Med Inform Assoc. 2011;18(3):327-34.

269. Simões A, Maia M, Gregório J, Couto I, Asfeldt A, Simonsen G, et al. Participatory implementation of an antibiotic stewardship programme supported by an innovative surveillance and clinical decision-support system. J Hosp Infect. 2018;100(3):257-64.

270. Varonen H, Kortteisto T, Kaila M, Group ES. What may help or hinder the implementation of computerized decision support systems (CDSSs): a focus group study with physicians. J Fam Pract. 2008;25(3):162-7.

271. Chow AL, Ang A, Chow CZ, Ng TM, Teng C, Ling LM, et al. Implementation hurdles of an interactive, integrated, point-of-care computerised decision support system for hospital antibiotic prescription. Int J Antimicrob Agents. 2016 Feb;47(2):132-9. DOI: 10.1016/j.ijantimicag.2015.12.006.
272. Ozkaynak M, Wu DTY, Hannah K, Dayan PS, Mistry RD. Examining Workflow in a Pediatric Emergency Department to Develop a Clinical Decision Support for an Antimicrobial Stewardship Program. Appl Clin Inform. 2018 2018/04//;9(2):248-60. DOI: 10.1055/s-0038-1641594.
273. Yusof MM, Kuljis J, Papazafeiropoulou A, Stergioulas LK. An evaluation framework for Health Information Systems: human, organization and technology-fit factors (HOT-fit). Int J Med Inform. 2008 2008/06/01/;77(6):386-98. DOI: https://doi.org/10.1016/j.ijmedinf.2007.08.011.
274. Jung SY, Hwang H, Lee K, Lee HY, Kim E, Kim M, et al. Barriers and Facilitators to Implementation of Medication Decision Support Systems in Electronic Medical Records: Mixed Methods Approach Based on Structural Equation Modeling and Qualitative Analysis. JMIR Med Inform. 2020 Jul 22;8(7):e18758. DOI: 10.2196/18758.
275. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003;15(3):261-6. DOI: 10.1093/intqhc/mzg031.
276. Abdulaziz K, Brehaut J, Taljaard M, Émond M, Sirois M-J, Lee JS, et al. National survey of physicians to determine the effect of unconditional incentives on response rates of physician postal surveys. BMJ Open. 2015;5(2):e007166. DOI: 10.1136/bmjopen-2014-007166.
277. Cunningham CT, Quan H, Hemmelgarn B, Noseworthy T, Beck CA, Dixon E, et al. Exploring physician specialist response rates to web-based surveys. BMC Medical Research Methodology. 2015 2015/04/09;15(1):32. DOI: 10.1186/s12874-015-0016-z.
278. Taylor T, Scott A. Do physicians prefer to complete online or mail surveys? Findings from a national longitudinal survey. Eval Health Prof. 2019;42(1):41-70.
279. Chung P, Scandlyn J, Dayan PS, Mistry RD. Working at the intersection of context, culture, and technology: Provider perspectives on antimicrobial stewardship in the emergency department using electronic health record clinical decision support. Am J Infect Control. 2017 Nov 1;45(11):1198-202. DOI: 10.1016/j.ajic.2017.06.005.
280. Broom J, Broom A, Plage S, Adams K, Post JJ. Barriers to uptake of antimicrobial advice in a UK hospital: a qualitative study. J Hosp Infect. 2016 Aug;93(4):418-22. DOI: 10.1016/j.jhin.2016.03.011.
281. Short D, Frischer M, Bashford J. The development and evaluation of a computerised decision support system for primary care based upon 'patient profile decision analysis'. J Innov Health

Inform. [decision analysis; decision support; patient profiles]. 2003:8. DOI: 10.14236/jhi.v11i4.567.

282. Rigopoulos G, Psarras J, Askounis D. A TAM model to evaluate user's attitude towards adoption of decision support systems. J Appl Sci. 2008;8(5):899-902.

283. Goh WP, Tao X, Zhang J, Yong J. Decision support systems for adoption in dental clinics: A survey. Knowledge-Based Systems. 2016 2016/07/15/;104:195-206. DOI: https://doi.org/10.1016/j.knosys.2016.04.022.

284. Zheng K, Padman R, Johnson MP, Diamond HS. Understanding technology adoption in clinical care: Clinician adoption behavior of a point-of-care reminder system. Int J Med Inform. 2005 2005/08/01/;74(7):535-43. DOI: https://doi.org/10.1016/j.ijmedinf.2005.03.007.

285. May L, Gudger G, Armstrong P, Brooks G, Hinds P, Bhat R, et al. Multisite exploration of clinical decision making for antibiotic use by emergency medicine providers using quantitative and qualitative methods. Infect Control Hosp Epidemiol. 2014;35(9):1114-25. DOI: 10.1086/677637.

286. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006 2006/01/01;3(2):77-101. DOI: 10.1191/1478088706qp063oa.

287. Corbin J, Strauss A. Basics of qualitative research: Techniques and procedures for developing grounded theory: Sage publications; 2014.

288. Lai F, Macmillan J, Daudelin DH, Kent DM. The Potential of Training to Increase Acceptance and Use of Computerized Decision Support Systems for Medical Diagnosis. Hum Factors. 2006 2006/03/01;48(1):95-108. DOI: 10.1518/001872006776412306.

289. Trivedi MH, Kern J, Marcee A, Grannemann B, Kleiber B, Bettinger T, et al. Development and implementation of computerized clinical guidelines: barriers and solutions. Methods Inf Med. 2002;41(05):435-42.

290. Tsiknakis M, Kouroubali A. Organizational factors affecting successful adoption of innovative eHealth services: a case study employing the FITT framework. Int J Med Inform. 2009 Jan;78(1):39-52. DOI: 10.1016/j.ijmedinf.2008.07.001.

291. Chan T, Brew S. Overcoming the barriers to using information systems. Nursing times. 2004;100(49):44-6.

292. Delone WH, Mclean ER. Measuring e-commerce success: Applying the DeLone & McLean information systems success model. International Journal of electronic commerce. 2004;9(1):31-47.

293. Lugtenberg M, Pasveer D, van der Weijden T, Westert GP, Kool RB. Exposure to and experiences with a computerized decision support intervention in primary care: results from a

process evaluation. BMC Fam Pract. 2015 2015/10/16;16(1):141. DOI: 10.1186/s12875-015-0364-0.

294. Lugtenberg M, Weenink J-W, van der Weijden T, Westert GP, Kool RB. Implementation of multiple-domain covering computerized decision support systems in primary care: a focus group study on perceived barriers. BMC Med Inform Decis Mak. 2015 2015/10/12;15(1):82. DOI: 10.1186/s12911-015-0205-z.

295. Khairat S, Marc D, Crosby W, Al Sanousi A. Reasons For Physicians Not Adopting Clinical Decision Support Systems: Critical Analysis. JMIR Med Inform. [Review]. 2018;6(2):e24. DOI: 10.2196/medinform.8912.

296. Shibl R, Lawley M, Debuse J. Factors influencing decision support system acceptance. Decis Support Syst. 2013 2013/01/01/;54(2):953-61. DOI: https://doi.org/10.1016/j.dss.2012.09.018.

297. Goud R, van Engen-Verheul M, de Keizer NF, Bal R, Hasman A, Hellemans IM, et al. The effect of computerized decision support on barriers to guideline implementation: A qualitative study in outpatient cardiac rehabilitation. International Journal of Medical Informatics. 2010 2010/06/01/;79(6):430-7. DOI: https://doi.org/10.1016/j.ijmedinf.2010.03.001.

298. Leslie SJ, Hartswood M, Meurig C, McKee SP, Slack R, Procter R, et al. Clinical decision support software for management of chronic heart failure: Development and evaluation. Comput Biol Med. 2006 2006/05/01/;36(5):495-506. DOI: https://doi.org/10.1016/j.compbiomed.2005.02.002.

299. Hor CP, O'Donnell JM, Murphy AW, O'Brien T, Kropmans TJB. General practitioners' attitudes and preparedness towards Clinical Decision Support in e-Prescribing (CDS-eP) adoption in the West of Ireland: a cross sectional study. BMC medical informatics and decision making. 2010;10:2-. DOI: 10.1186/1472-6947-10-2.

300. Afonso CM, Roldán Salgueiro JL, Sánchez Franco MJ, González MdlO. The moderator role of Gender in the Unified Theory of Acceptance and Use of Technology (UTAUT): A study on users of Electronic Document Management Systems. 2012.

301. Zuiderwijk A, Janssen M, Dwivedi YK. Acceptance and use predictors of open data technologies: Drawing upon the unified theory of acceptance and use of technology. Government information quarterly. 2015;32(4):429-40.

302. Bandyopadhyay K, Barnes C. An analysis of factors affecting user acceptance of ERP Systems in the United States. Int J Hum Cap Inf Technol Prof. 2012;3(1):1-14.

303. Jacob C, Sanchez-Vazquez A, Ivory C. Clinicians' role in the adoption of an oncology decision support app in Europe and its implications for organizational practices: qualitative case study. JMIR mHealth and uHealth. 2019;7(5):e13555.

304. Cho YI, Johnson TP, VanGeest JB. Enhancing Surveys of Health Care Professionals: A Meta-Analysis of Techniques to Improve Response. Eval Health Prof. 2013 2013/09/01;36(3):382-407. DOI: 10.1177/0163278713496425.
305. Joyce CM, Scott A, Jeon S-H, Humphreys J, Kalb G, Witt J, et al. The" Medicine in Australia: Balancing Employment and Life (MABEL)" longitudinal survey-Protocol and baseline data for a prospective cohort study of Australian doctors' workforce participation. BMC Health Serv Res. 2010;10(1):50.
306. Machowska A, Stålsby Lundborg C. Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health. 2019;16(1):27.
307. Hardy-Holbrook R, Aristidi S, Chandnani V, DeWindt D, Dinh K. Antibiotic resistance and prescribing in Australia: current attitudes and practice of GPs. Healthc infect. 2013;18(4):147-51.
308. Morse J, Blackburn L, Hannam JA, Voss L, Anderson BJ. Compliance with perioperative prophylaxis guidelines and the use of novel outcome measures. Paediatr Anaesth. 2018 Aug;28(8):686-93. DOI: 10.1111/pan.13428.
309. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and Strategies in Guideline Implementation—A Scoping Review. Healthcare. 2016;4(3):36. DOI: 10.3390/healthcare4030036.
310. Schwartz KL, Brown KA, Etches J, Langford BJ, Daneman N, Tu K, et al. Predictors and variability of antibiotic prescribing amongst family physicians. J Antimicrob Chemother. 2019 Jul 1;74(7):2098-105. DOI: 10.1093/jac/dkz112.
311. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, et al. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". Clin Infect Dis. 2013;57(2):188-96. DOI: 10.1093/cid/cit212.
312. Manne M, Deshpande A, Hu B, Patel A, Taksler GB, Misra-Hebert AD, et al. Provider Variation in Antibiotic Prescribing and Outcomes of Respiratory Tract Infections. South Med J. 2018 Apr;111(4):235-42. DOI: 10.14423/smj.0000000000000795.
313. Nowakowska M, van Staa T, Mölter A, Ashcroft DM, Tsang JY, White A, et al. Antibiotic choice in UK general practice: rates and drivers of potentially inappropriate antibiotic prescribing. J Antimicrob Chemother. 2019 Nov 1;74(11):3371-8. DOI: 10.1093/jac/dkz345.
314. Teixeira Rodrigues A, Roque F, Falcão A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. Int J Antimicrob Agents. 2013;41(3):203-12. DOI: 10.1016/j.ijantimicag.2012.09.003.

315. Dempsey PP, Businger AC, Whaley LE, Gagne JJ, Linder JA. Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. BMC Fam Pract. [journal article]. 2014 December 12;15(1):194. DOI: 10.1186/s12875-014-0194-5.
316. Neuendorf KA, Kumar A. Content analysis. The international encyclopedia of political communication. 2015:1-10.
317. Md Rezal RS, Hassali MA, Alrasheedy AA, Saleem F, Md Yusof FA, Godman B. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. Expert Rev Anti Infect Ther. 2015;13(5):665-80. DOI: 10.1586/14787210.2015.1025057.
318. Jeffs L, McIsaac W, Zahradnik M, Senthinathan A, Dresser L, McIntyre M, et al. Barriers and facilitators to the uptake of an antimicrobial stewardship program in primary care: A qualitative study. PloS one. 2020;15(3):e0223822-e. DOI: 10.1371/journal.pone.0223822.
319. Lum EPM, Page K, Whitty JA, Doust J, Graves N. Antibiotic prescribing in primary healthcare: Dominant factors and trade-offs in decision-making. Infect Dis Health. 2018;23(2):74-86. DOI: 10.1016/j.idh.2017.12.002.
320. Australian Commission on Safety and Quality in Health Care. AURA 2017- Second Australian report on antimicrobial use and resistance in human health. Sydney; 2017.
321. Pinder R, Berry D, Sallis A, Chadborn T. Behaviour change and antibiotic prescribing in healthcare settings: Literature review and behavioural analysis2015.
322. Mangione-Smith R, McGlynn EA, Elliott MN, McDonald L, Franz CE, Kravitz RL. Parent expectations for antibiotics, physician-parent communication, and satisfaction. Arch Pediatr Adolesc Med. 2001;155(7):800-6. DOI: 10.1001/archpedi.155.7.800.
323. Rose J, Crosbie M, Stewart A. A qualitative literature review exploring the drivers influencing antibiotic over-prescribing by GPs in primary care and recommendations to reduce unnecessary prescribing. Perspect Public Health. 2019:1757913919879183.
324. kianmehr H, Sabounchi NS, Seyedzadeh Sabounchi S, Cosler LE. Patient expectation trends on receiving antibiotic prescriptions for respiratory tract infections: A systematic review and meta-regression analysis. Int J Clin Pract. 2019;73(7):e13360. DOI: 10.1111/ijcp.13360.
325. Papoutsi C, Mattick K, Pearson M, Brennan N, Briscoe S, Wong G. Social and professional influences on antimicrobial prescribing for doctors-in-training: a realist review. J Antimicrob Chemother. 2017;72(9):2418-30. DOI: 10.1093/jac/dkx194.
326. Carlsen B, Glenton C, Pope C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. Br J Gen Pract. 2007;57(545):971-8.

327. Rodrigues AT, Roque F, Falcão A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. Int J Antimicrob Agents. 2013;41(3):203-12.
328. Simpkin AL, Schwartzstein RM. Tolerating uncertainty—the next medical revolution? New Eng J Med. 2016;375(18).
329. van Esch TE, Brabers AE, Hek K, van Dijk L, Verheij RA, de Jong JD. Does shared decision-making reduce antibiotic prescribing in primary care? J Antimicrob Chemother. 2018;73(11):3199-205.
330. Desveaux L, Shaw J, Wallace R, Bhattacharyya O, Bhatia RS, Jamieson T. Examining tensions that affect the evaluation of technology in health care: considerations for system decision makers from the perspective of industry and evaluators. JMIR Med Inform. 2017;5(4):e50.
331. Kelley LT, Fujioka J, Liang K, Cooper M, Jamieson T, Desveaux L. Barriers to Creating Scalable Business Models for Digital Health Innovation in Public Systems: Qualitative Case Study. JMIR Public Health Surveill. 2020;6(4):e20579.
332. Agrawal A. Bridging digital health divides. Science. 2020;369(6507):1050-2.
333. Evans RS. Electronic Health Records: Then, Now, and in the Future. Yearb Med Inform. 2016;Suppl 1(Suppl 1):S48-S61. DOI: 10.15265/IYS-2016-s006.
334. Fernandes M, Vieira SM, Leite F, Palos C, Finkelstein S, Sousa JMC. Clinical Decision Support Systems for Triage in the Emergency Department using Intelligent Systems: a Review. Artif Intell Med. 2020 Jan;102:101762. DOI: 10.1016/j.artmed.2019.101762.
335. Pearce R, Whyte I. Electronic medication management: is it a silver bullet? Aust Prescr. 2018;41(2):32-3. DOI: 10.18773/austprescr.2018.012.
336. Desveaux L, Soobiah C, Bhatia RS, Shaw J. Identifying and overcoming policy-level barriers to the implementation of digital health innovation: qualitative study. J Med Internet Res. 2019;21(12):e14994.
337. Andargoli AE. e-Health in Australia: A synthesis of thirty years of e-Health initiatives. Telemat Inform. 2021 2021/01/01/;56:101478. DOI: https://doi.org/10.1016/j.tele.2020.101478.
338. Andargoli AE. My Health Record Adoption and Utilisation Behaviour in Australia: Swinburne University of Technology, Australia; 2018.
339. Kraus S, Schiavone F, Pluzhnikova A, Invernizzi AC. Digital transformation in healthcare: Analyzing the current state-of-research. J Bus Res. 2021;123:557-67.
340. Morgan DL. Pragmatism as a paradigm for social research. Qual Inq. 2014;20(8):1045-53.

341. Hermes S, Riasanow T, Clemons EK, Böhm M, Krcmar H. The digital transformation of the healthcare industry: exploring the rise of emerging platform ecosystems and their influence on the role of patients. J Bus Res. 2020;13(3):1033-69.
342. Zikos D, DeLellis N. CDSS-RM: a clinical decision support system reference model. BMC Med Res Methodol. 2018;18(1):1-14.
343. Patton MQ. Qualitative research & evaluation methods: Integrating theory and practice: Sage publications; 2014.
344. Fox J, Glasspool D, Patkar V, Austin M, Black L, South M, et al. Delivering clinical decision support services: There is nothing as practical as a good theory. J Biomed Inform. 2010 2010/10/01/;43(5):831-43. DOI: https://doi.org/10.1016/j.jbi.2010.06.002.
345. Australian Health Ministers' Conference. National e-Health Strategy: Summary. 2008.
346. Dopp AR, Parisi KE, Munson SA, Lyon AR. Aligning implementation and user-centered design strategies to enhance the impact of health services: results from a concept mapping study. Implement Sci. 2020 2020/02/26;1(1):17. DOI: 10.1186/s43058-020-00020-w.
347. British Standard. ISO 9241-210: 2010-Ergonomics of human-system interaction-Part 210: Human-centred design for interactive systems. Geneva, Switzerland. 2010:27.
348. Medlock S, Wyatt JC, Patel VL, Shortliffe EH, Abu-Hanna A. Modeling information flows in clinical decision support: key insights for enhancing system effectiveness. J Am Med Inform Assoc. 2016;23(5):1001-6. DOI: 10.1093/jamia/ocv177.
349. Marcos M, Maldonado JA, Martínez-Salvador B, Boscá D, Robles M. Interoperability of clinical decision-support systems and electronic health records using archetypes: a case study in clinical trial eligibility. J Biomed Inform. 2013;46(4):676-89.
350. Kierkegaard P. Interoperability after deployment: persistent challenges and regional strategies in Denmark. Int J Qual Health Care. 2015;27(2):147-53.
351. Posnack S. Connecting health and care for the nation: a shared nationwide interoperability roadmap. 2015.
352. Wulff A, Haarbrandt B, Tute E, Marschollek M, Beerbaum P, Jack T. An interoperable clinical decision-support system for early detection of SIRS in pediatric intensive care using openEHR. Artif Intell Med. 2018 2018/07/01/;89:10-23. DOI: https://doi.org/10.1016/j.artmed.2018.04.012.
353. Mishuris RG, Palmisano J, McCullagh L, Hess R, Feldstein DA, Smith PD, et al. Using normalisation process theory to understand workflow implications of decision support implementation across diverse primary care settings. BMJ Health Care Inform. 2019;26(1):e100088.

354. Pope C, Halford S, Turnbull J, Prichard J, Calestani M, May C. Using computer decision support systems in NHS emergency and urgent care: ethnographic study using normalisation process theory. BMC Health Serv Res. 2013;13(1):1-13.
355. Olakotan OO, Mohd Yusof M. The appropriateness of clinical decision support systems alerts in supporting clinical workflows: A systematic review. Health Informatics J. 2021;27(2):14604582211007536.
356. Arts DL, Medlock SK, van Weert HCPM, Wyatt JC, Abu-Hanna A. Acceptance and barriers pertaining to a general practice decision support system for multiple clinical conditions: A mixed methods evaluation. PLOS ONE. 2018;13(4):e0193187. DOI: 10.1371/journal.pone.0193187.
357. Légat L, Van Laere S, Nyssen M, Steurbaut S, Dupont AG, Cornu P. Clinical Decision Support Systems for Drug Allergy Checking: Systematic Review. J Med Internet Res. [Review]. 2018;20(9):e258. DOI: 10.2196/jmir.8206.
358. Peiffer-Smadja N, Rawson TM, Ahmad R, Buchard A, Georgiou P, Lescure F-X, et al. Machine learning for clinical decision support in infectious diseases: a narrative review of current applications. Clin Microbiol Infect. 2020;26(5):584-95.
359. Horng S, Sontag DA, Halpern Y, Jernite Y, Shapiro NI, Nathanson LA. Creating an automated trigger for sepsis clinical decision support at emergency department triage using machine learning. PloS one. 2017;12(4):e0174708.
360. Lee EK, Wu TL, Senior T, Jose J. Medical alert management: a real-time adaptive decision support tool to reduce alert fatigue. AMIA Annu Symp Proc. 2014;2014:845-54.
361. Aljarboa S, Miah SJ. Assessing the acceptance of clinical decision support tools using an integrated technology acceptance model. In: 2020 IEEE Asia-Pacific Conference on Computer Science and Data Engineering (CSDE). 2020: IEEE; p. 1-6.
362. Sambasivan M, Esmaeilzadeh P, Kumar N, Nezakati H. Intention to adopt clinical decision support systems in a developing country: effect of Physician's perceived professional autonomy, involvement and belief: a cross-sectional study. BMC Med Inform Decis Mak. 2012 2012/12/05;12(1):142. DOI: 10.1186/1472-6947-12-142.
363. Wang X. Towards Better Interpretability of Machine Learning-Based Decision Support Systems: State University of New York at Buffalo; 2020.
364. Amann J, Blasimme A, Vayena E, Frey D, Madai VI. Explainability for artificial intelligence in healthcare: a multidisciplinary perspective. BMC Med Inform Decis Mak. 2020;20(1):1-9.
365. Zihni E, Madai VI, Livne M, Galinovic I, Khalil AA, Fiebach JB, et al. Opening the black box of artificial intelligence for clinical decision support: A study predicting stroke outcome. Plos one. 2020;15(4):e0231166.

366. O'Sullivan D, Fraccaro P, Carson E, Weller P. Decision time for clinical decision support systems. Clin Med (Lond). 2014;14(4):338-41. DOI: 10.7861/clinmedicine.14-4-338.
367. Fox J, Thomson R. Clinical decision support systems: a discussion of quality, safety and legal liability issues. In: AMIA Annu Symp Proc. 2002: American Medical Informatics Association; p. 265.
368. Challen R, Denny J, Pitt M, Gompels L, Edwards T, Tsaneva-Atanasova K. Artificial intelligence, bias and clinical safety. BMJ Qual Saf. 2019;28(3):231-7.
369. Trivedi MH, Daly EJ, Kern JK, Grannemann BD, Sunderajan P, Claassen CA. Barriers to implementation of a computerized decision support system for depression: an observational report on lessons learned in "real world" clinical settings. BMC Med Inform Decis Mak. 2009 2009/01/21;9(1):6. DOI: 10.1186/1472-6947-9-6.
370. Neter E, Brainin E. eHealth Literacy: Extending the Digital Divide to the Realm of Health Information. J Med Internet Res. [Original Paper]. 2012;14(1):e19. DOI: 10.2196/jmir.1619.
371. Duckett S, Willcox S. The Australian health care system: Oxford University Press; 2015.
372. Kemp E, Trigg J, Beatty L, Christensen C, Dhillon HM, Maeder A, et al. Health literacy, digital health literacy and the implementation of digital health technologies in cancer care: the need for a strategic approach. Health Promot J Austr. 2021;32:104-14.
373. Shaw J, Agarwal P, Desveaux L, Palma DC, Stamenova V, Jamieson T, et al. Beyond "implementation": digital health innovation and service design. npj Digital Medicine. 2018 2018/09/20;1(1):48. DOI: 10.1038/s41746-018-0059-8.
374. Jung SY, Hwang H, Lee K, Lee H-Y, Kim E, Kim M, et al. Barriers and facilitators to implementation of medication decision support systems in electronic medical records: Mixed methods approach based on structural equation modeling and qualitative analysis. JMIR Med Inform. 2020;8(7):e18758.
375. Kostkova P. Grand challenges in digital health. Public Health Front. 2015;3:134.
376. Fortuna KL, Brooks JM, Umucu E, Walker R, Chow PI. Peer support: A human factor to enhance engagement in digital health behavior change interventions. J Technol Behav Sci. 2019;4(2):152-61.
377. Campbell RJ. The five rights of clinical decision support: CDS tools helpful for meeting meaningful use. J AHIMA. 2013;84(10):42-7 (web version updated February 2016).
378. Australian Digital Health Agency. National Digital Health Workforce and Education Roadmap. Sydney, NSW: Australian Government; 2020.
379. O'Connor SM. Exploring eHealth implementation: understanding factors affecting engagement and enrolment in consumer digital health: University of Glasgow; 2020.

380. Shaw T, Hines M, Kielly-Carroll C. Impact of digital health on the safety and quality of health care. 2018.
381. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. Int J Qual Health Care. 2003;15(suppl_1):i49-i59. DOI: 10.1093/intqhc/mzg085.
382. Moghavvemi S, Salleh NAM, Sulaiman A, Abessi M. Effect of external factors on intention–behaviour gap. Behav Inf Technol. 2015;34(12):1171-85.
383. Bhattacherjee A, Sanford C. The intention–behaviour gap in technology usage: the moderating role of attitude strength. Behav Inf Technol. 2009;28(4):389-401.
384. Taylor S, Todd PA. Understanding information technology usage: A test of competing models. Information systems research. 1995;6(2):144-76.
385. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field methods. 2006;18(1):59-82.
386. Chung P, Scandlyn J, Dayan PS, Mistry RD. Working at the intersection of context, culture, and technology: Provider perspectives on antimicrobial stewardship in the emergency department using electronic health record clinical decision support. American Journal of Infection Control. 2017 2017/11/01/;45(11):1198-202. DOI: https://doi.org/10.1016/j.ajic.2017.06.005.
387. Short D, Frischer M, Bashford J. Barriers to the adoption of computerised decision support systems in general practice consultations: a qualitative study of GPs' perspectives. International Journal of Medical Informatics. 2004 2004/05/01/;73(4):357-62. DOI: https://doi.org/10.1016/j.ijmedinf.2004.02.001.