Evaluation of an antimicrobial stewardship program in an Australian tertiary paediatric hospital

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Certificate of Original Authorship

I, Mona Mostaghim declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health - Discipline of Pharmacy at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Abbreviations

ACSQHC	Australian Commission on Safety and Quality in Health Care
ADE	Adverse drug event
ADR	Adverse drug reaction
AMH-CDC	Australian Medicines Handbook-Children's Dosing Companion
AMS	Antimicrobial stewardship
AMR	Antimicrobial resistance
ANZPID	Australia New Zealand Paediatric Infectious Diseases Society-Antimicrobial Stewardship Interest Group
APR-DRG	All Patient Refined Diagnosis-Related Group
ARPEC	Antimicrobial resistance and prescribing in European children
ATC	World Health Organization Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical classification
AURA	Antimicrobial Use and Resistance in Australia
BNF	British National Formulary
BSA	Body Surface Area
BSI	Blood stream infection
CAP	Community-acquired pneumonia
CEC	Clinical Excellence Commission
CDC	United States Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CDSS	Computerised decision support and approval system, computerised clinical decision support system, computerised antimicrobial approval and decision support system
CICU	Children's intensive care unit
CPOE	Computerised prescriber order entry
DDD	Defined daily dose
DOT	Days of therapy
DTC	Drug and Therapeutics Committee
ED	Emergency Department
EMR	Electronic medical records
ESBL	Extended-spectrum beta-lactamase producing bacteria
FN	Febrile neutropenia
FTE	Full time equivalent

g	Grams
HO	Hospital-onset or hospital acquired
HSCT	Haemopoietic stem cell transplant
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems Australian Modification 10th Revision
ICU	Intensive Care Unit
ID	Infectious Diseases
IDSA	Infectious Diseases Society of America
IT	Information Technology
IV	Intravenous
JMO	Junior medical officer
LHD	Local health district
LOS	Length of stay
LOT	Length of antimicrobial therapy
MRO	Multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
NAPS	National antimicrobial prescribing survey
NIMC	National In-patient Medication Chart
NSQHS	National Safety and Quality Health Service
NICU	Neonatal intensive care unit
NSW	New South Wales
NWAU	National weighted activity unit
OBD	Occupied bed-day
OR	Odds ratio
PD	Patient bed-days
PICU	Paediatric intensive care unit
PBS	Pharmaceutical Benefits Scheme
PPS	Point Prevalence Survey
QI	Quality improvement
SS	Specific Syndrome
SSTI	Skin and soft tissue infection
TDM	Therapeutic Drug Monitoring
TGA	Therapeutic Goods Administration
WHO	World Health Organization
5x5	The 5x5 Antimicrobial Audit

Original Peer-Reviewed Manuscripts Generated Through This PhD Research

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Candidate designed the study and survey, collected the data, performed statistical analysis and wrote the manuscript. Beata V. Bajorek and Tom Snelling supervised the study design, data analysis and critically revised the manuscript. Pamela Konecny, Stuart Bond, Suman Adhikari, Adriana Chubaty and Cathy Lovell reviewed the survey design, facilitated data collection and critically revised the manuscript.

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Candidate was the primary author, wrote and organised manuscript. Beata V. Bajorek and Tom Snelling contributed to the idea, manuscript drafting and critical review of the manuscript.

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Candidate was the primary author, collected and analysed the data, wrote and organised manuscript. Beata V. Bajorek and Tom Snelling contributed to the idea, manuscript drafting and critical review of the manuscript. Yean Ewe assisted in data collection and reviewed the manuscript. Brendan McMullan critically reviewed the manuscript.

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M. Mostaghim, T. Snelling, H. Katf, B. V. Bajorek. “Paediatric antimicrobial stewardship and safe prescribing - an assessment of medical staff knowledge and behaviour.” *Pharmacy Practice* (Chapter 3, Section 3.1)

Candidate was the primary author, designed the survey, collected and analysed the data, wrote and organised manuscript. Beata V. Bajorek and Tom Snelling contributed to the idea, manuscript drafting and critical review of the manuscript. Hala Katf reviewed the survey and critically reviewed the manuscript.

M. Mostaghim, T. Snelling, B. V. Bajorek. “Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data.” (Chapter 4, Section 4.1)

Candidate was the primary author, collected and analysed the data, wrote and organised manuscript. Beata V. Bajorek and Tom Snelling contributed to the idea, manuscript drafting and critical review of the manuscript.

M. Mostaghim, T. Snelling, B. V. Bajorek. “Impact of computerised decision support on antibiotic utilisation trends in a Paediatric Intensive Care Unit.” (Chapter 4, Section 4.2)

Candidate was the primary author, collected and analysed the data, wrote and organised manuscript. Beata V. Bajorek and Tom Snelling contributed to the idea, manuscript drafting and critical review of the manuscript.

Other related peer-reviewed publications

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S. E. Bond, A. J. Chubaty, S. Adhikari, S. Miyakis, C. S. Boutlis, W. W. Yeo, M. J. Batterham, C. Dickson, B. J. McMullan, **M. Mostaghim,** S. Li-Yan Hui, K. R. Clezy, and P. Konecny, "Outcomes of multisite antimicrobial stewardship programme implementation with a shared clinical decision support system," *Journal of Antimicrobial Chemotherapy.*, vol. 72, no. 7, pp. 1–9, 2017.

Research presentations

Oral Presentations:

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M. Mostaghim. ‘Paediatric Antimicrobial Stewardship Programs’, National Centre for Antimicrobial Stewardship Seminar, July 2015, Melbourne, Australia

M. Mostaghim, T. Snelling, B.V. Bajorek. ‘Implementation of a Hospital Paediatric Antimicrobial Stewardship Program’, Western Australia Committee for Antimicrobials Symposium, June 2014, Perth, Australia.

M. Mostaghim, T. Snelling, B. McMullan, B.V. Bajorek. ‘Implementation of a Hospital Paediatric Antimicrobial Stewardship Program’, National Medicines Symposium, May 2014, Brisbane, Australia.

Poster Presentations:

M. Mostaghim, T. Snelling, B. McMullan, Y.H. Ewe, B.V. Bajorek. Impact of clinical decision support on empiric antibiotic prescribing for children with community-acquired pneumonia. New Horizons Conference, November 2017, Sydney, Australia.

M. Mostaghim, T. Snelling, B. McMullan, P. Palasanthiran, B.V. Bajorek. ‘Paediatric Antimicrobial Stewardship Programs: Driving Standardisation and Improved Clinical Evaluation’, New Horizons Conference, November 2015, Sydney, Australia.

Abstract

Background: The rise of antimicrobial resistance has been described as a threat to human health. Judicious use of antimicrobials, through antimicrobial stewardship (AMS) is a key component of the World Health Organization's Global action plan on antimicrobial resistance. AMS programs involve multiple strategies to ensure optimal antimicrobial selection, dosage, route of administration and duration of therapy to maximise the benefit of antimicrobials, whilst minimising the associated collateral damage. Although AMS has been a requirement for hospital accreditation in Australia since 2013 implementation and evaluation of AMS in Australian tertiary paediatric hospitals has been limited by the complexities in the patient population, and the local infrastructure and resources.

Aim: Evaluate an AMS program in an Australian tertiary paediatric hospital

Methods: The Centers for Disease Control and Prevention core elements of AMS for hospitals provided a framework for six studies, two studies focused on the use of the local computerised decision support and approval system (CDSS). The CDSS was assessed as an intervention to reduce inappropriate broad-spectrum antibiotic use for community-acquired pneumonia, compliance with the CDSS and its utility as a tracking tool were explored in a second study. Educational needs of nursing and non-consultant medical staff were determined using two different survey approaches. Candidate units of measure for antimicrobial surveillance were

developed and used to evaluate the impact of AMS in the paediatric intensive care setting in a quasi-experimental design study.

Results: Children with suspected uncomplicated community-acquired pneumonia were predominantly prescribed guideline-concordant narrow-spectrum penicillins at admission to hospital both before and after CDSS implementation. CDSS use was uncommon after standard pharmacy and AMS working hours, with ongoing implications for AMS involvement the next standard working day. Broad-spectrum antibiotics, potentially suitable for long term trend analysis were identified. Both standard adult defined daily doses and vial-based estimates did not identify an association between implementation of the CDSS and a reduction in restricted antibiotic use.

CHAPTER ONE

INTRODUCTION

1 GENERAL INTRODUCTION

1.1 Antimicrobial Use and Resistance

Antimicrobials have been called a miracle of modern medicine due to their critical role in preventing and treating infections, thereby supporting advancements in other fields of medicine and surgery.(1) However, antimicrobials are rapidly losing their effectiveness, largely due to increasing evidence of the development of resistance by microbes to these agents, posing a risk to global health security.(2) Antimicrobial resistance (AMR) is therefore cited to be “an urgent global health priority”, with the World Health Organization (WHO) describing it as a looming crisis in which common and treatable infections are becoming life threatening.(2) This has promoted the development of the Australian Government’s National Antimicrobial Resistance Strategy 2015-2019, which guides action aiming to reduce AMR in Australia, and which recognises that AMR is a “One Health” problem, i.e., it affects human health, animal health, agriculture, food, and the environment.(3)

A case in point regarding the development of AMR is that, in Australia, an estimated 10.7% of *Staphylococcus aureus* infections (*S. aureus* being a common pathogen associated with skin and soft tissue infections) are methicillin-resistant leading to a treatment-resistant infection, i.e., methicillin-resistant *Staphylococcus aureus* (MRSA).(4) In some parts of the United States, MRSA is the most common cause of skin or soft tissue infection that is diagnosed in hospital emergency departments, reflecting

widespread community-acquired MRSA.(5) Gram-negative resistant bacteria are a major concern in hospitals globally, as even those agents which have been reserved as “last-line” treatments, e.g., carbapenem and fluoroquinolone antibiotics, are no longer effective.(6)

The rising incidence of resistant bacteria, in not only hospitals but also in the community, coupled with a stagnant pipeline of new treatment options, has made AMR one of the greatest threats to human health.(2) Compared to treatment-susceptible organisms, infections caused by treatment-resistant organisms are associated with higher rates of mortality and longer hospitalisations, often requiring treatment with antimicrobial agents that possess greater individual and ecological side-effects as well as increased demands on healthcare systems (e.g., increased resources in administration and monitoring of these agents).(7)

It is widely understood that antimicrobial use and misuse increases selective pressure, and is one of the key drivers of AMR (Figure 1.1).(8) Misuse of antimicrobials largely comprises inappropriate use for the treatment of infections where the agent is not biologically active (e.g., using antibacterial agents for viral infections, using antimicrobials unnecessarily for mild, self-limiting infections such as the common cold, influenza, or otitis media) and/or using agents at suboptimal doses or for incorrect duration of time. Despite this understanding, antimicrobials remain among the most frequently dispensed medications under the Australian Pharmaceutical

Benefits Scheme (PBS).(9) In 2015, 44.7% of Australians received a prescription for an antimicrobial listed on the PBS, with higher than average rates of use among infants and children under 4 years of age (51%).(4) In the hospital setting, by 2012 estimates, 46% of hospitalised children nationally were prescribed at least one antimicrobial. The highest rates of inpatient antimicrobial use in paediatric hospitals was observed in paediatric intensive care units and in patients with malignancy (55 and 76% respectively).(10)

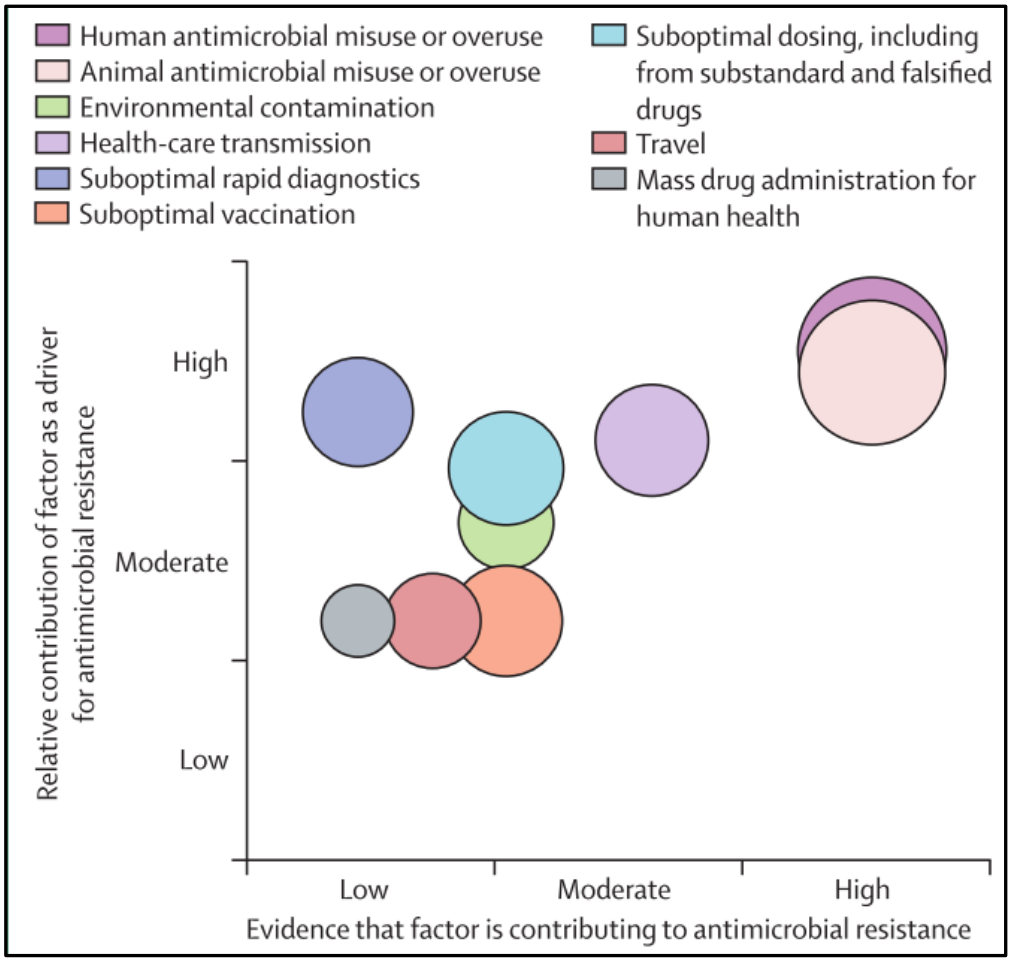

Figure 1.1 Role of modifiable drivers for antimicrobial resistance: a conceptual framework. Reprinted from The Lancet, Vol. 387 (10014), A. Holmes, Understanding the mechanisms and drivers of antimicrobial resistance, p180, Copyright 2016, with permission from Elsevier

1.2 Adverse and Unintended Consequences of Antimicrobial Use

Antimicrobials are not benign agents. Aside from AMR, antimicrobial use exposes patients to potential adverse outcomes such as side-effects, allergic reactions, and opportunistic infections (e.g., *Clostridium difficile* infection – CDI) which must be balanced against the potential benefits of therapy.(11) When used unnecessarily and/or inappropriately, antimicrobial use exposes patients to increased risk of harm without any clinical benefit.

1.2.1 Clostridium difficile

In recent years, symptomatic CDI has emerged as the most common healthcare-acquired infection among adults, and the most important cause of healthcare-associated diarrhoea in the United States.(12) Disruption of the normal colonic flora through repeated or lengthy exposure, and use of broad spectrum agents (e.g., third generation cephalosporins, fluoroquinolones, lincosamides) are among the key, albeit modifiable, risk factors for developing CDI, making it an important target for patient safety.(13) Among those at greatest risk of CDI are patients with comorbidities such as malignancy, prior solid organ transplant, inflammatory bowel disease and children with feeding tubes. Much like AMR, CDI is no longer limited to dedicated healthcare settings (e.g., hospitals) and is increasingly observed in the community.(14) The burden of CDI on both healthcare systems and individuals is substantial as CDI increases length of stay in hospital and health care costs. Most importantly,

CDI increases the risk of mortality (15), posing an immediate threat to patient safety.(13)

1.2.2 Inappropriate and Unnecessary Use

Suboptimal antimicrobial selection, dosage, route of administration, duration of treatment, as well as failure to perform the necessary diagnostic microbiological tests and/or therapeutic monitoring (i.e., patient response, measurement of drug serum levels) can result in ineffective treatment or prevention of infection, and/or lead to treatment-related toxicity.(16)

1.3 Antimicrobial Stewardship

In response to the rising threat of a “post-antibiotic” era, the WHO has called for stewardship of antimicrobial use (i.e., antimicrobial stewardship, AMS) in humans and animals as one of five strategic objectives that aim to retain the effectiveness of antimicrobials; these five strategies are cited as being:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimise the use of antimicrobial agents; and
- develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.(2)

In addition to minimising selective pressure, AMS programs aim to improve patient outcomes, minimise adverse events and reduce the healthcare costs associated with these outcomes.(17) AMS comprises *"coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration*".(18)

Since the term antimicrobial stewardship was first coined in 1997, AMS has predominantly taken the form of a structured program within a hospital setting. In 2007, when the first comprehensive AMS guidelines were published there was limited published evidence and examples of AMS for children, neonates and complex patients, and programs were still focused on hospital antimicrobial use.(17) AMS strategies are increasingly practiced in special populations of hospitalised patients, in emergency departments, and community setting such as general practice and nursing homes.(19,20)

1.3.1 CDC Core Elements of hospital AMS programs

There is no single method by which to optimise antimicrobial use, therefore, AMS strategies and priorities are highly adaptable, such that the strategies employed are determined by local resources available, clinical complexity of patients and organisational culture.(17) Allowing for this variation, the United States Centres for Disease Control and Prevention (CDC) outlines

seven core elements associated with effective stewardship that provide a framework for AMS in all hospitals across the United States (Figure 1.2).(21) Whilst there are local differences between healthcare systems internationally, the CDC elements are consistent with European and Australian recommendations for AMS in hospitals. (23,23) The first three elements, commitment, leadership and accountability focus on the structure of the AMS program, highlight the need for expertise, leadership support and multidisciplinary engagement and willingness to perform AMS related tasks (Table 1.1).

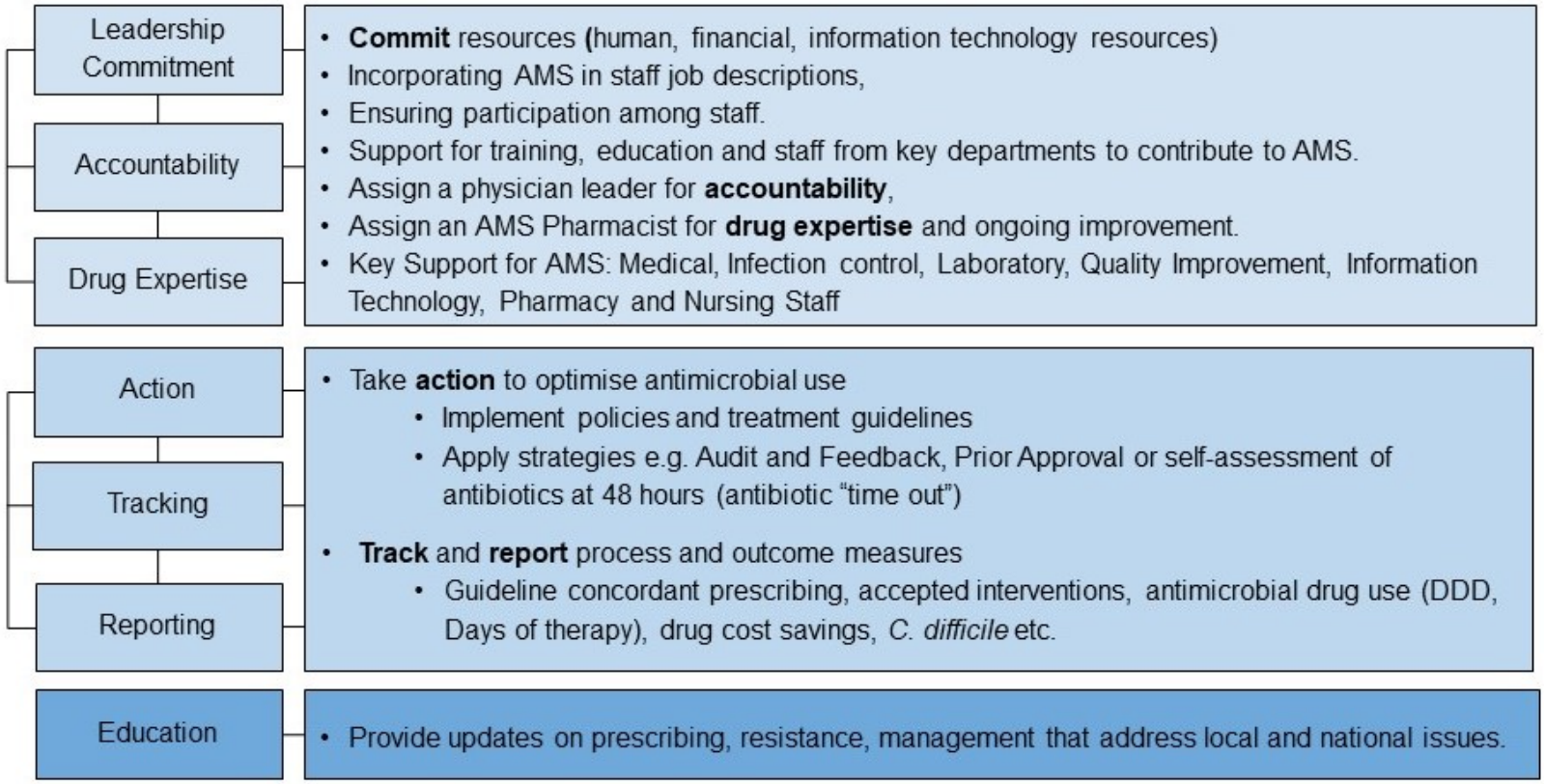

Figure 1.2 Core Elements of Antimicrobial Stewardship Programs. Adapted from Centers for Disease Control and Prevention (2014). Core Elements of Hospital Antibiotic Stewardship Programs. US Department of Health and Human Services, CDC. [Accessed 20 March 2018] Available from: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html

1.3.1.1 CDC Core Element: Action

AMS programs include one or more of a diverse range of strategies that target different aspects of antimicrobial use (Figure 1.3). In the following sections strategies are categorised as being either restrictive, persuasive or structural in regard to their intended approach to optimising antimicrobial use.(24,25)

1.3.1.2 CDC Core Element: Action - Restrictive Strategies

Actions to reduce opportunities for over- or mis-use of antimicrobials are designed to restrict prescribers direct access to selected agents, thereby requiring prescribers to obtain specific approval for use from designated AMS or Infectious diseases staff before prescribing those agents. Alternative restrictive strategies include:

- automatic stop orders in electronic prescribing systems (i.e., programming automatic discontinuation for specific indications or agents after a designated period, e.g., limiting post-surgical prophylaxis to 24 hours)
- mandating that fields for treatment indication/s and treatment review dates are populated when prescribing antimicrobials
- selectively reporting microbial susceptibility so that prescribers cannot choose the most broad-spectrum agents
- endorsing pharmacists to perform therapeutic substitutions without consulting prescribers (e.g., changing the dosage, frequency or

dosage form to optimise use, switching a non-formulary order to a formulary equivalent).(25)

1.3.1.3 CDC Core Element: Action - Persuasive Strategies

The most common persuasive actions are performing prospective audits of antimicrobial prescribing coupled with feedback and recommendations to the treating clinician alongside targeted educational programs.(24) Audit and feedback, or post-prescription review, are predominantly conducted by AMS teams after 48 to 72 hours of empiric antimicrobial use (e.g., Figure 1.3). As a result, there are opportunities to review microbial susceptibility and/or make targeted treatment recommendations (e.g., recommending switching from intravenous routes of administration to oral formulations, i.e., the so-called “IV to oral switch”; dose optimisation; discontinuation of antimicrobial therapy). In a recent Cochrane review of heterogenous AMS interventions for hospitalised children and adults, both restrictive and enabling strategies (i.e., audit and feedback, targeted education after patient review and reminders) were independently associated with improvements in antimicrobial prescribing. However, the preferred strategy for long term improvement is yet to be established, noting that current evidence suggests that prescribing improvements are lost after strategies are withdrawn.(24,25)

1.3.1.4 CDC Core Element: Action - Structural Strategies

Structural interventions refer to strategies that require leadership commitment in the form of resource investment, and these rely on the local setting's pre-existing capacity. Structural interventions include:

- diagnostic tools
- computerised prescriber order entry
- electronic medication administration
- rapid laboratory test reports
- computerised decision support tools.

Structure-based AMS strategies may facilitate or accompany restrictive and persuasive strategies. In the aforementioned Cochrane review of heterogenous AMS interventions, 7 of the 8 studies that evaluated structural strategies included education and also 4 included reminders.(25) Structural interventions, such as computerised decision support and electronic alerts that have been evaluated in the paediatric hospital setting are reported in Section 1.7 (Literature review).

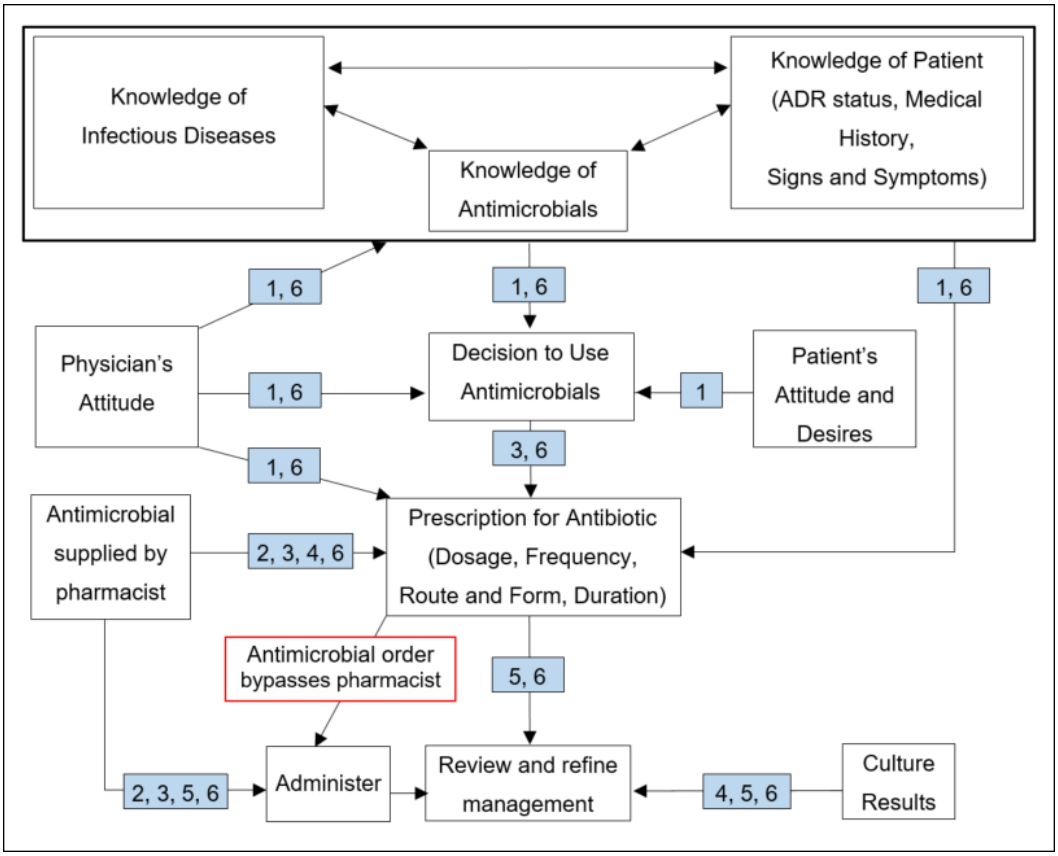

Figure Key: AMS Actions
1. Education 2. Formulary restriction 3. Prior approval 4. Mandatory indication in electronic prescribing system and antimicrobial order forms 5. Audit and Feedback 6. Computerised Decision Support; Electronic order sets

Figure 1.3 A conceptual framework for antimicrobial use Adapted from American Journal of Infection Control, 34 (5, S1), N. Fishman, Antimicrobial Stewardship., Copyright 2006 with permission from Association for Professionals in Infection Control and Epidemiology. and Elsevier.

	Nursing	Microbiology	Case Management	Pharmacy	Infectious Diseases	Infection Control	Inpatient Physician	Administration
Patient admission								
Triage and appropriate isolation	•					•		
Accurate allergy history	•			•	•		•	
Early and appropriate cultures	•				•		•	
Timely antibiotic initiation	•				•		•	•
Medication reconciliation	•			•			•	
Daily (24 h) clinical progress monitoring								
Progress monitor and report	•		•		•		•	
Preliminary micro results and antibiotic adjustment	•	•		•	•		•	
Antibiotic dosing and de-escalation	•			•	•		•	
Patient safety & quality monitoring								
Adverse events	•			•	•		•	
Change in patient condition	•				•		•	
Final culture report and antibiotic adjustment	•	•		•	•	•	•	
Antibiotic resistance identification	•	•			•	•	•	
Clinical progress/patient education/ discharge								
IV to PO antibiotic, outpatient antibiotic therapy	•		•	•	•		•	
Patient education	•				•	•	•	
Length of stay	•		•		•		•	•
Outpatient management, long-term care, readmission	•		•		•	•		•

Abbreviations: IV, intravenous; PO, per os [oral].

Table 1.1 Overlap of Nursing Activities with Function Attribution in Current Antimicrobial Stewardship Models Note: Reproduced from R. Olans, The Critical Role of the Staff Nurse in Antimicrobial Stewardship - Unrecognized, but Already There, Clinical Infectious Diseases, 2016, 62 (1), p 86, by permission of Oxford University Press and the Infectious Diseases Society of America

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1.4 Paediatric Medicine and Implications for AMS

Several aspects of paediatric medicine present unique challenges for AMS. Patients admitted to children's hospitals are hugely diverse, ranging from neonates within their first days of life through to teenagers up to 18 years old, representing a set of distinct patient groups with unique clinical needs. Safe and effective medication use requires adequate and specific knowledge of medications, disease states and patient factors. For children, there are specific age-related differences that must be recognised.(26) Therefore, when managing paediatric patients with infections, prescribers must have adequate knowledge of the:

- age-determined signs and symptoms
- diagnostic criteria and related diagnostic tests
- risks of clinical deterioration
- most likely causative pathogens
- clinical management

All of above aspects may vary with respect to patient age.(27) In addition, prescribers must have the skills to clearly communicate clinical decisions in a manner that will ensure correct preparation and administration of the prescribed therapy by nursing staff, patients and/or their families.(26)

1.4.1 Paediatric patients as “therapeutic orphans”

Paediatric patients have been called therapeutic orphans due to the low levels of evidence available to inform treatment guidelines and frequent off-label prescribing. In Australia, an estimated 35% and 47 % of prescribing for children and neonates, respectively, is regarded to be off-label. That is, the medication is used at a different dosage, frequency and/or for an age group or indication other than stated in its product licensing (NB/ In Australia, this would be the indication/s approved by the Therapeutic Goods Administration – TGA). Off-label prescribing is perceived to be an even greater challenge when prescribing therapy for pre-term neonates and patients with chronic complex or rare diseases.(28) Without adequate data, paediatric prescribing is prone to an increased risk of adverse effects in paediatric patients, leading to variable prescribing practices within individual hospitals.(29)

1.4.2 Pharmacokinetics and Pharmacodynamics

There are substantial changes in body composition, drug absorption and capacity to metabolise and eliminate medications among paediatric patients. These changes are most dramatic in the neonatal period, during which there are rapid changes in total and extracellular body water and metabolic enzymes, alongside slowly developing renal function. (Figure 1.4).(30) These are significant pharmacokinetic processes determining therapeutic efficacy (in terms of drug levels) and safety (in terms of toxicity from poor drug elimination). Failure to account for these differences may

lead to disastrous treatment outcomes. A notable example is the historical use of intravenous chloramphenicol for antimicrobial prophylaxis within the first days of a baby's life, which ultimately resulted in toxicity and increased mortality arising from impaired drug metabolism and elimination in neonates.(31) These issues are further compounded by the practical challenges in trying to account for these differences. For example, guidance on dose adjustments for renal function and obesity is limited, and may be underpowered resulting in extrapolation from studies in adults.(32,33)

1.4.3 Safe Prescribing and Administration

Inadequate knowledge of paediatric prescribing can contribute to ineffective treatment or prophylaxis of infection, toxicity or delayed access to antimicrobials in hospitals and the community setting, e.g.,

- Miscalculation of dose for weight or body surface area, incorrect weight documentation, or exceeding the maximum paediatric and adult dose,
- Dilution or calculation error when manipulating dosage formulations marketed for adults to obtain the prescribed paediatric dose,
- Lack of, or inappropriate dose rounding when prescribing antibiotics.(34)

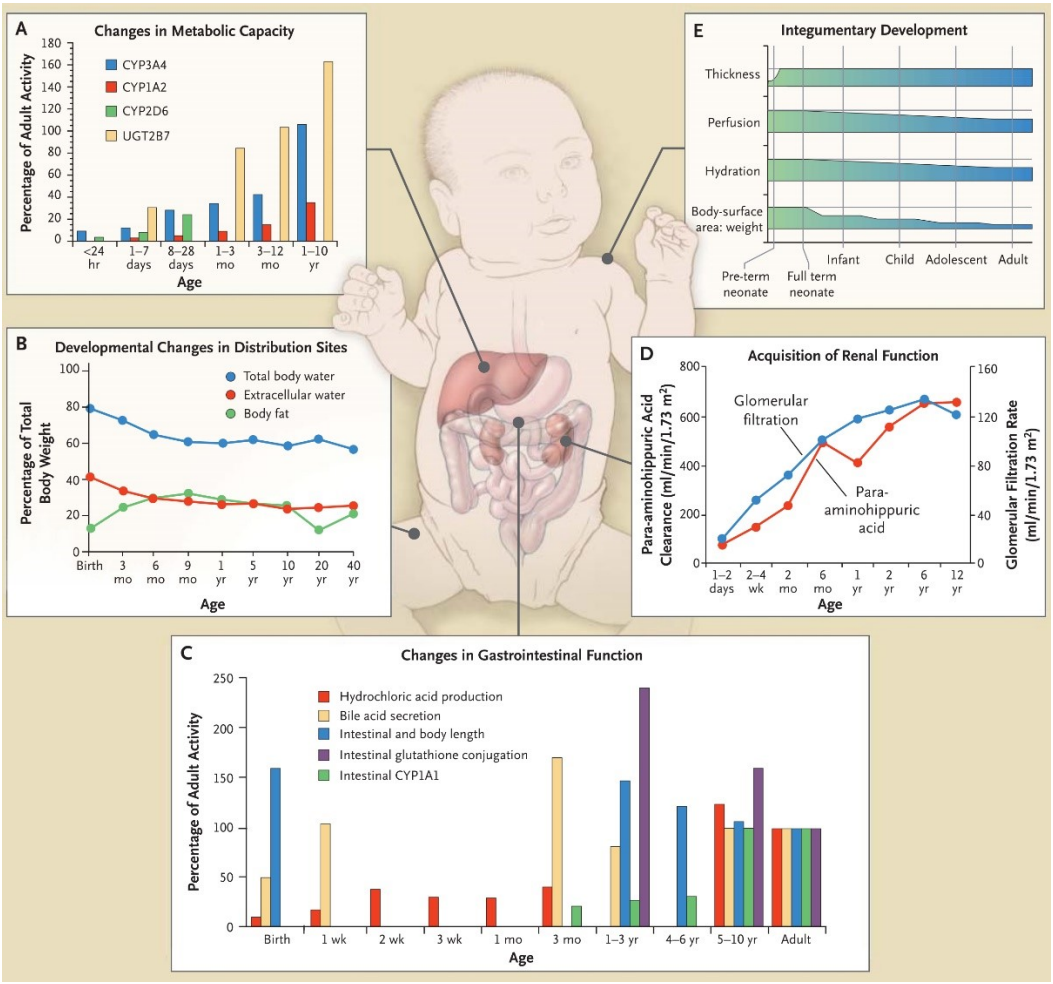

Figure 1.4 Developmental Changes in Physiologic Factors That Influence Drug Disposition in Infants, Children, and Adolescents

Reproduced with permission from G. Kearns, Developmental Pharmacology — Disposition, Action, and Therapy in Infants and Children, NEJM, 2003, Vol 349 (12) p 1160, Copyright Massachusetts Medical Society.

1.5 AMS in Australian Hospitals

In Australia, AMS programs are a key criterion of the National Safety and Quality Health Service (NSQHS) Standards.(35) As part of NSQHS Standards, hospitals are required to:

- have an AMS program in place,
- ensure prescribers have access to Australian national guidelines (*Therapeutic Guidelines: Antibiotic(27)*),
- monitor antimicrobial use and resistance,
- demonstrate that action has been taken to improve the program,
- produce an annual summary of local clinical isolates, (i.e., an antibiogram), and adjust empiric antimicrobial guidelines according to local susceptibility patterns.

1.5.1 AMS in the Local Hospital Setting

This thesis research was conducted in a tertiary paediatric hospital in Sydney, New South Wales (NSW), Australia that provides specialist paediatric care for patients undergoing oncologic and haemopoietic stem cell transplants (HSCT), solid organ transplants, cardiac surgery, or treatment for cystic fibrosis. The hospital employs and trains non-consultant level medical officers (as part of basic and advanced paediatric training) who are based in the study hospital or seconded to paediatric and neonatal units across NSW, Australian Capital Territory and the Northern Territory.

Since 2012, the study hospital has been in the process of transitioning from being part of a larger local health district (LHD) that predominantly comprised adult hospitals (adult-LHD), some of which had a general medical paediatric ward, to being a member of a specialist network of hospitals providing dedicated paediatric care (the so-called, children's hospital network). As such, the hospital's organisational structure, information technology platforms and governance processes have undergone substantial change throughout the study period, maintaining links to both the adult-LHD and the children's hospital network.

The study hospital is one of three hospitals on a shared city-based campus; the other two hospitals comprise an adult hospital with a separate infectious diseases (ID) service and AMS program, and a specialist women's and newborn care hospital with a neonatal intensive care unit (NICU). These campus hospitals share core services such as radiology, microbiology, operating theatres and pharmacy.

The study hospital's current AMS program is facilitated by a computerised decision support and approval system (CDSS, Guidance MS®, Guidance Group, Melbourne, Australia) that was implemented in October 2012. The content within the CDSS caters to the specialist services provided to a broad range of paediatric patients, including admitted and non-admitted patients, extending to outpatients, Hospital-in-the Home service patients,

and patients presenting acutely to the Emergency Department. No clinical areas are exempt from AMS interventions.

1.5.2 Local Antimicrobial Stewardship Program Prior to CDSS Implementation

Previous interventions to improve antimicrobial prescribing have included pocket cards for empiric antibiotic prescribing, education, ID consultant-led twice weekly ward rounds in the paediatric intensive care unit (PICU), attendance at oncology department meetings. In the pre-CDSS period, the ID department staff conducted annual Point Prevalence Studies (PPS) as part of the Antimicrobial Resistance and Prescribing in European Children (ARPEC) project. The hospital antimicrobial restriction policy was based on three restriction categories around antimicrobial use, including two main categories: unrestricted antimicrobials that could be used without any ID involvement, and "ID approval only" antimicrobials that required direct approval from the ID team, as arranged via telephone or face-to-face discussion. A third, intermediate category of "restricted" antimicrobials was a combination of indication- and department level- restrictions for specific medical specialties, i.e., those units that were expected to frequently prescribe certain agents for appropriate indications. Therefore, in many cases, antimicrobial agent selection, dosage and frequency for restricted antimicrobials was left to the discretion of the individual prescriber.

In anticipation of the NSQHS Standards, the adult-LHD supported the implementation of a centrally-deployed intranet-based CDSS utilising rules-based algorithms to enhance the pre-existing AMS strategies in each of the hospitals, helping to standardise the use of restricted antimicrobials across the adult-LHD. A multisite working party of Infectious Diseases Staff Specialists and AMS Pharmacists was formed with the support of the adult-LHD Drug and Therapeutics Committee (DTC) and Information Technology (IT) departments. The adult-focused CDSS was implemented between April and July 2012, reporting a 23% reduction in the use of those antibiotics that required CDSS approval (measured in WHO defined daily doses) in the immediate post implementation period, followed by a tendency for higher rates of use in the 24 months post implementation. Whilst the direct impact of CDSS for individual patients in those hospitals was not reported, introduction of the CDSS did not extend overall LOS nor did it increase standardised mortality ratios (i.e., observed/expected deaths) for those patients admitted with respiratory tract infections, urine and kidney infections and/or septicaemia.(36)

In another Australian hospital, AMS facilitated by CDSS has been associated with improved susceptibility of the microbe *Pseudomonas spp.* to imipenem (an intravenous beta-lactam antibiotic) and gentamicin.(37) However, these improvements were observed at least 2 years after the first CDSS was implemented as a pilot program in March 2001, and followed by a range of interventions including: a separate clinical decision support

platform for microbiology and pathology reports in the hospital's intensive care unit (June 2002); new empirical guidelines; and an expanded list of antimicrobials that required CDSS approval (January 2005).

CDSS users have reported perceived improvements in their knowledge of antibiotics and local treatment guidelines, alongside perceived improvements in their prescribing of antibiotics (in terms of guideline concordance and documentation).(38) In addition to promoting guideline-concordant prescribing, the CDSS identifies those patients whose antibiotic treatment requires auditing (with feedback to prescribers) by AMS teams.(39)

1.5.3 Paediatric CDSS Development and Implementation

The enhanced paediatric AMS program utilising CDSS was implemented in the study hospital in October 2012 after a 6-month consensus-building and content development period. At the time of implementation, the national standard antimicrobial guidelines, *Therapeutic Guidelines: Antibiotic* had few recommendations for children with chronic complex conditions.

As part of the paediatric CDSS implementation, a comprehensive review of paediatric antimicrobial guidelines, the primary literature and medication references for children was completed by the lead AMS ID Consultant (medical clinician specialising in infectious diseases) and AMS Pharmacist for comparison against the indication and recommendations in *Therapeutic*

Guidelines: Antibiotic. The resultant draft treatment recommendations were distributed to representatives from the medical and surgical paediatric departments, paediatric departments in the adult-LHD and the Campus NICU. Any changes to the local prescribing guidelines were negotiated, and consensus-based recommendations were developed. Recommendations defined the criteria for approval of antimicrobial agent use, according to the indication and patient factors (e.g., age, comorbidities) and provided the indication-specific doses, routes of administration, and duration of initial approval for all restricted antimicrobials (Figure 1.5).

Body Surface Area (BSA), paediatric renal function calculators, paediatric guidelines and management recommendations (e.g., duration of intravenous therapy, indications that required formal consultation from other medical or surgical specialty units) were incorporated into the approval process.

Guidelines for empiric antibiotic treatment, surgical prophylaxis, febrile neutropenia, empiric antifungal use in immunosuppressed patients, drug protocols for aminoglycoside, vancomycin and aciclovir dosing, monitoring and administration of therapy, were updated.

An AMS policy specifying the roles of medical staff, pharmacy staff, and dedicated AMS teams was adapted from the adult-LHD hospitals. CDSS recommendations and guidelines were ratified by the study hospital's Local

Drug and Therapeutics Committee (DTC) and programmed as CDSS algorithms by the paediatric AMS and adult-LHD project pharmacists.

A structured governance model was developed to support continuous monitoring of AMS recommendations and to coordinate decision-making with respect to changes embedded in the CDSS. All pharmacists and junior medical staff received CDSS training. Grand rounds, departmental meetings and a hospital-wide promotional campaign were led by the Chair of the local DTC. Nurses in designated education roles ("nurse educators", i.e., a registered nurse that either formally teaches at a nursing school or acts as a trainer in a health care facility) were introduced to the CDSS and AMS in general. Nurse educators were encouraged to organise education for their respective wards. Treatment recommendations for paediatric patients were adapted and adopted by all hospitals within the adult-LHD after consultation with paediatricians from each of their paediatric units. Paediatric and adult recommendations have formed the basis of electronic medication orders for children in the newly developed electronic prescribing systems throughout the adult-LHD.

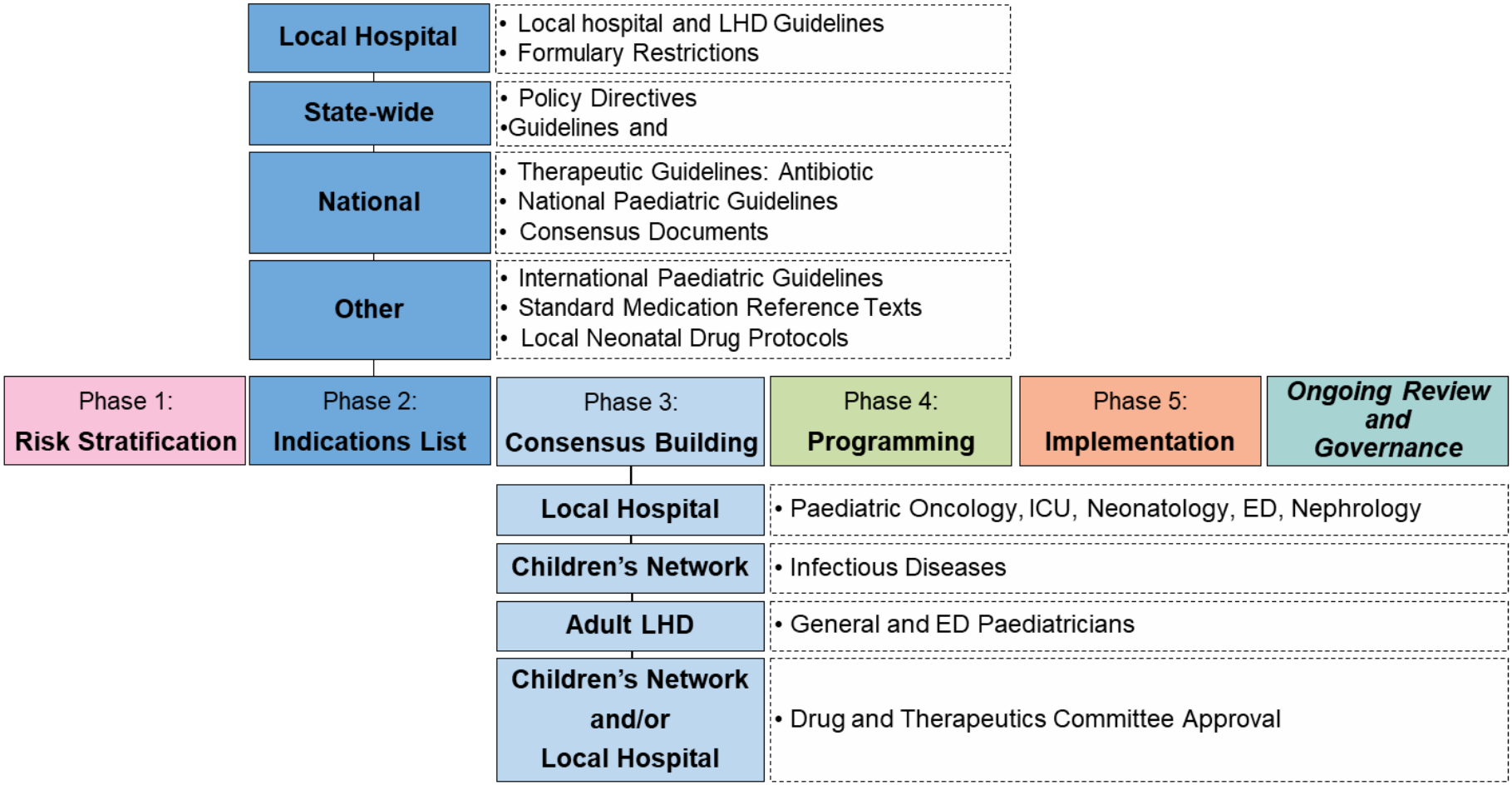

Figure 1.5 Development strategy for consensus-based paediatric CDSS indications

1.5.4 Local AMS Program Facilitated by CDSS

1.5.4.1 Staff Training

Since its implementation in 2012, orientation to the CDSS and the local antimicrobial policy is mandated for all medical residents and registrars (i.e., all junior medical officers - JMOs). All JMOs and pharmacists are provided, on an annual basis, with updated pocket cards that indicate the level of restriction for each formulary-listed antimicrobial, as well as the hospital's current empiric antibiotic prescribing guideline. The AMS pharmacist regularly attends meetings with the hospital nurse educators to provide updates on the AMS program and develops resources for antimicrobial administration, medicine information and pocket cards for dissemination to ward nurses.

1.5.4.2 Process for Approval and supply

As part of the local AMS policy, all prescribers must seek approval for the use of restricted antimicrobials by submitting an online request via the CDSS. During the hospital pharmacy department's standard operating hours (08:30 to 17:00, Monday to Friday), pharmacists conduct ward rounds where they review the treatments prescribed to their patients, as documented on paper medication charts. As part of these rounds, ward pharmacists may identify prescriptions for restricted or ID approval only antimicrobials that do not yet have valid approval; subsequently, the ward pharmacists will contact prescribers by telephone, detailing the exact action required, simultaneously lodging a 'pharmacist alert' within the CDSS.

Where a prescription for an antimicrobial requires the medication to be supplied by the pharmacy (i.e., the agent is not part of the ward's imprest stock), a limited quantity is initially dispensed to avoid treatment delay. Any use outside the pre-determined indications listed in the CDSS requires direct discussion with the AMS team and is considered a 'non-standard' use. One member of the AMS team reviews CDSS requisitions (i.e., requests for approval to use restricted antimicrobials) every day, Monday through to Friday, to identify CDSS approvals that may have expired, outstanding CDSS 'pharmacist alerts', and any 'non-standard' indications. AMS recommendations are made after consultation with the treating medical team; the AMS policy requires that any disagreements that cannot be resolved by non-consultant level prescribers and AMS approvers are escalated to the AMS-lead consultant and treating consultant. If necessary, these conflicts are escalated to the hospital executive (i.e., hospital administrators).

1.5.4.3 The Local Hospital AMS Team

The AMS program is supported by a half-time (0.5 full time equivalent - FTE) paediatric infectious diseases consultant (the AMS lead consultant) and a part-time (0.3 to 0.5 FTE) clinical AMS pharmacist. Two ID medical fellows are employed on a rotational basis, alternating between their AMS duties and consultations for paediatric patients across the state (NSW), against performing formal ID consultations for admitted patients as part of their role as infectious diseases clinicians. All clinical content within the

CDSS and its functionality are reviewed at least annually by the AMS lead consultant and AMS pharmacist. The AMS program has met the NSQHS Standards for AMS with “Merit” in each formal accreditation assessment since implementation.

1.6 CDC Element - Tracking and Reporting

AMS evaluation is inherently complex, due to the diverse range of strategies, resources, and contexts pertaining to the interventions used.(40) Most AMS studies report reductions in antimicrobial use as the primary evaluation measure, far outweighing the number of studies actually reporting the impact of AMS on microbial resistance (i.e., microbial resistance being a primary outcome underpinning AMS).(25) Antimicrobial resistance is complex and driven by multiple factors (Figure 1.1). In the hospital setting alone, microbial resistance is influenced by patient factors, community-acquired resistance, and adherence to infection control.(41) Also highlighting the complexities of AMS evaluation is that the findings from intervention studies have not been consistent in terms of demonstrating effectiveness.

CDI is internationally recognised as a key outcome for AMS, due to the burden of disease and impact on healthcare systems.(42) Blood stream infections,(43) antimicrobial drug utilisation rates, costs, prescribing assessments and a host of other evaluation measures relating to intervention processes and outcomes have been suggested for tracking

and reporting by hospital AMS programs (Table 1.2). However, very few clinically relevant metrics are clearly defined and validated.(44,45) Due to the complexity of antimicrobial therapy and patient factors, there is still a reluctance among some clinicians and/or sites to report actual clinical outcomes as part of routine AMS evaluation in hospitals. Even in those hospitals which have access to detailed electronic patients records (e.g., medical records/clinical progress notes, patient-level medication administration data, patient-level prescribing data) such reporting may not be feasible.(45)

Table 1.2 Suggested Measures and Metrics for AMS Evaluation

	United States CDC or IDSA	**Australia** ACSQHC
AMS Activity		
Prevalence surveys		*
AMS recommendations	*	*
Appropriate Prescribing	*	*
Concordance with susceptibility	*SS	*
Concordance with specific guidelines	*	*
Duration of therapy for specific indication	*	
Proportion of patients converted from intravenous to oral route	*	
Guideline concordant surgical prophylaxis by type of surgery		*
Patients with community-acquired pneumonia prescribed guideline concordant antimicrobials		*
Restricted antimicrobial prescriptions concordant with hospital approved indications		*
Patients with a toxic or subtherapeutic aminoglycoside concentration whose dosage has been adjusted or reviewed before the next dose (%)		*
Time to first antibiotic dose		*
AMS compliance		*
Prescriber acceptance rates upon receiving advice		*
Timeliness and appropriateness of therapy for a given infection		*

ACSQHC: Australian Commission on Safety and Quality in Healthcare (23); CDC: Centers for Disease Control and Prevention (21); IDSA: Infectious Diseases Society of America (42) SS: Specific Syndrome

Table continues on next page.

Table 1. 2 Suggested Measures and Metrics for AMS Evaluation *cont.*

	Guidelines		Published Consensus	
	CDC or IDSA	ACSQHC	Moehring (45)	Morris (46)
Antimicrobial Drug Utilisation	*	*	*	
National surveillance program metric	*	*	n/a	n/a
DOT per patient admissions			*	
DOT per patient days	*		*	*
DDD per patient days		*		
Redundant therapy events	*SS		*	* (CAP, SSTI, BSI)
Either DDD or DOT	*			
Cost	*			
Antibiotic cost per patient days	*			
Clinical Outcomes		*		
Mortality related to antimicrobial-resistant organisms				*
Hospital onset or healthcare facility acquired CDI	*SS	*	*	
Unplanned readmission to hospital within 30 days of discharge	*SS			* (CAP, SSTI, BSI)
30-day mortality	*SS			
Proportion of patients with an antibiotic related adverse drug event	*SS			
Proportion of patients or rate of clinical failure	*SS	*		
Hospital length of stay	*SS			
Microbial Resistance			*	
Incidence of drug-resistant infection			*	*

ACSQHC: Australian Commission on Safety and Quality in Healthcare (23); CDC: Centers for Disease Control and Prevention (21)
IDSA: Infectious Diseases Society of America (42) SS: Specific Syndrome, CAP: Community-Acquired Pneumonia; SSTI: Skin and soft tissue infection; BSI: Blood stream infection; DDD: Defined daily dose; DOT: Days of therapy; CDI: *Clostridium difficile* infection

1.6.1.1 CDC Element - Tracking and Reporting in Children's Hospitals

Evaluation of AMS in paediatric settings is associated with its own unique challenges. Assessments of antimicrobial prescribing for paediatric patients with co-morbidities are complicated by a lack of standard treatment guidelines,(47) alongside limited evidence to support prescribing, which may lead to discordant views among ID consultants.(48) Robust evaluation of patient outcomes is further limited by the inherent differences and risks at each phase of life in the paediatric patient, thus limiting the available sample sizes, leaving many studies underpowered to make relevant comparisons between individual AMS strategies and draw meaningful conclusions by controlling for other influential factors. Measures and metrics reported in studies that evaluated paediatric AMS strategies in hospitalised children published between 2000-2017 are included in Section 1.7 (Literature review). The units of measure reported in paediatric antimicrobial drug utilisation surveillance studies are described in Table 1.3.

In the absence of a standard unit of measure for the routine surveillance of antimicrobial use, the capacity of children's hospitals to routinely track, report and focus actions relating to optimal antimicrobial use is substantially limited.(49)

1.6.1.2 Paediatric Antimicrobial Surveillance

Two examples of typical antimicrobial therapy regimens for a 10-kilogram (kg) child are provided below.

Example A: Antimicrobial therapy comprises 3 concurrent agents for 5 days

- ampicillin 50 mg/kg 6-hourly = 500 mg 6-hourly
- gentamicin 7.5 mg/kg 24-hourly = 75 mg 24-hourly
- metronidazole 12.5 mg/kg 12-hourly = 125 mg 12-hourly

Example B: A single broad-spectrum antimicrobial for 5 days

- piperacillin-tazobactam 100 mg/kg (of piperacillin) 6-hourly = 1 g (of piperacillin) 6-hourly

Table 1.3 illustrates the attributes of the units of measure that have been applied for paediatric antimicrobial surveillance in such regimens.

Table 1.3 Reported units of measure for antimicrobial drug utilisation surveillance in hospitalised children

Unit of Measure (Abbreviation)	**Description** Example A and B are described in Section 1.6.1.2 Paediatric Antimicrobial surveillance
Defined Daily Dose (DDD)	The usual maintenance dose for the primary indication of an antimicrobial in an adult. Surrogate measure to capture the number of antibiotic treatment days in adults. The defined daily dose is not intended to reflect locally recommended dosing. DDD is not validated for use in children. (50) Ampicillin DDD = 2 g/day Metronidazole DDD = 1.5 g/day Gentamicin DDD = 0.24 g/day Piperacillin-tazobactam =14 g/day *NB/ These are the values assumed for a 70kg adult and not the calculated DDD for Examples A and B. This topic is explored in Section 4.1)*
Recommended Daily Dose (rDD)	The recommended daily dose for adults or children determined by local guidelines. rDD = recommended dose (mg/kg) × recommended frequency.(51)
Units	Count of the number of vials, tablets, or packs used or supplied.
Doses	Number of doses dispensed or administered. Example A: 35 doses Example B: 20 doses
Drug utilisation 90% (DU90%)	The antimicrobials that contribute to 90% of total use measured in DDD.(52) i.e., 1) Aggregate of DDD per period or site 2) Extract top 90% aggregate 3) Compare antimicrobials e.g. number of unrestricted or first line agents that contribute to DU90%

Table continues on next page

Table 1 3 Reported units of measure for antimicrobial drug utilisation surveillance in hospitalised children *cont.*

Unit of Measure (Abbreviation)	**Description** Example A and B described in Section 1.6.1.2 Paediatric Antimicrobial surveillance
Days of Therapy (DOT)	Sum of days of each antimicrobial prescribed or administered. i.e., antimicrobial agent-days Example A = 15 DOT Example B = 5 DOT
Length of Therapy (LOT)	Antimicrobial days irrespective of number of agents used. Example A: 5 LOT Example B: 5 LOT
Antimicrobial Courses	Number of distinct periods of consecutive days when a patient is prescribed or administered a *specific* antimicrobial. Courses refer to an antimicrobial of interest and would quantify a switch from one antimicrobial to another as 2 courses. Example A = 1 course Example B = 1 course
Patients exposed	Number of patients prescribed or administered an antimicrobial.
Agents	Number of antimicrobials prescribed or administered per patient.
Hospital Activity Measure	**Description**
Kilogram bed days	Sum of [expected weight in kg of patients at each age × the number of patient-days of that age]. i.e., Estimated weight from age for weight growth charts × patient LOS for that age) x 100 (51)

Note. Adapted from Table 2 - E. Fortin, Systematic Review of Measures, Journal of Antimicrobial Chemotherapy, 69 (6), 1447-1456.
Antimicrobial use measures are standardised for hospital activity e.g. patient bed-days, admissions, defined periods (months, years etc.) or days present.

1.6.2 Local hospital AMS Evaluation

The local hospital routinely reports on different aspects of antimicrobial use and compliance (Table 1.4).

Table 1.4 AMS tracking and reporting at the local hospital

Measure	Description and Reported Measure or Metric
AMS Activity	AMS actions (recommendations, agreement with prescribers, requests that are not approved) are not recorded for tracking
AMS Compliance	Bi-monthly CDSS activity reports are presented to the AMS and hospital Drug and Therapeutics Committee: • Number of approvals • Proportion of self-initiated medical staff approvals vs approvals generated in response to a pharmacist's request
	Peer-audit and feedback The lead AMS ID consultant and pharmacist support a JMO project that targets improved AMS compliance through fortnightly peer audit and feedback • Proportion of restricted antimicrobials with a CDSS approval
Appropriate prescribing	Clinical Excellence Commission "5x5" audit conducted weekly by AMS team, data collected include: • Documented indication • Guideline concordant (antimicrobial, dose, frequency) • Antimicrobial approval status of restricted antimicrobials
	An annual point prevalence survey is conducted by the AMS team and reported hospital-wide. The Australian National Antibiotic Prescribing Survey captures standardised assessments of prescribing across Australian hospitals. On a single day the AMS team collect: • Proportion of hospitalised patients prescribed antimicrobial/s and a record of each prescription (antimicrobial, dosage, frequency, route of administration) • Adherence to indicators for AMS (e.g. documented indication) • Compliance with guidelines, assessments for appropriateness (ranging from optimal to inadequate)

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Table 1.4 AMS tracking and reporting at the local hospital *cont.*

Measure *cont.*	Description and Reported Measure or Metric *cont.*
Balancing measure, Safety/ Clinical Outcome	All antimicrobial incidents and adverse drug reactions entered into the hospital's local incident reporting systems are reviewed by the AMS pharmacist. Incidents are assessed for possible error or harm caused or preventable with AMS input or CDSS utilisation. Action is taken in consultation with the Medication Safety Pharmacist. Findings are reported to the AMS subcommittee. • Number of incidents attributed to AMS; • Number of incidents possibly prevented by CDSS
Antimicrobial drug utilisation	Not formally measured
Healthcare cost	Not formally measured
Antimicrobial resistance	• A hospital specific antibiogram is prepared annually and reviewed by the AMS Subcommittee* • Multidrug-resistant organisms (MROs) are monitored by the hospital Infection Control Nurse and reported to the Infection Control and AMS Committees • Microbiology submitted to Antimicrobial Use and Resistance in Australia (AURA)(4) • CDI/10,000 occupied bed-days for patients 2 years and older is collected and reported to the hospital Infection Control Committee
Stakeholder Assessment	Annual user satisfaction survey of medical officers

*Antibiograms are a required action under the NSQHS criterion for AMS for the purpose of updating empiric antimicrobial guidelines.

1.6.2.1 Quality Improvement Activities and Research Projects

IV to Oral Switch Project

The so-named IV to Oral Switch Project is a joint pilot study led by the study hospital in conjunction with the NSW Clinical Excellence Commission (CEC). The study employs Quality Improvement (QI) methods (i.e., Plan-Do-Study-Act cycles) to minimise the duration of unnecessary intravenous antimicrobial therapy used for paediatric patients admitted to general medical and/or surgical units who meet the criteria for switching from IV to oral therapy. Eligibility is determined by patient and syndrome specific factors outlined in a published systematic review and consensus based guideline authored by the lead AMS consultant at the study hospital together with paediatric ID colleagues throughout Australia and New Zealand.(53) The systematic review has been adapted as a local guideline that includes guidance on suitable oral antibiotics, appropriate dosages for children and is further supported by posters and information for patients and families. Eligible patients are identified by manual screening of the medical notes for all patients admitted to medical and surgical units, and key outcomes recorded for discussion at monthly project meetings (Table 1.5).

Table 1.5 IV to Oral Switch Project Outcomes

Appropriate Prescribing	• Median time taken to switch eligible patients* to oral antibiotics • Percentage of eligible patients* on IV antibiotics that are stopped or switched to oral therapy within 24 hours (target ≥ 95%)
Antimicrobial use, Clinical outcomes	• Duration of intravenous antibiotic therapy in eligible patients • Length of stay in eligible patients • Line-associated complications in eligible patients • Number of readmissions due to infection within 7 days of discharge in eligible patients • Number of eligible patients recommenced on intravenous antibiotics within 48 hours after oral switch

*eligibility determined IV to Oral Switch guideline criteria.

1.6.2.2 Local AMS Evaluation Challenges

Tracking and reporting, in the form of antimicrobial drug surveillance at the local study hospital has previously been limited by the available information technology systems. Without accessible patient-level electronic medication records, manual screening of handwritten medication charts and time-consuming data collection would be required to perform antimicrobial surveillance activities, which is not a feasible strategy for routine monitoring and reporting. With the implementation of CDSS, tracking and reporting on antimicrobial drug utilisation (including data related to indications for use) has extended to the inclusion of additional, albeit still limited, surrogate measures such as recorded CDSS approvals. However, CDSS approvals do not necessarily reflect actual antimicrobial usage (Figure 1.6).

Concordance between CDSS approval rates and actual use is dependent on whether the prescriber obtains CDSS approval at the time of antimicrobial prescribing and complies with any subsequent advice received (i.e., whether the AMS team has approved – or not – the requested antimicrobial treatment). In adult hospitals, concurrent tracking of CDSS approval days and antimicrobials supply days (Figure 1.6) has been used to monitor CDSS utilisation trends (i.e., to demonstrate improved rates of CDSS utilisation in the context of stable antimicrobial supply).(54) As there is no standard unit of measure to monitor paediatric antimicrobial use, we are unable to estimate the degree to which prescribers use the CDSS to inform their prescribing or comply with the AMS policy, nor the actual number of patients prescribed restricted antimicrobials. Therefore, the program has not historically, been able to reliably monitor AMS activity or impact on patient care. No other electronic data portals were available prior to December 2015, when the patient medical records (clinical progress notes), but not the medication administration records (medication charts), were transitioned from paper to electronic medical records (EMR); unfortunately, the hospital's EMR did not have any surveillance functionality to identify hospitalised patients with infections or specific indications. Records of supply from the hospital pharmacy could, however, be obtained electronically from the hospital pharmacy information system. The CDSS, EMR, hospital pharmacy information system and the usual communication systems used in the hospital (pager, electronic email) were not integrated.

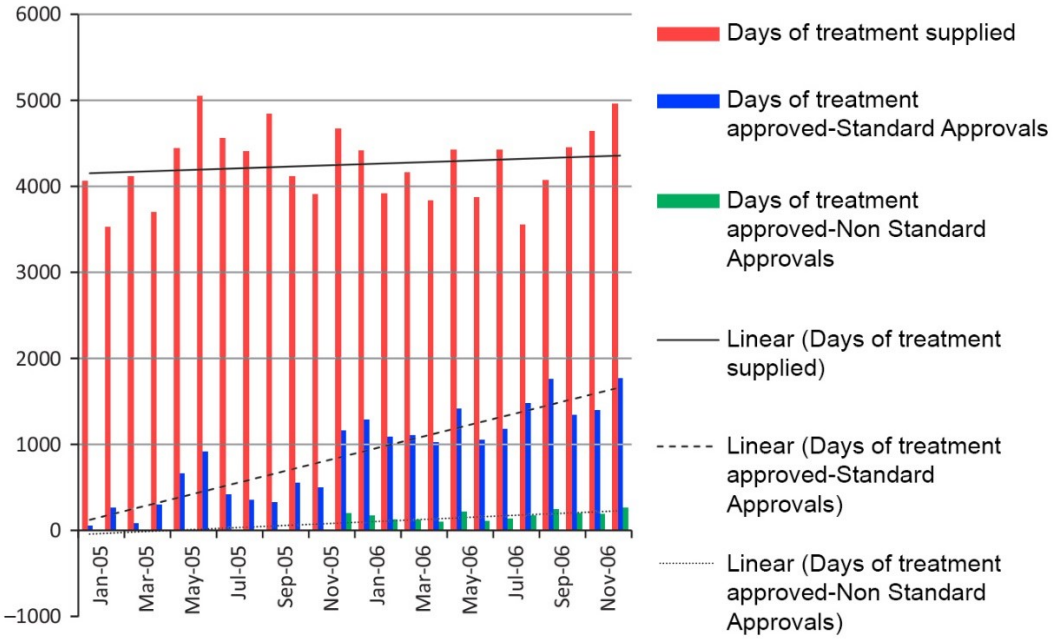


Figure 1.6 Tracking of CDSS approvals in relation to antibiotic use

Reprinted from “Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship”, by S. Zaidi, 2013, J Clin Pharm Ther. 38 (6), p 495.Figure 1. - Two year usage of iApprove® before and after the formative evaluation of the system Copyright 2013 John Wiley & Sons. Reprinted with permission. Note. Original figure converted to colour, Legend completed to include “Linear (Days of treatment approved-Non Standard approvals)” for dotted line. Data remains unaffected.

1.7 Strategies and measures for paediatric antimicrobial stewardship: a review of the literature

Manuscript 1
Mostaghim M, Snelling T, Bajorek, BV. **Antimicrobial stewardship for hospitalised children: A review of evaluation measures and metrics.**
Manuscript in submission (peer review)

1.7.1 Abstract:

Aim: Antimicrobial stewardship (AMS) is a complex and varied package of interventions which aim to improve the safety, quality and effectiveness of antimicrobial prescribing. There is no clear consensus regarding how such programs should be assessed across diverse settings and patient groups. Prescribing practices, treatment guidelines and age-specific patient factors distinguish paediatric patients from adults, thereby warranting focused AMS strategies and accompanying evaluation methods in paediatric hospitals. Therefore, we reviewed the process and outcome measures reported in published studies that evaluated the effectiveness of AMS strategies for hospitalised children.

Method: Embase, Medline (via Ovid), Scopus and Pubmed databases were searched for articles reporting individual or complex interventions (AMS) to improve antimicrobial prescribing for hospitalised paediatric patients published between January 2000 and December 2017. Measures that reported AMS performance, staff compliance, appropriate prescribing, drug

utilisation trends, healthcare cost, patient outcomes, and changes in antimicrobial resistance in the paediatric inpatient setting were extracted. Results: Most studies (32/46) were from hospitals in the United States, including two stakeholder assessments; twenty studies (43%) were from six hospitals. More than half of studies reported on programs that implemented some form of audit and feedback on prescribing (24/46). Many studies reported clinical outcomes (33/44) including duration of hospitalisation (23/33) and mortality (19/33). Studies variously reported on antimicrobial utilisation (28/44), antimicrobial resistance (12/44), and healthcare costs (18/44). Reporting on drug utilisation surveillance appeared to be reliant on access to electronic prescribing and administration data.

Conclusion: There is wide variation in how the effectiveness and impact of paediatric AMS programs are evaluated and reported in published evaluations. Standard process and outcome measures for paediatric AMS should be defined and included in published studies to inform local evaluation and facilitate benchmarking with comparable paediatric hospitals.

1.7.2 Introduction

Antimicrobials are frequently prescribed for hospitalised children, with variable rates of appropriate prescribing reported across hospitals and clinical specialties. (1) Inappropriate antimicrobial use can result in inadequate treatment of infection, expose patients to unnecessary toxicity

or complications, predispose patients to opportunistic infection, and promote the emergence of antimicrobial resistance. (2)

Antimicrobial stewardship (AMS) programs apply a range of strategies to optimize antimicrobial agent selection, dosage, route and duration in order to limit these adverse outcomes and maximise clinical benefits. Local AMS programs may involve one or more core strategies in combination with supplementary strategies that are selected and tailored according to the hospital culture and available resources. Core AMS strategies restrict direct access to targeted antimicrobials by requiring prescribers to obtain authorisation to prescribe targeted agents ("prior authorisation") and/or implement regular antimicrobial prescribing audits coupled with timely feedback to prescribers ("audit and feedback").(3) Supplementary AMS strategies include, but are not limited to, clinical decision support, automatic "stop orders", standardised ordering forms or electronic order sets that are consistent with local guidelines, and antimicrobial "time-outs" that prompt self-audit by prescribers. Infectious diseases (ID) clinicians and pharmacists are usually responsible for conceptualising and implementing programs, monitoring outcomes, and refining strategies to maximise effectiveness locally.(4)

AMS programs are complex interventions due to the diverse and evolving strategies employed, the broad range of stakeholders involved, and the seasonal, institutional, patient and microbial factors that may confound

measured outcomes.(5) In order to evaluate AMS implementation and to associate interventions with any observed changes in antimicrobial use, healthcare costs, clinical or antimicrobial resistance outcomes, it is recommended that AMS programs monitor both process and outcome measures (3,6).

AMS programs in paediatric hospitals may differ from those in adults, both in terms of the antimicrobials and treatment indications targeted, and the metrics selected for evaluation.(7) Quality assessments of paediatric antimicrobial prescribing may be complicated by very nature of prescribing in paediatric hospitals. That is, variation that results from more frequent off-label prescribing, presence of fewer standardised treatment guidelines and lower levels of evidence to support use.(8) In some countries drug utilisation surveillance for paediatric patients is hindered by the variable daily antimicrobial use requirements that result from age, body surface area or weight-based dosage calculations.(9)

In this review we describe the measures reported in published evaluations of AMS strategies for hospitalised children.

1.7.3 Methods

This review reports the findings of a literature search conducted in December 2017. Embase, Medline (via Ovid) and Scopus databases searches were performed using the search terms “antibiotic”,

“antimicrobial” and “control”, “restrict”, “approval”, “management team”, management program”, “management group” or “audit” with “feedback” in paediatric patients. A Pubmed search was conducted with these text words together with the medical subject heading (MeSH) “anti-infective agents”. Additional broad searches with the text word “stewardship” were performed in all databases. The search was limited to English language studies and conference abstracts in humans published between January 2000 and December 2017. Abstracts were screened to identify review articles, meta-analyses and studies (prospective, retrospective, observational) in hospitalised children. Reference lists from retrieved articles and international AMS guidelines were reviewed to identify additional papers. Conference abstracts were reviewed, but none were ultimately included in this review due to insufficient information.

Studies were excluded where they did not adequately describe the nature of the AMS intervention, assessed infection control, diagnostic tests or surgical prophylaxis only. All studies were restricted to paediatric inpatients, thereby excluding studies that focused solely on outpatient (ambulatory care), community practice programs and the neonatal intensive care setting where patients, interventions and outcomes are likely to differ.(10) Articles that reported AMS interventions involving both adult and paediatric patients, including neonates, were selected if paediatric outcomes, as identified by the authors, were reported separately (Figure 1.7).However, Studies that only reported outcomes for patients aged 14 years or older

were excluded. We did not exclude studies based on the grading of the evidence in order to identify a broader range of measures.

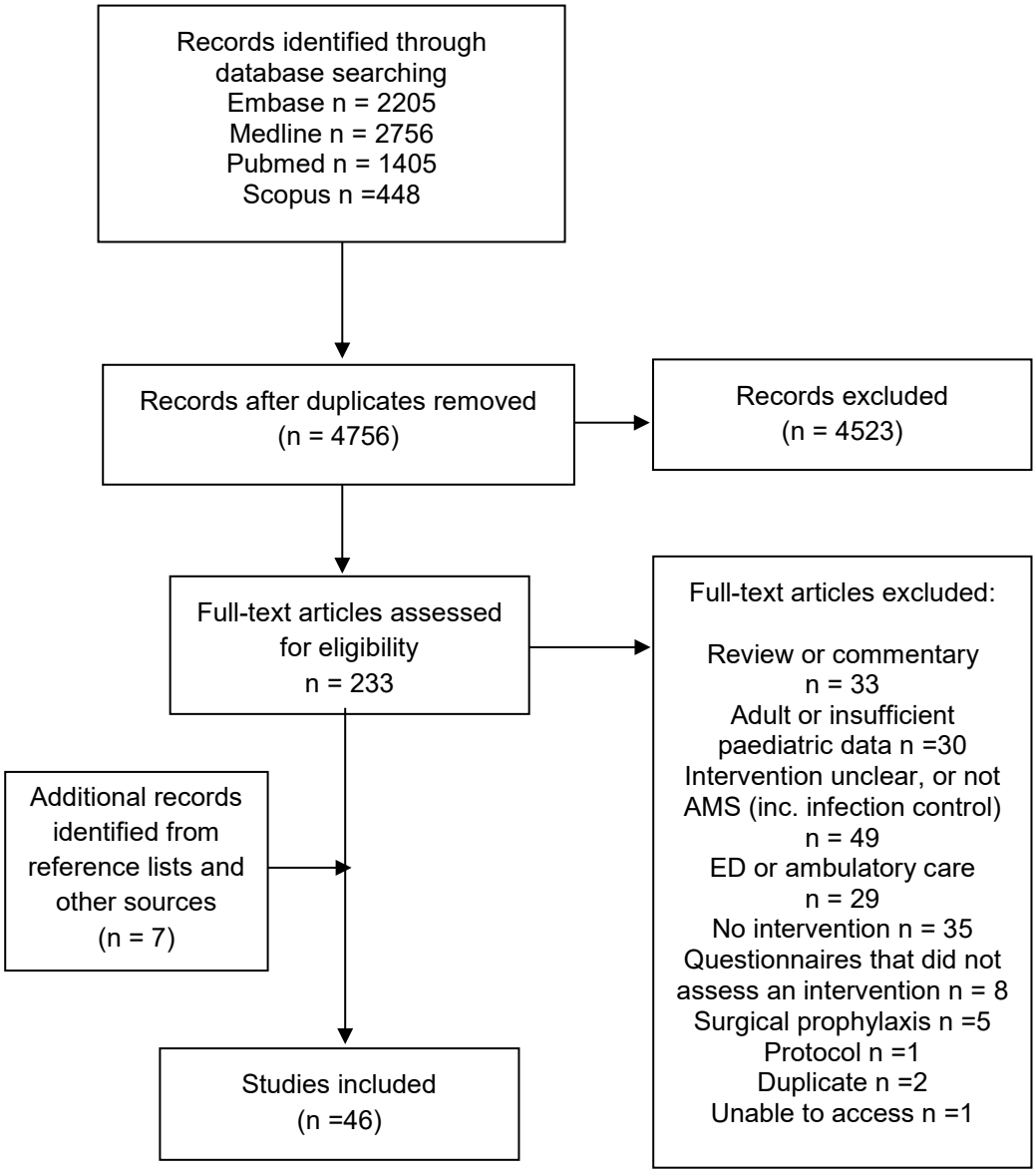


Figure 1.7 Flow diagram of study selection

1.7.4 Results

AMS strategies

Forty-six studies assessed AMS strategies implemented in a paediatric hospital setting, two of which were stakeholder evaluations.(11,12) More than half were published in 2014 or later (25/46), with close to one quarter of all studies published in 2017 (11/46). Most published evaluations were from hospitals in the United States (32/46); six hospitals accounted for 20 of the 46 published evaluations.

Most studies evaluated AMS programs that employed multiple strategies that were either implemented simultaneously or stepwise throughout the study period (Table 1.6). Approximately half of studies were of AMS programs that employed regular audit and feedback to prescribers (24/46). This included two novel approaches whereby stewardship advice was provided through teleconferences with a remote hospital, (13) and “handshake stewardship”, where feedback was presented as a suggestion rather than a mandate. (14) Twenty studies were of AMS programs that implemented some form of prior approval for prescribing selected broad spectrum or high cost agents, either as the primary intervention (9/46) or in combination with audit and feedback (11/46). One study focused on the impact of antimicrobial formulary restriction alone.(15) Three studies assessed the implementation of automatic antimicrobial stop orders together with audit and feedback (16,17) or prior approval. (18) The remaining studies assessed the impact of paper-based antibiotic order

forms (3/46),(19-21) computer-based point-of-care interventions (e.g. decision support, pathways or standard order sets, 6/46)(22-27) and a range of strategies to systematically promote guideline compliance (2/46); these included quality improvement methods and standard order sets, (28) education, and staff and consumer satisfaction. (29)

Some studies solely reported on specific patient groups or antimicrobial indications: community-acquired pneumonia (26,28-30), febrile neutropenia, (31,32) bronchiolitis. (24,25) Four studies evaluated interventions that focused primarily on the intensive care setting. (19,21,22,33)

Approximately half of the included studies reported on AMS programs with a dedicated AMS pharmacist (24/46)(12,14,16-18,30-48). Some AMS programs instead incorporated audit and feedback into clinical pharmacist's roles (2/46).(49,50) Elsewhere, multidisciplinary groups designed strategies, and facilitated compliance beyond enforcing restrictions to supply. (19,20,23,25,26,28,29,51) None of the evaluated AMS programs employed a designated AMS nurse, however, nurses were involved in the implementation of a treatment pathway (26) and training on infection control. (52)

**Table 1.6 Strategies and measures reported in published paediatric antimicrobial stewardship evaluations^*

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Newland, 2012	Primary strategy: Audit and feedback Country: United States Study Duration: 3 years, 3 months pre, ~2 years, 10 months post	Interrupted time series with external control to assess impact of audit and feedback on antibiotic use (inc. PICU).	AMS Activity: Number of patients and antibiotic orders reviewed. AMS Compliance: % initial recommendations accepted; overall agreement. Appropriate Prescribing: % of reviews that required recommendation; recommendation type. Drug Utilisation: DOT/1000/PD; LOT/1000/PD. Clinical Outcomes: Hospital-wide all-cause mortality; 30-day readmission rate. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
McCulloh, 2015	Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 5 years post	Retrospective study of patients with 1 AMS review during admission for clinical outcomes associated with AMS recommendations and prescriber agreement.	AMS Activity: Number of patients reviewed. AMS Compliance: % recommendations accepted. Appropriate Prescribing: % of reviews that required recommendation; recommendation type; indications. Drug Utilisation: Not reported. Clinical Outcomes: LOS; 30-day readmission rate. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Goldman, 2015	Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 5 years post	Retrospective study of AMS recommendations for indications and agents associated with an AMS recommendation and agreement (inc. PICU).	AMS Activity: Number of patients reviewed. AMS Compliance: % recommendations accepted. Appropriate Prescribing: % of reviews that required recommendation; recommendation type; indications. Drug Utilisation: Not reported. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Lee, 2017	Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 6 years	Retrospective study of patients with 1 review during admission for clinical outcomes associated with AMS recommendations and agreement (exc. PICU, NICU and oncology).	AMS Activity: Number of patients reviewed. AMS Compliance: % recommendations accepted. Appropriate Prescribing: % of reviews that required a recommendation. Drug Utilisation: Not reported. Clinical Outcomes: LOS; 30-day readmission rate. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Di Pentima, 2009	Primary strategy: Audit and feedback Other Strategies: Prior approval, guidelines, pocket cards Country: United States Study Duration: 12 months post	Prospective study to report on AMS recommendations and errors identified after daily AMS review of targeted antibiotics.	AMS Activity: Number of patients reviewed. AMS Compliance: Not reported. Appropriate Prescribing: % of reviews that required recommendation; % doses administered and hospital admissions with a recommendation. Drug Utilisation: Not reported. Clinical Outcomes: Adverse drug events; errors avoided. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Di Pentima, 2011	Primary strategy: Audit and feedback Other Strategies: Prior approval, Guidelines, Pocket cards Country: United States Study Duration: 3 years pre, 3 years post	Evaluate impact of audit and feedback on antimicrobial use, recommendations, patient outcomes, and rates of antimicrobial resistance (inc. PICU).	AMS Activity: Number of patients reviewed. AMS Compliance: % recommendations accepted. Appropriate Prescribing: % of reviews with a recommendation; % of hospital admissions with a recommendation. Drug Utilisation: Doses /1000 PD Doses/admission; % patients who received antibiotics. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: % sensitive isolates /year; hospital and community onset infections not differentiated.
Di Pentima 2010	Primary strategy: Audit and feedback Other strategies: Prior approval; Guidelines; Pocket cards Country: United States Study Duration: 1-year pre, 3 years post	Assess the impact of audit and feedback on vancomycin use, recommendations made, patient outcomes, rates of resistance.	AMS Activity: Number of patients reviewed. AMS Compliance: Not reported. Appropriate Prescribing: % doses administered concordant with local guidelines (indication, does, etc); Prescribing errors /100 PD/year. Drug Utilisation: Doses/1000 PD. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: % resistant staphylococcus; VRE cases/year. Infection control measures not discussed; hospital and community onset infections not differentiated.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Chan, 2014	Primary strategy: Prior approval Country: United States Study Duration: 21 months pre, 4 years post	Report on vancomycin use after transition from audit and feedback (pre) to prior approval after 2 doses of vancomycin and maximum approval duration of 7 days (post).	AMS Activity: Not reported (24/7 service). AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: Doses/1000 PD. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Molloy, 2017	Primary strategy: Audit and feedback Other strategies: Prior approval Country: United States Study Duration: 3 x 3 month	Prospective interventional study to assess impact of ID physician presence on agreement with AMS recommendations (inc. HSCT).	AMS Activity: Number of recommendations. AMS Compliance: % recommendations accepted. Appropriate Prescribing: Number and type of recommendation, method of communication to prescriber. Drug Utilisation: Not reported. Clinical Outcomes: All-cause readmission; All-cause inpatient mortality; Infections resolved, new infections, LOS. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Turner, 2017	Primary strategy: Audit and feedback Other Strategies: Electronic order sets and protocols Country: United States Study Duration: 12 months pre, 23 months post	Assess impact of protocol for cardiac surgical prophylaxis, FN (as electronic order set) and appendicitis and 72-hour audit and feedback by clinical pharmacists on antibiotic use (inc. PICU).	AMS Activity: Not reported (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: DOT/1000 PD; DOT/1000PD per CMI unit. Clinical Outcomes: LOS; Inpatient mortality. Healthcare Cost: Drug acquisition cost/1000 PD from electronic medication administration record. Antimicrobial Resistance: Not reported.
Lighter-Fisher, 2017	Primary strategy: Audit and feedback Other Strategies: Guideline and drug protocols implemented; prior approval Country: United States Study Duration: 2 years pre, 2 years post, (intervention year excluded)	Assess use and resistance changes after introduction of pharmacist led audit and feedback and guidelines to previous prior approval program (inc. PICU).	AMS Activity: Number of orders reviewed; Number of recommendations. AMS Compliance: % recommendations accepted within 24 hours. Appropriate Prescribing: % prescriptions concordant with local guidelines; % orders reviewed that resulted in a recommendation. Drug Utilisation: DOT/1000 PD; LOT/ 1000 PD; LOT/ admission (collected for patients on antibiotics). Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: % sensitive isolates (inc. HO MRSA).

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Nguyen-Ha, 2016	Primary strategy: Audit and feedback-caspofungin, meropenem, vancomycin Other Strategies: Guidelines Country: United States Study Duration: Variable, 16+ months pre, 40+ months post	Interrupted time series study to assess initiation and overall use of caspofungin, meropenem and vancomycin after introduction of guidelines and pharmacist led audit at 72 hours of use (inc. PICU).	AMS Activity: Not reported (24/7 service). AMS Compliance: % recommendations accepted within 24 hours. Appropriate Prescribing: Pharmacist notes/month. Drug Utilisation: Drug starts/1000 patients; DOT^/1000 PD. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Gillon, 2017	Primary strategy: Audit and feedback-vancomycin Other Strategies: Prior approval Country: United States Study Duration: 3 years 2 months pre, 27 months post	Interrupted time series study of vancomycin use, comparison with paediatric hospitals with and without AMS programs.	AMS Activity: Not reported (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: No. of recommendations. Drug Utilisation: Patients administered vancomycin/ month; DOT/1000 PD. Clinical Outcomes: Not reported. Healthcare Cost: vancomycin acquisition cost/1000 PD. Antimicrobial Resistance: MRSA skin, bloodstream and respiratory infections (risk ratio); hospital and community onset infections not differentiated.
Hurst, 2016	Primary strategy: Audit and Feedback-all antimicrobials Country: United States Study Duration: 1 year pre, 2 years planning, 1 year post	Assess introduction of audit and feedback and daily discussion with clinical teams on antibiotic use (inc. PICU).	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: % patients on antibacterial agents; DOT/1000 PD (all agents excl. topical agents only) for each clinical area. Clinical Outcomes: HO CDI /10,000 PD; Hospital-wide LOS, 30-day readmissions; mortality. Healthcare Cost: Antimicrobial drug costs/1000 PD. Antimicrobial Resistance: Not reported.
Seah, 2014	Primary strategy: Audit and feedback Country: Singapore Study Duration: 3 months pre, 2 years, 6 months post	Assess the impact of daily audit and feedback on carbapenem prescribing on appropriateness, usage rates and clinical outcomes.	AMS Activity: % orders reviewed; Number of recommendations. AMS Compliance: % recommendations accepted within 24 hours. Appropriate Prescribing: % courses concordant with local guidelines. Drug Utilisation: DDD/100 PD; DOT/100 PD; prescriptions/100 PD. Clinical Outcomes: Hospital wide (incl. non-paediatric wards):30-day all-cause mortality/100 PD; 30-day unplanned readmissions/100 PD; LOS. Healthcare Cost: Carbapenem billing cost to patient/100 PD. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Seah, 2017	Primary strategy: Audit and Feedback Country: Singapore Study Duration: ~3 years, 6 months post	Retrospective review of patients with an AMS recommendation for factors associated acceptance vs non-acceptance and patient, clinical and cost outcomes.	AMS Activity: Reported in original study (Seah, 2014). AMS Compliance: % recommendations accepted within 24 hours. Appropriate Prescribing: Reported in original study (Seah, et al 2014). Drug Utilisation: DDD/1000 PD; DOT/1000 PD. Clinical Outcomes: LOS; 30-day readmission; 30-day mortality; Clinical improvement after 7 days; Microbial clearance. Healthcare Cost: Hospitalisation charge/admission. Antimicrobial Resistance: Patients with carbapenem resistant organism detected within 30 days.
Kreitmeyr, 2017	Primary strategy: Audit and feedback Other Strategies: Prior approval; empiric antibiotic guidelines; pocket guide Country: Germany Study Duration: 4 months pre- and post-intervention (Sept – Dec 2014, Sept- Dec 2015)	Assess implementation of audit and feedback on antibiotic use, clinical outcomes and appropriate prescribing in a general medical ward (exc. surgical, HSCT, oncology, cystic fibrosis, chronic complex diseases).	AMS Activity: Number of recommendations (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: % courses appropriate dose (+/-30% of guideline); % CAP patients treated with ampicillin. Drug Utilisation: DOT/1000 PD; LOT/1000 PD; doses/1000 PD; % patients on antimicrobials. Clinical Outcomes: Inpatient mortality; LOS. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Lee, 2016	Primary strategy: Guidelines and Audit and feedback Country: United States Study Duration: 12 months pre, 1 year of implementation, 12 months post	Assess introduction of cardiac, neonatal and paediatric ICU guidelines and audit and feedback on antibiotic use, clinical outcomes and cost.	AMS Activity: Not reported (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: % concordance with PICU, and Cardiac ICU guidelines (HO blood stream infection, tracheitis, HAP, CAP, CA sepsis; cardiac surgical prophylaxis, NEC, neonatal sepsis). Drug Utilisation: DOT/1000 PD. Clinical Outcomes: LOS; Mortality (Number of deaths). Healthcare Cost: Drug acquisition cost ICU areas/period; Hospital-wide drug cost/period obtained from PHIS. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Murni, 2015	Primary strategy: Audit and feedback Other Strategies: Infection control, checklists, education, guidelines Country: Indonesia Study Duration: 12 months pre, 12 months post	Assess antimicrobial use and infection control education, guidelines and daily review of all antibiotics on guideline concordant prescribing, HOI and mortality (inc. PICU).	AMS Activity: Not reported (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: % patients on guideline concordant therapy (spectrum, dose +/-20% and duration +/-20%). Drug Utilisation: % patients on antibiotics. Clinical Outcomes: Mortality HOI /1000 PD; % patients with HOI. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Ceradini, 2017	Primary strategy: Audit and feedback-video case conference Other Strategies: Prior Approval Country: Italy Study Duration: 14 months pre, 12 months post	Assess impact of weekly video conference with ID physicians on antimicrobial use, cost, resistance outcomes in a specialist hospital.	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: Packs of antimicrobials. Clinical Outcomes: PICU LOS; Hospital LOS. Healthcare Cost: Pharmacy antimicrobial and "complex molecule" costs/admission. Antimicrobial Resistance: MDR bacteria/1000 PD.
Newman, 2012	Primary strategy: Audit and feedback program formed/CAP guideline Country: United States Study Duration: 12 months pre, 12 months post guideline implementation	Describe the impact of CAP guideline on antimicrobial prescribing and effectiveness of guideline concordant prescribing.	AMS Activity: Not reported. AMS Compliance: n/a. Appropriate Prescribing: % CAP patients on ampicillin or amoxycillin; % patients with blood cultures. Drug Utilisation: Not reported. Clinical Outcomes: % patients with ineffective therapy after 48 hours of use (agent changed or developed effusion/empyema) or readmission or change of antibiotic within 30 days of discharge. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Hennig, 2018	Primary strategy: Audit and Feedback-FN guideline Country: Australia Study Duration: 9 months pre, 15 months post	Assess impact of FN guideline with weekly audit and feedback on gentamicin use.	AMS Activity: Not reported. AMS Compliance: n/a. Appropriate Prescribing: % FN admissions treated empirically with gentamicin; % FN admission administered gentamicin >48 hours without confirmed Gram-negative infection; % FN admission administered gentamicin >48 hours without TDM; % FN admissions with blood culture. Drug Utilisation: DOT/ admission. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Wattier, 2017	Primary strategy: Audit and Feedback-FN guideline Country: United States Study Duration: 23 months pre, 22 months phase 1(oncology implementation, 12 months phase 2 HSCT implementation + Audit and feedback)	Interrupted time series analysis to assess tobramycin and ciprofloxacin use after phased implementation of FN guidelines audit and feedback for oncology and HSCT patients.	AMS Activity: Not reported (daily AMS review). AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: DOT/1000 PD. Clinical Outcomes: LOS; % patients admitted to ICU; PICU days/admission (e.g. oncology PICU days/all oncology admissions); Inpatient mortality; HO CDI/10,000 PD. Healthcare Cost: Not reported. Antimicrobial Resistance: Tobramycin and ciprofloxacin resistant Gram- negative isolates; hospital and community onset infections not differentiated.
Ambroggio, 2013	Primary strategy: QI methodology for CAP guideline Strategies: Education, pocket card, electronic order set, pre-formatted electronic medical record note Country: United States Study Duration: 6 months pre, 6 months post	Assess a QI initiative utilising systematic review and improvement on CAP guideline concordance.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % CAP case with guideline concordant antibiotic and choice. Drug Utilisation: Not reported. Clinical Outcomes: LOS. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Berild, 2002	Primary strategy: Audit and Feedback Other strategies: Empiric antibiotic guidelines, pocket guide Country: Norway Study Duration: ~3 years pre, 3 years post	Assess impact of empiric guidelines with audit and feedback on antibiotic use and cost in a paediatric ward.	AMS Activity: Not reported (weekly feedback). AMS Compliance: Not reported. Appropriate Prescribing: % patients on guideline concordant therapy. Drug Utilisation: % of patients prescribed antibiotics; DDD/100 PD. Clinical Outcomes: Not reported. Healthcare Cost: Drug acquisition cost to clinical area/100 PD; % of hospital drug costs attributed to antibiotics. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Sáez-llorens, 2000	Study: Sáez-llorens, 2000 Primary strategy: Prior approval Other strategies: Surgical prophylaxis <24 hours, rationalise empiric antibiotics for neonates at 72 hours; ID approval required for all antibiotics after 7 days Country: Panama Study Duration: 2 years pre, 2 years post	Before and after study to assess impact of antibiotic restriction on clinical and microbial outcomes, and antibiotic costs (inc. PICU).	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: Vials. Clinical Outcomes: All cause inpatient mortality; LOS. Patients with and without HOI reported separately. Healthcare Cost: Drug acquisition cost/period; Number of vials purchased/period. Antimicrobial Resistance: % sensitive isolates (stratified to Nursery, wards, PICU).
Metjian, 2008	Primary strategy: Prior approval Country: United States Study Duration: 4 months	Prospective cohort study describing the activities and cost outcomes of an established prior approval AMS program (inc. PICU).	AMS Activity: Number of requests for AMS approval. AMS Compliance: % recommendations accepted; intermittent assessments for compliance with standard approved indications. Appropriate Prescribing: % calls that required recommendation. Drug Utilisation: Not reported. Clinical Outcomes: Patients with ineffective therapy or re-infection within 48 hours of AMS changes to therapy; Unplanned readmission. Healthcare Cost: Difference of requested and approved antimicrobial drug acquisition cost/period. Antimicrobial Resistance: Not reported.
Ross, 2016	Primary strategy: Prior Approval with automated stop to antimicrobial orders without approval (see Metjian 2008) Country: United States Study Duration: Patients on antibiotics, ~2 years pre, 2 years post. Bacteraemia patients: 2 years, 8 months post	Retrospective evaluation of automatic stop orders on clinical outcomes with matched cohort of patients with mono-bacteraemic infections in a hospital with a prior approval AMS program.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: Not reported. Drug Utilisation: Not reported. Clinical Outcomes: All-cause inpatient mortality; 30-day hospital readmission; LOS. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Agwu, 2008	Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 12 months pre, 12 months post	Report on user satisfaction, and program improvements after transitioning from a telephone to web-based tool for prior approval.	AMS Activity: Number of requests per month; Time from request to dispensing. AMS Compliance: Not reported. Appropriate Prescribing: % of requests approved; % approved for initiation; % initiation approvals reapproved. Drug Utilisation: DOT/1000 PD; Doses/day. Clinical Outcomes: LOS. Healthcare Cost: Adjusted drug acquisition cost/1000 PD (exc. palivizumab and liposomal amphotericin). Antimicrobial Resistance: Not reported.
Venugopal, 2014	Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 4 years post	Retrospective evaluation of AMS requests for factors associated with approval patterns and trends over time (inc. PICU).	AMS Activity: Number of requests; Time taken for AMS decision. AMS Compliance: Number of automatic approvals. Appropriate Prescribing: % of requests approved; %approved for initiation, % initiation approvals that were reapproved. Drug Utilisation: Not reported. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Sick, 2013	Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 4 years post	Retrospective evaluation of antimicrobial approval rates for AMS generated cost savings (exc. PICU/ED).	AMS Activity: Number of requests for AMS approval. AMS Compliance: Not reported. Appropriate Prescribing: % of requests approved. Drug Utilisation: Doses/month. Clinical Outcomes: Hospital LOS. Healthcare Cost: Cost/1000 PD; Difference of requested and approved antimicrobial cost (inc. palivizumab and liposomal amphotericin). Antimicrobial Resistance: Not reported.
Horikoshi, 2016	Primary strategy: Prior approval via electronic medication management system Other strategies: Audit and feedback at 72 hours Country: Japan Study Duration: ~21 months pre, ~42 months post	Assess the impact of prior approval for antipseudomonal antibiotics on use and clinical outcomes.	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: DOT/1000 PD. Clinical Outcomes: All-cause inpatient mortality; Infection-related mortality (microbiological confirmation or clinical confirmation by ID physician, excluding palliative care); LOS. Healthcare Cost: Drug acquisition cost/1000 PD. Antimicrobial Resistance: % susceptible *P. aeruginosa* isolates.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Horikoshi, 2017	Primary strategy: Prior approval via electronic medication management system Other strategies: Audit and feedback at 72 hours Country: Japan Study Duration: 17 months pre, 66 months post	Interrupted time series analysis to assess impact of carbapenem prior approval on rates of use and correlation with resistance.	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: DOT/1000 PD. Clinical Outcomes: All-cause mortality/1000 PD; Infection related mortality (microbiological confirmation or clinical confirmation by ID physician, excluding palliative care); LOS. Healthcare Cost: Not reported. Antimicrobial Resistance: % non-susceptible Gram-negative isolates per year.
Lee, 2007	Primary strategy: Formulary Restriction Country: Korea Study Duration: 3 years pre, 4 years post	Assess the impact of cephalosporin formulary restriction on Extended spectrum beta-lactamase producing bacteria and mortality (exc. Surgical).	AMS Activity: n/a. AMS Compliance: Not reported. Appropriate Prescribing: Not reported. Drug Utilisation: DOT/1000 PD. Clinical Outcomes: Infection related mortality (% deaths 7 and 30 days of admission with ESBL vs non-ESBL cases); Number of adverse drug events. Healthcare Cost: Not reported. Antimicrobial Resistance: % Extended spectrum beta-lactamase producing *K. pneumoniae* and *E. coli.*
Karsies, 2014	Primary strategy: CPOE order set for suspected sepsis in PICU Country: United States Study Duration: 1 year pre (2004), 1 year post (2007) *Implemented in 2005/2006*	Assess the impact of an empiric antibiotic order set for critically ill patients on time to appropriate antibiotics.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % guideline concordant empiric antibiotic episodes; Time to guideline concordant antibiotic; % culture positive episodes with appropriate spectrum empiric antibiotic; Time from positive culture to appropriate spectrum antibiotic (i.e., drug-bug match). Drug Utilisation: Not reported. Clinical Outcomes: Inpatient mortality. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Rutman, 2017	Primary strategy: Pathway/Order set for CAP Country: United States Study Duration: 12 months pre, 12 months post	Assess the impact of a CAP pathway on ampicillin use, use of tests, LOS and hospitalisation costs.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % CAP patients prescribed ampicillin; % CAP patients with blood cultures; % CAP patients with viral test. Drug Utilisation: Not reported. Clinical Outcomes: LOS. Healthcare Cost: Hospitalisation cost/admission. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Smith, 2012	Primary strategy: AMS taskforce for CAP Other strategies: Education, pre-printed order form Country: United States Study Duration: 33 months, ~12 months post	Assess impact of CAP guidelines and education on empirical antibiotic choice.	AMS Activity: Not reported. AMS Compliance: n/a. Appropriate Prescribing: % CAP patients on ampicillin within 24 hours of admission. Drug Utilisation: Not reported. Clinical Outcomes: CAP mortality; Unplanned 30-day readmissions; LOS; Adverse events; % patients with infection caused by staphylococcus or pseudomonas treated with ampicillin. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Ding, 2008	Primary strategy: Order Form Order forms required documented indication, dose, frequency, and duration, signed by a Consultant Paediatrician. Country: China Study Duration: 2 years pre, 2 years post	Before and after study to assess impact of antibiograms and antibiotic order form for targeted antimicrobials on antibiotic use in PICU.	AMS Activity: Not reported. AMS Compliance: Not reported. Appropriate Prescribing: % patients on empiric vs targeted antibiotics; % patients on a single antibiotic. Drug Utilisation: antibiotics/patient; LOT/patient; % patients on antibiotics (first 15 patients admitted each month). Clinical Outcomes: PICU LOS. Healthcare Cost: Antibiotic cost/PD from audited records. Antimicrobial Resistance: % resistant clinical isolates.
Stocker, 2012	Study: Stocker, 2012 Primary strategy: Self-audit form/antibiotic “time out” at 48 hours and 5 days Country: United Kingdom Study Duration: 90 days pre, 110 days post	Before and after study assessing impact of a mandatory antibiotic checklist on appropriate treatment for suspected sepsis in PICU.	AMS Activity: n/a (no AMS activity, form promoted by pharmacists). AMS Compliance: % of antibiotic courses with a checklist. Appropriate Prescribing: % culture negative courses <3 days; % courses targeted based on cultures; % empiric courses > 3 days with a documented and rational indication for use. Drug Utilisation: Antibiotic courses (1 or more days of antibiotic). Clinical Outcomes: All-cause mortality; Infection related mortality; % antimicrobial courses initiated due to confirmed or suspected relapse. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
Bolon, 2005	Primary strategy: Order Form for vancomycin Country: United States Study Duration: 8 months pre- and post-form (November-June pre- and post-intervention); additional 2 months of for improved compliance	Assess the impact of a vancomycin order form on appropriateness and rates of use.	AMS Activity: Not reported. AMS Compliance: % vancomycin courses with an order form; % of forms with a documented indication. Appropriate Prescribing: % courses concordant with local guidelines. Drug Utilisation: Doses/1000 PD. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Abboud, 2006	Primary strategy: CPOE integrated alert for aminoglycoside TDM Country: United States Study Duration: 3 months pre, 3 months post	Before and after study to assess CPOE integrated prompt to order aminoglycoside levels on TDM.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % patients with sub-therapeutic levels; % patients with toxic levels; % aminoglycoside courses >= 4 days without TDM. Drug Utilisation: Not reported. Clinical Outcomes: Not reported. Healthcare Cost: Not reported. Antimicrobial Resistance: Not reported.
Mullett, 2001	Primary strategy: CDS for PICU Country: United States Study Duration: 6 months pre, 6 months post	Before and after study to assess impact of hospital information system integrated CDS at the bedside on PICU antimicrobial prescribing.	AMS Activity: n/a. AMS Compliance: Not reported. Appropriate Prescribing: Antimicrobial mismatch/100 admissions; Days of incorrect dosage/100 patient days; Pharmacist interventions /1000 orders. Drug Utilisation: % patients on antibiotics; Doses/patient; Number of antibiotics/patient. Clinical Outcomes: Adverse drug reactions/100 admissions; PICU LOS; Hospital LOS; Inpatient mortality. Healthcare Cost: Antimicrobial drug cost/admission. Antimicrobial Resistance: Not reported.

Author, Publication year	Primary Strategy, Country, Study Duration	Study Description	Reported Measures
King, 2007	Primary strategy: CPOE evidence alert for bronchiolitis management Country: Canada Study Duration: 5 months pre, 5 months post (bronchiolitis season pre- and post-intervention)	Before and after study to assess impact of CPOE integrated evidence summary on bronchiolitis management on antibiotic use and hospital LOS.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % bronchiolitis patients prescribed antibiotics. Drug Utilisation: Not reported. Clinical Outcomes: LOS. Healthcare Cost: Resource intensity weight. Antimicrobial Resistance: Not reported.
Wilson, 2002	Primary strategy: Electronic Pathway for bronchiolitis Country: United States Study Duration: 6 months	Assess impact of an electronic bronchiolitis pathway on frequency of antibiotic use and impact on hospital LOS and costs.	AMS Activity: n/a. AMS Compliance: n/a. Appropriate Prescribing: % bronchiolitis patients prescribed antibiotics. Drug Utilisation: Not reported. Clinical Outcomes: Readmission within 72 hours; LOS; Adverse drug events. Healthcare Cost: Hospitalisation cost. Antimicrobial Resistance: Not reported.

AMS: Antimicrobial stewardship; CA: Community-acquired; CAP: Community-Acquired Pneumonia; CDI: Clostridium difficile infection; CDS: Computerised decision support; CPOE: Computerised physician order entry; DOT: Days of antimicrobial therapy; *E. coli*: *Escherichia coli* ;ESBL: Extended-spectrum beta-lactamase producing bacteria; exc.: exclusions; FN: Febrile neutropenia; HO: Hospital-onset or hospital acquired; HSCT: Haemopoietic stem cell transplant; ICU: Intensive Care Unit; inc. : includes; *K. pneumoniae: Klebsiella pneumoniae;* LOS: Length of hospital stay; LOT: Length of antimicrobial therapy; NEC: Necrotising enterocolitis; NICU: Neonatal Intensive Care Unit; *P. aeruginosa: Pseudomonas aeruginosa*; PD: Patient bed-days; PICU: Paediatric Intensive Care Unit; QI: Quality improvement; TDM: Therapeutic drug monitoring; 24/7: 24-hours, 7 days per week

^Drug utilisation metrics consolidated for interpretation, authors may refer to metrics with different terminology in original studies

*Stakeholder surveys are not included in summary table

Measures of AMS activity

Where the frequency of audit and feedback was reported, the activity was conducted each weekday by the end of the study period (78%, 18/23), or once per week or fortnight (3/23). (13,31,51) The two studies that did not specify the frequency of audit and feedback activities did not report the number of audits conducted. (30,32) Among the programs that implemented prior authorisation for prescribing, half reported the extent of AMS activity in terms of antimicrobial prescriptions requested or reviewed. (45,53-55) Additional process measures such as the time taken for AMS decisions to be made were reported infrequently. (53,54)

Measures of appropriate prescribing and AMS compliance

Audit and feedback studies consistently reported the proportion of patients, orders or prescriptions audited that resulted in an AMS recommendation. Generally, recommendations were made with respect to local guidelines and were variously described as recommendations to: discontinue antimicrobials, change the antimicrobial agent (due to confirmed or suspected pathogen, adverse events or toxicity, formulary preference or cost), change the dosage or route (e.g. switch from IV to oral route), conduct additional tests or monitoring, or to seek a formal ID consultation. Across studies, doses were deemed ‘appropriate’ when between 10% to 30% of the recommended milligram per kilogram dose. One AMS program additionally assigned a risk of harm (minimum to severe) in the process of AMS audit and reported these antimicrobial errors in the local incident

reporting system.(16,17) Four studies of audit and feedback interventions included no assessments of the quality of prescribing (13,14,32,49). Studies of prior approval strategies reported the proportion of antimicrobial prescription requests that were approved as a measure of appropriateness (4/8),(45,53-55) only one study of a prior approval strategy reported the specific AMS recommendations that were made (e.g., discontinue, change agent, switch from IV to oral route). (45) Supplementary measures included: time taken to administer the most appropriate antibiotic, (23) the proportion of patients with blood cultures prior to empiric antibiotic therapy (26), and the rate of pharmacist interventions(Table 1.6). (22)

Compliance with AMS recommendations and processes were measured in a subset of studies in addition to appropriateness. Eleven studies reported the proportion of AMS recommendations that were accepted by prescribers, most often arising from audit and feedback (10/11), (34-38,40,42,43,46,50) six of these studies were of two AMS programs. The same programs also reported on 'agreement' with AMS recommendations, including the prescriber's reasoning for disagreement with AMS recommendations, (42) and agreement with an initial AMS recommendation vs agreement to a compromise recommendation reached after negotiation. (34) The single study of a prior approval strategy that directly monitored and reported on adherence measured adherence to recommendations made to change or discontinue therapy. (45)

There was a lack of studies which reported attempts by staff to circumvent AMS interventions. In the single study that investigated possible AMS 'workarounds' by staff, approval request patterns were studied over time to identify whether staff might be requesting approvals for unverified indications and choosing to list those indications that would be most likely to lead to AMS approval.(53) Two of the three studies that assessed antibiotic order forms monitored the utilisation of the forms and whether forms were completed. (19,20)

Measures of antimicrobial utilisation

We identified 28 studies that measured antimicrobial use according to a diverse range of metrics and methods (Table 1.6 and Table 1.7 respectively). Most studies assessed antimicrobial use in the context of baseline patient factors such as All Patient Refined Diagnosis-Related Group (APR-DRG), source of infection or indication, PICU admission rates or presence of comorbidities (23/28). Three studies assessed the impact of AMS strategies on antimicrobial utilisation without clinical outcomes or patient factors. (39,46,50)

The most common units of measure for antimicrobial utilisation across all 28 studies were 'days of therapy' per agent (16/28) and the number of doses used (8/28). The days of antimicrobial therapy was typically reported as the standard metric "DOT", an aggregate of the number of days each individual antimicrobial is prescribed or administered. DOT was sometimes

reported together with “LOT”, a measure of the length of therapy with any antimicrobial (i.e., 2 days of antimicrobial use with 2 agents = 4 DOTs or 2 LOTs). As DOT does not measure daily dose it is the preferred metric for paediatric utilisation, and the standard reporting measure for national surveillance in the United States. (6,56)

Non-standard paediatric units such as adult ‘defined-daily-doses’ (DDD), number of vials and packs were reported infrequently (n=5). Usage measures were most commonly standardised by the number of patient occupied bed-days (n=20) or patient admissions (n=7). In hospitals without electronic medication records, daily data collection or systematic patient sampling was used in order to monitor changes in actual use. (21,44)

Table 1.7 Characteristics and summary of selected findings in published paediatric antimicrobial stewardship evaluations[^#*]

Study details	Description	Summary of Reported Findings
Study: Newland, 2012 Primary strategy: Audit and feedback Country: United States Study Duration: 3 years, 3 months pre, ~2 years, 10 months post	Interrupted time series with external control to assess impact of audit and feedback on antibiotic use (inc. PICU)	Audit conducted at 48 hours of antimicrobial use; AMS program performed 8765 patient reviews with 2380 AMS recommendations over 30 months; 19% of patient reviews resulted in AMS recommendations, primary recommendation: discontinuation. Prescriber agreement ranged from 83% to 100% per month (p=0.34) Statistically significant decline in percentage of patient reviews that resulted in recommendations over the study period (p<0.001). Antimicrobials targeted (IV and oral) reduced by ~12% in DOT/1000 patient days and ~ 13% in LOT/1000 patient days (p<0.001). Total use (targeted and non-targeted agents) reduced ~6% (p<0.001); ~18% reduction in targeted antimicrobial DOT and LOT after dividing use by mean CMI/month (p<0.001) and when compared with external controls (other paediatric hospitals without AMS) (p<0.001). Interrupted time series of hospital-wide all-cause mortality and readmission rate were not statistically significant (p=0.40 and p=0.35 respectively). Rate of infection was not statistically significant (p=0.65)
Study: McCulloh, 2015 Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 5 years post	Retrospective study of patients with 1 AMS review during admission for clinical outcomes associated with AMS recommendations and prescriber agreement.	AMS review performed for 2178 patients; 83.8% required no intervention overall. Decline in reviews that required AMS recommendation years 1-5 (p<0.01), 23.5% year 1, 12.1% in year 3. Primary indication for recommendations was CAP (30%), primary recommendation discontinuation (28.6%). Overall agreement with AMS recommendation 86.9%, ID consult primary recommendation associated with disagreement (25%), CAP primary indication associated with disagreement (50%). No statistically significant difference in median LOS (agree 87.9 hours vs disagree 74.3 hours, p=0.123). After matching APR-DRG median LOS (agree=+15.3 hours, p=NS) and readmission (agree 1.1% vs disagree 2.2% p=NS)

Study details	Description	Summary of Reported Findings
Study: Goldman, 2015 Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 5 years post	Retrospective study of AMS recommendations for indications and agents associated with an AMS recommendation and agreement (inc. PICU)	Retrospectively review of AMS recommendations for indications and agents associated with an AMS recommendation and prescriber agreement. 2,317 recommendations from 15,016 AMS patient reviews. Decline in % reviews that resulted in recommendation 20% (year 1) to 14% (year 5). Primary recommendation was discontinuation (45%), primary indication for recommendation CAP (45%) Overall agreement 78%. Highest likelihood of disagreement: carbapenem and linezolid use, respiratory and ENT indications, NICU and haematology/oncology patients.
Study: Lee, 2017 Primary strategy: Audit and feedback Other Strategies: Prior approval Country: United States Study Duration: 6 years	Retrospective study of patients with 1 review during admission for clinical outcomes associated with AMS recommendations and agreement (exc. PICU, NICU, HSCT and oncology)	Retrospective review of patients with 1 AMS review during admission for clinical outcomes associated with AMS recommendations and prescriber agreement (exc. PICU, NICU, oncology) stratified for clinical or medical admission, with or without CCC code. Overall, 8038 reviews included in analysis. Recommendations: Highest in surgical with CCC (28.1%), lowest in surgical without CCC (8.9%). Median LOS recommendation vs no recommendation: No difference surgical with or without CCC ($p=0.998$ and $p=0.955$). Differences for medical patients with and without CCC statistically significant in adjusted model (medical without CCC 80.9 vs 67.6 hours, $p<0.001$; medical with CCC 184.3 vs 150.5 $p<0.001$). Median LOS agree vs disagree: No statistically significant difference in any group, trend toward shorter LOS when prescriber agreed across all groups. 30-day readmission recommendation vs no recommendation: Not statistically significant for surgical with or without CCC (without CCC unadjusted 0 vs 1.12%, $p=0.6$; surgical with CCC 0.56% vs 2.26%, $p=0.076$). Medical without CCC not statistically significant (2.44% vs 2.3% $p=0.83$). Medical with CCC (7.3% vs 4.2%, $p = 0.005$). 30-day readmission agree vs disagree: Not statistically significant for any group (medical without CCC 3.86 vs 2.93%, $p=0.655$; medical with CCC 4.87 vs 4.78% $p=0.97$).

Study details	Description	Summary of Reported Findings
Study: Di Pentima, 2009 Primary strategy: Audit and feedback Other Strategies: Prior approval, Guidelines, Pocket cards Country: United States Study Duration: 12 months post	Prospective study to report on AMS recommendations and errors identified after daily AMS review of targeted antibiotics.	Report on AMS recommendations and errors identified after daily AMS review of targeted antibiotics. AMS performed 5564 prescription reviews, 493 recommendations for 257 patients over 12 months. 67% of recommendations in targeted antibiotics considered errors, 48% of those classified as “significant”, 25% “severe”. Primary errors: dose was not within +/-10% recommendation (61%), indication (23%). Reported outcomes likely to result from recommendation: optimisation (47%), cost reduction (28%), ADR prevention (25%). Automatic stop orders ~9% of errors identified.
Study: Di Pentima, 2011 Primary strategy: Audit and feedback Other Strategies: Prior approval, Guidelines, Pocket cards Country: United States Study Duration: 3 years pre, 3 years post	Evaluate impact of audit and feedback on antimicrobial use, recommendations, patient outcomes, and rates of antimicrobial resistance (inc. PICU).	Daily AMS review resulted in 1673 recommendations for 973 patients (3% of admissions) % recommendations for IV to oral switch reduced (23% year 1 to <1%, p=0.015), acceptance by prescribers increased (83% to 92%, p<0.001) Targeted antimicrobial doses administered/1000 PD per year reduced by 21% (p< 0.001), prior approval antimicrobials reduced by 36%. % patients on antibiotics unchanged (~43%), median doses/admission unchanged (~4). No significant change in % of sensitive E. cloacae (n>41) E. coli (n>474) K. pneumoniae (n>76), P. aeruginosa isolates (n>182) Acuity determined by PICU admissions/1000 admissions/year (+7%)
Study: Chan, 2014 Primary strategy: Prior approval Country: United States Study Duration: 21 months pre, 4 years post	Report on vancomycin use after transition from audit and feedback (pre) to prior approval after 2 doses of vancomycin and maximum approval duration of 7 days (post).	Segmented regression analysis performed producing a post-intervention slope (prior approval) that was +3.9 doses/month (SE 1.51, p=0.012) compared to the pre-intervention slope (audit and feedback). The authors noted vancomycin dosage recommendations and TDM targets in hospital guidelines were increased 8 months prior to the transition from audit and feedback to prior approval.

Study details	Description	Summary of Reported Findings
Study: Molloy, 2017 Primary strategy: Audit and feedback Other strategies: Prior approval Country: United States Study Duration: 3 x 3 months	Prospective interventional study to assess impact of ID physician presence on agreement with AMS recommendations (inc. HSCT)	Prospective interventional study to assess impact of ID physician presence on agreement with AMS recommendations. 154 recommendations made over 3 phases. Phase 2: ID physician present for feedback, or feedback communicated via telephone framed as endorsed by ID physician. Patients with recommendations: phase 1 (n = 59), phase 2 (n = 55) phase 3 (n = 40). No statistically significant differences in monitored patient factors. Overall acceptance was 76% vs 87% (phase 1 and 2 vs phase 3, p=0.155). Nil statistically significant clinical outcomes. New infections occurred in 1 patient in each of phase 1 and 2;1 readmission reported in phase 2, 2 deaths in phase 2.
Study: Turner, 2017 Primary strategy: Audit and feedback Other Strategies: Electronic order sets and protocols Country: United States Study Duration: 12 months pre,23 months post	Assess impact of protocol for cardiac surgical prophylaxis, FN (as electronic order set) and appendicitis and 72-hour audit and feedback by clinical pharmacists on antibiotic use (inc. PICU).	Conducted at a non-freestanding hospital by clinical pharmacists with no specialty ID training. Daily review at 72 hours of antibiotic use with appropriateness judged by pharmacists. CMI adjusted DOT/1000 PD reduced by 16.8% (p<0.001) or 1.1% without CMI adjustment (p=0.35). No change to antipseudomonal beta lactam antibiotics. Mean LOS controlled for CMI was not statistically significant (2.9 days vs 3 days, p=0.19), differences in inpatient mortality was not statistically significant (0.56% vs 0.68%, p=0.68). AMS program reported $67,000 in antibiotic costs saved per year with no associated maintenance costs.

Study details	Description	Summary of Reported Findings
Study: Lighter-Fisher, 2017 Primary strategy: Audit and feedback Other Strategies: Guideline and drug protocols implemented; prior approval Country: United States Study Duration: 2 years pre, 2 years post, (intervention year excluded)	Assess use and resistance changes after introduction of pharmacist led audit and feedback and guidelines to previous prior approval program (inc. PICU).	Previous prior approval program led by ID fellows with no hospital guidelines for common indications (e.g. sepsis, MRSA decolonisation, FN, CDI) and antibiotics (aminoglycosides, vancomycin). Audit and feedback at 48-72 hours of therapy by pharmacists with training in neonatology and oncology. Feedback was communicated via e-mail or telephone, not documented in medical record. AMS performed 1211 antimicrobial orders reviewed, guidelines were available for 44% of all antimicrobial orders and guideline concordance ~88%. Thirty percent of orders resulted in a recommendation, primarily “optimisation” including use of extended interval infusions; 89% or recommendations accepted and changed within 24 hours, lower rates of acceptance for FN and suspected sepsis in ICU. Median aggregate use reduced from 803 DOT/1000 PD/month to 761 DOT/ 1000 PD/month p=0.03, Mann-Whitney U test) with a nonsignificant downward trend in targeted antibiotics. Median LOT/admission (5.2 vs 4.8, p<0.01). Statistically significant increases in ceftriaxone, cefoxitin, linezolid, ampicillin/sulbactam, and reduced aminoglycosides, piperacillin, ampicillin and vancomycin(p<0.05). Piperacillin/tazobactam sensitive K. pneumoniae increase (90 vs 97, p<0.05, n>31), cefoxitin sensitive E. coli increased (87% vs 97%, p<0.05, n>61), gentamicin sensitive P. aeruginosa increased (79 vs 89%, p<0.05, n>55)
Study: Nguyen-Ha, 2016 Primary strategy: Audit and feedback – caspofungin, meropenem, vancomycin Other Strategies: Guidelines Country: United States Study Duration: Variable, 16+ months pre, 40+ months post	Interrupted time series study to assess initiation and overall use of caspofungin, meropenem and vancomycin after introduction of guidelines and pharmacist led audit at 72 hours of use (inc. PICU).	Conducted at a freestanding paediatric hospital by clinical pharmacists with no specialty ID training. Daily audit after 72 hours of caspofungin, meropenem, vancomycin by clinical pharmacists during usual working hours, ID physicians on weekends and on-call pharmacists for all other patients. Feedback provided via electronic and verbal means to discontinue, continue, change antimicrobial, consult ID. Pharmacist dose optimisation activities were reported separately. Prescriber acceptance reported for 3 months of the study was >90%. Caspofungin introduced to replace liposomal amphotericin. Mean vancomycin drug starts reduced (137.7 patients/1000 patients vs 121.4 patients/1000 patients, p=0.005), DOT declined (138.2/1000 PD vs104.2/1000 PD, p<0.001) Mean meropenem drug starts (14.3 patients/1000 patients vs 11.3 patients/1000 patients, p=0.67), DOT 20.0/1000 PD to 13.8/1000 PD, p=0.21).

Study details	Description	Summary of Reported Findings
Study: Gillon, 2017 Primary strategy: Audit and feedback-vancomycin Other Strategies: Prior approval Country: United States Study Duration: 3 years 2 months pre, 27 months post	Interrupted time series study of vancomycin use, comparison with paediatric hospitals with and without AMS programs	AMS pharmacists performed daily reviews (Monday to Friday); 123 interventions, primary recommendations to discontinue (50%) or consult ID (29%). Mean patients who received vancomycin/month reduced (23 vs 20, p < 0.001) with reduction in mean DOT/1000 PD/month (114 vs 89, p< 0.001). No statistically significant difference in trend compared to other hospitals with AMS. Vancomycin cost reduced by 41%. No significant difference in MRSA bloodstream and respiratory infections (RR 1.2, 95% CI 0.8 - 2 and 1.6, 95% CI 0.9-3). MRSA skin/soft tissue infection increased by 1.6 (95% CI 1.5-1.8). Rates of vancomycin use compared with other paediatric hospitals with AMS programs; vancomycin, linezolid and clindamycin were compared with two paediatric hospitals without AMS programs.
Study: Hurst, 2016 Primary strategy: Audit and Feedback-all antimicrobials Country: United States Study Duration: 12 months pre, 24 months planning, 12 months post	Assess introduction of audit and feedback and daily discussion with clinical teams on antibiotic use (inc. PICU).	Pharmacist/ID physician review all antimicrobials at 24 and 72 hours of therapy with no supply restrictions. Feedback provided face-to-face. AMS reviews increased from 3 per week in first 8 months of post-intervention phase to 5 days per week in the final 4 months of the post-intervention phase. Patients on antimicrobials (pre- 59.9%, planning 56.2%, post- 50.2%). Interrupted time series analysis antimicrobial use across 3 phases: reduced aggregate antimicrobial use (pre- vs planning slope −10.4, 95% CI −19 to −1.8, p<0.05; pre- vs post- slope −15, 95% CI −26.4, to -3.5, p<0.05). Meropenem use reduced (pre-vs planning slope −2.2, 95% CI −3.8 to −0.5, p<0.05; pre- vs post slope −3.9, 95% CI −6.1 to −1.7, p<0.05). HO CDI declined from planning to post (8.3 vs 4.9 /10,000 PD, p<0.01), Intervention coincided with infection control activities. Hospital-wide mean LOS (pre- and planning phases 5.2 vs post phase 4.8 days), 30-day readmission (9.7% vs 10.4% vs 10.9%), inpatient mortality (pre- 1.1% vs 1.0 vs 0.9%). Proportion of patients within each APR—DRG category (1-4) similar across phases. Mean cost/100 PD/month unchanged ($10,546 vs $10,45, p=0.93). Activity and acceptance rates collected after the study period: 1250 patients, 1600 orders reviewed each month, 150 AMS recommendations made with 84% acceptance rate.

Study details	Description	Summary of Reported Findings
Study: Seah, 2014 Primary strategy: Audit and feedback Country: Singapore Study Duration: 3 months pre, 2 years, 6 months post	Assess the impact of daily audit and feedback on carbapenem prescribing on appropriateness, usage rates and clinical outcomes.	Daily review of carbapenems (Monday to Friday) in a hospital for women and children. AMS recommendations communicated as written case notes and verbally. 86.6%(350/404) reviews in paediatric patients. Hospital-wide 61.2% recommendations accepted, primary recommendation discontinue. Paediatric use reduced (0.9 vs 0.4 DDD/100 PD, p=0.013). Change in DOT/100 PD not statistically significant (1.5 vs 0.8, p=0.06). Prescriptions/ 100 PD unchanged (p=0.36). Hospital-wide 30-day all-cause mortality unchanged (0.16 vs 0.17, p=0.57), 30-day unplanned readmission reduced (0.26 vs 0.04, p=0.006), median LOS unchanged (3.1 days pre- and post, p=0.1). Mean cost/100 PD in paediatrics reduced ($175 vs $149, p=0.01).
Study: Seah, 2017 Primary strategy: Audit and Feedback Country: Singapore Study Duration: ~3 years, 6 months post	Retrospective review of patients with an AMS recommendation for factors associated acceptance vs nonacceptance and patient, clinical and cost outcomes	101 patients with carbapenem recommendations, acceptance(n=67) vs non-acceptance (n=34) of AMS and outcomes. No statistically significant difference between paediatric, neonate and obstetrics/gynaecology. Hospital-wide (accepted vs non-acceptance): DDD and DOT lower in accept group, p<0.001). Median LOS unchanged (26 vs 39, p=0.11), 30-day readmission rate (38% vs 52%, p= 0.212). Nil deaths within 30-days in accept group. No statistically significant difference in clinical improvement at 7 days or microbial clearance between groups. Differences in median hospital charges did not reach statistical significance ($10,843 vs $17,470, p=0.088) Number of patients with carbapenem resistant organism detected within 30-days of therapy was not statistically significant (2 vs 0, p=0.55).

Study details	Description	Summary of Reported Findings
Study: Kreitmeyr, 2017 Primary strategy: Audit and feedback Other Strategies: Prior approval; empiric antibiotic guidelines; pocket guide Country: Germany Study Duration: 4 months pre- and post-intervention (Sept - Dec 2014, Sept- Dec 2015)	Assess implementation of audit and feedback on antibiotic use, clinical outcomes and appropriate prescribing in a general medical ward (exc. surgical, HSCT, oncology, cystic fibrosis, chronic complex diseases)	Daily review by a pharmacist, weekly ID round. Written and verbal feedback. Over 4 months, 167 recommendations were made, primarily modification (48.5%, 81/167; discontinue 37/81 or de-escalate 12/81) Courses prescribed with dose within 30% of consensus recommendations increased (78.8% courses vs 97.6% courses, $p < 0.0001$) CAP patients treated with penicillins increased from 39.5% to 93.8% (n=38 and n=32 respectively). Overall use among study patients reduced (10.5% DoT/1000 PD, 483.6 vs 432.9, $p < 0.001$ LOT/1000 PD - 7.7%, 377.4 to 348.3, $p = 0.02$). Reduced 3rd generation cephalosporins (22.3%, $p < 0.05$), fluoroquinolones (59.9%, $p < 0.001$) and metronidazole (51.1%, $p< 0.001$). Increased carbapenem (80.8%, $p<0.001$), combination aminopenicillin-beta lactamase inhibitor (78.8%, $p<0.001$). Inpatient mortality and LOS unchanged (0.37% vs 0.38%, p=1 and 7 vs 6 days, p=0.86 respectively).
Study: Lee, 2016 Primary strategy: Guidelines and Audit and feedback Country: United States Study Duration: 1year pre, 1 year implementation, 1 year post	Assess introduction of cardiac, neonatal and paediatric ICU guidelines and audit and feedback on antibiotic use, clinical outcomes and cost.	Compliance with guidelines reached 90% in cardiac ICU. Combined meropenem, piperacillin/tazobactam and cefepime use reduced (pre=105 vs post 70 DOT/1000 PD, $p < 0.001$). Differences in mean hospital wide LOS and deaths pre- and post were not statistically significant (days, 6 vs 6.13 and deaths, 73 vs 98, p=0.31). Median cost/month ($19,389 vs $11,043, $p<0.001$).

Study details	Description	Summary of Reported Findings
Study: Murni, 2015 Primary strategy: Audit and feedback Other Strategies: Infection control, checklists, education, guidelines Country: Indonesia Study Duration: 12 months pre, 12 months post	Assess antimicrobial use and infection control education, guidelines and daily review of all antibiotics on guideline concordant prescribing, HOI and mortality (inc. PICU).	Daily review of all antimicrobial orders and monthly departmental presentation for first 3 months of intervention. Co-intervention of AMS and infection control. Inappropriate antibiotics decreased from 43% (336/780) to 20.6% (182/882) RR 0.46 (95% CI 0.4-0.55). Primary reason for inappropriate prescribing was incorrect spectrum. Proportion of patients on antibiotics did not change (63.6% and 62.2%, p=0.43). Adjusted OR for mortality post intervention was 0.72 (95% CI 0.54 to 0.94). HOI reduced post intervention from 29.1 to 9.3/1000 PD, patients with HOI reduced from 22.6% to 8.6% (RR 0.38, 95% CI 0.31-0.46 and adjusted OR 0.28, 95% CI 0.21 to 0.38, p<0.001)
Study: Ceradini, 2017 Primary strategy: Audit and feedback-video case conference Other Strategies: Prior Approval Country: Italy Study Duration: 14 months pre, 12 months post	Assess impact of weekly video conference with ID physicians on antimicrobial use, cost, resistance outcomes in a specialist hospital	All patients reviewed during video case conference with ID physician and microbiologist every 2 weeks. Similar APR-DRG acuity among patients pre- and post (n=683 and n= 531 respectively). No significant difference in mean PICU or hospital LOS (PICU= 6.2 vs 6.1 days, p=0.92; hospital =8.4, p=1). Changes in rate of HOI not statistically significant (9.5 vs 6.1 for 1000/PD, p=0.23), infection control measures were not directly discussed. Reduction in MDR infections (26% reduction, 104/1000PD vs 79/1000 PD, p=0.01). Annual antimicrobial drug cost reported cost savings, 25,000 EURO 12 months before intervention vs 15,000 EURO in the comparison period (2 months before and 8 months after intervention), or 43 EURO/admission before vs 27 EURO/admission after. Antimicrobial use in “packs” was lower post implementation (5296 vs 3779). Satisfaction survey completed but was not published.

Study details	Description	Summary of Reported Findings
Study: Newman, 2012 Primary strategy: Audit and feedback program formed/CAP guideline Country: United States Study Duration: 12 months pre, 12 months post guideline implementation	Describe the impact of CAP guideline on antimicrobial prescribing and effectiveness of guideline concordant prescribing.	Significant increase in CAP patients prescribed ampicillin (13% vs 63%, p < 0.001). AMS program formation was associated with 20% increase in ampicillin use and 22% increase amoxycillin use on discharge. No change in frequency of obtaining blood cultures (56 vs 54%, p=0.4); 1.5 vs 1% patients met study criteria for ineffective therapy. Patients with effusions treated with inappropriate antibiotics was higher post-intervention (65% vs 73.5%, 28/43 and 39/53 respectively).
Study: Hennig, 2018 Primary strategy: Audit and Feedback-FN guideline Country: Australia Study Duration: 9 months pre, 15 months post	Assess impact of FN guideline with weekly audit and feedback on gentamicin use.	AMS rounds and meetings with Oncologists held weekly. Cases pre- vs post-intervention (n=195 vs n=257). FN cases treated empirically with gentamicin reduced (79.0% vs 20.9%, p < 0.001). Gentamicin use >48 hours without confirmed Gram-negative infection declined (85.5 vs 46.2%, p < 0.001), however, more Gram-negative infections were reported post-intervention (12.9% vs. 42.6%, p< 0.001). Gentamicin use >48 hours without TDM decreased from 44 to 0% (p < 0.001); admissions with blood cultures improved (97 vs 100%) Mean DOT among patients on gentamicin unchanged (~3 DOT).
Study: Wattier, 2017 Primary strategy: Audit and Feedback-FN guideline Country: United States Study Duration: 23 months pre, 22 months phase 1(oncology implementation, 12 months phase 2 HSCT implementation + Audit and feedback)	Interrupted time series analysis to assess tobramycin and ciprofloxacin use after phased implementation of FN guidelines audit and feedback for oncology and HSCT patients.	Tobramycin DOT/1000 PD reductions achieved and sustained by phase 2. No significant change in antipseudomonal beta lactams in oncology, variable use in HSCT. Oncology (pre- vs phase 2): Mean LOS (7 vs 5.5 days), 7% patients admitted to ICU in each phase (p=0.60), ICU days/all oncology cases and inpatient mortality unchanged (0.43 vs 0.11; 1.1 vs 1.4, p=0.4). HSCT (pre- vs phase 2): Mean LOS (37 vs 42 days), ICU admissions (14% vs 16%), highest in phase 1(27%,). ICU days/all HSCT cases 1.1 vs 1.7 (highest in phase 2 2.1), inpatient mortality (5.8% vs 2.7%), highest in phase 2 (6.5%), overall p=0.6. Change in HO CDI/10,000 PD was not statistically significant (16 vs 18.81/10,000 PD). Reduction in tobramycin reduced tobramycin TDM from 30 tests/100 admissions to 0 in phase 2. Statistically significant increase in tobramycin resistant Gram-negative isolates in phase 2, (6%, 2% and 26%, pre, phase 1 and phase 2, p=0.01 n>19 in each phase). Ciprofloxacin resistance did not change (~13% pre- and phase 1, 16% phase 2, p=0.9).

Study details	Description	Summary of Reported Findings
Study: Ambroggio, 2013 Primary strategy: QI methodology-CAP guideline Strategies: Education, pocket card, electronic order set, preformatted electronic medical record note Country: United States Study Duration: 6 months pre, 6 months post	Assess a QI initiative utilising systematic review and improvement on CAP guideline concordance	% guideline concordant prescriptions increased from 30 to 100%. Median LOS in days increased slightly (pre = <1, IQR 0-1; post 1, IQR 0-2; p<0.001).
Study: Berild, 2002 Primary strategy: Audit and Feedback Other strategies: Empiric antibiotic Guidelines, Pocket guide Country: Norway Study Duration: ~3 years pre, 3 years post	Assess impact of empiric guidelines with audit and feedback on antibiotic use and cost in a paediatric ward.	Quarterly education as part of hospital orientation. Weekly meetings held with prescribers. Point prevalence surveys observed 94% patients prescribed guideline concordant antibiotics, 25% of patients prescribed antibiotics overall. Antimicrobial use in DDD/100 PD reduced (38 vs 19), 74% reduction in aminoglycosides (~11 vs 2), 59% reduction in cephalosporins (~5 vs <2). Cost in GBP/100 PD reduced (739 vs 169 GBP). Antibiotics reduced from 49% to 21% of hospital drug costs. Twenty-one percent of antibiotic cost savings in one year were generated from lower pharmacy costs.

Study details	Description	Summary of Reported Findings
Study: Sáez-llorens, 2000 Primary strategy: Prior approval Other strategies: Surgical prophylaxis <24 hours, rationalise empiric antibiotics for neonates at 72 hours; ID approval required for all antibiotics after 7 days Country: Panama Study Duration: 2 years pre, 2 years post	Before and after study to assess impact of antibiotic restriction on clinical and microbial outcomes, and antibiotic costs (inc. PICU).	Total number of vials post-intervention reduced by 34%, largest reductions piperacillin (98%), gentamicin (99%), vancomycin (88%), ceftriaxone (68%), cefotaxime (65%) all required prior approval, amikacin (+15%, unrestricted), clindamycin (+25%, unrestricted), ciprofloxacin introduced post-intervention. Drug costs reduced by 50% post-intervention (pre- vials and cost 199427 and $699,543 respectively) Restricted antibiotic vials and cost reduced 89% and 77% respectively. Unrestricted agent costs reduced by 3% and 1%. No statistically significant changes in all-cause mortality with or without HO infection: HO infection: Nursery (49.0 vs 44.4%), PICU (51.8 vs 51.9%), General ward area (4.3 vs 4.1%). Nursery (16.3 vs 16.1%), PICU (21.1 vs 23.0%), general wards (0.5 vs 0.4%). Mean LOS in days unchanged (p=NS) No change in the percentage of Gram-positive sensitive isolates. Piperacillin susceptibility increased for Acinetobacter (29 vs 48%, n>58, p<0.05) Pseudomonas (80 vs 87%, n>200, p<0.05).
Study: Metjian, 2008 Primary strategy: Prior approval Country: United States Study Duration: 4 months	Prospective cohort study describing the activities and cost outcomes of an established prior approval AMS program (inc. PICU)	Prior approval includes weekends and after-hours. Over the 4-month study period there were 856 antibiotic requests, 652 patients, 45% calls required an AMS recommendation; 558 recommendations were made. No change in rate of recommendations/ month. Primary recommendations: obtain an ID consult (42.5%), change antibiotic (20.4%); 89% adherence to recommendations to stop or change antibiotics (75/84 requests). Lowest compliance observed for recommendation to stop therapy (73%). Clinical outcomes assessed for 11% of patients (10% of recommendations), 3/62 patients with recommendation to change antibiotic required different antibiotics after 48 hours, 1 unplanned readmission. No reinfections were reported among patients who stopped antibiotic therapy on AMS recommendation.

Study details	Description	Summary of Reported Findings
Study: Ross, 2016 Primary strategy: Prior Approval with automated stop to antimicrobial orders without approval (see Metjian 2008) Country: United States Study Duration: Patients on antibiotics, ~2 years pre, 2 years post. Bacteraemia patients: 2 years, 8 months post	Retrospective evaluation of automatic stop orders on clinical outcomes with matched cohort of patients with mono-bacteraemic infections in a hospital with a prior approval AMS program	Overall 25,871 patients, 22.1% on restricted antibiotics: No statistically significant difference in mortality (level p=0.37, trend p=0.57), readmission (level p=0.88, trend p=0.28), length of stay (level p=0.75, trend p=0.43). In the matched cohort of patients (n=480 vs 334): Mortality (risk difference −0.9%, 95% CI −4.1 to 2.3) and 30-day readmission rate were not statistically significant (risk difference −0.4%, 95% CI −7.6 to 6.8)
Study: Agwu, 2008 Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 12 months pre, 12 months post	Report on user satisfaction, and program improvements after transitioning from a telephone to web-based tool for prior approval	AMS team reviewed more requests for approval after transition to the electronic system (220 vs 342 per month), time from prescription to dispensing for restricted antimicrobials was similar before and after implementation (2.59 hours vs 2.44 hours, p=0.24) but shorter for unrestricted antibiotics (2.87 hours vs 1.93 hours, p<0.001). During the study period 89.4% of requests approved, 12.2% were automatic approval that were pre-programmed in the system but hidden from prescribers, 53.1% of approvals were for a limited period (<3 days), 13.1% were reapproved. DOT reduced post implementation (485.4 vs 417.6), with an 11% reduction in restricted doses (125.5-11.8 doses per day), 12% reduction in unrestricted doses (227.5 to 201.0 doses per day). Mean APR-DRG was higher post implementation (2.17 vs. 2.22, p<0.001), LOS was similar before and after (6.78 vs 6.67 days, p=0.65). Prior approval antibiotic cost reduced by 21.6% ($370,069), unrestricted antibiotic costs were unaffected (~$570,000).

Study details	Description	Summary of Reported Findings
Study: Venugopal, 2014 Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 4 years post	Retrospective evaluation of AMS requests for factors associated with approval patterns and trends over time (inc. PICU)	Prior approval required to initiate antimicrobials with re-approval required for ongoing use. ED and PICU exempt from requirement for initiation approval. Approximately 16,229 antimicrobial requests made; time to approval decision shorter when the indication was approved. No change in the number of approvals that were pre-programmed within the system to generate an "automatic approval". Approval rates increased by 6.1% over study period (p <0.01). Re-approval was more likely than initial approval (aOR 1.72, 95% CI 1.45-2.04). Compared to medical teams, approval less likely for surgical teams (aOR 0.70 95% CI, 0.59-0.83) and more likely for PICU (OR, 1.18 95% CI, 1.00-1.40).
Study: Sick, 2013 Primary strategy: Prior approval via computerised approval system Country: United States Study Duration: 4 years post	Retrospective evaluation of antimicrobial approval rates for AMS generated cost savings (exc. PICU/ED)	Mean unrestricted antimicrobial use decreased by 162 doses/month (p <0.001), restricted agents were unchanged. Between 90.7% to 93.1% of restricted agents were approved. $86,497 saved per year after implementation and maintenance costs. Few high cost agents accounted for large proportion of antimicrobial costs palivizumab (21%), liposomal amphotericin B (18%), meropenem (10%).

Study details	Description	Summary of Reported Findings
Study: Horikoshi, 2016 Primary strategy: Prior approval via electronic medication management system Other strategies: Audit and feedback at 72 hours Country: Japan Study Duration: ~21 months pre, ~42 months post	Assess the impact of prior approval for antipseudomonal antibiotics on use and clinical outcomes	Cefepime, piperacillin/tazobactam, carbapenem, ciprofloxacin orders could not be processed without prior approval by ID in electronic ordering system. NICU, PICU were excluded. Haematology/Oncology orders for piperacillin/tazobactam and cefepime were also restricted, and carbapenems and ciprofloxacin could only be prescribed for immunosuppressed patients. Mean DOT/1000 PD reduced for carbapenem (7.3 DOT/1000 PD vs 3.48 DOT/1000 PD, p<0.001), piperacillin/tazobactam (6.27 DOT/1000 PD vs 3.61 DOT/1000 PD, p<0.001), ciprofloxacin and cefepime use unchanged (1.3 DOT/1000 PD vs 1.6 DOT/1000 PD, p>0.05 and 19.6 DOT/1000 PD vs 17.7 DOT/1000 PD, p=0.3 respectively). Unrestricted ceftazidime and piperacillin (without inhibitor) declined in use, piperacillin was not statistically significant (ceftazidime 5.51 DOT/1000 PD vs 3.9 DOT/100 PD, p=0.008; piperacillin without inhibitor 9.75 DOT/1000 PD vs 8.15 DOT/1000 PD, p=0.068). No statistically significant changes in all-cause mortality (0.4 vs 0.33, p=0.19) and infection related mortality (0.12 vs 0.09, p=0.37). LOS was shorter postimplementation (15.0 vs 13.9 days, p=0.02). Standardised costs in USD/ month for carbapenem and piperacillin-tazobactam were lower post intervention ($2583 vs $1595, p=0.02 and $4847-3301, p=0.011), no other statistically significant differences in cost observed in study drugs. No significant changes in P. aeruginosa susceptibility, number of isolates not reported).
Study: Horikoshi, 2017 Primary strategy: Prior approval via electronic medication management system Other strategies: Audit and feedback at 72 hours Country: Japan Study Duration: 17 months pre, 66 months post	Interrupted time series analysis to assess impact of carbapenem prior approval on rates of use and correlation with resistance	Prior approval required for initiation of carbapenems with audit and feedback at 72 hours. Enhanced TDM service and selective reporting of antimicrobial susceptibility. Shorter LOS (20.6 days vs 18.6 days, p<0.01). All-cause mortality/1000 PD unchanged (0.28 vs 0.23, p=0.22) and infection related mortality reduced (0.09 vs 0.05, p=0.05) P. aeruginosa resistance reduced from 13.7 to 3.8%, p<0.01, (number of isolates were not reported). No significant change in E. coli. One K. pneumoniae outbreak occurred in the post-implementation period. AMS program reported correlation between DOT/1000 PD/year and % non-susceptible isolates/year. P. aeruginosa =0.82 (p=0.02), K. pneumoniae = -0.17 (p=0.71).

Study details	Description	Summary of Reported Findings
Study: Lee, 2007 Primary strategy: Formulary Restriction Country: Korea Study Duration: 3 years pre, 4 years post (exc. Surgical)	Assess the impact of cephalosporin formulary restriction on Extended spectrum beta-lactamase producing bacteria and mortality	Increase in piperacillin-tazobactam as the preferred agent (2.2 vs 108.0, p< 0.001), and a reduction in cephalosporins (175.0 vs 96.9, p< 0.001). Carbapenem use increased but did not reach statistical significance (35.5 vs 45.2, p=0.34). Total antibiotic days of therapy increased (274.8 vs 315.4, p=0.053); Differences in infection related deaths at 7 and 30 days of admission were not statistically significant (9 vs 5.5, p=0.19 and 12.4 vs 11.0%, p=0.19 respectively) No adverse drug events were reported. ESBL K. pneumoniae (64.1 to 25.6%, n>=17, p<0.001), E. coli (25.0 to 19.4%, n>=36, p=0.514). The authors report there were no changes to infection control measures throughout the study.
Study: Karsies, 2014 Primary strategy: CPOE order set for suspected sepsis in PICU Country: United States Study Duration: 12 months pre (2004), 12 months post (2007), Implemented in 2005/2006	Assess the impact of an empiric antibiotic order set for critically ill patients on time to appropriate antibiotics	Pre- vs post episodes (n = 252 vs 304). Guideline concordant empiric antibiotic increased among high and low HOI risk episodes (15% vs 76%, p<0.001). Median time to first antibiotic unchanged (1.55 hours, p=0.99), reduced time to guideline concordant antibiotic (5.9 hours vs 4 hours, p=0.01). Culture positive appropriate antibiotic empiric antibiotic selection improved post-implementation (64% vs 89%, p<0.001, n=148 and 176 respectively). Time to culture appropriate antibiotic reduced (9.6 hours vs 5.9 hours, p<0.001). No statistically significant change in mortality (11.7-7.9%, p=0.17). No significant differences in mean PRISM or PELOD scores that were reported as measures of clinical status (7.4 vs 6.6, p=0.19 and 10.8 vs 11, p=0.87 respectively).
Study: Rutman, 2017 Primary strategy: Pathway/Order set for CAP Country: United States Study Duration: 12 months pre, 12 months post	Assess the impact of a CAP pathway on ampicillin use, use of tests, LOS and hospitalisation costs	Project led by multidisciplinary working group that involved nurses and clinical leaders. Pre- and postintervention admitted patients (n=113 vs 110) Ampicillin use increased (8% vs 54%, target >75%), patients with blood cultures increased (35% to 63%), viral testing was influenced by changes to hospital policy. No statistically significant change in cost identified, interrupted time series analysis intercept and trends were not statistically significant.

Study details	Description	Summary of Reported Findings
Study: Smith, 2012 Primary strategy: AMS taskforce for CAP Other strategies: Education, pre-printed order form Country: United States Study Duration: 33 months, ~12 months post	Assess impact of CAP guidelines and education on empirical antibiotic choice	CAP guideline concordant antibiotic within 24 hours of admission increased (2% vs 44%) ceftriaxone use reduced (56% vs 28%). There were Similar numbers of unplanned readmissions within 30 days (5 vs 7, 19/1246 patients overall), mean LOS unchanged (3.11 vs 3.13 days). No adverse events or complicated cases inappropriately treated with ampicillin.
Study: Ding, 2008 Primary strategy: Order Form Order forms required documented indication, dose, frequency, and duration, signed by a Consultant Paediatrician. Country: China Study Duration: 2 years pre, 2 years post	Before and after study to assess impact of antibiograms and antibiotic order form for targeted antimicrobials on antibiotic use in PICU.	Order forms specified indication (empiric, therapeutic, prophylaxis), dose, frequency, duration. Patients on empiric antibiotic reduced (83.4% vs 66.6%, p<0.01). Proportion of patients on antibiotics unchanged (98.7% vs 93.5%) Mean antibiotics per patient unchanged (1.4 vs 1.3). Mean days of therapy unchanged 6 vs 5.4, p>0.05). Patients on: 4th generation cephalosporins unchanged (1.3% vs 1.3%), 3rd generation cephalosporins reduced (52.9% vs 17.2%, p<0.01), 2nd generation cephalosporins increased (13.1 vs 47.9%, p<0.01), Combination beta-lactam + beta-lactamase inhibitors increased (0.6% vs 9.6%, p<0.01), macrolide use reduced (20% vs 11.5%, p<0.01). LOS was not statistically significant (9.1 to 7.9 days (p=NS), P. aeruginosa isolates (n=6 vs 20): imipenem resistant isolates reduced (21.7% vs 9.9%, p<0.05), cefepime resistant isolates reduced (22.5% vs 10.6%, p<0.05), ceftazidime resistant isolates reduced (14.6% vs 7.5%, p<0.05) Cefoperazone-sulbactam resistant isolates unchanged (14.0% vs 13.9%, p=NS). E. coli isolates (n=7% vs 15%): cefepime resistant isolates reduced (61.5% vs 42.7%, p<0.01). K. pneumonia (n=8 vs 24): % resistant cefepime resistant isolates reduced (66.4 vs 34.0 (p<0.01). Cost per patient day reduced post intervention from $17.3 to $12.7 (p<0.05).

Study details	Description	Summary of Reported Findings
Study: Stocker, 2012 Primary strategy: Self-audit form/antibiotic "time out" at 48 hours and 5 days Country: United Kingdom Study Duration: 90 days pre, 110 days post	Before and after study assessing impact of a mandatory antibiotic checklist on appropriate treatment for suspected sepsis in PICU	Antibiotic checklist to document and assess antibiotic use at initiation, 48 hours and 5 days. No addition resources, checklist promoted by pharmacists. Total admissions and courses (174 vs 185, p=0.48 and 194 vs 182, p=0.14). Checklist completed for 69% of antibiotic courses. Increase in culture negative courses <3 days (18% vs 35%, p=0.05) and courses targeted based on cultures (58% vs 83%, p=0.21). Courses >3 days with documented and rational indication improved (0 vs 40%). No statistically significant differences in all-cause mortality (0 vs 3, p=0.25) and no infection related mortality. Antimicrobial courses initiated due to confirmed or suspected relapse (6.2% vs 5.0%, p=0.62). Infection control measures unchanged.
Study: Bolon, 2005 Primary strategy: Order Form for vancomycin Country: United States Study Duration: 8 months pre- and post-form (November-June pre- and post-intervention); additional 2 months of for improved compliance	Assess the impact of a vancomycin order form on appropriateness and rates of use	Less than 50% of vancomycin courses had an order form during planned study period, ~80% in final 2 months. Indication for use was documented on 63% of forms. Improved compliance observed when forms were promoted by pharmacists. Fewer courses were concordant with local guidelines post implementation (pre=65%, phase 1= 61% phase 2= 49%). Guideline concordance was not associated with order form use. Increase in both piperacillin and vancomycin use after forms implemented.
Study: Abboud, 2006 Primary strategy: CPOE integrated alert for aminoglycoside TDM Country: United States Study Duration: 3 months pre, 3 months post	Before and after study to assess CPOE integrated prompt to order aminoglycoside levels on TDM	Intervention did not mandate a specific form of monitoring. No statistically significant improvements among patients with TDM (n=111 vs 125). Patients with sub-therapeutic levels slightly lower post implementation (7.2 vs 5.6%, p=0.81), patients with toxic levels appeared higher without reaching statistical significance (8.1% vs 12%, p<0.44); similar proportion of courses without TDM before and after alert implementation (19.5% vs 17.5%; 31/159 vs 31/177, p>0.05).

Study details	Description	Summary of Reported Findings
Study: Mullett, 2001 Primary strategy: CDS for PICU Country: United States Study Duration: 6 months pre, 6 months post	Before and after study to assess impact of hospital information system integrated CDS at the bedside on PICU antimicrobial prescribing	Antimicrobial mismatch unchanged (0.2/100 admissions). Incorrect doses reduced (15.8 vs 10.8 days/100 patient days, p<0.001), 59% reduction in pharmacist interventions for dose adjustment (35 vs 15/1000 orders). Fewer patients on antibiotics (66.5% vs 60.2%, p < 0.05), no difference in mean doses and antibiotics per patient (12.8 vs 13.4 and 1.85 vs 1.96, p>0.05) No significant change in adverse drug reactions (~2.4/100 admissions), mean PICU or hospital LOS (4.9 and 10.7 days respectively) or inpatient mortality (3.7%) with similar APR-DRG assigned acuity. Mean cost per patient reduced ($86.60 vs $78.43, p<0.05).
Study: King, 2007 Primary strategy: CPOE evidence alert for bronchiolitis management Country: Canada Study Duration: 5 months pre, 5 months post (bronchiolitis season pre- and post- intervention)	Before and after study to assess impact of CPOE integrated evidence summary on bronchiolitis management on antibiotic use and hospital LOS	Pre- and post-intervention (n=147 vs n=187). % patients on antibiotics reduced by 37%, (35 vs 22%, p=0.02), changes in hospital-wide and ward antibiotic use post intervention were not statistically significant (-7%, p=0.26) or ward (+4.5%, p=0.54). No statistically significant difference in median LOS (2.8 vs 2.9 days, p=0.125).
Study: Wilson, 2002 Primary strategy: Electronic Pathway for bronchiolitis Country: United States Study Duration: 6 months	Assess impact of an electronic bronchiolitis pathway on frequency of antibiotic use and impact on hospital LOS and costs	% patients on antibiotics reduced (9 vs 27, p<0.05) Readmission within 72 hours (3.3 vs 2.7, p>0.05) and LOS unchanged (2.09 vs 2.55 days, p<0.05). Nil adverse drug events reported. Hospitalisation cost $2241 vs 3257 (p<0.001). Hospitalisation cost include standard hospital room rate (inc. nursing care), pharmacy, radiology, laboratory, emergency room costs.

AMS: Antimicrobial stewardship; APR-DRG: All-patient refined diagnosis-related group; aOR: adjusted odds ratio; CA: Community-acquired; CAP: Community-Acquired Pneumonia; CDI: *Clostridium difficile* infection; CDS: Computerised decision support; CI: Confidence interval; CPOE: Computerised physician order entry; DOT: Days of antimicrobial therapy; *E. cloacae: Enterobacter cloacae*; *E. coli: Escherichia coli*; ESBL: Extended-spectrum beta-

lactamase producing bacteria; exc.: Exclusions; FN: Febrile neutropenia; HO: Hospital-onset or hospital-acquired; HSCT: Haemopoietic stem cell transplant; ICU: Intensive Care Unit; inc.: Inclusions; *K. pneumoniae: Klebsiella pneumoniae*; LOS: Length of hospital stay; LOT: Length of antimicrobial therapy; MRSA: Methicillin-resistant *Staphylococcus aureus*; n: number of isolates included in analysis; NICU: Neonatal Intensive Care Unit; OR: Odds ratio; *P. aeruginosa: Pseudomonas aeruginosa* ;PD: Patient bed-days; PELOD: Pediatric Logistic Organ Dysfunction; PICU: Paediatric Intensive Care Unit; PRISM: Pediatric Risk of Mortality; Relative risk: RR; TDM: Therapeutic drug monitoring; VRE: Vancomycin resistant Enterococcus

[#]Studies have not been screened for quality. ^Drug utilisation metrics consolidated for interpretation, authors may refer to metrics with different terminology in original studies *Stakeholder surveys are not included in summary table

Measures of cost

Seventeen studies reported the cost impact of AMS; most focused on direct antimicrobial costs sourced from pharmacy or patient billing reports (82%, 14/17). (13,14,21,22,33,41,42,45,47,49,51,54,55,57) Most standardised these costs by normalising them to the number of patient-occupied bed days (9/14). In some studies, cost impacts were estimated by comparing expenditure before and after the intervention, or by comparing the cost of antimicrobials requested by prescribers outside of the AMS program with that of antimicrobials approved or recommended by the AMS program. A standard unit price for each antimicrobial was usually applied regardless of fluctuations in the actual purchase price, however some studies reported actual costs including any savings conferred by price reductions over time. (13,51,57) Studies did not specify whether costs associated with staff time for drug preparation or administration, consumables or monitoring were included. Overall hospital costs (from administrative or billing records) (3/17), (25,26,43) and operational costs (AMS staffing costs, implementation costs etc) were rarely reported (2/17) .(54,55) Two studies reported on associated reductions in therapeutic drug monitoring for restricted agents without quantifying the actual cost savings. (31,32) Similarly, one study reported a measure of resource utilisation (e.g. “resource intensity weight”) , as a cost outcome without assigning an actual cost. (24)

Measures of clinical impact

Most included studies reported on one or more clinical outcomes (33/44). The most frequently reported clinical outcomes were duration of hospital stay (LOS) (23/33), all-cause (18/33) or infection-related mortality (5/33), and readmission rates (12/33). Fewer studies directly reported direct indices of clinical failure such as recurrence of infection, change in the anticipated clinical course, escalation in care including admission to intensive care (6/33). Two studies reported on the incidence of hospital-onset CDI. (14,32)

Measures of antimicrobial resistance

Twelve studies reported changes in antimicrobial resistance patterns for Gram-positive (17,21,41,46) or Gram-negative bacteria. (13,15,21,32,38,43,46-48,57) Isolates obtained from usual clinical care were used to summarise antimicrobial susceptibility; one study summarised susceptibility on only 7 isolates, (21) and two studies did not report the number of isolates. (47,48) Infections caused by antimicrobial-resistant pathogens were also reported, as the number of cases per year, (17) the incidence density (cases/1000 patient-days), (13) or the relative risk (pre- vs post- AMS). (41) One retrospective study monitored carbapenem resistance within 30 days of use with the aim of evaluating differences in cases where prescribers accepted or rejected AMS recommendations. (43) The potential for confounding of resistance rates by variation in infection control practice, in the form of adherence to hand hygiene, personal

protective equipment and appropriate patient isolation throughout the study period was rarely addressed (1/12), (15) hospital-onset infections and colonisation were rarely differentiated from those with community-onset when reporting resistance outcomes (Table 1.6).(43,46,57)

Measures of staff and consumer satisfaction

Six studies reported results from stakeholder surveys which primarily focused on medical staff. (11,12,22,24,54) Questions explored perceived delays in antibiotic therapy, (54) operational improvements, (12) satisfaction with AMS recommendations, (11) and prescribers' willingness to adhere to AMS interventions. (11) Pharmacists and nurse prescribers were invited to participate in only a subset of stakeholder evaluations. (12,54)

1.7.5 Discussion

This review of published evaluations of paediatric AMS programs identified a range of process and outcome measures for AMS activity, prescribing appropriateness, recommendation compliance, antimicrobial drug utilisation, healthcare costs, clinical outcomes and antimicrobial resistance across different countries and hospital settings.

Audit and feedback was the most frequently reported paediatric AMS strategy. Studies of audit and feedback predominantly monitored appropriate antimicrobial prescribing in terms of concordance with

guidelines and the number and types of AMS recommendations made. Studies of hospital-wide AMS programs provided similar insights and reassurances to studies that focused on AMS for specific syndromes such as community-acquired pneumonia, febrile neutropenia, bronchiolitis and hospital and community-acquired sepsis in PICU. (6,58) Conversely, studies of prescribing prior approval programs were more likely to report antimicrobial drug utilisation or rates of AMS approval as a surrogate of appropriate antimicrobial prescribing, with the implicit assumption that all approved use was appropriate. Staff perceptions, the existence of AMS workarounds, and other implications of restriction and audit and feedback were usually not explored.

Much of the literature focused on reporting reductions in antimicrobial use rather than appropriateness per se. Many studies assessed potential unintended consequences by reporting clinical outcomes such as LOS or mortality while addressing potential confounders such as changing patient case-mix. Few studies evaluated the direct individual-level effect of AMS strategies on antimicrobial use and clinical outcomes by focussing on changes to the prescriber's intended course of action; only a small number of studies attempted to differentiate infection from non-infection-related health outcomes. Despite recent guidelines setting hospital CDI as a high priority measure for AMS programs in both paediatric and adult facilities, (6) only two studies included incidence of hospital onset CDI as measure of clinical impact. Although curbing antimicrobial resistance is a primary aim

of AMS programs, rates of resistance, like CDI, are affected by a host of medication-, patient-, community- and infection control related factors and is rarely reported.

Crude antimicrobial expenditure is very often used as a surrogate for utilisation despite the fact that drug costs in children are influenced by patient weight, and can be impacted by drug shortages and changes in price that are not controlled by AMS programs. (59,60) The most recent Infectious Diseases Society of America AMS guidelines recommend programs report projected savings as drug costs normalised for patient bed days, acknowledging this excludes costs saved or incurred indirectly as a consequence of AMS, which are not easily captured. One of the concerns of reporting drug costs is that there is no explicit relationship between the cheapest and the most appropriate antimicrobial in terms of targeted activity or toxicity, which may lead to conflicting aims. (61)

The strategies, activities, and reported measures we identified were largely enabled by electronic prescribing or administration systems and real-time surveillance reports. There was a clear distinction between studies from the United States and the rest of the world, and an even greater distinction between hospitals with, and those without electronic medication administration or prescribing records. For hospitals without access to electronic patient level data, audit and feedback is more labour intensive, and access to reliable antimicrobial utilisation data for ongoing surveillance

remains a challenge. Surprisingly, few studies reported antimicrobial LOT, and, thus, may not have captured the total duration of antimicrobial use, nor changes in aggregate DOT that may be attributed to the choice and number of agents used.(62)

Measuring antimicrobial DOT is rarely feasible for hospitals without electronic prescribing or medication administration records. The alternative benchmarking and surveillance metric used for adults in this setting, the WHO DDD, is not valid for children. (63,64) The DDD is derived from the estimated maintenance dose for adults, and therefore unable to account for weight and/or age-related differences among patients in paediatric hospitals. (65) As a result, antimicrobial use data for hospitalised children is excluded from national antimicrobial utilisation surveillance programs in countries like Australia, where surveillance in children's hospitals is limited to intermittent point prevalence surveys, local utilisation metrics, or flawed metrics such as expenditure. (66,67) This may have some implications for the findings in this review; we identified only one study from Australia despite updates to hospital accreditation standards in 2013 requiring all Australian hospitals have an AMS program in place, demonstrate evidence of monitoring and improvement and produce an annual antibiogram. (68)

This study has a number of potential limitations. Activity and compliance measures, as well as staff and consumer evaluations conducted as part of local evaluations may have been under-represented due to the search

strategy or inclusion criteria selected. These measures may additionally be subject to an important publication bias, whereby routine monitoring and reporting is omitted from the published evaluation.

This review highlights some of the challenges associated with evaluating AMS strategies for hospitalised children, and emphasises the need for feasible and standardised measures to evaluate AMS strategies for children across different hospital settings. Drug utilisation studies are required to establish the most suitable metric for monitoring hospital antimicrobial use by AMS programs as well as contribute to aggregated population level surveillance. Measures that capture clinical, microbial and cost outcomes directly related to AMS interventions should be a research priority.

To ensure effectiveness, paediatric AMS programs must; report on the core activities they undertake; monitor guideline concordant and appropriate prescribing; review compliance with AMS policies and recommendations and their consequences, particularly if clinical, microbial and cost outcomes are reported. Reasons for disagreement with AMS recommendations may provide insights and inform our current understanding of prescribing behaviour, to facilitate program improvement.

1.7.6 Conclusion

We identified a range of metrics that described AMS activities, antimicrobial prescribing behaviour and adherence to AMS program policies in addition to clinical, microbial and cost outcomes; however, most studies reported strategies and metrics specific to hospitals with electronic medication administration records that may not be feasible in other settings. There is no single agreed upon metric for measuring antimicrobial utilisation in paediatric settings where DOT cannot be captured. Alternate measures and metrics for antimicrobial surveillance and benchmarking must be explored and validated.

1.7.7 References

1. Osowicki J, Gwee A, Noronha J, Palasanthiran P, McMullan B, Britton PN, et al. Australia-wide point prevalence survey of the use and appropriateness of antimicrobial prescribing for children in hospital. Med J Aust 2014;201(11):657-62.
2. Duguid M, Cruickshank M, editors. Antimicrobial Stewardship in Australian Hospitals. Sydney: Australian Commission on Safety and Quality in Health Care (ACSQHC); 2011.
3. 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.
4. Cosgrove SE, Hermsen ED, Rybak MJ, File TM, Parker SK, Barlam TF. Guidance for the knowledge and skills required for antimicrobial stewardship leaders. Infect Control Hosp Epidemiol 2014;35(12):1444-51.
5. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337(a1655).
6. 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):e51–77.

7. Newland JG, Banerjee R, Gerber JS, Hersh AL, Steinke L, Weissman SJ. Antimicrobial Stewardship in Pediatric Care: Strategies and Future Directions. Pharmacotherapy 2012;32(8):735-43.
8. Spyridis N, Syridou G, Goossens H, Versporten A, Kopsidas J, Kourlaba G, et al. Variation in paediatric hospital antibiotic guidelines in Europe. Arch Dis Child 2016;101:72–6.
9. Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2016: First Australian report on antimicrobial use and resistance in human health. (ACSQHC). Sydney: ACSQHC; 2016.
10. Patel SJ, Saiman L. Principles and Strategies of Antimicrobial Stewardship in the Neonatal Intensive Care Unit. Semin Perinatol 2012;36(6):431-6.
11. Flannery DD, Swami S, Chan S, Eppes S. Prescriber Perceptions of a Pediatric Antimicrobial Stewardship Program. Clin Pediatr (Phila) 2014;53(8):747-50.
12. Stach LM, Hedican EB, Herigon JC, Jackson MA, Newland JG. Clinicians' Attitudes Towards an Antimicrobial Stewardship Program at a Children's Hospital. J Pediatric Infect Dis Soc 2012;1(3):190-7.
13. Ceradini J, Tozzi AE, D'Argenio P, Bernaschi P, Manuri L, Brusco C, et al. Telemedicine as an effective intervention to improve antibiotic

appropriateness prescription and to reduce costs in pediatrics. Ital J Pediatr 2017;43(1):105.

14. Hurst AL, Child J, Pearce K, Palmer C, Todd JK, Parker SK. Handshake Stewardship: A Highly Effective Rounding-based Antimicrobial Optimization Service. Pediatr Infect Dis J 2016;35(10):1104-10.

15. Lee J, Pai H, Kim YK, Kim NH, Eun BW, Kang HJ, et al. Control of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. J Antimicrob Chemother 2007;60(3):629-37.

16. Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila) 2009;48(5):505-12.

17. Di Pentima MC, Chan S. Impact of Antimicrobial Stewardship Program on Vancomycin Use in a Pediatric Teaching Hospital. Pediatr Infect Dis J 2010;29(8):707-11.

18. Ross RK, Beus JM, Metjian TA, Localio RA, Shelov ED, Desai BR, et al. Safety of Automatic End Dates for Antimicrobial Orders to Facilitate Stewardship. Infect Control Hosp Epidemiol 2016;37(8):974-8.

19. Stocker M, Ferrao E, Banya W, Cheong J, Macrae D, Furck A. Antibiotic surveillance on a paediatric intensive care unit: easy

attainable strategy at low costs and resources. BMC Pediatr 2012;12:196.

20. Bolon MK, Arnold AD, Feldman HA, Goldmann DA, Wright SB. An antibiotic order form intervention does not improve or reduce vancomycin use. Pediatr Infect Dis J 2005;24(12):1053-8.

21. Ding H, Yang Y, Wei J, Fan S, Yu S, Yao K, et al. Influencing the use of antibiotics in a Chinese pediatric intensive care unit. Pharm World Sci 2008;30(6):787-93.

22. Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and Impact of a Computerized Pediatric Antiinfective Decision Support Program. Pediatrics 2001;108(4):e75.

23. 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 2014;11(10):1569-75.

24. King WJ, Le Saux N, Sampson M, Gaboury I, Norris M, Moher D. Effect of point of care information on inpatient management of bronchiolitis. BMC Pediatr 2007;7(4).

25. Wilson SD, Dahl BB, Wells RD. An evidence-based clinical pathway for bronchiolitis safely reduces antibiotic overuse. Am J Med Qual 2002;17(5):195-9.

26. Rutman L, Wright DR, O'Callaghan J, Spencer S, Lion KC, Kronman MP, et al. A Comprehensive Approach to Pediatric Pneumonia:

Relationship Between Standardization, Antimicrobial Stewardship, Clinical Testing, and Cost. J Healthc Qual 2017;39(4):e59-69.

27. Abboud PA, Ancheta R, McKibben M, Jacobs BR. Impact of workflow-integrated corollary orders on aminoglycoside monitoring in children. Health Informatics J 2006;12(3):187-98.

28. Ambroggio L, Thomson J, Kurowski EM, Courter J, Statile A, Graham C, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics 2013;131(5):e1623-e31.

29. Smith MJ, Kong M, Cambon A, Woods CR. Effectiveness of Antimicrobial Guidelines for Community-Acquired Pneumonia in Children. Pediatrics 2012;129(5):e1326-e33.

30. Newman RE, Hedican EB, Herigon JC, Williams DD, Williams AR, Newland JG. Impact of a Guideline on Management of Children Hospitalized With Community-Acquired Pneumonia. Pediatrics 2012;129(3):e597-e604.

31. Hennig S, Staatz CE, Natanek D, Bialkowski S, Consuelo Llanos Paez C, Lawson R, et al. Antimicrobial stewardship in paediatric oncology: Impact on optimising gentamicin use in febrile neutropenia. Pediatr Blood Cancer 2018;65(2):e26810.

32. Wattier RL, Levy ER, Sabnis AJ, Dvorak CC, Auerbach AD. Reducing Second Gram-Negative Antibiotic Therapy on Pediatric Oncology and Hematopoietic Stem Cell Transplantation Services. Infect Control Hosp Epidemiol 2017;38(9):1039-47.

33. Lee KR, Bagga B, Arnold SR. Reduction of Broad-Spectrum Antimicrobial Use in a Tertiary Children's Hospital Post Antimicrobial Stewardship Program Guideline Implementation. Pediatr Crit Care Med 2016;17(3):187-93.

34. Newland JG, Stach LM, De Lurgio SA, Hedican E, Yu D, Herigon JC, et al. Impact of a Prospective-Audit-With-Feedback Antimicrobial Stewardship Program at a Children's Hospital. J Pediatric Infect Dis Soc 2012;1(3):179-86.

35. McCulloh RJ, Queen MA, Lee B, Yu D, Stach L, Goldman J, et al. Clinical Impact of an Antimicrobial Stewardship Program on Pediatric Hospitalist Practice, a 5-Year Retrospective Analysis. Hospital Pediatrics 2015;5(10):520-7.

36. Goldman JL, Lee BR, Hersh AL, Yu D, Stach LM, Myers AL, et al. Clinical Diagnoses and Antimicrobials Predictive of Pediatric Antimicrobial Stewardship Recommendations: A Program Evaluation. Infect Control Hosp Epidemiol 2015;36(6):673-80.

37. Lee BR, Goldman JL, Yu D, Myers AL, Stach LM, Hedican E, et al. Clinical Impact of an Antibiotic Stewardship Program at a Children’s Hospital. Infect Dis Ther 2017;6(1):103-13.

38. Di Pentima MC, Chan S, Hossain J. Benefits of a Pediatric Antimicrobial Stewardship Program at a Children's Hospital. Pediatrics 2011;128(6):1062-70.

39. Chan S, Hossain J, Di Pentima MC. Implications and Impact of Prior Authorization Policy on Vancomycin Use at a Tertiary Pediatric Teaching Hospital. Pediatr Infect Dis J 2014;34(5):506-8.

40. Molloy L, McGrath E, Thomas R, Kaye KS, Rybak MJ. Acceptance of Pharmacist-Driven Antimicrobial Stewardship Recommendations With Differing Levels of Physician Involvement in a Children's Hospital. Clin Pediatr (Phila) 2017;56(8):744-51.

41. Gillon J, Xu M, Slaughter J, Di Pentima MC. Vancomycin Use: Room for Improvement Among Hospitalized Children. J Pharm Pract 2017;30(3):296-9.

42. Seah XFV, Ong YLR, Tan SW, Krishnaswamy G, Chong CY, Tan NWH, et al. Impact of an Antimicrobial Stewardship Program on the Use of Carbapenems in a Tertiary Women's and Children's Hospital, Singapore. Pharmacotherapy 2014;34(11):1141-50.

43. Seah VXF, Ong RYL, Lim ASY, Chong CY, Tan NWH, Thoon KC. Impact of a Carbapenem Antimicrobial Stewardship Program on Patient Outcomes. Antimicrob Agents Chemother 2017;61(9):e00736-17.

44. Kreitmeyr K, von Both U, Pecar A, Borde JP, Mikolajczyk R, Huebner J. Pediatric antibiotic stewardship: successful interventions to reduce broad-spectrum antibiotic use on general pediatric wards. Infection 2017;45(4):493-504.

45. Metjian TA, Prasad PA, Kogon A, Coffin SE, Zaoutis TE. Evaluation of an Antimicrobial Stewardship Program at a Pediatric Teaching Hospital. Pediatr Infect Dis J 2008;27(2):106–11.

46. Lighter-Fisher J, Desai S, Stachel A, Pham VP, Klejmont L, Dubrovskaya Y. Implementing an Inpatient Pediatric Prospective Audit and Feedback Antimicrobial Stewardship Program Within a Larger Medical Center. Hospital Pediatrics 2017;7(9):516-22.

47. Horikoshi Y, Higuchi H, Suwa J, Isogai M, Shoji T, Ito K. Impact of computerized pre-authorization of broad spectrum antibiotics in Pseudomonas aeruginosa at a children's hospital in Japan. J Infect Chemother 2016;22(8):532-5.

48. Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis 2017;64:69-73.

49. Turner RB, Valcarlos E, Loeffler AM, Gilbert M, Chan D. Impact of an Antimicrobial Stewardship Program on Antibiotic Use at a Nonfreestanding Children’s Hospital. Journal of the Pediatric Infectious Diseases Society 2017;6(3):e36-e40.

50. Nguyen-Ha P-T, Howrie D, Crowley K, Vetterly CG, McGhee W, Berry D, et al. A Quality Assessment of a Collaborative Model of a Pediatric Antimicrobial Stewardship Program. Pediatrics 2016;137(5):e20150316.

51. Berild D, Ringertz SH, Aabyholm G, Lelek M, Fosse B. Impact of an antibiotic policy on antibiotic use in a paediatric department. Individual based follow-up shows that antibiotics were chosen according to diagnoses and bacterial findings. Int J Antimicrob Agents 2002;20(5):333-8.

52. Murni IK, Duke T, Kinney S, Daley AJ, Soenarto Y. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. Arch Dis Child 2015;100(5):454-9.

53. Venugopal V, Lehmann CU, Diener-West M, Agwu AL. Longitudinal evaluation of a World Wide Web–based antimicrobial stewardship program: Assessing factors associated with approval patterns and trends over time. Am J Infect Control 2014;42(2):100-5.

54. Agwu AL, Lee CKK, Jain SK, Murray KL, Topolski J, Miller RE, et al. A World Wide Web–Based Antimicrobial Stewardship Program Improves Efficiency, Communication, and User Satisfaction and Reduces Cost in a Tertiary Care Pediatric Medical Center. Clin Infect Dis 2008;47(6):747-53.

55. Sick AC, Lehmann CU, Tamma PD, Lee CKK, Agwu AL. Sustained savings from a longitudinal cost analysis of an internet-based preapproval antimicrobial stewardship program. Infect Control Hosp Epidemiol 2013;34(6):573-80.

56. Fridkin SK, Srinivasan A. Implementing a Strategy for Monitoring Inpatient Antimicrobial Use Among Hospitals in the United States. Clin Infect Dis 2014;58(3):401-6.

57. Sáez-llorens X, Castrejón De Wong MM, Castaño E, De suman O, De morös D, De atencio I. Impact of an antibiotic restriction policy on hospital expenditures and bacterial susceptibilities: a lesson from a pediatric institution in a developing country. Pediatr Infect Dis J 2000;19(3):200-6.

58. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013;4(4):CD003543.

59. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a Structured Panel Process to Define Quality Metrics for Antimicrobial Stewardship Programs. Infect Control Hosp Epidemiol 2012;33(5):500-6.

60. Stevenson KB, Balada-Llasat J-M, Bauer K, Deutscher M, Goff D, Lustberg M, et al. The economics of antimicrobial stewardship: the current state of the art and applying the business case model. Infect Control Hosp Epidemiol 2012;33(4):389-97.

61. Cairns KA, Jenney AW, Abbott IJ, SkInner MJ, Doyle JS, Dooley M, et al. Prescribing trends before and after implementation of an antimicrobial stewardship program. Med J Aust 2013;198(5):262-6.

62. Ibrahim OM, Polk RE. Benchmarking antimicrobial drug use in hospitals. Expert Rev Anti Infect Ther 2012;10(4):445-57.

63. Berrington A. Antimicrobial prescribing in hospitals: be careful what you measure. J Antimicrob Chemother 2010;65(1):163-8.

64. Haug JB, Reikvam Å. WHO defined daily doses versus hospital-adjusted defined daily doses: impact on results of antibiotic use surveillance. J Antimicrob Chemother 2013;68(12):2940-7.

65. Amadeo B, Zarb P, Muller A, Drapier N, Vankerckhoven V, Rogues A-M, et al. European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. J Antimicrob Chemother 2010;65(10):2247-52.

66. Bryant PA, Australian Stewardship of Antimicrobials in Pediatrics Group. Antimicrobial stewardship resources and activities for children in tertiary hospitals in Australasia: a comprehensive survey. Med J Aust 2015;202(3):134-9.

67. Fortin É, Fontela PS, Manges AR, Platt RW, Buckeridge DL, Quach C. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to paediatrics. J Antimicrob Chemother 2014;69(6):1447-56.

68. Huttner B, Harbarth S, Nathwani D. Success stories of implementation of antimicrobial stewardship: a narrative review. Clin Microbiol Infect 2014;20(10):954-62.

1.8 THESIS AIMS

This thesis was borne out of my observations - as an AMS pharmacist in the local setting (the study hospital) - around medication management practices pertaining to antimicrobials (i.e., prescribing, dispensing and administration). Using this critical lens, it has been apparent to me that the local hospital has invested considerable resources (human resources in terms of staff time as well as funding) to develop tools to support evidence-based treatment recommendations to guide the use of restricted antimicrobials in our vulnerable paediatric patients (Chapter 1, Section 1.4). Despite this investment, my observations of practice together with hospital data on approvals for the use of restricted antimicrobials - as recorded in the CDSS – collectively suggest that the CDSS has not been used optimally in the way it was originally intended; i.e., rather than being used prospectively to guide decision-making early in the treatment, the CDSS is being accessed retrospectively, i.e., after clinical decision-making has taken place. More specifically, the CDSS has been used by medical staff, in direct response to requests from pharmacists to seek guidance on the treatment plan and to gain approval for the use of restricted antimicrobials.

Therefore, the overall aim of this thesis research was to evaluate the impact of an AMS program comprising CDSS in the local Australian tertiary paediatric hospital setting. The specific objectives of the research were to:

- Evaluate CDSS as a specific AMS intervention to improve antimicrobial use, focusing on assessing its effectiveness as a tool to track restricted antimicrobial use when prescribing antimicrobials:
    - for specific syndromes, such as uncomplicated community-acquired pneumonia (CAP) **(Section 2.1)**
    - in the afterhours context (i.e., prescribing outside of standard pharmacy and AMS operating hours) **(Section 2.2)**
- Explore measures for tracking and reporting paediatric antimicrobial use using pharmacy data, in the absence of patient-level antimicrobial use data **(Section 4.1)**
    - Evaluate the impact of CDSS in the paediatric intensive care unit by tracking antimicrobial use **(Section 4.2)**
- Determine the education requirements of non-consultant level prescribers (**Section 3.1)** and nurses (**Section 3.2**) with respect to AMS and optimal antimicrobial use.

The specific research objectives align with the core elements of AMS programs, as cited by the United States Centers for Disease Control and Prevention (Figure 1. 8).

Framework for this thesis

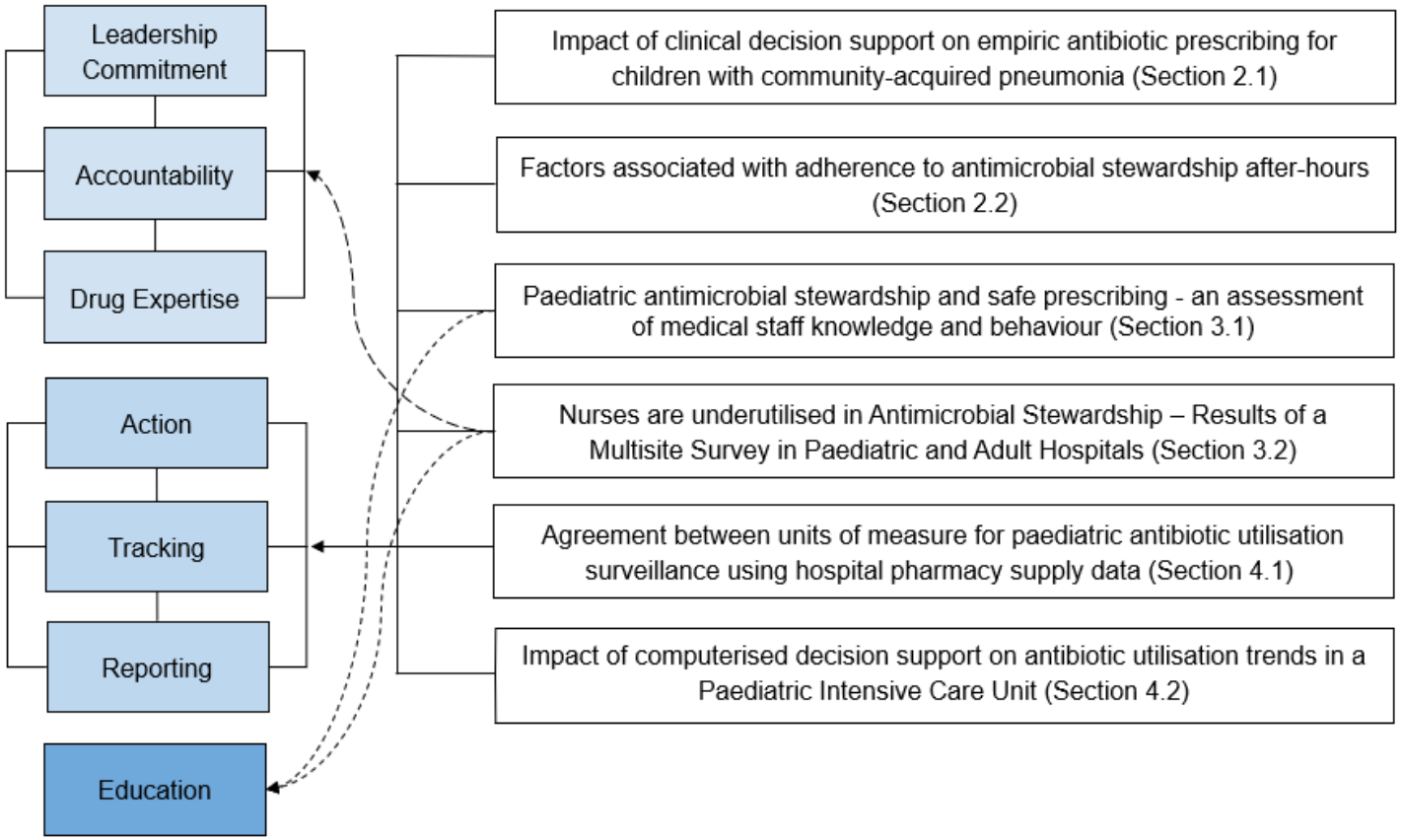


Figure 1.8 United States Centers for Disease Control and Prevention Core Elements of Antimicrobial Stewardship .

1.9 Overview of the Thesis

Chapter 1 Introduction

The first sections of this chapter (Sections 1.1 to 1.6) provides background information on the development of the CDSS and the local study hospital in which this thesis research was conducted.

The second section of this chapter (Section 1.7 Literature Review – Strategies and measures for paediatric antimicrobial stewardship) summarises the process and outcome measures reported in published evaluations of paediatric AMS strategies for hospitalised children. Embase, Medline (via Ovid), Scopus and Pubmed databases were searched for articles reporting individual or complex interventions (AMS) to improve antimicrobial prescribing for hospitalised paediatric patients published between January 2000 and December 2017 and reported measures categorised as one of the following: AMS activity, staff compliance, appropriate prescribing, drug utilisation trends, healthcare cost, patient outcomes, and changes in antimicrobial resistance.

Chapter 2 CDC Core Element – Tracking

This chapter comprises two studies and addresses the first objective of this thesis research, being to:

- Evaluate CDSS as a specific AMS intervention to improve antimicrobial use, focusing on assessing its effectiveness as a tool to **track** restricted antimicrobial use when prescribing antimicrobials:
    - for a specific syndrome, such as uncomplicated community-acquired pneumonia (CAP) **(Section 2.1)**
    - in the after-hours context (i.e., prescribing outside of standard pharmacy and AMS operating hours) **(Section 2.2)**

Manuscript 2 (Section 2.1): Impact of clinical decision support on empirical antibiotic prescribing for children with community-acquired pneumonia.

AIM: Assess the impact of an AMS program facilitated by a computerised clinical decision support and approval system (CDSS) on antibiotic use when treating children hospitalised with a presumptive diagnosis of uncomplicated community-acquired pneumonia (CAP).

SPECIFIC OBJECTIVES:

- Evaluate the impact of CDSS on inappropriate third generation cephalosporin use;
- track CDSS approvals for restricted antimicrobials.

This retrospective study used a broad range of International Statistical Classification of Diseases and Related Health Problems (ICD-10-AM)

codes to identify patients from birth to 18 years who were admitted to a tertiary paediatric hospital with presumptive diagnosis of uncomplicated CAP two years before and after the introduction of CDSS. Two independent investigators, a paediatric AMS pharmacist (MM) and a doctor training in paediatric medicine, assessed a random sample of cases according to the study inclusion criteria. The study assessed the impact of CDSS on guideline concordant prescribing and thus sought to assess the impact on unnecessary broad spectrum third generation cephalosporin use (non-concordance with guidelines). Empiric prescribing for presumptive CAP was specifically selected based on an underlying hypothesis that broad spectrum agents are likely to be overused at admission as a result of diagnostic uncertainty. The findings from the second objective of this study were explored further in the following section of this chapter (Section 2.2 Factors associated with adherence to antimicrobial stewardship after-hours).

Manuscript 3 (Section 2.2): Factors associated with adherence to antimicrobial stewardship after-hours.

AIM: Explore restricted antimicrobial use for antimicrobials acquired outside of standard hospital working hours (after-hours) within a paediatric hospital, when the extent of AMS monitoring and prescribing restriction are both reduced.

SPECIFIC OBJECTIVES:

- Determine the extent of AMS adherence at two time-points,
    - the time of antimicrobial acquisition after-hours, and
    - the next standard working day.
- Identify factors associated with AMS adherence at both time points.

This retrospective study tracked documented CDSS approval when restricted antimicrobials were acquired after standard pharmacy and AMS working hours over the course of 12 months, when nurses were responsible for drug acquisition. Drug acquisitions were deemed AMS adherent when there was a current CDSS approval at the time of drug utilisation reflecting the prescriber's response to a nurse's requests for approval, self-directed use of the CDSS by the prescriber as a clinical decision-making tool, or drug acquisition after a CDSS approval was obtained during standard pharmacy and AMS working hours. The use of CDSS the next standard-working day assessed the CDSS as a tracking tool for restricted antimicrobials and revealed only half of those restricted antimicrobials obtained after hours were reviewed by the AMS team. The study highlighted a need to explore the role of nurses in hospital AMS program (Section 3.2).

Chapter 3 CDC Element – EDUCATION

This chapter comprises two studies and addresses the thesis objective:

- Determine the **education** requirements of non-consultant level prescribers and nurses with respect to AMS and optimal antimicrobial use.

Manuscript 4 (Section 3.1): Antimicrobial stewardship and safe prescribing - an assessment of medical staff knowledge and behaviour.

AIM: Assess baseline AMS and paediatric safe prescribing knowledge among all non-consultant level medical staff (JMOs) at a tertiary paediatric hospital and evaluate subsequent prescribing behaviours.

SPECIFIC OBJECTIVES:

- Determine JMOs baseline knowledge of safe prescribing and good antimicrobial prescribing practice.

This study reports the findings of a knowledge assessment of safe paediatric prescribing and AMS among non-consultant level medical officers (JMOs), and the outcomes of prescribing audits over the first three months after the session. The knowledge assessment survey was conducted during a series of hospital orientation sessions attended by all

non-consultant level medical officers employed by the hospital with varying paediatric experience. Responses were collected anonymously throughout the sessions with the use of handheld keypad devices and reported as part of the education session. Prescribing audits focused on standard aspects of safe paediatric prescribing with implications for antimicrobials. Results were summarised and presented to JMOs each month after the education session by the chief resident medical officer.

Manuscript 5 (Section 3.2): Nurses are underutilised in antimicrobial stewardship–Results of a multisite survey in paediatric and adult hospitals.

AIM: Assess the attitudes held amongst nurses toward AMS programs and their perceptions regarding the role of nurses. A secondary aim was to explore differences in these perceptions and attitudes between paediatric nurses and those working in the adult setting.

SPECIFIC OBJECTIVES:

- Identify potential AMS roles that are acceptable to nurses and the education and support necessary to fulfil these roles;
- identify aspects of AMS that are most likely to engage paediatric nurses in AMS activities**.**

As outlined in Section 2.2 and Chapter 1 (Table 1.1) nurses perform many AMS related tasks and are therefore an important source of support. This study reports the findings of a multi-site survey of paediatric and adult-trained nurses working in hospitals that share the same centrally deployed CDSS. The results of this anonymous survey form a foundation by which to develop concrete responsibilities and targeted education strategies for nurses. Responses from paediatric and adult-trained nurses were compared to identify differences among paediatric and adult trained nurses.

Chapter 4 CDC Core Element- Tracking- Antimicrobial drug utilisation

This chapter comprises two studies addressing the following objectives of this thesis research:

- Explore measures for tracking and reporting paediatric antimicrobial use from pharmacy data in the absence of patient level antimicrobial use data
- Evaluate the impact of CDSS in the paediatric intensive care unit by tracking antimicrobial use

Manuscript 6 (Section 4.1): Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data.

AIM: Explore the levels of agreement between DDD and alternate estimates of the days of antimicrobial use in the context of a PICU that does not have access to individual patient-level antimicrobial use data.

SPECIFIC OBJECTIVES:

- Determine the minimum daily vial requirements for paediatric patients as reported in hospital pharmacy antimicrobial use reports.
- Measure levels of agreement between locally developed measures and adult defined daily doses used for national antimicrobial utilisation surveillance of hospitalised adults in Australia.
- Identify antibiotics that may be reliably monitored using hospital pharmacy data.

This study describes the development of candidate measures for antimicrobial surveillance in those paediatric hospitals without access to patient-level data. The study was devised after a review of the literature (Section 1.7), and guided by the original articles summarised in Table 1.3 Units of Measure (Chapter 1).

Two vial-based measures were the focus of this study, although a third measure was included for illustrative purposes. Vial-based measures were explored to account for state-wide medication handling and infection control policies that mandate the single (one time only) use of vials for the administration of doses by nurses who prepare most antimicrobials on the

ward. The vial-based measures were derived after estimating minimal daily vial requirements for paediatric patients after consulting standard paediatric medication references, PICU patient admission data, and hospital pharmacy records of antimicrobial use in the PICU over a period of 77 months (> 6 years). The estimated daily use of vials, a measure developed in this study, was applied to the sub-study reported in Section 4.2.

Manuscript 7 (Section 4.2): Impact of computerised decision support on antibiotic utilisation trends in a Paediatric Intensive Care Unit

AIM: Assess the impact of a structured AMS program on antibiotic use in a paediatric intensive care unit (PICU) that does not have access to patient level antimicrobial use data.

SPECIFIC OBJECTIVES:

- Evaluate the impact of CDSS on antimicrobial use from hospital pharmacy data in the PICU.
- Monitor and report potential confounders of antimicrobial use, hospital activity and clinical outcomes that coincided with CDSS implementation.

This sub-study assessed the impact of CDSS implementation on antimicrobial use in the PICU in addition to the pre-existing AMS activity of twice weekly consultant-led ID ward rounds that continued throughout the study period. Units of measure were chosen based on the preceding study

in this chapter (Section 4.1). The role of age and patient factors as potential confounders of data relating to antimicrobial use were explored. Multiple measures and methods are reported and contrasted.

Chapter 5 Discussion

This chapter synthesises the findings from each chapter, reflecting on the implications for practice, whilst acknowledging some of the limitations of the research and presenting recommendations for future research.

Chapter 6 Conclusion

This chapter presents the summary conclusions of the research.

NOTE:

The manuscripts presented within each of the ensuing chapters and related sections are formatted according to the variable submission requirements for each of the specific journals.

The abbreviation CDSS is used in reference to the hospital's computerised decision support and approval program (Guidance MS). Individual manuscripts may refer the same CDSS using a range of terms as decided by the authors and journal editors.

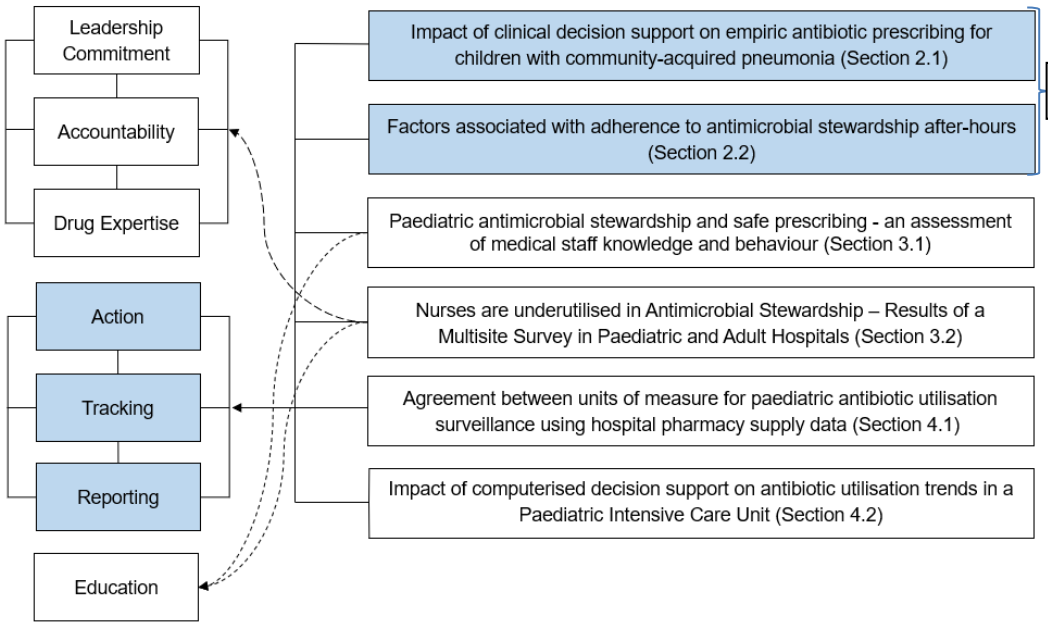
The data presented in each manuscript were obtained through specific sub-studies which were conducted according to ethical research principles.

Approval for the conduct of each sub-study was obtained from the relevant institutions' Human Research Ethics Committees.

CHAPTER TWO

TRACKING

2 CDC CORE ELEMENT – TRACKING



2.1 Impact of clinical decision support on empiric antibiotic prescribing for children with community-acquired pneumonia

This subsection will evaluate the impact of CDSS implementation as a specific AMS intervention. The substudy that follows assesses the impact of the CDSS on guideline concordant antibiotic prescribing for children admitted to hospital with a presumed diagnosis of non-severe CAP.

As detailed in the manuscript below, CAP has been identified as key contributor to the excessive use of third generation cephalosporins in paediatric hospitals in the US and a common indication for AMS intervention. Guideline concordant prescribing for CAP is recommended as an AMS outcome measure in national guidelines and among expert panels (Section 1.6). For these reasons, CAP is selected in preference to other infectious pathologies; hospital-acquired and aspiration pneumonia cases are excluded due to their distinct management and the lack of pre-existing, published guidelines at the study hospital.

Guideline concordant empirical prescribing for non-severe CAP in the study below is defined as the selection of ampicillin or benzylpenicillin. Third generation cephalosporins, ceftriaxone and cefotaxime are non-concordant with hospital guidelines. All other antibiotic choices recommended for mild to severe CAP in the pre- and post-CDSS hospital guidelines are additionally reported (e.g., vancomycin, lincomycin, macrolide antibiotics including clarithromycin and azithromycin). Restricted antibiotics

prescribed post-CDSS implementation are cross referenced with CDSS, thereby evaluating the effectiveness of the CDSS as a tracking tool. It should be noted that the terms narrow- and broad-spectrum refer to the primary objective of this study, that is the selection of ampicillin or benzylpenicillin (narrow spectrum penicillins) over third generation cephalosporins (broad-spectrum agents). The impact of the CDSS on the use of these agents in the PICU setting is reported in Section 4.2.

Manuscript 2
Mostaghim M, Snelling T, McMullan M, Ewe YH, Bajorek BV. **Impact of clinical decision support on empirical antibiotic prescribing for children with community-acquired pneumonia**. *Journal of Paediatrics and Child Health.* 2018. DOI 10.1111/jpc.14191
Manuscript published (peer reviewed)

2.1.1 Abstract

Aim: Assess the impact of a computerised clinical decision support system (CDSS) on antibiotic use in hospitalised children with a presumptive diagnosis of uncomplicated community-acquired pneumonia (CAP).

Methods: Codes associated with lower respiratory tract infection were used to identify cases of presumed uncomplicated CAP requiring admission to a tertiary paediatric hospital. Random sampling of the periods between 1 October 2010 to 30 September 2012 (pre-CDSS) and 1 October 2012 to 30 September 2014 (post-CDSS) determined the sequence of case

assessment by two independent investigators. Initial antibiotic therapy, associated CDSS approvals and documented signs of clinical deterioration prior to antibiotic decision-making were recorded.

Results: Statistically significant differences among cases pre- and post-CDSS implementation were minimal. High fever was observed in 57.5% (77/134) cases pre-CDSS, and 45.8% (49/107) cases post-CDSS (p=0.07). Supplemental oxygen was used in 30.6% pre-CDSS, and 54.2% post-CDSS cases (p<0.001). Narrow-spectrum penicillins were prescribed most often with no statistically significant change post-CDSS implementation (81.3% pre-CDSS, 77.6% post-CDSS, p=0.47). Macrolides were used consistently throughout the study period (53.7% pre-CDSS, 61.7% post-CDSS; p=0.21).

Conclusion: CDSS implementation did not reduce already low rates of broad-spectrum antibiotic use for uncomplicated CAP.

Keywords: Practice Guidelines as Topic; Practice Patterns, Physicians'; Community-Acquired Infections; Anti-infective Agents; Child

What is already known on this topic

- Community-acquired pneumonia (CAP) is a common cause for hospitalisation in children.
- High rates of inappropriate broad-spectrum antibiotic use for uncomplicated CAP have made adherence to CAP guidelines a focus for antimicrobial stewardship (AMS).

- Clinical decision support and approval systems (CDSS) are frequently used to promote guideline adherence and facilitate antimicrobial stewardship.

What this paper adds

- Over 80% of uncomplicated CAP cases in a tertiary paediatric hospital were treated with guideline concordant empirical antibiotics pre-CDSS.
- Restricted antibiotics were used infrequently post-CDSS. However, not one instance of restricted antibiotic use was associated with a documented CDSS approval.
- A standalone CDSS did not impact broad-spectrum antibiotic use for CAP (pre-CDSS 12.7%, post-CDSS 13.1%, p=0.927).

2.1.2 Background

Community-acquired pneumonia (CAP) in infants and children is predominantly due to viral infection, with bacterial pneumonias most often caused by *Streptococcus pneumoniae* and less frequently 'atypical' pathogens such as *Mycoplasma pneumoniae*.(1) Guidelines typically recommend hospitalised children with uncomplicated CAP are treated with narrow-spectrum penicillins, either alone or in combination with a macrolide antibiotic where infection with an atypical pathogen is suspected.(2) Broad-spectrum antibiotics such as third generation cephalosporins are generally

reserved for when penicillin-resistant pathogens are suspected, such as in unimmunised children or children with severe pneumonia and empyema.(2)

Despite published evidence indicating that treatment with narrow-spectrum antibiotics does not increase the length of hospitalisation (LOS), morbidity or hospital costs,(3) broad-spectrum antibiotics continue to be over-prescribed, even after guidelines are implemented locally.(4) Therefore, CAP is a common focus for antimicrobial stewardship (AMS) practice and research.

AMS involves the use of multiple strategies to optimise antimicrobial prescribing to achieve the best possible patient outcome and limit super-infection with opportunistic pathogens, toxicity, and the promotion of resistant organisms.(5) As CAP contributes substantially to antimicrobial use in tertiary paediatric hospitals, targeting adherence to CAP guidelines is likely to significantly impact the overall appropriateness of hospital antimicrobial use.(6)

We assessed the impact of an AMS programme with a computerised clinical decision support system (CDSS) on antibiotic use when treating children hospitalised with a presumptive diagnosis of uncomplicated CAP.

2.1.3 Methods

Setting

This study was conducted in a 170-bed university-affiliated tertiary paediatric hospital with specialist services in oncology, intensive care, solid organ transplant and cystic fibrosis in New South Wales, Australia.

Since October 2012 the hospital's AMS programme has been supported by a CDSS (Guidance MS, Melbourne Health, Australia) to facilitate approval to use restricted antimicrobials. Prescribers are required to seek approval via the CDSS prior to initiating restricted antimicrobials. Automatic CDSS approval can be obtained for restricted antimicrobials when prescribed according to hospital guidelines. Therefore, for severe or complicated CAP automatic CDSS approvals are generated for: third generation cephalosporins and lincosamides for CAP requiring intensive care and patients with empyema or pneumatocele; glycopeptides (vancomycin) for CAP with signs of sepsis; and azithromycin if CAP is severe and an atypical pathogen is suspected. However, roxithromycin is recommended for less severe cases (Figure 2.1). Where the intended use for a restricted antimicrobial is not consistent with hospital guidelines a limited 24-hour approval is granted, with further approval subject to direct consultation with the AMS team.

CONDITION	AGE	ANTIBIOTIC (MAXIMUM DOSE)
Pneumonia	< 3m	benzylpenicillin 60mg/kg 6 hourly & gentamicin** ADD azithromycin 10mg/kg daily if pertussis OR chlamydia suspected
Severe Pneumonia	< 3m	cefotaxime 50mg/kg 6 hourly & clindamycin± & azithromycin 10mg/kg daily ADD vancomycin†† if Shocked OR ICU ADD aciclovir if at risk of HSV Pneumonitis
Mild pneumonia	≥ 3m	ORAL amoxycillin 25mg/kg (500mg) 8 hourly *OR roxithromycin 4mg/kg (150mg) 12 hourly if considering mycoplasma*
Moderate pneumonia	≥ 3m	benzylpenicillin 30 to 60mg/kg (2.4g) 6 hourly & *ORAL roxithromycin 4mg/kg (150mg) 12 hourly if risk of mycoplasma*
Severe/ Complicated pneumonia **Consult respiratory**	≥ 3m	lincomycin 15mg/kg 8 hourly (600mg) & cefotaxime 25 to 50mg/kg (2g) 8 hourly *(OR ceftriaxone 50mg/kg (2g) daily)* ADD vancomycin†† if severe sepsis or requiring ventilatory support ADD azithromycin if considering atypicals
UNLESS OTHERWISE STATED MEDICATIONS ARE TO BE GIVEN INTRAVENOUSLY ** See Once Daily Gentamicin Guideline for dosing and monitoring recommendations †† See Vancomycin Guideline for dosing and monitoring recommendations ± Clindamycin dosing varies with age-see recommendations in Guidance MS		

Figure 2.1 Local empirical antibiotic guidelines for paediatric community-acquired pneumonia. Lanyard card supplied to local hospital staff 3m: 3 months of age

From May to October 2012 the Infectious Diseases team and Chair of the hospital's drug committee led a range of activities to prepare staff for the introduction of the CDSS. Activities included notifications to heads of department and discussions between infectious diseases and representatives from hospital departments for consensus on the antimicrobial restriction categories, approval requirements, indications suitable for automatic approval as well as the specific dosage and frequency recommended within the CDSS. As part of AMS implementation in October 2012, junior and senior medical staff were formally introduced

to the CDSS and trained on its use. Since then, AMS and CDSS orientation has been embedded within hospital orientation programs for junior medical staff at each new term rotation. Lanyard cards indicating the antimicrobial restriction categories and empirical antibiotic recommendations for common infections including CAP are available for all staff and given to all prescribers and pharmacists during hospital orientation.

Study design and data source

This retrospective clinical audit of medical records used the International Statistical Classification of Diseases and Related Health Problems Australian Modification 10th Revision (ICD-10-AM) codes associated with lower respiratory tract infections (Table 2.1) to identify potential cases of CAP in patients up to 18 years of age presenting between 1 October 2010 to 30 September 2012 (pre-CDSS) and 1 October 2012 to 30 September 2014 (post-CDSS). The hospital's health information unit extracted patient demographic and admission information for all potential cases, including the admission date, LOS and unplanned readmissions within 28 days. Patients directly transferred to the intensive care unit (ICU) and those admitted to hospital after being discharged within the previous 30 days were excluded.

Table 2.1 ICD-10-AM Diagnostic Codes to be used for data extraction from administrative records

ICD-10-AM code	Description
J13	Pneumococcal pneumonia
J18.1	Lobar pneumonia, unspecified
J10.0	Influenza with pneumonia, influenza virus identified
J11.0	Influenza with pneumonia, virus not identified
J12.0	Pneumonia due to adenovirus
J12.1	Pneumonia due to respiratory syncytial virus
J12.2	Pneumonia due to parainfluenza virus
J12.8	Pneumonia due to other virus not elsewhere classified
J12.9	Viral pneumonia, unspecified
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J15.2	Pneumonia due to Staphylococcus
J15.3	Pneumonia due to Streptococcus, group B
J15.4	Pneumonia due to other Streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other aerobic Gram-negative bacteria
J15.8	Other bacterial pneumonia
J15.7	Pneumonia due to Mycoplasma pneumoniae
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J17.0	Pneumonia in bacterial diseases classified elsewhere
J17.1	Pneumonia in viral diseases classified elsewhere
J17.2	Pneumonia in mycoses
J17.3	Pneumonia in parasitic diseases
J17.8	Pneumonia in other infectious diseases classified elsewhere
J15.9	Bacterial pneumonia, unspecified
J18.0	Bronchopneumonia, unspecified
J18.2	Hypostatic pneumonia, unspecified
J18.8	Other pneumonia, organism unspecified
J18.9	Pneumonia, organism unspecified
J85.1	Abscess of lung with pneumonia
B01.2	Varicella pneumonia
B05.2	Measles complicated by pneumonia
B37.1	Pulmonary candidiasis
B59	Pneumocystosis

ICD-10-AM: The International Statistical Classification of Diseases and Related Health Problems Australian Modification 10th Revision

Potential cases in each of the pre-CDSS and post-CDSS periods were numbered in chronological order. A random number generator was used to randomly sample potential cases in each period for independent assessment by two investigators. Both investigators reviewed medical records relating to each sampled admission. Cases were included where the emergency department (ED) physician or the admitting medical team physician clearly documented a clinical impression of pneumonia as the reason for admission with use of the terms “CAP”, “pneumonia”, “lower respiratory tract infection”, “LRTI”, “pneumonitis”, “mycoplasma”, “viral pneumonia”, or if there was evidence of a chest x-ray accompanied by a documented clinical impression of respiratory tract infection and prescription of at least one antibiotic.

We sought to limit cases to those for whom hospital guidelines recommend penicillin therapy, with or without a macrolide. Therefore, we excluded patients with documented chronic cardiac or respiratory disease (e.g. cystic fibrosis, chronic suppurative lung disease), immunodeficiency (cancer, solid organ transplant, or opportunistic infection), documented clinical impression of aspiration pneumonia, empyema or pleural effusion; patients assigned a ‘high acuity’ bed; or those who had not been immunised.

Cases were included if there was consensus among the investigators regarding eligibility. The process continued until a sufficient number of

eligible cases in each of the pre-CDSS and post-CDSS periods were identified.

Data collection

Investigators recorded the initial CAP diagnosis documented in the medical record and whether the initial antibiotic therapy prescribed on the medication chart included a penicillin, third generation cephalosporin, macrolide, lincosamide or glycopeptide. The specific macrolide antibiotic was also documented. Where a restricted antibiotic was prescribed post-CDSS the CDSS database was queried to confirm whether approval was obtained.

Observation charts were reviewed from the time of hospital presentation to the time of antibiotic selection. Where the time of selection could not be determined from the prescriber's note, the antibiotic administration time documented on the medication chart was used as a substitute. Investigators recorded whether there were any documented observations indicating respiratory distress, tachypnoea, tachycardia, altered consciousness (Alert Verbal Pain Unresponsive Scale or Glasgow Coma Scale), fever (temperature greater than 38.5^{O}C) and if supplemental oxygen was required at any time prior to antibiotic selection. Unless stated, high acuity ranges were determined from the hospital's age-specific criteria which mandate urgent clinical review by a medical officer (Figure 2.2).(7)

Tachypnoea (respiratory rate in breaths per minute): 3-12 months>65; 1-4 years>60; 5-11 years>50; 12 years and older>40

Tachycardia (heart rate in beats per minute) 3-12 months>180; 1-4 years>170; 5-11 years>160; 12 years and older>150

Respiratory Distress (any of): new onset stridor, imminent airway obstruction, drowsy, unable to cry, feed or suck, exhaustion, gasping, grunting, extreme pallor, cyanosis, absent breath sounds, apnoeic episodes, hypoxaemia not corrected with oxygen

Altered consciousness (Alert Voice Pain Unresponsive scale): rousable on central pain or unresponsive, or equivalent paediatric Glasgow Coma Scale

Figure 2.2 Criteria for mandatory clinical review by a medical officer within 5 minutes. Criteria used across all New South Wales hospitals.(7)

Sample size

Assuming that local prescribing was similar to published CAP evaluations we estimated the pre-CDSS rate of inappropriate third generation cephalosporin use in uncomplicated CAP to be 50%.(8) We determined that 170 cases in each of the pre- and post-CDSS periods would be required to demonstrate a 15% reduction (alpha 0.05, power 0.8; G*Power version 3.1.9.2; Heinrich Heine University Dusseldorf, Dusseldorf, Germany).(9)

Data analysis

Statistical analysis was performed in SPSS™ version 24 (IBM, Armonk NY, USA). Chi-square tests were used to compare differences in characteristics and antibiotic prescribing pre-CDSS and post-CDSS. LOS was measured in days and treated as a continuous variable. The median LOS before and after CDSS was compared using the Mann-Whitney *U*-test. All statistical tests were two-tailed with *P* values of <0.05 considered statistically significant.

2.1.4 Results

ICD-10-AM codes identified 697 potential cases overall. Investigators assessed 584 cases and included 134 pre-CDSS and 107 post-CDSS cases; 113 records were not available for review. Cases were frequently excluded due to a significant past medical history, complication, or treatment for an alternate condition at admission (Figure 2.3).

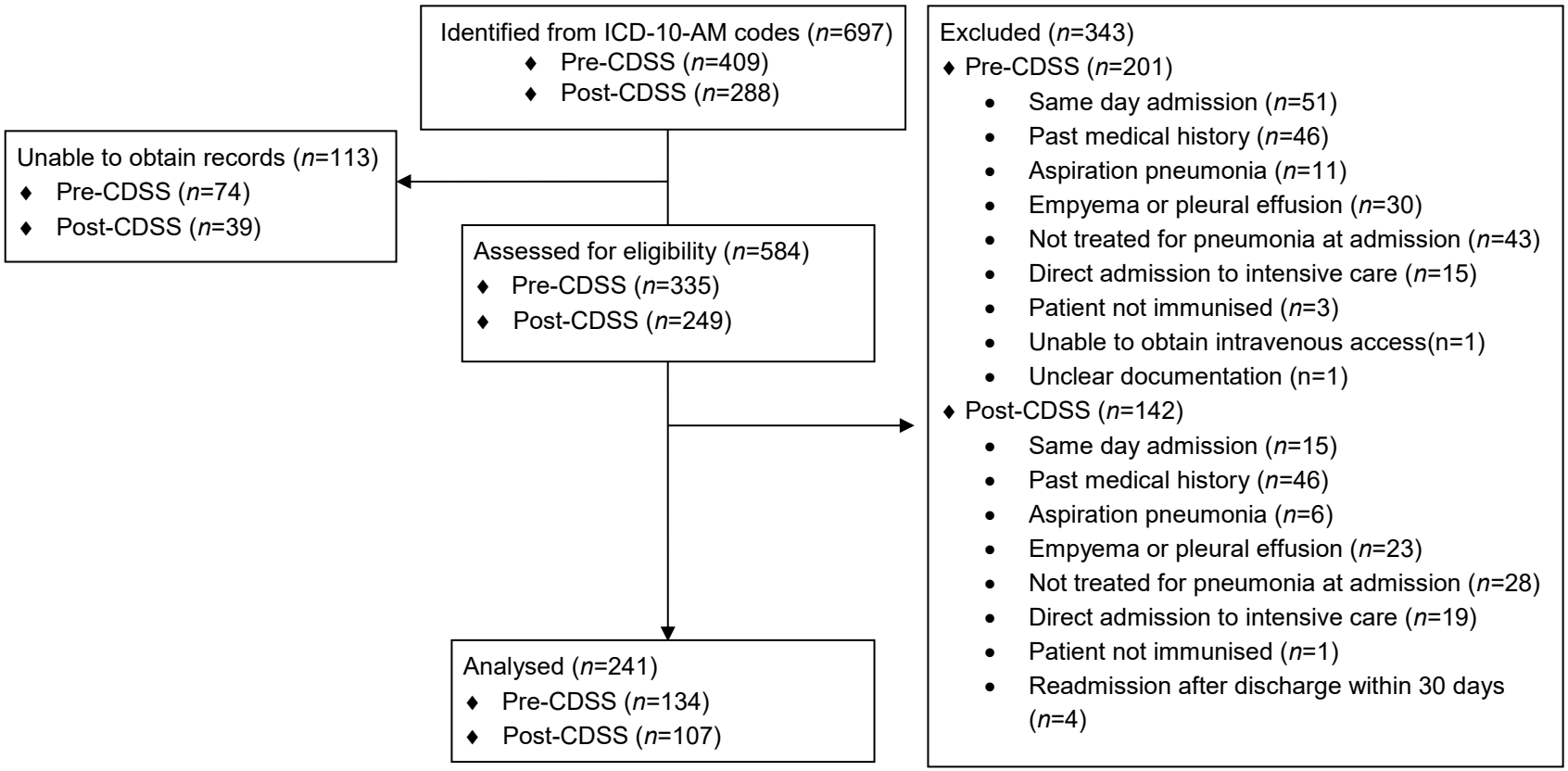


Figure 2.3 Process and criteria applied to identify cases of uncomplicated community-acquired pneumonia in children before and after implementation of clinical decision support and approval system for restricted antimicrobials

All cases were at least 3 months old, with a similar proportion under 12 months of age at admission (10.5% cases pre-CDSS, 8.4% cases post-CDSS). There were no significant differences in LOS or unplanned readmissions pre- and post-CDSS. Most cases did not have a presumed pathogen documented by the prescriber at the time of antibiotic selection (Table 2.2).

From the time of admission to antibiotic selection, one or more urgent reviews were required for tachypnoea (13.4% cases pre-CDSS versus 16.8% cases post-CDSS; p=0.46), respiratory distress (3.0% versus 3.7%; p=0.75), and tachycardia (13.4% versus 17.8%; p=0.36). High fever was observed in 57.5% and 45.8% of cases pre- and post-CDSS respectively (p=0.07). Supplemental oxygen was administered more often post-CDSS (30.6% cases pre-CDSS, 54.2% cases post-CDSS; p<0.001) (Table 2.2).

Table 2.2 Demographics and clinical status of study patients prior to antibiotic decision making

Characteristics	Pre-CDSS, *n* (%)	Post-CDSS, *n* (%)	Overall, *n* (%)
Cases of uncomplicated community-acquired pneumonia, *n*	134	107	241
Age at admission			
3-12 months of age	14 (10.4)	19 (8.4)	23 (9.5)
1-4 years	83 (61.9)	68 (63.6)	151 (62.7)
5-11 years	33 (24.6)	28 (26.2)	61 (25.3)
12 years or older	4 (2.9)	2 (1.9)	6 (2.5)
Female	68 (50.8)	49 (45.8)	117 (48.6)
Prescriber's documented indication at admission			
Bacterial Pneumonia	2 (1.5)	0	2 (0.8)
Atypical or Mycoplasma	13 (9.7)	9 (8.4)	22 (9.1)
Lower Respiratory Tract Infection Unspecified	105 (78.4)	90 (84.1)	195 (80.9)
Viral Pneumonia	14 (10.5)	8 (7.5)	22 (9.1)
Primary Diagnosis Code			
Viral Diagnosis Codes^	25 (18.7)	22 (20.6)	47 (19.5)
Bacterial Diagnosis Codes^^	19 (14.2)	19 (17.8)	38 (15.8)
Unspecified Diagnosis Codes^^^	90 (67.2)	66 (61.7)	156 (64.7)
Signs of Severity			
Tachypnoea (respiratory rate in "red zone")#	18 (13.4)	18 (16.8)	36 (14.9)
Sign of severe respiratory distress#	4 (3.0)	4 (3.7)	8 (3.3)
Supplemental oxygen administered**	41 (30.6)**	58 (54.2)**	99 (41.1)
Tachycardia#	18 (13.4)	19 (17.8)	37 (15.4)
Febrile (temperature >38.5 degrees Celsius)	77 (57.5)	49 (45.8)	126 (52.3)
Altered Consciousness#	0 (n/a)	0 (n/a)	0 (n/a)
Hospitalisation			
Duration of inpatient stay in days, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Readmission to any hospital within 28 days	6 (4.5)	3 (2.8)	9 (3.7)

*time of documented decision to treat with antibiotics where there was no recorded time on the prescriber's medical note the time of antibiotic administration was used; ^Viral diagnosis codes (J10.0, J11.0, J12.0, J12.1, J12.2, J12.8, J12.9); ^^Bacterial Diagnosis Codes (J13, J15.2, J15.9, J15.7);^^^Unspecified Diagnosis Codes (J18.0, J18.8, J18.9); #Any vital sign observation recorded on age appropriate standard paediatric observation chart prior to antibiotic decision making that required immediate clinical review by a medical officer as part of system to minimise clinical deterioration across all New South Wales public hospitals. Corresponding criteria are specified in **Figure 2.2**; ***P*<0.001, no other statistically significant differences observed. CDSS: Computerised clinical decision support and approval system; ICD-10-AM: The International Statistical Classification of Diseases and Related Health Problems Australian Modification 10th revision; IQR: Interquartile range

There were no statistically significant changes to antibiotic prescribing after CDSS implementation. Third generation cephalosporins were prescribed in only 12.7% of cases pre-CDSS and 13.1% of cases post-CDSS (Table 2.3). Of these, one case post-CDSS involved a possible penicillin allergy whereby the reaction, type and date of reaction were incompletely documented. Despite the initial choice to prescribe a broad-spectrum agent, narrow-spectrum penicillins were prescribed shortly thereafter. Penicillins were the initial antibiotic of choice prescribed in 81.3% and 77.6 % of cases pre- and post-CDSS($p=0.47$) respectively. Both macrolide prescribing and dual antibiotic therapy increased marginally post-CDSS, particularly where penicillins were used. Roxithromycin remained the macrolide of choice, used in 50.7% of cases pre-CDSS and 57.0% of cases post-CDSS implementation. Other antibiotics were used infrequently; neither clarithromycin nor glycopeptides were used for any episode of uncomplicated CAP. None of the 17 instances of restricted antibiotic use post-CDSS were associated with a CDSS approval.

Table 2.3 Initial antibiotic therapy selected for children hospitalised with uncomplicated community-acquired pneumonia[*#]

Antibiotics	Pre-CDSS *n* = 134, *n (%)*	Post-CDSS *n* = 107, *n (%)*	Total *n* = 241, *n (%)*
Third generation cephalosporin[^]	17 (12.7)	14 (13.1)	31 (12.9)
Narrow-spectrum penicillin[^^]	109 (81.3)	83 (77.6)	192 (79.7)
Macrolide	72 (53.7)	66 (61.7)	138 (57.26)
Azithromycin	2 (1.5)	3 (2.8)	5 (2.1)
Erythromycin	2 (1.5)	2 (1.9)	4 (1.7)
Roxithromycin	68 (50.7)	61 (57.0)	129 (53.5)
Lincosamide	0 (n/a)	2 (1.9)	2 (0.8)
Empirical antibiotic regimen selected at admission			
Single agent therapy	70 (52.2)	49 (45.8)	119 (49.4)
Macrolide alone	9 (6.7)	10 (9.4)	19 (7.9)
Narrow-spectrum penicillin alone	54 (40.3)	33 (30.8)	87 (36.1)
Third-generation cephalosporin alone	7 (5.2)	6 (5.6)	13 (5.4)
Dual agent therapy	64 (47.8)	58 (54.2)	122 (50.6)
Combination third generation cephalosporin and narrow spectrum penicillin	1 (0.8)	0 (n/a)	1 (0.4)
Combination third generation cephalosporin and macrolide	9 (6.7)	6 (5.6)	15 (6.2)
Combination third generation cephalosporin and lincosamide	0 (n/a)	2 (1.9)	2 (0.8)
Combination narrow spectrum penicillin and macrolide	54 (40.3)	50 (46.7)	104 (43.2)

*No statistically significant differences between pre- and post-CDSS; #percentages based on total within pre-CDSS and post-CDSS groups; ^Cefotaxime or ceftriaxone; ^^Ampicillin, amoxycillin or benzylpenicillin

CDSS: Computerised clinical decision support and approval system; n/a: not applicable

2.1.5 Discussion

There are no validated CAP severity scores for children,(10) and prognostic indicators are limited.(11) Therefore, we anticipated high rates of inappropriate prescribing and estimated approximately 50% of uncomplicated CAP would be treated with third generation cephalosporins.

However, almost 80% of cases over the entire study period were treated with penicillins. Third generation cephalosporins were used in only 13% of cases and varied by less than one percent pre- and post-CDSS. There was an apparent tendency toward the use of combination therapy in the post-CDSS period, although the difference in pre-CDSS versus post-CDSS usage was not statistically significant. Restricted antibiotics were infrequently used in both periods. Where restricted cephalosporins, azithromycin, or lincosamides were used, they were never accompanied by CDSS approval, suggesting the CDSS was not used when this antibiotic decision-making took place.

Published evaluations report varying CDSS utilisation rates and impact on prescribing.(12) Access to training, adequacy of computer skills, and a belief that a CDSS improves prescribing are considered facilitators to utilisation. These are reinforced by organisational support including senior staff endorsement. In contrast, poorly integrated systems—perceived to detract from patient–doctor interactions or create a divergence from usual workflow—are often considered barriers.(12)

Prescribing for CAP is usually initiated in the ED where antibiotic prescribing is predominantly monitored by pharmacists.(13) Unobstructed access to restricted antibiotics in our hospital's ED and general medical wards, together with a lack of pharmacist monitoring (i.e. absence of ED pharmacist rounds, limited pharmacist rounds on general medical wards)

might have further contributed to the apparent lack of impact of the CDSS on prescribing for CAP. Without regular pharmacist monitoring and poor integration with the prescriber's usual workflow, there were no prompts to use the CDSS at any point from antibiotic decision-making to the moment of administration. Thus, any theoretical improvement in prescribing or CDSS utilisation would have relied on general prescriber knowledge of AMS policy and routine AMS activity. As most assessed cases of CAP pre-CDSS were treated according to printed guidelines without the need for specific approval prescribers and nursing staff may have considered CDSS to be of minimal benefit.(12)

Antibiotic decision-making in ED occurs in the context of a busy working environment. There are constant interruptions,(14) limited diagnostic information,(15) and pressure to minimise patient waiting times.(16) Due to these constraints, the preferred strategies for AMS in ED are efficient, workflow-integrated systems with a degree of flexibility.(15) However, integration does not guarantee uptake,(17) and even efficient, integrated interventions have been poorly utilised in some EDs.(17) Locally, our CDSS platform has resulted in statistically significant reductions in the overall use of broad-spectrum antibiotics in adult hospitals.(18) However, third generation cephalosporins were still overused for moderate CAP in some hospitals, with rates only reduced after more intensive audit, feedback and education were introduced.(19) Similar assessments of CDSS impact on overall antimicrobial consumption in our hospital has been limited by a lack

of feasible and widely accepted measures to monitor use in paediatrics.(20) Unlike adult hospitals without electronic prescribing or administration records there is no paediatric equivalent for the World Health Organization's defined daily dose for adults.(21) As a result, the CDSS is often used by the local AMS to monitor antimicrobial use.

CAP guidelines for children supported by a range of AMS strategies have been reported to result in significant improvements in the rate of penicillin use. Guideline concordant prescribing increased from median baseline of 0% to 100% in ED and 30% to 100% among resident medical teams within 6 months by applying targeted quality improvement methodology with weekly reports on prescribing.(22) Elsewhere, prescribing improved but rates of broad-spectrum use remained higher than those observed in our study.(4) At our site, it may be that introducing a CDSS was insufficient to increase already comparatively guideline-concordant prescribing for CAP, without specific targeted intervention directed at CAP prescribing.

This study has several potential limitations. Our cohort of cases was identified using ICD-10-AM codes and the ED or admitting medical team's documented clinical impression. Coding relies on good clinical documentation and is therefore prone to insensitivity and non-specificity.(23) Acknowledging the potential influence of coding, we chose to include a broad range of ICD-10-AM codes associated with pneumonia and confirmed these as relevant cases only after review of medical records

and agreement between the two independent reviewers. Patients under 3 months of age may have been inadvertently excluded by coding or the clinician's initial risk assessment. We did not collect detailed age data in excluded patients and were therefore unable to confirm the underlying cause. We did not assess prior antibiotic use, either as a factor in antibiotic decision-making or as part of our exclusion criteria, although this may have influenced the prescriber's decisions. As we were unable to obtain adequate numbers of records and observed unexpectedly high rates of appropriate prescribing pre-CDSS our study was not sufficiently powered to exclude small improvements in prescribing. Finally, we were not able to consistently determine the oxygen saturation at the time of admission and exclude severe cases based on oxygen requirements which may have been an important consideration.(11)

Despite these limitations, the study has provided insights to inform targeted AMS activities that aim to maximise CDSS utilisation. Nurse-focussed strategies include rationalising the range and number of restricted agents stored in ward areas, integration of the traffic light system into ward medication rooms and resources used by nurses when preparing antibiotics. Since February 2017, utilisation among junior medical staff has been encouraged through regular peer audits of compliance, reported as departmental scorecards. In addition, the transition from paper-based to electronic medical records, in combination with a more streamlined CDSS

approval process via the electronic medical record has provided a platform to promote CDSS utilisation in ED.

Further studies are required to monitor CDSS utilisation and evaluate the impact on a broader set of indications and aspects of good antibiotic use, such as timely switch from intravenous to oral therapy and optimal treatment duration.

2.1.6 Conclusion

CDSS implementation and need for approval was not associated with a further reduction in already low rates of third generation cephalosporin use for children with presumed uncomplicated CAP.

2.1.7 References

1. McCulloh RJ, Patel K. Recent Developments in Pediatric Community-Acquired Pneumonia. Curr Infect Dis Rep 2016;18(5):14.
2. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53(7):e25-76.
3. Williams DJ, Hall M, Shah SS, Parikh K, Tyler A, Neuman MI, et al. Narrow Vs Broad-spectrum Antimicrobial Therapy for Children Hospitalized With Pneumonia. Pediatrics 2013;132(5):e1141-8.
4. Ross RK, Hersh AL, Kronman MP, Newland JG, Metjian TA, Localio AR, et al. Impact of Infectious Diseases Society of America/Pediatric Infectious Diseases Society Guidelines on Treatment of Community-Acquired Pneumonia in Hospitalized Children. Clin Infect Dis 2014;58(6):834-8.
5. MacDougall C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. Clin Microbiol Rev 2005;18(4):638-56.
6. Gerber JS, Kronman MP, Ross RK, Hersh AL, Newland JG, Metjian TA, et al. Identifying Targets for Antimicrobial Stewardship in Children's Hospitals. Infect Control Hosp Epidemiol 2015;34(12):1252-8.

7. Clinical Excellence Commission. Paediatric Quality Program: Between the flags. [Internet] Sydney, NSW: CEC; 2017 [cited 2017 16 August]; Available from: http://www.cec.health.nsw.gov.au/patient-safety-programs/paediatric-patient-safety/pqp-between-the-flags
8. Newman RE, Hedican EB, Herigon JC, Williams DD, Williams AR, Newland JG. Impact of a Guideline on Management of Children Hospitalized With Community-Acquired Pneumonia. Pediatrics 2012;129(3):e597-604.
9. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.
10. Usonis V, Ivaskevicius R, Diez-Domingo J, Esposito S, Falup-Pecurariu OG, Finn A, et al. Comparison between diagnosis and treatment of community-acquired pneumonia in children in various medical centres across Europe with the United States, United Kingdom and the World Health Organization guidelines. Pneumonia 2016;8(1):5.
11. Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? The rational clinical examination systematic review. JAMA 2017;318(5):462-71.
12. 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.

13. Welch S. Antimicrobial stewardship in Australian emergency departments. Emerg Med Australas 2015;27(5):427-30.
14. Coiera EW, Jayasuriya RA, Hardy J, Bannan A, Thorpe MEC. Communication loads on clinical staff in the emergency department. Med J Aust 2002;176(9):415-8.
15. 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;45(11):1198-202.
16. Health System Purchasing and Performance. Emergency Department Care. [Internet] Sydney: NSW Health; [updated 30 April 2018; cited 2017 5 September]; Available from: http://www.health.nsw.gov.au/Performance/Pages/emergency.aspx
17. Demonchy E, Dufour J-C, 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;69(10):2857-63.
18. 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.

19. Bond SE, Boutlis CS, Yeo WW, Miyakis S. Impact of an antimicrobial stewardship intervention on appropriateness of prescribing for community-acquired pneumonia in an Australian regional hospital. Intern Med J 2017;47(5):582-5.

20. Fortin É, Fontela PS, Manges AR, Platt RW, Buckeridge DL, Quach C. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to paediatrics. J Antimicrob Chemother 2014;69(6):1447-56.

21. Irwin A, Sharland M. Measuring antibiotic prescribing in hospitalised children in resource-poor countries: A systematic review. J Paediatr Child Health 2013;49(3):185-92.

22. Ambroggio L, Thomson J, Kurowski EM, Courter J, Statile A, Graham C, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics 2013;131(5):e1623-31.

23. Drees M, Gerber JS, Morgan DJ, Lee GM. Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship: Use of Administrative and Surveillance Databases. Infect Control Hosp Epidemiol 2016;37(11):1278-87.

2.2 Factors associated with adherence to antimicrobial stewardship after-hours

In the preceding section, cases of presumed non-severe CAP that required admission to hospital post-CDSS implementation were primarily treated with guideline concordant, unrestricted antibiotics that did not require approval via the CDSS. There was, however, no evidence of CDSS utilisation among CAP cases that were treated with restricted agents. Upon review of these findings a number of hypotheses were proposed, such as limited pharmacist involvement in ED and general paediatric wards, and readily available access to those agents.

In this part of the Thesis research, the effectiveness of the CDSS as a tool for tracking the use of restricted agents is assessed, specifically in the after-hours hospital setting. i.e., in the absence of pharmacy and AMS staff, when CDSS utilisation is dependent upon rostered prescribers and nursing staff.

Univariate tests and multivariable regression examine associations between variables and the likelihood of AMS adherence, in the form of a current CDSS approval, when restricted antimicrobials are acquired by nurses after-hours. Variables selected include the presence of any documented pharmacist request for a prescriber to obtain approval, the availability of restricted agents as routine “ward stock”, together with other

variables pertaining to the patient location, admitting clinical service and agent in question.

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2.2.1 Abstract

Objectives: Assess restricted antimicrobials acquired after standard working hours for adherence to antimicrobial stewardship (AMS) and identify factors associated with increased likelihood of adherence at the time of acquisition, and the next standard working day.

Methods: All documented antimicrobials acquired from a paediatric hospital after-hours drug room from 1 July 2014 to 30 June 2015 were reconciled with records of AMS approval, and documented AMS review in the medical record.

Key findings: Of the 758 antimicrobial acquisitions from the after-hours drug room, 62.3% were restricted. Only 29% were AMS adherent at the time of acquisition, 15% took place despite documented request for approval by a pharmacist. Antimicrobials for respiratory patients (OR 3.10, 95% CI 1.68–5.5) and antifungals (2.48, 95% CI 1.43–4.30) were more likely to be AMS adherent. Half of the acquisitions that required review the next standard

working day were adherent to AMS (51.8%, 129/249). Weekday acquisitions (2.10, 95% CI 1.20–3.69) and those for patients in paediatric intensive care (2.26, 95% CI 1.07–4.79) were associated with AMS adherence. Interactions with pharmacists prior to acquisition did not change the likelihood of AMS adherence the next standard working day. Access to restricted antimicrobial held as routine ward stock did not change the likelihood of AMS adherence at the time of acquisition, or the next standard working day.

Conclusion: Restricted antimicrobials acquired after-hours are not routinely AMS adherent at the time of acquisition or the next standard working day, limiting opportunities for AMS involvement.

2.2.2 Introduction

Hospitalised children are at increased risk of harm from medication error compared to adults.(1) Antimicrobials are among the classes of medicines that are most often associated with both medication errors and risk of harm.(1) Antimicrobial stewardship (AMS) programs have demonstrated a role in reducing medication errors associated with antimicrobial use by optimising antimicrobial choice, dose, route and duration.(2) By reducing unnecessary antimicrobial use, AMS programs may also limit the risk of adverse effects such as Clostridium difficile infection or allergic reaction,(2) that may otherwise be considered non preventable adverse drug events.(1)

Antimicrobial stewardship strategies are diverse but generally target the prescribing clinician, varying in the degree of autonomy left to the individual prescriber as well as the resources required. Specific AMS strategies range from education and issuance of practice guidelines with or without audit and feedback on prescribing, to more restrictive interventions requiring prescribers to obtain approval prior to the use of targeted antimicrobials from AMS teams.(3) Computerised tools, such as clinical decision support and web-based approval systems, are increasingly used to combine multiple strategies, and facilitate AMS.(4)

Each strategy has unique limitations and considerations. Restrictive strategies have demonstrated significant improvements in prescribing in the short term; however, these become less pronounced over time compared to more persuasive strategies.(5) Computerised clinical decision support systems for AMS show variable improvements in appropriate prescribing.(6) A possible explanation for these inconsistencies is the poor, or declining, adherence to AMS strategies as staff develop ‘workarounds’ to exploit inherent weaknesses in each system. For example, staff may acquire restricted antimicrobials without obtaining the necessary approvals,(7) or may falsify information to obtain AMS approval. Failure to recognise and address these system weaknesses, as well as the workarounds employed, can undermine and diminish the effectiveness of AMS.(8,9)

Pharmacists play a central role in AMS by optimising antimicrobial use and providing drug expertise, acting in leadership and accountability roles and providing clinical support to AMS teams. Despite these responsibilities in measuring, monitoring and managing medication use in hospitals, more than half of hospitals in high-income, well-resourced countries such as the United States do not have access to a complete 24-h, 7-day a week pharmacy service.(10)

Aim

This study explored how restricted antimicrobials were acquired for use outside of standard hospital working hours (after-hours) within a paediatric hospital, when the extent of AMS monitoring and prescribing restriction are both reduced. Specifically, the objectives were to determine the extent of AMS adherence as recorded at two timepoints: (1) at the time of antimicrobial acquisition after-hours, (2) retrospectively during the next standard working day, and to identify factors associated with AMS adherence at each timepoint.

Ethics approval

Approval to conduct the study was granted by the Human Research Ethics Committees of the local hospital (approval number LNR/16/SCHN/217, 7 July 2016) and of the University of Technology Sydney (approval number ETH16-0912).

2.2.3 Methods

Study Design

This retrospective single-centre study involved the extraction of data from all documented drug acquisition records from the hospital's designated after-hours drug room together with pharmacy dispensing records from 1 July 2014 to 30 June 2015.

Setting

The study was conducted in a 170-bed tertiary care paediatric hospital with specialist services including intensive care, oncology, and stem cell and kidney transplants. As part of the hospital's AMS program, antimicrobials are categorised as unrestricted, restricted, or Infectious Diseases approval only (ID approval only). Guideline-based algorithms programmed within a computerised antimicrobial approval and decision support system (CDSS, Guidance MS, Melbourne Health) are used promote optimal dosing for age and indication for all restricted antimicrobials used for admitted and non-admitted patients. In using the CDSS prescribers have 24-hour access to relevant management guidelines and may proceed to obtain automatic AMS approval for a predetermined duration depending on the indication selected. Approval to initiate ID approval only antimicrobials are determined on a case-by-case basis after telephone or face-to-face discussion with the Infectious Diseases (ID) team and recorded in the CDSS by the ID team member. Approvals that are due to expire are highlighted in the CDSS, and act as a prompt for clinical review by the AMS team and admitting clinical

specialty as the approval may only be extended by the ID/AMS team (Figure 2.4).

	Restriction Category		
	Unrestricted	**Restricted**	**ID Approval Only**
Approval Process	No approval required	Approval is facilitated by a CDSS accessible 24 hours a day. The CDSS processes approval requests, provides indication specific dose recommendations. Locally designed algorithms automate approval where use is compliant with local guidelines. Automated approvals expire after a timeframe based on the antimicrobial and indication but remain visible within the CDSS, prompting review by the AMS team.	Prescribers are required to contact the AMS or ID team directly for approval prior to use. The ID approver records the approval in the CDSS for a defined period.
Availability	Antimicrobials are available on wards as routine ward stock in high usage areas but may also be dispensed by the hospital pharmacy on prescription.	Some restricted antimicrobials are available on wards as routine ward stock in high usage areas but may also be dispensed by the hospital pharmacy on prescription.	Antimicrobials are not available outside the hospital pharmacy during pharmacy operating hours.
Supply during Pharmacy Hours (08:30 to 17:00 Monday to Friday)	Supplied to ward	Supplied after confirmation of approval in the CDSS. Pharmacists who identify prescriptions without existing approval notify the prescriber by telephone of the action required while also lodging an "alert" to the AMS team via the CDSS. Where a prescription for a restricted antimicrobial requires urgent supply, a limited quantity is dispensed to avoid delays in the commencement of therapy.	Supplied only after confirmation of approval in the CDSS or discussion with the ID or AMS team. Pharmacists who identify prescriptions for ID approval only antimicrobials without existing approval will notify the prescriber by telephone to contact the ID or AMS team and lodge an "alert" to the team via the CDSS.
Supply After-Hours (17:01 to 08:29 Monday to Friday, all weekends and public holidays)	Nursing staff acquire additional or newly prescribed medications that are not available on the ward by accessing a secure after-hours drug room after discussion with the hospital after-hours nurse coordinator.		
Records of After-Hours drug acquisition	The patient's details (patient name, medical record number, ward), medication name, dosage form, strength and quantity of drug stock taken are documented on a paper-based record held in the after-hours drug room.		
Records of CDSS approval	Approval numbers are generated by the CDSS and should be recorded on the medication chart by the prescriber. Medical, nursing and pharmacy staff may query the CDSS for current approvals, expired approvals and pharmacist alerts for current inpatients. The AMS team have access to activity logs that record all approval-related CDSS transactions including "alerts".		

Figure 2.4 Process of antimicrobial approval and supply during and after standard working hours. The after-hours drug room and paper-based records are reviewed by the hospital pharmacy the next standard working day. Stock levels are replenished, and the medications documented are retrospectively dispensed to individual patients. The AMS team regularly screen the CDSS for: any approval requests that are for indications that are not pre-programmed in the CDSS; approvals which have expired or are close to expiring; and any pharmacist-generated requests for approval('alert'). However, hospital policy stipulates that it is the prescriber's responsibility to obtain AMS approval. AMS, Antimicrobial Stewardship; CDSS, computerised antimicrobial approval system with decision support; ID, Infectious Diseases.

All CDSS guidelines and approvals may be viewed by medical, pharmacy and nursing staff; pharmacists cannot obtain approvals but are able to lodge ‘alerts’ within the CDSS when restricted antimicrobials are prescribed without the necessary approval. In addition to the documentation in the CDSS, prescribers and pharmacists record the CDSS-generated approval code on the medication chart. CDSS activity logs allow the AMS team to review and report all approval-related activity, including the date and time of each approval, alert and approval extension. Since its implementation in October 2012 education on the use of the CDSS has been available for all staff, and included as part of mandatory orientation for all junior medical staff. The restriction categories of all antimicrobials used at the hospital are listed on pocket cards that are issued to all staff members.

In standard working hours, pharmacists perform medication chart reviews and clinical interventions, document use of restricted antimicrobials and prompt prescribers to obtain the necessary approvals. For the latter, prescribers are advised on the specific action according to restriction category via face-to-face or telephone conversation whilst simultaneously lodging an ‘alert’ within the CDSS.

Where a prescription for a restricted antimicrobial requires urgent supply, a limited quantity is dispensed to avoid delays in the commencement of therapy. After-hours (17:01 to 08:29 hours, Monday to Friday, all weekends and public holidays), nursing staff review medication charts and acquire

restricted antimicrobials from a secure after-hours drug room (Figure 2.4) with no pharmacist intervention. Nursing staff record the date and time of acquisition, the patient's details and location, the medication name, dosage form, strength and quantity of drug stock taken on a paper-based record form held in the after-hours drug room. The next standard working day, a member of the pharmacy department reviews the paper-based record and physical stock on hand in the afterhours drug room to validate the information recorded on the form. Once validated, the details of the after-hours drug acquisitions (i.e. medication, strength, dosage form, quantity, date and ward at the time of acquisition) are recorded in the patient's profile within the pharmacy dispensing software. As these items are processed with an additional note (i.e. 'after hours, taken on dd/mm/yyyy'), they are easily identified in the dispensing record. Stock within the after-hours drug room is replenished before the end of the standard working day to ensure stock levels are adequate after-hours. As nurses are not required to secure the appropriate approval, prescribers are contacted by pharmacists the next standard working day if an approval is required.

Data Collection

Paper-based records used to document the antimicrobials acquired from the hospital's after-hours drug room were reviewed for patient identifiers (current ward location, treating clinical specialty), the medication acquired (dosage form, quantity), and date and time of acquisition as documented on the paper-based record; this information was cross-checked against

dispensing records from the hospital pharmacy dispensing software (*ipharmacy, CSC, Sydney, NSW*) to verify the quantity documented on the after-hours drug room record, expressed as World Health Organization defined daily doses (DDDs).(11)

The information was then used to query the CDSS activity log for evidence of (1) AMS adherence at the time restricted antimicrobials were acquired from the afterhours drug room, and (2) AMS adherence the next standard working day.

After-hours antimicrobial use was considered to be (1) AMS adherent at the time of antimicrobial acquisition if a CDSS approval was generated on or before the date and time documented on the after-hours drug room record and was yet to expire (2) AMS adherent the next standard working day if a CDSS approval was obtained retrospectively, that is after drug acquisition from the after-hours drug room, or there was a change in therapy accompanied by documented evidence of clinical review involving AMS/ID the next standard working day. Changes in therapy, clinical reviews and discharge from hospital were determined after investigators reviewed patients' progress notes and medication charts without a CDSS approval (Figure 2.5). Patients who were discharged and restricted antimicrobials that were discontinued before the next standard working day were excluded from the assessment of AMS adherence the next standard working day (i.e. retrospective CDSS approval or AMS/ID review). Whilst querying the CDSS

activity log, presence of a pre-existing ‘alert’ and/or expired CDSS approval were also documented.

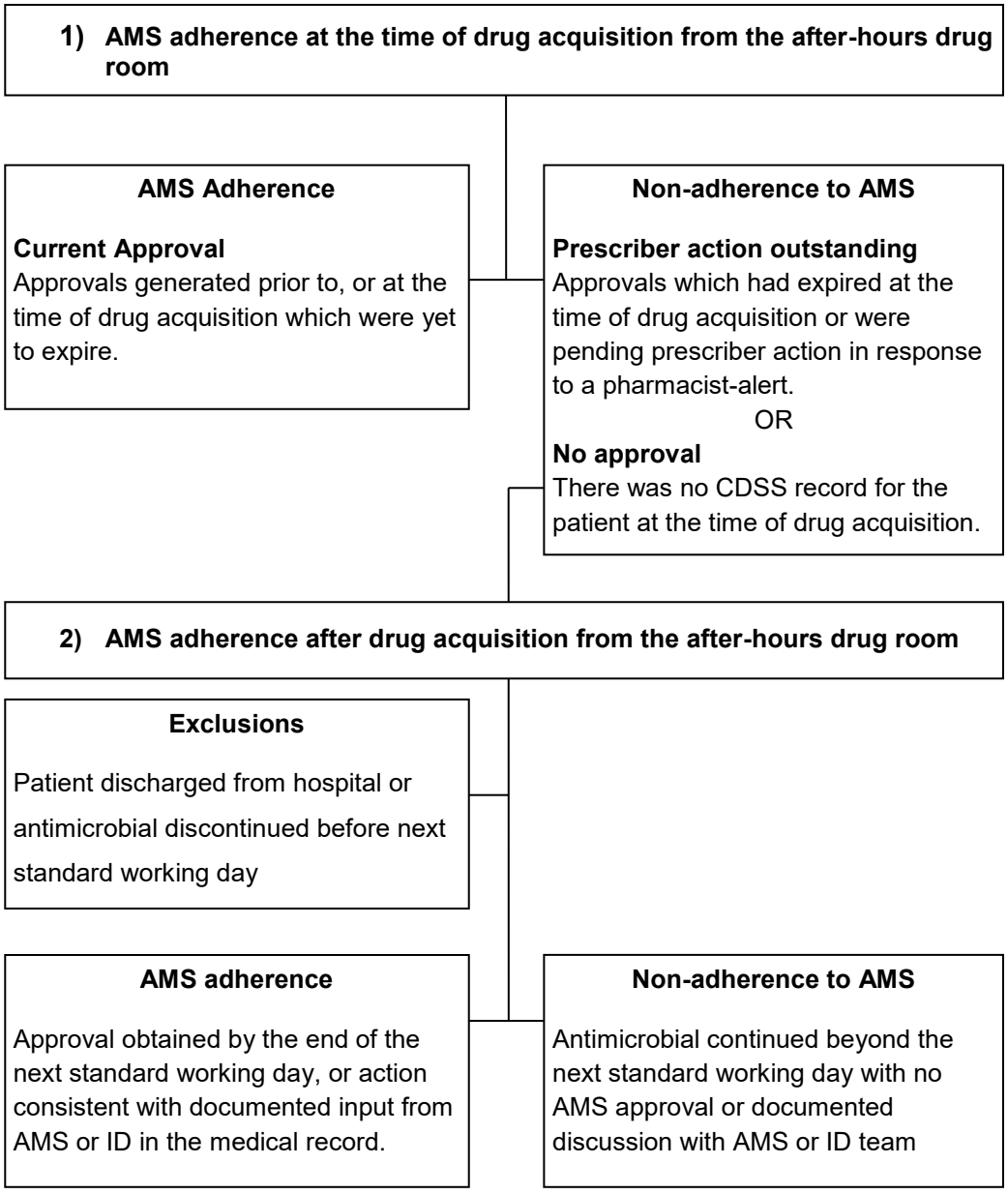

Figure 2.5 Assessment and classification of AMS adherence for restricted antimicrobials acquired from the after-hours drug room.
AMS, Antimicrobial Stewardship; ID, Infectious Diseases; CDSS, Computerised antimicrobial approval and decision support system.

Data Analysis

Data analysis was undertaken using IBM SPSS Statistics for Windows Version 24 (Armonk, NY, IBM Corp). Descriptive statistics were used to summarise data pertaining to antimicrobial acquisition from the after-hours drug room, and AMS adherence. The Mann–Whitney *U*-test was used to compare the quantity of restricted antimicrobial (in DDD) acquired for AMS adherent and non-adherent prescribing. Bland–Altman plots and one sample t-tests were used to explore differences between quantities documented on after-hours drug room and pharmacy dispensing records within each dosage form subgroup.(12)

Logistic regression analysis with purposeful selection was used to identify factors associated with AMS adherence at (1) the time of drug acquisition and (2) the next standard working day. Univariate analysis was performed to explore associations between variables and the likelihood of AMS approval at each time point. Where quasi-complete separation was detected within a variable categories were collapsed for univariate analysis.(13) All explanatory variables demonstrating an association with the outcome variable ($P < 0.25$) were included as potential factors in multivariable logistic regression models for each of the timepoints.(14) A backward likelihood ratio method was used to select the most parsimonious models. Variables with statistically significant *P* values were retained as factors; variables that influenced the odds ratio of statistically significant factors by more than 10% were retained as covariates. The final models

were reviewed for multicollinearity among the covariates. Unless otherwise stated, all statistical tests were two tailed and considered a *P* value <0.05 to denote statistical significance.

2.2.4 Results

After-hours retrievals for antimicrobials

There were 771 separate records for antimicrobial acquisitions from the after-hours drug room; 13 entries had incomplete, illegible or incorrect patient identifiers, these could not be matched to pharmacy dispensing records and were excluded from analysis. This resulted in 758 records being included in the analysis, the equivalent of approximately 2000 DDD used for 485 patients. Bland-Altman plots indicated injectable and solid oral quantities documented in the paper-based, after-hours drug room records and pharmacy dispensing records were almost always the same (Figure 2.6). Oral liquids and topical antimicrobials were in perfect agreement. As the largest discrepancies identified were recording errors related to pack size or the unit of measure, investigators used data from the pharmacy dispensing record for further analysis. Restricted antimicrobials were acquired most often (62.3%, 472/758) followed by those in the unrestricted (35%, 267/758), and ID approval only (2.5% 19/758) categories. Ceftriaxone (16.7%, 79/472), azithromycin (13.6%, 64/472) and clindamycin (10.8%, 51/472) were the restricted antimicrobials acquired most commonly after-hours.

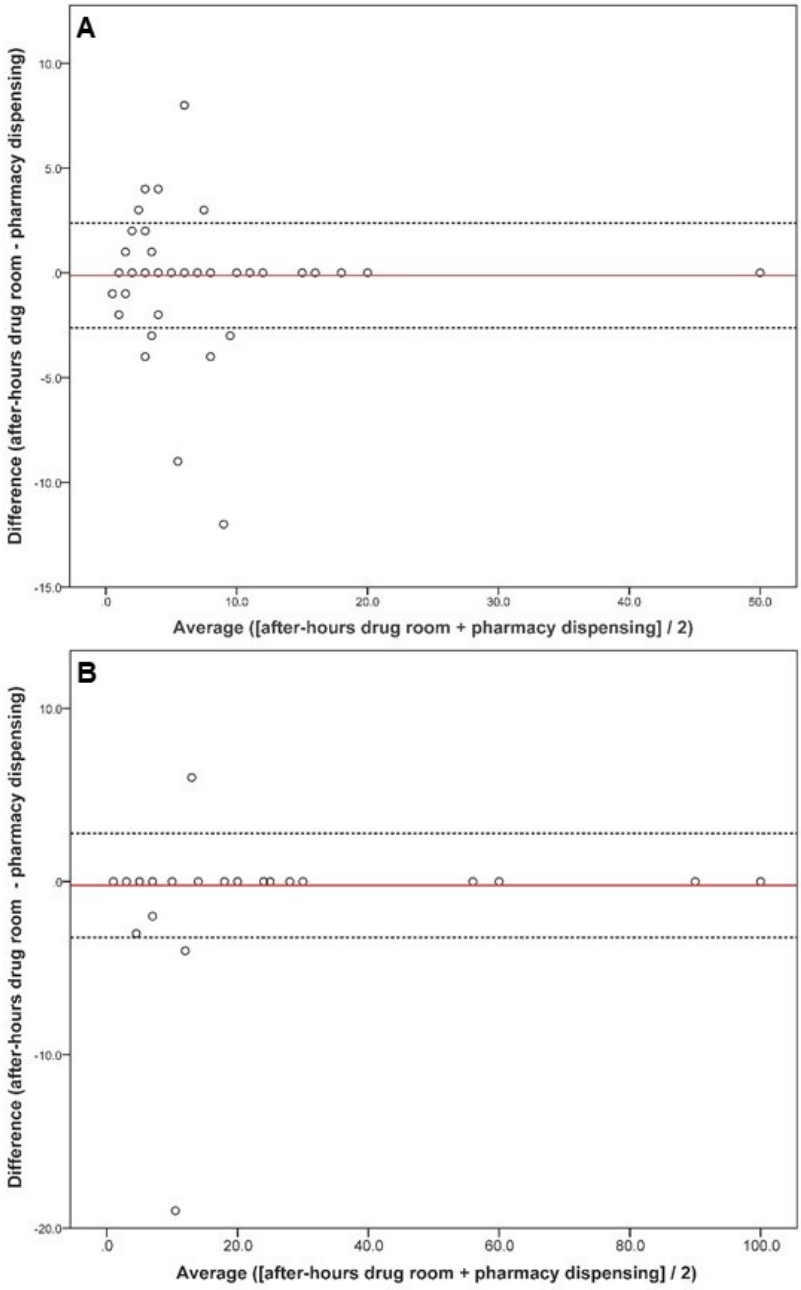

Figure 2.6 Agreement between after-hours drug room and pharmacy dispensing records (results of Bland-Altman analysis). A. Injectable antimicrobial drug acquisitions(N=419). Mean difference (quantity) -0.13 (limits of agreement 2.69 to -2.96). One sample t test p=0.06 **B.** Solid oral (tablets and capsules) antimicrobial drug acquisitions (N=96). Mean difference (quantity) -0.23 tablets or capsules (limits of agreement 3.90 to -4.36). One sample t test p=0.29.

AMS adherence at the time of drug acquisition from the after-hours drug room

The CDSS was infrequently used for decision support and approval after-hours (29.2%, 138/472). Over half of the restricted antimicrobial acquisitions after-hours were nonadherent to AMS because they had no associated CDSS approval whatsoever (55.2%, 261/472). The remaining were either associated with an expired AMS approval, or were acquired after the prescriber had disregarded a pharmacist's request to obtain approval during standard working hours (15.5%, 73/472).

Univariate analyses indicated there was no statistically significant difference in the likelihood of AMS adherence between winter and other seasons, weekdays versus weekends, intravenous versus oral or topical dosage forms, or wards where the restricted antimicrobial in question was routinely stored versus those where it was supplied for the individual patient after chart review from pharmacy. Antifungal prescriptions were more likely to be AMS adherent than prescriptions for antibacterials (Table 2.4).

Compared to respiratory patients, those admitted under surgical and oncology clinical specialties were less likely to be AMS adherent when acquiring restricted antimicrobials after-hours, and almost all wards were less likely to be AMS adherent when compared to the adolescent ward. Furthermore, there was no evidence of adherence to AMS in the emergency department (Table 2.4).

Table 2.4 Explanatory variables and multivariable model for potential factors associated with AMS adherence at the time of drug acquisition after-hours*

	Univariate Analysis			Multivariable Model[$]	
Characteristics	Approved restricted antimicrobials *n* (%)138 (29.2)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Clinical specialty			<0.001		
Other Medical Specialty[#] (*n*=28)	7 (25.0)	1 (Ref)	n/a		
Emergency Department (*n*=22)	0 (0)	1 (Ref)	n/a		
Respiratory (*n*=63)	35 (55.6)	7.68 (3.00–19.67)	<0.001	3.10 (1.72–5.62)[^]	<0.001
Surgical (*n*=98)	25 (25.5)	2.10 (0.84–5.27)	0.113		
Paediatric Intensive Care (*n*=89)	26 (29.2)	2.54 (1.01–6.36)	0.048		
General Paediatrics (*n*=60)	16 (26.7)	2.34 (0.84–5.97)	0.109		
Oncology (*n*=112)	29 (25.9)	2.15 (0.87–5.30)	0.098		
Access during standard working hours					
Available on ward as routine stock during standard working hours (*n*=114)	34 (29.8)	1 (Ref)	n/a		
Dispensed by pharmacy after medication chart review (*n*=358)	104 (29.1)	0.96 (0.61-1.53)	0.874		
Ward location			0.001		
Emergency Department (*n*=24)	0 (0)	1 (Ref)	n/a		
Surgical Short Stay (*n*=23)	3 (13.6)	1 (Ref)	n/a		
Adolescent (*n*=55)	26 (47.3)	13.15 (3.64–47.47)	<0.001	2.50 (1.28–4.90)[^]	0.008
Paediatric Intensive Care Unit (*n*=89)	26 (29.2)	6.05 (1.73–21.25)	0.005		
Acute Isolation (*n*=101)	34 (33.7)	7.44 (2.15–25.73)	0.002	1.61 (0.94–2.76)[^]	0.083
Oncology (*n*=41)	7 (17.1)	3.02 (0.73–12.55)	0.128		
Neurology (*n*=80)	29 (36.3)	8.34 (2.38–29.26)	0.001	2.09 (1.15–3.78)[^]	0.015
Surgical Long Stay (*n*=59)	13 (22.0)	4.15 (1.11–15.54)	0.035		
Dosage Form			0.119		
Injectable (*n*=349)	111 (31.8)	1 (Ref)	n/a		
Tablets or capsules (*n*=48)	10 (20.8)	0.56 (0.27–1.17)	0.130		
Oral liquids or topical (*n*=75)	17 (22.7)	0.63 (0.33–1.13)	0.120		
Antimicrobial classification			0.055		
Antibacterial (*n*=374)	105 28.1)	1 (Ref)	n/a		
Antifungal (*n*=77)	30 (39.0)	1.63 (0.98–2.72)	0.059	2.48 (1.43–4.30)[^]	0.001
Antiviral (*n*=21)	3 (14.3)	0.43 (0.12–1.48)	0.180		
Timing of drug acquisition					
Weekday (*n*=246)	74 (30.1)	1 (Ref)	n/a		
Weekend (*n*=226)	64 (28.3)	0.92 (0.61–1.37)	0.674		
Season[##]			0.301		
Winter (*n*=148)	48 (32.4)	1 (Ref)	n/a		
Spring (*n*=95)	27 (28.4)	0.83 (0.47–1.45)	0.509		
Summer (*n*=100)	22 (22.0)	0.59 (0.327–1.05)	0.075		
Autumn (*n*=129)	41 (31.8)	0.97 (0.59–1.61)	0.908		

AMS: Antimicrobial Stewardship, CI: Confidence Interval; *N=472; [#]Other clinical specialty: Nephrology, Neurology, Gastroenterology, Infectious Diseases, Rheumatology, Dermatology, Ophthalmology, Cardiology, Rehabilitation; [##]Seasons: Winter: 1 July to 30 September, Spring: 1 October to 31 December, Summer: 1 January to 31 March, Autumn: 1 April to 30 June; [^]Reference category is all other categories within the same variable; [$]Model Specification: -2 Log likelihood 529.38, Cox and Snell 0.08, Nagelkerke R Square 0.12, Chi square statistic=41.05, 5 degrees of freedom, *P* value < 0.001.

The multivariable model identified individual clinical specialties and wards with increased likelihood of being AMS adherent after-hours: respiratory patients were three times more likely to have the required CDSS approval afterhours compared to all other clinical specialties (OR 3.10, 95% CI 1.68–5.5). Patients admitted to the neurology and the adolescent wards were at least two times more likely to have approval than those on any other ward (OR 2.09, 95% CI 1.15–3.78 and OR 2.5, 95% CI 1.28–4.90, respectively). Antifungal drug acquisitions were more likely to be AMS adherent than those for antibacterials or antivirals (2.48, 95% CI 1.43–4.30). The acute isolation ward was retained in the model due to the influence on the other variables though it was not statistically significant (Table 2.4). No statistically significant interactions were identified.

The quantity of antimicrobial removed from the afterhours drug room, measured in DDDs, did not vary with respect to AMS adherence for most restricted antimicrobials. Clindamycin (median DDDs AMS adherent 2.50, IQR 1.67– 8.75; median DDDs non-adherent 1.67, IQR 0.50–1.67; P = 0.042), ticarcillin–clavulanate (median DDDs adherent 0.90, IQR 0.70–1.70; median DDDs non-adherent 0.60, IQR 0.40–0.80; P = 0.034) and ceftazidime (median DDDs adherent 1.5, IQR 1.00–2.00; median DDDs non-adherent 1.00, IQR 0.50–1.00; P = 0.005) were supplied in larger quantities when associated with adherence to AMS.

AMS adherence after drug acquisition from the after-hours drug room

The 334 records for restricted antimicrobials associated with non-adherence to AMS at the time of drug acquisition were further assessed for AMS adherence the next standard working day. Two hundred and forty-nine records remained evaluable after excluding acquisitions for patients who were discharged (12.6%, 42/334), had discontinued therapy before the next standard working day (11.1%, 37/334) or had missing documentation (1.8%, 6/334). AMS adherence and non-adherence occurred almost equally amongst patients who remained in hospital after acquiring restricted antimicrobials from the after-hours drug room (51.8% and 48.2%, respectively). In most instances, AMS adherence the next standard working day came in the form of a documented CDSS approval (93.8%, 121/129) with only a few cases discontinued after documented discussion between the treating and AMS team (6.2%, 8/129).

Univariate analysis suggested AMS adherence was more likely when antimicrobial acquisitions took place on weekdays compared to weekends. Antifungals were less likely to be AMS adherent than antibacterials and antivirals, and all clinical specialties were more likely to be adherent to AMS when compared to oncology. Whilst there was statistically significant variation among wards, ease of access to restricted antimicrobials during standard working hours did not contribute to the likelihood of AMS adherence. Univariate analysis also suggested there was a seasonal pattern, such that the likelihood of AMS adherence was higher in summer,

compared to winter months. Injectable antimicrobials appeared to be more likely to be associated with AMS adherence (Table 2.5).

The multivariable model (Table 2.5) indicated that AMS adherence was two times more likely to occur when antimicrobials were acquired on weekdays compared to weekends (OR 2.10, 95% CI 1.20–3.69) or for patients in intensive care compared to all other wards (OR 2.26, 95% CI 1.07–4.79). Prescribing for patients admitted under oncology was less likely to be AMS adherent the next standard working day when compared to other specialties. Injectable antimicrobials were more likely than other forms to be associated with AMS approval (OR 3.00, 95% CI 1.57–5.74).

Antimicrobial stewardship adherence was not significantly different for antifungals compared to other types of antimicrobials in the multivariable model. Interactions with pharmacists on the previous working day, either in the form of a request for AMS approval or an expired AMS approval, did not appear to influence AMS adherence after drug acquisition from the after-hours drug room.

Table 2.5 Explanatory variables and multivariable model for potential factors associated with retrospective AMS adherence after using after-hours procedures to acquire restricted antimicrobials[**]

	Univariate Analysis			Multivariable model[^^]	
Characteristic	AMS adherence n (%) 129 (51.8)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Clinical Specialty			<0.001		
Oncology (*n*=59)	18 (26.1)	1 (Ref)	n/a	0.22 (0.11–0.43)[#]	<0.001
Respiratory (*n*=26)	19 (73.1)	7.69 (2.77–21.32)	<0.001		
Surgical (*n*=48)	28 (58.3)	3.97 (1.81–8.71)	0.001		
Paediatric Intensive Care (*n*=52)	35 (67.3)	5.83 (2.65–12.86)	<0.001		
General Paediatrics (*n*=30)	15 (50.0)	2.83 (1.16–6.93)	0.023		
Emergency[^] (*n*=9)	6 (66.7)	5.67 (1.28–25.05)	0.022		
Other Clinical Specialty[$] (*n*=15)	8 (53.3)	3.24 (1.03–10.21)	0.045		
Access during standard working hours					
Available on ward as routine stock during standard working hours (*n*=57)	30 (52.6)	1 (Ref)	n/a		
Dispensed by pharmacy after medication chart review (*n*=192)	99 (51.6)	0.96 (0.53–1.73)	0.887		
Ward Location			0.004		
Paediatric Intensive Care Unit (*n*=52)	35 (67.3)	1 (Ref)	n/a	2.26 (1.07–4.79)[#]	0.033
Emergency[^] (*n*=11)	8 (72.7)	1 (Ref)	n/a		
Adolescent (*n*=21)	12 (57.1)	0.62 (0.22–1.71)	0.356		
Neurology (*n*=39)	25 (64.1)	0.83 (0.36–1.93)	0.666		
Surgical Short stay (*n*=13)	7 (53.8)	0.54 (0.16–1.82)	0.323		
Surgical Long stay (*n*=38)	18 (47.4)	0.42 (0.18–0.96)	0.039		
Acute Isolation (*n*=46)	16 (34.8)	0.25 (0.11–0.55)	0.001		
Oncology (*n*=29)	8 (27.6)	0.18 (0.67–0.47)	<0.001		
Dosage Form			0.125		
Injectable (*n*=179)	100 (55.9)	1 (Ref)	n/a	3.00 (1.57–5.74)[#]	0.001
Tablets and capsules (*n*=26)	11 (42.3)	0.58 (0.25–1.33)	0.199		
Oral liquids or topical[*] (*n*=44)	18 (40.9)	0.55 (0.28–1.07)	0.077		
Antimicrobial classification			0.013		
Antibacterial (*n*=197)	111 (56.4)	1 (Ref)	n/a		
Antifungal (*n*=40)	12 (30.0)	0.32 (0.16–0.69)	0.003		
Antiviral (*n*=12)	6 (50.0)	0.77 (0.24–2.49)	0.668		
Timing					
Weekend (*n*=118)	53 (44.9)	1 (Ref)	n/a		
Weekday (*n*=131)	76 (58.0)	1.69 (1.03–2.80)	0.039	2.10 (1.20–3.69)[#]	0.009
Season[##]			0.133		
Winter (*n*=79)	37 (46.8)	0.88 (0.46–1.71)	0.713		
Spring (*n*=46)	27 (58.7)	0.55 (0.25–1.18)	0.202		
Summer (*n*=60)	37 (61.7)	2.08 (1.01–4.24)	0.047		
Autumn (*n*=64)	28 (43.7)	1 (Ref)	n/a		
Interaction with AMS or Pharmacist previous working day					
Expired AMS approval or prior request for approval by pharmacist (*n*=60)	32 (53.3)	1.08 (0.61–1.94)	0.786		

AMS: Antimicrobials Stewardship; CI: Confidence Interval; OR: Odds Ratio [**]Adherence to AMS assessed the next standard working day after drug acquisition after-hours, N=249.[##]Seasons adjusted to study period: Winter: 1 July to 30 September, Spring: 1 October to 31 December, Summer: 1 January to 31 March, Autumn: 1 April to 30 June; [*]No restricted topical antimicrobials were approved. [#]reference is all other categories within variable; [^]Patients were admitted to Emergency ward or clinical specialty at the time of drug acquisition from the after-hours drug room and may have been transferred to a different ward or clinical specialty the next working day;[$]Other clinical specialty: Nephrology, Neurology, Gastroenterology, Infectious Diseases, Rheumatology, Dermatology, Ophthalmology, Cardiology, Rehabilitation; [^^]Model Chi square statistic 44.21 on 4 degrees of freedom, *P*<0.001, -2 Log likelihood 300.65, Nagelkerke R square 0.217, Cox and Snell R square 0.163.

2.2.5 Discussion

Antimicrobial stewardship adherence was suboptimal at the time of drug acquisition after-hours, only 29.2% of drug acquisitions had a current CDSS approval. There was no indication that the quantity of antimicrobial acquired by nurses after-hours was increased in instances where no prior approval had been obtained. Where retrospective approval or AMS review was required the next standard working day, adherence and non-adherence to AMS occurred almost equally (51.8% vs 48.2%, respectively). Alerts generated by pharmacists did not increase the likelihood of AMS adherence after hours, or the next standard working day. Unique factors were identified in each multivariable model. AMS adherence at the time of drug acquisition was more likely for antifungals compared to other antimicrobials; however, the antimicrobial classification was not significant in the multivariable analysis of retrospective approval. Whilst the neurology and adolescent wards were significant factors associated with adherence at drug acquisition, patients in intensive care were most likely to be AMS adherent retrospectively. Among the clinical specialties, adherence at the time of drug acquisition was most likely for patients admitted under respiratory.

Retrospective adherence for patients admitted under respiratory was higher than all other clinical specialties. The multivariable analysis of retrospective adherence identified admission under oncology as a significant factor associated with non-adherence. There was a distinction between weekday and weekend drug acquisitions at the two assessment

points; whilst AMS adherence recorded at the time of drug acquisitions did not differ on weekdays compared to weekends, retrospective approval or AMS review the next standard working day was more likely for when the acquisition took place on a weekday compared to weekends.

This study had a number of limitations. The findings may be specific to the local hospital and may not apply to other institutions. Although the multivariable model adjusted for a range of covariates selected a priori, the findings may have been influenced by unmeasured confounders, such as staffing levels or variability in pharmacy services across wards and departments. Comparisons of standard and after-hours AMS adherence, although ideal, were not feasible. Routine audits of AMS adherence at the hospital were not designed to differentiate between prescribing, CDSS approvals and drug acquisitions that take place during the standard working day and those that occur in the after-hours period. A comparative study would have require detailed records of nurse and prescriber activity during standard working hours, and was, therefore, not viable. Due to the retrospective assessment and reliance on existing documentation for AMS approval, there may have been instances where approval was granted verbally but not confirmed in the CDSS by the ID team. CDSS approvals generated by the AMS team and clinical specialty were not explicitly recorded; this may have meant specialties who received closer attention from the AMS team theoretically might have been more adherent. Finally, data collection methods did not account for omitted doses that were not

administered to patients, doses acquired from other ward areas or reallocated from other patients, which are other potential mechanisms for bypassing approval.

The limited use of the CDSS across the hospital, particularly the emergency department, suggests that it was not used to guide prescribing. Bypassing the CDSS is concerning in this setting, as the hours when pharmacists are not available on site have been associated with an increased risk of error among paediatric inpatients.(15) In the paediatric emergency setting, up to 10% of medication charts may have a prescribing error, with risk further increasing after-hours.(16) Unlike other AMS strategies that may be unavailable or have different modes of operation afterhours,(17) CDSS is available to guide safe and appropriate antimicrobial prescribing at all times and could be of considerable benefit in minimising these risks.

The local institution relies on paper-based medication charts with a standalone CDSS, requiring AMS adherent prescribers to deviate from their usual workflow to obtain the appropriate management recommendations and approvals for the use of restricted antimicrobials. Computerised prescriber order entry (CPOE) with integrated AMS clinical decision support has demonstrated improvements in antimicrobial prescribing and reductions in antimicrobial use and errors in paediatric hospitals.(2,18) Shifting from ‘opt in’ systems to workflow-integrated CDSS appears prudent, and in-keeping with ‘systems’ approaches used to ensure patient

safety.(19) However, results between institutions have not been consistent.(20)

Several findings from this study are noteworthy, and warrant further investigation. Minimising access to restricted antimicrobials on select wards did not influence the likelihood of adherence after-hours when compared to wards where restricted antimicrobials were freely available; although the cause cannot be determined within the current study, it might mean that restricted antimicrobials that are freely available in high use wards are not contained within those areas. The increased likelihood of approval following after-hours drug acquisition on weekdays compared to weekends could simply be due to poor documentation and miscommunication.(21) However, weekend antimicrobial prescribing has been associated with inappropriate, often excessive, prescribing elsewhere.(22) As such, there may be a need to consider alternate strategies on Mondays. For example, this may mean direct involvement by the AMS, or collaborating with clinical specialties and Administrators to facilitate communication.

There is no consensus on how to measure and report staff adherence to the day-to-day processes involved in AMS and no obvious workarounds have been reported in paediatric centres. Venugopal et al. observed approval patterns that suggest prescribers may have learnt how to frame requests to initiate restricted antimicrobials in a manner that would maximise the likelihood of approval. More specifically, as the AMS program

became more established requests to initiate restricted antimicrobials were increasingly approved; however, AMS approval for ongoing use after AMS prescription review remaining constant. Furthermore, those clinical specialties with junior medical staff who were less familiar with the local system were also less likely to have their antimicrobial requests approved.(7) Other AMS programs have reported evidence to suggest clinicians delayed prescribing antimicrobials that were unlikely to be AMS approved until the after-hours period.(23)

Whilst this study represents a small proportion of the hospital's overall antimicrobial use in use in DDDs, the assessment identified important factors associated with adherence, non-significant factors that warrant further review of day-to-day antimicrobial supply and storage functions, clinical specialties and days of the week (i.e. Mondays) that may require more proactive AMS involvement. Further studies are needed to better understand facilitators and barriers to AMS adherence and the most effective strategies for AMS after-hours. Adherence to AMS during standard AMS and pharmacy working hours and the after-hours period should be explored in comparative studies to more explicitly define the impact on process and outcome measures related to AMS.

2.2.6 Conclusion

Restricted antimicrobials acquired after-hours are most often non-adherent to AMS and are not consistently followed up the next standard working day.

Subverting the CDSS at the point of prescribing eliminates the expected benefits of computerised AMS strategies after-hours, with repercussions for AMS during standard working hours.

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Authors' contributions

All authors contributed to the design of this study. M Mostaghim collected the data, performed the data analysis, drafted and revised the manuscript. Dr T Snelling and A/Prof. Bajorek actively reviewed the data analysis and critically revised the manuscript. M. Mostaghim was the sole author with full access to the study data. All authors approved the final manuscript this study as submitted.

2.2.7 References

1. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285(16):2114-20.
2. Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila) 2009;48(5):505-12.
3. 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.
4. 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.
5. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013(4):CD003543.
6. 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;23(8):524-32.

7. Venugopal V, Lehmann CU, Diener-West M, Agwu AL. Longitudinal evaluation of a World Wide Web–based antimicrobial stewardship program: Assessing factors associated with approval patterns and trends over time. Am J Infect Control 2014;42(2):100-5.
8. Dunagan WC, Medoff G. Formulary control of antimicrobial usage: What price freedom? Diagn Microbiol Infect Dis 1993;16(3):265-74.
9. Seemungal IA, Bruno CJ. Attitudes of Housestaff toward a Prior-Authorization-Based Antibiotic Stewardship Program. Infect Control Hosp Epidemiol 2012;33(4):429-31.
10. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Monitoring and patient education—2015. Am J Health Syst Pharm 2016;73(17):1307-30.
11. WHO Collaborating Centre for Drug Statistics Methodology. Defined Daily Dose: Definition and general considerations of defined daily dose (DDD). [Internet] Oslo: Norwegian Institute of Public Health [cited 2017 3 December]. Available from: http://www.whocc.no/ddd/definition_and_general_considera/
12. Sedgwick P. Limits of agreement (Bland-Altman method). BMJ 2013;346:f1630.
13. Allison P. Convergence Problems in Logistic Regression. In: Altman M, Gill J, Mc Donald P.. Numerical Issues in Statistical Computing for the Social Scientist. Hoboken (NJ): John Wiley & Sons; 2003. p. 238-52.

14. Hosmer DW, Jnr, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. New York (NY): John Wiley & Sons; 2013.
15. Miller AD, Piro CC, Rudisill CN, Bookstaver PB, Bair JD, Bennett CL. Nighttime and Weekend Medication Error Rates in an Inpatient Pediatric Population. Ann Pharmacother 2010;44(11):1739-46.
16. Walsh KE, Kaushal R, Chessare JB. How to avoid paediatric medication errors: a user's guide to the literature. Arch Dis Child 2005;90(7):698-702.
17. Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a Hospital-Based Antimicrobial Management Program on Clinical and Economic Outcomes. Clin Infect Dis 2001;33(3):289-95.
18. Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and Impact of a Computerized Pediatric Antiinfective Decision Support Program. Pediatrics 2001;108(4):e75.
19. Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? Arch Pediatr Adolesc Med 2001;155(9):1002-7.
20. Demonchy E, Dufour J-C, 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;69(10):2857-63.
21. Linkin DR, Fishman NO, Landis JR, Barton TD, Gluckman S,

Kostman J, et al. Effect of Communication Errors During Calls to an Antimicrobial Stewardship Program. Infect Control Hosp Epidemiol 2007;28(12):1374-81.

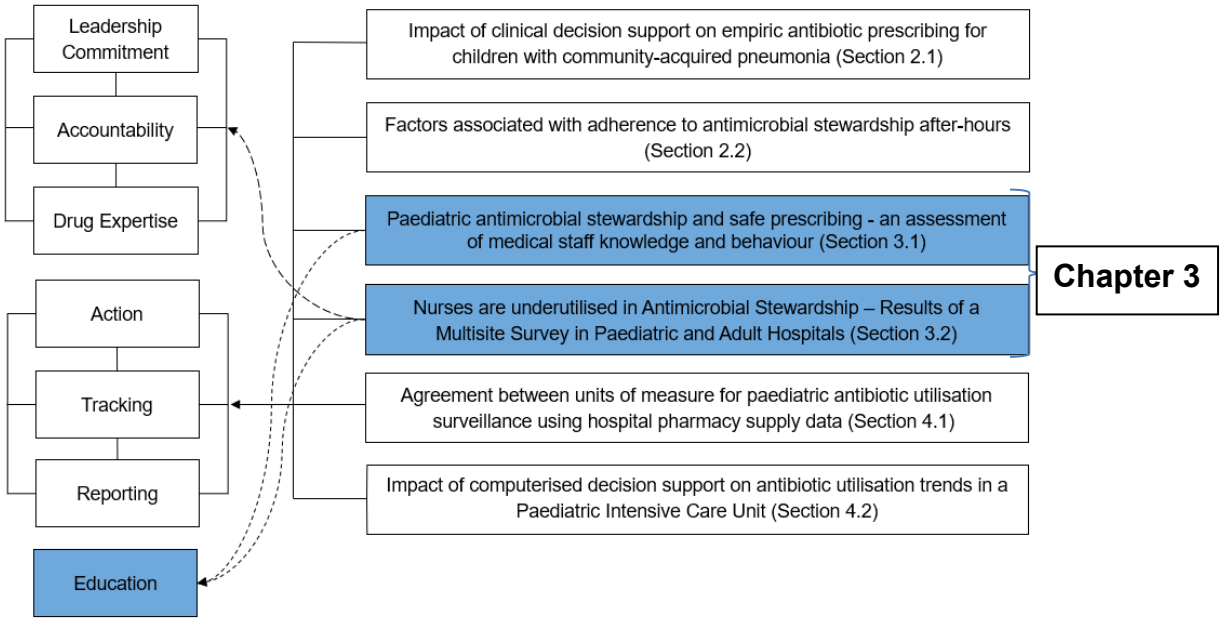
22. Kawanami GH, Fortaleza CMCB. Factors predictive of inappropriateness in requests for parenteral antimicrobials for therapeutic purposes: A study in a small teaching hospital in Brazil. Scand J Infect Dis 2011;43(6-7):528-35.

23. LaRosa LA, Fishman NO, Lautenbach E, Koppel RJ, Morales KH, Linkin DR. Evaluation of Antimicrobial Therapy Orders Circumventing an Antimicrobial Stewardship Program: Investigating the Strategy of “Stealth Dosing”. Infect Control Hosp Epidemiol 2007;28(5):551-6.

CHAPTER THREE

EDUCATION

3 CDC CORE ELEMENT – EDUCATION



3.1 Paediatric antimicrobial stewardship and safe prescribing - an assessment of medical staff knowledge and behaviour

The following subchapter focuses on the CDC core element “education” as it pertains to non-consultant medical staff. The intervention, i.e., education session, and accompanying knowledge assessment in this sub-section aim to determine the educational requirements of non-consultant level medical staff in relation to AMS principles and optimal antimicrobial use for children.

As previously described in the Chapter 1 (Section 1.4), all non-consultant level medical staff are categorised as junior medical officers (JMOs) at the study hospital, therefore, the same terminology has been applied in the manuscript below. Prescribing decisions are driven by consultants, however, the JMOs are primarily responsible for documentation in the medical records and the act of generating a prescription (i.e., prescribing the regimen on the medication chart).

Manuscript 4
Mostaghim M, Snelling T, Katf H, Bajorek BV. **Paediatric antimicrobial stewardship and safe prescribing - an assessment of medical staff knowledge and behaviour.** *Pharmacy Practice.* 2018 Apr-Jun;16(2):1198. DOI: 10.18549/PharmPract.2018.02.1198
Manuscript published (peer reviewed)

3.1.1 Abstract

Objective: Determine baseline knowledge of antimicrobial stewardship, and safe prescribing among junior medical officers, monitor their level of participation in interactive education during protected teaching time and assess day-to-day prescribing behaviours over the subsequent 3-month period.

Methods: A voluntary and anonymous survey of all non-consultant level medical officers was conducted with the use of an audience response system during mandatory face-to-face orientation sessions at a tertiary paediatric hospital. Routine prescribing audits monitored compliance with national and locally derived quality use of medicines indicators.

Results: Eighty-six percent of medical officers participated by responding to at least one question (171/200). Response rate for individual questions ranged between 31% and 78%. Questions that addressed adverse drug reactions, documentation and monitoring for empiric antibiotics and the error-prone abbreviations IU and U were correctly answered by over 90% of participants. Other nonstandard and error-prone abbreviations were less consistently identified. In practice, 68% of patients had complete adverse drug reaction documentation (113/166). Error-prone abbreviations were identified on 5% of audited medication orders (47/976), approximately half included a documented indication and intended dose.

Conclusions: Participants demonstrated a good understanding of safe prescribing and antimicrobial stewardship. Audits of prescribing identified potential discrepancies between prescribing knowledge and behaviours.

3.1.2 Introduction

Safe and appropriate prescribing requires knowledge of patient and medication factors as well as the skills to effectively gather information and communicate clinical decisions to staff and patients.(1,2) Medication errors may result from illegible or incomplete prescriptions, use of error-prone abbreviations, missed drug interactions or failure to adequately monitor treatment.(3)

Pharmacokinetic and pharmacodynamic changes in paediatric patients introduce unique sources of error in the paediatric setting. For example, paediatric dosing strategies are often age-specific and require individual dose calculations according to weight or body surface area.(4) In addition, paediatric prescribing is frequently off-label,(5) and practice may vary between hospitals(6) and prescribers.(7)

Strategies that aim to minimise erroneous and suboptimal prescribing include the use of standardised guidelines and terminology, as well as quality and safety initiatives that target medications associated with high risk of error or complication, such as antimicrobials.(8) Antimicrobial stewardship (AMS) programs have demonstrated significant contributions to hospital patient safety by detecting errors and educating staff on practices that optimise antimicrobial selection, dosage, route and duration.(9)

With a broad range of strategies and individualised hospital practices, there is a recognised need for practical orientation for medical officers.(8) In this study, we assessed baseline AMS and paediatric safe prescribing knowledge among all non-consultant level medical staff (JMOs) as part of mandatory orientation at a tertiary paediatric hospital and evaluated subsequent prescribing behaviours by conducting routine prescribing audits. The primary objective of the study was to determine the educational requirements for JMOs who were newly employed by the hospital and those with prior local experience. A secondary objective was to assess the quality of prescribing in the three months after completing baseline assessment and orientation.

3.1.3 Methods

On 2 February and 6 February 2017 all JMOs who attended one of three mandatory education sessions on AMS and safe prescribing were offered wireless keypad devices and invited to participate in an anonymous and voluntary survey. The survey questions were presented to JMOs throughout the AMS and safe prescribing session on presentation slides created in Microsoft PowerPoint (Microsoft Corporation, Redmond, Washington). JMO responses entered using the keypad devices were captured in real-time using an audience response system (KP1, Sydney, NSW) and presented as part of the session. From 8 February to 7 May 2017 weekly prescribing audits were conducted across the hospital using a convenience sampling technique whereby the sample was easily

accessible to the auditor.(10) Inpatient wards were scanned for patients with current and available medication charts with a target of 60 patients each month to ensure sustainability. Audit results were reported to JMOs by the JMO unit as part of the JMO newsletter. Approval to conduct the survey and prescribing audit was granted by the local hospital research ethics committee as a quality improvement project (QIE-2017-02-04), and ratified by the University of Technology Research Ethics Committee.

Setting

This study was conducted at a 170-bed university-affiliated tertiary paediatric hospital in Sydney, New South Wales. The hospital employs JMOs with two or more years of post-registration experience that may or may not include prior paediatric experience. During their employment, JMOs may be based onsite at the tertiary hospital or seconded to one of 23 different paediatric sites across New South Wales, Australian Capital Territory and the Northern Territory.

Orientation is mandatory for JMOs and includes attendance at a face-to-face AMS and safe prescribing session designed by medical and pharmacy staff. The session reinforces aspects of safe prescribing in children, introduces local practice expectations and includes demonstrations of how to access local medication-related resources. The information is also summarised in the hospital's Junior Medical Staff Handbook. The Handbook is updated annually and lists frequently used guidelines,

prescribing “tips” and prescriber responsibilities. The responsibilities include obtaining approval for the use of restricted antimicrobials according to the hospital’s computerised clinical decision support and approval system (CDSS, Guidance MS, Melbourne, Australia) as part of the local AMS policy. Technical training on the use of the CDSS has been in place since its implementation in 2012 and is addressed during a separate face-to-face session.

Since 2015, the time allocated for the safe prescribing session has been extended annually in order to cover broader aspects of paediatric medication use from the point of admission to discharge with a focus on antimicrobial use. However, JMO’s baseline knowledge and participation had never been formally assessed.

AMS and safe prescribing session and survey

JMOs who were employed by the hospital and working on site in the week before the start of term 1, 2017 (6 February 2017) attended one of two abridged face-to-face orientation programs that each included a 40 minute AMS and safe prescribing session. JMOs who had spent the previous 3-month term in another facility attended a longer face-to-face orientation program with a 60 minute AMS and safe prescribing session.

Presentation content and survey questions were designed by paediatric pharmacists with experience in quality use of medicines, medication safety and AMS. Content was finalised after feedback was received from: a

consultant paediatrician responsible for general paediatric training, the hospital's chief resident medical officer, an advanced trainee in paediatrics, and the lead infectious diseases consultant for AMS. Survey questions were not piloted among JMOs in order to limit pre-exposure to the assessment questions and maximise the number of responses.(11) The content included case studies, unidentified errors, and examples of best practice in vital aspects of safe and appropriate medication use in children from admission to discharge. The examples included:

- Medication history taking(12) and documentation of adverse drug reactions (ADRs).(13)
- Medication information resources.
- AMS principles, clinical standards and indicators for AMS,(14) local policies, and JMO roles.
- National standard terminology and error-prone abbreviations.(15)
- Safe prescribing in accordance with national quality use of medicines indicators (16) and the paediatric National Inpatient Medication Chart (NIMC).(13)
- Local, legislative and Commonwealth funding prescription requirements.
- Medication documentation requirements for hospital discharge summaries.

Priority areas were determined after consideration of current practice observed in local audits and the potential risk of harm. Survey questions presented throughout the session were designed to enhance participation, engage JMOs and assess basic concepts before each topic was introduced in the presentation slides

Informed consent was obtained from JMOs at the beginning of each session. JMOs in attendance were informed that their participation in the survey was voluntary, anonymous and there were no incentives encouraging involvement. Participating JMOs could elect not to respond to individual questions and withdraw at any time. Any data collected through the audience response system prior to their withdrawal could not, however, be excluded due to the anonymous nature of the assessment.

During the session, a presenter read aloud each assessment question and all answer options. The audience response system remained open to receive keypad responses until there was a consensus among the attending JMOs that responses had been submitted. Results were presented in the form of a graphical chart after the close of each survey question. The correct response was confirmed by the presenter; incorrect responses prompted further exploration of the topic and clarification as part of the session. All response options were multiple-choice, ranging from binary responses (yes or no, true or false) to a maximum of 5 response options.

Data collection and extraction

Responses captured during each session were extracted from each of the session presentations with the use of the audience response system software and combined into a single database. Codes were assigned to each session and keypad combination. Attendance records obtained from the Junior Medical Unit determined the sample frame.

Prescribing audits assessed all current medication orders for each patient. ADR documentation, error-prone abbreviations, paediatric prescribing, and orders for intermittent therapy (non-daily administration) were collected in accordance with national quality use of medicines indicator definitions.(16) Two additional NIMC criteria were also collected, the percentage of medication orders with a documented indication, and the percentage of “pro re nata” (PRN or “when necessary”) orders with the maximum number of doses in 24 hours specified.

Statistical Analysis

Descriptive statistics were performed in SPSS 24 (IBM, Armonk, NY). All survey responses and prescription audit criteria were analysed as categorical data and reported as percentages rounded to the closest whole number. Chi Square tests were used to explore differences in proportion of correct survey responses between JMOs who identified themselves as new employees and those who had previously worked in the institution.

Participation was reported for each survey question separately as the proportion of the sample frame with a captured keypad response (i.e. number of responses/number of JMOs in attendance). The extent of participation by individual JMOs throughout each session was reported as the percentage of questions with a response from a single keypad. Kruskal Wallis tests assessed differences in prescribing each month after the AMS and safe prescribing session. All statistical tests were two-tailed with *P* values <0.05 considered statistically significant.

3.1.4 Results

Survey

Two hundred JMOs attended orientation, 89 were assigned to an abridged program. Most JMOs had experience in paediatrics; more than half were in the process of completing either Basic or Advanced Paediatric training. A small proportion of JMOs were Training in other specialties such as general practice, surgical subspecialties, intensive care and emergency medicine (Figure 3.1). More than half of all JMOs present responded to at least 80% of the survey questions in their session (Figure 3.2). The response rate for individual questions ranged between 31% and 78%. Thirty-nine percent of JMOs (77/200) reported working at the hospital in the previous 12 months and 33% (65/200) indicated they had not.

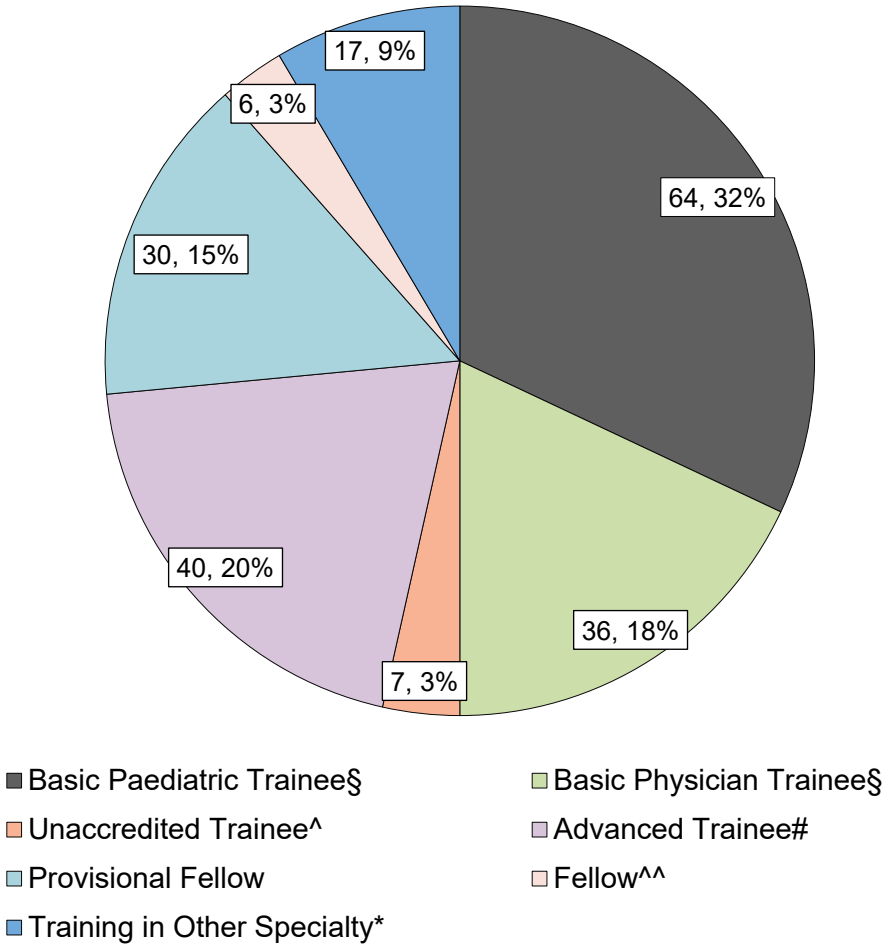


Figure 3.1 Medical staff in attendance during safe prescribing and antimicrobial stewardship orientation §Basic Physician or Paediatric Trainees have committed to, or are in the process of completing Paediatric Training, with 2 or more years of experience; ^Unaccredited Trainees hold registrar positions but may not have participated in the full College training program; #Advanced Trainees have completed Basic Training; ^^Fellows have completed training; *Training in Other Specialty includes: Intensive Care, Emergency Medicine, Surgical Subspecialties, General Practice and Dermatology

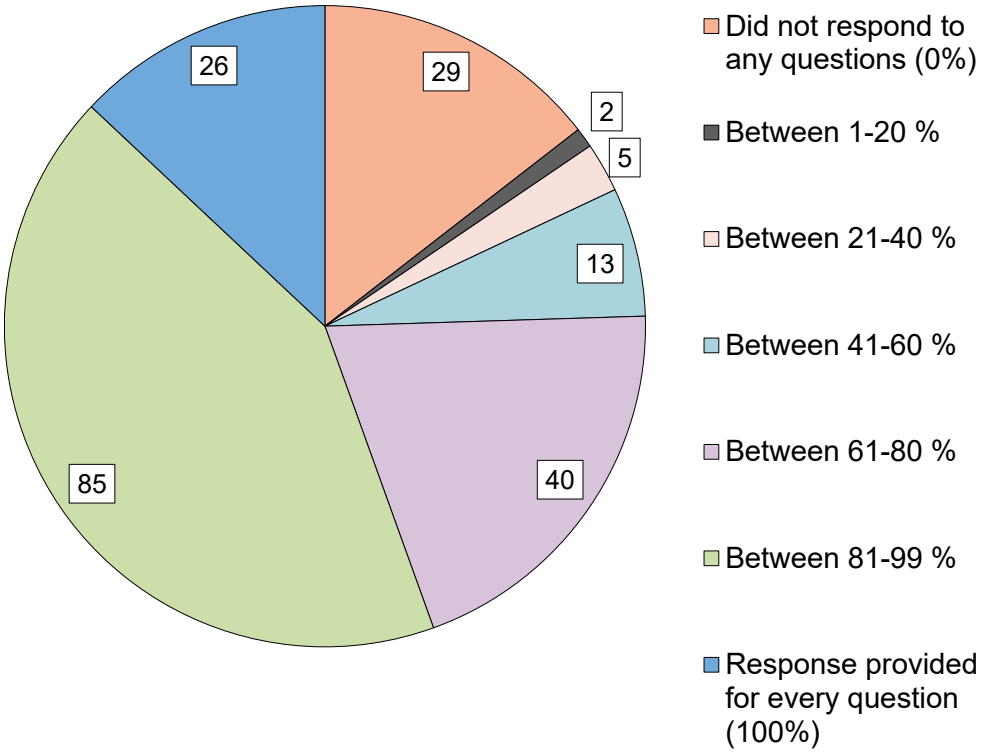


Figure 3.2 Medical staff participation throughout orientation.

Proportion of questions with responses from JMOs in 40 minute session (14 questions) and 1 hour session (17 questions).

Information Gathering and clinical decision-making

Almost all JMOs (98%) were aware of NIMC requirement to record the specific reaction, reaction type and the date of occurrence as part of complete documentation. Overall, 85% (132/155) of participating JMOs correctly identified the national paediatric medication reference as the preferred guide for medicines information and dosing at the institution. Among those who reported their prior local experience, the correct option was selected by 96% of JMOs who had worked at the hospital in the previous 12 months and 71% of those who had not (P=0.001) (Table 3.1).

Communicating and reviewing decisions

Between 70% and 74% of JMOs responded to questions about antimicrobial prescribing. Among those who participated, 95% had heard the term antimicrobial stewardship, and knew that prescriptions for empiric antibiotics should document both the indication and a planned review date in the medical record. Very few respondents considered it appropriate to wait until 72 hours of antibiotic therapy or the next consultant ward round to review empiric antibiotic therapy. The majority indicated reviews should take place at least daily (78%) or every 48 hours (20%). Almost all JMOs recognised that fever alone was not an exclusion for intravenous to oral antimicrobial switch (94%).

Table 3.1 Assessment survey questions and JMO responses according to self-identified previous work experience at the study hospital[#]

Assessment questions and responses (Responses rate, all responses/all JMOs, %)	Overall JMO responses, *n* (%)	Previous work experience unknown[^], *n* (%)	JMOs worked at the hospital in the previous year, *n* (%)	JMOs who did not work at the hospital in the previous year, *n* (%)
Have you heard of the term "Antimicrobial Stewardship" or AMS?				
Responses (RR 140/200, 70%)	140	20	63	57
Heard of AMS	133 (95)	20 (100)	61 (97)	52 (91)
Have not heard of AMS	7 (5)	0	2 (3)	5 (9)
In addition to name, signature and date, which of the following indicates a correct example of adverse drug reaction documentation?				
Responses (RR 148/200, 74%)	148	19	69	60
Rash, 20/11/2001	0(0)	0(0)	0 (0)	0 (0)
Amoxycillin, 20/11/2001	0(0)	0(0)	0 (0)	0 (0)
Amoxycillin, Rash, 20/11/2001	3(2)	1(5)	1(1)	1(2)
Amoxycillin, Rash - urticaria, 20/11/2001 (correct)	145 (98*)	18 (95)	68 (99)	59 (98)
For general prescribing the first reference should be:				
Responses (RR 155/200, 78%)	155	23	70	62
Meds4Kids[§]	21 (14)	2 (9)	2 (3)	17 (27)
Uptodate	0	0	0	0
BNF for Children	2 (1)	0	1 (1)	1 (2)
AMH-CDC (correct)	132 (85*)	21 (91)	67 (96)	44 (71)
Prescriptions for empiric antimicrobial use should document both the indication and planned review date				
Responses (RR 141/200, 71%)	141	23	65	53
True (correct)	136 (96*)	22 (96)	63 (97)	51 (96)
False	5 (4)	1 (4)	2 (3)	2 (4)
It is unnecessary to document the date on a ceased medication order as long as both the prescription and administration sections of a medication chart are crossed out.				
Responses (RR 135/200, 68%)	135	18	63	54
True	11 (8)	1 (6)	7 (11)	3 (6)
False (correct)	124 (92*)	17 (94)	56 (89)	51 (94)
"Flucloxacillin PO 500mg 6/24 for 1/7" is a safe prescription if one day of antibiotic therapy is required before discharge				
Responses (RR 141/200, 71%)	141	18	69	54
True	27 (19)	5 (28)	13 (19)	9 (17)
False (correct)	114 (81*)	13 (72)	56 (81)	45 (83)
How many of the following are acceptable when prescribing once DAILY prescriptions: OD, d, o.d., qd, QD, mane, M, N nocte?				
Responses (153/200, 77%)	153	20	71	62
One	16(10)	3(15)	6(8)	7(11)
Three	24(16)	4(20)	8(11)	12(19)
Two (correct)	112 (73*)	13 (65)	56 (79)	43 (69)
Five	1 (<1)	0	1 (1)	0 (0)

Assessment questions and responses (Responses rate, all responses/all JMOs, %)	Overall JMO responses, *n* (%)	Previous work experience unknown^, *n* (%)	JMOs worked at the hospital in the previous year, *n* (%)	JMOs who did not work at the hospital in the previous year, *n* (%)
How many of the following abbreviations are appropriate: subcut, sc, S/C, SC, S/L, SL, IO, D/C?				
Responses (RR 148/200, 74%)	148	23	67	58
Three	30 (20)	4 (17)	12 (18)	14 (24)
One (correct)	79 (53*)	13(57)	39 (58)	27 (47)
Two	32 (22)	4 (17)	14 (21)	14 (24)
Five	4 (3)	2 (9)	1 (1)	1 (2)
Eight	3 (2)	0	1 (1)	2 (3)
U and IU are acceptable abbreviations for units				
Responses (RR 149/200, 75%)	149	21	69	59
True	8 (5)	2 (10)	4 (6)	2 (3)
False (correct)	141 (95*)	19 (90)	65 (94)	57 (97)
How many errors (abbreviations symbols etc.) are there in the prescription “clonidine PO .030 mcg 8° x3d then review”				
Responses (RR 144/200, 72%)	144	22	66	56
Five (correct)	86 (60*)	14 (64)	41 (62)	31 (55)
Two	1 (<1)	0 (0)	1 (2)	0 (0)
Three	37 (26)	7 (32)	14 (21)	16 (29)
Six	20 (14)	1 (4)	10 (15)	9 (16)
Chemical symbols (MgSo4, KCl etc.) should be used when ordering electrolytes				
Responses (62/200, 31%)	62	7	47	8
True	8(12.9)	1(14.3)	7(14.9)	0
False (correct)	54 (87.1*)	6 (85.7)	40 (85.1)	8 (100)
Empiric antibiotic therapy should be reviewed:				
Responses (RR 147/200, 74%)	147	23	67	57
48 hours after initiation	29 (20)	4 (17)	13 (19)	12 (21)
At least daily (correct)	114 (78*)	19 (83)	50 (75)	45 (79)
72 hours after initiation	1 (<1)	0	1 (1)	0
On Consultant Ward Round	3 (2)	0	3 (5)	0
Paediatric patients should remain on IV antimicrobials as long as they are febrile				
Responses (RR 145/200, 73%)	145	22	63	60
True	8 (6)	3 (14)	1 (2)	4 (7)
False (correct)	137 (94*)	19 (86)	62 (98)	56 (93)

[#]Unless otherwise stated there were no statistically significant differences in the proportion of correct responses between groups; ^JMOs who did not respond when asked if they had worked in the study hospital in the previous year; [§]Intranet resource belonging to another tertiary paediatric hospital with links to their own hospital specific guidelines;**P=0.001; *Overall percentage correct BNF for Children: British National Formulary for Children; AMH CDC: Australian Medicines Handbook-Children’s Dosing Companion; Uptodate®; IV:Intravenous; RR: Response rate; JMO: Non-consultant level medical officer

Ninety-two percent were aware of the correct method by which to cease an order on the NIMC, specifically, the need to document the date of cessation on the order (124/135). Non-standard terminology (i.e., “6/24” and “1/7) in the order “flucloxacillin PO 500mg 6/24 for 1/7” was identified by 85% of JMOs.

Almost all JMOs recognised that the error-prone abbreviations “IU” and “U” were unacceptable when prescribing medications measured in “international units” and “units” (95%, 141/149). Almost 30% of JMOs were unable to identify the standard terms “mane” and “nocte” from terms that should not be used (OD, D, o.d, M, N, QD, qd). Only 53% could differentiate the standard term “subcut” from the error-prone abbreviations. When asked to count the erroneous and non-standard terms present in the order “clonidine PO .030 mcg 8° x3d then review”, only 60% correctly identified all five (Table 3.1). Although the response rate was considerably lower than any other question (31%, 62/200), 87% of participants were aware that chemical symbols should not be used when prescribing electrolytes.

Discharge prescriptions

The 60-minute AMS and safe prescribing session included three additional assessment questions to gauge awareness of prescribing requirements for special authority and Schedule 8 medicine (drugs of addiction, e.g. oxycodone, fentanyl, etc.). Approximately 90% of JMOs were reportedly aware that standard hospital prescription forms were unsuitable for supply

from a retail pharmacy. Over 90% were aware that multiple Schedule 8 medicines could not be prescribed on a single discharge prescription, and that pre-printed patient identification should not be used for Schedule 8 discharge prescriptions (Table 3.2)

Table 3.2 Discharge Prescription Assessment Questions

Assessment Question and response options (*n*=111)	Overall, *n* (%)	Previous work experience unknown^, *n* (%)	JMOs worked at the hospital in the previous year, *n* (%)	JMOs who did not work at the hospital in the previous year, *n* (%)
A PBS Authority may be obtained from an outside (community) pharmacy with a hospital discharge prescription?				
Responses (RR 77/111)	77	11	19	47
True	8 (10)	2 (18)	2 (11)	4 (9)
False(correct)	69 (90*)	9 (82)	17 (89)	43 (91)
When prescribing Schedule 8 medications a separate discharge prescription is required for each form of the medication?				
Responses (RR 83/111)	83	13	20	50
True(correct)	78 (94*)	11 (85)	20 (100)	47 (94)
False	5 (6)	2 (15)	0 (0)	3 (6)
Addressograph (Patient ID stickers) may be used on discharge prescriptions for Schedule 8 medications				
Responses (RR 84/111)	84	12	20	52
True	7 (8)	0 (0)	2 (10)	5 (10)
False(correct)	77 (92*)	12 (100)	18 (90)	47 (90)

#No statistically significant differences between groups; ^ Unknown=No response provided when asked if they had worked in the study hospital in the previous year; *Overall percentage correct. Schedule 8: Drugs of Dependence (oxycodone, morphine, fentanyl etc); PBS: Pharmaceutical Benefits Scheme; Patient ID: Patient identification; JMO: non-consultant medical officer

Prescribing Audit

Nine hundred and seventy-six medication orders were reviewed for 166 patients between 7 February and 6 May 2017. No statistically significant changes in prescribing were observed during the auditing period. Over the three months of auditing, between 63 to 75% of audited patients had an appropriately documented ADR (Table 3.3). The maximum number of PRN doses was included on 77% of PRN orders, ranging from 84% of orders in period 1 and 70% in period 3 (P=0.08); on average 46% of orders included a documented indication.

Error-prone abbreviations were observed in 5 to 8% of medication orders in the first two months and 2% in period 3 (P=0.09). Almost all intermittent medications were documented according to the national QUM indicator with the non-administration days crossed out (27/28). Dose calculations were consistently documented in approximately half of all orders.

Table 3.3 Prescribing behaviour observed after AMS and Safe Prescribing session*

Prescription characteristics	Period 1 *n* (%)	Period 2 *n* (%)	Period 3 *n* (%)	*P* value
Patients reviewed, *n*	40	65	61	
Prescriptions per patient, median (IQR)	6.5 (4–10)	4 (3–8)	5 (4–7)	0.03
National quality use of medicines Indicators+				
Patients with ADR documented on current medication chart	26/40 (65)	41/65 (63)	46/61(75)	0.30
Prescriptions with error prone abbreviations	13/284 (5)	27/345 (8)	7/347 (2)	0.09
Paediatric medication orders that include the correct dose per kilogram or BSA	91/183 (50)	107/221 (48)	135/262 (52)	0.88
Medication orders for intermittent therapy prescribed safely	14/14 (100)	5/6 (83)	8/8 (100)	0.22
Local Indicators				
Order with indication documented	147/284 (52)	157/345 (46)	145/347 (42)	0.37
PRN orders that specified the maximum number of doses every 24 hours	61/73 (84)	83/103 (81)	80/115 (70)	0.08

*Period 1: 7 February-6 March 2017, Period 2: 7 March to 6 April, Period 3: 7 April to 6 May 2017

+ National quality use of medicines indicators specified as:

Indicator 3.2 ADR status must be documented as nil known, unknown or include the drug, reaction, type and date.

Indicator 3.3 Error prone abbreviations: Qd, OD, U, mcg, trailing zeros or failure to include a leading zero when the dose is less than a one. Adapted to include abbreviations IT, SC and µ

Indicator 3.4 Paediatric dose must be documented, safe and effective,

Indicator 3.5 Intermittent therapy non-administration days must be crossed out days of therapy specified

ADR: Adverse drug reaction; BSA: Body surface area; IQR: Interquartile range;
PRN: When required

3.1.5 Discussion

JMOs who participated in this baseline assessment survey demonstrated an excellent understanding of best practice for safe and appropriate prescribing. Almost all JMOs were familiar with AMS and were aware of the national AMS clinical indicators for empiric antimicrobial therapy that require prescribers to document the indication and date of clinical review in the medical record.(14) JMOs also recognised that fever alone was not an indication for intravenous antibiotic therapy, and that empiric antibiotic therapy should be reassessed at regular intervals. Standard and error-prone terminology was generally differentiated by JMOs. However, the very low response rate to our question about the use of chemical symbols suggests that some JMOs might have chosen not to participate due to uncertainty. If true, this could have implications elsewhere in our survey.

By conducting our survey during face-to-face orientation, we had direct contact with all JMOs. In addition to assessing knowledge amongst respondents, we were able to report participation at each assessment question during the AMS and safe prescribing session. Response rate in this survey is of particular importance due to the conditions in which it was conducted; attendance was mandatory and the sessions were held during protected teaching time so that JMOs were not distracted by their day-to-day tasks. The 1-hour orientation was held at the beginning of the new term, before JMOs were assigned any designated responsibilities to a medical unit or cohort of patients that might prevent them from attending or

concentrating on formal teaching.(8) Despite the ideal conditions, 15% of JMOs overall did not respond to a single question during the AMS and safe prescribing session, and only 13% responded to all the survey questions in their session.

JMOs in our study most readily participated when asked to identify preferred medication information resources, in keeping with other research that suggests JMOs view information on guidelines and protocols favourably,(8) and rely heavily on online sources of information.(17)

It is widely recognised that prescribing is complex, and influenced by a range of personal factors such as baseline knowledge, awareness and attitudes, as well as environmental interruptions and social dynamics.(1,18) The results of our prescribing audits reinforce these conclusions and are consistent with other evaluations that target prescribing behaviour. Documentation was not ideal at any point in the months following the session despite the results of our baseline survey and the prompts incorporated into the paediatric NIMC that outline where to record the maximum PRN dose in 24 hours, indication for use, the prescriber's dose calculations and how to document an ADR. Incomplete ADR documentation is of particular interest for AMS programs, as patients labelled with allergies to commonly used first line antimicrobials (e.g., penicillins) may be treated with alternate broad-spectrum agents that are associated with greater risk of adverse effects.(19)

This study has several limitations. We were unable to determine whether the decision to participate during the session reflected individual JMOs confidence or their interest in the content. We also cannot exclude alternate scenarios such as temporary audience response system malfunctions or JMOs using the keypad incorrectly by accidentally or intentionally selecting incorrect answers. In all these scenarios, our results could underreport JMO knowledge and participation. Our survey questions were relatively basic for our cohort of JMOs who had prior hospital experience, and in some cases, were close to completing their paediatric training. Nevertheless, even without JMO's usual workplace distractions we identified gaps in knowledge and observed examples of error-prone prescribing and incomplete documentation. Finally, our study design was not ideal. A sufficiently powered randomised control trial was not feasible in our setting and may have been inappropriate. We did not limit our prescribing audit to JMOs and may have included prescriptions written by Consultant Paediatricians. However, this would be rare as JMOs are most frequently tasked with prescription writing responsibilities, even if they are not responsible for prescribing decisions.(8)

Further studies are needed to determine whether face-to-face education adopted here improves prescribing behaviours, and how suboptimal prescribing can be addressed despite excellent or adequate knowledge of the expected prescribing practice. Targeted behaviour change strategies

underpinned by a deeper understanding of prescriber's perceptions and motivations are warranted and should be further explored.

3.1.6 Conclusion

JMO respondents demonstrated sound baseline knowledge of safe prescribing and good antibiotic prescribing practices. Potential gaps in knowledge included the use of chemical symbols and error-prone abbreviations. Participation in a baseline assessment survey facilitated by an audience response system was adequate but not ideal despite eradicating distractions such as clinical or administrative responsibilities. Suboptimal documentation in the months following the knowledge assessment suggests prescribing is influenced by factors beyond knowledge and awareness.

3.1.7 References

1. Page MA, Bajorek BV, Brien J-aE. Prescribing in Teaching Hospitals: a Qualitative Study of Social and Cultural Dynamics. Journal of Pharmacy Practice and Research 2008;38(4):286-91.
2. Likic R, Maxwell SRJ. Prevention of medication errors: teaching and training. Br J Clin Pharmacol 2009;67(6):656-61.
3. Coombes ID, Reid C, McDougall D, Stowasser D, Duiguid M, Mitchell C. Pilot of a National Inpatient Medication Chart in Australia: improving prescribing safety and enabling prescribing training. Br J Clin Pharmacol 2011;72(2):338-49.
4. Ghaleb MA, Barber N, Dean Franklin B, Wong ICK. What constitutes a prescribing error in paediatrics? BMJ Quality & Safety 2005;14(5):352-7.
5. Le Doare K, Barker CIS, Irwin A, Sharland M. Improving antibiotic prescribing for children in the resource-poor setting. Br J Clin Pharmacol 2015;79(3):446-55.
6. Porta A, Hsia Y, Doerholt K, Spyridis N, Bielicki J, Menson E, et al. Comparing neonatal and paediatric antibiotic prescribing between hospitals: a new algorithm to help international benchmarking. J Antimicrob Chemother 2012;67(5):1278-86.
7. Bowes J, Yasseen III AS, Barrowman N, Murchison B, Dennis J, Moreau KA, et al. Antimicrobial stewardship in pediatrics: focusing on the challenges clinicians face. BMC Pediatr 2014;14(1):212.
8. Mattick K, Kelly N, Rees C. A window into the lives of junior doctors:

narrative interviews exploring antimicrobial prescribing experiences. J Antimicrob Chemother 2014;69(8):2274-83.

9. Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila) 2009;48(5):505-12.
10. Sedgwick P. Convenience sampling. BMJ 2013;347:f6304.
11. Ruel E, Wagner WE, Gillespie BJ. The Practice of Survey Research. Thousand Oaks(CA): SAGE Publications; 2015.
12. Clinical Excellence Commission. Continuity of Medication Management: Medication Reconciliation Toolkit. Sydney: Clinical Excellence Commission; 2014;
13. Australian Commission on Safety and Quality in Health Care (ACSQHC). NIMC Auditing. [Internet] Sydney: ACSQHC; [cited 2017 January 21]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/medication-chart/nimc/national-inpatient-medicationchart-audit/
14. Australian Commission on Safety and Quality in Health Care (ACSQHC). Indicator Specification: Antimicrobial Stewardship Clinical Care Standard. Sydney: ACSQHC; 2014.
15. Australian Commission on Safety and Quality in Health Care (ACSQHC). Recommendations for Terminology, Abbreviations and Symbols used in the Prescribing and Administration of Medicines.

Sydney: ACSQHC; 2011.

16. Australian Commission on Safety and Quality in Health Care (ACSQHC) and NSW Therapeutic Advisory Group. National Quality Use of Medicines Indicators for Australian Hospitals. Sydney; 2014.
17. Chong HT, Weightman MJ, Sirichai P, Jones A. How do junior medical officers use online information resources? A survey. BMC Med Educ 2016;16:120.
18. Brennan N, Mattick K. A systematic review of educational interventions to change behaviour of prescribers in hospital settings, with a particular emphasis on new prescribers. Br J Clin Pharmacol 2013;75(2):359-72.
19. Unger NR, Gauthier TP, Cheung LW. Penicillin Skin Testing: Potential Implications for Antimicrobial Stewardship. Pharmacotherapy 2013;33(8):856-67.

3.2 Nurses are underutilised in Antimicrobial Stewardship – Results of a Multisite Survey in Paediatric and Adult Hospitals

In the preceding subchapter, the education requirements of non-consultant medical staff were determined during an interactive education session. The proceeding sub-section aims to determine the education requirements of nurses in adult and paediatric hospitals in relation to AMS and optimal antimicrobial use. Additionally, nurses perceived roles and their willingness to undertake AMS related tasks, including those highlighted in Chapter 2, are explored.

Manuscript 5
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3.2.1 Abstract

Objectives: Explore perceptions and attitudes of nurses in regard to antimicrobial stewardship (AMS), their roles as nurses, and identify differences in perceptions and attitudes across paediatric and adult settings.

Methods: Electronic survey administered to nursing staff across three public Australian tertiary institutions with AMS facilitated by a shared electronic approval and decision support system.

Results: Overall 65% (93/142) of nurses who completed the survey were familiar with the term AMS, and 75% recognised that they were expected to have a role alongside other disciplines, including ward pharmacists (paediatric 88%, adult 73%; p = 0.03). Hand hygiene and infection control (86%), patient advocacy (85%) and knowledge of antimicrobials (84%) were identified most often as AMS roles for nurses. However, 57% of nurses reported that their knowledge of antimicrobials was minimal or limited. Nurses generally agreed that requirement to obtain approval is an effective way to reduce inappropriate antimicrobial use (median scores: paediatric: 2.0 [agree], adult 1.0 [strongly agree]; p = 0.001). Only 35% of paediatric and 58% of adult nurses perceived that their role includes ensuring approval for restricted antimicrobials (p <0.01). Most nurses identified AMS teams (85%), pharmacists (83%) and infection control teams (paediatric 68%, adult 84%; p = 0.04) as sources of AMS support. Areas of interest for support and education included appropriate antimicrobial selection (73%) and intravenous to oral antimicrobial switch (paediatric 65%, adult 81%, p = 0.03).

Conclusion: Nurses consider AMS activities within their roles, but are underutilised in AMS programs. Further engagement, education, support and acknowledgement are required to improve nursing participation.

Keywords: Health personnel; Hospitals; Antimicrobial stewardship; Antimicrobials; Quality of health care

Highlights

- The role of nurses in hospital AMS programs is not yet defined.
- Infection control and patient advocacy were considered key nursing roles.
- Antimicrobial knowledge was self-rated as limited or minimal by 57% of nurses.
- AMS teams and pharmacists are a source of support for nurse involvement in AMS.
- Opportunity exists for nursing education on intravenous to oral switch.

3.2.2 Introduction

Antimicrobial stewardship (AMS) programs provide a multifaceted and systematic approach to optimising antimicrobial use. International guidelines for implementing AMS programs call for a designated AMS pharmacist and Infectious Diseases (ID) physician to act as core members of the AMS team, responsible for engaging relevant stakeholders including other clinicians, pharmacists, nurses, hospital executives and patients,(1) although these may not be available in certain settings (e.g., smaller hospitals in Australia). For this reason it is imperative to consider the role that nurses can play in AMS.

Nurses have a consistent ward presence and are involved in AMS related aspects of care from the point of admission to discharge. Nurses are responsible for patient monitoring, timely and accurate documentation and antimicrobial administration. In addition to facilitating communication between disciplines and departments, nurses provide education and support to patients.(2) Furthermore, nurses are frequently involved in quality and safety programs and executive committees, and contribute to the overall organisation culture and memory.(3,2) These activities place nurses in an ideal position to positively impact antimicrobial management (4–6). However, there is limited evidence on the impact of nurses in AMS and the role of the nurse in hospital AMS programs is not yet defined.(2,4,7)

There are other unknowns in regard to the role of nurses when considering the differences between paediatric and adult care settings. Paediatric patients are at an increased risk of prescribing and administration errors compared to adult patients due to the vast variation in body size across age groups and need to calculate specific doses according to weight.(8) Young children may not be able to communicate symptoms in the same manner as adults, and may present with non-specific illness resulting in diagnostic uncertainty.(9) In the tertiary paediatric setting where organ and bone marrow transplantation takes place there are also fewer paediatric specific antimicrobial guidelines, and these often rely on lower levels of

evidence.(10) We believe these factors may differentially influence nurses' perceptions of AMS programs and support required for nursing staff.

We conducted a survey of nursing staff at three Australian institutions with established AMS programs to assess the attitudes held amongst nurses toward AMS programs and their perceptions regarding the role of nurses. A secondary objective was to explore differences in these perceptions and attitudes between paediatric nurses and those working in the adult setting.

3.2.3 Methods

On 9 December 2015 nursing staff were contacted via local electronic mail distribution lists and invited to participate in an anonymous and voluntary internet-based survey hosted on Survey Monkey (SurveyMonkey Inc. Palo Alto, California, USA). Paper surveys were available at one hospital for those who were unfamiliar with electronic surveys and manually entered by a designated investigator. There were no incentives for participation. The survey was closed on 26 January 2016.

Program and setting

The survey was conducted across three tertiary public hospitals in New South Wales, Australia. Hospital A, a 600 bed metropolitan hospital with one paediatric ward, is a referral hospital for eight smaller hospital sites within a non-metropolitan health district. Hospital B is a 660 bed metropolitan hospital with one paediatric ward. Hospital C is a 170 bed tertiary paediatric metropolitan hospital with highly specialised services including haematology, oncology, transplant and a paediatric intensive care. The collective sampling frame (i.e., number of nurses on email distribution lists) is approximately 4345: 2044 in Hospital A, 1670 in Hospital B and 631 in Hospital C.

AMS programs are established in all three institutions. Consultant led AMS rounds are conducted at least once a week at all hospitals with staff access to both ID consultation and endorsed antimicrobial guidelines. Principles of

appropriate antimicrobial management are promoted at junior medical staff orientation and across all hospitals during antibiotic awareness week and include appropriate timing of blood cultures, guideline concordant prescribing, performing an antibiotic “time-out” at 48 hours to re-evaluate antimicrobial therapy.

All hospitals have nurse representation on local AMS Committees, and training is made available to nurses in the form of ward in-services and presentations at hospital nurse education meetings.

A computerised antimicrobial approval system with decision support (CDSS; Guidance MS, Melbourne, Australia) is shared across the hospitals to facilitate AMS activities, and has been in operation since April 2012 at hospitals A and B, and October 2012 in hospital C. The CDSS contains defined guideline concordant indications for children and adults, with specific patient management recommendations, doses and fixed duration of AMS approval for “restricted” antimicrobials that are frequently prescribed and targeted by the AMS team.(11)

A traffic light colour coding system has been established as part of the local AMS policy at each hospital in order for staff to easily distinguish the level of restriction for each antimicrobial (based on risk of toxicity, promotion of resistance, or cost). Printed lanyard cards indicating antimicrobial classification are disseminated to all staff at Hospitals B and C. According

to the AMS policies “unrestricted” (green) antimicrobials do not require approval for their use, the aforementioned “restricted” (yellow) antimicrobials require approval via the CDSS, and “highly restricted” (red) antimicrobials may only be prescribed after direct consultation and approval from the local ID or AMS team. As such, the CDSS is intended to prompt appropriate antimicrobial selection by prescribers upon initiation prescription and is endorsed as a compendium of antimicrobial guidelines for staff.

New and expiring approvals in the CDSS are reviewed daily by the local AMS team alerting them to any antimicrobial use that may be inconsistent with local guidelines, or require further AMS input. Once alerted, AMS teams undertake “audit and feedback” whereby the AMS team review the appropriateness of antimicrobial prescribing and provide feedback on: relevant patient management, antimicrobial choice, dose, therapeutic drug monitoring and duration of therapy. AMS team feedback is communicated to treating teams either in person or documented in the medical record. Where ongoing use of “restricted” or “highly restricted” antimicrobials is deemed appropriate, CDSS approval is extended by the AMS team, endorsing further use and supply from Pharmacy.

Survey design

The survey comprised questions adapted from AMS surveys of medical practitioners previously conducted at the study sites and a recent survey of

nurses and midwives undertaken by the Scottish Antimicrobial Prescribing Group.(12) The survey was reviewed and tested by two staff nurses prior to dissemination.

The questionnaire (Table 3.4) included 18 questions, of which three related to participant demographics, qualifications, site of employment and whether participants were based in a paediatric or adult unit. Two questions were open-ended; one was visible only when the respondent indicated familiarity with the term “antimicrobial stewardship” or “AMS”, the other invited participants to comment on AMS in general or their local hospital AMS program.

Likert-type questions canvassed self-perceptions of knowledge about AMS and attitudes about the local AMS program. Response options were based on 5 point scales with options ranging from minimal to excellent (1 = minimal, 2 = limited, 3 = average, 4 = good, 5 = excellent) and attitudes strongly agree to strongly disagree (1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree). The remaining 9 questions were multiple-choice answers with an option to add supplementary comments or alternate responses.

Table 3.4 Survey questions used across all hospitals

1. Have you heard of the term “Antimicrobial Stewardship” or AMS?
2. If yes, in your opinion, what is the purpose of Antimicrobial Stewardship (AMS) in hospitals?
3. According to local antimicrobial restriction policy “green” antimicrobials are (select one)
    - Highly restricted -Infectious Diseases approval required
    - Unrestricted
    - Electronic approval required
4. How would you rate your knowledge of antimicrobials?
    - Minimal
    - Limited
    - Average
    - Good
    - Excellent
5. Who would you expect to be involved in antimicrobial stewardship in your area?(check all that apply)
    - Doctor
    - Infectious Diseases Doctor
    - Microbiologist
    - Nurse
    - Infection Control Nurse
    - Ward Pharmacist
    - Dispensary Pharmacist
    - Infectious Diseases/AMS Pharmacist
    - Other
6. What do you think the nurse’s role in antimicrobial stewardship should involve? (check all that apply)
    - Ensuring appropriate antimicrobial use (indication, dose, frequency)
    - Knowledge of antimicrobials
    - Educating colleagues / patients / public
    - Challenging prescribing decisions
    - Role model / raising awareness
    - Communication / Participation in multi-disciplinary discussions
    - Hand Hygiene/ Infection Control
    - Patient advocacy
    - Monitoring side-effects and response to treatment
    - AMS is not the role of the nurse
    - Checking restriction category and ensuring antimicrobials are approved
    - Prompting prescribers to consider switching to oral antimicrobials
    - Prompting prescribers to perform Therapeutic Drug Monitoring (TDM)
7. What ongoing support would you need to take on an AMS role on the ward? (check all that apply
    - Updates of information
    - Expert contacts / Mentors
    - Protected time for teaching / learning
    - Continued education (i.e., online learning, posters, ward sessions/lectures)
    - I could not ever support AMS on the ward
    - Other

Table 3.4 Survey questions used across all hospitals *cont.*

8. Who would you like to receive support from? (check all that apply)
    - Nursing colleagues
    - Management / senior staff
    - Pharmacy
    - Infection Control Team
    - Infectious Diseases/AMS team
    - Junior Doctors
    - Senior Doctors
    - Microbiology Lab
    - Nurse Educators / Nurse Prescribers
9. Select the areas where you would like greater input, guidelines or education from the AMS team: (check all that apply)
    - Appropriate antimicrobial selection
    - Antimicrobial dosing and frequency
    - Appropriate use of IV or oral (including IV to oral switch)
    - Selecting the appropriate duration (De-escalation to narrow spectrum or discontinuing therapy)
    - Therapeutic drug monitoring (timing of levels, dose adjustment etc)
    - Interpreting microbiology
    - Appropriate administration
    - Checking Guidance MS for antimicrobial approvals
    - I do not need input from the AMS team
    - Other
10. Which of the following do you feel impacts the most on prescribers getting antimicrobial approvals on time for your patients? (select top 3 impacts)
    - Waiting for ward rounds to finish
    - Consultant opinion
    - Other ward jobs taking priority for prescribers
    - Limited access to a computer
    - Prescribers having difficulty logging into and navigating Guidance MS
    - They forgot to get an approval
    - They are not sure which patients are prescribed restricted antimicrobials (yellow or red drugs)
    - Requiring input from the ID registrar or consultant
    - I do not know
    - Other
11. Requirement to get antimicrobial approvals is an effective way to reduce inappropriate antimicrobial use
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly Disagree

Table 3.4 Survey questions used across all hospitals *cont.*

12. Verbal and written advice from the AMS team has improved my patients' care
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly Disagree
13. Verbal and written advice from the AMS team has improved my patients' care
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly Disagree
14. I would question a prescriber if an antimicrobial was charted for an inappropriate indication
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly Disagree
15. If I think that antimicrobial approval is unlikely I will try to bypass the system
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly Disagree
16. You are invited to share any other comments/issues regarding Guidance MS or AMS below:

17. Which Hospital are you currently working in?*
    - *Hospital A*
    - *Hospital B*
    - *Hospital C*
18. In which area are you currently working?
    - Paediatric
    - Adult
19. Your current qualifications:
    - NUM (Nurse Unit Manager)
    - CNC (Clinical Nurse Consultant)
    - CNE (Clinical Nurse Educator)
    - CNS (Clinical Nurse Specialist)
    - RN (Grades 2-8)
    - TRN (Transitional RN, used to be new graduates)
    - EEN (Endorsed Enrolled Nurse)
    - EN (Enrolled Nurse)
    - AIN (Assistant in Nursing)

**Response options have been amended according to manuscript*

Statistical Analysis

Descriptive statistics were performed in IBM SPSS Statistics for Windows Version 23 (IBM Corp, Armonk, NY) for completed surveys only. Categorical data were reported as percentages rounded to the closest whole number. Five point Likert-type scale responses were considered continuous variables and reported as the median ± interquartile range (IQR). Differences between responses from paediatric and adult nurses were explored by using chi-square tests for questions with categorical responses and Mann-Whitney tests for Likert-type scales. All tests were two tailed, with p values < 0.05 considered statistically significant. Responses to open-ended questions were reviewed for key terms or concepts.

3.2.4 Results

One hundred and forty-two surveys were completed and included in the analysis (approximately, 3.3% of the overall sampling frame). Overall 40% (n = 57) of participants worked in paediatric settings; primarily based in hospital C (55/57). The largest group of respondents were registered nurses with 2–8 years of experience (45%, n = 64), followed by clinical nurse specialists (16.2%; n = 23) (Figure 3.3). There were no statistically significant differences in qualifications between the two groups.

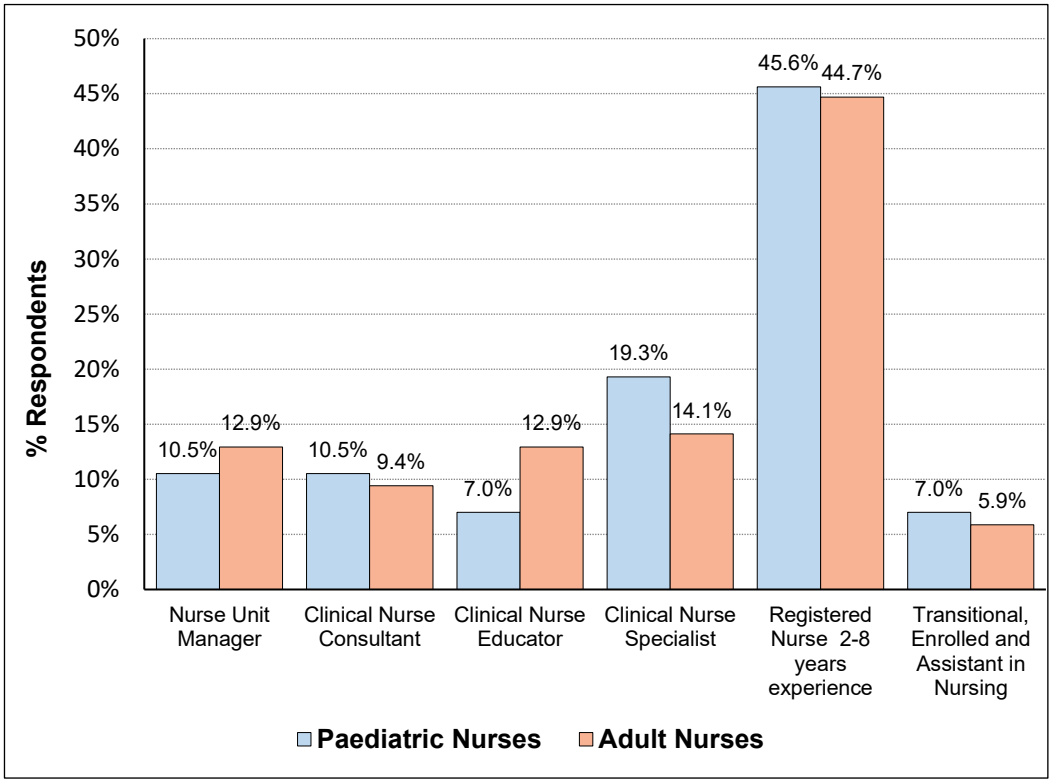

Figure 3.3 Respondent Qualifications and Training. Clinical Nurse Specialists = Registered Nurse with ≥ 12 months experience in a specific clinical area PLUS post-registration qualifications, OR 4 years of post-registration experience with ≥ 3 years of experience in their relevant clinical area. Clinical Nurse Consultant = Registered Nurse with ≥ 5 years of experience post-registration with approved post-registration qualifications relevant to their clinical area.

Knowledge and Awareness

Sixty-five percent of nurses (93/142) had heard of the terms “antimicrobial stewardship” or “AMS” at the time the survey was completed (paediatric 60%, adult 69%; p = 0.23). Among those familiar with AMS, the vast majority (82%, 77/ 93) described the purpose of AMS as promoting “correct”, “proper”, “right”, or “evidence-based” use, or as reducing

“unnecessary” or “overuse” of antimicrobials (paediatric 82%, adult 83%; p = 0.93).

Overall 76% (108/142) of respondents were aware of the categories in the local antimicrobial restriction policy, correctly indicated that “green” antimicrobials were unrestricted (paediatric 75%, adult 77%; p = 0.9).

More than half of all nurses rated their knowledge of antimicrobials as minimal or limited (57%, 82/142). The median rating in both paediatrics and adults was 2.0 (limited) (paediatric IQR 1–3.0; adult IQR 2.0–3.0; p = 0.9). Only 6% (9/142) rated their knowledge as good or excellent.

Staff Roles and Responsibilities

When asked to select which health care professionals expected to be involved in AMS nurses most often expected doctors to participate. Doctors in general were selected more often than ID doctors. The majority of nurses also expected infection control nurses and ward pharmacists to have a role in AMS; with the latter selected by a significantly greater proportion of paediatric nurses (paediatric 88%, adult 73%; p = 0.03) (Table 3.5).

Close to 75% of respondents expected nurses and ID or AMS pharmacists to take part in AMS. Microbiologists and dispensary pharmacists were perceived to participate in AMS least often, and fewer than half of

respondents selected all the listed roles as being involved in AMS (Table 3.5).

Table 3.5 Nurses' responses about which health professionals they expect to be involved in Antimicrobial Stewardship

	Overall, *n* (%)	Paediatric nurses, *n* (%)	Adult nurses, *n* (%)	*P*-value
Doctor (General)	126 (89)	52 (91)	74 (87)	0.44
ID Doctor	120 (85)	50 (88)	70 (82)	0.39
Microbiologist	99 (70)	37 (65)	62 (73)	0.30
Nurse	107 (75)	44 (77)	63 (74)	0.68
Infection Control Nurse	112 (79)	46 (81)	66 (78)	0.66
Ward Pharmacist	112 (79)	50 (88)	62 (73)	0.03
Dispensary Pharmacist	86 (61)	37 (65)	49 (58)	0.39
ID/AMS* Pharmacist	104 (73)	46 (81)	58 (68)	0.10

*ID: Infectious Diseases; AMS: Antimicrobial Stewardship. N = 142; Paediatric Nurses, n = 57

The nurse's role in AMS

In keeping with nurses' understanding of how AMS positively contributed to the appropriate use of antimicrobials, nurses rarely excluded AMS from their professional role (Table 3.6). More specifically, hand hygiene and infection control, patient advocacy and knowledge of antimicrobials were commonly recognised as nursing roles in AMS and selected more often

than tasks such as ensuring appropriate indication, dose and frequency, with no significant differences between the two groups (Table 3.6).

Prompting switch from IV to oral formulation (46%), prompting therapeutic drug monitoring (TDM) (51%) and checking restriction category for prescribed antimicrobials and ensuring antimicrobials were approved (49%) were less frequently considered nursing responsibilities in AMS.

In both the adult and paediatric setting, ensuring prescribers had obtained antimicrobial approval was selected less often than ensuring appropriate use (indication, dose and frequency), participating in multidisciplinary discussions and challenging prescribing decisions (Table 3.6).

Compared to adult nurses, those working in paediatrics more often felt that prompting prescribers to perform TDM was an AMS role for nurses (paediatric 61%, adult 45%; $p = 0.05$). Respondents working in paediatrics were also less inclined to associate checking restriction and approval status of antimicrobials as a nurse's responsibility (paediatric 35%, adult 58%; $p < 0.01$).

Table 3.6 Perceived roles for nurses participating in Antimicrobial Stewardship

	Overall, *n* (%)	Paediatric Nurses, *n* (%)	Adult Nurses, *n* (%)	*P*-value
Ensuring appropriate antimicrobial use *(indication, dose, frequency)*	104 (73)	44 (77)	60 (71)	0.38
Knowledge of antimicrobials	119 (84)	46 (81)	73 (86)	0.41
Role model / raising awareness	102 (72)	39 (68)	63 (74)	0.46
Communication / Participation in multi-disciplinary discussions	100 (70)	40 (70)	60 (71)	0.96
Patient advocacy	120 (85)	51 (90)	69 (81)	0.18
AMS* is not the role of the nurse	4 (3)	2 (4)	2 (2)	0.68
Prompting prescribers to consider switching to oral antimicrobials	65 (46)	24 (42)	41(48)	0.47
Checking restriction category and ensuring antimicrobials are approved	69 (49)	20 (35)	49 (58)	<0.01
Monitoring side-effects and response to treatment	115 (81)	48 (84)	67 (79)	0.42
Prompting prescribers to perform TDM#	73 (51)	35 (61)	38 (45)	0.05
Hand Hygiene/ Infection Control	123 (86)	50 (88)	73 (86)	0.75
Challenging prescribing decisions	98 (69)	42 (74)	56 (66)	0.32
Educating colleagues / patients / public	115 (81)	43 (75)	72 (85)	0.17

*AMS, Antimicrobial Stewardship; #TDM, Therapeutic Drug Monitoring. N = 142; Paediatric Nurses, n = 57.

Sixty-eight percent of nursing staff agreed that they would question a prescriber if an antimicrobial was prescribed for an inappropriate indication with no significant difference between paediatric and adult nurses (median score paediatric and adult 2.0 [agree], paediatric IQR 2.0–3.0, adult IQR 1.0–3.0; p = 0.37). Few respondents indicated that they would not question a prescription for an inappropriate indication (paediatric 7%, adult 4.7%).

Scores for the statement “if I think that antimicrobial approval is unlikely I will try to bypass the system” suggested that nurses in both the adult and paediatric setting would not intentionally bypass the CDSS (median paediatric and adult 4.0 [disagree], IQR paediatric and adult 3.0–4.0; p = 0.67).

Perceptions of the local AMS program

There were significant differences in the perceived impact of the AMS team’s input on patient care. Nurses working in adult medicine agreed more often that verbal and written advice from the AMS team had improved their patient’s care (median score paediatric 3.0 [neutral], IQR 2.0–3.0, median score adult 2.0 [agree], IQR 2.0–3.0; p = 0.004). No respondents working in adult medicine strongly disagreed with the statement “verbal and written advice from the AMS team has improved my patients’ care”.

The majority of respondents (87%) agreed to some extent that the requirement to get antimicrobial approval is an effective way to reduce inappropriate antimicrobial use. Responses from adult nurses were significantly more positive than those working in paediatrics (median score paediatric 2.0 [agree], IQR 1.5–2.0, median score adult 1.0 [strongly agree], IQR 1.0¬2.0; p = 0.001). Furthermore, no respondents working in adult medicine disagreed with the statement.

Support for nurses in AMS

The preferred form of support for nurse participation in AMS was similar in both groups. Respondents rated information updates and continued education highly (>90%), followed by expert contacts or mentors (76%) and protected teaching time (77%). Only 2 respondents indicated that they could not, ever, support AMS on the ward.

The majority of nurses were interested in receiving support from the AMS or ID team and pharmacists, and acknowledged the role of nurse prescribers and educators (78% overall). Infection control teams were more likely to be considered a potential source of support in the adult setting (paediatric 68%, adult 84%; p = 0.04). Of the potential staff members listed in the survey junior doctors were least often recognised as a potential source of support (Table 3.7a).

Common areas for further guidance or support from AMS teams for nurses in the paediatric and adult setting included: appropriate antimicrobial selection and appropriate dosing and frequency. Switch from IV to oral antimicrobial formulation was of marked interest in amongst adult nurses compared to those in paediatrics (paediatric 68%, adult 81%; p = 0.03) (Table 3.7b). Requests for AMS support to appropriately administer antimicrobials did not differ significantly between the adult and paediatric nurses. Nurses in both groups rated guidance on the use of the CDSS to check antimicrobial approvals, interpretation of microbiology and appropriate duration of therapy least often.

Table 3.7 Support required for nurse involvement in Antimicrobial Stewardship

	Overall, *n* (%)	Paediatric nurses, *n* (%)	Adult nurses, *n* (%)	*P*-value
a: Who would you like support from?				
Nursing colleagues	89 (63)	34 (60)	55 (65)	0.54
Management / senior staff	79 (56)	30 (53)	49 (58)	0.56
Junior Doctors	44 (31)	14 (25)	30 (35)	0.18
Microbiology Lab	68 (48)	22 (39)	46 (54)	0.07
Nurse Educators / Nurse Prescribers	111 (78)	42 (74)	69 (81)	0.29
Senior Doctors	68 (48)	24 (42)	44 (52)	0.26
Infection Control Team	110 (78)	39 (68)	71 (84)	0.04
Pharmacy	118 (83)	45 (79)	73 (86)	0.28
ID*/AMS** team	120 (85)	46 (81)	74 (87)	0.31
b: Areas where you would like greater input, guidelines or education from the AMS team**				
Interpreting microbiology	72 (51)	27 (47)	45 (53)	0.52
Selecting the appropriate duration *(De-escalation to narrow)*	80 (56)	29 (51)	51 (60)	0.28
TDM# *(timing of levels, dose adjustment etc.)*	93 (66)	39 (68)	54 (64)	0.55
Appropriate use of IV$ or oral *(including IV$ to oral switch)*	106 (75)	37 (65)	69 (81)	0.03
Appropriate administration	88 (62)	32 (56)	56 (66)	0.24
Antimicrobial dosing and frequency	94 (66)	35 (61)	59 (69)	0.32
I do not need input from the AMS** team	5 (4)	3 (5)	2 (2)	0.36
Appropriate antimicrobial selection	104 (73)	40 (70)	64 (75)	0.5
Checking the CDSS^ for antimicrobial approvals	71 (50)	26 (46)	45 (53)	0.39

*ID, Infectious Diseases; **AMS, Antimicrobial Stewardship; #TDM, Therapeutic Drug Monitoring; $IV, Intravenous; ^CDSS, Computerised Decision Support System. N = 142; Paediatric Nurses, n = 57.

3.2.5 Discussion

To our knowledge, our study is the first to focus on Australian nurses' views of AMS programs across multiple hospitals with similar AMS activities. Furthermore, the comparison of paediatric and adult nurses' survey responses on AMS is novel. These findings provide further insights into nursing roles in AMS, and build on the limited research undertaken in this area. A survey by Cotta et al., conducted in the private sector before AMS implementation, reported that 22% of nurses had heard the term "AMS", and 43% would be willing to participate in clinical interventions.(13)

This study has a number of important findings. Nurses working in hospitals with established AMS programs showed some familiarity with the term AMS and were able to describe the overarching goal of AMS as promoting optimal antimicrobial use. Three out of four survey participants acknowledged that nurses would be expected to have a role in AMS, more so than dispensary pharmacists and microbiologists. It is also encouraging that the overwhelming majority of nurses recognised that patient advocacy, a key competency for nursing staff,(14) embedded within the very definition of nursing,(15) applies to AMS.

Respondents primarily identified traditional nursing roles as nursing functions in AMS such as hand hygiene and infection control, an area where nurses have clearly demonstrated their impact as clinical leaders, researchers and program participants.(16) As patient advocates, nurses

recognised the importance of antimicrobial knowledge and their contribution to AMS when monitoring adverse effects from therapy and educating patients and colleagues about antimicrobial use. Effective patient advocacy requires an adequate understanding of risks, training, up-to-date information and a degree of authority.(17) However, self-rated knowledge of antimicrobials was limited, emphasising a need for more education on antimicrobial use for nursing students and staff, particularly when considering the critical need for timely and appropriate antibiotic administration.(18,19)

Current best practice international guidelines for AMS recommend education on AMS principles as part of undergraduate and postgraduate nurse education.(20) Recent surveys of nursing schools in the United Kingdom found that more than half included AMS in their curriculum, but fewer than 13% incorporated all aspects of good antimicrobial prescribing and stewardship.(21) A recent article by Manning et al., has called for robust education of all nurses, addressing the administration of antimicrobials, risks and benefits of therapy, and most importantly, the role of the nurse in AMS.(22)

For nurses in the professional environment, our study suggests education promoting AMS principles and antimicrobial knowledge by the AMS team and pharmacists would be acceptable to staff nurses and nurse educators, in accordance with AMS guidelines.(1,20)

In our survey, 68% of respondents indicated they would question a prescriber if the indication for an antimicrobial was inappropriate. In comparison, more than 90% of nurses surveyed before and after an IV to oral switch campaign in another Australian hospital indicated they would question a prescriber if they thought an antibiotic was inappropriate.(23) This higher rate may be due to numerous factors including greater motivation or confidence amongst those involved in a new initiative, differences in questionnaire design, or local differences amongst participants. Elsewhere, developing nurses' skills and confidence in questioning prescribers on antibiotic use has been highlighted as an area for enhancing nursing involvement in AMS.(7)

There is increasing recognition that nurse involvement in AMS is critical.(2,22) Areas for potential nurse involvement in AMS have included promoting optimal antimicrobial dose, route and duration by interpreting microbiology, encouraging switch from IV to oral route and prompting transition to outpatient antimicrobial therapy.(4,7,23) One such mechanism to prompt AMS initiatives by nurses is antimicrobial "time-outs" to re-evaluate antimicrobial therapy.(22)

The key area of interest amongst adult nurses in our survey was IV to oral switch, identified by 81% adult nurses as an area for further education or support, compared to only 68% of those in paediatrics. We believe the

variation observed in our survey warrants further study and could be related to contextual factors such as the perception that IV therapy in paediatric patients is minimised due to the pain and stress associated with inserting needles,(24) or that the duration of therapy is already limited by poor intravenous catheter patency in young children.(25) Due to the additional calculations and manipulations required to administer paediatric doses from larger adult dosage forms, and the subsequent risk of error, we expected paediatric nurses to be most interested in appropriate antimicrobial administration. However, there was no statistically significant difference observed.

Three-quarters of the nurses surveyed had adequate knowledge of the local antimicrobial restriction categories and considered their role to involve multidisciplinary discussions, ensuring appropriate indication, dose and frequency, and expressed a willingness to question inappropriate prescribing.

Furthermore, the majority of participants agreed that antimicrobial approval is effective in reducing inappropriate antimicrobial use. However, checking antimicrobial restriction category and CDSS approval was of little interest as a current role, or an area for further education, particularly amongst paediatric nurses. These findings suggest a disconnect between the intended role of the CDSS in supporting optimal antimicrobial choice, dose, route and duration, and the perception held by nurses, reiterating the

importance of multidisciplinary colleagues in providing tailored AMS support to meet the needs of each unique setting.

This study has a number of limitations. The modest number of responses may not be representative of all nursing staff within these institutions, and likely reflects the views of those most interested in AMS, a finding we believe further reinforces the need for greater nursing engagement. The response rate may have also impacted our secondary objective and precluded our ability to identify more significant differences between paediatric and adult nurses. Due to the study sites selected our findings may not be transferable to other institutions without similar AMS programs (i.e. combining audit and feedback with preapproval via a CDSS). Nevertheless, the findings provide local insights to facilitate greater nurse involvement in the daily management of AMS and have identified initial directions for antimicrobial education by AMS teams. Future questionnaires across the hospitals will aim to further clarify the best approach to involve nurses in the daily management of AMS.

3.2.6 Conclusion

The majority of nurses surveyed recognised that they have some role in AMS. Greater support and targeted education, and clarification of the specific roles for nurses in AMS are required for nursing staff in both the paediatric and adult setting to incorporate AMS into their daily tasks, and to apply AMS principles to their care of patients.

Ethics

Approval to conduct the study was granted by the Sydney Children's Hospital and University of Technology Human Research Ethics Committees with research governance approval at each institution (LNR/15/SCHN/430).

Authorship statement

MM designed the study and survey, collected the data, performed statistical analysis and wrote the manuscript. BB and TS supervised the study design, data analysis and critically revised the manuscript. SB, AC, SA, PK, BM, CL reviewed the survey design, facilitated data collection and critically revised the manuscript.

Conflicts of interest

All authors report no conflicts of interest relevant to this manuscript.

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Provenance and peer review

Not commissioned; externally peer reviewed.

3.2.7 References

1. 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.
2. Olans RN, Olans RD, DeMaria JA. The Critical Role of the Staff Nurse in Antimicrobial Stewardship—Unrecognized, but Already There. Clin Infect Dis 2016;62(1):84-9.
3. Charani E, Castro-Sánchez E, Holmes A. The Role of Behavior Change in Antimicrobial Stewardship. Infect Dis Clin North Am 2014;28(2):169-75.
4. Edwards R, Drumright L, Kiernan M, Holmes A. Covering more territory to fight resistance: considering nurses' role in antimicrobial stewardship. J Infect Prev 2011;12(1):6-10.
5. Manning ML, Giannuzzi D. Keeping Patients Safe: Antibiotic Resistance and the Role of Nurse Executives in Antibiotic Stewardship. J Nurs Adm 2015;45(2):67-9.
6. Edwards R, Loveday H, Drumright LN, Holmes A. Should nurses be more involved in antimicrobial management? J Infect Prev 2011;12(1):4-5.
7. Olans RD, Nicholas PK, Hanley D, DeMaria A, Jnr. Defining a Role for Nursing Education in Staff Nurse Participation in Antimicrobial Stewardship. J Contin Educ Nurs 2015;46(7):318-21.

8. Rinke ML, Bundy DG, Velasquez CA, Rao S, Zerhouni Y, Lobner K, et al. Interventions to Reduce Pediatric Medication Errors: A Systematic Review. Pediatrics 2014;134(2):338-60.
9. Magsarili HK, Girotto JE, Bennett NJ, Nicolau DP. Making a Case for Pediatric Antimicrobial Stewardship Programs. Pharmacotherapy 2015;35(11):1026-36.
10. Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J 2014;44(12b):1283-97.
11. 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.
12. Scottish Antimicrobial Prescribing Group. Exploring the role of nurses and midwives in antimicrobial stewardship. 2014 [Accessed 2016 10 December]; Available from: http://www.nes.scot.nhs.uk/media/3065666/exploring_role_of_nurses_and_midwives_in_antimicrobial_stewardship_report.pdf
13. Cotta MO, Robertson MS, Tacey M, Marshall C, Thursky KA, Liew D, et al. Attitudes towards antimicrobial stewardship: results from a large private hospital in Australia. Healthcare infection 2014;19(3):89-94.

14. Nursing and Midwifery Board of Australia. Registered nurse standards for practice. Nursing and Midwifery Board of Australia; 2016 [accessed 2016 10 December]; Available from: http://www.nursingmidwiferyboard.gov.au/Codes-Guidelines-Statements/Professional-standards.aspx
15. International Council of Nurses. Definition of Nursing. [Internet]: International Council of Nurses; [cited 2016 7 August]; Available from: https://www.icn.ch/about-icn/icn-definition-of-nursing/
16. Perry C. The infection control nurse in England: past, present and future. British Journal of Infection Control 2005;6(5):18-21.
17. Mallik M. Advocacy in nursing — a review of the literature. J Adv Nurs 1997;25(1):130-8.
18. Haeusler GM, Sung L, Ammann RA, Phillips B. Management of fever and neutropenia in paediatric cancer patients: room for improvement? Curr Opin Infect Dis 2015;28(6):532-8.
19. Ladenheim D, Rosembert D, Hallam C, Micallef C. Antimicrobial stewardship: the role of the nurse. Nurs Stand 2013;28(6):46-9.
20. 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):e51–77.
21. Castro-Sánchez E, Drumright LN, Gharbi M, Farrell S, Holmes AH. Mapping Antimicrobial Stewardship in Undergraduate Medical,

Dental, Pharmacy, Nursing and Veterinary Education in the United Kingdom. PLoS One 2016;11(2):e0150056.

22. Manning ML, Pfeiffer J, Larson EL. Combating antibiotic resistance: The role of nursing in antibiotic stewardship. Am J Infect Control 2016;44(12):1454-7.

23. Gillespie E, Rodrigues A, Wright L, Williams N, Stuart RL. Improving antibiotic stewardship by involving nurses. Am J Infect Control 2013;41(4):365-7.

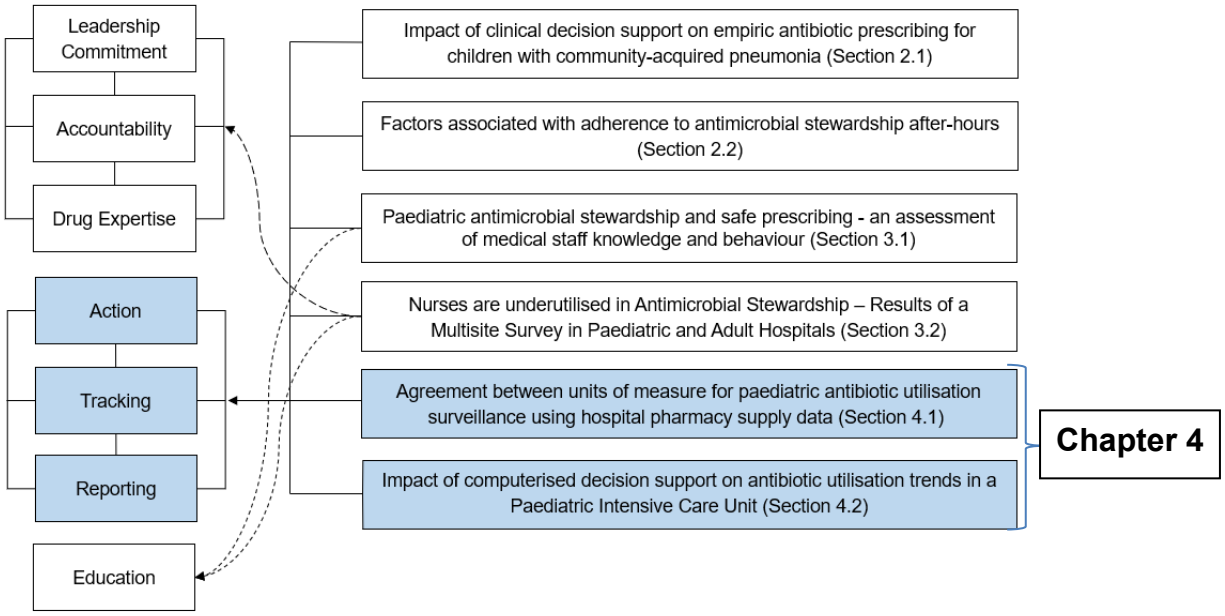
24. Kennedy RM, Luhmann J, Zempsky WT. Clinical Implications of Unmanaged Needle-Insertion Pain and Distress in Children. Pediatrics 2008;122(Suppl 3):S130-3.

25. Foster L, Wallis M, Paterson B, James H. A Descriptive Study of Peripheral Intravenous Catheters in Patients Admitted to a Pediatric Unit in One Australian Hospital. J Infus Nurs 2002;25(3):159-67.

CHAPTER FOUR

TRACKING ANTIMICROBIAL USE

4 CDC CORE ELEMENT – TRACKING ANTIMICROBIAL USE



4.1 Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data

Chapter 4 revisits the CDC core elements for AMS of “tracking and reporting”. Following the studies in Chapter 2, which confirmed that CDSS utilisation rates alone underestimate antimicrobial use, pharmacy supply data was re-examined as a potential source of information for tracking and reporting.

This subchapter explores the units of measure available for tracking and reporting antibiotics using pharmacy supply data as applied to the local context. The published units of measure for monitoring antimicrobial use (Sub-section 1.6.1.2 and Section 1.7) and the principles underpinning the use of the adult DDD measure inform the measures selected for this study.

The PICU is selected as the site for this study to maximise the range of injectable antibiotics available for examination.

Manuscript 6
Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data.
Manuscript in submission (peer review)

4.1.1 Abstract

Aim: Explore agreement between standard adult-based measures and alternate paediatric estimates of days of antibiotic use in a Paediatric Intensive Care Unit that does not have access to individual patient-level data.

Methods: Hospital pharmacy antimicrobial use reports and age-specific occupied bed-day data from 1 January 2010 to 31 May 2016 were extracted. Local paediatric and neonatal dosage recommendations and extracted data were used to develop three paediatric estimates of days of antibiotic use, accounting for age, weight, and potential wastage. Agreement between adult-based defined daily doses and each of the paediatric measures was assessed visually via Bland-Altman plots for each antibiotic.

Results: Thirty-one different antibiotics were used throughout the study period. Despite varying daily dose estimates in grams, for 39% of antibiotics the daily use of vials was unchanged from birth to 18 years. Vial-based metrics and defined daily doses were superior recommended daily dose estimates that did not account for wastage during preparation and administration. Vial-based measures were unaffected by vial size changes due to drug shortage.

Conclusion: Vial-based estimates of days of antimicrobial use should be further explored; detailed understanding of hospital practice is needed before inter-hospital comparisons are made.

Key Notes

Robust paediatric metrics of antimicrobial use are needed for children's hospitals without access to electronic prescribing or administration data. Drug use reports from pharmacy data are dependent on drug distribution systems, medication handling policies and medications guidelines. Vial-based estimates that account for waste warrant further evaluation in hospitals with single vial policies.

4.1.2 Introduction

Monitoring hospital antimicrobial use and resistance is key to antimicrobial stewardship efforts to curtail the rise of antimicrobial resistance. Antimicrobial stewardship (AMS) programs monitor compliance with interventions that aim to optimise therapy and identify antimicrobial utilisation patterns that warrant further investigation. In many countries hospital-level data also contribute to large-scale surveillance programs that enable benchmarking and epidemiological research.(1)

In the absence of patient-level data (typically from electronic prescribing or medication administration systems), antimicrobial use in hospitals is frequently sourced from pharmacy information systems and reported as the number of defined daily doses (DDD) for adult patients. The DDD is defined by the World Health Organization as an estimate of the average daily dose of each agent according to its most common indication in a 70kg patient. Therefore, reporting antimicrobial use in terms of DDD is considered to give

an approximate measure of the number of days in a given month that an antimicrobial was used within an adult population.(2)

There has been debate over the applicability of DDD as a measure for antimicrobial surveillance in both adults and children. One major concern is the propensity for DDD to over- or underestimate the actual days of use when DDD does not reflect the actual prescribed or recommended dose. The relationship between “consumed” and “administered” antimicrobial is further complicated in children as a considerable amount of drug is likely to be discarded in the process of preparing individualised doses from available standard sized vials.(3,4) Due to these variations, DDD is not validated or endorsed for use in children, and consequently, data from paediatric patients is often excluded from larger antimicrobial surveillance programs.(5)

AMS programs in children’s hospitals are expected to monitor antimicrobial usage patterns (6), and demonstrate cost-effective antimicrobial therapy.(7) Surveys of actual prescribing, though ideal, are resource intensive in the absence of electronic prescribing systems and may not be feasible for routine surveillance, pharmacy information systems continue to be used as the primary data source in paediatric hospitals, with use reported in terms of total drug costs, DDD and paediatric (modified) defined daily doses.(8)

Given the limitations of DDD and the absence of any endorsed measure, there is a need for individual hospitals to identify alternate broadly applicable measures that can account for age, waste and usual maintenance doses in their patient population.

This study explored the levels of agreement between DDD and alternate estimates of the days of antimicrobial use in the context of a Paediatric Intensive Care Unit (PICU) that does not have access to individual patient-level data.

4.1.3 Methods

Setting

This retrospective study was conducted in a 170-bed university affiliated tertiary paediatric hospital in New South Wales, Australia. The hospital is adjoined by two public hospitals for general adult and specialist women's and newborn care. A range of services are shared across the campus including operating theatres, radiology and pharmacy. The PICU accepts complex surgical and oncology patients from birth to 18 years, including preterm neonates transferred from the neonatal intensive care unit (NICU) at the adjoining hospital.

Nursing staff order routinely prescribed antimicrobials that have been approved as "imprest" items from a pharmacy warehouse shared between the adult and paediatric hospitals. Pharmacy warehouse staff distribute

imprest items to individual wards with limited or no direct contact with pharmacists; non-imprest antimicrobials are dispensed to individual patients by pharmacists. All injectable medications, other than those associated with high cost or special handling requirements, are prepared by nurses on the ward. State-wide infection control and medication handling policies mandate the use of single dose vials over multi-dose products, and require nurses to discard any unused portions of injectable medicine.(9)

Data collection and analysis

Antimicrobial and patient demographic data

Records of antimicrobial supply to PICU inpatients from 1 January 2010 to 31 May 2016 were extracted from the hospital pharmacy information system (iPharmacy, CSC, Sydney Australia). In keeping with the National Antimicrobial Utilisation and Surveillance Program methods used for adults, the data combined records of imprest distribution from the pharmacy warehouse and individual inpatient dispensing by pharmacists.(5) Discharge and outpatient dispensing associated with the PICU cost centre code were excluded. All agents within the WHO Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) classification system for antimicrobials (categories J01, J02, J05, J04AB02) were included in the extraction.(2)

ATC category J01 and J04AB02 injectables were included in the study. Tobramycin and colistin for injection and inhalation could not be

differentiated consistently throughout the study period and were excluded from further analysis. Injectable erythromycin was also excluded because it is more commonly prescribed for gastric motility in our PICU. Data entry errors were corrected after confirmation from pharmacy and warehouse managers; records of unused items returned to stock after initial supply were subtracted from the original month of supply. Antibiotic use was reported as monthly vial counts according to vial size.

Date of birth and occupied bed-day data were obtained from the hospital performance unit. Patient age (in months) was calculated for each patient at each day of their PICU admission and used to create a database of monthly age-specific PICU occupied bed-days.

Paediatric measures of antibiotic use

We derived three new metrics in an attempt to capture daily antimicrobial consumption for children and compared each of these to WHO ATC DDD (2016). Monthly antimicrobial use was measured in DDDs and was calculated by dividing grams used by the WHO assigned DDD value, i.e., (Vial size (grams) × Number of vials)/DDD.

Alternative metrics were derived from the dosage and frequency recommendations published in national paediatric medication references texts and New South Wales Neonatal Medicine Consensus Formularies. (10,11) Where there were no local or national recommendations we

referred to Lexi-Comp®(12), and the British National Formulary for Children.(13) Median weight for age was extrapolated from the U.S. Centers for Disease Control and Prevention weight-for-age percentile reference ranges for girls.(14) For consistency (i.e., alignment with DDD), the specific dose and frequency selected was equal or equivalent to the adult values assigned by WHO. For example, DDD assignments for beta-lactams with beta-lactamase inhibitors were an average of two commonly prescribed dosage schedules, therefore, we took the same approach for our derived paediatric metrics.

Local measure 1: Estimated daily use of vials

Estimated daily use of vials ("estimated daily vials") was derived from the recommended frequency of antimicrobial administration for children. A single vial was assumed to equate to a single dose irrespective of the weight and age of the child, and the dose actually delivered. Monthly PICU antibiotic use measured according to the estimated daily vials metric was calculated by dividing the total number of vials supplied to PICU each month by the estimated daily vials metric, i.e., Number of vials /Estimated daily vials.

Local measure 2: Age-adjusted estimated daily use of vials

The estimated daily use of vials was further adjusted to account for age-specific recommendations and estimated weight. Average doses were calculated for each antibiotic from birth to 18 years old. Vial sizes from

antibiotic use reports determined the number of vials required to deliver each average dose; doses were allowed to be rounded down to the nearest whole number of vials where the delivered dose would still remain within 5% of the average dose. Average daily vial requirements were then calculated according to the recommended dose frequency for each age. Average daily vial requirements for each specific age were then summed according to the age-specific PICU occupied bed-days each month to form the age-adjusted estimated daily use of vials ("age-adjusted estimated daily vials"), i.e., ∑ (Average daily vial requirement for age × Proportion of occupied bed-days for age).

Average doses for neonates broadly accounted for gestational age by taking the lowest or most commonly used frequency in neonates. Unless otherwise stated, gestational and postnatal age-adjustment was applied to all patients under 3 months old to account for possible preterm birth. Neonatal dose adjustments were not performed for antibiotics that were deemed rare or unsuitable for neonatal use. The proportion of occupied bed-days for age was recalculated accordingly.

Monthly PICU antibiotic use measured according to age-adjusted estimated daily vials was calculated by dividing the total number of vials by the age-adjusted estimated daily vials metric, i.e., Number of vials /Age-adjusted estimated daily vials.

Local measure 3: Recommended daily dose

The total recommended daily dose was calculated according to the median admission weight and age without accounting for discarded antibiotic, i.e., Dose in milligram per kilogram × usual dose frequency × 50^{th} percentile weight).

Monthly PICU antibiotic use measured according to total recommended daily doses was calculated by dividing the total use in grams by the total recommended daily dose for each month, i.e., (Vial size(grams) × Number of vials)/Total recommended daily dose(grams)).

Ethics

Ethics approval was granted by the hospital Human Research Ethics Committee (LNR/16/SCHN/445) and ratified by the University of Technology Sydney.

Statistical analysis

Data was extracted to a Microsoft Excel 2016 database (Microsoft Corporation, Redmond, WA, USA) for initial calculations. Statistical analysis was performed in R version 3.3.1(R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were used to report the age-adjusted estimated daily vials metrics that resulted from the PICU patient population throughout the

study period. Agreement between the DDD and the estimated daily use in vials, the DDD and the age-adjusted daily use in vials, and the DDD and the total recommended daily doses was assessed visually via Bland-Altman plots for each antibiotic with at least 10 months of use (10 observations).

Differences in estimated monthly use between DDD and each of the derived paediatric use metrics were plotted against the Average of the two measures, i.e., y = Differences = use in DDD – use in derived metric, x=Averages = (use in DDD + use in derived metric)/2. Shapiro-Wilk tests and visual inspection of Bland-Altman and quantile-quantile plots confirmed whether the calculated differences were normally distributed. Where the assumption of normality was not met linear regression was used to describe the mean difference as a function of Averages. As described by Bland and Altman, the mean differences are obtained from a fitted regression model (model 1), $B_0 + B_1 Averages = Differences$. The limits of agreement are then derived from a second linear regression model, $C_0 + C_1 Averages = Residuals$, where the residuals are the absolute residuals from model 1. Statistical significance was determined by the p-value of the coefficients of the Averages, B_1 and C_1. The limits of agreement were calculated as ± 2.46 ($C_0 + C_1 Averages$) of the mean difference ($B_0 + B_1 Averages$).(15) Where distributions varied between antibiotics the most common distribution determined the method of analysis, and a single approach was applied to antibiotics. All tests were two-tailed, and P values <0.05 were considered statistically significant.

4.1.4 Results

Of the 31 antibiotics used in the PICU throughout the study period, 61% (19/31) were consistently supplied in one vial size. Cefotaxime was the only antibiotic supplied in more than two sizes. Estimated daily vials were assigned for almost all antibiotics (30/31). Gentamicin was excluded because there was no clear relationship between vial size and usual dosage and/or frequency. For 13 antibiotics (42%) that were limited to a single size, the estimated daily use in vials for children was equal to DDD in terms of the reported grams of use, and the number of vials required (Table 4.1).

Table 4.1 Antibiotic dosage recommendations and references for paediatric estimates of days of antibiotic use

Antibiotic (ATC code)	WHO DDD 2016	Vial Sizes used in PICU	Recommended paediatric and neonatal antibiotic dosage: mg/kg (max. dose), frequency[$£]	Estimated daily use of vials - usual dosage *frequency* for children, Number of vials (grams of use)	Reference ranges for estimates of daily use[++]	Age-specific average daily vial requirements derived from reference ranges, vial size and extrapolated weight for age[++]	Age-adjusted estimated daily vials[^], Mean (range)
Amikacin (J01GB06)	1g	0.5g	Paediatric: 1 month – 10 years: 22.5mg/kg >10 years: 18mg/kg (1.5g) Neonatal: ≥ 32 weeks: daily	1 (0.5g)	1 month – 10 years: 22.5mg/kg daily >10 years: 18mg/kg (1.5g)	≤ 7 years, 2 months: 1 vial per day ≥ 7 years, 3 months: 2 vials per day	1.2 (1.1–1.4)
Ampicillin (J01CA01)	2g	0.5g, 1g	Paediatric: 25-50mg/kg (2g) 6-8 hourly Neonatal[£]: <30 weeks & <28 days, 30 – 36 weeks & < 14 days, & ≥ 37 weeks & < 7 days: 12 hourly ≥ 45 weeks: 6 hourly	4 (2 - 4g)	25mg/kg (1g) 6 hourly	< 3 months: 2 vials per day ≥ 3 months: 4 vials per day	3.5 (3.0–3.8)
Azithromycin (J01FA10)	0.5g	0.5g	Paediatric: 10mg/kg/day (0.5g) Neonatal (term): once daily	1 (0.5g)	10mg/kg/day (0.5g)	All patients: 1 vial per day	n/a
Aztreonam (J01DF01)	4g	1g	Paediatric: 30-50mg/kg (2g) 6-8 hourly Neonatal[^^]: >2kg and ≤7 days: 8 hourly	3 (3g)	30m/kg (2g) 8 hourly	<10 years, 5 months: 3 vials per day ≥ 10 years, 6 months: 6 vials per day	3.4 (3.1–3.9)
Benzathine penicillin (J01CE08)	3.6g	0.9g	>20kg: 900mg <20kg: 450mg	1 (0.9g)	>20kg: 900mg <20kg: 450mg	All patients: 1 vial per dose	n/a

Benzylpenicillin (J01CE01)	3.6g	0.6g, 1.2g	Paediatric: 30-60mg/kg (1.2g - 2.4g) 4-6 hourly Neonatal[£]: <30 weeks & <28 days, 30 - 36weeks & < 14 days, & ≥ 37 weeks & < 7 days: 12 hourly ≥ 45 weeks: 6 hourly	4 (2.4 -4.8g)	30mg/kg (1.2g) 6 hourly	< 3 months: 2 vials per day ≥ 3 months: 4 vials per day	3.5 (3.0–3.8)
Cefalotin (J01DB03)	4g	1g	Paediatric: 25mg/kg (1g) 4-6 hourly OR, 50mg/kg (2g) 6 hourly Neonatal: Not used	4 (4g)	25mg/kg (1g) 6 hourly	All patients: 4 vials per day	n/a
Cefazolin (J01DB04)	3g	1g	Paediatric: 6.25-25mg/kg (1g) 6 hourly OR, 50mg/kg (2g) 8 hourly Neonatal[£]: ≤ 7 days 12 hourly >8 days: 8 hourly	3 (3g)	25mg/kg (1g) 8 hourly)	<1 month of age: 2 vials per day >1 month: 3 vials per day	2.9 (2.7–3.0)
Cefepime (J01DE01)	2g	1g, 2g	Paediatric: 50mg/kg(2g) 8-12 hourly Neonatal[^^]: >2kg: 8-12 hourly	2 (2 - 4g)	50mg/kg (2g) 12 hourly	All patients: 2 vials per day	n/a
Cefotaxime (J01DD01)	4g	0.5g, 1g, 2g**	Paediatric: 25-50mg/kg (2g) 6-8 hourly Neonatal[£]: < 30 weeks & >28 days, 30 - 36 weeks & >14 days: 8 hourly ≥ 37 weeks & >7 days: 6 hourly	4 (2-8g)	25mg/kg (1g) 6 hourly	< 3 months: 3 vials per day ≥ 3 months: 4 vials per day	3.7 (3.5–3.9)

Cefoxitin (J01DC01)	6g	1g	Paediatric: 20-40mg/kg (2g) 6-8 hourly Neonatal: Not used	3 (3g)	40mg/kg (2g) 8 hourly	≤ 8 years, 2 months: 3 vials per day ≥ 8 years, 4 months: 6 vials per day	3.9 (3.3–4.6)
Ceftazidime (J01DD02)	4g	1g, 2g	Paediatric: 25-50mg/kg (2g) 8 hourly Neonatal: 12 hourly	3 (3 - 6g)		<3 months: 2 vials per day ≥ 3 months: 3 vials per day	2.7 (2.5–2.9)
Ceftriaxone (J01DD04)	2g	0.5g, 1g	Paediatric: 50–75 mg/kg (2g) once daily OR 100 mg/kg (4g) once daily OR 50 mg/kg (2 g) 12 hourly Neonatal: Not used	1 (0.5 -1g)	50mg/kg/day (2g) once daily	≥ 5 months - ≤ 6 years, 3 months: 1 vial per day ≥ 6 years 4 months: 2 vials per day	1.3 (1.1–1.6)
Ciprofloxacin (J01MA02)	0.5g	0.1g, 0.2g	Paediatric: 10mg/kg (0.4g) 8-12 hourly Neonatal: ≥ 32 weeks: 12 hourly	2 (0.2 - 0.4g)	10mg/kg (0.4g) 12 hourly	≤ 6 years, 3 months: 2 vials per day ≥ 6 years 4 months: 4 vials per day	2.5 (2.2–2.8)
Clindamycin (J01FF01)	1.8g	0.3g, 0.6g	Paediatric: 5-15mg/kg (0.6g) 8 hourly Neonatal[$]: >38 weeks <8 days: 8 hourly ≥ 7 days: 6 hourly	3 (0.9 - 1.8g)	15mg/kg (0.6g) 8 hourly	All patients: 3 vials per day	n/a
Daptomycin (01XX09)	0.28g	0.5g	Paediatric[^^]: 1-2 years:10mg/kg 2-6 years: 9mg/kg 7-11 years: 7mg/kg 12-17 years: 5mg/kg daily Neonatal: Not used	1 (0.5g)	According to paediatric doses[^^]	All patients: 1 vial per day	n/a

Flucloxacillin (J01CF05)	2g	0.5g, 1g	Paediatric: 25mg/kg (1g) OR 50mg/kg (2g) 4-6 hourly Neonatal[£] (any age): <7 days: 12 hourly 8-28 days: 8 hourly	4 (2 - 4g)	25mg/kg (1g) 6 hourly	<1 month: 2 vials per day >1 month: 4 vials per day	3.7 (3.4–4.0)
Gentamicin (J01GB03)	0.24g	0.01g, 0.08g	Paediatric: < 10 years: 7.5mg/kg (0.32g) >10 years: 6-7mg/kg (0.56g) Neonatal: 8 hourly OR daily	1 (0.08g)		Excluded	Excluded
Imipenem (J01DH51)	2g	0.5g	Paediatric: 15-25mg/kg (1g) 6 hourly Neonatal: Not used	4 (2g)	15mg/kg (0.5g) 6 hourly	All patients: 4 vials per day	n/a
Lincomycin (J01FF02)	1.8g	0.6g	Paediatric: 15 mg/kg (0.6g) 8 hourly Neonatal: Not used	3 (1.8g)	15 mg/kg (0.6g) 8 hourly	≥ 5 months: 3 vials per day	n/a
Linezolid (J01XX08)	1.2g	0.6g	Paediatric: 1 month-12 years: 10mg/kg (0.6g) 8 hourly 12-18 years: 0.6g 12 hourly Neonatal[^^]: 8 or 12 hourly	3 (1.8g)	<12 years: 10mg/kg (0.6g) 8 hourly ≥ 12-18 years: 0.6g 12 hourly	<12 years: 3 vials per day ≥ 12 years: 2 vials per day	2.9 (2.7–3.0)
Meropenem (J01DH02)	2g	0.5g, 1g	Paediatric: 20-40mg/kg (2g) 8-12 hourly Neonatal: 8 hourly	3 (1.5 - 3g)	20mg/kg (1g) 8 hourly	All patients: 3 vials per day	n/a
Metronidazole (J01XD01)	1.5g	0.5g	Paediatric: 12.5mg/kg (0.5g) 12 hourly OR, 7.5mg/kg (0.5g) 8 hourly Neonatal: 34 – < 41weeks: 8 hourly[£] 37 weeks: 12 hourly[$]	3 (1.5g)	7.5mg/kg (0.5g) 8 hourly	< 1 month: 2 vials per day ≥ 1 month: 3 vials per day	2.9 (2.7–3.0)

Moxifloxacin (J01MA14)	0.4g	0.4g	Paediatric[^^]: 10 mg/kg (0.4g) daily Neonatal: Not used	1 (0.4g)	10 mg/kg (0.4g) daily	All patients: 1 vial per day	n/a
Piperacillin–tazobactam (J01CR05)[#]	14g	4g	Paediatric: 100mg/kg (4g) 6-8 hourly Neonatal: <30 weeks 8 hourly >30 weeks 6 hourly	3.5 (14g)	100mg/kg (4g) 6-8 hourly	All patients: 3.5 vials per day	n/a
Rifampicin (J04AB02)	0.6g	0.6g	Paediatric: 10-20mg/kg (0.6g) daily Neonatal: Not used	1 (0.6g)	10-20mg/kg (0.6g) daily	All patients: 1 vial per day	n/a
Teicoplanin (J01XA02)	0.4g	0.4g	Paediatric: 10mg/kg (0.4g) daily Neonatal (term): daily	1 (0.4g)	10mg/kg (0.4g) daily	All patients: 1 vial per day	n/a
Ticarcillin–clavulanic acid (J01CR03)[#]	15g	3g	Paediatric: 50mg/kg (3g) 4-6 hourly Neonatal[£]: <28 days: 12 hourly	5 (15g)	50mg/kg (3g) 4-6 hourly	≤ 1 month: 2 vials per day >1 month: 5 vials per day	4.6 (4.2–5.0)
Tigecycline (J01AA12)	0.1g	0.05g	Paediatric[^^]: 1.2 mg/kg (0.05g) 12 hourly Neonatal: not used	2 (0.1g)	1.2 mg/kg (0.05g) 12 hourly	All patients: 2 vials per day	n/a
Trimethoprim–sulfamethoxazole (J01EE01)[#]	20mL	5mL	Paediatric: 5-8mg/kg (320mg, 20mL) 12 hourly Neonatal: Not used	2 (10mL)	4mg/kg (160mg, 10mL) 12 hourly	≥ 5 months - ≤ 6 years, 3 months: 2 vials per day ≥ 6 years, 4 months: 4 vials per day	2.7 (2.3–3.2)
Vancomycin (J01XA01)	2g	0.5g, 1g[§]	Paediatric: 15mg/kg (0.75g) 6 hourly Neonatal: 15mg/kg 12-8 hourly	4 (2g)	15mg/kg (0.75g) 6 hourly	< 3 months: 2 vials per day ≥ 3 months - ≤ 10 years,5 months: 4 vials per day ≥ 10 years, 6 months - 18 years: 8 vials per day	4.0 (3.3–5.0)

DDD: World Health Organisation defined daily dose; g: Grams; PICU: Paediatric Intensive Care Unit; WHO ATC: World Health Organization Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical Classification
++ Reference ranges for age-adjusted estimated daily vials or the average daily vial requirement for age calculated from 50th percentile weight-for-age;
^ Age-adjustment derived from the proportion of monthly patient bed days for each age (in years, months) and the estimated number of vials required for one day of use at the stated doses (see ++), antibiotics marked n/a do not require age-adjustment;
**Cefotaxime 0.5 g vial size available January 2010 to July 2012 and August 2014 to November 2015, cefotaxime 2g vial size supplied during cefotaxime shortage March 2013 to April 2013 and August 2013 to November 2013;
$Australian Medicines Handbook Children's Dosing Companion (10);
£ New South Wales Neonatal Medicine Consensus Formularies (11);
^^Lexi-Comp (12);
#Dosage refers to piperacillin, ticarcillin or trimethoprim component only;
§ Vancomycin 1g vial size supplied over 77 months was not incorporated into the daily measure

Twelve antibiotics (39%) had an estimated daily use in vials that accounted for DDD equivalent doses regardless of age, including neonates and teenagers. These were; azithromycin, benzathine penicillin, cefalotin, cefepime, clindamycin, daptomycin, imipenem, meropenem, moxifloxacin, piperacillin-tazobactam, rifampicin, teicoplanin, tigecycline. Nine antibiotics were further adjusted to account for neonatal dosage regimens (ampicillin, benzylpenicillin, cefazolin, cefotaxime, ceftazidime, flucloxacillin, metronidazole and ticarcillin-clavulanic acid). Eight changes were made for weight or age in children. Only vancomycin was adjusted for both neonates and children. Month-to-month variation attributed to age-adjustment was largest for vancomycin (range 3.3–5.0 vials), cefoxitin (range 3.3–4.6 vials) and trimethoprim/sulfamethoxazole (2.3–3.2 vials) (Figure 4.1).

Comparison of measures for monitoring PICU antibiotic use

Agreement between reported use in DDD and local units of measure was completed for 20 different antibiotics that were supplied to the PICU over at least 10 months of the study period. Bland-Altman plots of PICU use in DDD and estimated daily vials showed perfect agreement for azithromycin, cefalotin, cefazolin, lincomycin, metronidazole and penicillins with beta-lactamase inhibitors (7/20). Shapiro-Wilk tests of the differences confirmed normal distributions for only two antibiotics and thus regression methods were used to determine the mean difference and limits of agreement.

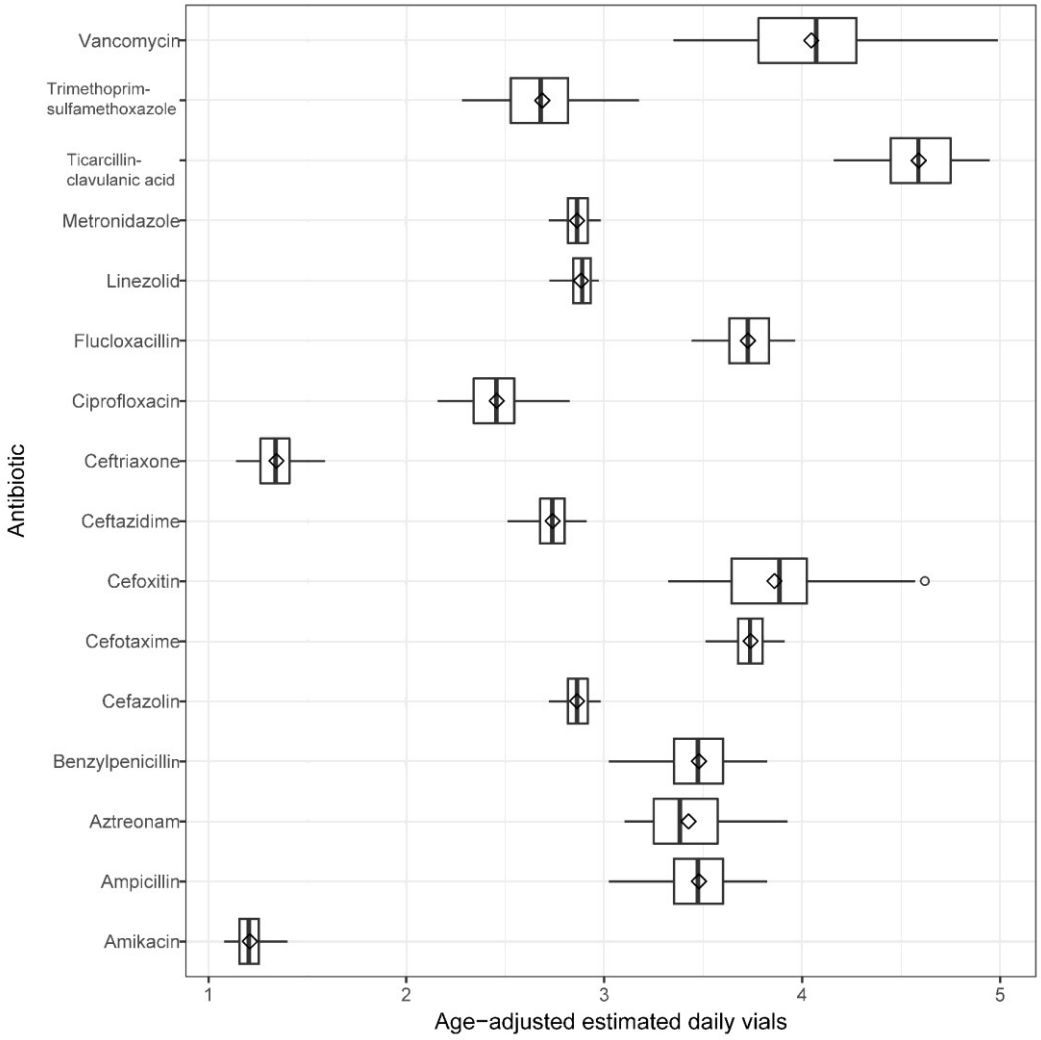


Figure 4.1 Age-adjusted estimated daily vials generated from age-specific occupied bed-days in the Paediatric Intensive Care Unit

The relationship between the differences in terms of the averages of use in DDD and estimated daily vials was perfectly linear for amikacin, trimethoprim-sulfamethoxazole and linezolid, with no deviations from the regression line (Figure 4.2). The mean difference for vancomycin in DDD and estimated daily vials was not statistically significant despite three deviations attributed to a small number of larger sized vancomycin vials (*p* = 0.059). Agreement varied for antibiotics that were supplied in various size vials.

Estimated daily vials for 7 antibiotics accounted for all paediatric doses despite 2-fold or greater variation in reported DDD (ampicillin or flucloxacillin = 1.0–2.0 DDD, meropenem and ceftazidime = 0.75–1.5 DDD, clindamycin = 0.5–1.0 DDD, benzylpenicillin ~0.67–1.33 DDD, cefotaxime = 0.5–2.0 DDD). However, comparisons of use in DDD and estimated daily vials for the antibiotics were variable. Flucloxacillin plots exhibited the narrowest limits of agreement, and the most prominent slope (Table 4.2 and Figure 4.2). The steep incline suggested that higher usage months measured in DDD may vastly overestimate use compared to estimated daily vials. Bland-Altman plots for others produced wider limits of agreement as various vial sizes were more consistently used, including low usage months.

Approximately one in every four monthly cefotaxime usage observations were in perfect agreement (19/75, difference = 0) without a statistically

significant change in relation to the magnitude of the averages (p = 0.922). Differences between cefotaxime DDD and estimated vials were both negative and positive, suggesting DDD measures may have potentially under- and over-reported use. The largest negative difference and most extreme positive outlier occurred during periods of high cefotaxime use predominantly supplied as small and large vials respectively (difference = -43.73, 67% vials 0.5g; +72.5, 100% of vials 2g) (Figure 4.2).

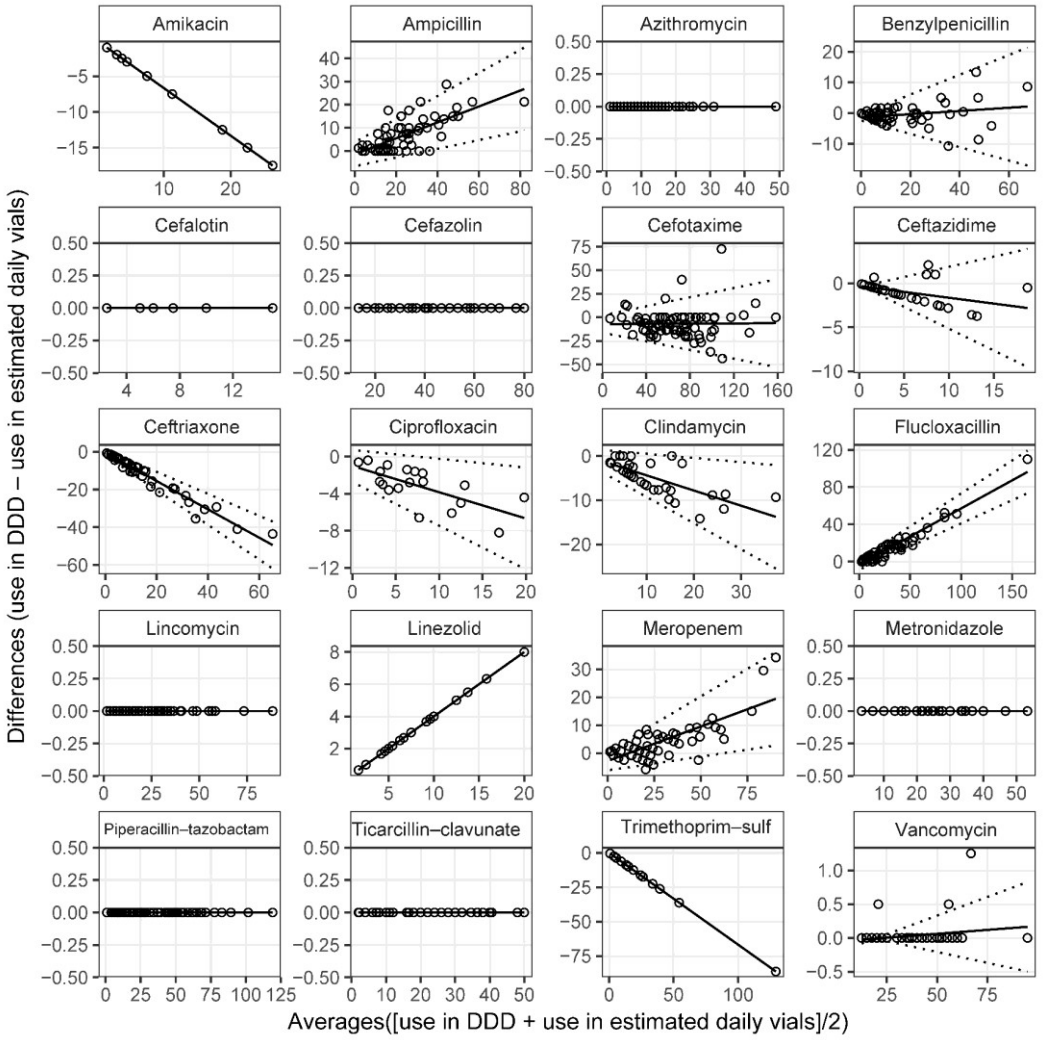


Figure 4.2 Bland-Altman plots of PICU antibiotic use measured in World Health Organization defined daily doses and estimated daily use of vials. Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Table 4.2).

Table 4.2 Differences and limits of agreement between defined daily doses and locally derived measures to estimate days of PICU antimicrobial use[#]

	DDD vs Estimated daily vials						DDD vs Age-adjusted estimated daily vials						DDD vs Recommended daily dose					
	Mean difference = B_0+ B_1Averages			Limits = Mean difference +/-2.46 (C_0+ C_1Averages)			Mean difference= B_0+ B_1Averages			Limits = Mean difference +/-2.46 (C_0+ C_1Averages)			Mean difference= B_0+ B_1Averages			Limits = Mean difference +/-2.46 (C_0+ C_1Averages)		
Antibiotic (n)	B_0	B_1	p*	C_0	C_1	p*	B_0	B_1	p*	C_0	C_1	p*	B_0	B_1	p*	C_0	C_1	p*
Amikacin (16)	0.0	-0.7	<0.001	0.0	0.0	0.818	0.1	-0.5	<0.001	0.2	0.0	0.075	-0.4	-1.1	<0.001	-0.2	0.1	0.046
Ampicillin (67)	-1.4	0.3	<0.001	2.1	0.1	0.026	-1.0	0.2	<0.001	2.0	0.1	0.003	3.5	-0.7	<0.001	2.1	0.1	0.004
Azithromycin (58)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	2.0	-1.3	<0.001	1.6	0.0	0.013
Benzylpenicillin (60)	-1.4	0.1	0.072	0.4	0.1	<0.001	-1.2	-0.1	<0.001	0.6	0.1	<0.001	2.3	-1.1	<0.001	0.4	0.1	<0.001
Cefalotin (19)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.2	-1.2	<0.001	0.7	0.0	0.541
Cefazolin (77)	0.0	0.0	n/a	0.0	0.0	n/a	-0.6	0.0	<0.001	0.0	0.0	<0.001	12.4	-1.3	<0.001	1.6	0.1	0.001
Cefotaxime (76)	-7.1	0.0	0.922	3.8	0.1	0.026	-6.5	-0.1	0.219	3.3	0.1	0.016	16.2	-1.3	<0.001	2.5	0.1	<0.001
Ceftazidime (39)	-0.3	-0.1	0.003	-0.1	0.2	<0.001	-0.3	-0.2	<0.001	0.0	0.1	<0.001	0.7	-1.0	<0.001	0.4	0.1	0.001
Ceftriaxone (48)	-0.5	-0.8	<0.001	0.6	0.1	<0.001	-0.4	-0.5	<0.001	0.4	0.1	<0.001	-0.3	-1.2	<0.001	0.1	0.1	<0.001
Ciprofloxacin (19)	-1.0	-0.3	0.001	0.7	0.1	0.034	-1.2	0.0	0.754	0.6	0.1	0.077	0.6	-0.9	<0.001	0.8	0.1	0.304
Clindamycin (39)	-1.0	-0.3	<0.001	1.0	0.1	0.001	-1.0	-0.3	<0.001	1.0	0.1	0.001	0.2	-1.1	<0.001	0.0	0.1	<0.001
Flucloxacillin (66)	-3.1	0.6	<0.001	2.3	0.0	<0.001	-3.0	0.5	<0.001	2.6	0.0	0.006	0.2	-0.6	<0.001	-0.8	0.1	<0.001
Lincomycin (53)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	2.3	-1.2	<0.001	0.7	0.1	<0.001
Linezolid (18)	0.0	0.4	<0.001	0.0	0.0	<0.001	0.1	0.4	<0.001	0.1	0.0	0.065	0.0	-1.2	<0.001	1.8	0.0	0.811
Meropenem (69)	-2.8	0.3	<0.001	1.4	0.1	<0.001	-2.8	0.3	<0.001	1.4	0.1	<0.001	3.1	-1.1	<0.001	-0.3	0.1	<0.001
Metronidazole (76)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	-0.1	<0.001	0.1	0.0	<0.001	2.1	-1.5	<0.001	1.2	0.0	<0.001
Piperacillin–tazobactam (63)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	7.9	-1.3	<0.001	4.0	0.1	0.002
Ticarcillin–clavulanate (42)	0.0	0.0	n/a	0.0	0.0	n/a	-0.1	-0.1	<0.001	0.1	0.0	<0.001	4.0	-1.5	<0.001	0.8	0.1	<0.001
Trimethoprim–sulfamethoxazole (14)	0.0	-0.7	<0.001	0.0	0.0	0.901	1.3	-0.5	<0.001	1.1	0.0	0.052	1.1	-1.2	<0.001	2.7	0.0	0.353
Vancomycin (77)	-0.1	0.0	0.059	-0.1	0.0	0.001	-1.2	0.1	0.070	0.6	0.1	<0.001	12.8	-1.2	<0.001	3.5	0.1	0.010

DDD: Defined daily doses; Limits: Limits of Agreement; n: observations (months of use); n/a: Not applicable; PICU: Paediatric Intensive Care Unit;
[#]Shapiro Wilk test of differences p>0.05 for DDD vs Estimated daily vials (ceftazidime, ciprofloxacin), DDD vs age-adjusted estimated daily vials (linezolid, vancomycin), DDD vs recommended daily dose (amikacin, cefazolin, lincomycin).
*p values for the coefficient of the Averages (B_1 and C_1);

Adjustment for neonatal recommendations and paediatric weight introduced additional variation to each of the Bland-Altman plots. Metronidazole, cefazolin and ticarcillin/clavulanate were no longer in perfect agreement (Figure 4.3). Ampicillin and flucloxacillin continued to exhibit statistically significant and positive differences in relation to the averages. Despite changes in the appearance of the plots, the mean difference for both cefotaxime and vancomycin did not reach statistical significance; limits of agreement were, however, narrower and wider respectively as expected. The magnitude of the mean difference in relation to the averages changed significantly after age adjustment to benzylpenicillin and ciprofloxacin as demonstrated by the changes to the slopes (benzylpenicillin + $0.1Averages_{DDDvials}$, $p = 0.072$ to $-0.1Averages_{DDDageadj}$, $p<0.001$; ciprofloxacin $-0.3Averages_{DDDvials}$, $p = 0.001$ to $0.0Averages_{DDDageadj}$, $p = 0.754$).

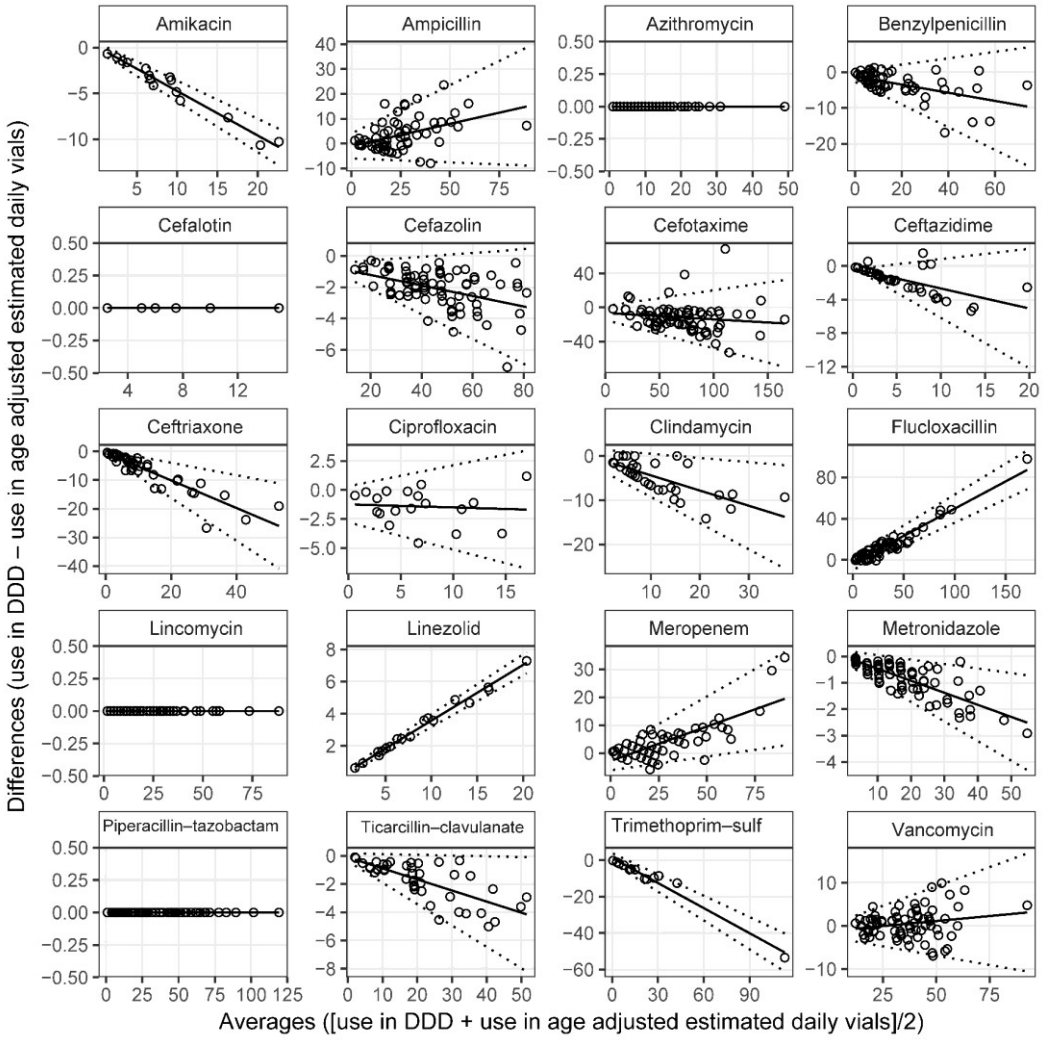


Figure 4.3 Bland-Altman plots of PICU antibiotic use measured in World Health Organization defined daily doses and age-adjusted estimated daily use of vials. Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Table 4.2).

Agreement between DDD and total recommended daily doses was poor. Visual inspection of Bland-Altman plots and linear regression showed an obvious and statistically significant relationship between the differences and the averages that was inversely proportional (Table 4.2 and Figure 4.4). Differences between DDD and total recommended daily doses increased dramatically with higher average use; negative differences indicated that the estimated days of antibiotic use measured in recommended doses far exceeded that which was reported in DDD.

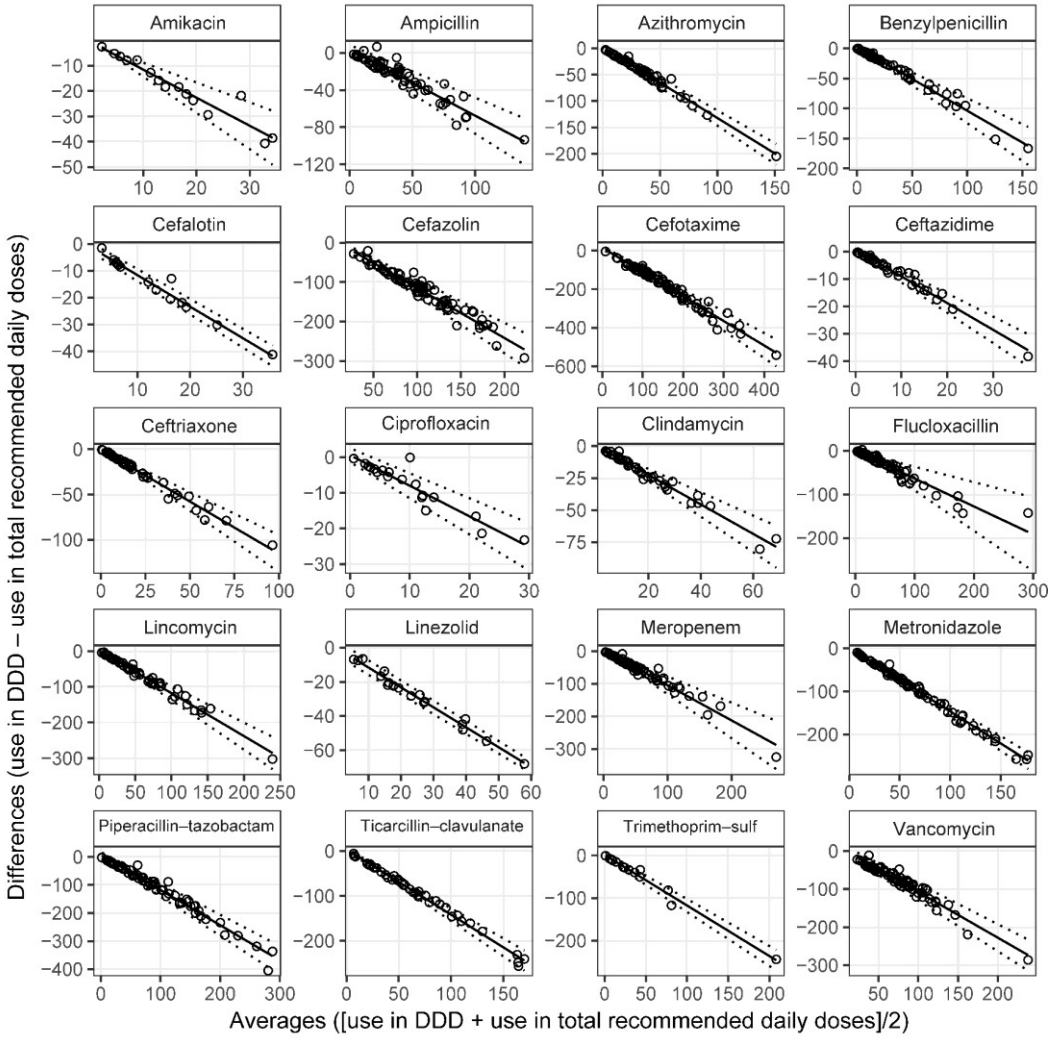


Figure 4.4 Bland-Altman plots of PICU antibiotic use measured in World Health Organization defined daily doses and total recommended daily doses. Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Table 4.2).

4.1.5 Discussion

Despite its exploratory nature, this study offers some insight into a range of patient and organisational factors that influence the approach to antimicrobial surveillance in children's hospitals. Extracted records of use together with medication reference texts identified thirteen antibiotics that are likely to be reliably reported in children and teenagers in DDD without any adjustment, and with only minor adjustment in neonates. This list of 13 agents includes 10 that are restricted or highly restricted agents in our hospital. Also included is injectable metronidazole, which, while unrestricted, is a potential target for antimicrobial stewardship activities that promote IV to oral switch or reduce therapeutic duplication. Approximately half of the antibiotics used in PICU required estimated daily vials metric to be adjusted for age and weight and only one antibiotic, vancomycin, required adjustment for both neonates and children.

Bland-Altman plots of antibiotic use measured agreement between each of the derived paediatric use metrics and DDD, illustrating how vial size, age and waste may impact drug usage reports. Compared to DDD, vial-based units of measure that focused on the dosage frequency were more robust against formulary changes and drug shortages. In contrast, agreement between total recommended daily doses and DDD was poor. Use in total recommended daily doses resulted in considerably higher estimates of monthly use, even where all other measures were equal or similar.

To the best of our knowledge, previous weight-adjusted methods in similar settings have largely reported use according to total recommended daily doses or proportions of DDD rather than vials.(3,4,16,17) Others have argued against weight-based adjustments due to the broad range of paediatric doses and the wide range of indications, choosing to use DDD for benchmarking and trend analysis.(18) Whilst DDD generally appeared to be closer to the minimum quantity reported for a single day of use in our setting, these conclusions may not be generalisable to hospitals without single vial policies, and different vial sizes in use. Similarly, these variations are likely to limit the capacity for benchmarking between hospitals and comparisons with published surveillance reports internationally.

This study has a number of limitations. The metrics developed in this study were modelled similarly to DDD and share some of the same limitations, including that they might be based on recommended dosages that do not accurately reflect the most common dosage regimens actually used in hospitals. Prescribers may choose alternate regimens within the medication reference ranges for either convenience or based on severity of infection. However, these concerns are not limited to vial-based measures, or children. Vial-based measures are also unlikely to identify high dose use unless the number of vials is higher than expected, and may overestimate use when multiple smaller vials are used to deliver doses. Furthermore, the age adjustments applied in our study are estimates. We did not have access to complete records of gestational age and assumed all patients

under 3 months old were neonates if dose adjustment was needed. In addition to possibly over-estimating the adjustments required for neonates, this also meant we could not account for all the post-natal dose changes. Vial requirements for children and teenagers were extrapolated from paediatric reference ranges for standard weight-for-age and not actual patient weight. Whilst these are limitations of our study, they may be overcome in future studies as gestational and postnatal age are collected by Australian PICU's and weight estimates have since become available for electronic data extraction in our hospital. Age-adjustments may also be influenced by the ordering process if antibiotics were supplied and administered in separate months. Finally, we were unable to validate our measures against actual days of use. Such validation would require a prospective observational study and/or access to electronic medication administration or prescribing data, which were neither feasible nor available during this study.

Further research is needed to assess whether agreement between estimated vial-based measures and actual use are acceptable for local surveillance, benchmarking and/or epidemiological studies. Initial studies should investigate drug distribution systems, medication handling policies, hospital formularies and medication dosage guidelines for similarities. Consensus based methods may be required to reconcile discrepancies between prescribed doses and reference ranges used to define metrics.

4.1.6 Conclusion

Paediatric antibiotic use reports generated from pharmacy information systems may not reflect actual administration because of the influence of variable vial size, patient age, pharmacy distribution systems and local medication handling and infection control policies. Agreement between estimated daily vials and age-adjusted daily vials and DDD were superior to total recommended daily doses and unchanged by drug shortages. A considerable number of antibiotics targeted by AMS programs may be reported in DDD when used for children and teenagers.

4.1.7 References

1. Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2017: Second Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2017.
2. WHO Collaborating Centre for Drug Statistics Methodology. Defined Daily Dose: Definition and general considerations of defined daily dose (DDD). Oslo: Norwegian Institute of Public Health [Internet]. Available from: http://www.whocc.no/ddd/definition_and_general_considera/
3. Antachopoulos C, Dotis J, Pentsioglou V. Development of a paediatric daily defined dose system for the measurement of antibiotic consumption in paediatric units. In: 14th European Congress of Clinical Microbiology and Infectious Diseases; Prague, Czech Republic; 2004.
4. Raastad R, Tvete IF, Abrahamsen TG, Berild D, Leegaard TM, Walberg M, et al. A worrying trend in weight-adjusted paediatric antibiotic use in a Norwegian tertiary care hospital. Acta Paediatr 2015;104(7):687-92.
5. SA Health. National Antimicrobial Utilisation Surveillance Program(NAUSP) [Internet]; Available from: http://www.sahealth.sa.gov.au/nausp
6. Australian Commission on Safety and Quality in Health Care (ACSQHC). Standard 3: Preventing and Controlling Healthcare Associated Infections. In: National Safety and Quality Health Service

Standards. Sydney: ACSQHC; 2012. p. 26-33.

7. MacDougall C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. Clin Microbiol Rev 2005;18(4):638-56.

8. Fortin É, Fontela PS, Manges AR, Platt RW, Buckeridge DL, Quach C. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to paediatrics. J Antimicrob Chemother 2014;69(6):1447-56.

9. NSW Ministry of Health. Medication Handling in NSW Public Health Facilities. Policy Directive (PD2013_043) [Internet] Sydney, NSW: NSW Health; 2013 [updated 27 November 2013, cited 2018 20 January]; Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2013_043.pdf

10. Australian Medicines Handbook. Australian Medicines Handbook Children's Dosing Companion. Adelaide: Australian Medicines Handbook Pty Ltd.

11. Neonatal Medicines Formulary (NMF) Consensus Group. Newborn Care Centre Clinical resources – Medications. Neomed Formularies. [Internet] Sydney, NSW [cited 2018 20 January]; Available from: www.seslhd.health.nsw.gov.au/rhw/Newborn_Care/guidelines_med.asp

12. American Pharmaceutical Association (APA). Lexi-Comp Online in UptoDate Hudson, Ohio: APA; 2017.

13. Paediatric Formulary Committee. British National Formulary for

Children [Internet]. UK: BMJ Group and Royal Pharmacuetical Society; 2017 [cited 20 January 2018].

14. Centers for Disease Control and Prevention(CDC). Clinical Growth Charts. [Internet] Atlanta (GA) CDC; Available from: https://www.cdc.gov/growthcharts/cdc_charts.htm

15. Bland JM, Altman DG. Measuring Agreement in Method Comparison Studies. Stat Methods Med Res 1999;8:135-60.

16. Liem TBY, Heerdink ER, Egberts ACG, Rademaker CMA. Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. Eur J Clin Microbiol Infect Dis 2010;29(10):1301-3.

17. Zou X-x, Fang Z, Min R, Bai X, Zhang Y, Xu D, et al. Is nationwide special campaign on antibiotic stewardship program effective on ameliorating irrational antibiotic use in China? Study on the antibiotic use of specialized hospitals in China in 2011–2012. Journal of Huazhong University of Science and Technology [Medical Sciences] 2014;34(3):456-63.

18. Zhang W, Shen X, Bergman U, Wang Y, Chen Y, Huang M, et al. Drug utilisation 90% (DU90%) profiles of antibiotics in five Chinese children's hospitals (2002-2006). Int J Antimicrob Agents 2008;32(3):250-5.

4.2 Impact of computerised decision support on antibiotic utilisation trends in a Paediatric Intensive Care Unit

In the previous sub-chapter three potential measures for tracking and reporting antibiotic use from pharmacy supply data were explored. Age-specific average daily vial requirements were calculated and agreement between adult DDD and each of the proposed measures was assessed. Agreement between the total recommended daily dose (local measure 3) and DDD was poor. Agreement between vial-based measures and DDD were dependent upon the agent in question. However, a substantial proportion of restriction agents were equal or close to DDD.

Therefore, in this chapter both DDD and estimated daily use of vials, are applied to pharmacy supply data for the purpose of tracking and reporting injectable antibiotic usage trends in the PICU. An interrupted time series analysis is performed to evaluate the impact of the CDSS on restricted agents in the PICU. Age-specific occupied bed days are tracked together with antibiotic use to identify variation that may be attributed to patient age or weight. The PICU is again selected as the site of this subsequent study as the antibiotics supplied were predominantly injectable dosage forms.

Manuscript 7
Impact of computerised decision support on antibiotic utilisation trends in a Paediatric Intensive Care Unit
Manuscript in submission (peer review)

4.2.1 Abstract

Rationale: Antimicrobial use surveillance is an essential component of antimicrobial stewardship but may be limited in hospitals without access to patient level usage data.

Aims and objectives: To assess the impact of a computerised decision support and approval system (CDSS) on antibiotic use in a paediatric intensive care unit that does not have access to electronic patient level antimicrobial use data.

Methods: Pharmacy and patient admission data from 1 January 2010 to 30 October 2015 were used to assess changes in patient characteristics and antibiotic use by hospital stay and PICU occupied bed-day (OBD). Interrupted time series analysis (ITS) was performed on antibiotic use in defined daily doses (DDD) and the estimated daily use of vials (daily vials) and patient factors to identify immediate or long-term impact.

Results: Post-CDSS implementation occupancy in the PICU increased (355 [IQR 319–374] pre-CDSS vs 417 [345-437] post CDSS). Most patients were between 1 month up to 6 years of age (64% PICU OBD pre- and post-CDSS, p = 0.527), neonatal occupancy days declined slightly (13.5 pre-CDSS vs 12.5% PICU OBD post CDSS). Primary diagnosis codes for

respiratory illness was assigned more often post-CDSS, for discharges (27.0 vs 36.4% discharges) and PICU OBD (24.4 vs 33.8% PICU).

On ITS, discharge during the first month post-CDSS coincided with longer time in PICU (+7.9 hours, 95% CI 0.3 to 15.5) and risk of mortality (1.50, 95% CI 0.71 to 3.23; p = 0.245) compared to the baseline level (48.51 hours [95% CI 42.10 to 54.92] and 0.03 [95% CI, 0.02 to 0.05]). Long term, mortality was unaffected trend-change 1.00(95% CI 0.97–1.03, p = 0.953). Restricted agents managed via the CDSS were preferred over unrestricted agents. On ITS, there was an immediate increase from the baseline level (post-CDSS level change 178.8 DDD/1000 OBD [95% CI 7.7 to 350.07] and 123.4 daily vials/1000 OBD [95% CI -42.6 to 289.3]). Post-CDSS trend changes for both metrics indicated the level change was not sustained long term (-3.5 DDD/1000 OBD 95% CI [-12.5 to 5.5]; 123.4 daily vials of use/1000 OBD -0.9 [95% CI -9.6 to 7.8]).

Conclusion: CDSS implementation did not reduce the use of restricted injectable antibiotics measured in DDD or the locally developed estimated daily use of vials in PICU. Usage rates may have been affected by changes in PICU activity and patient characteristics.

4.2.2 Background

Inappropriate and excessive antimicrobial use can lead to ineffective treatment of infection, avoidable complications or adverse events that impact patient care, hospital resources and increase selective pressure, promoting antimicrobial resistance. (1)

Antimicrobial Stewardship (AMS) programs aim to maximise the clinical benefit of antimicrobial therapy while minimizing these consequences through one or more of a range of interventions, including antimicrobial restrictions, audit and feedback of prescribing, and provision of resources and tools to facilitate evidence based antimicrobial use. A core component of AMS is routine monitoring and reporting of process and outcome measures to identify areas for improvement and ensure strategies are safe and effective.(2) Antimicrobial drug utilisation data is widely recommended as a standard reporting measure, drug utilisation data are commonly used to identify patterns of use that are unexpectedly high and warrant further investigation by AMS teams or report reductions that may be attributed to AMS implementation.(3)

AMS strategies are now commonplace in hospitals and include high risk and vulnerable populations such as children admitted to intensive care. However, evidence to support AMS in these settings is still limited and the most effective and acceptable AMS strategies for paediatric intensive care units is not yet established.(4) One of the barriers to routine antimicrobial

drug utilisation monitoring for children's hospitals without patient level electronic records of medication use is a lack of validated metrics by which to standardise use. The World Health Organization's standard unit of measure, the defined daily dose (DDD) has not been validated for children as the daily estimates of use in grams are derived from maintenance doses for a 70-kilogram adult. As paediatric doses are dependent on patient weight or body surface area, there is no single defined daily dose that applies to all paediatric patients.(5)

This study assessed the impact of a structured AMS program on antibiotic use in a paediatric intensive care unit (PICU) that does not have access to patient level antimicrobial use data. The specific objective of the study was to assess the impact of a hospital-wide AMS policy and computerised decision support and approval system on the use of restricted antibiotics in PICU and report potential confounders related to antimicrobial use, hospital activity and clinical outcomes.

4.2.3 Methods

Study Design

This retrospective quasi-experimental study used interrupted time series analysis to assess the impact of a hospital-wide computerised antimicrobial approval and decision support system (CDSS, GuidanceMS, Melbourne Health, Australia) introduced in October 2012 on PICU antimicrobial utilisation rates.

Setting

The PICU services a 170-bed tertiary paediatric hospital in Sydney, New South Wales that provides specialty paediatric services including bone marrow and renal transplantation, oncology, cystic fibrosis and cardiac care. In addition, the PICU also provides post-surgical care to neonates transferred from a Neonatal Intensive Care Unit (NICU) located at an adjoining hospital for Women and Newborn Care.

Prior to implementation of the structured AMS program with CDSS most antimicrobials were available for use in PICU without any restriction. A select group of antimicrobials with broad-spectrum or associated with high-cost or risk of toxicity were classified as “ID approval only”, and were only released from the hospital pharmacy after approval by the infectious diseases team.

ID consultant-led stewardship rounds were conducted in the PICU twice weekly and involved face-to-face review of all PICU patients with PICU consultants. ID approval only antimicrobials were discussed and approved where appropriate during ward rounds; most restricted and unrestricted antimicrobials were freely available for ordering by PICU nursing staff and stored on the ward for use as needed.

AMS program implementation

The AMS program was implemented in October 2012 after extensive consultation and consensus building between May 2012 and October 2012 led by a paediatric infectious diseases consultant.

During the consensus building phase, formulary antimicrobials were classified into three categories “unrestricted”, “restricted” or “ID approval only”. Hospital guidelines and drug protocols were revised or created; standard hospital approved indications, dosage recommendations and approval durations were established for all restricted antimicrobials in conjunction with medical specialties and clinical pharmacists. All consensus-derived recommendations were ratified by the hospital Drug and Therapeutics Committee (DTC); restricted antimicrobial indications, corresponding dosage and frequency recommendations and an automatic-approval duration were programmed as CDSS algorithms. Additional content was linked to each algorithm to facilitate access to local and international management guidelines, infection control requirements and comprehensive medicines information.

Indications for use that did not align with the hospital’s approved CDSS indications generated an interim 24-hour CDSS approval whilst directing prescribers to empiric antimicrobial guidelines and paediatric medicines information resources. Extended use beyond the CDSS generated approval duration required discussion with the AMS team.

After implementation of the CDSS, all prescribers were required to obtain CDSS approvals before prescribing restricted antimicrobials. PICU imprest antimicrobials and nurse's authority to order and access restricted antimicrobials were unchanged post-intervention; antimicrobials supplied by the hospital pharmacy were supplied in limited quantities (up to 24 hours) for interim approvals, with larger quantities dispensed after approval was obtained. ID consultant-led wards rounds in PICU continued throughout the study period.

Data Source and Cleaning

Antimicrobial transactions for ATC codes J01, J02, J05, J04AB02 from 1 January 2010 to 30 October 2015 were extracted from the hospital pharmacy information system (iPharmacy®, CSC, Sydney, Australia). Unused antimicrobials returned to the hospital pharmacy from PICU were reconciled with the original month of supply; data entry errors were corrected after confirmation with pharmacy managers.

Antimicrobial supply records dispensed on discharge or for outpatient use were excluded as were antimicrobials for intrathecal, intravitreal, inhaled, oral and topical use, or where the route of administration could not be determined (colistin, gentamicin, tobramycin); erythromycin was excluded as it is used almost exclusively as a pro-motility agent in our PICU.

The remaining injectable formulations were categorised by antimicrobial restriction category (unrestricted, restricted or ID approval only) and the corresponding World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) code at the 3rd and 4th level of classification.(6) The total number of vials and corresponding vial sizes were aggregated to give monthly counts of use measured as WHO defined daily doses (DDD) 2016 and the estimated daily use of vials, a local estimate of daily use based on the usual maintenance dosage frequency for children (Table 4.3).

The hospital's health information unit provided for each PICU episode: the date of birth, discharge medical specialty, primary International Statistical Classification of Diseases and Related Health Problems, 9th edition 10th revision-Australian Modification (ICD-10-AM) code, hospital length of stay (LOS), PICU LOS and the National Weighted Activity Unit version 14 (NWAU). The NWAU is a standardised measure of use of healthcare resources, developed to compare services and activity across hospitals.(7)

Table 4.3 Restriction category and classifications for injectable antibiotics

Antibiotic (ATC code)	Restriction level[€]	WHO DDD 2016	Vial size	Recommended dose in mg/kg (max dose) dosage frequency[$^^]	Estimated daily use of vials (Min-Max grams[§])
Amikacin (J01GB06)	Highly restricted	1g	0.5g	1 month-10 years: 22.5mg/kg daily >10 years: 18mg/kg (1.5g) daily	1 (0.5g)
Ampicillin (J01CA01)	Unrestricted	2g	0.5g, 1g	25-50mg/kg (2g) 6-8 hourly	4 (2–4g)
Azithromycin (J01FA10)	Restricted	0.5g	0.5g	10mg/kg/day (500mg)	1 (0.5g)
Aztreonam (J01DF01)	Highly restricted	4g	1g	30-50mg/kg (2g) 6-8 hourly	3 (3g)
Benzathine penicillin (J01CE08)	Unrestricted	3.6g	0.9g	>20kg: 900mg <20kg: 450mg	1 (0.9g)
Benzylpenicillin (J01CE01)	Unrestricted	3.6g	0.6g, 1.2g	30-60mg/kg 4-6 hourly (1.2g - 2.4g)	4 (2.4–4.8g)
Cefalotin (J01DB03)	Unrestricted	4g	1g	25mg/kg (1g) 4-6 hourly OR, 50mg/kg (2g) 6 hourly	4 (4g)
Cefazolin (J01DB04)	Unrestricted	3g	1g	6.25-25mg/kg (1g) 6 hourly OR, 50mg/kg (2g) 8 hourly	3 (3g)
Cefepime (J01DE01)	Restricted	2g	1g, 2g	50mg/kg (2g) 8-12 hourly	2 (2–4g)
Cefotaxime (J01DD01)	Restricted	4g	0.5g, 1g, 2g**	25-50mg/kg (2g) 6-8 hourly	4 (2-8g)
Cefoxitin (J01DC01)	Highly restricted	6g	1g	20-40mg/kg (2g) 6-8 hourly	3(3g)
Ceftazidime (J01DD02)	Restricted	4g	1g, 2g	25-50mg/kg(2g), 8 hourly	3 (3–6g)
Ceftriaxone (J01DD04)	Restricted	2g	0.5g, 1g	50–75 mg/kg (2 g) once daily OR, 100 mg/kg (4 g) once daily OR 50 mg/kg (2 g) 12 hourly	1 (0.5–1g)
Ciprofloxacin (J01MA02)	Restricted	0.5g	0.1g, 0.2g	10mg/kg (400mg) 8-12 hourly	2 (0.2–0.4g)
Clindamycin (J01FF01)	Restricted	1.8g	0.3g, 0.6g	5-15mg/kg (600mg) 8 hourly	3 (0.9–1.8g)
Daptomycin (01XX09)	Highly restricted	0.28g	0.5g	1-2 years:10mg/kg daily 2-6 years: 9mg/kg daily 7-11 years: 7mg/kg daily 12-17 years: 5mg/kg daily[^^]	1 (0.5g)
Flucloxacillin (J01CF05)	Unrestricted	2g	0.5g, 1g	25mg/kg(1g) OR 50mg/kg (2g) 4-6 hourly	4 (2–4g)
Gentamicin (J01GB03)	Restricted>3 doses	0.24g	0.01g[$$], 0.08g	< 10 years: 7.5mg/kg (320mg) >10 years: 6-7mg/kg (560mg)	1 (0.08g)
Imipenem (J01DH51)	Highly restricted	2g	0.5g	15-25mg/kg (1g) 6 hourly	4 (2g)
Lincomycin (J01FF02)	Restricted	1.8g	0.6g	15 mg/kg (600 mg) 8 hourly	3 (1.8g)

Table continues on next page

Table 4.3 Restriction category and classifications for injectable antibiotics *cont.*

Antibiotic (ATC code)	Restriction level€	WHO DDD 2016	Vial size	Recommended dose in mg/kg (max dose) dosage frequency$^^	Estimated daily use of vials (Min-Max grams§)
Linezolid (J01XX08)	Highly restricted	1.2g	0.6g	1 month-12 years: 10mg/kg (600mg) 8 hourly; 12-18 years: 600mg 12 hourly	3 (1.8g)
Meropenem (J01DH02)	Restricted	2g	0.5g, 1g	20-40mg/kg (2g) 8-12 hourly	3 (1.5–3g)
Metronidazole (J01XD01)	Restricted >5 days	1.5g	0.5g	12.5mg/kg (500mg) 12 hourly OR 7.5mg/kg (500mg) 8 hourly	3 (1.5g)
Moxifloxacin (J01MA14)	Highly restricted	0.4g	0.4g	10 mg/kg (400mg) daily^^	1 (0.4g)
Piperacillin–Tazobactam (J01CR05)#	Restricted	14g	4g	100mg/kg (4g) 6-8 hourly	3.5 (14g)
Rifampicin (J04AB02)	Highly restricted	0.6g	0.6g	10-20mg/kg (600mg) daily	1 (0.6g)
Teicoplanin (J01XA02)	Restricted	0.4g	0.4g	10mg/kg (400mg) daily	1 (0.4g)
Ticarcillin-clavulanic acid (J01CR03)#	Restricted	15g	3g	50 mg/kg (3g) 4-6 hourly	5 (15g)
Tigecycline (J01AA12)	Highly restricted	0.1g	0.05	1.2 mg/kg (50mg) 12 hourly^^	2 (0.1g)
Trimethoprim-sulfamethoxazole (J01EE01)#	Restricted	20mL (16mg/mL)	5mL (160mg)	5-8mg/kg (320mg) 12 hourly	2 (10mL)
Vancomycin (J01XA01)	Restricted	2g	0.5g, 1g	15mg/kg (750mg) 6 hourly	4 (2g)

Abbreviations: DDD: World Health Organisation defined daily dose; g: Grams; Min: Minimum; Max: Maximum; WHO ATC: World Health Organization Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical classification

€Highly restricted agents require direct consultation with infectious diseases ("ID approval only")

$ Australian Medicines Handbook. Australian Medicines Handbook Children's Dosing Companion. Adelaide: *Australian Medicines Handbook Pty Ltd*.

§ Number of daily doses is the locally developed estimated daily use of vials, the alternate unit of measure for antimicrobial use outcomes in the study

^^Lexi-Comp AP Association. Lexi-Comp Online in *UptoDate*. Hudson, Ohio: *AP Association*, 2017.

#Dosage refers to piperacillin, ticarcillin or trimethoprim component only

Hospital activity

Monthly PICU occupied bed-days (OBD) were calculated including PICU episodes of exceeding 24 hours to standardise antimicrobial utilisation rates (DDD/1000 PICU OBD and estimated daily use of vials/1000 PICU OBD). To account for changes in the PICU patient population throughout the study period PICU OBD were calculated by primary ICD-10-AM categories and patient age.

Patient demographic and clinical factors and outcomes were extracted for each unique hospital stay of at least 24 hours that required admission to PICU for any period of time. A unique hospital stay was defined as a distinct combination of hospital stay number, episode start date and time, episode end date and time, the episode's mode of separation and NWAU.

Multiple PICU admissions throughout each unique hospital stay were aggregated and reported as the total PICU LOS for the entire stay and the proportion of the unique hospital stay spent in PICU (total PICU LOS/ hospital LOS, "proportion time in PICU"). These measures were chosen to avoid administrative discharge and readmissions to PICU. Episode separations for the purpose of code reassignment (e.g. for transition from acute care to rehabilitation) for the same patient were treated as unique hospital stays.

Patient factors and outcomes were summarised by the last date of PICU discharge and included: mortality rate (proportion of episodes resulting in death), total hospital LOS, total PICU LOS, proportion time in PICU and episode NWAU.

Statistical Analysis

Segmented regression analysis of interrupted time series was performed for restricted antimicrobial use and patient outcomes after reporting descriptive statistics. The pre-CDSS period (from 1 January 2010 to 30 October 2012) was compared to the CDSS period (from 1 January 2013 to 30 October 2015), allowing a two-month phase-in period that was excluded from analysis.

As described elsewhere, monthly outcomes were estimated using the segmented regression equation $Y_t = \beta0 + \beta*time_t + \beta*intervention_t + \beta*trend\ change_t + \varepsilon_t$ where β0 represents a baseline level, $\beta*time_t$ is the pre-intervention trend, $\beta*level_t$ the immediate impact of the intervention (the change between the month before and after the intervention) and β*trend-change, the *change* in trend after the intervention (8,9).

Linear regression was performed for continuous outcomes and beta-regression with bias correction for outcomes measured as proportions. Mortality risk was assessed by modelling the number of the deaths each month as a count outcome in a quasi-poisson regression model, thereby

allowing for over-dispersion; the number of PICU separations each month was added to the model as an offset term.

To account for potential seasonality, month and quarter terms were entered in each of the models and retained when statistically significant. Autocorrelation and heteroskedasticity in the residuals (ε_t) were examined in each of the models by visually inspecting the autocorrelation function (ACF) and partial autocorrelation function (PACF), together with Durbin-Watson and Breusch-Godfrey tests of up to 12 lags.(10) Residual plots (residuals vs time, histograms and quantile-quantile plots) were generated to assess model fit, Breusch-Pagan tests confirmed homoscedasticity. Confidence intervals were obtained from Newey-West robust standard errors and lags where indicated. Outliers that could not be confirmed as erroneous were retained in the analysis.(11)

Mann–Whitney *U* tests and Chi-square tests were additionally performed to compare continuous and categorical outcomes (respectively) pre- and post-CDSS.

Statistical analysis was performed in R Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 0.99.903 (RStudio Inc, Boston, United States). All tests were 2-tailed with p-values ≤0.05 considered significant.

Ethics

Approval was granted by the hospital Human Research Ethics Committee (LNR/16/SCHN/445) and ratified by the University of Technology Sydney.

4.2.4 Results

PICU Activity

There were 5038 separations that involved at least one admission to PICU throughout the study period. Mann-Whitney U tests of the pre- and post-CDSS outcomes indicated a substantial increase in overall PICU activity post-CDSS (Table 4.4). On average there were more PICU OBD and separations post-CDSS (median 355 vs 417 OBD and 66 vs 83 separations, p<0.001). PICU patients had a shorter overall hospital LOS post-CDSS (median 7 vs 6 days, p<0.001), but more time was spent in PICU (median proportion time in PICU 42% vs 55%, p<0.001; median hours in PICU 60.0 vs 65.0, p = 0.005).

After adjusting for seasonal variation interrupted time series analysis suggested the baseline median monthly PICU LOS was approximately 48 hours (95% CI 42.0 to 54.9) with a small but increasing trend pre-CDSS (0.29 hours per month (95% CI, -0.01 to 0.59). CDSS implementation coincided with an immediate increase in PICU LOS (7.9 hours, 95% CI 0.3 to 15.5). Post-CDSS there was a trend change of 0.72 hours each month (95% CI -1.09 to -0.35 hours per month) (Table 4.5).

Table 4.4 Paediatric Intensive Care Unit activity and patient factors

	Pre-CDSS	Post-CDSS	*P*-value§
PICU Occupied Bed-days	**11707**	**13427**	
OBD, median (IQR)	355 (319–374)	417 (345–437)	<0.001
Age, OBD (%)			
Neonate, %	13.5	12.5	0.017
Infant up to 6 years, %	64.4	64.0	0.527
6–12 years, %	11.7	11.3	0.295
12 years or older, %	10.1	11.9	<0.001
Primary ICD-10-AM classification*, *n* (%)			
Circulatory system (I)	102 (4.5)	79 (2.9)	0.002
Respiratory (J)	2859 (24.4)	4542 (33.8)	<0.001
Congenital malformations, chromosomal abnormalities (Q)	3139 (26.8)	2866 (21.3)	<0.001
Neoplasms (C)	836 (7.1)	889 (6.6)	0.104
Nervous system (G)	556 (4.7)	836 (6.2)	<0.001
Infectious Diseases (A)	504 (4.3)	653 (4.9)	0.035
Neonatal (P)	948 (8.1)	765 (5.7)	<0.001
Diseases of blood, blood forming organs and the immune system (D)	436 (3.7)	443 (3.3)	0.067
Separations, Total# (N=5038)	**2262**	**2776**	
Separations per month, median (IQR)	66 (61–73)	83 (77–89)	<0.001
Age, median years (IQR)	1 (0–7)	1 (0–6)	0.204
NWAU, median (IQR)	5.4 (3.0–9.9)	5.1 (3.1–9.2)	0.304
Total PICU LOS, median hours (IQR)**	60.0 (27–122)	65.0 (34–121)	0.005
Hospital LOS, median days (IQR,)	7 (4–13)	6 (3–11)	<0.001
Mortality, %	2.90	3.00	0.808
Proportion time in PICU^, median (IQR)	42% (21–72)	55% (28-85)	<0.001
Primary ICD-10-AM classification*, *n* (%)			
Circulatory system (I)	102 (4.5)	79 (2.8)	0.002
Respiratory (J)	611 (27.0)	1010 (36.4)	<0.001
Congenital malformations, chromosomal abnormalities (Q)	425 (18.8)	445 (16.0)	0.010
Neoplasms (C)	137 (6.1)	152 (5.5)	0.378
Nervous system (G)	172 (7.6)	206 (7.4)	0.806
Infectious Diseases (A)	79 (3.5)	107 (3.8)	0.498
Neonatal (P)	105 (4.6)	113 (4.1)	0.322
Diseases of blood, blood forming organs and the immune system (D)	98 (4.3)	93 (3.35)	0.069

ICD-10-AM: International Statistical Classification of Diseases and Related Health Problems, 9th edition 10th revision-Australian Modification; IQR: Interquartile range: LOS: Length of stay; OBD: Occupied bed-days; NWAU: National Weighted Activity Unit; PICU: Paediatric Intensive Care Unit;
§ *P*-value for categorical outcomes from Chi square test, *P*-value for continuous outcomes from Mann–Whitney U test;
#Pre-CDSS 1 January 2010- 30 October 2012, Post-CDSS: 1 January 2013-30 October 2015;
* Primary ICD-10-AM classification determined by first letter of ICD-10-AM code assigned to primary diagnosis;
**Total PICU LOS includes readmissions to PICU during the same unique hospital admission;
^ Proportion time in PICU is the proportion of the unique hospital admission spent in PICU (total PICU LOS/ hospital LOS)

Table 4.5 Interrupted time series analysis of patient factors before and after CDSS

	Model terms							
Outcome	Baseline Level (95% CI)	*P* value	Trend pre-CDSS (95% CI)	*P* value	Level change post-CDSS (95% CI)	*P* value	Trend change post-CDSS (95% CI)	*P* value
Mortality, *risk*[*]	0.03 (0.02 to 0.05)	<0.001	0.98 (0.97 to 1.01)	0.391	1.50 (0.71 to 3.23)	0.245	1.00 (0.97 to 1.03)	0.953
PICU LOS, *hours*[^]	48.51 (42.10 to 54.92)	<0.001	0.29 (-0.01 to 0.59)	0.055	7.93 (0.32 to 15.54)	0.041	-0.72 (-1.09 to -0.35)	<0.001
Discharge age, *years*[±]	2.18 (1.80 to 2.60)	<0.001	0.00(-0.02 to 0.01)	0.823	-0.36 (-0.88 to 0.16)	0.283	0.01 (-0.01 to 0.04)	0.505
NWAU[§]	5.29 (4.74 to 5.84)	<0.001	0.01(-0.01 to 0.03)	0.446	-0.36 (-0.90 to 0.19)	0.198	-0.02 (-0.05 to 0.01)	0.230

CI: Confidence Interval; LOS: length of stay; NWAU: National Weighted activity unit; PICU: Paediatric intensive care unit;

*Mortality risk and relative risk estimated from a quasi-poisson regression model, (95% CI of Newey-West robust standard errors lag = 2);

^PICU LOS linear regression model with Newey-West robust standard errors, lag = 1, adjusted for seasonality (April-June 6.4 hours [95% CI 0.25 to 12.55], *p* = 0.041; July-September 10.2 hours [95% CI 4.28 to 16.15], p=0.001; October-December 3.47[95% CI -3.45 to 10.40], *p* = 0.319);

±Discharge age linear model with Newey-West robust standard errors, lag = 0, adjusted for seasonality (April-June -0.6 years [95% CI -0.93 to -0.28], *p* = 0.009);

§NWAU linear model of median NWAU at last discharge from PICU, 95 % CI of Newey-West robust standard errors, lag=0;

Patient Age

Infants and children between 29 days up to 6 years old accounted for the vast majority of PICU OBD (64% pre- and post-CDSS, $p = 0.527$). Overall, PICU OBD by age varied most for the youngest and the oldest patients, with one percent reduction in neonatal PICU OBD (13.5% vs 12.5%, $p = 0.017$) and a 1.8% increase in OBD for patients 12 years or older (10.1 vs 11.9%) in the context of an increased total PICU OBD (Table 4.4).

Despite these differences the median age in years at discharge from PICU was no different between the two periods (1 year, IQR 0 to 7 vs 0 to 6 years old, pre- vs post-CDSS), interrupted time series analysis also did not uncover any statistically significant trends or level changes (Table 4.5).

Clinical Factors and Outcomes

Patients with primary diagnosis related to a respiratory illness accounted for a much larger proportion of PICU OBD and separations post-CDSS implementation, with an approximate increase of 9.4% (1683 OBD or 399 separations, $p<0.001$). Infectious diseases diagnostic codes were assigned to more OBD post-CDSS (4.3% vs 4.9%, $p = 0.035$), whilst OBD for malignancy, haematological or immune-related illness were similar in each period. Fewer PICU OBD were required for patients with congenital malformations, deformations and abnormalities post-intervention (-5.5%, 273 OBD; $p<0.001$).

On average, the NWAU assigned to PICU patients was similar pre-and post-CDSS (median NWAU 5.4 vs 5.1, $p = 0.304$). Likewise, the time series model's estimated baseline NWAU in January 2010 (median 5.29, 95 % CI 4.74 to 5.84) was largely unchanged throughout the study period.

Mortality was approximately 3% throughout the entire study period (2.9% vs 3.0%, p=0.808), the quasi-poisson model estimated a similar baseline risk of mortality (0.03 ,95% CI, 0.02 to 0.05), the pre-CDSS trend was similar (0.98 ,95% CI 0.97 to 1.01). However, the level change suggested a higher risk in the first month of the post-CDSS period (1.5, 95% CI 0.71 to 3.31, $p = 0.245$) that then returned to the pre-CDSS risk (1.0, 95% CI 0.97–1.03, $p = 0.953$) (Table 4.5).

Antibiotic Use

Restricted antimicrobial use measured in both DDD and estimated daily use of vials was significantly greater post-CDSS. On average, monthly DDD per 1000 OBD increased from 479.7 (IQR, 384.5–587.5) to 673.3 (IQR, 530.6–744.1), with a similar increase when measured as the estimated daily use of vials per 1000 OBD (530.3, IQR, 421.3–614.4 to 701.1, IQR 580.3–783.1).

In the post-CDSS period the PICU used more injectable azithromycin (median pre-CDSS vs post-CDSS, 3.0 vs 26.8), combination beta-lactam with beta-lactamase inhibitors active against *Pseudomonas* (median pre-

CDSS vs post-CDSS, 88.5 vs 130.89) and lincosamides (median pre-CDSS vs post CDSS, 16.1 vs 64.9). There were discrepancies between the two measure's estimates of combined cefotaxime and ceftriaxone use; when measured in DDDs use went from 176.5 DDD/1000 OBD each month (IQR, 111.8–210.1) pre-CDSS to 195.6 DDD/1000 OBD each month (IQR, 141.3–25.0) post-CDSS. However, when measured as the estimated daily use of vials median monthly use was similar in each period (median pre-CDSS vs post-CDSS, 211.2 [IQR 161.6–259.9] vs 215.9 [IQR 176.1–289.3]). The use of vancomycin was roughly the same in each period; differences in meropenem use were not significant (Table 4.6).

The increase in restricted antimicrobial use coincided with significant reductions in unrestricted antibiotic use; DDD declined in the post-intervention period once normalised for OBD (median unrestricted use in DDD/1000 OBD pre-CDSS vs post-CDSS, 370.8 vs 302.9; IQR 291.9–504.8 and 183.1–401.4 respectively). This was supported by the vial-based measure of use (Table 4.6). The post-CDSS decline was sizeable, and significant, for first generation cephalosporins, flucloxacillin and metronidazole in both DDD and estimated daily use of vials.

Table 4.6 Injectable antibiotic use in the PICU classified by AMS restriction category before and after CDSS implementation

Antibiotics and AMS restriction categories	Pre-CDSS, median **DDD** (IQR)	Post-CDSS, median **DDD** (IQR)	*P*-value*	Pre-CDSS, median **estimated daily use of vials** (IQR)	Post-CDSS, median **estimated daily use of vials** (IQR)	*P*-value*
Restricted Agents						
Total restricted agent use	152.4 (123.3 - 198.2)	255.0 (188.1 - 310.3)	<0.001	173.0 (139.5 - 214.0)	278.0 (201.5 - 333.4)	<0.001
Restricted agent use/1000 OBD	479.7 (384.5 - 587.5)	673.3 (530.6 - 744.1)	<0.001	530.3 (421.3 - 614.4)	701.1(580.3 - 783.1)	<0.001
Azithromycin	3.0 (0.0 - 26.2)	26.8 (13.5 - 42.7)	<0.001	3.0 (0.0 - 26.2)	26.8 (13.5 - 42.7)	<0.001
Cefotaxime and ceftriaxone**	176.5 (111.8 - 210.1)	195.6 (141.3 - 25.0)	0.041	211.21 (161.6 - 259.9)	215.86 (176.1 - 289.3)	0.264
Cephalosporins (*Pseudomonas* active)§§	0.7 (0.0 - 13.8)	0.9 (0 - 8.2)	0.979	0.9 (0.0 - 17.1)	1.19 (0.0 - 9.7)	0.886
Ciprofloxacin	0.0 (0.0 - 0.0)	0.0 (0.0 - 5.6)	0.214	0.0 (0.0 - 0.0)	0.0 (0.0 - 11.5)	0.22
Lincosamides	16.1 (0.0 - 44.6)	64.9 (42.8 - 90.7)	<0.001	20.4 (0.0 - 48.6)	71.51 (51.1 - 96.6)	<0.001
Meropenem	39.2 (12.7 - 84.5)	52.0 (31.7 - 100.3)	0.234	35.4 (9.23 - 83.6)	43.8 (31.0 - 93.6)	0.244
Combination beta-lactam + beta-lactamase inhibitor (*Pseudomonas* active)§	88.5 (68.3 - 111.2)	130.89 (96.0 - 159.4)	0.002	88.5 (68.31 - 111.2)	130.9 (96 - 159.4)	0.002
Trimethoprim-sulfamethoxazole	0.0 (0.0 - 3.3)	0.0 (0.0 - 11.0)	0.385	0.0 (0.0 - 1.5)	0.0 (0.0 - 22.1)	0.247
Glycopeptides	103.84 (63.0 - 128.1)	94.73 (70.45 - 122.1)	0.552	103.8 (63.0 - 128.1)	94.73 (70.5 - 122.1)	0.552
Unrestricted Agents						
Total unrestricted agent use	127.5 (95.2 - 179.8)	103.33 (66.3 - 157.3)	0.146	116.2 (90.0 - 144.3)	84.0 (62.2 - 142.8)	0.067
Unrestricted agent use/1000 OBD	370.8 (291.9 - 504.8)	302.9 (183.1 - 401.4)	0.019	333.3 (242.3 - 465.3)	271.0 (171.8 - 351.5)	0.008
Ampicillin	61.6 (36.8 - 92.7)	51.8 (14.5 - 93.1)	0.311	55.6 (32.0 - 70.5)	33.2 (12.8 – 63.0)	0.064
Benzylpenicillin	17.0 (0.0 - 30.5)	25.97 (9.3 – 56.0)	0.11	17.8 (0.0 - 35.1)	26.13 (11.6 - 53.6)	0.143
Cefazolin and cefalotin	133.5 (114.8 - 159.6)	113.8 (77.9 - 134.6)	0.017	133.5 (114.8 - 159.6)	113.8 (77.9 - 134.6)	0.017
Flucloxacillin	92.0 (44.6 - 142.8)	44.4 (11.9 - 88.6)	0.021	60.8 (28.4 - 94.2)	29.9 (9.7 - 48.1)	0.010
Metronidazole	66.0 (38.7 - 90.2)	29.2 (19.4 - 44.6)	<0.001	66.0 (38.7 - 90.2)	29.24 (19.4 - 44.6)	<0.001

Table continues on next page

Table 4.6 Injectable antibiotic use in the PICU classified by AMS restriction category before and after CDSS implementation *cont.*

Antibiotics and AMS restriction categories	Pre-CDSS, median **DDD** (IQR)	Post-CDSS, median **DDD** (IQR)	*P*-value*	Pre-CDSS, median **estimated daily use of vials** (IQR)	Post-CDSS, median **estimated daily use of vials** (IQR)	*P*-value*
ID Approval Only Agents^						
Total ID approval only agent use	0.0 (0.0 - 10.2)	0.0 (0.0 - 3.5)	0.222	0.0 (0.0 - 10.1)	0.0 (0.0 - 4.5)	0.190
ID approval only agent use/1000 OBD	0.0 (0.0 - 30.6)	0.0 (0.0-8.1)	0.185	0.0 (0.0 - 26.5)	0.0 (0.0 - 9.4)	0.151
Amikacin	0.0 (0.0 - 10.6)	0.0 (0.0 - 0.0)	0.057	0.0 (0.0 - 21.2)	0.0 (0.0 - 0.0)	0.057

AMS: Antimicrobial Stewardship; CDSS: Computerised decision support and approval system; CI: Confidence Interval; DDD: World Health Organization adult defined daily dose; IQR: Interquartile range; OBD: Occupied bed-days; PICU: Paediatric Intensive Care Unit

*Mann–Whitney U test of use Pre-CDSS 1 January 2010 to 30 October 2012, Post-CDSS 1 January 2013 to 30 October 2015

§ Cephalosporins (*Pseudomonas* active): cefepime, ceftazidime; combination beta-lactam + beta-lactamase inhibitor (*Pseudomonas* active): piperacillin-tazobactam and ticarcillin-clavulanic acid

^ID approval only agents used during study not listed in table: tigecycline and moxifloxacin (pre-intervention only); cefoxitin, daptomycin, imipenem, rifampicin (post intervention only). Linezolid total DDD/1000 occupied bed-days pre-CDSS vs post-CDSS 194.8 vs 258.6 in 8 vs 7 months of pre- and post-CDSS periods) All ID approval only agents are included in total ID approval only agent use and ID approval only agent use/1000 occupied bed-days.

Antibiotics classified as ID approval only were used infrequently throughout both periods; the PICU did not use any ID approval only antibiotics in 18 (53%) and 23 (68%) of the months in the pre- and post-CDSS periods respectively. Amikacin was the most common ID approval only agent used pre-intervention, and it appeared to be used less frequently in the post-CDSS period (10 months of use vs 4 months of use) and smaller quantities during those months.

Total restricted antibiotic DDD and estimated daily use of vials adjusted for OBD demonstrated marked month-to-month variation, with no evidence of seasonality; the units of measure gave different estimates of the baseline level (467.6 DDD/1000 OBD vs 517.5 estimated daily use of vials/1000 OBD), the pre-CDSS trend was almost identical using the two measures (DDD vs estimated daily use of vials 1.1 vs 1.0 [95% CI -5.1 to 7.4 DDD 1000 OBD vs -5.0 to 7.2 estimated daily use of vials/1000 OBD]). The two units of measure gave different estimates of use post-CDSS, with more pronounced shift in level when reported as DDD, 178.8 (95% CI 7.7 to 350.1) compared to 123.4 estimated daily use of vials (95% -42.6 to 289.3). Though neither measure reported a statistically significant trend change after CDSS was implemented both were negative and suggested the immediate rise in use was not sustained long term (Table 4.7**)**. Review of the regression models and plots of actual use suggested an upward trend in restricted antibiotic use in the months before CDSS implementation (Figure 4.5 and Figure 4.6).

Table 4.7 Interrupted time series of restricted injectable antibiotics in the PICU before and after CDSS implementation

	Model terms							
Outcome	Baseline Level (95% CI)	*P*-value	Trend Pre-CDSS (95% CI)	*P*-value	Level Change Post-CDSS (95% CI)	*P*-value	Trend Change Post-CDSS (95% CI)	*P*-value
All restricted agents								
DDD/1000 OBD	467.6 (341.1 to 594.2)	<0.001	1.1 (-5.1 to 7.4)	0.720	178.8 (7.7 to 350.07)	0.041	-3.5 (-12.5 to 5.5)	0.439
Daily vials/1000 OBD	517.5 (394.7 to 640.5)	<0.001	1.0 (-5.0 to 7.2)	0.723	123.4 (-42.6 to 289.3)	0.142	-0.9 (-9.6 to 7.8)	0.837
	Baseline Level (95% CI)	*P*-value	Trend Pre-CDSS (95% CI)	*P*-value	Level Change post-CDSS (95% CI)	*P*-value	Trend change post-CDSS (95% CI)	*P*-value
Restricted agents as a proportion of total antibiotic use‡								
DDD	0.039 (-0.30 to 0.38)	0.800	0.007(-0.01 to 0.02)	0.335	0.066 (-0.25 to 0.52)	0.763	0.01 (-0.01 to 0.04)	0.194
Daily vials	0.19 (-0.04 to 0.42)	0.082	0.005 (-0.01 to 0.02)	0.306	0.003 (-0.29 to 0.29)	0.987	0.02 (0.00 to -0.04)	0.035
	Baseline Level (95% CI)	*P*-value	Trend Pre-CDSS (95% CI)	*P*-value	Level Change post-CDSS (95% CI)	*P*-value	Trend change post-CDSS (95% CI)	*P*-value
Cefotaxime and ceftriaxone								
DDD/1000 OBD	153.73 (114.2 to 193.2)	<0.001	0.46 (-1.65 to 2.56)	0.663	91.4 (23.4 to 159.4)	0.009	-2.99 (-6.2 to 0.21)	0.069
Daily vials/1000 OBD	206.0 (164.5 to 247.5)	<0.001	0.30 (-2.1 to 2.7)	0.800	46.9 (-29.1 to 122.9)	0.222	-1.20 (-4.9 to 2.5)	0.516
	Baseline Level (95% CI)	*P*-value	Trend Pre-CDSS (95% CI)	P-value	Level Change post-CDSS (95% CI)	*P*-value	Trend change post-CDSS (95% CI)	*P*-value
Pseudomonas* active restricted agents*								
DDD/1000 OBD	192.3 (109.30 to 275.25)	<0.001	-1.6 (-5.6 to 2.52)	0.455	147.5 (37.3 to 257.7)	0.010	-1.6 (-7.5 to 4.33)	0.600
Daily vials/1000 OBD	187.31 (112.7 to 261.8)	<0.001	-1.47 (-5.1 to 2.2)	0.434	151.4 (52.4 to 250.4)	0.003	-2.2 (-7.6 to 3.1)	0.415

AMS: Antimicrobial Stewardship; CDSS: Computerised decision support and approval system; CI: Confidence Interval Daily vials: Estimated daily use of vials; DDD: World Health Organization adult defined daily dose; OBD: Occupied bed-days; PICU: Paediatric Intensive Care Unit

**Meropenem, piperacillin-tazobactam, ticarcillin-clavulanic acid, ceftazidime, cefepime, ciprofloxacin

‡ Total injectable antibiotic use, beta-regression model selected according to best fit determined by likelihood ratio test

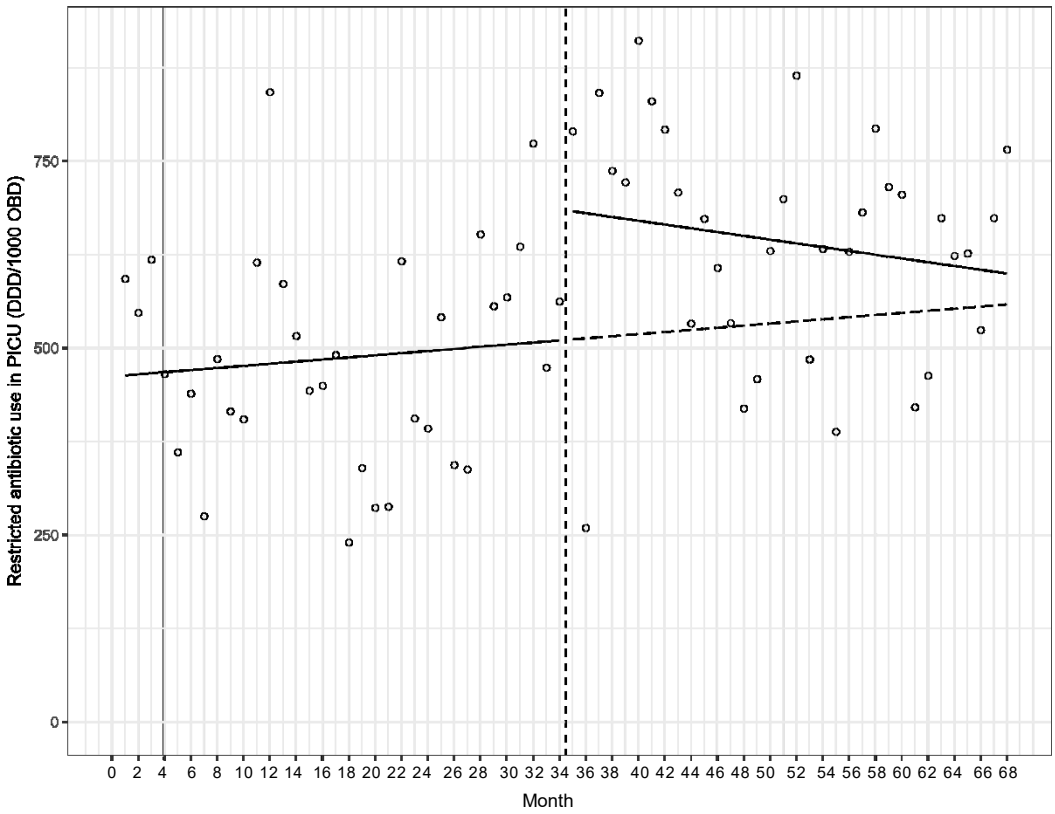


Figure 4.5 Injectable restricted antibiotic use measured in adult defined daily doses in PICU . DDD: World Health Organization adult defined daily dose; OBD: Occupied bed-days; PICU: Paediatric Intensive Care Unit. Solid line is obtained from the fitted model, dashed line is the projected outcome without the intervention (vertical line); See Table 4.7 for statistically significant terms.

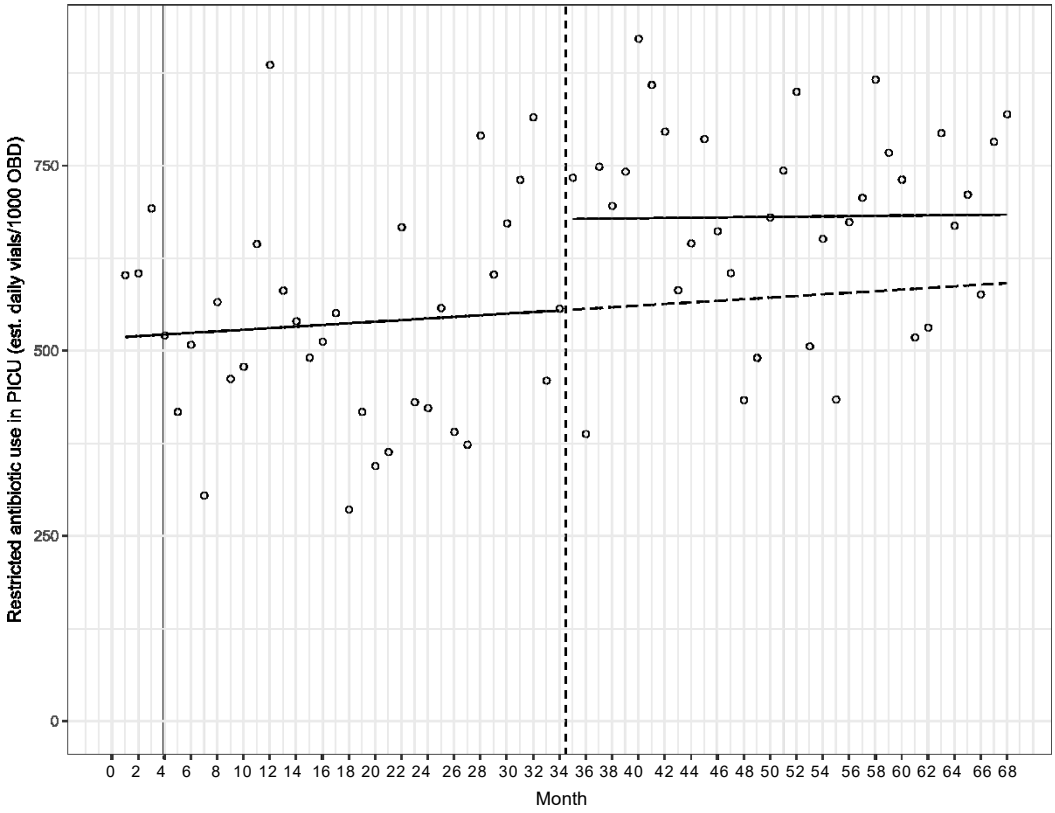


Figure 4.6 Injectable restricted antibiotic use measured in estimated daily use of vials in PICU. est daily vials: Estimated daily use of vials; OBD: Occupied bed-days; PICU: Paediatric Intensive Care Unit. Solid line is obtained from the fitted model, dashed line is the projected outcome without the intervention (vertical line); See Table 4.7 for statistically significant terms.

In order to assess restricted antibiotic use in relation to overall antibiotic use we performed the interrupted time series analysis on restricted antibiotic use as a proportion of total PICU injectable antibiotic use (sum of unrestricted, restricted and ID approval only antibiotics); both DDD (Figure 4.7) and estimated daily use of vials (Figure 4.8) provided weak evidence to suggest a tendency toward more restricted antibiotic use over time.

Restricted antibiotics active against *Pseudomonas* estimated a baseline monthly DDD of 192.3 (95% CI 109.3 to 275.2, $p<0.001$) with a declining trend pre-CDSS (pre-trend -1.6, 95% CI -5.6 to 2.5, $p = 0.455$) and a statistically significant level change of 147.5 DDD/1000 OBD (95% CI 37.3 to 257.7) and a subsequent trend-change post-CDSS of -1.6 (95% CI -7.5 to 4.3), similar patterns were observed when measured as estimated daily use of vials/1000 OBD (Table 4.7).

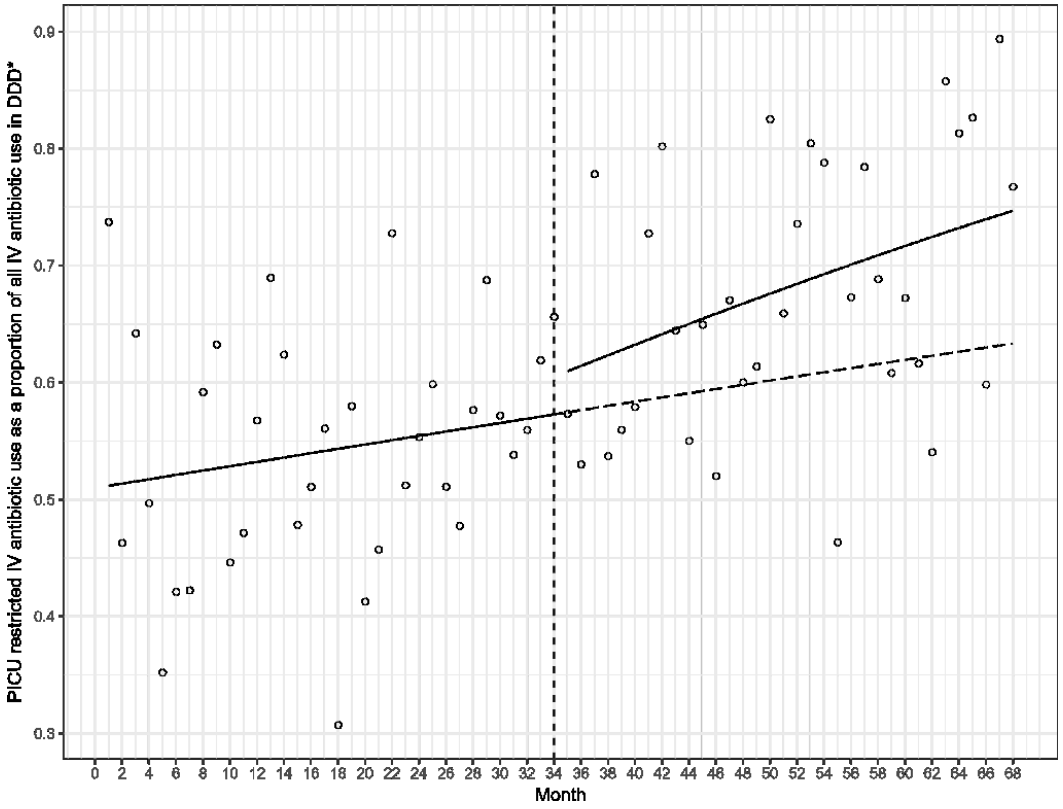


Figure 4.7 Restricted antibiotics as a proportion of total injectable antibiotic use measured in adult defined daily doses in PICU. DDD: World Health Organization adult defined daily dose; PICU: Paediatric Intensive Care Unit; Solid line is obtained from the fitted model, dashed line is the projected outcome without the intervention (vertical line). See Table 4.7 for statistically significant terms.

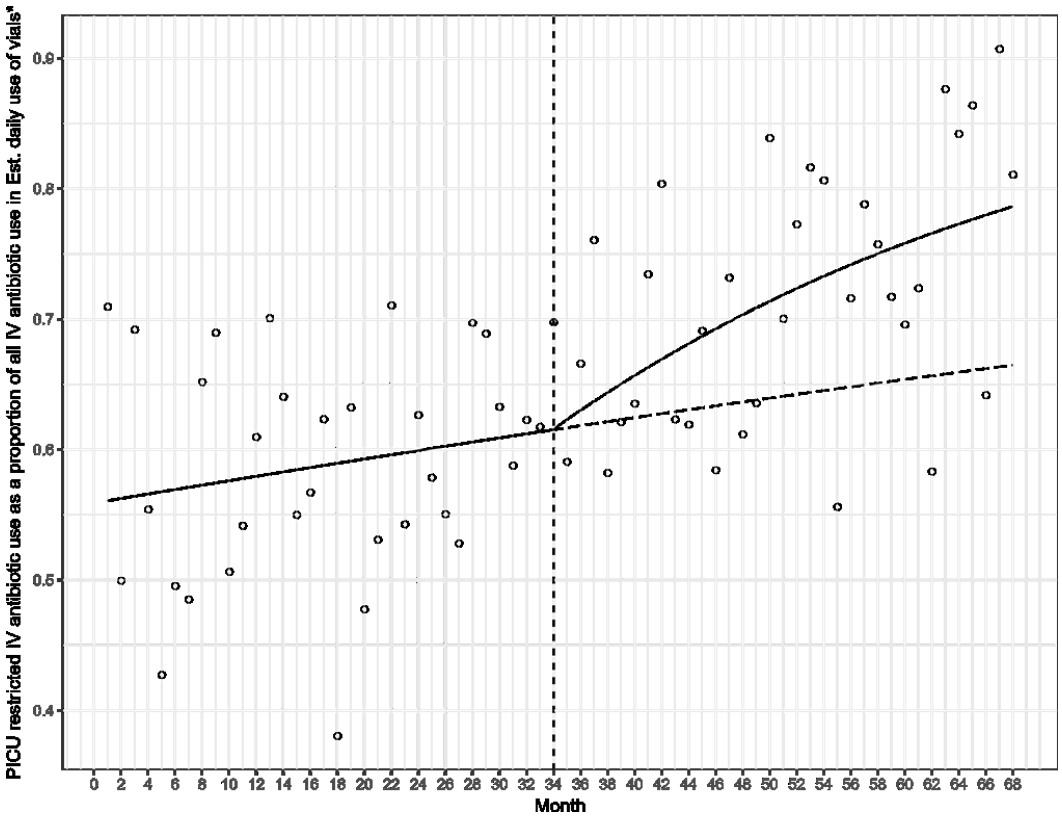


Figure 4.8 Restricted antibiotics as a proportion of total injectable antibiotic use measured in estimated daily use of vials in PICU. Est. daily use of vials: Estimated daily use of vials; PICU: Paediatric Intensive Care Unit. Solid line is obtained from the fitted model, dashed line is the projected outcome without the intervention See Table 4.7 for statistically significant terms.

4.2.5 Discussion

This study describes the changes in antibiotic use after introduction of a structured AMS program facilitated by a CDSS in the context of a PICU without access to patient level medication use data. Overall the findings this study provided suggest selected restricted antibiotics were used more frequently after CDSS implementation whilst the use of unrestricted antibiotics declined. Interrupted time series analysis added a different dimension to assessment and suggested the higher average usage identified in the before and after assessment might be attributed to an immediate rise in use. Despite suboptimal fit of the individual terms in the beta-regression models there was an indication that restricted antibiotics were increasingly favoured, either appropriately or inappropriately.

The combination of patient factors and PICU activity reported in this study are an indication of the multiple and varied factors that may influence antimicrobial use. Throughout the study period, there were more unique episodes with time in PICU and more PICU occupied bed days post-CDSS, with more respiratory diagnoses assigned to hospital stays that required admission to PICU and PICU occupied bed-days. The level-change reported from our analyses suggest implementation may have coincided with a longer LOS and a higher than usual mortality risk (though this was not significant) together with a rise in antimicrobial use. This highlights one of the limitations of using ward-level data to monitor antimicrobial usage trends without knowledge of the patients, indications and doses used. Even

where this information is accessible from comprehensive electronic records, there is no validated method to adjust for patient factors, and there are mixed views as to whether clinical outcomes should be reported as indicators for individual AMS programs. (12)

This study has a number of other limitations. Antimicrobial use was obtained from pharmacy records that combined orders by nurses as well as individual patient dispensing by pharmacists. Therefore, antibiotics may have been ordered and left unused for extended periods. Furthermore, we used administrative codes assigned after separation from hospital that do not reflect the working diagnosis at admission when a child's symptoms may be non-specific. (13) Similarly, the NWAU is a combination of factors that are non-specific to infectious diseases or the severity of illness. In addition to patient factors, the analysis of antibiotic use was influenced by unstable patterns of smaller cefotaxime vials (0.5 grams) that were later discontinued. This was further complicated by an extended cefotaxime shortage that resulted in a single month during which no cefotaxime was supplied to PICU and intermittent use of larger cefotaxime vials (2 grams) that had not previously been supplied to the PICU. Whilst the latter appeared to affect outcomes based on DDD, the estimated daily use of vials was unaffected as the dosage frequency was unchanged. The inclusion of a shortage term in the interrupted time series model did not consistently change the reported outcomes, likely due to the compensatory use of other antibiotics during this period, and so we chose not to include

the outlier term in our analysis. However, we cannot rule out the potential impact on drug distribution practice in the lead up to, and during, the shortage. Finally, this study does not include any process related outcomes to differentiate between inappropriate, excess use and clinically appropriate use which is fundamental when evaluating multifaceted interventions.

4.2.6 Conclusion

Introduction of a hospital-wide CDSS did not reduce the use of restricted antibiotics in an Australian PICU without access to electronic patient medical use data. CDSS implementation coincided with marked changes in PICU activity, and changes in individual patient factors that may have led to higher rates of antimicrobial use.

4.2.7 References

1. MacDougall C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. Clin Microbiol Rev 2005;18(4):638-56.
2. Pollack LA, Srinivasan A. Core Elements of Hospital Antibiotic Stewardship Programs From the Centers for Disease Control and Prevention. Clin Infect Dis. 2014;59(supplement 3):S97–100.
3. 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.
4. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in children: a systematic review. J Hosp Infect 2018;99(2):117-23.
5. Irwin A, Sharland M. Measuring antibiotic prescribing in hospitalised children in resource-poor countries: A systematic review. J Paediatr Child Health 2013;49(3):185-92.
6. World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) :Structure and principles. [Internet] Oslo: Norwegian Institute of Public Health; 2016; Available from: http://www.whocc.no/atc/structure_and_principles/
7. Independent Hospital Pricing Authority. Technical Specifications

2014 - 2015. Sydney2014;

8. Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. J Antimicrob Chemother 2003;52(5):842-8.
9. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. J Antimicrob Chemother 2003;52(5):764-71.
10. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol 2017;46(1):348-55.
11. Jandoc R, Burden AM, Mamdani M, Lévesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol 2015;68(8):950-6.
12. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES, et al. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis 2017;64(3):377-83.
13. Bowes J, Yasseen III AS, Barrowman N, Murchison B, Dennis J, Moreau KA, et al. Antimicrobial stewardship in pediatrics: focusing on the challenges clinicians face. BMC Pediatr 2014;14(1):212.

CHAPTER FIVE

DISCUSSION

5 DISCUSSION

This thesis research evaluated a structured AMS program facilitated by a CDSS in a tertiary paediatric hospital that provides medical and surgical services for neonates, infants, children and adolescent patients including those with rare and complex conditions. As outlined in section 1.4 paediatric prescribing is inherently error-prone and supported by lower levels of evidence. Like adults, paediatric patients may experience unwanted adverse effects, such as opportunistic infections such as CDI and are not immune to the effects of antimicrobial resistance. Despite these facts, there is a paucity of data on paediatric-specific AMS interventions and antimicrobial drug utilisation in Australia.

Overall, the separate studies in this thesis suggest deficiencies in the planning and implementation of AMS which may have been avoided by more rigorous pre-implementation assessments of the local medication distribution systems, staffing levels (across disciplines and within the AMS team), key stakeholders, and IT infrastructure as well as the capacity of the CDSS to perform a set of expected day-to-day and longer term AMS functions. That is, as an intervention to guide clinical decision-making, identify and track patients for AMS review and report on process-related trends.

The following chapter summarises each of the studies, followed by a discussion of the implications and limitations of the research.

5.1 Overview of findings

Chapter 2 of this thesis assessed the use of CDSS as an AMS intervention to support clinical decision-making by prescribers and to track restricted antimicrobial use, as part of audit and feedback processes by the AMS team.

In the retrospective study presented in subchapter 2.1, cases of patients admitted to hospital with a presumed diagnosis of uncomplicated pneumonia were tracked for compliance with the pre-existing guideline that recommends the use of narrow-spectrum penicillins over broad-spectrum third-generation cephalosporins (the latter being regarded as unnecessary and associated with adverse outcomes such as CDI). Community-acquired pneumonia is one of the main drivers of antimicrobial overuse in children's hospitals, and among the diagnoses that most often warrant an AMS recommendation.(1) Community-acquired pneumonia was selected specifically as a focus of this study after it was identified as a specific target syndrome for AMS programs in both consensus-based and national AMS guidelines (Section 1.6 Introduction). When prescribing for infants and children at admission, diagnostic uncertainty, prescriber concerns around clinical deterioration, and the inconvenience of more frequent intravenous administration of narrow-spectrum agents, suggest that broad-spectrum third-generation cephalosporins were likely to be over-used. However, this study revealed high rates of guideline-concordant prescribing at admission prior to CDSS implementation, with no discernible variation in empiric

broad-spectrum third generation cephalosporin use after CDSS implementation. Any reported gains would not have been attributed to CDSS as there were no instances of restricted antimicrobial approval among study patients. This finding suggests that CDSS was not used at the time of clinical decision-making and did not track the use of restricted agents, as was originally intended.

The second study in this chapter tracked CDSS compliance when antimicrobials were prescribed in the after-hours context, i.e., after standard AMS and pharmacy operating hours. The specific aim was to identify factors associated with AMS adherence when alternate antimicrobial supply methods were utilised, and the subsequent impact on AMS actions the next standard working day. This study reinforced the finding of the study presented in Section 2.1. CDSS compliance at the time of initial drug acquisition was poor. Of greater concern is that approximately half the restricted antimicrobial drug acquisitions for patients who remained in hospital were continued beyond the next standard working day without any documented CDSS approval, nor interaction with the AMS team. No differences were identified between wards with or without routine access to antimicrobials that were classified as being restricted, and prior requests by pharmacists to prescribers to obtain approval were not associated with an increased likelihood of CDSS approval.

Chapter 3 determined the education requirements of nursing and medical staff for paediatric AMS. Sub-study 3.1 assessed knowledge of AMS and safe paediatric prescribing with a focus on antimicrobials among non-consultant level medical staff (JMOs) with varying paediatric experience. Paediatric prescribing is inherently error-prone, and, therefore, clear documentation, correct dose calculation and dosage capping, and age-appropriate antimicrobial selection are required to prevent delays in therapy. As previously described (Section 1.4.1), there are substantial practice differences across different paediatric sites when prescribing high risk antimicrobials, making adequate assessment and education an important stewardship activity. JMOs who participated in this voluntary survey demonstrated excellent knowledge of the requirements for adverse drug reaction documentation, principles of appropriate antimicrobial prescribing and awareness of AMS. However, this knowledge was not translated to practice and, despite strong support from the Junior Medical Unit and feedback to JMOs from their direct supervisors, there were no substantial improvements in prescribing practices.

Section 3.2 revealed a willingness among nurses to participate in AMS as patient advocates and educators, with a central role in infection control. Respondents working in adult hospitals tended to view AMS more favourably than paediatric nurses, and more often indicated that the nurse's role in AMS involves checking restriction and approval status. Most nurses indicated they would not intentionally bypass AMS, expressed a willingness

to receive education and training on AMS and question inappropriate prescribing. Self-rated knowledge of antimicrobials among nurses suggests greater education and training may be required for nurses to confidently perform AMS roles.

Chapter 4 returned to the CDC elements of tracking and reporting. Shifting from CDSS utilisation (Chapter 2) to focus on tracking and reporting antimicrobial drug use with hospital pharmacy supply data, as is done in most adult hospitals in Australia. Lack of standard, acceptable antimicrobial use measures continue to be a major barrier to tracking and reporting antimicrobial use in those paediatric hospitals without access to patient level electronic records, and therefore limits opportunities for AMS programs to intervene and improve antimicrobial use.

Section 4.1 explored the use of two vial-based measures. The estimated daily use of vials was determined by the usual dosage frequency for infants and children, without accounting for weight-based differences. A second measure, the age-adjusted daily use of vials incorporated PICU occupied bed days for each age and minimum daily vial requirements for each age, thereby providing a crude estimate of the proportion of drug wasted when preparing antimicrobial doses for neonate, infants, children and adolescent patients that required partial or multiple vials. Bland-Altman plots displayed agreement between each of the measures and adult DDD. Linear regression analysis was performed to measure the mean difference as a

function of the averages, as recommended by Bland and Altman. A third measure that did not account for wastage was reported to demonstrate the need to account for the discarded portion of the vial. The study identified broad-spectrum, restricted antimicrobials that required no adjustment for children in our local setting, and which may therefore be suitable for antimicrobial surveillance locally (as markers of use), and contribute to NAUSP.

The findings from Chapter 4.1 were applied to Chapter 4.2 to track antimicrobial utilisation before and after CDSS implementation using interrupted time series with segmented regression analysis and a conventional before and after technique. In the before-and-after analysis of the most commonly used antimicrobials it was evident that azithromycin, clindamycin and broad-spectrum antibiotics active against *Pseudomonas spp.,* (predominantly combined beta-lactam beta-lactamase antibiotics) were used more often post-CDSS implementation, whilst unrestricted antibiotic use generally declined. The quasi-experimental design employed in this study did not identify any reductions in broad-spectrum restricted antibiotics that may be attributed to the implementation of CDSS, even after inclusion of age- and diagnosis-related occupied bed days and antibiotic shortages were entered in each of the models as explanatory variables.

5.2 Limitations

The methodological limitations of the individual studies are outlined within each of the manuscripts that form Chapters 2, 3 and 4. As previously stated in Section 2.1, a major limitation of our evaluation of CDSS impact on CAP was the use of published overseas data for our power analysis which vastly overstated the extent of inappropriate prescribing compared with our local hospital. Additionally, there were no internal prospective audits undertaken to confirm that the selected ICD-10-AM codes selected would identify patients with uncomplicated CAP. Similarly, the PICU patient factors monitored in Section 4.2 were sourced from the hospital's health information unit and did not capture the true sickness severity of patients.

The use of a self-administered questionnaire to examine nurses perceptions of AMS (section 3.2) and the limited number of responses are notable and potentially compounded by the lack of information available in regard to the roles and qualifications held by the nurses within the sampling frame and general nursing population.(2) Self-administered questionnaires are subject to potential non-response error due to self-selection, whereby those with pre-existing knowledge or interest may be more willing to participate.(2,3) Therefore, nurses without prior knowledge of AMS or a lack of interest may have chosen not to take part despite attempts to encourage participation by sending reminders.(3) These limitations are reflected in the recommendations future research (Section 5.5).

Overall, a potential limitation of this thesis research is the specific focus on process and operational measures which may be considered less significant than the expected outcomes of AMS.(4) That is, clinical and/or health outcomes, antimicrobial resistance, adverse events such as CDI, and a reduction in healthcare costs. As this thesis was conducted in our local hospital, it complements the current evaluation framework (Chapter 1, Section 1.6.2). A number of obstacles prevented more comprehensive evaluation of these measures and are reflected in the suggestions listed in Section 5.4.

5.3 Adapting to a multidisciplinary model for antimicrobial stewardship

Nurses were identified as having an independent role in the supply of restricted antimicrobials in the studies presented in Sections 2.2 and 4.2, but were hesitant to perform the tasks normally expected of pharmacists when supplying restricted antimicrobials, such as checking for antimicrobial approval (Section 3.2). These findings raise a number of questions with respect to delineating AMS roles, and whether responsibilities should be assigned to a discipline or to the function needed to be performed. In the local study hospital there were no direct AMS responsibilities assigned to ward nurses, creating a degree of ambiguity.

Prior stewardship guidelines and descriptions of AMS teams are based on IDSA guidelines,(5,6) being focused primarily on prescribers and

pharmacists; whilst the role of the nurse is increasing discussed, there remain few examples of nursing involvement in paediatric AMS programs as reported in Section 1.7.

In this context, pharmacists, who represent only a small proportion of the overall clinical workforce when compared to medical and nursing professions, are tasked with the responsibility of identifying the use of restricted antimicrobials without CDSS approval, generating CDSS alerts (aptly named “pharmacist alerts” in our CDSS), and contacting prescribers to request that CDSS approval be sought, thereby taking on a “policing role”,(7) whilst having only partial authority over access to these agents. As demonstrated in Section 2.2, the strategies assigned to the pharmacy department (i.e., the aforementioned requests for approval and location-based restriction) did not translate to an increased likelihood of AMS compliance. This is consistent with research conducted in other Australian hospitals; nurses and pharmacists describe mechanisms by which nursing staff circumvent antimicrobial restrictions. (8,9).

The multiple and varied roles of nurses highlighted in chapters 1 (Table 1.1), 2 (Section 2.2) and 4 (Section 4.2) identify nurses as key stakeholders in AMS, and the engagement of this large and ever-present workforce is vital.

5.4 Need for comprehensive and adaptable electronic tools to facilitate AMS

This thesis research prompted a critical review of the CDSS as a tool for systematic tracking and reporting of AMS activity and antimicrobial use. As reported by others, currently available stand-alone CDSS platforms cannot guard against prescribers misrepresenting the intended indication to obtain approval and remains somewhat voluntary.(9) The quality of documentation among the different CDSS *approvers* in our studies has also been variable (e.g., some did not document an indication at all in the CDSS or did not consistently enter approvals), a challenge also identified in other AMS research conducted in the Australian hospital setting.(10)

Flexible solutions capable of local adaptation are needed to facilitate AMS in the Australian hospital setting. This thesis research highlights that specific adaptations and resource investments that should be considered when investing in electronic systems.

- Systems should recognise the role of nurses as prescribers and independent suppliers of restricted agents, giving nurses equal access to CDSS (just as for doctors and pharmacists) when performing similar functions.

- Shift focus from day-to-day approval and tracking to support reporting aspects of AMS activity such as documenting the number

of patients that are reviewed, assessments of appropriateness, recommendations provided, and information about the most acceptable interventions.

- Resources should be made available to integrate dispensing systems, electronic medical records, paging and electronic mail.

5.5 Future research

The individual studies within each of the manuscripts that form Chapters 2, 3 and 4 highlight areas of future research. A number of findings in this compilation of research warrant further exploration.

The exploratory work performed in defining paediatric measures for tracking and reporting antibiotic utilisation from pharmacy supply data by assigning “usual” doses, average daily vial requirements and applying age-adjustment to OBD, provide valuable input into the development and evaluation of paediatric antimicrobial utilisation measures. Future studies should be carried out to assess the validity and utility of vial-based paediatric measures and DDD from pharmacy supply data against records of actual use. The extent to which staff workarounds, as highlighted in this research, impact tracking and reporting should additionally be considered.

Considerably more work will need to be done to adapt to a multidisciplinary model for AMS and identify most effective roles for pharmacists and nurses.

Future studies focusing on the perceptions of nurses in clinical, education and administration roles, are advisable to ensure the views of each of these groups are adequately represented. These initial findings may be progressed by analysing current and future education strategies for nurses.

It is anticipated that the implementation of electronic prescribing and administration records at the study hospital will substantially enhance the tracking and reporting deficiencies identified in this Thesis research. Despite the relative abundance of paediatric AMS studies that utilised EMR-driven AMS strategies, experience in the Australian context is scarce but essential to ensuring the most efficient and effective AMS strategies are identified within this new medication management system.

6 CONCLUSION

Antimicrobial resistance is a global threat, that requires stewardship of the antimicrobials currently available. Effective AMS programs share core elements that enable AMS programs to track, report and act to optimise antimicrobial use. This thesis research identified current barriers to effective AMS and provides suggestions by which they may be overcome.

APPENDICES AND BIBLIOGRAPHY

7 APPENDICES

APPENDIX A: ETHICS APPROVAL (Section 2.1)

The Sydney children's Hospitals Network
care, advocacy, research, education

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ABN 53 188 579 090

2 November 2016

Ms Mona Mostaghim
Clinical Pharmacology
Sydney Children's Hospital, Randwick

Dear Ms Mostaghim,

HREC Reference: **LNR/16/SCHN/398**

Project title: **Impact of Antimicrobial Stewardship on Third Generation Cephalosporin use in Paediatric Community Acquired Pneumonia**

Sites: **Sydney Children's Hospital, Randwick**

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive Committee ("the Committee") at its meeting **31 October 2016**.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the Committee has granted ethical approval of this research project. Your approval is valid for one (1) year, effective the date of this letter.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

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The Sydney children's Hospitals Network

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The documents reviewed and approved by the Committee are:

Document Reviewed	*Version*	*Date*
LNR Submission Code, AU/6/AD99212		22 October 2016
CAP Data Collection Tool		Received 25 October 2016
AMS and 3rd Generation Cephalosporin in pCAP Study Protocol		Received 25 October 2016

Please note the following conditions of approval:

1. This approval is restricted to research being conducted in accordance with the approved documents, and the review of the medical records you have nominated. There is to be no contact with patients, parents/guardians or other family members.

2. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

3. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

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

5. The co-ordinating investigator will provide a final report to the HREC on completion of the study.

6. Your approval is valid for one (1) year from the date of the final approval letter. If your project extends beyond that one year period please submit an application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

7. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

Production Note:
Signature removed prior to publication.

Dr Peter Cooper
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee
Sydney Children's Hospitals Network Human Research Ethics Committee

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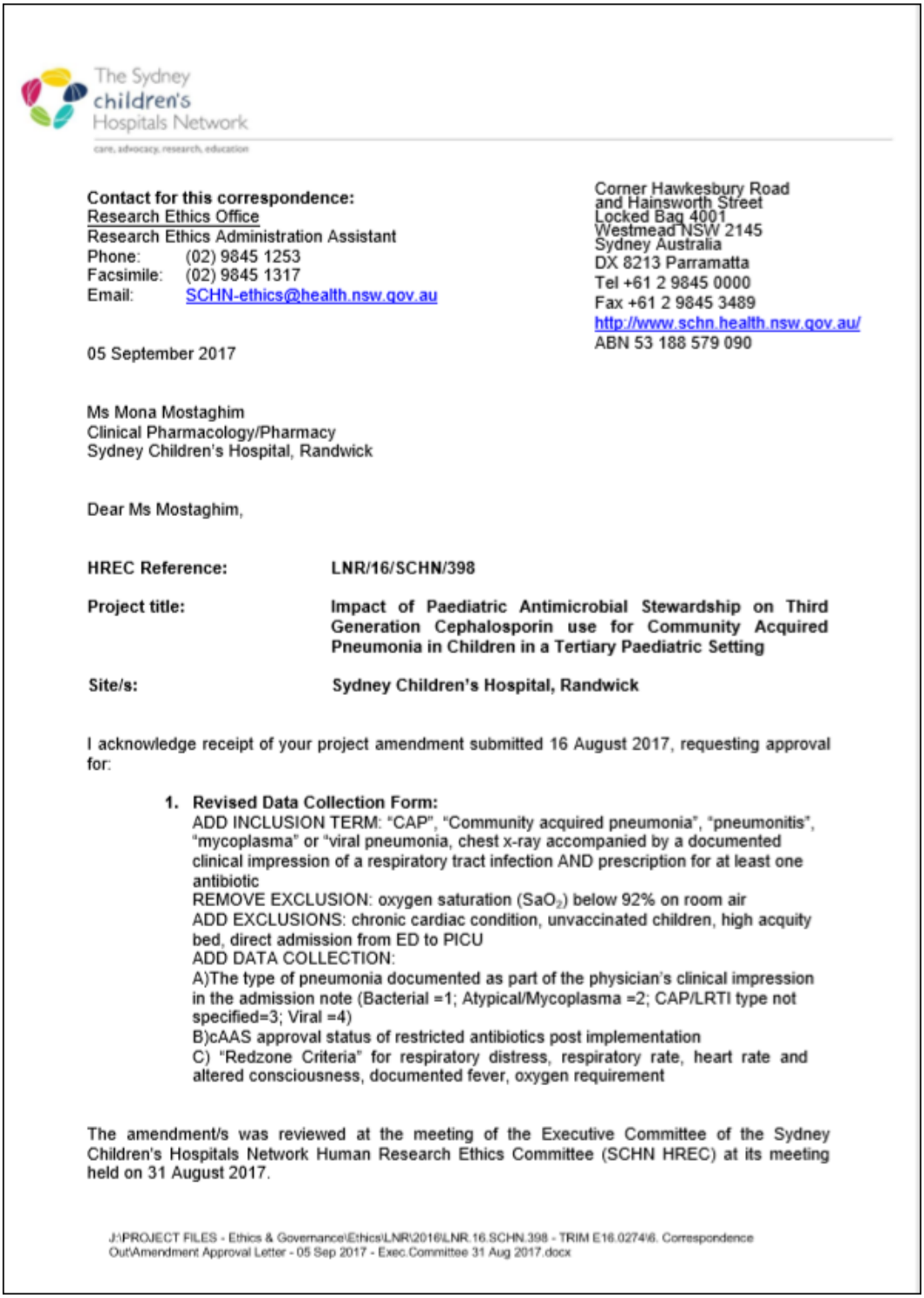
APPENDIX B: DATA COLLECTION TOOL (Section 2.1)

Criteria	
Allocated Number	
Pre=0, Post =1 Period	
admission_age (years)	
age in months (if < 1year)	
DOB	
sex (male=1, female=2)	
stay_number	
episode_sequence_number	
readmitted_within_28_days	
episode_start_date	
episode_end_date	
length_of_stay_total	
diagnosis_code	
Exclusion criteria (1= Assigned High Acuity/High Dependency), (2=Past Medical History of immunodeficiency i.e., cancer, Solid Organ Transplant, opportunistic infection OR cystic fibrosis/CSLD OR cardiac risk factors), (3=aspiration pneumonia) (4=empyema, pneumatocele, pleural effusion) (5= Unimmunised) (6=discharged within 30 days, admitted to intensive care, not admitted)	
Include (1)/ Exclude (0) / Record Not Available (3) (Investigator 1)	
Include (1)/ Exclude (0)/Record Not Available (3) (Investigator 2)	
Include (1)/ Exclude (0)/Not Available (3) Confirmed by Investigators 1 AND 2	
Documented indication: Bacterial CAP=1; Atypical/Mycoplasma CAP=2; CAP/LRTI type not specified=3; Viral CAP=4	
Respiratory Rate in red zone for age any time prior to antibiotics Y (1), N (0)	
Respiratory Distress in red zone for age any time prior to antibiotics Y (1), N (0)	
On oxygen to maintain oxygen saturation any time prior to antibiotics Y (1), N (0)	
Heart Rate in red zone for age any time prior to antibiotics Y (1), N (0)	
Blood pressure in red zone for age any time prior to antibiotics Y (1), N (0)	
Temperature>38.5 C any time prior to antibiotics Y (1), N (0)	
Level of Consciousness AVPU Scale Pain/Unresponsive or GCS<14 Y (1), N (0)	
3rd generation cephalosporin (ceftriaxone/ cefotaxime/ cefepime/ ceftazidime) Y (1), N (0)	
Benzylpenicillin/ampicillin Y (1), N (0)	
Macrolide antibiotic (one of roxithromycin/azithromycin/erythromycin, clarithromycin) Y (1), N (0)	
List Macrolide if applicable (R=roxithromycin, A=azithromycin, C=clarithromycin, E=erythromycin)	
Lincosamide (clindamycin/ lincomycin) Y (1), N (0)	
Glycopeptide (vancomycin/ teicoplanin) Y (1), N (0)	
Number of restricted antibiotics with approval	

APPENDIX C: ETHICS APPROVAL-PROTOCOL AMENDMENT (Section 2.1)



The Sydney children's Hospitals Network
care, advocacy, research, education

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05 September 2017

Ms Mona Mostaghim
Clinical Pharmacology/Pharmacy
Sydney Children's Hospital, Randwick

Dear Ms Mostaghim,

HREC Reference: **LNR/16/SCHN/398**

Project title: **Impact of Paediatric Antimicrobial Stewardship on Third Generation Cephalosporin use for Community Acquired Pneumonia in Children in a Tertiary Paediatric Setting**

Site/s: **Sydney Children's Hospital, Randwick**

I acknowledge receipt of your project amendment submitted 16 August 2017, requesting approval for:

1. **Revised Data Collection Form:**
   ADD INCLUSION TERM: "CAP", "Community acquired pneumonia", "pneumonitis", "mycoplasma" or "viral pneumonia, chest x-ray accompanied by a documented clinical impression of a respiratory tract infection AND prescription for at least one antibiotic
   REMOVE EXCLUSION: oxygen saturation (SaO_2) below 92% on room air
   ADD EXCLUSIONS: chronic cardiac condition, unvaccinated children, high acquity bed, direct admission from ED to PICU
   ADD DATA COLLECTION:
   A)The type of pneumonia documented as part of the physician's clinical impression in the admission note (Bacterial =1; Atypical/Mycoplasma =2; CAP/LRTI type not specified=3; Viral =4)
   B)cAAS approval status of restricted antibiotics post implementation
   C) "Redzone Criteria" for respiratory distress, respiratory rate, heart rate and altered consciousness, documented fever, oxygen requirement

The amendment/s was reviewed at the meeting of the Executive Committee of the Sydney Children's Hospitals Network Human Research Ethics Committee (SCHN HREC) at its meeting held on 31 August 2017.

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.398 - TRIM E16.0274\6. Correspondence Out\Amendment Approval Letter - 05 Sep 2017 - Exec.Committee 31 Aug 2017.docx

The Sydney children's Hospitals Network

care, advocacy, research, education

I am pleased to advise that the documents reviewed and approved at the meeting were:

Documents Reviewed	*Version*	*Date*
Amendment Form	-	16 August 2017
Amended Data Collection Tool	-	Rec'd 16 August 2017
Protocol	-	Rec'd 16 August 2017

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

This letter constitutes ethics amendment approval ONLY. A copy of this letter must be forwarded to the Research Governance Officer at each site for governance approval.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

Should you require any further information, please do not hesitate to contact the Research Ethics Office at SCHN-ethics@health.nsw.gov.au or on (02) 9845 1253.

Yours sincerely,

Production Note:
Signature removed prior to publication.

Associate Professor Sarah Garnett
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee
Sydney Children's Hospitals Network Human Research Ethics Committee

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.398 - TRIM E16.0274\6. Correspondence Out\Amendment Approval Letter - 05 Sep 2017 - Exec.Committee 31 Aug 2017.docx

APPENDIX D ETHICS RATIFICATION (Section 2.1)

UTS HREC Approval - ETH17-1854

Research.Ethics@uts.edu.au

Fri 13/04/2018 8:28 AM

To:Mona Mostaghim <Mona.Mostaghim@student.uts.edu.au>; Beata Bajorek <Beata.Bajorek@uts.edu.au>; tom.snelling@telethonkids.org.au <tom.snelling@telethonkids.org.au>; Research Ethics <research.ethics@uts.edu.au>; Gilkrist@gmail.com <Gilkrist@gmail.com>;

Dear Applicant

[External Ratification: Sydney Children's Hospitals Network Human Research Ethics Committee HREC approval – LNR/16/SCHN/398 – 12 months]

The UTS Human Research Ethics Expedited Review Committee has reviewed your application titled, "Impact of Paediatric Antimicrobial Stewardship on Third Generation Cephalosporin use for Community Acquired Pneumonia in Children in a Tertiary Paediatric Setting", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. ETH17-1854.

Approval will be for the period specified above and subject to the provision of evidence of continued support from the above-named Committee.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year).

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au , and click on " RM6 – Production" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go

to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Associate Professor Beata Bajorek
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
E: Research.Ethics@uts.edu.au
I:
https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/human-research-ethics.aspx

E13-6

APPENDIX E ETHICS APPROVAL (Section 2.2)

The Sydney children's Hospitals Network
care, advocacy, research, education

Contact for this correspondence:
Research Ethics Office
Research Ethics Administration Assistant
Phone: (02) 9845 1253
Facsimile: (02) 9845 1317
Email: SCHN-ethics@health.nsw.gov.au

Corner Hawkesbury Road
and Hainsworth Street
Locked Bag 4001
Westmead NSW 2145
Sydney Australia
DX 8213 Parramatta
Tel +61 2 9845 0000
Fax +61 2 9845 3489
http://www.schn.health.nsw.gov.au/
ABN 53 188 579 090

7 July 2016

Ms Mona Mostaghim
Clinical Pharmacology
Sydney Children's Hospital, Randwick

Dear Ms Mostaghim,

HREC Reference: **LNR/16/SCHN/217**

Project title: **After Hours Drug Room Antimicrobial Access**

Sites: **Sydney Children's Hospital, Randwick**

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive Committee ("the Committee") at its meeting **15 June 2016**, and subsequently out of session on the **4 July 2016**.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the Committee has granted ethical approval of this research project. Your approval is valid for one (1) year, effective the date of this letter.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

The documents reviewed and approved by the Committee are:

Document Reviewed	*Version*	*Date*
LNR, Submission Code: AU/6/4F9623		3 June 2016

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.217 - TRIM E16.0167\6. Correspondence Out\2016-07-07 - REO 04-07-2016 - Ethics Approval Letter.docx

The Sydney children's Hospitals Network

care, advocacy, research, education

Project Plan		Received 3 June 2016
SCHN HREC After Hours Drug Room Antimicrobial Access		22 June 2016

Please note the following conditions of approval:

1. This approval is restricted to research being conducted in accordance with the approved documents, and the review of the medical records you have nominated. There is to be no contact with patients, parents/guardians or other family members.

2. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

3. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

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

5. The co-ordinating investigator will provide a final report to the HREC on completion of the study.

6. Your approval is valid for one (1) year from the date of the final approval letter. If your project extends beyond that one year period please submit an application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

7. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

Production Note:
Signature removed prior to publication.

Dr Peter Cooper
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee
Sydney Children's Hospitals Network Human Research Ethics Committee

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.217 - TRIM E16.0167\6. Correspondence Out\2016-07-07 - REO 04-07-2016 - Ethics Approval Letter.docx

APPENDIX F: DATA COLLECTION INSTRUMENT (Section 2.2)

Code	
Day	
Month	
Column1	
Date on EDR record	
Day of the Week	
Pt ID	
Documented Ward on EDR record	
Imprest (0) Non-Imprest (1)	
Clinical Specialty at acquisition time	
Antimicrobial	
Dose Formulation (tablet or capsule, injectable, topical, oral liquid)	
Strength of dosage form	
New drug order patient per EDR	
Quantity documented on EDR record	
Quantity dispensed	
Unit of measure	
Unrestricted (1)	
Yellow (1)	
Red (1)	
If restricted is there a current approval Y(1), N (0)	
Is there an expired pharmacist alert, Y(1) N(0) or NA (unrestricted or approved)	
If no approval or expired approval was approval sought? Y(1), N (0)	
Days to approval since drug acquired	
Approved by end of next business day Y (1), N (0), NA (3)	
AMS follow up Approval or review by ID (1) vs NO follow up and antimicrobial continued (2)	
Next working day Discharge (1), Discontinued by team (2), Continued (3), Discontinued by ID (4) Not recorded on medication chart (5)	
Additional Notes	
Repeat access without next day approval, Y (1) N (0)	

APPENDIX G: ETHICS APPROVAL (Section 2.2)

UTS HREC Approval - ETH16-0912 - CORRECTION

Valeria Passo on behalf of Research Ethics

Fri 10/03/2017 5:05 PM

To: Beata Bajorek <Beata.Bajorek@uts.edu.au>; Mona Mostaghim <Mona.Mostaghim@student.uts.edu.au>;

Cc: Research Ethics <research.ethics@uts.edu.au>;

Dear Applicant

[External Ratification: Sydney Children's Hospitals Network Human Research Ethics Committee: LNR/16/SCHN/217
– 01/07/16 to 01/07/17]

The UTS Human Research Ethics Expedited Review Committee has reviewed your application titled,, "After Hours Drug Room Antimicrobial Access", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. ETH16-0912.

Approval will be for the period specified above and subject to the provision of annual reports and evidence of continued support from the above-named Committee.
Your approval number must be included in all participant material and advertisements. Any advertisements on the UTS Staff Connect without an approval number will be removed.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au , and click on " RM6 – Production " after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Associate Professor Beata Bajorek

Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
E: Research.Ethics@uts.edu.au

APPENDIX H: ETHICS APPROVAL (Section 3.1)

Activity ethically reviewed after initial approval by Reporting To
CHARLI Notification [SCHN-ITDevelopment@health.nsw.gov.au]
Sent: Monday, December 11, 2017 3:45 PM
To: Mona Mostaghim (SCHN)
Cc: Hala Katf (SCHN)

Activity name: INTERACTIVE SAFE PRESCRIBING AND AMS EDUCATION FOR JUNIOR MEDICAL OFFICERS
Activity number: 5636
Ethics Application No: QIE-2017-02-04
CGU approval status: Approved
CGU review comment: CGU has reviewed your request to include audit results in your evaluation and have approved this amendment. In the future please contact CGU prior to making any changes to your project.
Action required: For information only.
http://apps.jb.schn.health.nsw.gov.au/charli/email_link/show/ACT/5636
This is an automated message - please do not reply as the account is not monitored. Please direct all enquiries to the Clinical Governance Unit for your facility.

APPENDIX I: ETHICS APPROVAL (Section 3.1)

UTS HREC Letter of Noting - ETH17-1859

Research.Ethics@uts.edu.au

Thu 8/03/2018 2:46 PM

To: Mona Mostaghim <Mona.Mostaghim@student.uts.edu.au>; Beata Bajorek <Beata.Bajorek@uts.edu.au>; tom.snelling@telethonkids.org.au <tom.snelling@telethonkids.org.au>; Research Ethics <research.ethics@uts.edu.au>;

Dear Applicant,

The Faculty has considered your Nil/Negligible Risk Declaration Form for your project titled, "Junior Medical Staff Knowledge and Awareness of Safe Prescribing and Antimicrobial Stewardship", and agree your research does not require review from the UTS Human Research Ethics Committee. Please keep a copy of your Declaration form on file to show you have considered risk.

For tracking purposes, you have been provided with an ethics application number, which is UTS HREC ETH17-1859.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of noting.

Instructions for saving the declaration form can be downloaded from:
https://staff.uts.edu.au/howdoi/Pages/Researching/Research%20ethics%20and%20Integrity/Human%20research%20ethics/submit-my-human-research-ethics-application.aspx

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au, and click on "RM6 - Production" after logging in.

If you or anyone connected with this research have any queries please do not hesitate to contact Research.Ethics@uts.edu.au

Yours sincerely,

Associate Professor Beata Bajorek
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney

E: Research.Ethics@uts.edu.au
https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/human-research-ethics.aspx
PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]

REF: E28

APPENDIX J: ETHICS APPROVAL (Section 3.2)

The Sydney children's Hospitals Network
care, advocacy, research, education

Contact for this correspondence:
Research and Development
Ethics Administration Assistant
Phone: (02) 9845 1253
Facsimile: (02) 9845 1317
Email: SCHN-ethics@health.nsw.gov.au

Corner Hawkesbury Road
and Hainsworth Street
Locked Bag 4001
Westmead NSW 2145
Sydney Australia
DX 8213 Parramatta
Tel +61 2 9845 0000
Fax +61 2 9845 3489
http://www.schn.health.nsw.gov.au/
ABN 53 188 579 090

6 November 2015

Ms Mona Mostaghim
Clinical Pharmacology
Sydney Children's Hospital, Randwick

Dear Ms Mostaghim,

HREC Reference: **LNR/15/SCHN/430**

Project title: **Evaluation of nursing and medical staff knowledge and perceptions of Antimicrobial Stewardship Programs**

Sites: **Sydney Children's Hospital, Randwick**
Prince of Wales Hospital
Wollongong Hospital
St George Hospital
Sutherland Hospital

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive Committee ("the Committee") at its meeting 28 October 2015, and subsequently out of session on 4 and 6 November 2015.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that after receiving the further information required on 6 November 2015, the Committee has granted ethical approval of this research project. Your approval is valid for three (3) years, effective the date of this letter.

The documents reviewed and approved by the Committee are:

Document Reviewed	*Version*	*Date*
LNR, Submission Code: AU/6/D802216		22 October 2015
Questionnaire Summary (project Plan)		undated

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2015\LNR.15.SCHN.430 - TRIM E15.0422 @/6. Correspondence Out\LNR.15.SCHN.430 - Ethics Approval Letter - 6 November 2015.docx

The Sydney children's Hospitals Network

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AMS and Nursing Questionnaire	V1.1	
Prescriber Survey AMS	V1.1	
Response to Executive Committee		2 November 2015
Response to Executive Committee		5 November 2015
Response to Executive Committee		6 November 2015

Please note the following conditions of approval:

1. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

2. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

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

4. The co-ordinating investigator will provide an annual report to the HREC on the anniversary of this approval letter, and a final report on completion of the study.

5. Your approval is valid for three (3) years from the date of the final approval letter. If your project extends beyond that three year period and you are still actively recruiting you will be required to resubmit your application incorporating any amendments within six (6) months of that approval expiry date. If your project is in follow up on, or analysis, please submit and application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

6. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

Production Note:
Signature removed prior to publication.

Mrs Jillian Bunting
Executive Officer
Sydney Children's Hospitals Network Human Research Ethics Committee

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APPENDIX K: ETHICS APPROVAL (Section 3.2)

UTS HREC Approval - ETH16-0225 - CORRECTION

Valeria Passo on behalf of Research Ethics

Fri 10/03/2017 4:52 PM

To:Beata Bajorek <Beata.Bajorek@uts.edu.au>; Mona Mostaghim <Mona.Mostaghim@student.uts.edu.au>;

Cc:Research Ethics <research.ethics@uts.edu.au>;

Dear Applicant

[External Ratification: Sydney Children's Hospitals Network HREC approval –LNR/15/SCHN/430 – 06/11/15-06/11/18]

The UTS Human Research Ethics Expedited Review Committee has reviewed your application titled, "Evaluation of nursing and medical staff knowledge and perceptions of Antimicrobial Stewardship Programs", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. ETH16-0225.

Approval will be for the period specified above and subject to the provision of annual reports and evidence of continued support from the above-named Committee.

Your approval number must be included in all participant material and advertisements. Any advertisements on the UTS Staff Connect without an approval number will be removed.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au , and click on " RM6 – Production " after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Associate Professor Beata Bajorek
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
E: Research.Ethics@uts.edu.au

APPENDIX L: ETHICS APPROVAL (Sections 4.1 and 4.2)

The Sydney children's Hospitals Network
care, advocacy, research, education

Contact for this correspondence:
Research Ethics Office
Research Ethics Administration Assistant
Phone: (02) 9845 1253
Facsimile: (02) 9845 1317
Email: SCHN-ethics@health.nsw.gov.au

Corner Hawkesbury Road
and Hainsworth Street
Locked Bag 4001
Westmead NSW 2145
Sydney Australia
DX 8213 Parramatta
Tel +61 2 9845 0000
Fax +61 2 9845 3489
http://www.schn.health.nsw.gov.au/
ABN 53 188 579 090

29 November 2016

Ms Mona Mostaghim
Clinical Pharmacology
Sydney Children's Hospital, Randwick

Dear Ms Mostaghim,

HREC Reference: **LNR/16/SCHN/445**

Project title: **Trends in Antimicrobial Consumption in a Paediatric Hospital – Assessing the Impact of Antimicrobial Stewardship**

Sites: **Sydney Children's Hospital, Randwick**

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive Committee ("the Committee") at its meeting 28 November 2016.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the Committee has granted ethical approval of this research project. Your approval is valid for one (1) year, effective the date of this letter.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

The documents reviewed and approved by the Committee are:

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.445 - TRIM E16.0299\6. Correspondence Out\2016-11-29 - Exec. Officer 28-11-2016 - Ethics Approval letter.docx

The Sydney children's Hospitals Network

care, advocacy, research, education

Document Reviewed	*Version*	*Date*
LNR Submission Code, AU/6/CA3A219		20 November 2016
Project Summary		Received 22 November 2016
Appendix 1: International Classification of Disease (10th edition) codes		Received 22 November 2016

Please note the following conditions of approval:

1. This approval is restricted to research being conducted in accordance with the approved documents, and the review of the medical records you have nominated. There is to be no contact with patients, parents/guardians or other family members.

2. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

3. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

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

5. The co-ordinating investigator will provide a final report to the HREC on completion of the study.

6. Your approval is valid for one (1) year from the date of the final approval letter. If your project extends beyond that one year period please submit an application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

7. In the event of a project not having commenced within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

Production Note:
Signature removed prior to publication.

Dr Peter Cooper
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee
Sydney Children's Hospitals Network Human Research Ethics Committee

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.445 - TRIM E16.0299\6. Correspondence Out\2016-11-29 - Exec. Officer 28-11-2016 - Ethics Approval letter.docx

APPENDIX M: ETHICS APPROVAL (Sections 4.1 and 4.2)

UTS HREC Approval - ETH17-1193

Research.Ethics@uts.edu.au

Wed 8/03/2017 11:41 AM

To:Mona Mostaghim <Mona.Mostaghim@student.uts.edu.au>; Beata Bajorek <Beata.Bajorek@uts.edu.au>; Research Ethics <research.ethics@uts.edu.au>; tom.snelling@telethonkids.org.au <tom.snelling@telethonkids.org.au>;

Dear Applicant

[External Ratification: Sydney Children's Hospitals Network Human Research Ethics Committee HREC approval – LNR/16/SCHN/445 – 29/11/16 to 29/11/17]

The UTS Human Research Ethics Expedited Review Committee has reviewed your application titled, "Trends in Antimicrobial Consumption in a Paediatric Hospital – Assessing the Impact of Antimicrobial Stewardship", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. ETH17-1193
Approval will be for the period specified above and subject to the provision of annual reports and evidence of continued support from the above-named Committee.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au , and click on " RM6 – Production" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

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APPENDIX N: Reference List (Chapter 1, Sections 1.0-1.6)

1. Laxminarayan R, Matsoso P, Pant S, Brower C, Rottingen J-a, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. Lancet 2016;387(10014):168-75.
2. World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva: World Health Organization; 2015.
3. Australian Government Departments of Health and Agriculture. Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015-2019. Canberra: Australian Government 30 June 2015.
4. Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2017: Second Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2017.
5. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. Clin Infect Dis 2011;52(3): e18-55.
6. Gottlieb T, Nimmo GR. Antibiotic resistance is an emerging threat to public health: an urgent call to action at the Antimicrobial Resistance Summit 2011. Med J Aust 2011;194(6):281-3.
7. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance—the need for global solutions. Lancet Infect Dis 2013;13(12):1057-98.
8. Holmes A, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 2015;387(10014):176-87.
9. Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee. Australian Statistics on Medicines 2015. Canberra: Australian Government Department of Health; 2016.

10. Osowicki J, Gwee A, Noronha J, Palasanthiran P, McMullan B, Britton PN, et al. Australia-wide point prevalence survey of the use and appropriateness of antimicrobial prescribing for children in hospital. Med J Aust 2014;201(11):657-62.
11. Gyssens IC. Antibiotic policy. Int J Antimicrob Agents 2011;38(Supplement):11-20.
12. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66(7):e1–48.
13. Davey P, Sneddon J, Nathwani D. Overview of strategies for overcoming the challenge of antimicrobial resistance. Expert Rev Clin Pharmacol 2010;3(5):667-86.
14. Tamma PD, Sandora TJ. Clostridium difficile Infection in Children: Current State and Unanswered Questions. Journal of the Pediatric Infectious Diseases Society 2012;1(3):230-43.
15. Dubberke ER, Carling P, Carrico R, Donskey CJ, Loo VG, McDonald LC, et al. Strategies to Prevent Clostridium difficile Infections in Acute Care Hospitals: 2014 Update. Infect Control Hosp Epidemiol 2014;35(6):628-45.
16. Tamma PD, Holmes A, Dodds Ashley ES. Antimicrobial stewardship: another focus for patient safety? Curr Opin Infect Dis 2014;27(4):348-55.
17. 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.
18. Fishman NO, Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Society PID. Policy Statement on Antimicrobial Stewardship by the Society for

Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33(4):322-7.

19. Rutman L, Wright DR, O'Callaghan J, Spencer S, Lion KC, Kronman MP, et al. A Comprehensive Approach to Pediatric Pneumonia: Relationship Between Standardization, Antimicrobial Stewardship, Clinical Testing, and Cost. J Healthc Qual 2017;39(4):e59-69.
20. van Buul LW, Sikkens JJ, van Agtmael MA, Kramer MHH, van der Steen JT, Hertogh CMPM. Participatory action research in antimicrobial stewardship: a novel approach to improving antimicrobial prescribing in hospitals and long-term care facilities. J Antimicrob Chemother 2014;69(7):1734-41.
21. Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs [Internet]: Atlanta (GA) US Department of Health and Human Services, CDC; 2014 [cited February 23, 2017]. Available from: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html.
22. Pollack LA, Plachouras D, Sinkowitz-Cochran R, Gruhler H, Monnet DL, Weber JT. A concise set of structure and process indicators to assess and compare antimicrobial stewardship programs among EU and US Hospitals: Results from a multinational expert panel. Infect Control Hosp Epidemiol 2016;37(10):1201-11.
23. Duguid M, Cruickshank M, editors. Antimicrobial Stewardship in Australian Hospitals. Sydney: Australian Commission on Safety and Quality in Health Care (ACSQHC); 2011.
24. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013;4(4):CD003543.
25. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for

hospital inpatients. Cochrane Database Syst Rev. 2017(2):CD003543.

26. Coombes ID, Reid C, McDougall D, Stowasser D, Duiguid M, Mitchell C. Pilot of a National Inpatient Medication Chart in Australia: improving prescribing safety and enabling prescribing training. Br J Clin Pharmacol 2011;72(2):338-49.
27. Antibiotic Expert Groups. Therapeutic guidelines: Antibiotic. Melbourne: Therapeutic Guidelines Limited; 2014.
28. Committee on Drugs. Off-Label Use of Drugs in Children. Pediatrics 2014;133(3):563-7.
29. Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ. Trough Concentrations of Vancomycin: Adult Therapeutic Targets Are Not Appropriate for Children. The Pediatric Infectious Disease Journal 2012;31(12):1269-71.
30. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. N Engl J Med 2003;349(12):1157-67.
31. Robertson AF. Reflections on Errors in Neonatology: II. The “Heroic” Years, 1950 to 1970. J Perinatol 2003; 23:154-61.
32. Kendrick JG, Carr RR, Ensom MHH. Pediatric Obesity: Pharmacokinetics and Implications for Drug Dosing. Clin Ther 2015;37(9):1897-923.
33. Daschner M. Drug dosage in children with reduced renal function. Pediatr Nephrol 2005;20(12):1675-86.
34. Australian Medicines Handbook. Australian Medicines Handbook Children's Dosing Companion. Adelaide: Australian Medicines Handbook Pty Ltd.
35. Australian Commission on Safety and Quality in Health Care (ACSQHC). Standard 3: Preventing and Controlling Healthcare Associated Infections. In: National Safety and Quality Health Service Standards. Sydney: ACSQHC; 2012. p. 26-33.

36. 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.
37. Buising KL, 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.
38. Zaidi STR, Marriott JL, Nation RL. The role of perceptions of clinicians in their adoption of a web-based antibiotic approval system: do perceptions translate into actions? Int J Med Inform 2008;77(1):33-40.
39. 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(1):35.
40. Pulcini C, Huttner A. CMI policy on antimicrobial stewardship research. Clin Microbiol Infect 2018;28(2):91-2.
41. McGowan JE. Antimicrobial stewardship—the State of the Art in 2011: Focus on Outcome and Methods. Infect Control Hosp Epidemiol 2012;33(4):331-7.
42. 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):e51-77.
43. Coulter S, Roberts JA, Hajkowicz K, Halton K. The use of bloodstream infection mortality to measure the impact of antimicrobial stewardship interventions: assessing the evidence. Infect Dis Rep 2017;9(1).

44. Dodds Ashley ES, Kaye KS, DePestel DD, Hermsen ED. Antimicrobial Stewardship: Philosophy Versus Practice. Clin Infect Dis 2014;59(Supplement 3):S112-21.
45. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES, et al. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis 2017;64(3):377-83.
46. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a Structured Panel Process to Define Quality Metrics for Antimicrobial Stewardship Programs. Infect Control Hosp Epidemiol 2012;33(5):500-6.
47. Spyridis N, Syridou G, Goossens H, Versporten A, Kopsidas J, Kourlaba G, et al. Variation in paediatric hospital antibiotic guidelines in Europe. Arch Dis Child 2016;101:72–6.
48. Levy ER, Swami S, Dubois SG, Wendt R, Banerjee R. Rates and Appropriateness of Antimicrobial Prescribing at an Academic Children's Hospital, 2017-2010. Infect Control Hosp Epidemiol 2012;33(4):346-53.
49. Bryant PA, Australian Stewardship of Antimicrobials in Pediatrics Group. Antimicrobial stewardship resources and activities for children in tertiary hospitals in Australasia: a comprehensive survey. Med J Aust 2015;202(3):134-9.
50. WHO Collaborating Centre for Drug Statistics Methodology. Defined Daily Dose: Definition and general considerations of defined daily dose (DDD) [Internet]. Oslo: Norwegian Institute of Public Health; [cited 2017 3 December]. Available from: http://www.whocc.no/ddd/definition_and_general_considera/135.html
51. Raastad R, Tvete IF, Abrahamsen TG, Berild D, Leegaard TM, Walberg M, et al. A worrying trend in weight-adjusted paediatric antibiotic use in a Norwegian tertiary care hospital. Acta Paediatr 2015;104(7):687-92.

52. Zhang W, Shen X, Bergman U, Wang Y, Chen Y, Huang M, et al. Drug utilisation 90% (DU90%) profiles of antibiotics in five Chinese children's hospitals (2002-2006). Int J Antimicrob Agents 2008;32(3):250-5.
53. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. The Lancet Infectious Diseases 2016;16(8): e139-52.
54. Zaidi STR, Thursky KA. Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship. J Clin Pharm Ther 2013;38(6):490-7

APPENDIX O: Reference List (Chapter 5)

1. Goldman JL, Lee BR, Hersh AL, Yu D, Stach LM, Myers AL, et al. Clinical Diagnoses and Antimicrobials Predictive of Pediatric Antimicrobial Stewardship Recommendations: A Program Evaluation. Infect Control Hosp Epidemiol 2015;36(6):673-80.
2. Parker RA, Rea LM. Designing and Conducting Survey Research: A Comprehensive Guide. 4th Edition ed. San Francisco (CA): Jossey-Bass; 2014.
3. Fogli J, Herkenhoff L. Conducting Survey Research: A Practical Guide. New York(NY): Business Expert Press; 2018.
4. Khadem TM, Dodds Ashley E, Wrobel MJ, Brown J. Antimicrobial Stewardship: A Matter of Process or Outcome? Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2012;32(8):688-706. 5.
5. 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. 6.
6. Hyun DY, Hersh AL, Namtu K, et al. Antimicrobial stewardship in pediatrics: How every pediatrician can be a steward. JAMA Pediatrics 2013;167(9):859-66.
7. Broom A, Broom J, Kirby E, Scambler G. The path of least resistance? Jurisdictions, responsibility and professional asymmetries in pharmacists' accounts of antibiotic decisions in hospitals. Soc Sci Med 2015;146:95-103.
8. Broom A, Broom J, Kirby E, Scambler G. Nurses as Antibiotic Brokers: Institutionalized Praxis in the Hospital. Qual Health Res 2017;27(13):1924-35.
9. Zaidi STR, Thursky KA. Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship. J Clin Pharm Ther 2013;38(6):490-7.

10. Baysari MT, Oliver K, Egan B, Li L, Richardson K, Sandaradura I, et al. Audit and feedback of antibiotic use: utilising electronic prescription data. Appl Clin Inform 2013;4(4):583-95.

8 BIBLIOGRAPHY

Abboud PA, Ancheta R, McKibben M, Jacobs BR. Impact of workflow-integrated corollary orders on aminoglycoside monitoring in children. Health Informatics J 2006;12(3):187-98.

Agwu AL, Lee CKK, Jain SK, Murray KL, Topolski J, Miller RE, et al. A World Wide Web–Based Antimicrobial Stewardship Program Improves Efficiency, Communication, and User Satisfaction and Reduces Cost in a Tertiary Care Pediatric Medical Center. Clin Infect Dis 2008;47(6):747-53.

Allison P. Convergence Problems in Logistic Regression. In: Altman M, Gill J, Mc Donald P. Numerical Issues in Statistical Computing for the Social Scientist. Hoboken (NJ): John Wiley & Sons; 2003. p. 238-52.

Amadeo B, Zarb P, Muller A, Drapier N, Vankerckhoven V, Rogues A-M, et al. European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. J Antimicrob Chemother 2010;65(10):2247-52.

Ambroggio L, Thomson J, Kurowski EM, Courter J, Statile A, Graham C, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Pediatrics 2013;131(5):e1623-e31.

American Pharmaceutical Association (APA). Lexi-Comp Online in UptoDate [Internet]. Hudson, Ohio: APA; 2017 [cited 20 January 2018].

Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. J Antimicrob Chemother 2003;52(5):842-8.

Antachopoulos C, Dotis J, Pentsioglou V. Development of a paediatric daily defined dose system for the measurement of antibiotic consumption in paediatric units. In: 14th European Congress of Clinical Microbiology and Infectious Diseases; Prague, Czech Republic; 2004.

Antibiotic Expert Groups. Therapeutic guidelines: Antibiotic. Melbourne: Therapeutic Guidelines Limited; 2014.

Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in children: a systematic review. J Hosp Infect 2018;99(2):117-23.

Australian Commission on Safety and Quality in Health Care (ACSQHC). NIMC Auditing. [Internet] Sydney: ACSQHC; [cited 2017 January 21]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/medication-chart/nimc/national-inpatient-medicationchart-audit/

Australian Commission on Safety and Quality in Health Care (ACSQHC). Recommendations for Terminology, Abbreviations and Symbols used in the Prescribing and Administration of Medicines. Sydney: ACSQHC; 2011.

Australian Commission on Safety and Quality in Health Care (ACSQHC). Standard 3: Preventing and Controlling Healthcare Associated Infections. In: National Safety and Quality Health Service Standards. Sydney: ACSQHC; 2012. p. 26-33.

Australian Commission on Safety and Quality in Health Care (ACSQHC). Indicator Specification: Antimicrobial Stewardship Clinical Care Standard. Sydney: ACSQHC; 2014.

Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2016: First Australian report on antimicrobial use and resistance in human health. (ACSQHC) Sydney: ACSQHC; 2016.

Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2017: Second Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2017.

Australian Commission on Safety and Quality in Health Care (ACSQHC) and NSW Therapeutic Advisory Group. National Quality Use of Medicines Indicators for Australian Hospitals. Sydney; 2014.

Australian Government Departments of Health and Agriculture. Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015-2019. Canberra: Australian Government June 2015.

Australian Medicines Handbook. Australian Medicines Handbook Children's Dosing Companion. Adelaide: Australian Medicines Handbook Pty Ltd.

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.

Baysari MT, Oliver K, Egan B, Li L, Richardson K, Sandaradura I, et al. Audit and feedback of antibiotic use: utilising electronic prescription data. Appl Clin Inform 2013;4(4):583-95.

Bergman U, Grimsson A, Wahba A, Westerholm B, editors. Studies in drug utilization: methods and applications. In World Health Organization Regional Publications. European Series: no. 8 ; Copenhagen: WHO; 1979.

Berild D, Ringertz SH, Aabyholm G, Lelek M, Fosse B. Impact of an antibiotic policy on antibiotic use in a paediatric department. Individual based follow-up shows that antibiotics were chosen according to diagnoses and bacterial findings. Int J Antimicrob Agents 2002;20(5):333-8.

Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol 2017;46(1):348-55.

Berrington A. Antimicrobial prescribing in hospitals: be careful what you measure. J Antimicrob Chemother 2010;65(1):163-8.

Bland JM, Altman DG. Measuring Agreement in Method Comparison Studies. Stat Methods Med Res 1999;8:135-60.

Bolon MK, Arnold AD, Feldman HA, Goldmann DA, Wright SB. An antibiotic order form intervention does not improve or reduce vancomycin use. Pediatr Infect Dis J 2005;24(12):1053-8.

Bond SE, Boutlis CS, Yeo WW, Miyakis S. Impact of an antimicrobial stewardship intervention on appropriateness of prescribing for community-acquired pneumonia in an Australian regional hospital. Intern Med J 2017;47(5):582-5.

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.

Bowes J, Yasseen III AS, Barrowman N, Murchison B, Dennis J, Moreau KA, et al. Antimicrobial stewardship in pediatrics: focusing on the challenges clinicians face. BMC Pediatr 2014;14(1):212.

Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53(7):e25-76.

Brennan N, Mattick K. A systematic review of educational interventions to change behaviour of prescribers in hospital settings, with a particular emphasis on new prescribers. Br J Clin Pharmacol 2013;75(2):359-72.

Broom A, Broom J, Kirby E, Scambler G. The path of least resistance? Jurisdictions, responsibility and professional asymmetries in pharmacists' accounts of antibiotic decisions in hospitals. Soc Sci Med 2015;146:95-103.

Broom A, Broom J, Kirby E, Scambler G. Nurses as Antibiotic Brokers: Institutionalized Praxis in the Hospital. Qual Health Res 2017;27(13):1924-35.

Bryant PA, Australian Stewardship of Antimicrobials in Pediatrics Group. Antimicrobial stewardship resources and activities for children in tertiary hospitals in Australasia: a comprehensive survey. Med J Aust 2015;202(3):134-9.

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(1):35.

Buising KL, 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.

Cairns KA, Jenney AW, Abbott IJ, Skinner MJ, Doyle JS, Dooley M, et al. Prescribing trends before and after implementation of an antimicrobial stewardship program. Med J Aust 2013;198(5):262-6.

Castro-Sánchez E, Drumright LN, Gharbi M, Farrell S, Holmes AH. Mapping Antimicrobial Stewardship in Undergraduate Medical, Dental, Pharmacy, Nursing and Veterinary Education in the United Kingdom. PLoS One 2016;11(2):e0150056.

Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs [Internet]. Atlanta, GA: US Department of Health and Human Services, CDC; 2014 [cited February 23, 2017]. Available from: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html.

Centers for Disease Control and Prevention(CDC). Clinical Growth Charts. [Internet] Atlanta (GA) CDC; Available from: https://www.cdc.gov/growthcharts/cdc_charts.htm

Ceradini J, Tozzi AE, D'Argenio P, Bernaschi P, Manuri L, Brusco C, et al. Telemedicine as an effective intervention to improve antibiotic appropriateness prescription and to reduce costs in pediatrics. Ital J Pediatr 2017;43(1):105.

Chan S, Hossain J, Di Pentima MC. Implications and Impact of Prior Authorization Policy on Vancomycin Use at a Tertiary Pediatric Teaching Hospital. Pediatr Infect Dis J 2014;34(5):506-8.

Charani E, Castro-Sánchez E, Holmes A. The Role of Behavior Change in Antimicrobial Stewardship. Infect Dis Clin North Am 2014;28(2):169-75.

Chong HT, Weightman MJ, Sirichai P, Jones A. How do junior medical officers use online information resources? A survey. BMC Med Educ 2016;16(1):120.

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;45(11):1198-202.

Clinical Excellence Commission(CEC). Continuity of Medication Management: Medication Reconciliation Toolkit. Sydney, NSW :CEC; 2014;

Clinical Excellence Commission. Paediatric Quality Program: Between the flags. [Internet] Sydney, NSW: CEC; 2017 [cited 2017 16 August]; Available from: http://www.cec.health.nsw.gov.au/patient-safety-programs/paediatric-patient-safety/pqp-between-the-flags

Coiera EW, Jayasuriya RA, Hardy J, Bannan A, Thorpe MEC. Communication loads on clinical staff in the emergency department. Med J Aust 2002;176(9):415-8.

Committee on Drugs. Off-Label Use of Drugs in Children. Pediatrics 2014;133(3):563-7.

Coombes ID, Reid C, McDougall D, Stowasser D, Duiguid M, Mitchell C. Pilot of a National Inpatient Medication Chart in Australia: improving prescribing safety and enabling prescribing training. Br J Clin Pharmacol 2011;72(2):338-49.

Cosgrove SE, Hermsen ED, Rybak MJ, File TM, Parker SK, Barlam TF. Guidance for the knowledge and skills required for antimicrobial stewardship leaders. Infect Control Hosp Epidemiol 2014;35(12):1444-51.

Cotta MO, Robertson MS, Tacey M, Marshall C, Thursky KA, Liew D, et al. Attitudes towards antimicrobial stewardship: results from a large private hospital in Australia. Healthcare infection 2014;19(3):89-94.

Coulter S, Roberts JA, Hajkowicz K, Halton K. The use of bloodstream infection mortality to measure the impact of antimicrobial stewardship interventions: assessing the evidence. Infect Dis Rep 2017;9(1).

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337(a1655).

Daschner M. Drug dosage in children with reduced renal function. Pediatr Nephrol 2005;20(12):1675-86.

Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2013(4):CD003543.

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017(2):CD003543.

Davey P, Sneddon J, Nathwani D. Overview of strategies for overcoming the challenge of antimicrobial resistance. Expert Rev Clin Pharmacol 2010;3(5):667-86.

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.

Demonchy E, Dufour J-C, 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;69(10):2857-63.

Di Pentima MC, Chan S. Impact of Antimicrobial Stewardship Program on Vancomycin Use in a Pediatric Teaching Hospital. Pediatr Infect Dis J 2010;29(8):707-11.

Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila) 2009;48(5):505-12.

Di Pentima MC, Chan S, Hossain J. Benefits of a Pediatric Antimicrobial Stewardship Program at a Children's Hospital. Pediatrics 2011;128(6):1062-70.

Dik J-WH, Vemer P, Friedrich AW, Hendrix R, Lo-Ten-Foe JR, Sinha B, et al. Financial evaluations of antibiotic stewardship programs - a systematic review. Front Microbiol 2015;6:317.

Ding H, Yang Y, Wei J, Fan S, Yu S, Yao K, et al. Influencing the use of antibiotics in a Chinese pediatric intensive care unit. Pharm World Sci 2008;30(6):787-93.

Dodds Ashley ES, Kaye KS, DePestel DD, Hermsen ED. Antimicrobial Stewardship: Philosophy Versus Practice. Clin Infect Dis 2014;59(Suppl. 3):S112-21.

Drees M, Gerber JS, Morgan DJ, Lee GM. Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship: Use of Administrative and Surveillance Databases. Infect Control Hosp Epidemiol 2016;37(11):1278-87.

Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee. Australian Statistics on Medicines 2015. Canberra: Commonwealth of Australia; 2016 18 November 2016.

Dubberke ER, Carling P, Carrico R, Donskey CJ, Loo VG, McDonald LC, et al. Strategies to Prevent Clostridium difficile Infections in Acute Care Hospitals: 2014 Update. Infect Control Hosp Epidemiol 2014;35(6):628-45.

Duguid M, Cruickshank M, editors. Antimicrobial Stewardship in Australian Hospitals. Sydney: Australian Commission on Safety and Quality in Health Care (ACSQHC); 2011.

Dunagan WC, Medoff G. Formulary control of antimicrobial usage: What price freedom? Diagn Microbiol Infect Dis 1993;16(3):265-74.

Edwards R, Drumright L, Kiernan M, Holmes A. Covering more territory to fight resistance: considering nurses' role in antimicrobial stewardship. J Infect Prev 2011;12(1):6-10.

Edwards R, Loveday H, Drumright LN, Holmes A. Should nurses be more involved in antimicrobial management? J Infect Prev 2011;12(1):4-5.

Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.

Fishman NO. Antimicrobial stewardship. Am J Infect Control 2006;34(5):S55-63. Figure 3, A conceptual framework for antimicrobial use; p. S58.

Fishman NO, Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Society PID. Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33(4):322-7.

Flannery DD, Swami S, Chan S, Eppes S. Prescriber Perceptions of a Pediatric Antimicrobial Stewardship Program. Clin Pediatr (Phila) 2014;53(8):747-50.

Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J 2014;44(12b):1283-97.

Fogli J, Herkenhoff L. Conducting Survey Research: A Practical Guide. New York(NY): Business Expert Press; 2018.

Fortin É, Fontela PS, Manges AR, Platt RW, Buckeridge DL, Quach C. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to paediatrics. J Antimicrob Chemother 2014;69(6):1447-56.

Foster L, Wallis M, Paterson B, James H. A Descriptive Study of Peripheral Intravenous Catheters in Patients Admitted to a Pediatric Unit in One Australian Hospital. J Infus Nurs 2002;25(3):159-67.

Fridkin SK, Srinivasan A. Implementing a Strategy for Monitoring Inpatient Antimicrobial Use Among Hospitals in the United States. Clin Infect Dis 2014;58(3):401-6.

Gerber JS, Kronman MP, Ross RK, Hersh AL, Newland JG, Metjian TA, et al. Identifying Targets for Antimicrobial Stewardship in Children's Hospitals. Infect Control Hosp Epidemiol 2015;34(12):1252-8.

Ghaleb MA, Barber N, Dean Franklin B, Wong ICK. What constitutes a prescribing error in paediatrics? Qual Saf Health Care 2005;14(5):352-7.

Gillespie E, Rodrigues A, Wright L, Williams N, Stuart RL. Improving antibiotic stewardship by involving nurses. Am J Infect Control 2013;41(4):365-7.

Gillon J, Xu M, Slaughter J, Di Pentima MC. Vancomycin Use: Room for Improvement Among Hospitalized Children. J Pharm Pract 2017;30(3):296-9.

Goldman JL, Lee BR, Hersh AL, Yu D, Stach LM, Myers AL, et al. Clinical Diagnoses and Antimicrobials Predictive of Pediatric Antimicrobial Stewardship Recommendations: A Program Evaluation. Infect Control Hosp Epidemiol 2015;36(6):673-80.

Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ. Trough Concentrations of Vancomycin: Adult Therapeutic Targets Are Not Appropriate for Children. Pediatr Infect Dis J 2012;31(12):1269-71.

Gottlieb T, Nimmo GR. Antibiotic resistance is an emerging threat to public health: an urgent call to action at the Antimicrobial Resistance Summit 2011. Med J Aust 2011;194(6):281-3.

Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a Hospital-Based Antimicrobial Management Program on Clinical and Economic Outcomes. Clin Infect Dis 2001;33(3):289-95.

Gyssens IC. Antibiotic policy. Int J Antimicrob Agents 2011;38(Supplement):11-20.

Haeusler GM, Sung L, Ammann RA, Phillips B. Management of fever and neutropenia in paediatric cancer patients: room for improvement? Curr Opin Infect Dis 2015;28(6):532-8.

Haug JB, Reikvam Å. WHO defined daily doses versus hospital-adjusted defined daily doses: impact on results of antibiotic use surveillance. J Antimicrob Chemother 2013;68(12):2940-7.

Health System Purchasing and Performance. Emergency Department Care. [Internet] Sydney: NSW Health; [updated 30 April 2018; cited 2017 5 September]; Available from: http://www.health.nsw.gov.au/Performance/Pages/emergency.aspx

Hennig S, Staatz CE, Natanek D, Bialkowski S, Consuelo Llanos Paez C, Lawson R, et al. Antimicrobial stewardship in paediatric oncology: Impact on optimising gentamicin use in febrile neutropenia. Pediatr Blood Cancer 2018;65(2):e26810.

Holmes A, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 2015;387(10014):176-87.

Horikoshi Y, Higuchi H, Suwa J, Isogai M, Shoji T, Ito K. Impact of computerized pre-authorization of broad spectrum antibiotics in Pseudomonas aeruginosa at a children's hospital in Japan. J Infect Chemother 2016;22(8):532-5.

Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis 2017;64:69-73.

Hosmer DW, Jnr, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. New York (NY): John Wiley & Sons; 2013.

Hurst AL, Child J, Pearce K, Palmer C, Todd JK, Parker SK. Handshake Stewardship: A Highly Effective Rounding-based Antimicrobial Optimization Service. Pediatr Infect Dis J 2016;35(10):1104-10.

Huttner B, Harbarth S, Nathwani D. Success stories of implementation of antimicrobial stewardship: a narrative review. Clin Microbiol Infect 2014;20(10):954-62.

Hyun DY, Hersh AL, Namtu K, et al. Antimicrobial stewardship in pediatrics: How every pediatrician can be a steward. JAMA Pediatrics 2013;167(9):859-66.

Ibrahim OM, Polk RE. Benchmarking antimicrobial drug use in hospitals. Expert Rev Anti Infect Ther 2012;10(4):445-57.

Independent Hospital Pricing Authority. Technical Specifications 2014 - 2015. Sydney, NSW, 2014;

International Council of Nurses. Definition of Nursing. [Internet]: International Council of Nurses; [cited 2016 7 August]; Available from: https://www.icn.ch/about-icn/icn-definition-of-nursing/

Irwin A, Sharland M. Measuring antibiotic prescribing in hospitalised children in resource-poor countries: A systematic review. J Paediatr Child Health 2013;49(3):185-92.

Jandoc R, Burden AM, Mamdani M, Lévesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol 2015;68(8):950-6.

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 2014;11(10):1569-75.

Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? Arch Pediatr Adolesc Med 2001;155(9):1002-7.

Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285(16):2114-20.

Kawanami GH, Fortaleza CMCB. Factors predictive of inappropriateness in requests for parenteral antimicrobials for therapeutic purposes: A study in a small teaching hospital in Brazil. Scand J Infect Dis 2011;43(6-7):528-35.

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology — Drug Disposition,

Action, and Therapy in Infants and Children. N Engl J Med 2003;349(12):1157-67.

Kendrick JG, Carr RR, Ensom MHH. Pediatric Obesity: Pharmacokinetics and Implications for Drug Dosing. Clin Ther 2015;37(9):1897-923.

Kennedy RM, Luhmann J, Zempsky WT. Clinical Implications of Unmanaged Needle-Insertion Pain and Distress in Children. Pediatrics 2008;122(Suppl. 3):S130-3.

Khadem TM, Dodds Ashley E, Wrobel MJ, Brown J. Antimicrobial Stewardship: A Matter of Process or Outcome? Pharmacotherapy 2012;32(8):688-706.

King WJ, Le Saux N, Sampson M, Gaboury I, Norris M, Moher D. Effect of point of care information on inpatient management of bronchiolitis. BMC Pediatr 2007;7(4).

Kuster SP, Ruef C, Bollinger AK, Ledergerber B, Hintermann A, Deplazes C, et al. Correlation between case mix index and antibiotic use in hospitals. J Antimicrob Chemother 2008;62(4):837-42.

Kuster SP, Ruef C, Ledergerber B, Hintermann A, Deplazes C, Neuber L, et al. Quantitative Antibiotic Use in Hospitals: Comparison of Measurements, Literature Review, and Recommendations for a Standard of Reporting. Infection 2008;36(6):549-59.

Kreitmeyr K, von Both U, Pecar A, Borde JP, Mikolajczyk R, Huebner J. Pediatric antibiotic stewardship: successful interventions to reduce broad-spectrum antibiotic use on general pediatric wards. Infection 2017;45(4):493-504.

Ladenheim D, Rosembert D, Hallam C, Micallef C. Antimicrobial stewardship: the role of the nurse. Nurs Stand 2013;28(6):46-9.

LaRosa LA, Fishman NO, Lautenbach E, Koppel RJ, Morales KH, Linkin DR. Evaluation of Antimicrobial Therapy Orders Circumventing an Antimicrobial Stewardship Program: Investigating the Strategy of “Stealth Dosing”. Infect Control Hosp Epidemiol 2007;28(5):551-6.

Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance—the need for global solutions. The Lancet Infectious Diseases 2013;13(12):1057-98.

Laxminarayan R, Matsoso P, Pant S, Brower C, Rottingen J-a, Klugman K, et al. Access to effective antimicrobials : a worldwide challenge. The Lancet 2016;387(10014):168-75.

Le Doare K, Barker CIS, Irwin A, Sharland M. Improving antibiotic prescribing for children in the resource-poor setting. Br J Clin Pharmacol 2015;79(3):446-55.

Lee BR, Goldman JL, Yu D, Myers AL, Stach LM, Hedican E, et al. Clinical Impact of an Antibiotic Stewardship Program at a Children’s Hospital. Infect Dis Ther 2017;6(1):103-13.

Lee J, Pai H, Kim YK, Kim NH, Eun BW, Kang HJ, et al. Control of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a children's hospital by changing antimicrobial agent usage policy. J Antimicrob Chemother 2007;60(3):629-37.

Lee KR, Bagga B, Arnold SR. Reduction of Broad-Spectrum Antimicrobial Use in a Tertiary Children's Hospital Post Antimicrobial Stewardship Program Guideline Implementation. Pediatr Crit Care Med 2016;17(3):187-93.

Levy ER, Swami S, Dubois SG, Wendt R, Banerjee R. Rates and Appropriateness of Antimicrobial Prescribing at an Academic Children's Hospital, 2017-2010. Infect Control Hosp Epidemiol 2012;33(4):346-53.

Liem TBY, Heerdink ER, Egberts ACG, Rademaker CMA. Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. Eur J Clin Microbiol Infect Dis 2010;29(10):1301-3.

Lighter-Fisher J, Desai S, Stachel A, Pham VP, Klejmont L, Dubrovskaya Y. Implementing an Inpatient Pediatric Prospective Audit and Feedback Antimicrobial Stewardship Program Within a Larger Medical Center. Hospital Pediatrics 2017;7(9):516-22.

Likic R, Maxwell SRJ. Prevention of medication errors: teaching and training. Br J Clin Pharmacol 2009;67(6):656-61.

Linkin DR, Fishman NO, Landis JR, Barton TD, Gluckman S, Kostman J, et al. Effect of Communication Errors During Calls to an Antimicrobial Stewardship Program. Infect Control Hosp Epidemiol 2007;28(12):1374-81.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus

Aureus Infections in Adults and Children. Clin Infect Dis 2011;52(3):e18-e55.

MacDougall C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. Clin Microbiol Rev 2005;18(4):638-56.

Magsarili HK, Girotto JE, Bennett NJ, Nicolau DP. Making a Case for Pediatric Antimicrobial Stewardship Programs. Pharmacotherapy: 2015;35(11):1026-36.

Mallik M. Advocacy in nursing — a review of the literature. J Adv Nurs 1997;25(1):130-8.

Manning ML, Giannuzzi D. Keeping Patients Safe: Antibiotic Resistance and the Role of Nurse Executives in Antibiotic Stewardship. J Nurs Adm 2015;45(2):67-9.

Manning ML, Pfeiffer J, Larson EL. Combating antibiotic resistance: The role of nursing in antibiotic stewardship. Am J Infect Control 2016;44(12):1454-7.

Mattick K, Kelly N, Rees C. A window into the lives of junior doctors: narrative interviews exploring antimicrobial prescribing experiences. J Antimicrob Chemother 2014;69(8):2274-83.

McCulloh RJ, Patel K. Recent Developments in Pediatric Community-Acquired Pneumonia. Curr Infect Dis Rep 2016;18(5):14.

McCulloh RJ, Queen MA, Lee B, Yu D, Stach L, Goldman J, et al. Clinical Impact of an Antimicrobial Stewardship Program on Pediatric Hospitalist Practice, a 5-Year Retrospective Analysis. Hospital Pediatrics 2015;5(10):520-7.

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66(7):e1–e48.

McGowan JE. Antimicrobial stewardship—the State of the Art in 2011: Focus on Outcome and Methods. Infect Control Hosp Epidemiol 2012;33(4):331-7.

McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. The Lancet Infectious Diseases 2016;16(8):e139-e52.

Metjian TA, Prasad PA, Kogon A, Coffin SE, Zaoutis TE. Evaluation of an Antimicrobial Stewardship Program at a Pediatric Teaching Hospital. Pediatr Infect Dis J 2008;27(2):106–11.

Miller AD, Piro CC, Rudisill CN, Bookstaver PB, Bair JD, Bennett CL. Nighttime and Weekend Medication Error Rates in an Inpatient Pediatric Population. Ann Pharmacother 2010;44(11):1739-46.

Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES, et al. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis 2017;64(3):377-83.

Molloy L, McGrath E, Thomas R, Kaye KS, Rybak MJ. Acceptance of Pharmacist-Driven Antimicrobial Stewardship Recommendations

With Differing Levels of Physician Involvement in a Children's Hospital. Clin Pediatr (Phila) 2017;56(8):744-51.

Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a Structured Panel Process to Define Quality Metrics for Antimicrobial Stewardship Programs. Infect Control Hosp Epidemiol 2012;33(5):500-6.

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.

Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and Impact of a Computerized Pediatric Antiinfective Decision Support Program. Pediatrics 2001;108(4):e75.

Murni IK, Duke T, Kinney S, Daley AJ, Soenarto Y. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. Arch Dis Child 2015;100(5):454-9.

Neonatal Medicines Formulary (NMF) Consensus Group. Newborn Care Centre Clinical resources – Medications. Neomed Formularies. [Internet] Sydney, NSW [cited 2018 20 January]; Available from: www.seslhd.health.nsw.gov.au/rhw/Newborn_Care/guidelines_med.asp

Newland JG, Banerjee R, Gerber JS, Hersh AL, Steinke L, Weissman SJ. Antimicrobial Stewardship in Pediatric Care: Strategies and Future Directions. Pharmacotherapy 2012;32(8):735-43.

Newland JG, Stach LM, De Lurgio SA, Hedican E, Yu D, Herigon JC, et al. Impact of a Prospective-Audit-With-Feedback Antimicrobial Stewardship Program at a Children's Hospital. J Pediatric Infect Dis Soc 2012;1(3):179-86.

Newman RE, Hedican EB, Herigon JC, Williams DD, Williams AR, Newland JG. Impact of a Guideline on Management of Children Hospitalized With Community-Acquired Pneumonia. Pediatrics 2012;129(3):e597-604.

Nguyen-Ha P-T, Howrie D, Crowley K, Vetterly CG, McGhee W, Berry D, et al. A Quality Assessment of a Collaborative Model of a Pediatric Antimicrobial Stewardship Program. Pediatrics 2016;137(5):e20150316.

NSW Ministry of Health. Medication Handling in NSW Public Health Facilities. Policy Directive (PD2013_043) [Internet] Sydney: NSW Health; 2013 [updated 27 November 2013 cited 2018 20 January]; Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2013_043.pdf

Nursing and Midwifery Board of Australia. Registered nurse standards for practice. Nursing and Midwifery Board of Australia; 2016 Available

from: http://www.nursingmidwiferyboard.gov.au/Codes-Guidelines-Statements/Professional-standards.aspx

Olans RD, Nicholas PK, Hanley D, DeMaria A, Jnr. Defining a Role for Nursing Education in Staff Nurse Participation in Antimicrobial Stewardship. J Contin Educ Nurs 2015;46(7):318-21.

Olans RN, Olans RD, DeMaria JA. The Critical Role of the Staff Nurse in Antimicrobial Stewardship—Unrecognized, but Already There. Clin Infect Dis 2016;62(1):84-9.

Osowicki J, Gwee A, Noronha J, Palasanthiran P, McMullan B, Britton PN, et al. Australia-wide point prevalence survey of the use and appropriateness of antimicrobial prescribing for children in hospital. Med J Aust 2014;201(11):657-62.

Paediatric Formulary Committee. British National Formulary for Children [Internet]. UK: BMJ Group and Royal Pharmacuetical Society; 2017 [cited 20 January 2018].

Page MA, Bajorek BV, Brien J-aE. Prescribing in Teaching Hospitals: a Qualitative Study of Social and Cultural Dynamics. Journal of Pharmacy Practice and Research 2008;38(4):286-91.

Parker RA, Rea LM. Designing and Conducting Survey Research: A Comprehensive Guide. 4th Edition ed. San Francisco (CA): Jossey-Bass; 2014.

Patel SJ, Saiman L. Principles and Strategies of Antimicrobial Stewardship in the Neonatal Intensive Care Unit. Semin Perinatol 2012;36(6):431-6.

Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Monitoring and patient education—2015. Am J Health Syst Pharm 2016;73(17):1307-30.

Perry C. The infection control nurse in England: past, present and future. British Journal of Infection Control 2005;6(5):18-21.

Pollack LA, Plachouras D, Sinkowitz-Cochran R, Gruhler H, Monnet DL, Weber JT. A concise set of structure and process indicators to assess and compare antimicrobial stewardship programs among EU and US Hospitals: Results from a multinational expert panel. Infect Control Hosp Epidemiol 2016;37(10):1201-11.

Porta A, Hsia Y, Doerholt K, Spyridis N, Bielicki J, Menson E, et al. Comparing neonatal and paediatric antibiotic prescribing between hospitals: a new algorithm to help international benchmarking. J Antimicrob Chemother 2012;67(5):1278-86.

Pulcini C, Huttner A. CMI policy on antimicrobial stewardship research. Clin Microbiol Infect 2018;28(2):91-2.

Raastad R, Tvete IF, Abrahamsen TG, Berild D, Leegaard TM, Walberg M, et al. A worrying trend in weight-adjusted paediatric antibiotic use in a Norwegian tertiary care hospital. Acta Paediatr 2015;104(7):687-92.

Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. J Antimicrob Chemother 2003;52(5):764-71.

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;23(8):524-32.

Rinke ML, Bundy DG, Velasquez CA, Rao S, Zerhouni Y, Lobner K, et al. Interventions to Reduce Pediatric Medication Errors: A Systematic Review. Pediatrics 2014;134(2):338-60.

Robertson AF. Reflections on Errors in Neonatology: II. The “Heroic” Years, 1950 to 1970. J Perinatol 2003;23:154-61.

Ross RK, Beus JM, Metjian TA, Localio RA, Shelov ED, Desai BR, et al. Safety of Automatic End Dates for Antimicrobial Orders to Facilitate Stewardship. Infect Control Hosp Epidemiol 2016;37(8):974-8.

Ross RK, Hersh AL, Kronman MP, Newland JG, Metjian TA, Localio AR, et al. Impact of Infectious Diseases Society of America/Pediatric Infectious Diseases Society Guidelines on Treatment of Community-Acquired Pneumonia in Hospitalized Children. Clin Infect Dis 2014;58(6):834-8.

Ruel E, Wagner WE, Gillespie BJ. The Practice of Survey Research. Thousand Oaks (CA): SAGE Publications; 2015.

Rutman L, Wright DR, O'Callaghan J, Spencer S, Lion KC, Kronman MP, et al. A Comprehensive Approach to Pediatric Pneumonia: Relationship Between Standardization, Antimicrobial Stewardship, Clinical Testing, and Cost. The J Healthc Qual 2017;39(4):e59-e69.

SA Health. National Antimicrobial Utilisation Surveillance Program(NAUSP). [Internet] 2017; Available from: http://www.sahealth.sa.gov.au/nausp

Sáez-llorens X, Castrejón De Wong MM, Castaño E, De suman O, De morös D, De atencio I. Impact of an antibiotic restriction policy on hospital expenditures and bacterial susceptibilities: a lesson from a pediatric institution in a developing country. Pediatr Infect Dis J 2000;19(3):200-6.

Schwartz DN, Evans RS, Camins BC, Khan YM, Lloyd JF, Shehab N, et al. Deriving Measures of Intensive Care Unit Antimicrobial Use from Computerized Pharmacy Data Methods, Validation, and Overcoming Barriers. Infect Control Hosp Epidemiol 2011;32(5):472-80.

Scottish Antimicrobial Prescribing Group. Exploring the role of nurses and midwives in antimicrobial stewardship. 2014 [cited 2016 10 December]; Available from: http://www.nes.scot.nhs.uk/media/3065666/exploring_role_of_nurses_and_midwives_in_antimicrobial_stewardship_report.pdf

Seah VXF, Ong RYL, Lim ASY, Chong CY, Tan NWH, Thoon KC. Impact of a Carbapenem Antimicrobial Stewardship Program on Patient Outcomes. Antimicrob Agents Chemother 2017;61(9):e00736-17.

Seah XFV, Ong YLR, Tan SW, Krishnaswamy G, Chong CY, Tan NWH, et al. Impact of an Antimicrobial Stewardship Program on the Use of

Carbapenems in a Tertiary Women's and Children's Hospital, Singapore. Pharmacotherapy 2014;34(11):1141-50.

Sedgwick P. Limits of agreement (Bland-Altman method). BMJ 2013;346:f1630.

Sedgwick P. Convenience sampling. BMJ 2013;347:f6304.

Seemungal IA, Bruno CJ. Attitudes of Housestaff toward a Prior-Authorization-Based Antibiotic Stewardship Program. Infect Control Hosp Epidemiol 2012;33(4):429-31.

Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? The rational clinical examination systematic review. JAMA 2017;318(5):462-71.

Sick AC, Lehmann CU, Tamma PD, Lee CKK, Agwu AL. Sustained savings from a longitudinal cost analysis of an internet-based preapproval antimicrobial stewardship program. Infect Control Hosp Epidemiol 2013;34(6):573-80.

Smith MJ, Kong M, Cambon A, Woods CR. Effectiveness of Antimicrobial Guidelines for Community-Acquired Pneumonia in Children. Pediatrics 2012;129(5):e1326-e33.

Spyridis N, Syridou G, Goossens H, Versporten A, Kopsidas J, Kourlaba G, et al. Variation in paediatric hospital antibiotic guidelines in Europe. Arch Dis Child 2016;101:72–6.

Srinivasan A, Pollack LA. Core Elements of Hospital Antibiotic Stewardship Programs From the Centers for Disease Control and Prevention. Clin Infect Dis 2014;59(suppl. 3):S97-100.

Stach LM, Hedican EB, Herigon JC, Jackson MA, Newland JG. Clinicians' Attitudes Towards an Antimicrobial Stewardship Program at a Children's Hospital. J Pediatric Infect Dis Soc 2012;1(3):190-7.

Stevenson KB, Balada-Llasat J-M, Bauer K, Deutscher M, Goff D, Lustberg M, et al. The economics of antimicrobial stewardship: the current state of the art and applying the business case model. Infect Control Hosp Epidemiol 2012;33(4):389-97.

Stocker M, Ferrao E, Banya W, Cheong J, Macrae D, Furck A. Antibiotic surveillance on a paediatric intensive care unit: easy attainable strategy at low costs and resources. BMC Pediatr 2012;12:196.

Tamma PD, Holmes A, Dodds Ashley ES. Antimicrobial stewardship: another focus for patient safety? Curr Opin Infect Dis 2014;27(4):348-55.

Tamma PD, Sandora TJ. Clostridium difficile Infection in Children: Current State and Unanswered Questions. J Pediatric Infect Dis Soc 2012;1(3):230-43.

Turner RB, Valcarlos E, Loeffler AM, Gilbert M, Chan D. Impact of an Antimicrobial Stewardship Program on Antibiotic Use at a Nonfreestanding Children's Hospital. J Pediatric Infect Dis Soc 2017;6(3):e36-e40.

Unger NR, Gauthier TP, Cheung LW. Penicillin Skin Testing: Potential Implications for Antimicrobial Stewardship. Pharmacotherapy 2013;33(8):856-67.

Usonis V, Ivaskevicius R, Diez-Domingo J, Esposito S, Falup-Pecurariu OG, Finn A, et al. Comparison between diagnosis and treatment of community-acquired pneumonia in children in various medical centres across Europe with the United States, United Kingdom and the World Health Organization guidelines. Pneumonia 2016;8(1):5.

van Buul LW, Sikkens JJ, van Agtmael MA, Kramer MHH, van der Steen JT, Hertogh CMPM. Participatory action research in antimicrobial stewardship: a novel approach to improving antimicrobial prescribing in hospitals and long-term care facilities. J Antimicrob Chemother 2014;69(7):1734-41.

Venugopal V, Lehmann CU, Diener-West M, Agwu AL. Longitudinal evaluation of a World Wide Web–based antimicrobial stewardship program: Assessing factors associated with approval patterns and trends over time. Am J Infect Control 2014;42(2):100-5.

Walsh KE, Kaushal R, Chessare JB. How to avoid paediatric medication errors: a user's guide to the literature. Arch Dis Child 2005;90(7):698-702.

Wattier RL, Levy ER, Sabnis AJ, Dvorak CC, Auerbach AD. Reducing Second Gram-Negative Antibiotic Therapy on Pediatric Oncology and Hematopoietic Stem Cell Transplantation Services. Infect Control Hosp Epidemiol 2017;38(9):1039-47.

Weissman C. Analyzing intensive care unit length of stay data: Problems and possible solutions. Crit Care Med 1997;25(9):1594-600.

Welch S. Antimicrobial stewardship in Australian emergency departments. Emerg Med Australas 2015;27(5):427-30.

Williams DJ, Hall M, Shah SS, Parikh K, Tyler A, Neuman MI, et al. Narrow Vs Broad-spectrum Antimicrobial Therapy for Children Hospitalized With Pneumonia. Pediatrics 2013;132(5):e1141-e8.

Wilson SD, Dahl BB, Wells RD. An evidence-based clinical pathway for bronchiolitis safely reduces antibiotic overuse. Am J Med Qual 2002;17(5):195-9.

World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva: World Health Organization; 2015.

World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) :Structure and principles. [Internet] Oslo: Norwegian Institute of Public Health; Available from: http://www.whocc.no/atc/structure_and_principles/

World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Defined Daily Dose: Definition and general considerations of defined daily dose (DDD). Oslo, Norwegian Institute of Public Health; Available from: http://www.whocc.no/ddd/definition_and_general_considera/

Zaidi STR, Marriott JL, Nation RL. The role of perceptions of clinicians in their adoption of a web-based antibiotic approval system: do perceptions translate into actions? Int J Med Inform 2008;77(1):33-40.

Zaidi STR, Thursky KA. Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship. J Clin Pharm Ther 2013;38(6):490-7.

Zhang W, Shen X, Bergman U, Wang Y, Chen Y, Huang M, et al. Drug utilisation 90% (DU90%) profiles of antibiotics in five Chinese children's hospitals (2002-2006). Int J Antimicrob Agents 2008;32(3):250-5.

Zou X-x, Fang Z, Min R, Bai X, Zhang Y, Xu D, et al. Is nationwide special campaign on antibiotic stewardship program effective on ameliorating irrational antibiotic use in China? Study on the antibiotic use of specialized hospitals in China in 2011–2012. Journal of Huazhong University of Science and Technology [Medical Sciences] 2014;34(3):456-63.