Evaluating, Understanding and Managing Medication Incidents with High-Risk Antibiotics
2015_Hamad_Anas_1045375_ethesis

Hamad, Anas Ahmad E A

Awarding institution: King's College London

The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without proper acknowledgement.

END USER LICENCE AGREEMENT

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence. https://creativecommons.org/licenses/by-nc-nd/4.0/

You are free to:

- Share: to copy, distribute and transmit the work

Under the following conditions:

- Attribution: You must attribute the work in the manner specified by the author (but not in any way that suggests that they endorse you or your use of the work).
- Non Commercial: You may not use this work for commercial purposes.
- No Derivative Works - You may not alter, transform, or build upon this work.

Any of these conditions can be waived if you receive permission from the author. Your fair dealings and other rights are in no way affected by the above.

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Evaluating, Understanding and Managing Medication Incidents with High-Risk Antibiotics

Submitted by

Anas Ahmad Hamad

to King's College London as a thesis for the degree of

Doctor of Philosophy
Abstract

Medication incidents (MIs) were one of the top 3 patient-safety incidents reported to the National Reporting and Learning System in England and Wales over the last 10 years. Reported rates of MIs vary widely as different study methods and definitions are often used. Preventable medication harms could cost the National Health Service (NHS) in England alone £774 million a year. Antimicrobials are a drug class most often implicated in MIs. At least one-third of hospital inpatients are prescribed an antibiotic at some point during their stay.

Retrospective incident report analysis was performed to evaluate the prevalence, incidence and nature of antibiotic-associated MIs reported at two large acute teaching Trusts. This analysis confirmed that antibiotic MIs are common especially in the prescribing and administration stages. Omission and wrong dose/frequency were the most common MI types. It was also highlighted that detailed analysis of data from reports is essential in understanding MIs and in developing strategies to prevent their recurrence. A novel approach was used in the analysis of reported MIs by applying the concept of defined daily doses (DDDs), a measure of antibiotic consumption, to establish a more accurate picture of the magnitude of risk of error with this class of drugs. Using DDDs in the analysis of MIs allowed an incident rate to be determined, which provided additional information about the relative frequency of error with particular antibiotic agents than the absolute numbers alone. It also highlighted the disproportionate risk associated with less commonly prescribed antibiotics not identified using MI reporting rates alone, especially if data is analysed over shorter time periods. Therefore, incident data should be interpreted alongside consumption data when determining which drugs are most ‘risky’ in practice. Important information (e.g. drug name) was missing in some reports, therefore it is necessary to make all essential fields in incident reporting systems mandatory. As data could only be compared once categories used for MI classification had been standardised, this highlights the importance of harmonised MI categories for comparison between different hospitals.

The analysis of reported antibiotic-associated MIs at one large acute teaching Trust identified that one-third of dose/frequency errors reported were related to gentamicin and vancomycin. A local Failure Modes and Effects Analysis for gentamicin identified that risks with dose calculation and prescribing were greater than risks with preparation of infusions. A systematic review was conducted to identify interventions to manage the risks identified with dosing gentamicin and vancomycin. This review identified electronic clinical decision support (CDS) as an effective intervention. The existence of electronic prescribing and patient record systems at the Trust facilitated the development of electronic dose calculators for calculating initial treatment doses of gentamicin and vancomycin. A pre-post intervention study was conducted to assess the impact of these calculators on the accuracy of initial doses. This study showed that introduction of the calculators led to a significant improvement in the prescribing of initial doses of these agents. Use of such CDS tools can give rise to improvements in clinical care and this study suggests that organisations implementing electronic prescribing systems strongly consider including such CDS tools in their programmes.

An interview-based study was undertaken to explore the views and experiences of doctors in prescribing gentamicin and vancomycin and the resources and methods they use to calculate the initial dose of these drugs. The main patterns for accurate dosing found in this study were being a SHO or JCF, using the Trust dosing tools, and treating a non-
elderly patient with normal renal function. Prescribers who used the calculators or guidelines accurately were more likely to prescribe a correct dose compared to those who used standard doses (e.g. 5mg/kg gentamicin). However, some prescribers could not use the calculators properly which shows that more education on their use is needed. The main factors identified by prescribers to influence dose selection were patient parameters, Trust dosing tools, Microbiology advice, and clinical condition of the patient. A number of prescribers who obtained a correct dose using the calculators did not know some of the underlying calculations/values needed for dosing (e.g. ideal body weight). This identified that some prescribers may have an overreliance on CDS tools without a sufficient understanding of the parameters required which masks a potential source of error. Some doctors criticised the design of the calculators and preferred more accessible, user-friendly calculators that are integrated with other electronic systems in the Trust (e.g. electronic patient records). Taking doctors’ comments and recommendations into consideration in designing and updating dosing tools would increase the ownership of these tools and potentially their use to enhance safe and effective prescribing.
This thesis is dedicated to my late father, Dr Ahmad Hamad.

It is your shining example that I try to emulate in all that I do.

Thank you for everything.
Acknowledgements

First of all, I sincerely thank ALLAH the Most High for giving me the health, strength and determination to complete this PhD research.

During this research study, I have had the great honour and privilege of working alongside many experts and professionals. First and foremost, I would like to express sincere gratitude to my supervisors for providing me with the opportunity to undertake this research. I have learnt a lot from Dr Cate Whittlesea and I am indebted to her for nurturing my research skills, critical thinking, and scientific writing. Her continuous guidance and support throughout this research were absolutely invaluable. I am also grateful to Mrs Gillian Cavell for adding her practical experience into the research, for facilitating everything for me in the research site, and for providing constant advice and assistance. Both provided continuous inspiration, motivation and encouragement.

I am really thankful to both of my research advisers, Dr James Hinton from King’s College Hospital and Mr Paul Wade from Guy’s and St Thomas’ Hospital, for participating in this research with their antimicrobial expertise and for providing the antibiotic data required from each hospital. I much appreciate their support and guidance. I would also like to thank Peter Milligan for his expertise in statistical analysis. I am very grateful to my sponsor, Hamad Medical Corporation, for funding my PhD and securing everything I needed.

This research would not have been possible without the help and support of many people. I am thankful to Moira Talpaert for teaching me how to calculate drug consumption and providing the required data, Alice Oborne for providing the incident reporting data from Guy’s and St Thomas’ Hospital, Mimoza Neziri for providing the required patient notes from Patient Records Department, Karen Poole for her help in setting the search strategy of the systematic review, Hardeep Sahota and Peter Hughes for their help in updating and promoting the dose calculators, and Liam Slater for providing the data on usage of the dose calculators. I would especially like to thank all of the staff at the Pharmacy Department at King’s College Hospital for providing me with help and support. Thanks to nurses and nurse aids in the hospital who helped me when I was collecting data on the wards. I am also grateful to the doctors who dedicated their time and participated in the interviews. Finally, thanks to my colleagues and friends who supported me in writing and strengthened me to strive towards my goal.

Last but not least, I would like to thank my lovely family. Words cannot express how grateful I am to my precious mother, Maha, who have actually encouraged me to pursue a PhD degree. Her unconditional love, motivation and prayers were what sustained me that far. I would also like to thank my dear brother, Mohammed, for being always there for me. Very special thanks to my beloved wife, Maisa, for all the support, encouragement and reassurance she provided me with during this research. Without her being by my side, completing this PhD would not have been possible. My adorable little angel, Layan, was the best thing happened to me in the 4 years of this research. I would like to thank her for the extreme joy and happiness she brought into my life.
Table of Contents

ABSTRACT .................................................................................................................. 2
ACKNOWLEDGEMENTS ............................................................................................ 5
TABLE OF CONTENTS ............................................................................................... 6
LIST OF TABLES ......................................................................................................... 10
LIST OF FIGURES ...................................................................................................... 12
LIST OF APPENDICES .............................................................................................. 14
GLOSSARY OF TERMS ................................................................................................. 15
CHAPTER 1 .................................................................................................................. 17
GENERAL INTRODUCTION ....................................................................................... 17
1.1. BACKGROUND ..................................................................................................... 18
1.2. PATIENT SAFETY AND HEALTHCARE QUALITY ............................................. 19
  1.2.1. Patient safety .................................................................................................. 19
  1.2.2. Clinical governance and risk management ...................................................... 21
  1.2.3. Safety culture .................................................................................................. 23
  1.2.4. Safety models .................................................................................................. 24
  1.2.5. Taxonomy ....................................................................................................... 28
  1.2.6. Incidence and burden of patient safety incidents ............................................ 32
1.3. MEDICATION SAFETY INCIDENTS .................................................................... 33
  1.3.1. Medication-use process .................................................................................. 33
  1.3.2. Definition ........................................................................................................ 36
  1.3.3. Classification ................................................................................................... 37
  1.3.4. Detection methods .......................................................................................... 41
  1.3.5. Prevalence ....................................................................................................... 45
  1.3.6. Cost .................................................................................................................. 46
1.4. MEDICATION SAFETY WITH ANTIBIOTICS .................................................... 46
1.5. MEDICATION INCIDENTS BASED ON THE STAGE OF OCCURRENCE IN THE MEDICATION-USE PROCESS, WITH A FOCUS ON ANTIBIOTICS ...................................................................................................................... 48
  1.5.1. Prescribing and transcribing errors ................................................................. 48
  1.5.2. Administration errors ...................................................................................... 52
  1.5.3. Dispensing errors ............................................................................................ 55
  1.5.4. Monitoring errors ............................................................................................ 56
1.6. IMPLICATIONS FOR THE PRESENT RESEARCH ............................................. 57
1.7. THESIS AIMS AND OBJECTIVES ....................................................................... 58
CHAPTER 2 .................................................................................................................. 59
RISK OF MEDICATION SAFETY INCIDENTS WITH ANTIBIOTIC USE .................... 59
2.1. INTRODUCTION ................................................................................................... 60
  2.1.1. Patient safety incident reporting ................................................................. 60
  2.1.2. Characteristics and requirements of successful incident reporting systems ...... 61
  2.1.3. International incident reporting systems ....................................................... 62
  2.1.4. Incident reporting system in the UK ............................................................. 62
  2.1.5. Strengths of incident reporting systems ....................................................... 65
  2.1.6. Limitations of incident reporting systems ................................................... 66
  2.1.7. Actions to improve incident reporting ......................................................... 67
  2.1.8. Rates of medication incident reporting ....................................................... 69
  2.1.9. Reporting of antibiotic incidents ................................................................. 69
2.2. AIM AND OBJECTIVES ....................................................................................... 70
  2.2.1. Aim of study .................................................................................................... 70
  2.2.2. Study objectives ............................................................................................. 70
# Table of contents

2.3. METHODS ........................................................................................................... 70
  2.3.1. Study design ................................................................................................. 70
  2.3.2. Study setting ................................................................................................. 71
  2.3.3. Inclusion/exclusion criteria ......................................................................... 71
  2.3.4. Research permission ................................................................................. 71
  2.3.5. Definitions .................................................................................................. 72
  2.3.6. Medication incident reporting process ..................................................... 72
  2.3.7. Data collection and processing ................................................................. 72

2.4. RESULTS ........................................................................................................... 74
  2.4.1. Reported medication incidents ................................................................. 74
  2.4.2. Stages and types of medication incidents ................................................. 75
  2.4.3. Antibiotics involved in medication incidents ........................................... 76
  2.4.4. Severity of medication incidents .............................................................. 78
  2.4.5. The relationship between medication incidents and defined daily doses ... 80
  2.4.6. Reports of medication incidents by clinical staff ....................................... 81
  2.4.7. Specialties associated with medication incidents ...................................... 81

2.5. DISCUSSION ................................................................................................... 83
  2.5.1. Rate of antibiotic-related medication incidents ....................................... 83
  2.5.2. The relationship between medication incidents and defined daily doses ... 83
  2.5.3. Stages and types of medication incidents ................................................. 84
  2.5.4. Severity of medication incidents .............................................................. 85
  2.5.5. Medication incidents associated with paediatrics .................................... 86
  2.5.6. Clinical staff who reported medication incidents ...................................... 86
  2.5.7. Quality of information in medication incident reports ......................... 87
  2.5.8. The issue of under-reporting ................................................................. 88
  2.5.9. Limitations ................................................................................................. 89

2.6. FURTHER WORK ............................................................................................ 90

2.7. CONCLUSION ................................................................................................. 90

CHAPTER 3 ............................................................................................................ 91

## INTRODUCTION TO IMPROVE THE ACCURACY OF GENTAMICIN AND VANCYMYCIN DOSING: A SYSTEMATIC REVIEW ................................................................. 91

3.1. INTRODUCTION .............................................................................................. 92

3.2. AIM AND OBJECTIVES ................................................................................. 93
  3.2.1. Aim of study .............................................................................................. 93
  3.2.2. Study objectives ....................................................................................... 93

3.3. METHODS ....................................................................................................... 93
  3.3.1. Criteria for considering studies for this review ....................................... 93
  3.3.2. Search strategy for identification of studies ........................................... 94
  3.3.3. Data collection and analysis ................................................................. 95

3.4. RESULTS ......................................................................................................... 97
  3.4.1. Results of the study search .................................................................... 97
  3.4.2. Study characteristics ............................................................................. 99
  3.4.3. Quality of studies ................................................................................. 103
  3.4.4. Risk of bias ............................................................................................. 104
  3.4.5. Definition of an appropriate dose ......................................................... 107
  3.4.6. Impact of interventions ........................................................................ 109

3.5. DISCUSSION ................................................................................................ 111
  3.5.1. Dosing outcomes evidence .................................................................... 111
  3.5.2. Clinical outcomes evidence ................................................................. 113
  3.5.3. Which type of intervention to use? ....................................................... 113
  3.5.4. Limitations ............................................................................................ 114
AN EVALUATION OF THE IMPACT OF DOSE CALCULATORS ON THE ACCURACY OF GENTAMICIN AND VANCOMYCIN INITIAL DOSES .............................................. 116

1. INTRODUCTION ........................................................................................................ 117
2. AIM AND OBJECTIVES ............................................................................................. 128
3. METHODS .................................................................................................................. 128
4. RESULTS .................................................................................................................... 137
5. DISCUSSION .............................................................................................................. 148
6. FURTHER WORK ....................................................................................................... 152
7. CONCLUSION .......................................................................................................... 153

AN INTERVIEW-BASED STUDY TO EXPLORE PRESCRIBING OF INITIAL DOSES OF GENTAMICIN AND VANCOMYCIN ........................................... 154

1. INTRODUCTION ....................................................................................................... 155
2. CAUSES AND FACTORS ........................................................................................... 156
3. QUALITATIVE RESEARCH STUDIES ..................................................................... 158
4. UNDERSTANDING ANTIMICROBIAL PRESCRIBING PRACTICE ........................... 160
5. INVESTIGATING GENTAMICIN AND VANCOMYCIN PRESCRIBING ..................... 162
Table of contents

5.1.6. Problems with gentamicin and vancomycin dosing .................................................. 164
5.2. AIMS AND OBJECTIVES ................................................................................................. 165
  5.2.1. Aim of study .................................................................................................................. 165
  5.2.2. Study objectives .............................................................................................................. 165
5.3. METHODS ......................................................................................................................... 166
  5.3.1. Study design ..................................................................................................................... 166
  5.3.2. Study setting .................................................................................................................... 166
  5.3.3. Research permission ....................................................................................................... 168
  5.3.4. Development of data collection tools ............................................................................. 168
  5.3.5. Study participants .......................................................................................................... 170
  5.3.6. Participant recruitment process ...................................................................................... 172
  5.3.7. Data collection and processing ...................................................................................... 174
5.4. RESULTS ......................................................................................................................... 175
  5.4.1. Study participants .......................................................................................................... 175
  5.4.2. Interview results ............................................................................................................. 177
  5.4.3. Dose calculation resources ........................................................................................... 178
  5.4.4. Therapy monitoring ....................................................................................................... 190
  5.4.5. Conditions and factors that might affect dose prescribing decision ....................... 195
  5.4.6. Doctor views and opinions about drug dosing .............................................................. 200
  5.4.7. Common patterns for accurate prescribing ................................................................. 214
5.5. DISCUSSION ................................................................................................................... 214
  5.5.1. Main findings of the study ............................................................................................ 214
  5.5.2. Dose calculation resources ........................................................................................... 216
  5.5.3. Therapy monitoring ...................................................................................................... 218
  5.5.4. Conditions and factors that might affect dose prescribing decision ....................... 219
  5.5.5. Possible sources of dosing errors and recommendations to avoid their occurrence ... 220
  5.5.6. Limitations .................................................................................................................... 225
5.6. FURTHER WORK ............................................................................................................. 226
5.7. CONCLUSION ............................................................................................................... 227

CHAPTER 6 .............................................................................................................................. 228

GENERAL DISCUSSION ............................................................................................................ 228
6.1. OVERVIEW ......................................................................................................................... 229
6.2. EVALUATING ANTIBIOTIC-RELATED MEDICATION SAFETY INCIDENTS ................. 230
6.3. UNDERSTANDING PRESCRIBING OF GENTAMICIN AND VANCOMYCIN INITIAL DOSES 234
6.4. MANAGING DOSING ERRORS IN GENTAMICIN AND VANCOMYCIN ......................... 237
6.5. IMPLICATIONS FOR POLICY AND PRACTICE ............................................................ 240
6.6. LIMITATIONS .................................................................................................................... 243
6.7. FURTHER WORK .............................................................................................................. 244
6.8. SUMMARY OF FINDINGS ............................................................................................... 246
6.9. OVERALL CONCLUSION ................................................................................................. 247

REFERENCES .......................................................................................................................... 248

APPENDICES .......................................................................................................................... 274

RESEARCH OUTCOMES .......................................................................................................... 311
List of Tables

Table 1.1. The National Patient Safety Agency patient safety incident taxonomy (adapted from NPSA, 2004, p.97) .......................................................... 28
Table 1.2. Comparison of the medication-use process between hospitals in the UK, US and Europe (adapted from James, 2009, p.36) ......................................................... 35
Table 1.3. Examples of psychological classes of medication errors with potential preventive strategies (from Ferner and Aronson, 2006, p.8-9) ........................................ 38
Table 1.4. Summary of medication incident detection methods (adapted from James, 2009, p.28-29) ............................................................................................. 43
Table 1.5. Some large scale studies that reported on the detection and rate of prescribing errors (PEs) with antibiotics ........................................................................ 51
Table 1.6. Some large scale studies that reported on the detection and rate of administration errors (AEs) with antibiotics ................................................................. 54

Table 2.1. Demographics of the submitted medication incident reports .................. 75
Table 2.2. Analysis of the stages of medication-use process in which antibiotic medication incidents occurred .................................................................................. 75
Table 2.3. Analysis of antibiotic medication incident types .................................... 76
Table 2.4. Analysis of antibiotic classes associated with medication incidents........ 77
Table 2.5. Analysis of antibiotic agents associated with medication incidents ........ 78
Table 2.6. Analysis of severity of antibiotic medication incidents ....................... 79
Table 2.7. The relationship between antibiotic medication incidents and consumption in terms of defined daily doses ........................................................................ 81
Table 2.8. Analysis of clinical staff who reported antibiotic medication incidents ...... 82
Table 2.9. Analysis of divisions/specialties associated with medication incidents ...... 82
Table 2.10. Quality of data in medication incident reports submitted to the National Reporting and Learning System (NHS England, 2014) compared to reports in this study ........................................................... 88
Table 2.11. Rates of medication incident reporting at both research Trusts compared to the UK national average .................................................................................. 89
Table 3.1. Criteria used to select studies to be included in the systematic review ...... 95
Table 3.2. Summary of the 12 studies included in the systematic review ............. 101
Table 3.3. Quality of the included studies assessed using the TREND checklist with section and overall scores .................................................................105

Table 3.4. Risk of bias in the included studies for each EPOC criteria and overall....106

Table 3.5. The definition of an appropriate dose/regimen in the included studies.... 108

Table 4.1. Barriers to optimal adoption and effectiveness of clinical decision support systems for medication management and general solutions to overcome them (adapted from Teich et al, 2005) ........................................................................................................124

Table 4.2. Equations/calculations used in gentamicin and vancomycin dose calculators .................................................................134

Table 4.3. Demographic data of gentamicin patients ..................................................139

Table 4.4. Demographic data of vancomycin patients ..............................................139

Table 4.5. Analysis of the accuracy of gentamicin initial doses .................................140

Table 4.6. Analysis of the accuracy of vancomycin initial doses ...............................143

Table 4.7. Sub-analysis of the accuracy of vancomycin initiation regimens ..............143

Table 4.8. Accuracy of gentamicin doses based on the specialty of prescribers ...... 144

Table 4.9. Accuracy of vancomycin regimens based on the specialty of prescribers ..145

Table 4.10. The difference in gentamicin dose accuracy between high risk and non-high risk patients .................................................................146

Table 4.11. The difference in vancomycin dose accuracy between high risk and non-high risk patients .................................................................147

Table 5.1. Conditions in which prescribers at the Trust should contact Clinical Microbiology .........................................................................................167

Table 5.2. Demographics of the participant doctors and their dosing accuracy ........176

Table 5.3. Rates of drug prescribing, usage of Trust dosing tools, and dose accuracy by the participant doctors ........................................................................177

Table 5.4. The process of creating research themes out of the identified codes .........178

Table 5.5. The working conditions described by study participants when prescribed gentamicin and vancomycin .......................................................................197

Table 5.6. The possible sources of dosing errors with gentamicin and vancomycin identified by participants ........................................................................212

Table 5.7. The recommendations suggested by participants to avoid dosing errors with gentamicin and vancomycin .................................................................213
List of Figures

**Figure 1.1.** Integrating approaches of clinical governance (from Scally and Donaldson, 1998) ................................................................. 21

**Figure 1.2.** Reason’s psychological classification of human errors (from Reason, 1990, p.207) ................................................................. 25

**Figure 1.3.** Reason’s Swiss cheese model of accident causation (from Reason *et al*, 2001, p.ii21) ................................................................. 26

**Figure 1.4.** Vincent’s accident model for healthcare organisations (from Vincent *et al*, 1998, p.1155) ................................................................. 27

**Figure 1.5.** Conceptual framework for the international classification for patient safety (from WHO, 2009, p.8) ................................................................. 30

**Figure 1.6.** The National Patient Safety Agency matrix for classifying the risk of associated with patient safety incidents (adapted from NPSA, 2008, p.6-10)......... 31

**Figure 1.7.** Medication-use process in hospitals (adapted from IoM, 2007, p.68) ....... 34

**Figure 1.8.** The relationship between the different kinds of medication incidents in the context of all patient safety incidents (adapted from Ferner and Aronson, 2006, p.1012) ......................................................... 36

**Figure 1.9.** Index for categorising medication incidents (from NCC MERP, 2001) ..... 40

**Figure 1.10.** The medication error iceberg (from Smith, 2004, p.22)....................... 41

**Figure 2.1.** The Medicines and Healthcare products Regulatory Agency and NHS England model for the flow of information needed to improve reporting of medication incidents in the NHS (from NHS England, 2014, p.6)......................................................... 64

**Figure 3.1.** Study search flow chart........................................................................ 98

**Figure 3.2.** Main characteristics of the studies included in the systematic review .... 99

**Figure 4.1.** Computerised prescriber order entry (CPOE) and clinical decision support systems (CDSS) integrated within the structure–process–outcome framework of Donabedian model of patient safety (from Chang *et al*, 2011, p.350)............... 121

**Figure 4.2.** A step-by-step summary of the data collection, intervention implementation and data analysis stages of the study............................................. 129
List of Figures

Figure 4.3. Study participant flow chart................................................................. 138

Figure 4.4. Distribution of gentamicin doses before and after the calculator .......... 141

Figure 4.5. Distribution of vancomycin loading doses before and after the calculator 142

Figure 4.6. Distribution of vancomycin maintenance doses before and after the calculator ................................................................. 142

Figure 5.1. Prescribing error producing conditions identified by Dean et al (2002c, p.3) .......................................................................................................................... 159

Figure 5.2. A flow diagram of the study process ..................................................... 173

Figure 6.1. Miller’s framework for clinical assessment (1990, p.63)...................... 242
List of Appendices

Appendix 2.1. Adverse incident report form at Trust A ..........................................................275

Appendix 2.2. The terms used for stage of medication-use process and type of
medication incident in each Trust and the agreed terms used in this study ............277

Appendix 2.3. Risk matrix to grade the severity of adverse incidents ..................278

Appendix 3.1. Strategy used to search databases for relevant articles: Embase ........279

Appendix 3.2. Data extraction form: systematic review .....................................................283

Appendix 3.3. PRISMA checklist for assessing the reporting quality of systematic
reviews (from PRISMA Statement, 2009) .................................................................284

Appendix 3.4. TREND checklist for assessing the quality of non-randomised
comparative studies (from CDC, 2010) .................................................................285

Appendix 3.5. EPOC risk of bias criteria for assessing RCTs, CCTs and CBAs
(adapted from EPOC, 2009) ......................................................................................288

Appendix 4.1. Gentamicin calculator for males .................................................................289

Appendix 4.2. Vancomycin calculator for females ............................................................290

Appendix 4.3. Calculators’ promotion information ............................................................291

Appendix 4.4. Data collection form used in the study ......................................................296

Appendix 5.1. Pre-study information email sent to all doctors in the Trust ............297

Appendix 5.2. Invitation letter sent to all eligible doctors who prescribed a treatment
dose of gentamicin or vancomycin .................................................................298

Appendix 5.3. Participant information leaflet sent to all eligible doctors who
prescribed a treatment dose of gentamicin or vancomycin ..................................300

Appendix 5.4. Consent form signed by all interview participants ...............................302

Appendix 5.5. Final interview schedule used for interviewing participants ..........304

Appendix 5.6. An example of the process used to code the data collected through
interviews ..............................................................................................................308

Appendix 5.7. Characteristics of the prescribers of correct and incorrect doses of
gentamicin and vancomycin ...............................................................................309
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&amp;E</td>
<td>Accident and emergency</td>
</tr>
<tr>
<td>AE</td>
<td>Administration error</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>ASHP</td>
<td>American Society of Health-System Pharmacists</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>CBA</td>
<td>Controlled before-after study</td>
</tr>
<tr>
<td>CCT</td>
<td>Non-randomised controlled trial</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDS</td>
<td>Clinical decision support</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
</tr>
<tr>
<td>CME</td>
<td>Continuous medical education</td>
</tr>
<tr>
<td>CPOE</td>
<td>Computerised prescriber order entry</td>
</tr>
<tr>
<td>CQC</td>
<td>Care Quality Commission</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined daily dose</td>
</tr>
<tr>
<td>DE</td>
<td>Dosing error</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>eGFR</td>
<td>Electronic glomerular filtration rate</td>
</tr>
<tr>
<td>EPMA</td>
<td>Electronic prescribing and medicines administration system</td>
</tr>
<tr>
<td>EPOC</td>
<td>Effective Practice and Organisation of Care Group</td>
</tr>
<tr>
<td>EPR</td>
<td>Electronic patient records</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>FMEA</td>
<td>Failure modes and effects analysis</td>
</tr>
<tr>
<td>HMIC</td>
<td>Global Health, Health Management Information Consortium</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>IHI</td>
<td>Institute for Healthcare Improvement</td>
</tr>
<tr>
<td>IoM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>IPA</td>
<td>International Pharmaceutical Abstracts</td>
</tr>
<tr>
<td>ISMP</td>
<td>Institute for Safe Medication Practices</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MI</td>
<td>Medication incident</td>
</tr>
<tr>
<td>MUP</td>
<td>Medication-use process</td>
</tr>
<tr>
<td>NCC MERP</td>
<td>National Co-ordinating Council for Medication Error Reporting and Prevention</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NPSA</td>
<td>National Patient Safety Agency</td>
</tr>
<tr>
<td>NRLS</td>
<td>National Reporting and Learning System</td>
</tr>
<tr>
<td>OQE</td>
<td>Other quasi-experimental study</td>
</tr>
<tr>
<td>PE</td>
<td>Prescribing error</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PSI</td>
<td>Patient safety incident</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SrCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>TREND</td>
<td>Transparent Reporting of Evaluations with Nonrandomized Designs</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WoS</td>
<td>Web of Science Core Collection</td>
</tr>
</tbody>
</table>
Chapter 1

General Introduction
1.1. Background

Healthcare is one of the basic needs of any society. It helps to cure diseases, relieve suffering, and save lives. Although there has been a tremendous improvement in healthcare so that many previously fatal diseases have become easily treatable, healthcare itself is still considered a source of patient harm. Vincent (2011, p.ix) stated that

“While healthcare brings enormous benefits to us all, errors are common and patients are frequently harmed. The nature and scale of this harm is hard to comprehend. It is made up, worldwide, of hundreds of thousands of individual tragedies every year in which patients are traumatised, suffer unnecessary pain, are left disabled or die. Many more people have their care interrupted or delayed by minor errors and problems; these incidents are not as serious for patients but are a massive and relentless drain on scarce healthcare resources.”

There were mixed opinions about medicine in early times in which the double idea of death and doctor riding together was widely impending. In ancient Greece, Apollo was the god of physic and sender of diseases at the same time. The word ‘pharmakos’ meant both remedy and poison and the words kill and cure were nearly indistinguishable (Porter, 1999). Beauchamp and Childress (2001) identified 4 ethical principles in healthcare. Besides respect for autonomy (respect the decision making capacities of autonomous persons), justice (fair distribution of benefits and risks), and beneficence (provide benefits), non-maleficence was one of these principles which means that healthcare providers should not harm the patient or put him/her at risk of being harmed. Hippocrates, the legendary Greek doctor, had a famous dictum that says ‘first, do no harm’ (Vincent, 2011). In the context of modern medicine, Florence Nightingale was one of the first to address healthcare-associated risks, particularly in hospitals. She introduced her book Notes on Hospitals (1863, p.iii) with

“It may seem a strange principle to enunciate as the very first requirement in a Hospital that it should do the sick no harm.”

Over the past 30 years, several reports have been published on the size and burden of healthcare-related injuries. This has led to more recognition by governments and national regulatory agencies of the issue of patient safety and health service quality which has now
become widely accepted as a problem that needs to be tackled on both national and international levels. (Legido-Quigley et al, 2008)

1.2. Patient safety and healthcare quality

1.2.1. Patient safety

The potential harm of medicine was more recognised in the 1920s when the term ‘iatrogenic disease’ was first used. This term came from the Greek words ‘iatros’ and ‘genesis’, which mean physician and disease. So somehow it is the illness induced by a physician (Vincent, 2011). The World Health Organization (WHO, 2012) defined patient safety broadly as

“The absence of preventable harm to a patient during the process of health care.”

A more describing definition was provided by a group of world experts in patient safety (Emanuel et al, 2008, p.6);

“Patient safety is a discipline in the health care sector that applies safety science methods toward the goal of achieving a trustworthy system of health care delivery. Patient safety is also an attribute of health care systems; it minimizes the incidence and impact of, and maximizes recovery from, adverse events.”

One of the first publications in relation to patient safety was by Schimmel (1964) who encouraged the junior doctors at 3 hospital wards to report any adverse episodes that result from acceptable diagnostic/treatment procedures. He found that adverse episodes were reported for 20% of the 1,000 patients investigated in the study, including 16 that were fatal. Brennan et al (1991) conducted the Harvard Medical Practice Study, the first large-scale study on safety and quality in healthcare. They reviewed the records of 30,121 patients from 51 New York hospitals in 1984 and found that adverse incidents occurred in 3.7% of these patients; 27.6% of which were preventable. Another large study was conducted by Thomas et al (1999) where they assessed the records of 14,732 patients discharged from 28 hospitals in Utah and Colorado in 1992. They identified that 3.1% of these discharges were associated with errors; 57.7% of which were preventable.
Based on the two previous studies, the Institute of Medicine (IoM) published a landmark report ‘To Err is Human’ (Kohn et al, 2000) on the incidence and consequences of healthcare-associated harm in the US. The first sentence in the report (p.1) was

“The knowledgeable health reporter for the Boston Globe, Betsy Lehman, died from an overdose during chemotherapy. Willie King had the wrong leg amputated. Ben Kolb was eight years old when he died during ‘minor’ surgery due to a drug mix-up.”

This report estimated that up to 98,000 patients die every year due to poor patient care (Kohn et al, 2000) and has led to a significant response nationwide and globally by clinicians, researchers and politicians to tackle the issue. In 2004, the WHO launched the WHO Patient Safety programme with the aim of coordinating and accelerating improvements in patient safety on a global level (WHO, 2012).

Recently in the UK, an inquiry about Mid Staffordshire NHS Foundation Trust chaired by Sir Robert Francis (2010) found that poor patient care between 2005 and 2009 led to significantly high rates of avoidable patient harm (including death) when compared to the national average. This scandal sparked public and political debate which led the government to assign Professor Donald Berwick to review the issue and give his recommendations. In his report, Berwick (2013) emphasised the highly important role of patient safety in improving the quality of healthcare across the National Health Service (NHS). He stated (p.14) that

“Patient safety should be the ever-present concern of every person working in or affecting NHS-funded care. The quality of patient care should come before all other considerations in the leadership and conduct of the NHS, and patient safety is the keystone dimension of quality.”

Several other studies and reports have been published on the scope and extent of problems with patient safety (discussed further in section 1.2.6). In his final report about the Mid Staffordshire events which included a comprehensive review of the scandal, Francis (2013) addressed that the absence of effective clinical governance at the hospital was one of the main reasons for the tragedy. Clinical governance had been introduced as a comprehensive strategy to tackle the issue of patient safety and improve the quality of patient care on both individual and organisational levels (Scally and Donaldson, 1998).
1.2.2. Clinical governance and risk management

Clinical governance was introduced to the NHS in the late 1990s to enhance patient safety and health service quality. This strategy was first used in the business field with the aim to amend failures in providing standard services. Scally and Donaldson (1998, p.62) defined clinical governance as

“A system through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.”

The complexity and the rapid advancement of medicine increased the need for systems to assure consistency in providing high quality care to everyone (Kohn et al, 2000). Clinical governance is a comprehensive system which involves different approaches integrated together in order to achieve high quality healthcare (Figure 1.1).

Figure 1.1. Integrating approaches of clinical governance (from Scally and Donaldson, 1998)
Chapter 1: General Introduction

The WHO (1983) recognised four aspects of healthcare quality including professional performance, efficiency, risk management, and patients' satisfaction with the service provided. In 2001, the IoM identified six dimensions of quality in healthcare. These included the WHO aspects with slightly different terms (effectiveness, efficiency, safety, and patient-centeredness) in addition to timeliness and equitability.

In 1998, the Department of Health (DoH) published a paper about the quality in the new NHS. This paper emphasised that clinical governance was essential to introduce continuous improvement into the NHS and allow quality assurance of clinical decisions. This report defined the key activities needed to make an effective clinical governance system. These included conducting quality improvement activities (e.g. clinical audit), monitoring of clinical care (e.g. electronic patient records), implementing clinical guidelines (e.g. National Institute for Health and Care Excellence guidance), supporting and applying evidence-based medicine, continuing professional development, assessing and managing risk (e.g. critical incident reporting), and making clear lines of responsibility and accountability.

Therefore, risk management was recommended by the WHO, IoM, and DoH as one of the key approaches towards achieving effective clinical governance. Risk management was defined by Dickson (1995, p.75) as

“A mechanism for managing exposure to risk that enables us to recognise the events that may result in unfortunate or damaging consequences in the future, their severity, and how they can be controlled.”

Three main principles of risk management were identified by Dickson (1995); identify risks (ideally using a combination of methods), analyse their impacts, and control them (by reducing their burden and cost). Risk management was introduced into healthcare initially as a response to increased litigation costs. However, it proved to be a more useful strategy that helped in the establishment of mechanisms to reduce the incidence of harm, identify and report adverse events, and care for patients who were harmed. So, in addition to reducing the chance of claims being made and controlling the cost of those claims, clinical risk management aims to reduce the occurrence of preventable adverse events and minimise the associated patient and financial harm (Vincent and Moss, 1995). One of the main approaches to clinical governance is the creation of an open and participative
culture which is seen by some researchers as a feature that characterises the best healthcare organisations (Scally and Donaldson, 1998).

1.2.3. Safety culture

One of the main recommendations in the Berwick report (2013) to enhance patient safety in England was to get rid of the dominant culture of blame and fear and the top-down, control-oriented, and requirement-driven management. Instead, the NHS should strive to create a culture of trust, appreciation, transparency, openness, teamwork, involvement, and continuous learning and improvement. Regarding the importance of such a culture in improving patient safety, Berwick (2013, p.11) stated that

“Culture will trump rules, standards and control strategies every single time, and achieving a vastly safer NHS will depend far more on major cultural change than on a new regulatory regime.”

The endeavour to achieve a safety culture in the UK goes back to the early 1990s. The UK Health and Safety Commission published a report (1993, p.23) that addressed the importance of creating a safety culture and defined it as

“The product of individual and group values, attitudes, perceptions, competencies, and patterns of behaviour that determine commitment to, and the style and proficiency of, an organisation’s health and safety management.”

The domination of a blame culture in the NHS and the need to change it to a culture of trust and openness was identified in the late 1990s (DoH, 2000; NPSA, 2004). However, the Mid Staffordshire failings as emphasised by both Francis (2013) and Berwick (2013) showed that this blame culture still exists in the NHS. Reason (1997) identified 4 key sub-components of a positive safety culture which have also been adopted by the DoH (2000):

- A reporting culture in which staff are ready to report their errors. Proper data analysis and feedback to staff are essential to show the actions being taken
- A just culture of trust that encourages staff to provide information related to safety, but at the same time holds them accountable for their actions
- A flexible culture that respects the frontline staff skills and abilities, but still allows task experts to interfere when necessary
- A learning culture in which staff are competent and determined to learn from their errors, and implement major reforms where needed.
The patient safety performance at healthcare organisations can be enhanced by the presence of a good safety culture. A US study (Singer et al, 2009) assessed the impact of safety culture on hospitals’ performance on patient safety indicators derived from the Agency for Healthcare Research and Quality (AHRQ) indicators (2007). The safety culture was assessed by a 38-question survey on safety-related topics sent to healthcare staff from different professions. The survey was sent to 35,006 staff in 91 hospitals and a 52% response rate was achieved. Higher levels of safety culture were associated with higher safety performance (IRR=1.034, P<0.05). It was also found that hospitals which had more staff reporting problems about fear of shame (IRR=1.050, P<0.05) or blame (IRR=1.013, P<0.01) were associated with lower rates of safety performance. Another US study (Mardon et al, 2010) assessed the relationship between safety culture and safety performance based on data from 179 hospitals. AHRQ safety culture composites (2009) and patient safety indicators (2007) were used in this study. Data from the 56,480 respondents (51% response rate) showed that all of the safety culture-performance relationships were positively associated, including 47% that were significant.

One of the challenges with introducing changes to healthcare services is that some staff feel the change does not apply to them, especially if they had no previous incidents. Another challenge is that staff consider learning as a one-off event. Therefore, active learning is needed to incorporate such changes into the daily workflow of staff. It is also common that healthcare organisations focus intensively on a certain issue and then forget about it in a short time if new priorities emerge or leadership goals changed. This highlights the need for making any change implemented sustainable so it will be in place when needed. (NPSA, 2004)

1.2.4. Safety models

Safety models were developed to help the analysis and understanding of the nature and causes of healthcare-related errors which would potentially lead to better preventive strategies. In 1990, Reason developed a model of human error which viewed the problem in two different ways; the person approach (active failures) and the system approach (latent failures). The person approach divides the human unsafe acts psychologically into unintended and intended actions. Unintended unsafe actions occur due to the failure to perform a good plan while the intended unsafe actions occur with the good performing of an inappropriate or incorrect plan. (Figure 1.2)
According to Reason (1990), the unintended actions are generally skill-based and they can be either slips (i.e. the clinician intend to do something, but did something else by mistake) or lapses (i.e. memory failure or unconscious mental errors). Leape (1994) divided the slips to capture and description errors. Capture errors occur when a more common action is performed instead of a similar but less familiar one. For example, dispense a drug very commonly used instead of the prescribed look-alike/sound-alike drug. Description errors are ones in which the right action is performed on the wrong object such as administering the drug for a wrong patient. Two types of lapses were mentioned by Leape (1994). The first type was the associative activation errors in which ideas are mentally associated (e.g. answering the phone when the bell rings). The second type was the loss of activation errors which result from temporary memory losses (e.g. starting something and forgetting why it is being done).
Reason (1990) divided the intended actions into mistakes which are either rule-based (i.e. misapply good rules or apply bad rules) or knowledge-based (e.g. unaware of committed error) and violations (i.e. intentional policy violation). Leape (1994) stated that rule-based errors can be due to the misperception of a situation or the misapplication of expertise. The knowledge-based errors were linked to four habits of thought. The first was biased memory in which decisions are made based on familiar patterns that exist in the memory (e.g. overgeneralising a rare case treatment). Availability heuristic was the second habit. This is the tendency to use information that comes to mind first. The third habit was confirmation bias, which is the tendency to seek evidence that supports an already existing perception and ignore any contradicting data. Overconfidence was the fourth habit where there is a tendency to be extra certain of the chosen action and to focus only on the evidence in its favour (Leape, 1994).

The second approach in which Reason (1990) viewed human error was the system approach (latent failures) which was seen as the most important and the origin of the problem. Latent failures (or conditions) occur due to strategic decisions by organisation decision makers (e.g. chief executives) which have the potential to introduce risks into the system. These decisions can create conditions where errors can be incited (e.g. time pressure, fatigue) and can also lead to longstanding problems in the system (e.g. untrustworthy alarms). Latent failures may exist for many years before local prompts and active failures formulate and cause incidents. In his Swiss cheese model, Reason (1990) showed how these conditions can create holes in the system defence layers through which errors can pass and cause incidents (Figure 1.3).

![Figure 1.3. Reason’s Swiss cheese model of accident causation (from Reason et al, 2001, p.ii21)](image-url)
Based mainly on Reason’s (1990) model which was originally developed to analyse organisational accidents in other complex industries such as nuclear plants, Vincent et al. (1998) developed a framework to analyse adverse incidents in healthcare organisations (Figure 1.4). This framework sets a hierarchy of factors that affect clinical practice. The most influential are the latent factors including institutional context and organisational/management factors. These factors such as low staffing levels, improper facilities, or poor support create the conditions staff work in which, if not appropriate, can facilitate errors. Such factors lead to error-producing conditions and include work environment (e.g. high workload), team factors (e.g. lack of supervision), individual factors (e.g. knowledge deficiency), task factors (e.g. poor equipment), and patient characteristics (e.g. communication difficulties). These factors facilitate the human unsafe acts to be committed especially in the absence of effective defences (e.g. checklists).

Figure 1.4. Vincent’s accident model for healthcare organisations (from Vincent et al., 1998, p.1155)
1.2.5. Taxonomy

1.2.5.1. Terms used for patient safety incidents

Many terms and definitions have been used for incidents occurring in patient care. A review by Yu et al (2005) identified 25 different terms with 119 definitions used for incidents of medication safety and patient safety in general. In general the patient safety term ‘adverse event’ was the term most commonly used (21 definitions) followed by ‘error’ (13 definitions), ‘incident’ (8 definitions) and ‘near-miss’ (8 definitions). This review found that no standard definitions or classification systems were available to describe patient safety data which would affect the consistency in their reporting. The National Patient Safety Agency (NPSA, 2004) selected the term patient safety incident (PSI) to cover all of these terms and created its own taxonomy (Table 1.1). This taxonomy is adopted in this research and is applied to all incidents occurring to patients while receiving healthcare in any setting.

<table>
<thead>
<tr>
<th>Old term</th>
<th>New term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk</td>
<td>Patient safety</td>
<td>The identification, analysis and management of patient-related risks and incidents, in order to make patient care safer and minimise harm to patients</td>
</tr>
<tr>
<td>Adverse incident</td>
<td>Patient safety incident</td>
<td>Any unintended or unexpected incident(s) that could have or did lead to harm for one or more persons receiving healthcare</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical incident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical incident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical mistake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sentinel event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No harm event</td>
<td>Patient safety incident</td>
<td>A patient safety incident that caused no harm but was not prevented (‘impact not prevented’) or a patient safety incident that was prevented</td>
</tr>
<tr>
<td>(level of severity no harm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near miss/close call</td>
<td>Patient safety incident</td>
<td>Any patient safety incident that had the potential to cause harm but was prevented, resulting in no harm to patients receiving healthcare</td>
</tr>
<tr>
<td>(prevented)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In 2009, the WHO published a conceptual framework for an international classification of patient safety terms. This classification identified 10 high level classes (Figure 1.5) that are essential to focus on in order to improve patient safety. This classification is aiming to enhance the understanding of the patient safety domain and so facilitate identification, prevention, detection, and reduction of PSIs and associated risks. In addition, it aims to enable incident recovery and system resilience.

Two of these classes, incident type and patient outcomes, help in translating PSIs into categories with a clinical meaning. Four classes, patient characteristics, incident characteristics, contributing factors/hazards, and organisational outcomes, provide descriptive information on the incident and help in understanding the context. Finally, detection, mitigating factors, ameliorating actions and actions taken to reduce risk, are the four classes that capture information about incident prevention, recovery, and system resilience. The WHO is still developing the final classification which has not yet been published. (WHO, 2009)
1.2.5.2. **Harm Classification**

The NPSA developed a matrix for grading the risk of PSIs (2008) based on the severity and likelihood of the incident (Figure 1.6). Based on how likely the incident would occur and the consequences it causes, it is assigned a score from 1–25 (the higher the score the higher the incident risk). Since grading the potential harm of incidents is subjective and depends on the reporter’s knowledge and experience, it is not required by the NPSA to grade reported incidents for potential impact or recurrence (NPSA, 2004).

---

**Figure 1.5.** Conceptual framework for the international classification for patient safety (from WHO, 2009, p.8)
Chapter 1: General Introduction

<table>
<thead>
<tr>
<th>Likelihood score</th>
<th>1 (Rare)</th>
<th>2 (Unlikely)</th>
<th>3 (Possibly)</th>
<th>4 (Likely)</th>
<th>5 (Almost certain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (broadly)</td>
<td>This will probably never happen/recur</td>
<td>Do not expect it to happen/recur but it is possible it may do so</td>
<td>Might happen or recur occasionally</td>
<td>Will probably happen/recur, but it is not a persisting issue/circumstances</td>
<td>Will undoubtedly happen/ recur, possibly frequently</td>
</tr>
<tr>
<td>Frequency (time-framed)</td>
<td>Not expected to occur for years</td>
<td>Expected to occur at least annually</td>
<td>Expected to occur at least monthly</td>
<td>Expected to occur at least weekly</td>
<td>Expected to occur at least daily</td>
</tr>
<tr>
<td>Probability</td>
<td>&lt;0.1%</td>
<td>0.1 – 1%</td>
<td>1 – 10%</td>
<td>10 – 50%</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity level</th>
<th>1 (Negligible)</th>
<th>2 (Minor)</th>
<th>3 (Moderate)</th>
<th>4 (Major)</th>
<th>5 (Catastrophic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on the safety of patients, staff or public (physical/psychological harm)</td>
<td>Minimal injury requiring no/minimal intervention or treatment</td>
<td>Minor injury or illness requiring minor intervention</td>
<td>Moderate injury requiring professional intervention</td>
<td>Major injury leading to long-term incapacity/disability</td>
<td>Incident leading to death</td>
</tr>
<tr>
<td>Probability</td>
<td>&lt;0.1%</td>
<td>0.1 – 1%</td>
<td>1 – 10%</td>
<td>10 – 50%</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity \ Likelihood</th>
<th>1 (Rare)</th>
<th>2 (Unlikely)</th>
<th>3 (Possibly)</th>
<th>4 (Likely)</th>
<th>5 (Almost certain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (Catastrophic)</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>4 (Major)</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>3 (Moderate)</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>2 (Minor)</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>1 (Negligible)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1–3 Low risk  4–6 Moderate risk  8–12 High risk  15–25 Extreme risk

Figure 1.6. The National Patient Safety Agency matrix for classifying the risk of associated with patient safety incidents (adapted from NPSA, 2008, p.6-10)
1.2.6. Incidence and burden of patient safety incidents

PSIs affect a significant number of patients and lead to undesirable clinical and financial consequences. The IoM report ‘To Err is Human’ (Kohn et al., 2000) reported that PSIs occur in 2.9% to 3.7% of hospital admissions and that half of these could be prevented. It was estimated that at least 44,000 and up to 98,000 American patients die every year because of preventable PSIs. These numbers were based on extrapolation of data from two large studies which were linked to the annual number of hospital admissions in the US in 1997. The total national cost of these preventable PSIs was estimated to be between $17–29 billion. A later study (James, 2013) stated that the number of serious preventable PSIs and deaths associated with them is even larger. This study estimated that a minimum of 2 million serious injuries and 210,000 deaths occur every year in the US because of preventable PSIs. These estimations were based on the extrapolation of a weighted average rate from four large studies that used the Institute for Healthcare Improvement (IHI) Global Trigger Tool (Griffin and Resar, 2009) to detect PSIs from hospital medical records. When the estimated number of incidents not detected by the Global Trigger Tool was added (e.g. omission errors due to failure to follow guidelines, commission errors that were not documented), it was estimated that up to 4 million serious injuries and 440,000 deaths occur annually due to preventable PSIs.

A study by Wilson et al. (1995) assessed the quality of Australian healthcare by investigating the medical records of 14,179 patients admitted to 28 hospitals. This study identified a PSI rate of 16.6% (n=2,302), half of which (8.3%) were preventable. Of these incidents, 13.7% (n=315) led to permanent harm and 4.9% (n=112) led to death. The WHO (2013) reported that PSIs occur in 8–12% of hospitalised patients in the European Union (EU). It also stated that 23% of the EU citizens claim to have experienced a PSI, 18% claim to have experienced a serious PSI in a hospital, and 11% claim to have been prescribed a wrong medication. Since 50–70% of PSIs can be prevented, the WHO estimated that strategies to reduce the rate of these incidents in the EU would lead to the prevention of more than 750,000 harmful PSIs per year. This would save 3.2 million hospitalisation days, and prevent 260,000 permanent disabilities and 95,000 deaths per year.
The (DoH) in the UK published a report ‘An Organisation with a Memory’ (2000) that estimated harmful PSIs occur in 10% of patients admitted to UK hospitals, and that half of them were preventable. Vincent et al conducted a study (2001) to estimate the incidence and costs of PSIs in UK acute hospitals. This study found that of 1,014 patients, 110 (10.8%) experienced 119 PSIs (11.7%). These PSIs led to an average of 8.5 extra days at hospital with a direct cost of £290,268. Almost half of the PSIs (48%, n=53) and extra bed days (46%, n=460) were preventable. The outcomes for one-third of the patients affected (34%, n=37) were moderate/greater disability or death. After extrapolation, preventable PSIs could cost the NHS in England and Wales around £1bn a year in terms of additional bed days alone. Recent data presented by the UK DoH and Secretary of State for Health (2013) stated that in 2011/2012, half a million NHS patients (0.4%) were harmed and 3,000 (0.003%) died as a result of preventable PSIs.

1.3. Medication safety incidents

1.3.1. Medication-use process

The medication-use process (MUP) is a complex process involving multiple stages through which the medication passes before reaching to the patient. These stages are prescribing, transcribing, dispensing, administering, and monitoring (IoM, 2007) (Figure 1.7). Medication safety incidents (MIs) can occur in any of these stages. The MUP involves almost 20 steps which means there are approximately 20 opportunities for a MI to occur. The five classic incident types called the ‘five wrongs’ (wrong drug, wrong dose, wrong route, wrong time, and wrong patient) can happen in any of the first four stages of the MUP. In addition, healthcare staff monitoring/following-up of patient responses (therapeutic or toxic) to medication therapy is not always performed sufficiently. (Vogenberg and Benjamin, 2011)

In US hospitals, prescribing and administration are the MUP stages in which most MIs occur, followed by the dispensing, transcribing, and monitoring stages (Bates et al, 1995; Kaushal et al, 2001). Leape et al (1995) analysed the type of MIs found within each MUP stage in a US hospital. They found that the most common MIs in the prescribing stage were wrong dose (38%), wrong drug (19%), and known allergy (12%). In the administration stage, the most common MIs were wrong dose (27%), wrong technique (14%), wrong drug (12%), omission (8%), and wrong time (7%). Wrong frequency
(25%), missed dose (23%), wrong dose (13%), and known allergy (13%) were the most common transcription errors, while wrong time (32%), wrong drug (29%), and wrong dose (16%) were the most common dispensing errors.

There are no large research studies (e.g. observational) on the incidence of MIs in UK hospitals. However, most MIs reported from hospitals occur during drug prescribing (usually involve transcribing) and administration, followed by dispensing and monitoring (NPSA, 2009A; Ashcroft and Cooke, 2006). Similarities with the US results in the MI types within each MUP stage were found in an incident-report analysis at a UK hospital (Ashcroft and Cooke, 2006). The prescribing MIs most reported include wrong dose (40%), wrong drug (14%), omission (16%), and possible ADR (9%). The administration MIs most reported include wrong dose (34%), wrong drug (14%), omission (12%), and wrong time (9%). The dispensing MIs most reported include wrong drug (26%), wrong dose (21%), and wrong directions (13.7%).

Though, the comparison of MUP between UK hospitals and other hospitals in Europe or the US is not very reliable due to the various differences in the process. James (2009) summarised the differences in the MUP between these countries (see Table 1.2).

---

**Figure 1.7. Medication-use process in hospitals (adapted from IoM, 2007, p.68)**
Table 1.2. Comparison of the medication-use process between hospitals in the UK, US and Europe (adapted from James, 2009, p.36)

<table>
<thead>
<tr>
<th>MUP</th>
<th>UK hospitals</th>
<th>US hospitals</th>
<th>European hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>Prescriptions are handwritten or computer generated by doctors, nurses, and pharmacist supplementary / independent prescribers. Prescription types include medication charts and discharge and outpatient prescriptions.</td>
<td>Prescriptions are handwritten or generated using computerised physician order entry systems by doctors. Prescription types include medication charts and outpatient prescriptions.</td>
<td>Prescriptions are handwritten or computer generated by doctors. Prescription types include medication charts and discharge and outpatient prescriptions.</td>
</tr>
<tr>
<td>Transcription</td>
<td>Medication orders may be transcribed from a prescription to a pharmacy requisition by nurses, pharmacists, and pharmacy technicians.</td>
<td>Nurses transcribe details from a handwritten prescription to pharmacy requisition or medication administration record. Computerised physician order entry generated prescriptions are accessed directly by pharmacy via the computer system.</td>
<td>Nurses transcribe details from a prescription to a pharmacy requisition.</td>
</tr>
<tr>
<td>Dispensing</td>
<td>Pharmacists review patient’s drug chart, prescription and pharmacy requisition on the ward to identify prescribing and transcribing errors (clinical checks). Centralised pharmacy departments assemble medications. Patients are supplied with an original manufactures’ packed labelled with patient name, date of dispensing, drug name, strength, form, directions for administration and warning/cautionary advice. Some pharmacies will dispense discharge prescriptions at ward level using patients’ own drugs or previously supplied medications. All total parenteral nutrition and parenteral cytotoxic medications are prepared by pharmacy. Some pharmacies prepare a limited number of intravenous medications.</td>
<td>Pharmacy staff review medication orders for safety from a decentralised pharmacy unit at ward level. Unit doses of each drug ordered for a patient are assembled by the decentralised pharmacy. All intravenous medications for patients are prepared and supplied by the decentralised pharmacy department.</td>
<td>Pharmacist and pharmacy staff work solely from the centralised pharmacy departments. Medication charts, discharged and outpatient prescriptions are checked by pharmacists for accuracy and appropriateness of prescribing and transcribing. Pharmacy supplies patients with manufactures’ original packs of medication without a dispensing label giving details of drug or directions.</td>
</tr>
<tr>
<td>Administration</td>
<td>Medication is stored in a locked drug trolley or individual patient locker. Nurses administer medications to patients and document supply on the medication chart which is both a prescription and a record of medication administration.</td>
<td>Medication is stored in computerised drug cabinets. Nurses document administration of medications to patients on a medication administration chart.</td>
<td>Medication is stored in locked cupboards on the wards. Nurses document administration of medications to patients on a medication administration chart.</td>
</tr>
</tbody>
</table>
1.3.2. Definition

The NPSA definition of a MI, which is used in this research, is

“Any incident where there has been an error in the process of prescribing, dispensing, preparing, administering, monitoring or providing medicines advice, regardless of whether any harm occurred or was possible.” (NPSA, 2009A, p.6)

MIs can occur in the form of adverse drug reactions (ADRs) including error-based (preventable) and idiopathic (non-preventable), medication errors that lead to patient harm that is not an ADR (preventable adverse drug events (ADEs), or unharmful medication errors including those with potential to cause harm (ADR or ADE). The relationship between these kinds of MIs in the context of all PSIs is visually explained in Figure 1.8.

ADR: adverse drug reaction; ADE: adverse drug event.

Figure 1.8. The relationship between the different kinds of medication incidents in the context of all patient safety incidents (adapted from Ferner and Aronson, 2006, p.1012)
1.3.3. Classification

MIs can be classified according to the stage of the MUP during which they occur (prescribing, transcribing, dispensing, administration or monitoring), the way in which they occur (e.g. omission, wrong dose, wrong drug), or based on a psychological classification of human errors (knowledge-, rule-, action- or memory-based) (Ferner and Aronson, 2006). Reason’s (1990) psychological classification (section 1.2.4) was applied to MIs by Ferner and Aronson (2006). They suggested that this classification facilitates the understanding of incidents rather than just describing them which would help in developing strategies to prevent their recurrence. For example, knowledge-based mistakes can be prevented by improving clinicians’ knowledge or introducing computerised decision support (CDS) tools while rule-based mistakes can be prevented by improving rules. Training can help in preventing action-based errors (slips) whereas check lists and computerised systems can help with memory failures (lapses). Table 1.3 includes examples for each psychological class of MIs with potential preventive strategies.

MIs were also classified by Morimoto et al (2004) based on their severity, preventability/ameliorability, and the staff responsible for them (e.g. pharmacist). MI severity can be significant (e.g. rash), serious (e.g. gastrointestinal bleeding), life-threatening (e.g. anaphylactic shock) or fatal. In 1999, Dean and Barber developed a scale to score the severity of MIs based on their potential outcome from 0 (no effect) to 10 (death). The rating of MIs using this scale was consistent across different healthcare professions. An index for grading the severity of MIs was developed by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) in 2001 to ensure consistency in MI reporting (Figure 1.9).

A preventable ADE is an injury that results from an error during any stage of the MUP (e.g. coma due to a sedative overdose) while non-preventable ADE is an injury due to a medication where there is no error (e.g. reaction in a patient not previously known to be allergic to the medication). An ameliorable ADE is an injury where the severity/duration could have been substantially reduced if different actions had been taken (e.g. sexual dysfunction for several months while taking a selective serotonin reuptake inhibitor). A non-ameliorable ADE is an injury where the severity/duration cannot be reduced using currently available methods (e.g. bradycardia after the first usual dose of beta-blocker). (Morimoto et al, 2004)
Table 1.3. Examples of psychological classes of medication errors with potential preventive strategies (from Ferner and Aronson, 2006, p.8-9)

<table>
<thead>
<tr>
<th>Potential strategy for avoiding error</th>
<th>Stage of treatment process</th>
<th>Examples</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge-based errors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved teaching: computerised decision-support systems</td>
<td>Deciding to treat</td>
<td>Being unaware of value of sodium bicarbonate in amitriptyline poisoning[^24]</td>
<td>Death from arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>Being unaware of the interaction between warfarin and azapropazone</td>
<td>Warfarin: toxicity[^25]</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>Failing to know that chloroform and chloroform water are different</td>
<td>Poisoning with chloroform[^26]</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>Not knowing that para-phenyldissolves plastic syringes[^27]</td>
<td>Difficulty of administration</td>
</tr>
<tr>
<td></td>
<td>Administering the medicine</td>
<td>Being ignorant of the course of the sciatic nerve</td>
<td>Sciatic nerve palsy from intramuscular injection[^28]</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>Taking blood for lithium concentration into a heparin tube, unaware that it contains lithium heparin</td>
<td>Erroneous lithium concentration[^29]</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>Continuing after 2 weeks to give amiodarone at the loading dose</td>
<td>Amiodarone poisoning</td>
</tr>
<tr>
<td><strong>Rule-based errors: misapplying a good rule</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved teaching: computerised decision-support systems</td>
<td>Deciding to treat</td>
<td>Instituting cardiac massage in a patient who has failed</td>
<td>Alarm, chest trauma</td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>Prescribing oral treatment in a patient with dysphagia</td>
<td>Aspiration or failure to treat</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>Withdrawing necessary treatment while checks are made</td>
<td>Delay in necessary treatment</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Administering the medicine</td>
<td>Giving an intramuscular injection of diclofenac into the thigh</td>
<td>Skin necrosis[^30]</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>Taking a blood sample at the time of trough lithium concentration</td>
<td>Misleading serum lithium concentration</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>Giving a short course of antibacterial treatment</td>
<td>Under treating some infections</td>
</tr>
<tr>
<td><strong>Rule-based errors: applying a bad rule or failing to apply a good rule</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic examination of and improvement to rules</td>
<td>Deciding to treat</td>
<td>Prescribing amoxicillin for sore throat</td>
<td>Rash in a patient with glandular fever[^31]</td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>Printing drugs chart without space to record allergies</td>
<td>Failure to record significant allergy</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>Dispensing intravenous vincristine and intrathecal methotrexate together</td>
<td>Opportunity for confusion; death[^32]</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>Using multidose vials</td>
<td>Contamination, malaria, death[^33]</td>
</tr>
</tbody>
</table>

*Continued next page*
Table 1.3. (Continued) Examples of psychological classes of medication errors with potential preventive strategies (from Ferner and Aronson, 2006, p.8-9)

<table>
<thead>
<tr>
<th>Potential strategy for avoiding error</th>
<th>Stage of treatment process</th>
<th>Examples</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action-based errors (slips)</td>
<td>Administering the medicine</td>
<td>Not taking aspirin tablets with water</td>
<td>Oesophagogastric damage[^1][^2]</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>Monitoring for agranulocytosis when giving carbamazepine</td>
<td>Extra trouble, but no likelihood of benefit</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>Prolonging antibacterial treatment unnecessarily</td>
<td>Increased bacterial resistance[^3][^4]</td>
</tr>
<tr>
<td></td>
<td>Deciding to treat</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>-</td>
<td>Hypoglycaemia[^5]</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>-</td>
<td>Death[^6]</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>-</td>
<td>Cardiac arrest[^7]</td>
</tr>
<tr>
<td></td>
<td>Administering the medicine</td>
<td>-</td>
<td>Infection, poisoning, thrombosis</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>-</td>
<td>Uncontrolled warfarin treatment</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>-</td>
<td>Recurrent thromboembolism</td>
</tr>
<tr>
<td>Technical slips</td>
<td>Deciding to treat</td>
<td>Writing illegibly, so that ‘Daonil’[^8] (glibenclamide) is dispensed for ‘Amodi[^9] (amodiolin)</td>
<td>Hypoglycaemia, brain damage[^10]</td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>-</td>
<td>Undertreatment or toxicity[^11]</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>-</td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>-</td>
<td>Pain, loss of efficacy, tissue damage</td>
</tr>
<tr>
<td></td>
<td>Administering the medicine</td>
<td>-</td>
<td>Over treatment or undertreatment</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>-</td>
<td>Air embolism[^12], oversedation[^13]</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Memory-based errors (tapses)</td>
<td>Deciding to treat</td>
<td>Forgetting that the patient is allergic to penicillin</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Writing the prescription</td>
<td>Omitting a date on which to stop treatment</td>
<td>Poisoning or unnecessary treatment</td>
</tr>
<tr>
<td></td>
<td>Dispensing the medicine</td>
<td>Leaving a bottle of tablets on the counter when dispensing</td>
<td>Treatment failure</td>
</tr>
<tr>
<td></td>
<td>Preparing for administration</td>
<td>-</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Administering the medicine</td>
<td>-</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Monitoring the treatment</td>
<td>-</td>
<td>Uncontrolled warfarin treatment</td>
</tr>
<tr>
<td></td>
<td>Adjusting or ceasing treatment</td>
<td>-</td>
<td>Unnecessary risk and expense</td>
</tr>
</tbody>
</table>
Figure 1.9. Index for categorising medication incidents (from NCC MERP, 2001)
1.3.4. Detection methods

Many MIs go undetected and many of those detected are not reported (Smith, 2004). It is now believed that the MIs reported are just the tip of the iceberg (Figure 1.10). Detection of MIs is the first step towards reporting incidents, preventing them and building safer healthcare systems. Reports, alerts, and recommendations are needed to raise awareness about MIs and their risks and encourage healthcare organisations to improve their pharmacovigilance performance. These reports are usually published by national healthcare systems and regulatory agencies such as the Food and Drug Administration (FDA), United States Pharmacopeia (USP), Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), European Medicines Agency (EMEA), Australian Patient Safety Foundation (APSF), Medicines and Healthcare Products Regulatory Agency (MHRA), and NPSA (Montesi and Lechi, 2009).

![Figure 1.10. The medication error iceberg (from Smith, 2004, p.22)](image-url)
Given the available resources, different methods are used to detect MIs. The most common methods used are observation, medical record review, and incident report analysis. Observation was proved to be the best and most accurate method in detecting MIs, however it is the most expensive. A study by Flynn et al (2002) in 36 US healthcare facilities compared the three methods of detecting MIs among 2,556 doses. Observation detected 300 MIs (11.7%), while record review detected 17 (0.7%) and incident report analysis detected only 1 (0.04%). The average cost of error detection was much higher with observation ($4.82) compared to chart review ($0.63). A UK study used 3 different methods simultaneously to detect adverse events in the same patient group. Out of 288 prospectively-assessed discharges, real-time record review detected 67 MIs, pharmacy surveillance (proactive surveillance by pharmacists of inpatient prescriptions and medication administration) found 30 MIs, and incident reporting detected 11 MIs (Olsen et al, 2007).

Recently, computerised alert systems (e.g. trigger tools) were developed as a cost-effective MI detection method that required less manpower. A US study (Jha et al, 1998) compared a computerised system that issued alerts for possible MIs based on predefined rules (e.g. new medication, laboratory results above or below certain values) to medical note review and voluntary reporting in detecting MIs at a tertiary-care hospital. This study found that the computerised system generated 2,620 alerts, of which 275 were actually MIs. Medical record review identified 389 MIs while report analysis found only 23. Noticeably, 76 of the total 617 MIs were identified by both chart review and computer monitor and only 3 were identified by both incident reporting and the computer monitor. MIs detected by the computer monitoring system had a higher proportion of severe incidents compared to chart review (51% vs 42%, P=0.04). In the Olsen et al (2007) study, only 3 MIs were detected by both record review and pharmacist surveillance, while only 1 MI was detected by both record review and incident reporting. These studies showed that it is useful to use more than one tool to detect MIs as each tool detects different incidents. James (2009) summarised all methods used in the literature to detect MIs and documented the advantages and disadvantages of each method (Table 1.4).
<table>
<thead>
<tr>
<th>Research method</th>
<th>Data collection</th>
<th>Incident type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluntary reporting (official incident reports and</td>
<td>Details of incident reported by staff on standardised forms or in interviews</td>
<td>ADE, potential ADEs, ADRs and medication</td>
<td>• An ongoing reporting mechanism</td>
<td>• Reporting requires an awareness of incident occurrence</td>
</tr>
<tr>
<td>anonymous reports)</td>
<td></td>
<td>errors.</td>
<td>• Anonymity eliminates fear of disciplinary action</td>
<td>• Under-reporting due to fear of disciplinary action</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inexpensive</td>
<td>• Incidents may not be reported if considered harmless or advised against reporting by peer</td>
</tr>
<tr>
<td>Case note review</td>
<td>Trained reviewers screen patient’s case note using pre-defined criteria to identify</td>
<td>ADEs, ADRs and medication errors (mainly</td>
<td>• Large amount of information obtained</td>
<td></td>
</tr>
<tr>
<td></td>
<td>incidents.</td>
<td>prescribing and administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Litigation claims data</td>
<td>Review of litigation claims</td>
<td>ADEs and medication errors</td>
<td>• Inexpensive</td>
<td>• Less sensitive data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Limited data</td>
</tr>
<tr>
<td>Critical incident technique</td>
<td>Observation or interviews of staff to identify casual factors</td>
<td>ADEs, potential ADEs and medication</td>
<td>• Detailed information on case incidents</td>
<td>• Difficult analysis of data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>errors</td>
<td></td>
<td>• Difficult interpretation of data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Multiple sources of bias</td>
</tr>
<tr>
<td>Computerised monitoring</td>
<td>Computer systems screen administrative data and clinical database using</td>
<td>ADEs and potential ADEs</td>
<td>• Sensitive</td>
<td>• Requires advanced information systems (e.g. electronic patient records) and programming</td>
</tr>
<tr>
<td></td>
<td>pre-programmed criteria. Case note review is undertaken for identified incidents</td>
<td></td>
<td>• Large amount of data obtained for identified incidents</td>
<td>• Number of identified incidents depends on the information system links</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Automatic</td>
<td>• Limited information on potential ADEs</td>
</tr>
</tbody>
</table>
Table 1.4. (Continued) Summary of medication incident detection methods (adapted from James, 2009, p.28-29)

<table>
<thead>
<tr>
<th>Research method</th>
<th>Data collection</th>
<th>Incident type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct observation (disguised or participant observation)</td>
<td>Researchers observe member of staff and document any incidents witnessed</td>
<td>Potential ADEs and medication errors (mainly administration)</td>
<td>• Highly sensitive</td>
<td>• Requires trained observer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Large amount of data obtained in a short time</td>
<td>• Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Does not rely on awareness of incidents or willingness of staff to report</td>
<td>• Time-consuming</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Casual links can be identified</td>
<td>• Presence of observer may influence staff (Hawthorne effect)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Observer may misinterpret observation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Limited information on prescribing errors</td>
</tr>
<tr>
<td>Pharmacist intervention</td>
<td>Documentation of errors or issues identified and rectified by pharmacists during review of medication charts/case notes</td>
<td>Potential ADEs, ADRs and medication errors</td>
<td>• Large amount of information</td>
<td>• Depends on knowledge and experience of pharmacist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Practical</td>
<td>• Limited information on administrative errors</td>
</tr>
<tr>
<td>Patient surveys</td>
<td>Postal surveys, telephone or direct interviews with patients to identify adverse events experienced following period of hospitalisation or outpatients appointment</td>
<td>ADEs, potential ADEs and medication errors</td>
<td>• Can be used for outpatients</td>
<td>• Relies on patients awareness of incidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Detects incidents not documented in case note</td>
<td>• Highly subjective, relying on patient recall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Resource intensive</td>
</tr>
<tr>
<td>Focus group</td>
<td>Multi-disciplinary discussion used to identify major incidents</td>
<td>ADEs, potential ADEs and medication errors</td>
<td>• Target major issues</td>
<td>• Does not address daily events or trends</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Rapid identification of issues in need of addressing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

ADR: adverse drug reaction; ADE: adverse drug event.
1.3.5. Prevalence

MI rates vary widely, as a result of the variety of different study methods and definitions used. The rate of MIs varies between 2 and 14% of patients admitted to hospital (Williams, 2007). The IoM report ‘To Err is Human’ (Kohn et al, 2000) stated that almost 2% of hospitalised patients in the US are affected by preventable MIs. Preventable MIs have been estimated to kill 7,000 patients per year and accounts for nearly 1 in 20 hospital admissions in the US. In both studies that this report findings were extrapolated from, 19% of the PSIs identified were MIs; the most common type in the Harvard Medical Practice Study (Leape et al, 1991) and the 2nd most common in the Utah and Colorado study (Thomas et al, 2000).

Furthermore, a US study of 4,031 adult patients conducted by Bates et al (1995) identified 441 (10.9%) MIs, 247 ADEs and 194 potential ADEs, through incident report analysis and prospective record review. Of these, 264 (60%) were preventable (70 ADEs & all potential ADEs). Forty-two percent of serious and life-threatening ADEs (44/103) were preventable. A study by Barker et al (2002) in 36 healthcare facilities across 2 American states (24 hospitals & 12 nursing homes) found that 19% of assessed doses were associated with preventable MIs (605/3,216). The rate of MIs was slightly lower at hospitals (16.4%, 290/1,765) compared to nursing homes (21.7%, 315/1,451), but the difference was not statistically significant (P=0.82).

In Australia, Wilson et al (1995) found that 249 (10.8%) of the retrospectively identified PSIs (n=2,302) were ADEs, of which 43% (n=108) were highly preventable. These errors caused 20 (8%) deaths and 42 (17%) permanent disabilities. Another study (Runciman et al, 2003) showed that 2–4% of all hospital admissions in Australia, up to 30% in patients aged over 75 years, are medication-related. Three quarters of these medication-related hospital admissions were preventable. The study also showed that MIs are affecting 1% of hospitalised patients, and are occurring with 15–20% of dose administrations when ward stock systems are used and 5–8% when individual patient supply systems are used.

A Spanish observational study by Otero-Lopez et al (2006) identified 191 ADEs among 2,643 hospitalised patients (7.2%). Of which 19.9% (n=38) were preventable. In 2011, MIs were the second most common type of PSIs (after patient accidents) reported by hospitals in England and Wales; n=149,409, 11.4% of all incidents (NRLS, 2013A). A study conducted in 2 large hospitals in England and involved 18,820 patients has
identified that 6.5% (n=1,225) of hospital admissions were related to ADRs. Of these, 72% were judged as avoidable ADRs (Pirmohamed et al, 2004). Moreover, Ghaleb et al (2006) conducted a systematic review on the incidence of MIs in paediatric inpatients. They found 32 studies which used different methods to detect MIs; 14 used chart review, 10 used spontaneous reporting, and 8 used observation. Although there was a great variation in the incident rates reported (probably due to the different definitions and methodologies employed), this review confirmed that MIs are common among hospitalised paediatrics.

All of the studies above are large-scale well recognised studies. Despite the different settings, methodologies, and MI rates reported in these studies, they demonstrate that MIs are a common problem that affects both adult and paediatric inpatients worldwide. They also show the high preventability of MIs.

1.3.6. Cost

In addition to the harm and poor care quality caused by MIs, they can have significant financial consequences. The IoM (2007) estimated that injuries occurring in hospitals due to preventable MIs cost the US healthcare system $3.5 billion per year. This estimation was based on the extra costs of treating 400,000 avoidable medication-related injuries annually; it did not include extra wages or additional healthcare costs. In Australia, it was estimated that 190,000 medication-related admissions (2-3% of all hospital admissions) occur annually with a cost of $660 million. Of these admissions, around 50% were considered avoidable (Roughead and Semple, 2009).

In the UK, the NPSA published a report in 2007 estimating that preventable MIs cost the NHS £774 million per year. This amount was based on the cost of avoidable hospital admissions (£359m), avoidable inpatient harms (£411m), and litigation costs (£4m). An extrapolation from the results of the study by Pirmohamed et al (2004) estimated that avoidable ADR-related admissions cost the NHS £466 million per year.

1.4. Medication safety with antibiotics

Antibiotics are widely used in hospitals. A recent report by the Centers for Disease Control and Prevention (CDC) in the US (Fridkin et al, 2014) stated that in 2010, 55.7% of patients in 323 hospitals received an antibiotic for at least one day during their
hospitalisation. A UK study of 2,656 patients across 4 London NHS hospitals found that one-third of inpatients (n=865) received at least one antibiotic at some point during their hospital stay (Dean et al, 2002B).

Recently and especially with the rise in antibiotic resistance, there has been an increased focus on the proper and safe use of antibiotics. The Chief Medical Officer in England emphasised that antibiotic resistance should be treated as a national threat and included on the National Risk Register. In her annual report (Davies, 2013, p.16), she stated

“Antimicrobial resistance is a ticking time bomb not only for the UK but also for the world. We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality. This is a threat arguably as important as climate change for the world.”

Six months later, the DoH published a UK 5-year strategy to tackle antimicrobial resistance (2013) through raising the awareness about the issue, stewarding the effectiveness of existing antibiotics, and stimulating the development of new antibiotics and novel therapies. One of this report’s recommendations to tackle resistance was to optimise the antimicrobial prescribing practice, ideally through antibiotic stewardship committees. A Cochrane review by Davey et al (2013) found that interventions to improve antibiotic prescribing in hospitalised patients can reduce antimicrobial resistance. Therefore, reducing MIs with antibiotics is an essential measure to tackle the issue of antimicrobial resistance.

Antibiotics is a class of drugs frequently associated with MIs. Antibiotics was the drug class most associated with MIs (12.9%, 30/233) in Wilson et al (1995) study, 30% of which had high preventability. Bates et al (1995) found that antibiotics was the second drug class most commonly associated with ADEs (24%, n=59), of which 10% were preventable, and potential ADEs (n=46). In Otero-Lopez et al (2006) study, 22.9% (11/48) of the preventable ADEs identified were associated with anti-infectives. Moreover, a study by Winterstein et al (2004) at a US tertiary-care hospital found that 41.7% (n=100) of the 240 preventable MIs prospectively identified by a multidisciplinary team were related to anti-infectives. Antimicrobials was also the drug class most associated with MIs (32.1%, n=162) in the emergency department at 4 US academic hospitals (Rothschild et al, 2010).
Furthermore, antibiotic-associated MIs are common among paediatrics. A UK study identified that 44% (48/109) of all MIs reported over 5 years at a large paediatric teaching hospital were associated with antimicrobial agents (Ross et al., 2000). Kunac and Reith (2008) found in a prospective observational study at a paediatric teaching hospital in New Zealand that antibiotics had a MI rate of 21/100 medication orders. Antibiotics were also the drug class most commonly associated with paediatric MIs in the systematic review by Ghaleb et al. (2006).

Two of the studies above have linked the frequent association of antibiotics with MIs to the common prescribing of these drugs. Winterstein et al. (2004) commented that the inclusion of oncology, transplantation, and critical care units, which commonly prescribe anti-infectives, may have contributed to making them the drug class most frequently associated with MIs in their study. Ghaleb et al. (2006) noted in their review that because antibiotics and sedatives are the most widely prescribed drugs, this makes them the drug classes most commonly associated with MIs.

1.5. Medication incidents based on the stage of occurrence in the medication-use process, with a focus on antibiotics

1.5.1. Prescribing and transcribing errors

Many medication errors occur as a result of poor prescribing and often involve relatively inexperienced medical staff, who are responsible for the majority of prescribing in hospitals (Williams, 2007). Dean et al. (2000, p.235) used the Delphi technique to develop a general definition of a prescribing error (PE), which is used in this research;

“A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.”

This definition includes transcription errors committed by prescribers (e.g. transcribing a medication order incorrectly when rewriting a patient’s drug chart) and has been used in most UK studies. PE incidence rates vary between different studies due to the use of different methodologies (Franklin et al., 2009). Bates et al. (1995) identified that among the 264 preventable ADEs found in 2 US tertiary-care hospitals, 49% (n=128) were PEs
and 11% were transcription errors (n=29). In addition, Winterstein et al (2004) found that 72.5% (174/240) of the MIs detected in a US tertiary-care hospital occurred in the prescribing stage and 6.3% (15/240) occurred in the transcribing stage.

In the UK, Dornan et al (2009) conducted the EQUIP study across 19 hospitals in England to investigate PEs committed by junior doctors. This study evaluated 124,260 medication orders and found 11,077 PEs (8.9%). Another study across 9 English hospitals (Seden et al, 2013) assessed 4,238 prescriptions and found that 1,857 (43.8%) contained at least one PE; the total number of PEs was 3,011 PEs. A recent study, PROTECT, was conducted across 8 Scottish hospitals to explore the outcomes of junior doctors’ prescribing after engagement in a training programme (Ryan et al, 2014). This study screened 4,710 drug charts which included 44,726 prescribed medications. It found that 36.1% (n=1,700) of drug charts and 7.5% (n=3,364) of medications were associated with PEs. In addition, Dean et al (2002A) found that 1.5% out of 36,168 prescriptions (n=538) in a 550-bed London hospital included a PE, 25% of which were potentially serious. The NPSA report ‘Safety in Doses’ (2009A) revealed that 17.5% of MIs reported from secondary care settings in 2007 were PEs (n=11,180). Furthermore, PEs are also significant in the paediatric population. A study of 1,120 patients performed in the US by Kaushal et al (2001) showed that among all stages, 74% (454/616) of medication errors occurred in prescribing stage while 10% (62/414) occurred in transcribing stage. In the UK, Ghaleb et al (2010) conducted a study across five London NHS hospitals which found 391 PEs in 2,955 paediatric prescriptions (13.2%).

The studies above involved large numbers of patients and have all used the prospective observational design which is deemed as the most effective in detecting MIs (Flynn et al, 2002; Olsen et al, 2007). Although these studies showed variant rates of PEs, they confirm that this type of MIs is common in hospitals among both adult and paediatric patients. A systematic review of 65 studies (including 25 from the US & 22 from the UK) on PEs in adults and/or paediatrics identified that they are affecting 7% of medication orders, 2.4% of patient days, and 52% of hospital admissions (Lewis et al, 2009).

Incidence of PEs is common with antibiotics. A 9-year study by Lesar et al (1997A) indicated that out of 11,186 PEs occurred in a tertiary-care hospital, 35.7% were associated with antibiotics. Jayawardena et al (2007) found in a US study that 53.9% of the 3,321 PEs detected in a teaching hospital were related to antibiotics. A lower
proportion was reported in UK studies such as Dornan et al (2009) study which indicated that 6.2% of PEs (n=685) detected were related to antibiotics, yet it was the second drug class mostly associated with PEs. In the Seden et al (2013) study, prescriptions included antibiotics (n=724) were the most associated with PEs (18%). A Turkish study (Ceyhan et al, 2010) of 1,302 paediatric patients from 12 different hospitals showed that 46.7% of patients who received an antimicrobial (n=711) received at least one inappropriately prescribed drug. Lewis et al (2009) review identified that out of 22 studies which specified the medications most commonly associated with PEs, antimicrobials was the drug class most commonly associated (32% median prevalence). Table 1.5 includes more details about these studies.


<table>
<thead>
<tr>
<th>Study, country</th>
<th>Design, methods</th>
<th>Setting, participants, sample size</th>
<th>Antibiotic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesar et al, 1997A</td>
<td>Prospective cohort study; pharmacists used any available information sources, including the pharmacy computer system which had automated checking functions, to evaluate prescriptions prior to dispensing.</td>
<td>A tertiary-care teaching hospital. All prescriptions handwritten by a physician during the 9-year study period were assessed. Size of the included sample was 3,903,433 prescriptions.</td>
<td>11,186 PEs were detected (0.29% of all prescriptions assessed). Of these, 35.7% (n=3,997) related to antibiotics.</td>
</tr>
<tr>
<td>Jayawardena et al, 2007</td>
<td>Retrospective cohort study; the pharmacist reviewed prescriptions placed before the medication was released to the nursing staff. If there was any doubt about a particular order, the pharmacist would directly clarify the prescription with the resident.</td>
<td>A community teaching hospital. All prescriptions placed through the computerised prescription order entry system (the emergency department did not have this system) over 1 year were assessed. Size of the included sample was 466,311 prescriptions.</td>
<td>3,321 PEs were detected (0.71% of all prescriptions assessed). Of these, 53.9% (n=1,790) related to antibiotics.</td>
</tr>
<tr>
<td>Dornan et al, 2009</td>
<td>Prospective cohort study; pharmacists identified errors in new prescriptions as part of their routine practice.</td>
<td>19 acute teaching hospitals. All new prescriptions made on seven monthly-separated weekdays were assessed. Size of the included sample was 124,260 prescriptions.</td>
<td>11,077 PEs were detected (8.9% of all prescriptions assessed). Of these, 6.2% (n=1,790) related to antibiotics.</td>
</tr>
<tr>
<td>Ceyhan et al, 2010</td>
<td>Prospective cross-sectional study; paediatricians and infection control nurses collected all data related to new paediatric antimicrobial orders (e.g. dosage, indication).</td>
<td>12 paediatric hospitals. All patients who were receiving antimicrobials during a 10-hour period on 3rd Oct 2007 were included. Size of the included sample was 1,302 patients.</td>
<td>711 patients (54.6%) were receiving antimicrobials. Of these, 46.7% (n=332) received at least one inappropriately prescribed drug.</td>
</tr>
<tr>
<td>Seden et al, 2013</td>
<td>Prospective cross-sectional study; ward-based clinical pharmacists prospectively documented prescribing errors at the point of clinically checking admission or discharge prescriptions.</td>
<td>9 hospitals (3 teaching; 3 district; 3 specialist). Each hospital was asked to audit a minimum of 400 prescriptions. All types of medication orders were audited. Size of the included sample was 4,238 prescriptions.</td>
<td>3,011 PEs were detected in 1,857 prescriptions (43.8% of all prescriptions assessed). Of these prescriptions, 423 (22.8%) contained antibiotics. These included 130 (30.7%) antibiotic-related PEs (18% of all 724 antibiotic prescriptions).</td>
</tr>
<tr>
<td>Lewis et al, 2009</td>
<td>Systematic review; authors searched 4 clinical databases (Medline; Embase; CINAHL; International Pharmaceutical Abstracts) to identify eligible studies.</td>
<td>All studies published in English between 1985 and 2007 that reported on the detection and rate of PEs in prescriptions handwritten for hospital inpatients were reviewed. Size of the included sample was 65 studies (including 25 from the US and 22 from the UK).</td>
<td>22 studies specified the medications most commonly associated with PEs. In these, the median prevalence of antimicrobial PEs was 32%.</td>
</tr>
</tbody>
</table>
1.5.2. Administration errors

Drug administration has long been the focus of review and research especially because administration errors (AEs) have a direct impact on patient outcomes and might affect his/her morbidity and mortality. The determination to provide patients with safe and quality care encourages researchers to develop strategies to reduce the occurrence of AEs. However, AEs are still occurring (McBride-Henry and Foureur, 2006). The definition of an administration error as described by Ghaleb et al (2010, p.114) is

“The administration of a dose of medication that deviates from the prescription, as written on the patient medication chart, or from standard hospital policy and procedures. This includes errors in the preparation, and administration of intravenous medicines on the ward.”

Different studies have shown the high prevalence of AEs in hospitals. A Malaysian study that observed 1,118 dose administrations has shown a high incidence of AEs (11.4%, n=127); 10.4% of these were considered as potentially life-threatening (Chua et al, 2009). A Spanish study by Rodriguez-Gonzalez et al (2012) at two medical units in Spain with automated prescribing and dispensing systems found that 22% of all dose administrations (509/2,314) were associated with AEs. A German study by Bertsche et al (2008) identified that out of 1,376 drug handling processes (i.e. storage, preparation, and administration), 833 involved (60.5%) errors; 99% of these were during preparation and administration. More than half of the MIs reported to the NPSA (2009A) from secondary care settings in 2007 occurred during administration/supply of medicines (53.4%, n=34,137). Timing errors is one of the most common types of AEs. A French study found that 27.6% (415/1,501) of total opportunities for error (i.e. all doses given plus all doses omitted) were associated with at least one AE. Of these errors, 75.2% (n=312) were timing errors (Berdot et al, 2012).

In paediatrics, Prot et al (2005) conducted a 1-year study in France (2005) to quantify drug AEs in paediatric inpatients. They observed 1,719 administrations, of which 538 were associated with AEs (31.3%). In the UK, Ghaleb et al (2010) observed 161 nurses preparing and administering doses to 265 paediatric patients and recorded 429 AEs (19.1%) in 2,249 opportunities for error. A systematic review of 91 studies (including 25 from the US & 22 from the UK) on AEs in adults and/or paediatrics showed a median
error rate of 19.6%. When timing errors were excluded, the median rate became 8.0% (Keers et al., 2013). McLeod et al (2013) conducted a UK-specific systematic review of 16 AE studies. The overall adult AE rates were 5.6% of a total of 21,533 non-intravenous opportunities for error and 35% of a total of 154 intravenous opportunities for error. AEs were 5 times more likely in intravenous than non-intravenous doses (pooled OR=5.1; 95%CI 3.5–7.5). This review excluded timing errors from the reported rates.

Antibiotics are commonly associated with AEs. A multinational study (involved 113 units from 27 countries, including 17 from the UK) conducted by Valentin et al (2009) showed the incidence of 179 (9.4%) AEs among 1,905 antimicrobial administrations (16.2% of all administrations assessed), and among a total of 857 AEs (20.9%). In the Bertsche et al (2008) study, antibiotics was the drug class most associated with handling errors (29.5%, n=246). Out of 150 antimicrobial administrations in the Berdot et al (2012) study, 50 were associated with AEs (33.3%) which make 12% of all AEs in the study. Rodriguez-Gonzalez et al (2012) identified the use of antibiotics as a risk for AEs as there was a significant correlation between antibiotics and AE incidence (OR=3.1, 95%CI: 1.98–4.85). In the Keers et al (2013) review, antimicrobials was identified as one of the top 3 drug classes associated with AEs in 4 out of the 10 studies that stated details on medications involved in errors. Prot et al (2005) identified that 19.7% (n=339) of paediatric dose administrations assessed were for anti-infectives which had the third highest incidence of AEs (OR=2.57, 95%CI: 1.01–6.57). Further details on these studies can be found in Table 1.6.
**Table 1.6. Some large scale studies that reported on the detection and rate of administration errors (AEs) with antibiotics**

<table>
<thead>
<tr>
<th>Study, country</th>
<th>Design, methods</th>
<th>Setting, participants, sample size</th>
<th>Antibiotic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prot et al, 2005 (France)</td>
<td>Prospective cohort study; twelve 5th year pharmacy students accompanied nurses giving medications (undisguised) and witnessed the preparation and administration of drugs to find discrepancies between physicians’ orders and actual drug administration</td>
<td>A paediatric teaching hospital. On 4 wards, all drugs given to all patients on all weekday mornings over a 1-year period were observed. Size of the included sample was 336 patients for whom there were 485 nurse-observation periods.</td>
<td>538 AEs (31.3%) out of 1,719 opportunities for error. Of these, 19.7% related to anti-infectives which were the 3rd highest drug class associated with errors (OR=2.57, 95%CI: 1.01–6.57).</td>
</tr>
<tr>
<td>Bertsche et al, 2008 (Germany)</td>
<td>Prospective cohort study; three trained pharmacy students monitored drug handling (storage, preparation and administration) and assessed the prevalence of 20 predefined errors.</td>
<td>A tertiary-care teaching hospital. Each ward was visited by one monitor in the busy morning hours from 7 to 10 for 10 days. Size of the included sample was 87 nurses for whom there were 1,376 observed processes.</td>
<td>833 handling errors (60.5%) including 30 (1%) in storage, 254 (30.5%) in administration and 571 (68.5%) in preparation. Of these, 29.5% (n=246) related to antibiotics which was the drug class most associated with errors.</td>
</tr>
<tr>
<td>Valentin et al, 2009 (Multinational)</td>
<td>Prospective cross-sectional study; All nurses and physicians on duty in the participating units were asked to fill in a single multi-entry questionnaire (self-reporting) available at the bedside of each patient that ask if, and at what time, an error in parenteral medication had occurred.</td>
<td>113 intensive care units in 27 countries (including 17 from the UK). Drug administrations to all adult patients staying in the units, including those admitted or discharged during a 24-hour period. Size of the included sample was 1,328 patients (including 200 from the UK) who received 11,725 drug administrations.</td>
<td>861 AEs affected 441 patients (33.2% of all patients observed). Of these AEs, 179 (20.8%) related to antimicrobials which was the 2nd drug class most commonly associated with errors (9.4% of all 1,905 antimicrobial administrations).</td>
</tr>
<tr>
<td>Rodriguez-Gonzalez et al, 2012 (Spain)</td>
<td>Prospective cohort study; six pharmacists and five nurses disguisedly observed drug administrations and assessed the AE rate.</td>
<td>A tertiary-care teaching hospital. On 2 adult gastroenterology units, all drug administrations during all shifts over a 1-week period were observed. Size of the included sample was 73 patients who received 213 drugs.</td>
<td>509 AEs (22.0%) out of 2,314 opportunities for error. Of these opportunities, 297 (12.8%) were for antibiotic AEs (no. of errors not mentioned). There was a significant correlation between antibiotics and AE incidence (OR=3.1, 95%CI: 1.98–4.85).</td>
</tr>
<tr>
<td>Berdot et al, 2012 (France)</td>
<td>Prospective cohort study; a pharmacist disguisedly observed AEs while accompanying nurses and witnessing the preparation and administration of drugs. Directly after the round, the pharmacist compared the drug administrations to the physician order.</td>
<td>A teaching hospital. On 4 adult wards, drug administrations to all patients during the three drug rounds on each of six days per ward were observed. Size of the included sample was 28 nurses caring for 108 patients.</td>
<td>430 AEs occurred in 415 (27.6%) out of 1,501 opportunities for error. Of these, 55 (12.8%) AEs occurred in 50 anti-infective (12.0%) opportunities for error (33.3% of all 150 anti-infectives opportunities for error).</td>
</tr>
<tr>
<td>Keers et al, 2013 (UK)</td>
<td>Systematic review; authors searched 10 clinical databases (Medline; Embase; International Pharmaceutical Abstracts; Scopus; Applied Social Sciences Index &amp; Abstracts; PsycINFO; Cochrane Reviews &amp; Trials; British Nursing Index; CINAHL; HMIC) to identify eligible studies.</td>
<td>All studies published in English between 1985 and May 2012 and reported on the rate of AEs derived only from direct observation at long-term care or hospital settings were reviewed. Size of the included sample was 91 studies (including 25 from the US and 22 from the UK).</td>
<td>Median AE rate was 19.6% (IQR 8.6–28.3%); 18.8% in the US (4.9–23.5%) and 21.7% in the UK (6.4–35.9%). Out of 10 studies specified the medications most commonly associated with AEs, 4 reported that antimicrobials was 1 of the top 3 drug classes associated with AEs.</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Interval; IQR: interquartile range.
1.5.3. Dispensing errors

Dispensing is the core function of pharmacy professionals. More than 900 million items are dispensed annually by hospital and community pharmacies in England and Wales (James et al., 2009). Although dispensing errors can result in significant harm for patients, most of the research has been focusing on prescribing and administration errors (Beso et al., 2005). Cheung et al. (2009, p.676) defined a dispensing error as

“A discrepancy between a prescription and the medicine that the pharmacy delivers to the patient or distributes to the ward on the basis of this prescription, including the dispensing of a medicine with inferior pharmaceutical or informational quality.”

Dispensing error rates are generally lower than those of PEs and AEs. A study by Bohand et al. (2009) investigated 734 filled medication cassettes in a French hospital and found 179 dispensing errors (2.5%) with the 7,249 unit doses investigated. Up to 12.5% of items dispensed in US hospital pharmacies are associated with dispensing errors (Beso et al., 2005). A study of 140,755 doses dispensed at a US tertiary-care hospital identified 5,075 dispensing errors (3.6%), of which 20.9% (n=1,059) were not detected by the verifying pharmacist (Cina et al., 2006). A study at a paediatric unit in Brazil identified at least one dispensing error with all doses (n=705) of high-alert medications (based on the classification of the Institute for Safe Medication Practices (ISMP). The total number of dispensing errors associated with these doses was 1,707 (Silva et al., 2011). In the UK, a memorandum presented to the Parliament by Franklin and Barber (2009) stated that dispensing errors account for up to 9.8% of dispensed items in secondary care. The NPSA report ‘Safety in Doses’ (2009A) showed that 11.1% (n=7,436) of MIs reported from England and Wales secondary care settings in 2007 occurred during medicines preparation and dispensing.

A structured literature review of 60 studies (including 29 from the US & 24 from the UK) by James et al. (2009) investigated the incidence of dispensing errors. The incidence results were divided into prevented dispensing errors (i.e. detected within the pharmacy) and unprevented dispensing errors (i.e. detected after the medication has left the pharmacy). In the US, 16 studies investigated prevented dispensing errors in hospitals and reported an incidence between 0.06–18%, while only one study (from the 16) reported a 0.75% rate of unprevented dispensing errors. Lower rates were found in the UK hospitals where 14 studies investigated dispensing error rates (3 studies investigated both
prevented and unprevented). Eight studies reported a rate of prevented errors between 0.11–2.7%, and 9 studies reported a rate of unprevented errors between 0.008–0.02%.

Very limited data are available on the rate of dispensing errors with antibiotics, particularly in hospitals. One study in the US by Kuo et al (2013) showed that 12.7% (n=77) of the 605 inpatient MIs reported by 53 clinical pharmacists from across the US were dispensing errors. Of these, 39% (n=30) were associated with systemic anti-infectives (89% of which were antibiotics).

1.5.4. Monitoring errors

Monitoring medication effects on the patient is the last stage of the MUP. This stage is essential to ensure the treatment is effective and safe for the patient at the same time. Alldred et al (2008, p.318) developed a consensus definition of a monitoring error:

“A monitoring error occurs when a prescribed medicine is not monitored in the way which would be considered acceptable in routine general practice. It includes the absence of tests being carried out at the frequency listed in the criteria, with tolerance of +50%. This means, for example, that if a drug requires liver function tests at 3 monthly intervals, we would class as an error if a test has not been conducted within 18 weeks. If a patient refused to give consent for a test, then this would not constitute an error.”

Errors in the monitoring stage are less investigated compared to other stages of the MUP, especially in the hospital setting. In 2007, at least 2,424 (3.8%) of the MIs reported to the NPSA from secondary care occurred in the monitoring stage (NPSA, 2009A). There have been a number of studies conducted in care homes that reported rates of monitoring errors. Barber et al (2008) assessed the prevalence of MIs in 256 patients from 55 care homes. They found that among 218 medicines given to patients that need monitoring, 14.7% (n=32) were associated with monitoring errors. Gurwitz et al (2005) assessed the MIs associated with 1,247 elderly patients in two Canadian academic long-term facilities and found a higher rate of monitoring errors. They found 815 MIs, 42% of which were preventable (n=338). Of these, monitoring errors were the most common category of MIs (80.2%, n=271). Monitoring errors in this study included those similar to the definition above (72.7%, n=197), but also included the failure to act on monitoring (66.4%, n=180).
Data on the incidence of monitoring errors with antibiotics are uncommon in the literature. In the Kuo et al (2013) study, 14% of inpatient MIs (85/605) were monitoring errors. Of which, 55.3% (n=47) were associated with anti-infectives. However, most of the studies available usually concentrate on the monitoring of a specific issue with certain antibiotics (e.g. therapeutic drug monitoring with aminoglycosides). A study conducted at 2 tertiary-care teaching hospitals in Australia found that out of 413 gentamicin serum concentrations measured for 161 patients, 19.6% (n=81) were done inappropriately, mostly as samples taken at the wrong time (Martin et al, 2012).

### 1.6. Implications for the present research

Research has found that MIs are one of the most common PSIs. Antibiotics are also one of the drug classes most commonly associated with MIs. Antibiotics are commonly used in hospitals and recently antibiotic resistance has been rising. Therefore, enhancing appropriate use of antibiotics, including avoiding MIs, is essential in controlling antibiotic resistance and providing safe and effective care for patients.

This thesis explores the issue of antibiotic-related MIs in hospital settings. The research is primarily guided by Reason's (1990) model of human error and Vincent et al’s (1998) framework for healthcare organisation accidents. This research will investigate the incidence and nature of antibiotic-related MIs and how the risk of incident occurrence can be analysed. In addition, it will review the most effective interventions to improve the use of high-risk antibiotics. The prescribing process of such antibiotics along with the causes of error and recommendations to avoid these errors will also be explored.
1.7. Thesis aims and objectives

- **Aim 1:** To determine the prevalence, incidence and nature of reported antibiotic-associated MIs occurring among inpatients at two NHS Foundation Trusts.
  
  Objectives:
  
  - To determine the number, incidence, and type of antibiotic MIs reported
  - To identify the antibiotics involved in MIs
  - To investigate the relationship between MIs and antibiotic consumption/usage
  - To assess the severity of MIs, clinical staff who reported them and divisions (specialties) from which they originated.

- **Aim 2:** To evaluate the impact of an intervention on improving the prescribing of specific high-risk antibiotics at an NHS Foundation Trust.
  
  Objectives:
  
  - To identify potential evidence-based interventions to improve prescribing accuracy in specific high-risk antibiotics
  - To apply an evidence-based intervention identified
  - To assess the impact of the intervention on prescribing accuracy by determining the significance of the difference between the number/rate of correct doses of these antibiotics before and after the intervention
  - To determine the usage of the intervention by prescribers.

- **Aim 3:** To explore the views and experiences of doctors in prescribing specific high-risk antibiotics at an NHS Foundation Trust and the resources and methods they use to prescribe these antibiotics.
  
  Objectives:
  
  - To gain an understanding of the prescribing process of specific high-risk antibiotics
  - To identify the resources and methods doctors use to prescribe these antibiotics, for both correct and incorrect doses
  - To assess prescribers’ knowledge and experience of using these antibiotics and the factors that might affect their prescribing accuracy
  - To explore prescribers’ views of the sources of error and preventive strategies.
Chapter 2

Risk of Medication Safety Incidents with Antibiotic Use
2.1. Introduction

As discussed in Chapter 1, antibiotics is one of the drug classes most frequently associated with medication incidents (MIs). In addition, incident reporting was identified as one of the methods most commonly used to detect MIs. This chapter investigates antibiotic-associated MIs through an incident report analysis.

2.1.1. Patient safety incident reporting

The history of incident reporting goes back to the 1940s when the critical incident technique was introduced to examine military aircraft training accidents and to improve safety and performance among pilots. This technique involves the identification of behaviours/incidents that led or had the potential to lead to an adverse outcome. These behaviours/incidents should be reported by the staff directly involved in the questionable process as soon as they are discovered. (Flanagan, 1954)

The failure of some healthcare systems to learn from their mistakes appears to be a major barrier to patient safety improvement. One solution to this problem is adverse incident reporting by staff within healthcare organisations, and then by organisations to a regional or national reporting system. This would enhance learning from errors and allow sharing experiences with a wider audience. An effective reporting system can be the keystone of safe care practice and a measure of progress towards creating a safety culture within healthcare organisations. (Leape and Abookire, 2005)

Incident reporting is one of numerous tracking systems and techniques for collecting and analysing patient safety incidents (PSIs). Audits, retrospective record reviews, confidential enquiries, and litigation databases are all other methods for tracking incidents. The major difference between these methods and incident reporting is that reporting relies on the gaining of real-time data from the healthcare staff directly involved in the incident. (Simon et al, 2005)

Subsequently, the purpose of incident reporting is collecting qualitative data from the frontline healthcare providers about undesired clinical outcomes or deviations from standard clinical practice and providing quantitative data for these incidents. Incident reporting systems may be voluntary or mandatory, include adverse incidents, no-harm
incidents or near misses, be limited to specific incidents such as adverse drug events (ADEs) or be more comprehensive. (Simon et al, 2005)

The World Health Organization (WHO) created draft guidelines for adverse incident reporting and learning systems (Leape and Abookire, 2005) to facilitate the development/improvement of incident reporting systems. According to these guidelines, the primary purpose of reporting systems is for healthcare organisations to learn from their experience. Reporting systems must provide clear and valuable reactions in order to stimulate further reporting and justify the consumed resources. In order to prevent the recurrence of PSIs, results of incident data analysis should be used to articulate and circulate practice recommendations for changes in the system. This is seen by the guidelines as the most important role of reporting systems.

2.1.2. Characteristics and requirements of successful incident reporting systems

Voluntary medical incident reporting systems are struggling to find an effective design to solve the issues of staff acceptance and usage. Leadership support, blame culture, punitive environment, clinician involvement, legislation issues, and system usability affect the adoption of these systems by staff and have substantial effects on the quantity and quality of data collected using them. (Hua and Gong, 2011)

In their WHO guidelines, Leape and Abookire (2005) determined 7 characteristics for a successful national reporting system; non-punitive, confidential, independent, expert analysis, timely, systems-oriented, and responsive. In addition, the guidelines specified 9 requirements that healthcare systems need in order to build a successful reporting system. These were clear objectives, clarity about who should report, clarity about what gets reported, mechanisms for receiving reports and managing the data, expertise for analysis, capacity to respond to reports, a method for classifying and making sense of reported incidents, capacity to disseminate findings, and technical infrastructure and data security.

The US Agency for Healthcare Research and Quality (AHRQ) have identified four key components incident reporting systems should have in order to be effective (2012); a supportive reporting environment that protects the privacy of reporting staff, staff from a wide range of departments/professions reporting incidents, dissemination of incident data summaries in a regular and timely manner, and the existence of structured mechanisms for analysing data and formulating action plans.
Chapter 2: Risk of Medication Safety Incidents with Antibiotic Use

The 8 articles in the Hua and Gong (2011) review on voluntary medical incident reporting systems demonstrated the existence of different challenges in the design and adoption of such systems which affect the quality of incident reports submitted. These challenges included voluntariness, terminology/taxonomy/nomenclature, blame-free environment, reporting culture, usability and utility concerns, feedback, and administrative issues.

2.1.3. International incident reporting systems

National incident reporting systems have great variations in sponsorship, support, participation, and function. While some were developed by governmental agencies (e.g. UK, Denmark, Czech Republic, Sweden, Netherlands, Ireland), others were developed within the private or non-governmental sector (e.g. Australia, Japan, USA). (Leape and Abookire, 2005).

Terzibanjan (2007) found in a study reviewing MI reporting systems in 16 countries, in affiliation with the International Pharmaceutical Federation (FIP), that a reporting system existed in 11 countries; 5 national (Canada, Japan, Sweden, Norway, Zambia) and 6 local (Australia, Hungary, Finland, Czech republic, Rwanda, Austria) while it didn’t exist in 5 countries (Ghana, India, Kosovo, Latvia, Serbia). MI reporting systems were more likely to exist in the countries which had national patient-safety (Austria, Canada, Hungary, Japan, Norway, Sweden and Zambia) and/or medication-safety (Australia, Austria, Canada, Japan, Norway, Sweden and Zambia) authorities.

These findings demonstrate the vital role of national authorities in the development, implementation and maintenance of MI reporting systems. The study also showed that some countries had a local reporting system without the existence of a separate authority for medication safety. This indicates that healthcare systems need to have an independent authority for medication safety to lead and regulate the process, especially when developing a national MI reporting system. (Terzibanjan, 2007)

2.1.4. Incident reporting system in the UK

2.1.4.1. England and Wales

Over the last 15 years, the issue of patient safety became very important within the National Health Service (NHS) due to rising concerns about the preventable harm associated with patient safety incidents (PSIs). The report ‘An Organisation with a
Memory’ (2000) by the Department of Health (DoH) emphasised on the importance of enhancing patient safety by learning from these incidents. Thus, numerous recommendations were made to encourage and facilitate reporting of PSIs. One year later, ‘Building a safer NHS’ (DoH, 2001) was published. This report provided an action plan for specific patient safety recommendations to be implemented in the UK. One of these was the establishment of the National Patient Safety Agency (NPSA) which was a national system for collecting and analysing PSI reports from all NHS Trusts in England and Wales. (Alrwisan et al, 2011)

The National Reporting and Learning System (NRLS) was launched in 2003 under the umbrella of the NPSA. This system enables PSI reports from England and Wales to be submitted to a national database. NRLS mission is to identify and reduce risks to the NHS patients. It also conducts nation-wide initiatives to improve patient safety. Since the NRLS was established, over four million PSI reports were submitted by healthcare staff. (NRLS, 2013B)

PSIs can be reported by NHS staff via local reporting systems by using confidential online reports. NHS staff are encouraged to report all incidents to these local systems, whether they result in patient harm or not. These reports are then transferred to the NRLS database. From 1st April 2010 it became mandatory for NHS Trusts in England to report all serious PSIs as part of the Care Quality Commission (CQC) registration process. These incidents (including death and severe harm incidents) should be submitted by the Trusts to NRLS who would then transfer them to CQC. Clinicians and safety experts analyse the reports to identify hazards, risks, and opportunities to improve the safety of patient care. Afterwards, healthcare organisations are provided with feedback and guidance to improve patient safety practice. This can be in the form of (NRLS, 2013B):

- Resources, including quarterly reports on incidents, alerts to address specific safety risks, and tools to build a strong safety culture
- National campaigns on specific topics (e.g. clean your hands, patient safety first, save 1000 lives)
- Collaborations with international organisations on global campaigns and initiatives.

From 1st June 2012, the NPSA key functions for patient safety have been transferred to the NHS Commissioning Board Special Health Authority, NHS England. This included the Authority harnessing the power of NRLS. (NPSA, 2012)
The Medicines and Healthcare products Regulatory Agency (MHRA) operates a pharmacovigilance system to monitor the use of medicines in the UK. MHRA and NHS England have started a strategic partnership to improve the reporting of and learning from MIs (including those causing adverse drug reactions (ADRs)). NRLS would act as an integrated reporting route for MIs as part of this partnership (Figure 2.1). ADRs not arising from medication errors should be reported to MHRA through Yellow Card Scheme. (NHS England, 2014)


Figure 2.1. The Medicines and Healthcare products Regulatory Agency and NHS England model for the flow of information needed to improve reporting of medication incidents in the NHS (from NHS England, 2014, p.6)

2.1.4.2. Scotland

ADRs occurring in Scotland are reported to the MHRA Yellow Card Scheme. Many Scottish hospitals are using incident reporting systems (e.g. Datix®) to report PSIs locally. However, there is no national system (equivalent to NRLS) to collate and analyse incident data from all of these hospitals (Mair, 2014).
2.1.4.3. **Northern Ireland**

The Northern Ireland Medicine Governance Team was established in 2002, as part of the Health and Social Care in Northern Ireland (HSCNI), to enhance medicines risk management across the secondary care sector. The Team, which is totally run by medicines governance pharmacists, was expanded to cover primary care in 2010 (Medicines Governance Northern Ireland, 2014A).

The Team collects MI data voluntarily reported by healthcare staff, from different professions, in all hospitals in Northern Ireland (not anonymised) as well as data reported from community pharmacies (anonymised). Then, they analyse these data and publish quarterly reports which are sent back to all Trusts to provide them with feedback. However, these data are not published publicly due to confidentiality issues (Carrington, 2014). The Team also publishes different guidelines, policies, newsletters and reports (e.g. Medication Safety Today, Medication Safety Matters) to facilitate learning and provide recommendations for practice improvement and error reduction (Medicines Governance Northern Ireland, 2014B).

2.1.5. **Strengths of incident reporting systems**

Incident reporting systems are an important tool for monitoring patient safety at hospitals. One of the main strengths identified for these systems is that they can provide a broad database of incidents in a specific time period, especially as minor incidents occur much more than serious accidents, which can help in anticipating potentially harmful incidents. (Staender, 2000). It was stated by Leape *et al* (1997, p.216) that

“*The objective of initial data collection is to obtain a stable and reproducible measure of the problem in order to be able to determine the effect of an intervention*”.

The analysis of reported incidents provides an opportunity for learning from dangerous situations which would help in finding potential solutions. This is not possible with serious accidents as there is no recovery. Analysing reported incidents can lead to their root-causes which help in guiding effective actions to improve the quality of patient care. Furthermore, proper monitoring of incidents can help in maintaining the quality of certain activities over time and over change in policies (Staender, 2000). Healthcare teams and individual staff can learn much from the exchange of experiences that occurs through
incident reporting. Moreover, the costs of incident reporting systems are relatively low compared to other patient-safety monitoring tools (Staender, 2000).

2.1.6. Limitations of incident reporting systems

Shojania (2010) identified four main disadvantages for incident reporting systems; under-reporting of serious incidents, frequent reporting of events not suitable for individual analysis, can become discouraging if staff do not notice any improvements resulting from the PSIs they report, and cannot measure safety changes in relation to time.

Under-reporting reduces the quantity and quality of information that can be used to improve patient care and avoid recurrence of errors. A study by Cullen et al (1995) identified that only 6% out of 54 ADEs occurred over a 6-month period were reported. This study also emphasised that only 2 of the 26 serious/life-threatening ADEs were reported. A UK study showed that out of 196 PSIs identified from 500 deliveries at two maternity units in London, 23% were reported by staff and further 22% by risk managers. The remaining 55% of incidents were identified only by record review. Staff reported about half of the serious incidents (48%), but comparatively few of the moderately serious (24%) or minor ones (15%) (Stanhope et al, 1999). Other studies comparing incident reporting to other detection methods are presented in section 1.3.4. A systematic review of 37 studies from 12 countries showed a median ADR under-reporting of 94% (interquartile range 82-98%). No significant differences in under-reporting rates were found between general practice and hospital-based studies. The average under-reporting rate was slightly lower (85%) in the 19 studies that investigated specific severe and serious ADRs (Hazell and Shakir, 2006).

The reasons for under-reporting could be unfamiliarity with the reporting process, cultural issues (e.g. fear of punitive action), discrimination at the workplace, and legal consequences. The doctors’ poor reporting practices may reflect a deeply embedded belief in medicine that only bad doctors make mistakes. Lack of clarity about what should be reported and about the way in which the reports may lead to practice improvement are other possible factors for under-reporting (Mahajan, 2010). A study by Evans et al (2006) showed that the main barriers for doctors to report PSIs were the lack of feedback (57.7%), the long time needed to complete the incident form (54.2%), and a belief that insignificant incidents do not need to be reported (51.2%). For nurses, the main barriers
were the lack of feedback (61.8%), a belief that near misses should not be reported (49.0%), and forgetting to make a report because of the high workload (48.1%).

It is not possible to validate the information in reports submitted to anonymous incident reporting systems, the majority, therefore this is an important limitation that might lead to reporting bias in these systems. In addition, ambiguity about who should report and what should be reported is another limitation of such systems (Stanhope et al, 1999).

Knowing the outcome of a certain incident can influence the chances of it being reported. Evans et al (2006) showed that the incidents which were immediate and/or witnessed (e.g. falls, drug errors) were more often reported than the incidents which had a gradual development and could not be linked to a single cause, or were considered as known complications of hospitalisation (e.g. nosocomial infections, pressure ulcers). However, this outcome bias is minimised with incidents in comparison to accidents as there is no adverse outcome in the majority of cases; which is another advantage of analysing incidents instead of only harmful accidents (Staender, 2000).

2.1.7. Actions to improve incident reporting

Different actions can be taken in order to improve incident reporting. In 2008, the NHS Confederation, in combination with NPSA, published a briefing on actions to improve patient safety reporting. In this briefing, five major changes were required in order to achieve good reporting practice across all NHS organisations:

1. Give feedback to staff:
The staff need to see the outcomes of the effort they make to report PSIs and that the organisation is using these reports to provide better services. The lack of feedback makes incident reporting a boring bureaucratic process instead of a powerful mechanism for system change. Feedback mechanisms can be in the form of local ward-level meetings to discuss incidents, central team visits to provide feedback, regular newsletters highlighting the action-prompting incident reports, trend analysis, or case study reports.

2. Focus on learning:
Rather than blame, understanding the root causes of incidents, learning from them and accordingly taking actions to minimise risks to patients should be the main focus of incident reporting. Reporting should be used to motivate local safety improvement by
identifying topics and themes that need an in-depth review. The influence of incident reporting on the organisational decisions and practice should be noticed by senior staff, especially clinicians, in order to encourage and sustain good reporting levels.

3. Engage frontline staff:
The briefing stated that in Healthcare Commission annual staff surveys, the high-reporting organisations are scoring above-average in safety culture ratings. Data from the surveys showed that most staff from these organisations had sufficient knowledge on how to report, felt their organisation is supporting them, and believed they were receiving feedback on their reports. Training on the ‘what, how and why’ is essential to increase reporting levels and acquire useful data that can be analysed and generate actions.

4. Make it easy to report:
While capturing the required information, incident reporting forms should be made as simple as possible. Online reporting systems increase the consistency and efficiency throughout the reporting cycle. However, paper forms may still be needed in some cases (e.g. in busy wards with restricted computer access). New ways of encouraging staff to report have also been developed (e.g. a short form on medication trolleys for immediate reporting of MIs, linking the reporting system to central electronic records so that patient and staff details can be automatically populated).

5. Make reporting matter:
The boards and senior managers of the organisations with high incident reporting rates show strong and visible safety leadership. That is practically articulated by investing in robust systems and using the data from incident reports in supporting decision making at the highest level of the organisation.

A survey conducted by the UK National Audit Office (2005) found that 78% of 256 healthcare Trusts found that their focus on encouraging incident reporting was having an annual positive impact on the number of PSIs reported. However, Trusts recognised that a substantial amount of incidents still go unreported. On average, it was estimated that 22% of PSIs go unreported, mostly MIs and serious incidents. In addition, there was a low rate of near-miss reporting as 39% were estimated to go unreported. A main reason for that was the different perceptions by staff of what is considered a near miss.
2.1.8. Rates of medication incident reporting

Reported rates of MIs vary widely as different study methods and definitions are often used. According to a report by David Cousins (2011), MIs were the second most common PSI reported (9.7%, n=525,186) to the NPSA in England and Wales over a six-year period (2005-2010) after patient accidents. In the first year, 8.2% (n=42,398) of all PSIs reported were MIs. This increased to 11.0% in the sixth year (n=132,069). This rate seems to remain stable as data from the NRLS (2013A), on the 2 following years, showed that MIs are still the second most common incident reported with relatively similar proportions in 2011 (11.4%, n=149,409) and 2012 (11.1%, n=158,951). In hospital settings, MIs make almost the same proportion of PSIs to that in all healthcare settings (2011: 11.5%, n=108,108; 2012: 10.9%, n=112,710).

Data from the Australian Incident Monitoring System (AIMS) showed that 26.5% of 27,000 (n=7,155) reported hospital-based incidents were MIs, as were 36.2% (n=723) of 2,000 anaesthesia-related incidents, and 50.1% (n=1,294) of 2,582 general-practice incidents (Runciman et al, 2003). A study by Nuckols et al (2007) analysed 3,875 randomly selected PSIs reported to the incident reporting system at two US hospitals (an academic hospital and a community hospital). In this study, 28.8% (n=1,094) of reported incidents were MIs. Of which, 93% (n=1,017) were judged to be preventable; 45.3% of all preventable incidents in the study (n=2,246). This showed that the preventability of MIs is high compared to other types of PSIs.

2.1.9. Reporting of antibiotic incidents

Antibiotics is one of the drug classes most reported for MIs. A UK study identified that 14.3% out of 495 MIs submitted to the incident reporting system of an NHS hospital were related to anti-infectives (Ashcroft and Cooke, 2006). A US study on elderly patients identified that out of 861 MIs submitted to the hospital incident reporting system, 17.6% were associated with antibiotics (Picone et al, 2008). Furthermore, a Spanish study found that 19.7% of the reported 173 MIs involved anti-infectives (Menéndez et al, 2008). In a UK study on paediatric admissions, 44% of the 109 MIs reported for intravenous drugs were related to antibiotics (including antivirals) which made it the drug class most commonly reported (Ross et al, 2000).
Antibiotics are also commonly reported for serious incidents. It was the second drug class mostly reported in association with death or severe harm in Cousin’s (2011) report (5.8% of all death/severe harm incidents, n=48) after opioids. In a review to all harmful MIs reported to MEDMARX®, the US Pharmacopeia MI reporting system, over 5 years, antimicrobials were the second most commonly reported drug class (7.5%, n=61) after opioids (Hicks et al, 2006). A Canadian study on paediatrics (Doherty and McDonnell, 2012) found that out of 6,643 MIs reported to the hospital reporting system over 5 years, 3.8% (n=252) were 10-fold medication errors. Of these, antimicrobials was the second drug class most commonly reported (12.3%, n=31), again after opioids. Therefore, this study will investigate the MIs reported in association with antibiotics in the hospital setting. This will help in identifying the most important issues with antibiotic use in order to develop potential solutions.

2.2. Aim and Objectives

2.2.1. Aim of study

The aim of this study was to determine the prevalence, incidence, and nature of reported antibiotic-associated MIs occurring in inpatients at two NHS Foundation Trusts.

2.2.2. Study objectives

- To determine the number, incidence, and type of antibiotic MIs reported by staff
- To identify the antibiotics involved in MIs
- To investigate the relationship between MIs and defined daily doses (DDDs)
- To assess the severity of MIs reported (the harm caused to patients)
- To identify the clinical staff who reported MIs
- To determine the divisions (specialties) where MIs originated.

2.3. Methods

2.3.1. Study design

As discussed earlier, incident report analysis is useful to provide a broad database of MIs within a specific period of time. It also offers an opportunity to learn from high-risk conditions which can be helpful in finding potential solutions (Staender, 2000). In this
study, a retrospective secondary quantitative analysis was performed on antibiotic-associated MIs reported individually to Datix® system, a web-based patient safety software for healthcare risk management applications. Datix® is used at both study sites to report all PSIs (e.g. including accidental injuries, damages, MIs). In addition, the relationship between MIs and defined daily doses (DDDs) was assessed to check if there is any relation between the amount of drug consumed and the risk of it being associated with an incident.

2.3.2. Study setting

The study was performed in two London NHS Foundation Trusts; King’s College Hospital Foundation Trust (Trust A) and Guy’s and St Thomas’ Foundation Trust (Trust B), which have an overall capacity of 2,150 beds (Trust A=1,200; Trust B=950). Both Trusts are teaching hundreds of doctors every year. They both provide secondary and tertiary care including many medicine and surgery sub-specialties, haematology/oncology, critical care, women and children, and accident and emergency. Electronic prescribing was available in most wards of Trust A, except of critical care wards which used paper prescribing. In contrast, critical care wards were the only ones using electronic prescribing in Trust B, while all other wards used paper prescribing.

2.3.3. Inclusion/exclusion criteria

All inpatients (adults and paediatrics) for whom a MI report about a systemic antibiotic was submitted between 1st June 2009 and 31st May 2011 were included in this analysis regardless of age, division (specialty), or location. Reports related to topical antibiotics (e.g. creams, ointments, drops), all antifungals, antivirals, and antiprotozoals were excluded from the study. Reports related to idiopathic adverse drug reactions and outpatients were also excluded.

2.3.4. Research permission

This retrospective study did not require ethical approval as confidential patient data were not extracted or recorded and there was no direct contact with patients. The study was determined to be a clinical audit/service evaluation and was registered with the Clinical Effectiveness and Audit Departments at both Trusts (Project No. 2360).
2.3.5. Definitions

2.3.5.1. Antibiotic

The term antibiotic strictly refers to antimicrobial agents that are synthesised and released by microorganisms. In practice, the term antibiotic has become synonymous with all antibacterial agents, whether natural or synthetic (Barnes, 2006). This ‘practical’ term was used as such in this study.

2.3.5.2. Defined Daily Dose

The DDD is defined as

“The assumed average maintenance dose per day for a drug used for its main indication in adults”. (WHO Collaborating Centre for Drug Statistics Methodology, 2009)

However, it should be emphasised that DDD is a unit of measurement and does not necessarily reflect the recommended daily dose. The WHO has a standard DDD for each drug, and for each dosage form of this drug. That DDD is used to standardise the comparison of drug usage between different drugs or between different health care settings.

2.3.6. Medication incident reporting process

At both Trusts, each MI is submitted through an adverse incident report form on Datix® (Appendix 2.1) by an anonymous reporter (the name field is not mandatory) who should record his/her profession (e.g. pharmacist, medical specialist, registered nurse). The incident type in the form should be chosen and if ‘medication’ was selected, the incident is then categorised as a MI by the system. Once reported on Datix®, an incident notification will be sent electronically to the appropriate manager for action, risk grading and approval on the web system.

2.3.7. Data collection and processing

2.3.7.1. Data extraction

All MI reports occurred in the study period (1st June 2009 – 31st May 2011) were extracted from Datix® by the Medication Safety Consultant at each Trust who anonymised them and exported the data to an Excel® spreadsheet. The data were encrypted and access was
limited only to the research team. Using the Excel\textsuperscript® filter application, MI reports associated with antibiotics were then extracted and transferred to another spreadsheet. In order to identify these reports, each antibiotic including different spellings was separately filtered within the spreadsheet columns of drug name, drug administered, correct drug, and synopsis to find all MI reports related to antibiotics.

The data extracted from each MI report were date, division (specialty), location, stage of the medication-use process (MUP), incident type, severity, synopsis, drug involved, reporter’s profession, drug administered, correct drug, dose administered, correct dose, form administered, correct form, route administered, correct route, action taken, and investigation.

2.3.7.2. Data cleansing

Quality assurance measures were undertaken before analysing the data. Differences in the categories used to classify MIs at each Trust were identified. Following discussions with the Medication Safety Consultants at both Trusts, these categories were harmonised and used to analyse data (Appendix 2.2).

Each antibiotic MI was reviewed, and re-classified if needed, in order to ensure that the reported incident type, severity, and stage of the MUP were accurately classified. If not mentioned in the drug name category, the drug involved in the MI was searched for in all other fields. Furthermore, any MI which was duplicated or did not fulfil the inclusion criteria was removed.

2.3.7.3. Data analysis

Quantitative analysis was undertaken using Microsoft Excel\textsuperscript® 2010. The total number of MIs associated with antibiotics was calculated. Excel\textsuperscript® filters were used to count each type of MIs; in Datix\textsuperscript®, the reporter categorises each MI into one of 6 stages of the MUP (e.g. prescribing, administration) and 24 incident types (e.g. omission, wrong dose, allergy).

The antibiotics involved in MIs were categorised according to the BNF classification of 74 drugs classified into 13 antibiotic groups (Joint Formulary Committee, 2011). Then, the number of MIs associated with each antibiotic group and drug was identified.
The relationship between MIs and DDDs was determined for the top 10 antibiotics most commonly associated with MIs at each Trust. The ratio of MIs to the total quantity consumed of each antibiotic (in DDDs) was calculated, and thus the MI rate for these antibiotics was determined. Drug consumption/utilisation (in DDDs) can be calculated using the following equation adopted from the antibiotic consumption calculator created by Monnet (2006):

\[
\text{Drug consumption (DDDs)} = \frac{\text{No. of items issued} \times \text{Amount of drug per item (in grams)}}{\text{DDD (assigned by WHO)}}
\]

The data needed to calculate the total quantity consumed of each antibiotic was obtained from the pharmacy internal system at each Trust (Ascribe\textsuperscript{®} at Trust A and JAC\textsuperscript{®} at Trust B) (i.e. number of items issued) and the ATC/DDD index (2011) by the WHO Collaborating Centre for Drug Statistics Methodology (i.e. drug’s standard DDD).

The severity assigned to each MI was evaluated using a local risk matrix (Appendix 2.3) inspired from the NPSA risk matrix (2008). Based on this matrix, severity was divided into 5 categories based on the degree of harm the MI caused: no harm, low harm, moderate harm, serious harm, and death.

The clinical staff who reported MIs (e.g. pharmacists, nurses, doctors) were reviewed. The number of MIs reported by each clinical profession and associated grades was calculated. Moreover, the divisions from where these reports came were also assessed to determine which departments in the Trust were reporting most MIs. Therefore, the number of MI reports originated from each division (specialty) in both Trusts was determined.

2.4. Results

2.4.1. Reported medication incidents

In the 2-year study period, 6,756 MI reports were submitted to the risk management systems across both Trusts, of which 885 (13.1%) were associated with antibiotics. These reports included 959 MIs (Table 2.1). Some reports recorded multiple MIs with the same antibiotic or a MI with different antibiotics; 53 reports included 2 MIs, 9 included 3 MIs, and 1 included 4 MIs.
These reports were submitted to Datix® from different areas including all patient wards, intensive-care units, emergency departments, day-care units, radiology, dental-care practices, recovery areas, medical-assessment units, sexual health centre, and pharmacy. Of the 959 MIs submitted, 54.6% (n=524) were submitted in the first year (June 2009–May 2010) and 45.4% (n=435) in the second year (June 2010–May 2011) of the study.

Table 2.1. Demographics of the submitted medication incident reports

<table>
<thead>
<tr>
<th>Category</th>
<th>Trust A</th>
<th>Trust B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI reports submitted</td>
<td>2,850 (42.2)</td>
<td>3,906 (57.8)</td>
<td>6,756 (100)</td>
</tr>
<tr>
<td>Antibiotic-associated MI reports</td>
<td>372 (42.1)</td>
<td>513 (57.9)</td>
<td>885 (100)</td>
</tr>
<tr>
<td>Antibiotic-associated MIs</td>
<td>397 (41.4)</td>
<td>562 (58.6)</td>
<td>959 (100)</td>
</tr>
<tr>
<td>MIs in the 1st year</td>
<td>221 (42.2)</td>
<td>303 (57.8)</td>
<td>524 (100)</td>
</tr>
<tr>
<td>MIs in the 2nd year</td>
<td>176 (40.5)</td>
<td>259 (59.5)</td>
<td>435 (100)</td>
</tr>
</tbody>
</table>

2.4.2. Stages and types of medication incidents

Most MI reports involved prescribing (42.4%, n=407) and administration (40.0%, n=384) incidents. Only 8.0% of MIs (n=77) occurred during dispensing. The MI types most reported were omission/delay (26.3%, n=252), most of which (74.6%, n=188) occurred during administration, followed by wrong dose/frequency (18.0%, n=173) and allergy MIs (17.0%, n=163). Allergy MIs were divided into two types; ‘allergy status not documented’ (n=28) and ‘drug used despite known allergy’ (n=135). Details related to the MI stages and types can be found in Tables 2.2 and 2.3.

Table 2.2. Analysis of the stages of medication-use process in which antibiotic medication incidents occurred

<table>
<thead>
<tr>
<th>Stage of medication-use process</th>
<th>Trust A</th>
<th>Trust B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>185 (46.6)</td>
<td>222 (39.5)</td>
<td>407 (42.4)</td>
</tr>
<tr>
<td>Administration</td>
<td>161 (40.6)</td>
<td>223 (39.7)</td>
<td>384 (40.0)</td>
</tr>
<tr>
<td>Dispensing</td>
<td>31 (7.8)</td>
<td>46 (8.2)</td>
<td>77 (8.0)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>7 (1.8)</td>
<td>35 (6.2)</td>
<td>42 (4.4)</td>
</tr>
<tr>
<td>Drug Management System</td>
<td>9 (2.3)</td>
<td>30 (5.3)</td>
<td>39 (4.1)</td>
</tr>
<tr>
<td>Medical Advice</td>
<td>3 (0.8)</td>
<td>3 (0.5)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3)</td>
<td>3 (0.5)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>397 (100)</td>
<td>562 (100)</td>
<td>959 (100)</td>
</tr>
</tbody>
</table>
Table 2.3. Analysis of antibiotic medication incident types

<table>
<thead>
<tr>
<th>MI Type</th>
<th>Number of incidents (%)</th>
<th>Trust A</th>
<th>Trust B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omission</td>
<td>81 (20.4)</td>
<td>117 (20.8)</td>
<td>198 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>58 (14.6)</td>
<td>105 (18.7)</td>
<td>163 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Wrong Dose</td>
<td>66 (16.6)</td>
<td>57 (10.1)</td>
<td>123 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Delay*</td>
<td>25 (6.3)</td>
<td>29 (5.2)</td>
<td>54 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Wrong Frequency</td>
<td>30 (7.6)</td>
<td>20 (3.6)</td>
<td>50 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Wrong Drug</td>
<td>24 (6.0)</td>
<td>17 (3.0)</td>
<td>41 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Wrong Patient</td>
<td>14 (3.5)</td>
<td>22 (3.9)</td>
<td>36 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Documentation*</td>
<td>10 (2.5)</td>
<td>21 (3.7)</td>
<td>31 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Wrong Preparation</td>
<td>16 (4.0)</td>
<td>13 (2.3)</td>
<td>29 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Delay / Failure to Monitor</td>
<td>5 (1.3)</td>
<td>21 (3.7)</td>
<td>26 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Failure to Discontinue</td>
<td>8 (2.0)</td>
<td>18 (3.2)</td>
<td>26 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Inadequate Medicine Systems or Records*</td>
<td>3 (0.8)</td>
<td>22 (3.9)</td>
<td>25 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Drug Duplication</td>
<td>5 (1.3)</td>
<td>17 (3.0)</td>
<td>22 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Dose Duplications</td>
<td>6 (1.5)</td>
<td>10 (1.8)</td>
<td>16 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Wrong Route</td>
<td>4 (1.0)</td>
<td>12 (2.1)</td>
<td>16 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Expired Drug</td>
<td>11 (2.8)</td>
<td>3 (0.5)</td>
<td>14 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Contraindication</td>
<td>3 (0.8)</td>
<td>9 (1.6)</td>
<td>12 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Wrong Rate</td>
<td>6 (1.5)</td>
<td>5 (0.9)</td>
<td>11 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Inappropriate Storage</td>
<td>1 (0.3)</td>
<td>6 (1.1)</td>
<td>7 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Wrong Formulation</td>
<td>5 (1.3)</td>
<td>2 (0.4)</td>
<td>7 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Wrong Time</td>
<td>4 (1.0)</td>
<td>3 (0.5)</td>
<td>7 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Wrong Quantity</td>
<td>1 (0.3)</td>
<td>4 (0.7)</td>
<td>5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Wrong / Omitted Patient Information Leaflet</td>
<td>3 (0.8)</td>
<td>2 (0.4)</td>
<td>5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Not Indicated</td>
<td>3 (0.8)</td>
<td>0 (0)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.3)</td>
<td>27 (4.8)</td>
<td>32 (3.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>397 (100)</strong></td>
<td><strong>562 (100)</strong></td>
<td><strong>959 (100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Giving the dose > 2hr after the scheduled time but before the next dose is due
" Errors in documenting drug administration, signing prescription/drug chart, or taking drug history
# Includes finding drugs of other patients in the locker, storing drugs in the wrong place on wards, referring outpatients to take drugs on ward, missing drugs from ward stock without records of what happened to them, and problems in storing drugs in the automated supply cabinet.

2.4.3. Antibiotics involved in medication incidents

The reported MIs were related to 45 drugs from 12 BNF antibiotic classes. Penicillins was the drug class most frequently reported (34.5%, n=331) followed by aminoglycosides (16.6%, n=159), ‘some other antibacterials’, i.e. vancomycin, linezolid, teicoplanin, daptomycin, colistin and chloramphenicol (13.5%, n=129), and cephalosporins, carbapenems & other beta-lactams (13.5%, n=129). The drugs most commonly reported were co-amoxiclav (16.8%, n=161), gentamicin (14.1%, n=135), and vancomycin (9.9%, n=95). Most of the reported co-amoxiclav MIs occurred during prescribing (65.8%, n=106).
Twenty-eight MIs were reported for antibiotic agents although the name was not specified. In addition, there were 4 cases in which the allergy status was documented as ‘no known drug allergies’, but on investigation the patients were allergic to penicillin. These were categorised as penicillin group MIs and as no named drug had been prescribed, these were categorised as ‘not applicable’ in the drug category. Furthermore, there were 8 reports concerning antibiotics that had been indicated but not prescribed for patients. Unlike most drugs identified, cefotaxime MIs were predominantly associated with paediatrics (92.3%, 24/26). Tables 2.4 and 2.5 provide further details on the antibiotics involved in MIs.

<table>
<thead>
<tr>
<th>BNF Antibiotic Class</th>
<th>Number of incidents (%)</th>
<th>Trust A</th>
<th>Trust B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>139 (35.8)</td>
<td>192 (34.2)</td>
<td>331 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>51 (12.8)</td>
<td>108 (19.2)</td>
<td>159 (16.6)</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, carbapenems &amp; other beta-lactams</td>
<td>46 (11.6)</td>
<td>83 (14.8)</td>
<td>129 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Some other antibacterials*</td>
<td>77 (19.4)</td>
<td>52 (9.3)</td>
<td>129 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>13 (3.3)</td>
<td>26 (4.6)</td>
<td>39 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Metronidazole and tinidazole</td>
<td>11 (2.8)</td>
<td>26 (4.6)</td>
<td>37 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides and trimethoprim</td>
<td>11 (2.8)</td>
<td>18 (3.2)</td>
<td>29 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>9 (2.3)</td>
<td>19 (3.4)</td>
<td>28 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Anti-TB</td>
<td>8 (2.0)</td>
<td>11 (2.0)</td>
<td>19 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>8 (2.0)</td>
<td>5 (0.9)</td>
<td>13 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1 (0.3)</td>
<td>5 (0.9)</td>
<td>6 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>1 (0.3)</td>
<td>3 (0.5)</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>15 (3.8)</td>
<td>13 (2.3)</td>
<td>28 (2.9)</td>
<td></td>
</tr>
<tr>
<td>No antibiotic although indicated</td>
<td>7 (1.8)</td>
<td>1 (0.2)</td>
<td>8 (0.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>397 (100)</strong></td>
<td><strong>562 (100)</strong></td>
<td><strong>959 (100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Vancomycin, linezolid, teicoplanin, daptomycin, colistin and chloramphenicol.
Chapter 2: Risk of Medication Safety Incidents with Antibiotic Use

Table 2.5. Analysis of antibiotic agents associated with medication incidents

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of incidents (%)</th>
<th>Trust A</th>
<th>Trust B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-Amoxiclav</td>
<td></td>
<td>54 (13.6)</td>
<td>107 (19.0)</td>
<td>161 (16.8)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td>39 (9.8)</td>
<td>96 (17.1)</td>
<td>135 (14.1)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td>52 (13.1)</td>
<td>43 (7.7)</td>
<td>95 (9.9)</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td></td>
<td>15 (3.8)</td>
<td>35 (6.2)</td>
<td>50 (5.2)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td></td>
<td>35 (8.8)</td>
<td>13 (2.3)</td>
<td>48 (5.0)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
<td>14 (3.5)</td>
<td>28 (5.0)</td>
<td>42 (4.4)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
<td>24 (6.0)</td>
<td>15 (2.7)</td>
<td>39 (4.1)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td>11 (2.8)</td>
<td>26 (4.6)</td>
<td>37 (3.9)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td>4 (1.0)</td>
<td>22 (3.9)</td>
<td>26 (2.7)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td>6 (1.5)</td>
<td>19 (3.4)</td>
<td>25 (2.6)</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td>7 (1.8)</td>
<td>13 (2.3)</td>
<td>20 (2.1)</td>
</tr>
<tr>
<td>Cefalexin</td>
<td></td>
<td>8 (2.0)</td>
<td>12 (2.1)</td>
<td>20 (2.1)</td>
</tr>
<tr>
<td>Clarithromycins</td>
<td></td>
<td>6 (1.5)</td>
<td>13 (2.3)</td>
<td>19 (2.0)</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>12 (3.0)</td>
<td>6 (1.1)</td>
<td>18 (1.9)</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td>5 (1.3)</td>
<td>12 (2.1)</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
<td>2 (0.5)</td>
<td>14 (2.5)</td>
<td>16 (1.7)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td>8 (2.0)</td>
<td>5 (0.9)</td>
<td>13 (1.4)</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>11 (2.8)</td>
<td>2 (0.4)</td>
<td>13 (1.4)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>4 (1.0)</td>
<td>7 (1.2)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Co-Trimoxazole</td>
<td></td>
<td>8 (2.0)</td>
<td>3 (0.5)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>4 (1.0)</td>
<td>7 (1.2)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td></td>
<td>8 (2.0)</td>
<td>3 (0.5)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Other (less than 10 incidents)</td>
<td></td>
<td>37 (9.3)</td>
<td>44 (7.8)</td>
<td>81 (8.4)</td>
</tr>
<tr>
<td>Not specified</td>
<td></td>
<td>15 (3.8)</td>
<td>13 (2.3)</td>
<td>28 (2.9)</td>
</tr>
<tr>
<td>Not applicable</td>
<td></td>
<td>1 (0.3)</td>
<td>3 (0.5)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>No antibiotic although indicated</td>
<td></td>
<td>7 (1.8)</td>
<td>1 (0.2)</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>397 (100)</strong></td>
<td><strong>562 (100)</strong></td>
<td><strong>959 (100)</strong></td>
</tr>
</tbody>
</table>

2.4.4. Severity of medication incidents

The no-harm category was dominant among the submitted reports (78.2%, n=750); Trust A=78.3% (311/397) & Trust B=78.1% (439/562), followed by low-harm (19.9%, n=191); Trust A=19.6% (78/397) & Trust B=20.1% (113/562). There were few moderate-harm (1.6%, n=15); Trust A=1.8% (7/397) & Trust B=1.4% (8/562) and no serious-harm or death incidents reported. In 3 cases, the clinical outcome for the patient was not evident at time of reporting. Reports submitted with harm unrecorded were categorised as ‘outcome unknown’. (Table 2.6)

Most incidents reporting low and moderate harm (n=206) were associated with penicillins (24.8%, n=51), aminoglycosides (22.3%, n=46), ‘some other antibacterials’ (18.0%, n=37), and cephalosporins, carbapenems and other beta-lactams (15.0%, n=31) classes. The drugs involved in most of these incidents were gentamicin (19.4%, n=40), co-amoxiclav (14.1%, n=29), and vancomycin (13.6%, n=28).
Table 2.6. Analysis of severity of antibiotic medication incidents

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Incident Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No harm</td>
</tr>
<tr>
<td></td>
<td>(n=750)</td>
</tr>
<tr>
<td>Penicillins (331 incidents)</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>36</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>16</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>132</td>
</tr>
<tr>
<td>Co-fluampicil</td>
<td>1</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>48</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>7</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>37</td>
</tr>
<tr>
<td>Timentin</td>
<td>1</td>
</tr>
<tr>
<td>Not Specified</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
</tr>
<tr>
<td>Aminoglycosides (159 incidents)</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>14</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>95</td>
</tr>
<tr>
<td>Neomycin</td>
<td>1</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
</tr>
<tr>
<td>Some Other Antibacterials (129 incidents)</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1</td>
</tr>
<tr>
<td>Colistin</td>
<td>3</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>3</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>8</td>
</tr>
<tr>
<td>Vancomycin*</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
</tr>
<tr>
<td>Cephalosporins, Carbapenems and Other Beta-Lactams (129 incidents)</td>
<td></td>
</tr>
<tr>
<td>Cefalexin</td>
<td>16</td>
</tr>
<tr>
<td>Cefixime</td>
<td>1</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>20</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>5</td>
</tr>
<tr>
<td>Ceftriaxone*</td>
<td>4</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>34</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>13</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
</tr>
<tr>
<td>Macrolides (39 incidents)</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>6</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>13</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
</tr>
<tr>
<td>Metronidazole and Tinidazole (37 incidents)</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 6. (Continued) Analysis of severity of antibiotic medication incidents

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Incident Severity</th>
<th>No harm (n=750)</th>
<th>Low harm (n=191)</th>
<th>Moderate harm (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides and Trimethoprim (29 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-Trimoxazole</td>
<td></td>
<td>10</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td></td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
<td>14</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>24</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Quinolones (28 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td>17</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td></td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TB (19 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td>6</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Rifater</td>
<td></td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rifinah</td>
<td></td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>18</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Tetracyclines (13 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td>11</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Clindamycin (6 incidents)</td>
<td></td>
<td>5</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Urinary Tract Infection (4 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td></td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Others (36 incidents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>23</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Not given although indicated</td>
<td></td>
<td>6</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>29</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

*1 report submitted without being clear about the severity at time of reporting
*2 reports submitted without being clear about the severity at time of reporting.

2.4.5. The relationship between medication incidents and defined daily doses

DDD were used to assess MI incidence according to volume of drugs used (Table 2.7). This identified cefotaxime (105.4 MIs/10,000 DDDs), gentamicin (25.7 MIs/10,000 DDDs), and vancomycin (23.7 MIs/10,000 DDDs) as having the highest incident rates. The incident rate for co-amoxiclav, the drug most commonly reported, was 2.7 MIs/10,000 DDDs. In the 2-year study period, the number of patient-days was 650,216 in Trust A and 672,422 in Trust B. Rate of DDD/100 patient-days for these antibiotics can be found in Table 2.7.
Table 2.7. The relationship between antibiotic medication incidents and consumption in terms of defined daily doses

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>ATC code</th>
<th>DDDs Trust A</th>
<th>DDDs Trust B</th>
<th>DDD/100 pt-days Trust A</th>
<th>DDD/100 pt-days Trust B</th>
<th>MI / 10,000 DDDs Trust A</th>
<th>MI / 10,000 DDDs Trust B</th>
<th>MI / 10,000 DDDs Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime&quot;</td>
<td>J01DD01</td>
<td>1,284</td>
<td>1,183</td>
<td>0.2</td>
<td>0.2</td>
<td>31.2</td>
<td>186.0</td>
<td>105.4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>J01GB03</td>
<td>19,546</td>
<td>33,041</td>
<td>3.0</td>
<td>4.9</td>
<td>20</td>
<td>29.1</td>
<td>25.7</td>
</tr>
<tr>
<td>Vancomycin IV</td>
<td>J01XA01</td>
<td>26,429</td>
<td>13,669</td>
<td>4.1</td>
<td>2.1</td>
<td>21</td>
<td>31.5</td>
<td>23.7</td>
</tr>
<tr>
<td>Linezolid*</td>
<td>J01XX08</td>
<td>5,456</td>
<td>2,130</td>
<td>0.8</td>
<td>0.4</td>
<td>20.2</td>
<td>9.4</td>
<td>17.1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>J01DC02</td>
<td>17,323</td>
<td>25,140</td>
<td>2.7</td>
<td>3.7</td>
<td>8.1</td>
<td>11.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Piperacillin/ tazobactam*</td>
<td>J01CR05</td>
<td>45,427</td>
<td>7,447</td>
<td>7.0</td>
<td>1.1</td>
<td>7.7</td>
<td>17.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Ciprofloxacin&quot;</td>
<td>J01MA02</td>
<td>44,655</td>
<td>38,462</td>
<td>6.9</td>
<td>12.3</td>
<td>1.3</td>
<td>4.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Co-Amoxiclav</td>
<td>J01CR02</td>
<td>223,232</td>
<td>374,676</td>
<td>34.3</td>
<td>70.1</td>
<td>2.4</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>J01CF05</td>
<td>78,313</td>
<td>103,758</td>
<td>12.0</td>
<td>21.1</td>
<td>1.9</td>
<td>3.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Meropenem*</td>
<td>J01DH02</td>
<td>54,975</td>
<td>14,873</td>
<td>8.5</td>
<td>2.2</td>
<td>2.2</td>
<td>4.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>J01XD01</td>
<td>76,436</td>
<td>82,459</td>
<td>11.8</td>
<td>15.9</td>
<td>1.4</td>
<td>3.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Trimethoprim&quot;</td>
<td>J01EA01</td>
<td>49,683</td>
<td>31,640</td>
<td>7.6</td>
<td>6.9</td>
<td>0.4</td>
<td>4.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>J01CA04</td>
<td>261,247</td>
<td>135,353</td>
<td>40.2</td>
<td>30.5</td>
<td>0.9</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

MI: medication incident; DDD: defined daily dose; IV: intravenous; ATC: Anatomical Therapeutic Chemical

* From the top 10 antibiotics reported for MIs at Trust B but not A
* From the top 10 antibiotics reported for MIs at Trust A but not B.

2.4.6. Reports of medication incidents by clinical staff

Nurses reported most MIs (44.5%, n=427) followed by pharmacy staff (36.2%, n=347) and doctors (9.3%, n=89). In addition, MIs were reported by midwives (4.1%, n=39), other clinical staff (3.5%, n=34), and patients (0.4%, n=4). Eighteen reports (1.9%), all from Trust B, were submitted without reporters specifying their profession. (Table 2.8)

2.4.7. Specialties associated with medication incidents

Paediatrics was the division/specialty who reported the highest number of MIs (24.2%, n=232) followed by internal medicine (18.9%, n=181), surgery (13.9%, n=133), critical care (9.5%, n=91), and obstetrics/gynaecology and women's health (7.5%, n=72). Further information can be found in Table 2.9.
### Table 2.8. Analysis of clinical staff who reported antibiotic medication incidents

<table>
<thead>
<tr>
<th>Reporter</th>
<th>Number of incidents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trust A</td>
</tr>
<tr>
<td>Nurses</td>
<td>143 (36.0)</td>
</tr>
<tr>
<td>Student</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Registered / Clinical nurse</td>
<td>108 (27.2)</td>
</tr>
<tr>
<td>Dental nurse</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Ward manager / Sister</td>
<td>29 (7.3)</td>
</tr>
<tr>
<td>Matron / Head of nursing</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pharmacy Staff</td>
<td>180 (45.3)</td>
</tr>
<tr>
<td>Pharmacist / Clinical pharmacist</td>
<td>180 (45.3)</td>
</tr>
<tr>
<td>Pharmacy technician</td>
<td>-</td>
</tr>
<tr>
<td>Doctors</td>
<td>38 (9.6)</td>
</tr>
<tr>
<td>Training grades FY1 &amp; FY2</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Speciality training grade</td>
<td>25 (6.3)</td>
</tr>
<tr>
<td>Staff &amp; associate specialist</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Consultant</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Midwives</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Midwife</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Others</td>
<td>30 (7.6)</td>
</tr>
<tr>
<td>Other clinical</td>
<td>30 (7.6)</td>
</tr>
<tr>
<td>Patient</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>397 (100)</td>
</tr>
</tbody>
</table>

FY: Foundation Year.

### Table 2.9. Analysis of divisions/specialties associated with medication incidents

<table>
<thead>
<tr>
<th>Division / Specialty</th>
<th>Number of incidents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trust A</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>118 (29.7)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>59 (14.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>32 (8.1)</td>
</tr>
<tr>
<td>Critical care &amp; theatres</td>
<td>31 (7.8)</td>
</tr>
<tr>
<td>Women’s health, obstetrics &amp; gynaecology</td>
<td>21 (5.3)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Renal</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Haematology / Oncology</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Other specialties</td>
<td>89 (22.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>397 (100)</strong></td>
</tr>
</tbody>
</table>
Chapter 2: Risk of Medication Safety Incidents with Antibiotic Use

2.5. Discussion

2.5.1. Rate of antibiotic-related medication incidents

Analysis of 6,756 reports identified 885 (13.1%) reports containing 959 MIs associated with antibiotics. This rate is comparable to other studies in the literature which used a similar methodology. A UK study conducted in a 1000-bed hospital identified that of the 495 MIs submitted to the hospital’s incident reporting system during the 26-month study period, 71 (14.3%) were related to anti-infectives (Ashcroft and Cooke, 2006). A 42-month study on elderly patients in an 843-bed hospital in the US identified that 861 MIs were submitted to the hospital’s voluntary incident reporting system, 152 of which (17.6%) were associated with antibiotics (Picone et al, 2008).

In a Spanish study at a 200-bed hospital, 173 (6.4%) MIs were reported for 2,696 hospitalisations over a 2-year period, of which 34 (19.7%) involved anti-infectives (Menéndez et al, 2008). In a UK five-year study (1994-1999) of 112,536 paediatric admissions (Ross et al, 2000), antibiotics (including antivirals) were the drug class most reported for errors involving intravenous drugs (44%, 48/109) compared to 24.2% in this study (n=232).

2.5.2. The relationship between medication incidents and defined daily doses

Most studies of medication-related incidents report overall prevalence and do not compare this with drug consumption data (in DDDs). A commonly used drug might be associated with a high number of MI reports and therefore assumed to be of a 'higher risk'. A drug used rarely may be associated with very few MIs and will therefore be assumed to be 'less risky'. The application of antibiotic DDDs to the analysis of incident reports allows measuring prevalence against consumption. Therefore, when DDDs are taken into account, a rarely used drug associated with few MIs might appear to be a 'higher-risk' drug than a drug which is very commonly used and associated with more MIs.

This is best illustrated by cefotaxime which was associated with 2.7% of MIs and was 9th in the list of drugs most frequently associated with reported MIs (Table 2.5). Cefotaxime is used less often than other antibiotics. However when number of incidents was compared to consumption data (Table 2.7), cefotaxime became the antibiotic most
frequently associated with MIs (105.4 MIs/10,000 DDDs). It became even 'riskier' than co-amoxiclav which had a much lower incidence (2.7 MIs/10,000 DDDs), although it is more commonly used and was the drug most associated with MIs (16.8%). This also applies to linezolid (1.4% of MIs & 17.1 MIs/10,000 DDDs) and cefuroxime (4.4% of MIs & 9.9 MIs/10,000 DDDs).

Piperacillin/tazobactam was associated with almost 4 times more MIs in Trust A (8.8%, 35/397) than in Trust B (2.3%, 13/562) but when DDDs are taken into consideration, the MI incidence is more than twice higher in Trust B (17.5 MIs/10,000 DDDs) than in Trust A (7.7 MIs/10,000 DDDs). The same for vancomycin which was associated with almost twice as many MIs in Trust A (13.1%, 52/397) than in Trust B (7.7%, 43/562) but when consumption data are taken into account, the MI incidence is 1.5 times more in Trust B (31.5 MIs/10,000 DDDs) than in Trust A (21 MIs/10,000 DDDs).

When tables 2.5 and 2.7 were compared, two additional antibiotics (linezolid and trimethoprim) were identified as of a higher risk because DDDs were taken into account. Based on reporting rates alone, trends in incidents with these two antibiotics were unlikely to be investigated. Thus, opportunities to take action to reduce risk may be missed. This analysis identified that the number of MIs associated with each antibiotic does not necessarily reflect the risk of a MI occurring with this antibiotic, especially where data might be analysed over shorter time periods.

2.5.3. Stages and types of medication incidents

Hua and Gong (2011) review has identified terminology/taxonomy/nomenclature as one of the challenges for designing an effective incident reporting system. It stated that the lack of consistent terminology can disrupt the communication between different PSI reporting systems on larger levels. One solution suggested by the review for this issue was the use of a widely recognised PSI taxonomy such as the National Co-ordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy for Medication Errors (2001). In the current study, different categories were used to classify MI stages and types at each Trust. Inconsistency in these categories across the NHS would make comparison of MI prevalence and incidence between different hospitals more difficult and less reliable. Therefore, efforts should be made to unify MI categories across all NHS organisations. Unifying the categories for this study was an important aspect of the research and may enable future benchmarking of other incident data.
In 2007, administration MIs were the incident type most frequently reported to the NPSA from the acute-care sector (53.4%, n=34,137) followed by prescribing (17.5%, n=11,180) and preparation/dispensing (11.6%, n=7,436) MIs (NPSA, 2009A). Ashcroft and Cooke (2006) identified that 46.5% of MIs (n=230) occurred in drug administration, 38.8% (n=192) in prescribing, and 14.7% (n=73) in dispensing. In this study, MIs occurred the most during prescribing (42.4%, n=407) and administration (40.0%, n=384), while only 8.0% (n=77) were dispensing incidents. The high proportion of prescribing errors in this study might be because of the MIs related to allergy, a known area of risk with antibiotics with potential to cause serious harm to patients. Healthcare staff at both Trusts are aware of this MI and encouraged to report it by hospital policies. Allergy MIs accounted for 40.0% (n=163) of all prescribing MIs reported highlighting awareness of the risk and willingness of staff to report relevant incidents.

Omission/delay was the most common type of MIs (26.3%, n=252) in this study followed by wrong dose/frequency (17.9%, n=172). These two types were commonly reported in similar studies. Out of all incidents in Ashcroft and Cooke (2006) study, since there was no sub-analysis for each drug class, dose/frequency incidents were the most common type of MIs (34.9%, n=173), whereas omission incidents were the third most common type with 11.9% (n=59). Of the 152 antibiotic MIs in Picone et al (2008) study, omission errors occurred most frequently (59.2%, n=90), while there were only 5.3% (n=8) wrong-dose errors. Between 2006 and 2009, there were 95 incidents of patient death or severe harm due to omitted/delayed medicines in UK hospitals; of which 31 (32.6%) involved anti-infectives (NPSA, 2010). A third of all death/severe-harm MIs reported to the NPSA in 2007 were wrong dose/frequency (33/100) incidents (NPSA, 2009A).

2.5.4. Severity of medication incidents

The NPSA report ‘Safety in Doses’ showed that 80% (n=58,326) of reported MIs resulted in no harm, 16% (n=11,338) in low harm, 4% (n=2,710) in moderate harm, 0.001% (n=63) in severe harm, and 0.0005% (n=37) caused death (NPSA, 2009A). In comparison, this study determined that 78.2% (n=750) of MIs resulted in no harm, 19.9% (n=191) in low harm, 1.6% (n=15) in moderate harm, and no MIs resulted in serious harm or death.

Although there is a risk matrix to rate MIs reported to NRLS (NPSA, 2008) which all hospitals adapt and use in their local systems, the rating of incident severity is often based
on individual perceptions and professional backgrounds. A UK study (Williams and Ashcroft, 2009) revealed noticeable differences in the severity ratings for MIs against NRLS criteria. On two separate occasions, participants were required to answer a questionnaire including 9 MI scenarios and rate the severity of each. There was a wide variation in the severity scores of MIs both within and between different healthcare professions. Nurses and pharmacy technicians gave higher severity scores for the MIs than pharmacists or doctors.

2.5.5. Medication incidents associated with paediatrics

Paediatrics was the specialty most associated with MIs (24.2%, n=232) in this study. The NPSA report ‘Review of Patient Safety for Children and Young People’ (2009B) showed that MIs were the PSI type most commonly reported for paediatrics. In this age group, most drug doses are individualised and the majority of drugs used are unlicensed or off-label. This may increase the potential for medication errors and risks associated with extemporaneous dispensing as adult dosage forms are used for paediatrics. (Ghaleb et al, 2010). Within paediatrics, prescribing was the most common stage in which MIs occurred (48.7%, n=113) followed by administration (40.9%, n=95), and monitoring (4.7%, n=11).

The most frequently reported MI types in this age group were wrong dose/frequency (38.8%, n=90), omission/delay (22.4%, n=52), and wrong drug (5.6%, n=13). These results echo the NPSA data in which wrong dose/frequency was the most commonly reported incident type for paediatrics (31% for children & neonates) followed by omission (10% for children & 18% for neonates) and wrong drug (8% for children & 5% for neonates) (NPSA, 2009B). Interestingly, there were 8 times fewer allergy errors in paediatrics (2.6%, n=6) compared to adults (21.6%, n=153). However, wrong dose/frequency was reported 3.5 times more often in paediatrics (38.8%, n=90) than adults (11.3%, n=82). There were also fewer dispensing errors in paediatrics (3.9%, n=9) than adults (9.4%, n=68).

2.5.6. Clinical staff who reported medication incidents

Regarding the staff who reported MIs, a UK based study (Ashcroft and Cooke, 2006) showed similar results compared to Trust A in this study with pharmacists reporting 51.9% (n=257) of MIs, nurses 37.6% (n=186), and doctors only 9.1% (n=45). In another study conducted by Alrwisan et al (2011), nurses/midwives reported most MIs (80.4%,
m=2,143) compared to doctors (2.1%, n=56) and other healthcare professionals, including pharmacists (9.1%, n=242). These results are similar in comparison with Trust B and overall in this study.

A qualitative study conducted in Australia by Kingston et al (2004) showed that cultural differences between doctors and nurses reinforce their attitudes to incident reporting. The doctors’ culture was less transparent, less dependent on instructions, and preferred to deal with incidents internally, which probably led them to report less incidents than nurses. Nurses were reporting more regularly due to a culture which depend on clear instructions and protocols and have the concept of security embedded within. In the US, a study by Gavaza et al (2011) investigated the influence of pharmacists’ attitudes on intention to report serious MIs. Most pharmacists intended to report serious MIs (78.8%, n=297) and believed that incident reporting would improve patient safety (89.7%, n=338). However, many of them indicated that reporting was time consuming (72.6%, n=274) and disrupting the workflow (55.5%, n=209).

2.5.7. Quality of information in medication incident reports

As identified by Hua and Gong (2011), the quality of submitted incident reports can be affected by different challenges in relation to design and adoption. The quality of the information provided by some MI reports in this study was poor. Twenty-eight reports were submitted without documenting the drug involved and identifying it only as an antibiotic. Some reports had a blank ‘drug name’ or ‘error type’ field, but this information was identified from the synopsis. So, despite quality assurance procedures used, it is possible that some relevant reports may not have been detected. This might be because some essential fields in the Datix® incident form were not mandatory. Therefore, making all essential fields mandatory would enhance the quality of reported data.

The issue of poor information in incident reports was also identified by others. An Australian study (Thomas et al, 2011) found that only 10.7% of 487 incident reports (n=52) provided sufficient information to classify specific incident aetiology, and 59.1% of reports (n=288) had sufficient detailed information to classify a specific incident recovery mechanism. This showed that existing systems do not provide enough useful information on the incident underlying aetiology or recovery functions. The authors suggested that new approaches should be innovated to sample incidents and produce more
detailed data especially for those of high-risk. These approaches could involve targeting specific incident types and using telephone interview or survey techniques to elicit more detailed information.

Moreover, an analysis of the MI reports (n=12,355) submitted to NRLS in March 2013 (NHS England, 2014) revealed that poor quality of data and lack of essential information in incident reports is common across the NHS. Comparing the results of the current study to this report analysis showed that the quality-assurance measures applied (described in section 2.3.7.2) were effective and improved the quality of collected data. (Table 2.10)

Table 2.10. Quality of data in medication incident reports submitted to the National Reporting and Learning System (NHS England, 2014) compared to reports in this study

<table>
<thead>
<tr>
<th>Data Quality Issue</th>
<th>Description</th>
<th>% in NRLS data* (n=12,355)</th>
<th>% in this study (n=959)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data not recorded</td>
<td>Staff type reporting the incident. Options include: doctor, nurse, pharmacist etc.</td>
<td>71</td>
<td>1.9</td>
</tr>
<tr>
<td>Data not recorded</td>
<td>Medicine name</td>
<td>32</td>
<td>2.9</td>
</tr>
<tr>
<td>Data miscoded</td>
<td>Clinical outcome codes indicating death or severe harm</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Data miscoded</td>
<td>Use of the term ‘other’ in type of medication error. Options include wrong patient, medicine, route, dose, frequency, quantity, omitted etc.</td>
<td>25</td>
<td>3.3</td>
</tr>
<tr>
<td>Data miscoded</td>
<td>Use of the term ‘other’ in the medication process field. Options include prescribing, preparation, dispensing, administration, monitoring etc.</td>
<td>12</td>
<td>0.4</td>
</tr>
</tbody>
</table>

NRLS: National Reporting and Learning System
* Data from reports submitted to NRLS in March 2013 (NHS England, 2014)

2.5.8. The issue of under-reporting

Under-reporting of MIs limits the accuracy of determining the true prevalence and incidence of MIs (Cullen et al, 1995; Stanhope et al, 1999; Hazell and Shakir, 2006). However, voluntary reporting is universally accepted as a tool for routinely collecting incident data (Leape and Abookire, 2005). It should be noted that under-reporting may have occurred in this study and therefore the identified incident rates are the lowest possible and true rates are probably higher.
Despite the assumed under-reporting it should be noted that over the study period, the rate of MI reporting from both Trusts of the study was higher than the national reporting rate from all acute teaching organisations in England and Wales (Table 2.11) as per the NRLS online database of organisations’ PSI reports. (NRLS, 2013C)

Table 2.11. Rates of medication incident reporting at both research Trusts compared to the UK national average

<table>
<thead>
<tr>
<th>Time period</th>
<th>Trust A</th>
<th>Trust B</th>
<th>National average</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/04/2009 – 30/09/2009</td>
<td>15.8%</td>
<td>13.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>01/10/2009 – 31/03/2010</td>
<td>18.0%</td>
<td>19.6%</td>
<td>12.8%</td>
</tr>
<tr>
<td>01/04/2010 – 30/09/2010</td>
<td>20.0%</td>
<td>19.7%</td>
<td>13.2%</td>
</tr>
<tr>
<td>01/10/2010 – 31/03/2011</td>
<td>21.4%</td>
<td>16.8%</td>
<td>13.1%</td>
</tr>
<tr>
<td>01/04/2011 – 30/09/2011</td>
<td>19.3%</td>
<td>21.5%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Average over the whole period</td>
<td>18.9%</td>
<td>18.2%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

2.5.9. Limitations

Paediatric data could not be excluded from the Trusts’ antibiotic consumption and in this case, the MIs occurred with paediatrics were also included in the DDD analysis. As the DDDs are applied only to adults, it was not accurate to measure the incident rates of paediatric MIs using DDDs. This was considered a study limitation. Another measurement should be considered in future studies to calculate the incident rates of paediatric MIs, for example calculating the number of MIs per number of prescriptions written.

The use of DDDs, whilst not perfect, allowed standardisation of antibiotic consumption between the two Trusts and therefore direct comparison of the incidence of MIs for each antibiotic. Prescribed Daily Doses (PDDs) are an alternative option for the standardisation of antibiotic consumption. However since many hospitals already collect and share DDD information, this was deemed by the research team as the most appropriate method to standardise the MI incidence for each antibiotic.
2.6. Further Work

Omission/delay, particularly in administration, was the MI type most commonly reported. Further work is needed to identify appropriate strategies (e.g. reminders, alerts) to reduce omission errors. An experimental study could be undertaken to implement such strategies and evaluate their impact. Allergy errors, particularly in prescribing, were also one of the MI types most commonly reported. Some solutions for this issue (e.g. redesigned drug charts, electronic prescribing alerts) should be identified, implemented, and evaluated in an experimental study.

Dose/frequency errors were the second most commonly reported MI type. Gentamicin and vancomycin alone were associated with more than one-third of these errors (36.4%, 63/173). A systematic literature review on all interventions used to improve the dosing of gentamicin and vancomycin is required to assess the options available to address this issue and identify potential solutions (e.g. electronic tools, new policies).

2.7. Conclusion

This study confirms that antibiotic MIs are common in UK hospitals especially in the prescribing and administration stages and shows that rates may be comparable between similar acute Trusts. It also highlights that detailed analysis of data from reports is essential to understand MIs and develop strategies to prevent their recurrence. Using DDDs in the analysis of MIs allowed an incident rate to be determined, which provided more useful information than the absolute numbers alone. It also highlighted the disproportionate risk associated with less commonly prescribed antibiotics not identified using MI reporting rates alone, especially where data might be analysed over shorter time periods. Therefore, incident data should be interpreted alongside consumption data when determining which drugs are most ‘risky’ in practice.

The results of this study are comparable to other studies showing similar rates of antibiotic MI reporting with omission and wrong dose being the most common MI types. Important information was missing in some reports, therefore it is necessary to make all essential fields in incident reporting systems mandatory. As data could only be compared once categories used for MI classification had been standardised, this highlights the importance of harmonised MI categories for comparison between different hospitals.
Chapter 3

Interventions to Improve the Accuracy of Gentamicin and Vancomycin Dosing

A Systematic Review
3.1. Introduction

The incident report analysis in Chapter 2 identified that dose/frequency errors were the second most commonly reported incident type (18%, n=173). Gentamicin and vancomycin alone were associated with 36.4% (n=63) of these errors. Therefore, this chapter features a systematic review to identify and assess all interventions used to improve gentamicin and vancomycin dosing in order to address this issue and develop potential solutions.

Gentamicin and vancomycin are narrow-therapeutic-index antibiotics known for their high toxicity and need for dose individualisation with continuous therapeutic drug monitoring. Side effects of gentamicin and vancomycin are dose related. Common side effects of gentamicin include nephrotoxicity and irreversible ototoxicity while the main side effects of vancomycin include nephrotoxicity, ototoxicity, and blood disorders including neutropaenia. Doses of gentamicin and vancomycin are individualised according to patient parameters. For both drugs, dose calculations are relatively complex and doses are not always appropriately calculated which is a potential risk of overdosing that may lead to toxicity or underdosing that may lead to treatment failure. (Martin et al, 2010; Gonçalves-Pereira et al, 2010)

In a US study conducted at a large tertiary-care hospital, antibiotics were the most common medications associated with prescribing errors (39.7%, 276/696). Overdosing and underdosing accounted for more than half (58.3%, 406/696) of these errors (Lesar et al, 1997B). An Australian study by Leong et al (2006) showed that only 30.3% (n=40) of all gentamicin initial doses (n=132) were in accordance with hospital guidelines. Another study conducted in Australia found that of 60 gentamicin initial doses, only 46.7% (n=28) were consistent with local guidelines (Martin et al, 2012). A US study conducted by Swartling et al (2012) in a tertiary-care hospital identified that only 50.6% (128/253) of vancomycin initial doses were appropriate according to the American Society of Health-System Pharmacists / Infectious Diseases Society of America (ASHP/IDSA) guidelines. Moreover, Fuller et al (2013) found that less than a quarter (22.1%, n=980) of all vancomycin doses prescribed at a US emergency department (ED), for patients whose weight was known at the time of prescribing (n=4,441), were correct as per the ASHP/IDSA guidelines. The studies above have demonstrated that gentamicin and vancomycin are commonly associated with dosing errors (DEs) in hospital settings.
Chapter 3: Interventions to Improve the Accuracy of Gentamicin and Vancomycin Dosing

3.2. Aim and Objectives

3.2.1. Aim of study

The aim of this systematic review was to identify potential evidence-based interventions to improve gentamicin and vancomycin dosing accuracy at one NHS Foundation Trust.

3.2.2. Study objectives

- To identify all interventions used to improve gentamicin and vancomycin dosing
- To assess the impact of the identified interventions on dosing accuracy
- To find the most effective intervention(s) that can be applied in the Trust.

3.3. Methods

3.3.1. Criteria for considering studies for this review

3.3.1.1. Types of studies

All randomised controlled clinical trials (RCTs), non-randomised controlled clinical trials (CCTs), controlled before-after studies (CBAs), and other quasi-experimental studies (OQEs) that had analysable results on the accuracy of gentamicin and/or vancomycin doses with and without the intervention (e.g. control/study, before/after) were included in this systematic review (Table 3.1). Conference abstracts were included if they had sufficient method description and analysable results. Studies that did not include analysable data on dose accuracy with and without the intervention (e.g. ongoing studies with temporary results, intervention evaluations without control comparator) were excluded.

3.3.1.2. Types of participants

Studies were included where populations consisted of adult inpatients treated at a hospital setting regardless of their diseases, conditions, or the unit where they were treated. Studies on paediatrics were excluded because of the differences in dosing guidelines and considerations. Studies with a population of mixed ages were included only if results were analysed separately for adult patients. Studies of interventions in care homes, primary care, or hospital outpatient clinics were excluded.
3.3.1.3. Types of interventions

Interventions implemented to reduce DEs with gentamicin and vancomycin and improve their dose accuracy were included in the review. These interventions were classified according to a classification derived from a Cochrane review on interventions to improve hospital antibiotic prescribing (Davey et al., 2013). This classification was originally influenced from the Effective Practice and Organisation of Care Group (EPOC) Taxonomy of interventions (2002). The three classes in this classification are persuasive interventions (e.g. education/academic detailing, audit and feedback, protocols/guidelines), restrictive interventions (e.g. standardised order forms, dose pre-authorisation by pharmacists), and structural interventions (electronic prescribing, computerised clinical decision support tools).

3.3.1.4. Types of outcome measures

The primary outcome measure in the review was the accuracy of gentamicin and vancomycin doses. Secondary outcome measures included clinical (e.g. serum levels, length of hospitalisation) and financial (e.g. cost savings) impacts of the intervention. Discrepancies in these measures between intervention and non-intervention groups were assessed.

3.3.2. Search strategy for identification of studies

Seven databases were searched to identify relevant articles conducted between 01/01/1980-31/03/2013. These were Embase, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science Core Collection (WoS), Global Health, Health Management Information Consortium (HMIC), and International Pharmaceutical Abstracts (IPA). The search terms used in the review were identified by the research team in consultation with a Clinical Information Specialist at King’s College London. The main terms used were gentamicin, vancomycin, intervention(s), calculator(s), electronic prescribing, decision support system(s)/tool(s), policy(ies), guideline(s), safety management, reduce, enhance, improve, dose(s), dosing, dosage(s), error(s), incident(s), prescribing, and accuracy. Boolean operators (OR & AND) were used to link and combine the identified search terms. There was no limitation on study language. The detailed search strategy including all terms used with each database can be found in Appendix 3.1.
3.3.3. Data collection and analysis

3.3.3.1. Study selection process

The studies included in the review were selected using a 2-stage process (Table 3.1). In stage 1, two authors (AH and CW) independently reviewed the title and abstract of all identified articles. Any study that had data on interventions to improve antibiotic prescribing was selected, unless it was primarily about paediatrics or specific drugs other than gentamicin or vancomycin, or it was not conducted in a hospital setting. Reference lists of the identified articles were screened to identify any additional relevant articles. In stage 2, two authors (AH and GC) independently reviewed the full text of the articles selected in stage 1, unless they were conference abstracts. Only studies that had analysable data (e.g. percentages, p-values, odds ratios) about the impact of interventions to improve gentamicin and vancomycin dosing (i.e. included results on dose accuracy with and without the intervention) in adult patients were selected. In case of disagreement between the two authors about a study selection in any of the 2 stages, the third author, who was blind to the decisions of other authors reviewing the article, reviewed the study independently and their decision to include/exclude the study was followed. Finally, decisions regarding all the included articles were reached by consensus between research team members (AH, GC, CW).

Table 3.1. Criteria used to select studies to be included in the systematic review

<table>
<thead>
<tr>
<th>1st selection stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Contain data about antibiotics, unless it is clear that the study was on specific antibiotics other than gentamicin or vancomycin</td>
</tr>
<tr>
<td>• Involve intervention(s) (e.g. clinical decision support tool, guideline, policy) to improve the use of antibiotics, unless it is clear that the study was on a specific issue(s) not related to dosing</td>
</tr>
<tr>
<td>• Show that study design was either before-after intervention, interrupted time series, randomised, or non-randomised controlled trial</td>
</tr>
<tr>
<td>• Show that study was conducted in a hospital setting, or at least it doesn’t state that it was conducted in another setting</td>
</tr>
<tr>
<td>• Involves adult patients (i.e. conducted on adults only or on adults and children)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd selection stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Contains findings on the accuracy of dose prescribing with and without the intervention (e.g. dose calculation errors, dose compliance to guidelines, improving number of correct doses)</td>
</tr>
<tr>
<td>• Includes clear analysable results on gentamicin and/or vancomycin (e.g. numbers, percentages, p-values, odds ratios)</td>
</tr>
<tr>
<td>• Have adults analysed separately when study population is mixed</td>
</tr>
</tbody>
</table>
3.3.3.2. **Data extraction**

One reviewer (AH) independently extracted data from the studies using a standardised form (Appendix 3.2). When needed, additional checking and clarification was provided by another reviewer (GC; CW). The key aspects of all selected studies were collected and summarised using the PICOS approach (participants, interventions, comparators, outcomes, and study design) which is recommended by the Cochrane Handbook for Systematic Reviews of Interventions (O'Connor *et al.*, 2011). In addition, data about the country, nature of hospital/department, inclusion/exclusion criteria, and duration of study were collected. The impact of the intervention on the outcomes mentioned above (section 3.3.1.4) was also collected from the selected studies.

3.3.3.3. **Quality assessment strategy**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Liberati, 2009) was used to assure the robustness and transparency in reporting this systematic review (Appendix 3.3). Quality of data in the included studies was assessed using two separate checklists depending on the study design. The Consolidated Standards of Reporting Trials (CONSORT) checklist (Schulz *et al.*, 2010) was assigned to assess RCTs. This 25-item checklist focuses on how the study design, analysis, and interpretation were reported. The main parameters considered were randomisation, allocation concealment, and blinding which were identified by Schulz *et al.* (1995) as the most influential.

The quality of non-randomised comparative studies (CCTs, CBAs and OQEs) was assessed using a checklist by the US Centers for Disease Control and Prevention (CDC) (Des Jarlais *et al.*, 2004). This checklist (Appendix 3.4), the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement, is used to assess the reporting quality of non-randomised evaluations of behavioural and public health interventions. It comprises of 22 items that involve 57 points. In each study, availability of these points was assessed and the percentage of the ones reported was measured.

Risk of bias in the included studies was assessed using the EPOC criteria (2009) for RCTs, CCTs, and CBAs which consist of 9 items (Appendix 3.5). The main points to assess when using these criteria are selection bias, performance bias, detection bias, attrition bias, and reporting bias. Based on the information reported in each study, it was
awarded a risk score for each section of the criteria; low risk, unclear risk, or high risk. As in the Davey et al (2013) Cochrane review, overall risk of bias for each study was considered ‘low’ when all criteria were scored as low, ‘medium’ when one or two criteria were scored as high or unclear, and ‘high’ when more than two criteria were scored as high or unclear.

3.3.3.4. Measures of intervention effect

The impact of interventions was assessed by study design. The median effect size was calculated across studies of the same design. Intervention outcomes were reported in three separate sections; prescribing, clinical, and financial. The prescribing section included data from all studies about the dose accuracy of gentamicin/vancomycin with and without the intervention. The clinical section included data from the studies that reported clinical impact of the intervention including number of therapeutic serum levels and length of hospitalisation. The financial section included the studies that reported the cost of interventions and any savings achieved by their implementation.

3.4. Results

3.4.1. Results of the study search

The initial research retrieved 1,274 articles, including 315 duplicates. The title and abstract of the identified 959 articles were screened (stage 1) and 893 were excluded because they did not meet the inclusion criteria. Of the remaining 66 articles, the reference lists of the full-text articles (n=45) were screened and 15 additional articles were identified. Therefore, 81 studies (60 full-texts & 21 conference abstracts) qualified for stage 2 of the selection criteria. Of these, 69 studies were excluded in stage 2 as they had no data about the intervention impact on dosing accuracy (n=42) or they had no analysable data on gentamicin and/or vancomycin (n=27). Subsequently, the remaining 12 studies (11 full-texts & 1 conference abstract) were included in the final analysis. In the first stage of study selection, the 2 authors (AH and CW) agreed on 97.4% of the title/abstract decisions (934/959). The 2 authors in the second selection stage (AH and GC) agreed on 86.4% of the full-article decisions (70/81). Figure 3.1 illustrates the studies reviewed and included in the systematic review.
Figure 3.1. Study search flow chart
3.4.2. Study characteristics

Twelve studies were included in the final analysis (Figure 3.2). All were published in English. Eight studies were specifically about gentamicin (Johnson et al., 1982; Smith and Rindone, 1998; Hwang et al., 2004; Rogers et al., 2005; Chan et al., 2006; Egan et al., 2012; Manjaly et al., 2012; Qureshi et al., 2012), three specifically about vancomycin (Parker et al., 2004; McCluggage et al., 2010; Swartling et al., 2012), and one on gentamicin and vancomycin in addition to other renally cleared drugs (Roberts et al., 2010). No RCTs were included. Most of the studies were CBAs (n=9; Johnson et al., 1982; Smith and Rindone, 1998; Parker et al., 2004; Rogers et al., 2005; Chan et al., 2006; McCluggage et al., 2010; Roberts et al., 2010; Qureshi et al., 2012; Swartling et al., 2012) and the rest were one CCT (Hwang et al., 2004) and two OQEs. Both OQEs involved series of interventions with dose accuracy being assessed after the implementation of each intervention; Manjaly et al. (2012) involved 2 interventions and Egan et al. (2012) involved 3 interventions. All CBAs were ‘partially’ controlled as rather than describing two populations that were both assessed before and after the intervention, one population was assessed before the implementation of an intervention and a second, matched population was assessed after the intervention.

Figure 3.2. Main characteristics of the studies included in the systematic review

* n=13; one study included data on both gentamicin and vancomycin
# n=15; one study reported 3 interventions and one reported 2 interventions.

<table>
<thead>
<tr>
<th>Drug studied</th>
<th>Study design</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin (n=9, 69%)</td>
<td>Non-randomised controlled trial (n=1, 8%)</td>
<td>Structural (n=7, 47%)</td>
</tr>
<tr>
<td>Vancomycin (n=4, 31%)</td>
<td>Controlled before-after (n=9, 75%)</td>
<td>Persuasive (n=6, 40%)</td>
</tr>
<tr>
<td></td>
<td>Other quasi-experimental (n=2, 17%)</td>
<td>Restrictive (n=2, 13%)</td>
</tr>
</tbody>
</table>
Five studies were conducted in the US (Johnson et al., 1982; Smith and Rindone, 1998; Parker et al., 2004; McCluggage et al., 2010; Swartling et al., 2012), three in the UK (Rogers et al., 2005; Manjaly et al., 2012; Qureshi et al., 2012), and two in Taiwan (Hwang et al., 2004; Chan et al., 2006). Single studies from Ireland (Egan et al., 2012) and Australia (Roberts et al., 2010) were also included. All studies were conducted in a single hospital. Eight studies were not undertaken in specific departments or specialties (Johnson et al., 1982; Smith and Rindone, 1998; Hwang et al., 2004; Rogers et al., 2005; McCluggage et al., 2010; Egan et al., 2012; Manjaly et al., 2012; Swartling et al., 2012). One study was conducted in only general medicine and surgery wards (Roberts et al., 2010). The other three studies were specific to critical care (n=1; Chan et al., 2006), general medicine (n=1; Parker et al., 2004), and surgery (n=1; Qureshi et al., 2012).

Fifteen interventions were reported in the 12 studies which met the inclusion criteria. One study reported three interventions (Egan et al., 2012) and another reported two interventions (Manjaly et al., 2012). Of the 15 interventions, 7 (47%) were classified as structural interventions, all of which were computerised clinical decision support (CDS) tools (Hwang et al., 2004; Chan et al., 2006; McCluggage et al., 2010; Roberts et al., 2010; Egan et al., 2012; Manjaly et al., 2012; Qureshi et al., 2012). Six of the interventions (40%) were classified as persuasive interventions including three in the form of new guidelines (Johnson et al., 1982; Egan et al., 2012; Swartling et al., 2012) and three as prescriber education programmes (Parker et al., 2004; Egan et al., 2012; Manjaly et al., 2012). The remaining two interventions (13%) were standardised prescribing forms which were classified as restrictive interventions (Smith and Rindone, 1998; Rogers et al., 2005). A summary for all included studies can be found in Table 3.2.
## Table 3.2. Summary of the 12 studies included in the systematic review

<table>
<thead>
<tr>
<th>Study, country, type of intervention</th>
<th>Study design, drug studied</th>
<th>Setting, participants</th>
<th>Data collection period</th>
<th>Intervention description</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Hwang *et al*, 2004 (Taiwan)        | CCT                       | 1 hospital; 63 patients in control group & 58 in intervention group | Not available          | Pharmacokinetics-based CDS system embedded in a personal digital assistant | - Dosing: not available  
- Clinical: lower no. of undesired peak SS levels (24.1% vs 46%) & nephrotoxicity (17.2% vs 22.2%). Higher mean peak (P=0.035) & lower mean trough (P<0.001) SS levels |
| Chan *et al*, 2006 (Taiwan)         | CBA                       | 1 hospital, all adult CCUs; 465 regimens before & 297 after intervention | Unknown durations before July 2002 (intervention implementation) & in July 2003 | Pharmacokinetics-based dose calculator installed in the CPOE system | - Dosing: not available  
- Clinical: lower no. of undesired peak (7.7% vs 19.8%) & trough (5.7% vs 12.9%) levels |
| Qureshi *et al*, 2012 (UK)          | CBA                       | 1 hospital, all surgical wards; 50 patients before & 50 after intervention | Unknown; post-intervention data were collected after 6 months of implementation | Online dose calculator in which prescriber enters patient parameters & it provides the appropriate dose | - Dosing: incorrect doses reduced from 70% to 8%  
- Clinical: not available |
| Roberts *et al*, 2010 (Australia)   | CBA                       | 1 hospital; general medical & surgical wards; 73 gentamicin patients before & 38 after intervention; 34 vancomycin patients before & 17 after intervention | 6 months before (Mar-Aug 2004) & 5 months after (Jul-Nov 2005) intervention | CDS tool that automatically populate & update patient parameters was implemented with academic detailing | - Dosing: gentamicin incorrect doses reduced from 37% to 13% (P=0.01); vancomycin incorrect doses reduced from 53% to 23% (P=0.07)  
- Clinical: not available |
| McCluggage *et al*, 2010 (US)       | CBA                       | 1 hospital; 279 patients before & 243 after intervention | 2 months before (Aug-Sep 2006) & 2 months after (Mar-Apr 2007) intervention | Nomogram dosing guidelines embedded into a CPOE system | - Dosing: incorrect doses reduced from 64.5% to 53.1% (P=0.008); incorrect intervals reduced from 35.1% to 24.7% (P=0.009)  
- Clinical: not available |
| Manjaly *et al*, 2012 (UK)          | OQE                       | 1 hospital; 31 patients in cycle 1, 32 in cycle 2 & 27 in cycle 3 | 2 months (Aug-Sep) in cycle 1 (2008), cycle 2 (2009) & cycle 3 (2010) | 3-cycle audit. Cycle 1: baseline; Cycle 2: online dose calculator in which prescriber enters patient parameters & it provides the appropriate dose; Cycle 3: it was advertised by updating the prescribing charts | - Dosing: no difference in non-obese incorrect doses (22% average); obese incorrect doses reduced from 43% to 42% to 20%; incorrect frequency reduced from 12.2% to 3.8% to 4% (P=0.017)  
- Clinical: not available |
Table 3.2. (Continued) Summary of the 12 studies included in the systematic review

<table>
<thead>
<tr>
<th>Study, country, type of intervention</th>
<th>Study design, drug studied</th>
<th>Setting, participants</th>
<th>Data collection period</th>
<th>Intervention description</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egan et al, 2012 (Ireland) 2 Persuasive &amp; 1 Structural</td>
<td>OQE</td>
<td>1 hospital; 21 patients at baseline, 35 in audit 1, 19 in audit 2 &amp; 21 in audit 3</td>
<td>4 weeks in each of baseline (Apr 2008), audit 1 (Aug 2009), audit 2 (Mar 2010) &amp; audit 3 (Aug 2011)</td>
<td>Six sigma approach; Audit 1: new dosing &amp; monitoring schedule; Audit 2: education (lectures and audit &amp; feedback); Audit 3: policy-based dose calculator</td>
<td>- Dosing: incorrect initial doses reduced from 90% to 34% to 32% to 24% (P&lt;0.0001) - Clinical: not available</td>
</tr>
<tr>
<td>Johnson et al, 1982 (US) Persuasive</td>
<td>CBA</td>
<td>1 hospital; 92 patients (109 courses) before &amp; 102 (120 courses) after intervention</td>
<td>72 days before (Oct 1977 - Jan 1978) &amp; 72 days after (Oct 1978 - Jan 1979) intervention</td>
<td>New guidelines followed by 3-stage educational programme: 1) presenting initial review results; 2) devoting an issue of a hospital monthly publication to the drug acceptable use criteria; 3) copies of the criteria placed in all hospital nursing stations</td>
<td>- Dosing: Excessive doses (&gt;5mg/kg) reduced from 21% to 7% (P&lt;0.005) - Clinical: Nephrotoxicity reduced from 8.3% to 7.5% (NS). Undesired trough levels were 50% at both periods</td>
</tr>
<tr>
<td>Parker et al, 2004 (US) Persuasive</td>
<td>CBA</td>
<td>1 hospital, 3 general medicine wards; 36 patients (262 doses) before &amp; 43 (400 doses) after intervention</td>
<td>8 weeks before &amp; 8 weeks after intervention</td>
<td>Pharmacy education for medical residents on hospital guidelines</td>
<td>- Dosing: 24% incorrect initial doses in both groups - Clinical: not available</td>
</tr>
<tr>
<td>Swartling et al, 2012 (US) Persuasive</td>
<td>CBA</td>
<td>1 hospital; 253 patients before &amp; 200 after intervention</td>
<td>30-day period before (in Mar-Apr 2009) &amp; after (in Dec 2009- Jan 2010) intervention</td>
<td>New 1-page dosing guidelines disseminated by emails, links on the intranet, &amp; included on antimicrobial dosing cards</td>
<td>- Dosing: incorrect initial doses reduced from 49% to 22% (P&lt;0.0001) - Clinical: not available</td>
</tr>
<tr>
<td>Smith &amp; Rindone, 1998 (US) Restrictive</td>
<td>CBA</td>
<td>1 hospital; 39 patients before &amp; 47 after intervention</td>
<td>6 months before &amp; 14 months after intervention (introduced Nov 1995)</td>
<td>Physician-initiated standardised order form that integrates a dosing table into a concise, step-by-step approach to the drug dosing and monitoring. A group of doctors and nurses was trained on how to use the form prior to introduction.</td>
<td>- Dosing: incorrect initial doses reduced from 100% to 8.5% (P&lt;0.001) - Clinical: lower undesired peak levels (8.5% vs 56.4%, P&lt;0.001) &amp; similar undesired trough levels (89.4% vs 89.7%, P&lt;0.001)</td>
</tr>
<tr>
<td>Rogers et al, 2005 (UK) Restrictive</td>
<td>CBA</td>
<td>1 hospital; 20 patients before &amp; 20 after intervention</td>
<td>3 months in 2002 before and unknown period in 2003 after intervention</td>
<td>Standardised prescription, administration &amp; monitoring form with guidance on the reverse about calculating CrCl &amp; initial dose &amp; monitoring serum levels</td>
<td>- Dosing: incorrect initial doses reduced from 35% to 10% (P=0.074) - Clinical: no nephro- or oto-toxicity reported in both groups</td>
</tr>
</tbody>
</table>

CBA: controlled before-after; CCT: non-randomised controlled clinical trial; OQE: other quasi-experimental; CDS: clinical decision support; CPOE: computerised prescriber order entry; SS level; steady state level (i.e. after the 4th dose); CrCl: creatinine clearance; NS: not significant.
3.4.3. Quality of studies

Since no RCTs were included in the review, the TREND checklist for assessing the quality of non-randomised intervention evaluations was applied to all studies in this review apart from the study by Parker et al (2004) which was a conference abstract. This abstract was included in the final analysis as it provided sufficient data about the intervention and its effects on dosing accuracy including statistical analysis. It also covered the 3 quality criteria for title and abstract in the TREND checklist.

The overall quality of the included studies was low, with the 11 assessed studies having an average quality of 62% (range 42% to 84%) assessed by the 57 points in the TREND checklist (Table 3.3). None of the studies employed a sample size calculation or were blinded. Although the baseline audit in Egan et al study (2012) was blind to the clinicians. In addition, no study described any adverse events (i.e. unexpected adverse event from the intervention) or unintended effects (i.e. unintended exposure to factors that might bias the results). Furthermore, the generalisability of the included studies was poor. Although 3 studies (27%) were considered generalisable (Johnson et al, 1982; Smith and Rindone 1998; McCluggage et al, 2010), the other 8 (73%) had poor generalisability. This was primarily due to baseline participant characteristics (i.e. demographic data including relevant clinical information such as renal function). Seven studies (64%) did not report or compare the baseline characteristics of participants (Hwang et al, 2004; Rogers et al, 2005; Chan et al, 2006; Manjaly et al, 2012; Qureshi et al, 2012; Swartling et al, 2012; Egan et al, 2012) and one study (9%) had a significant difference in the population size between pre- and post-intervention groups for both gentamicin and vancomycin (Roberts et al, 2010).

Only two studies (18%) stated the software/programme used to perform statistical analysis for the outcomes (McCluggage et al, 2010; Manjaly et al, 2012), while in 2 other studies (18%) no statistical analysis was conducted (Chan et al, 2006; Qureshi et al, 2012). Five studies (45%) reported data on the baseline study group equivalence (Johnson et al, 1982; Smith and Rindone 1998; Hwang et al, 2004; Roberts et al, 2010; McCluggage et al, 2010). The baseline data were also not well reported with an average of 2.1 out of 4 points (range 0 to 4) about them in the TREND checklist covered.

The studies which met the inclusion criteria achieved high scores in some of the quality criteria. All studies stated the objectives and outcome measures. Although the
intervention deliverer was only stated in 3 studies (27%) (Johnson et al, 1982; Smith and Rindone 1998; Egan et al, 2012), the implemented interventions were generally well described with an average of 6.3/8 points (range 4 to 8). Background, assignment methods, and outcomes interpretation were also well covered with averages of 1.7/2 points (range 1 to 2), 2.5/3 points (range 1 to 3), and 3.5/4 points (range 2 to 4), respectively. Six studies (55%) demonstrated their overall evidence in the context of available literature and after balancing the potential benefits and harms (Johnson et al, 1982; Hwang et al, 2004; Roberts et al, 2010; McCluggage et al, 2010; Swartling et al, 2012; Egan et al, 2012).

3.4.4. Risk of bias

The overall risk of bias was high in all studies as they had more than 2 criteria assessed as high or unclear risk, mainly due to the design of studies as no RCTs were included. In total, 47% of the assessed items were scored as low risk, 41% as high risk, and 12% as unclear risk (Table 3.4). No study was blind and therefore all were assessed as high risk for blinding (i.e. detection and performance bias). According to EPOC criteria, CBAs (n=9) by the nature of their design are scored as high risk for sequence generation and allocation concealment (i.e. selection bias). The other 3 studies (2 OQEs and 1 CCT) were also not randomised and therefore scored as high risk for these two criteria.

However, the studies generally scored well in other criteria. Eleven of the 12 studies (92%) were assessed as low risk for group contamination (i.e. it is unlikely that the control group received the intervention) and baseline outcome measures (i.e. no important differences in performance or patient outcomes prior to the intervention). Ten studies (83%) were assessed as low risk for selective outcome reporting (i.e. no reporting bias) while nine (75%) were assessed as low risk for incomplete outcome data (i.e. no missing outcome measures or they were unlikely to bias the results). It was not surprising that the studies which achieved the three highest quality scores (McCluggage et al, 2010=84%; Johnson et al, 1982=74%; Roberts et al, 2010=74%) had the lowest scores for risk of bias. The three studies scored low risk in 6 out of the 9 criteria, with the exception of randomisation and blinding criteria.
Table 3.3. Quality of the included studies assessed using the TREND checklist with section and overall scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Title and abstract</th>
<th>Background</th>
<th>Participants</th>
<th>Interventions</th>
<th>Objectives</th>
<th>Outcomes</th>
<th>Sample size</th>
<th>Assignment method</th>
<th>Blinding</th>
<th>Unit of analysis</th>
<th>Statistical methods</th>
<th>Participant flow</th>
<th>Recruitment</th>
<th>Baseline equivalence</th>
<th>Numbers analysed</th>
<th>Outcomes and estimation</th>
<th>Ancillary analyses</th>
<th>Adverse events</th>
<th>Interpretation</th>
<th>Generalisability</th>
<th>Overall evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCluggage et al. 2010</td>
<td>3/3</td>
<td>2/2</td>
<td>4/4</td>
<td>7/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>3/4</td>
<td>6/6</td>
<td>1/1</td>
<td>4/4</td>
<td>1/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>1/1</td>
<td>4/4</td>
<td>1/1</td>
</tr>
<tr>
<td>Johnson et al. 1982</td>
<td>1/3</td>
<td>2/2</td>
<td>2/4</td>
<td>8/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>2/4</td>
<td>4/6</td>
<td>1/1</td>
<td>4/4</td>
<td>1/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>1/1</td>
</tr>
<tr>
<td>Roberts et al. 2010</td>
<td>3/3</td>
<td>2/2</td>
<td>3/4</td>
<td>7/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>2/3</td>
<td>0/1</td>
<td>1/2</td>
<td>2/4</td>
<td>4/6</td>
<td>1/1</td>
<td>4/4</td>
<td>1/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Swartling et al. 2012</td>
<td>3/3</td>
<td>2/2</td>
<td>4/4</td>
<td>6/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>2/3</td>
<td>0/1</td>
<td>1/2</td>
<td>1/4</td>
<td>6/6</td>
<td>1/1</td>
<td>2/4</td>
<td>0/1</td>
<td>2/2</td>
<td>1/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Egan et al. 2012</td>
<td>2/3</td>
<td>2/2</td>
<td>2/4</td>
<td>7/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>2/4</td>
<td>4/6</td>
<td>1/1</td>
<td>0/4</td>
<td>0/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Smith &amp; Rindone 1998</td>
<td>1/3</td>
<td>1/2</td>
<td>3/4</td>
<td>6/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>2/3</td>
<td>0/1</td>
<td>1/2</td>
<td>2/4</td>
<td>4/6</td>
<td>0/1</td>
<td>4/4</td>
<td>1/1</td>
<td>1/2</td>
<td>1/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>1/1</td>
</tr>
<tr>
<td>Manjaly et al. 2012</td>
<td>3/3</td>
<td>1/2</td>
<td>3/4</td>
<td>6/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>2/4</td>
<td>4/6</td>
<td>1/1</td>
<td>2/4</td>
<td>0/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>2/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Hwang et al. 2004</td>
<td>1/3</td>
<td>2/2</td>
<td>2/4</td>
<td>5/8</td>
<td>1/1</td>
<td>1/3</td>
<td>0/1</td>
<td>1/3</td>
<td>0/1</td>
<td>1/2</td>
<td>1/4</td>
<td>4/6</td>
<td>0/1</td>
<td>2/4</td>
<td>1/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>4/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Rogers et al. 2005</td>
<td>2/3</td>
<td>2/2</td>
<td>2/4</td>
<td>4/8</td>
<td>1/1</td>
<td>2/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>1/4</td>
<td>4/6</td>
<td>0/1</td>
<td>1/4</td>
<td>0/1</td>
<td>1/2</td>
<td>2/3</td>
<td>1/1</td>
<td>0/1</td>
<td>3/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Chan et al. 2006</td>
<td>0/3</td>
<td>2/2</td>
<td>3/4</td>
<td>6/8</td>
<td>1/1</td>
<td>1/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>0/4</td>
<td>4/6</td>
<td>1/1</td>
<td>0/4</td>
<td>0/1</td>
<td>1/2</td>
<td>1/3</td>
<td>0/1</td>
<td>0/1</td>
<td>3/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Qureshi et al. 2012</td>
<td>0/3</td>
<td>1/2</td>
<td>2/4</td>
<td>7/8</td>
<td>1/1</td>
<td>1/3</td>
<td>0/1</td>
<td>3/3</td>
<td>0/1</td>
<td>1/2</td>
<td>0/4</td>
<td>4/6</td>
<td>0/1</td>
<td>0/4</td>
<td>0/1</td>
<td>1/2</td>
<td>1/3</td>
<td>0/1</td>
<td>0/1</td>
<td>2/4</td>
<td>0/1</td>
</tr>
<tr>
<td>Average</td>
<td>1.7</td>
<td>1.7</td>
<td>2.7</td>
<td>6.3</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>2.5</td>
<td>0/1</td>
<td>1.5</td>
<td>4.4</td>
<td>0.6</td>
<td>0.5</td>
<td>1.1</td>
<td>1.6</td>
<td>0.8</td>
<td>3.5</td>
<td>0.3</td>
<td>0.5</td>
<td>35.5</td>
<td>62%</td>
</tr>
</tbody>
</table>
### Table 3.4. Risk of bias in the included studies for each EPOC criteria and overall

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding (detection &amp; performance bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective outcome reporting (reporting bias)</th>
<th>Other bias</th>
<th>Groups contamination</th>
<th>Baseline outcomes</th>
<th>Baseline characteristics</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Johnson et al, 1982</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9 (75)</td>
<td>10 (83)</td>
<td>6 (50)</td>
<td>11 (92)</td>
<td>11 (92)</td>
<td>4 (33)</td>
<td>51/108</td>
</tr>
<tr>
<td></td>
<td>Roberts et al, 2010</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>44/108</td>
</tr>
<tr>
<td></td>
<td>McCullage et al, 2010</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13/108</td>
</tr>
<tr>
<td></td>
<td>Rogers et al, 2005</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Qureshi et al, 2012</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swartling et al, 2012</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smith &amp; Rimbune 1998</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hwang et al, 2004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chan et al, 2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parker et al, 2004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manjaly et al, 2012</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Egan et al, 2012</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* Total scores were based on the 108 items assessed; 9 in each of the 12 studies.
3.4.5. Definition of an appropriate dose

In the included studies, different definitions have been used to identify an appropriate dose/regimen (Table 3.5). For gentamicin, the definition in 5 studies was based on a standard dose of 5 mg/kg adjusted according to patient’s renal function. However, these studies had different interpretations of the appropriate dose. One study (Johnson et al, 1982) focused on the maximum daily maintenance dose (ranging from 5 to 1 mg/kg) that should be prescribed based on predefined ranges of creatinine clearance (CrCl) without setting any lower limit. Manjaly et al (2012) rounded the 5 mg/kg dose to the nearest multiple of 40mg and prolonging the dosing interval (to 36 or 48 hours) in case of decreased renal function (based on predefined ranges). Rogers et al (2005) considered the dose appropriate if it was within a certain range from 5 mg/kg and did not include patients with renal insufficiency (CrCl <30 ml/min). Egan et al (2012) used 5 mg/kg as a reference dose adjusted to 3mg/kg in renal insufficiency (CrCl <30 ml/min). Another study (Qureshi et al, 2012) also used 5 mg/kg as a reference dose adjusted based on CrCl.

Smith and Rindone (1998) specified a loading dose (LD) for gentamicin (2mg/kg) while the maintenance dose (MD) was a predefined percentage of this LD based on patient’s serum creatinine (SrCr). Chan et al (2006) considered the doses appropriate when they led to desirable peak and trough drug serum levels. Hwang et al (2004) also linked the dose appropriateness to drug serum levels. However, in this study the steady state serum levels (i.e. after the 4th dose) were required within defined levels to consider the dosing regimen as appropriate. A study that assessed doses of renally cleared drugs including both gentamicin and vancomycin (Roberts et al, 2010) considered their doses appropriate if they were within a specified range of the recommended dose. This was the hospital guidelines dose pre-intervention (no details provided) and the calculator dose post-intervention (no sufficient details on how this dose was calculated).

The other 3 vancomycin studies each had a different definition of an appropriate dose. One (McCluggage et al, 2010) defined this as 15 mg/kg rounded to the nearest 250mg while interval is adjusted (from 12 to 48 hours) according to predefined ranges of the patient’s CrCl. Another study (Swartling et al, 2012) defined this as the dose recommended by the combined guidelines of the American Society of Health-System Pharmacists (ASHP) and Infectious Diseases Society of America (IDSA) which is based on predefined CrCl ranges. The third article, a conference abstract, assessed the dose
appropriateness based on the hospital guidelines, however it included insufficient information on how it was calculated.

Despite the differences, all studies considered the patient’s renal function in their definition of an appropriate dose. Nine studies clearly detailed whether initial/loading doses (Parker et al, 2004; Rogers et al, 2005; Egan et al, 2012; Swartling et al, 2012), maintenance doses (Johnson et al, 1982; McCluggage et al, 2010), or both (Smith and Rindone, 1998; Hwang et al, 2004; Chan et al, 2006) were assessed.

Table 3.5. The definition of an appropriate dose/regimen in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al, 1982</td>
<td>Gentamicin</td>
<td>Any daily maintenance dose below the maximum defined in the hospital criteria for patient’s SrCr (e.g. 4mg/kg is the maximum dose when SrCr is 97-141 mmol/L)</td>
</tr>
<tr>
<td>Smith &amp; Rindone, 1998</td>
<td>Gentamicin</td>
<td>LD is 2mg/kg; MD is a percentage of LD based on patient’s CrCl (e.g. 85% of LD q12h if CrCl is 60-80 ml/min)</td>
</tr>
<tr>
<td>Hwang et al, 2004</td>
<td>Gentamicin</td>
<td>The dosing regimen that leads to desirable steady state (i.e. after 4 doses) peak (4-8 mg/L) and trough (&lt;2mg/L) levels</td>
</tr>
<tr>
<td>Rogers et al, 2005</td>
<td>Gentamicin</td>
<td>An initial dose of 5mg/kg plus or minus 1 mg (=20% range)</td>
</tr>
<tr>
<td>Chan et al, 2006</td>
<td>Gentamicin</td>
<td>The dose that leads to desirable peak (≥4mg/L) and trough (&lt;2mg/L) levels</td>
</tr>
<tr>
<td>Egan et al, 2012</td>
<td>Gentamicin</td>
<td>The same initial dose as recommended by hospital guidelines (5mg/kg q24h adjusted to 3mg/kg q24h if CrCl is &lt;30 ml/min)</td>
</tr>
<tr>
<td>Manjaly et al, 2012</td>
<td>Gentamicin</td>
<td>The same dose as recommended by hospital guidelines (5 mg/kg rounded to the nearest multiple of 40mg)</td>
</tr>
<tr>
<td>Qureshi et al, 2012</td>
<td>Gentamicin</td>
<td>The dose provided by the CDS tool (3.5 mg/kg individualised based on CrCl that is provided from patient specific parameters)</td>
</tr>
<tr>
<td>Roberts et al, 2010</td>
<td>Gentamicin &amp; Vancomycin</td>
<td>Any dose within one-third range plus or minus the recommended dose (by hospital guidelines in the pre-intervention phase and by the CDS tool in the post-intervention phase)</td>
</tr>
<tr>
<td>Parker et al, 2004</td>
<td>Vancomycin</td>
<td>The same initial dose as recommended by hospital guidelines (no further details)</td>
</tr>
<tr>
<td>McCluggage et al, 2010</td>
<td>Vancomycin</td>
<td>The same dose as recommended by hospital guidelines (15mg/kg rounded to the nearest 250mg)</td>
</tr>
<tr>
<td>Swartling et al, 2012</td>
<td>Vancomycin</td>
<td>The same initial dose as recommended by ASHP/IDSA guidelines which is based on patient’s CrCl (e.g. 5-10 mg/kg q24h if CrCl is 20-40 ml/min)</td>
</tr>
</tbody>
</table>

LD: loading dose; MD: maintenance dose; SrCr: serum creatinine; CrCl: creatinine clearance; CDS: clinical decision support; ASHP/IDSA: American Society of Health-System Pharmacists/Infectious Diseases Society of America.
3.4.6. Impact of interventions

Ten studies (83%) involving 13 interventions (87%) reported results of dosing accuracy with and without the intervention. In general, these studies showed that the interventions have led to improvement in dosing accuracy and clinical effects (details provided in Table 3.2). The financial impacts of the intervention were not reported in any of the studies.

3.4.6.1. Structural interventions

3.4.6.1.1. Dosing outcomes

Five of the 7 studies (71%) that included a structural intervention (3 on gentamicin, 1 on vancomycin, and 1 on both) assessed the difference in dosing accuracy between the intervention and control groups. All of these studies showed improvements in dosing accuracy. The median improvement was 45% in the 2 OQEs (Manjaly et al., 2012; Egan et al., 2012) and 27% in the 3 CBAs, which was calculated out of 4 change values since the intervention in one study was applied on both gentamicin and vancomycin and therefore assessed separately (Roberts et al., 2010; McCluggage et al., 2010; Qureshi et al., 2012). The improvement was statistically significant in 2 gentamicin (Roberts et al., 2010; Egan et al., 2012) and 1 vancomycin (McCluggage et al., 2010) interventions. One vancomycin intervention showed an improvement that was statistically insignificant (Roberts et al., 2010) while two gentamicin interventions showed improvements without statistical evidence (Manjaly et al., 2012; Qureshi et al., 2012). Two interventions showed statistically significant improvements in dosing frequency; 10.4% in McCluggage et al. (2010) and 8.2% in Manjaly et al. (2012). All interventions in this section were multifaceted with educational efforts (assessed as a separate intervention in 2 studies) including providing education for end-users (n=4), publicising (n=2), and audit and feedback (n=1).

3.4.6.1.2. Clinical outcomes

The clinical outcomes of dose-accuracy improvement were assessed as primary outcomes in 2 of the 7 (29%) structural-intervention studies. Both studies showed improvement in the number of desired peak serum levels. Hwang et al., 2004 (CCT) showed a 21.9% improvement while Chan et al., 2006 (CBA) showed a 12.9% improvement. However, neither studies conducted statistical analysis for this change. In addition, Chan et al. (2006)
showed a 7.2%-improvement in the number of desired trough serum levels. Hwang *et al* (2004) showed significantly higher mean peak and lower mean trough steady state serum levels, i.e. after the 4th dose, though the mean levels in both pre- and post-intervention groups were within the desired levels. This study showed a 5%-reduction in the number of patients who had nephrotoxicity.

### 3.4.6.2. Persuasive interventions

#### 3.4.6.2.1. Dosing outcomes

Five studies involving 6 persuasive interventions were included in this review. The Egan *et al* (2012) OQE study involved new guidelines and an associated education campaign, each assessed separately. Three of these studies investigated gentamicin and two investigated vancomycin. The 2 OQEs (Egan *et al*, 2012; Manjaly *et al*, 2012) involved 3 persuasive interventions (2 educational and 1 guideline) which showed a median improvement of 22%. The persuasive interventions (2 guidelines and 1 educational) in the 3 CBAs (Johnson *et al*, 1982; Parker *et al*, 2004; Swartling *et al*, 2012) showed a median improvement of 14%. The improvement was statistically significant with 2 gentamicin interventions (Johnson *et al*, 1982; Egan *et al*, 2012) and 1 vancomycin intervention (Swartling *et al*, 2012). Another vancomycin intervention showed no improvement (0%) in dosing accuracy (Parker *et al*, 2004). While the Manjaly *et al* (2012) study did not provide statistical evidence for the improvement in gentamicin dose-accuracy, it showed a statistically significant 8.2%-improvement in dose frequency. The 3 guideline interventions were multifaceted with educational activities (assessed as a separate intervention in one study) including publicising (n=2), audit and feedback (n=2), and providing education for end-users (n=1).

#### 3.4.6.2.2. Clinical outcomes

Only one study (17%) reported data on clinical outcomes (Johnson *et al*, 1982). This study showed a statistically insignificant 1.2%-decrease in nephrotoxicity and identified no difference in the number of undesired serum levels (50% in both groups).
3.4.6.3. Restrictive interventions

3.4.6.3.1. Dosing outcomes

Two restrictive interventions were assessed in this review (Smith and Rindone, 1998; Rogers et al, 2005). Both interventions were standardised gentamicin ordering forms multifaceted with educational materials. They both showed improvement in initial dose accuracy with a median effect of 58.3%. The improvement was statistically significant in one study (Smith and Rindone, 1998) and insignificant in the second (Rogers et al, 2005). Although the objective of Smith and Rindone (1998) study was to evaluate the accuracy of completing the vancomycin order form (which included both loading and maintenance doses), the maintenance dose accuracy was not reported in the study outcomes.

3.4.6.3.2. Clinical outcomes

Smith and Rindone (1998) reported that the number of desired peak serum levels was significantly improved (+47.9%) following the intervention while the number of desired trough serum levels was unchanged (+0.3%). Rogers et al (2005) study stated that no cases of nephrotoxicity or ototoxicity were reported in either group.

3.5. Discussion

This systematic review investigated the impact of different interventions on the accuracy of gentamicin and vancomycin dosing. It also reviewed any clinical or financial impacts reported for the interventions identified. Fifteen interventions were evaluated including 11 solely for gentamicin, 3 solely for vancomycin, and one for renally cleared drugs including both gentamicin and vancomycin. Quality assessment of the included studies showed some criteria were inadequately covered including blinding, randomisation, sample size calculation, and generalisability. In addition, all studies had a high risk of bias especially with respect to randomisation and blinding.

3.5.1. Dosing outcomes evidence

Thirteen of the 15 interventions (87%) have been assessed for dosing outcomes including 6 persuasive, 5 structural (Roberts et al’s (2010) intervention was assessed once for gentamicin and once for vancomycin which makes the structural interventions count as 6
in this analysis), and 2 restrictive interventions. Thirteen of these 14 interventions (93%) showed improvements in dosing accuracy including 9 (69%) that were statistically significant (7/10 for gentamicin and 2/3 for vancomycin). All structural interventions (n=6) were associated with improvements (including 4 with statistical significance) in addition to 5 persuasive (including 4 with statistical significance) and both restrictive (including 1 with statistical significance) interventions. The restrictive interventions had the highest median effect (58.3%) followed by structural (27-45%) and persuasive interventions (14-22%). In addition, the outcomes of only three of the 13 (23%) interventions were judged as generalisable (one of each type of intervention), which was also limited because they were assessed at one hospital only.

Providing educational material(s) in association with interventions has shown improvements in intervention adoption and dosing outcomes. Manjaly et al (2010) implemented an online dose calculator without providing either education or promotion. One year after the baseline assessment, the dosing accuracy was unchanged (58% vs 57%). The calculator was then advertised by removing the previously-existing dosing formulas on the prescribing charts and replacing them with information about the new calculator. One year later, an improvement was observed in dosing accuracy (58% vs 80%). However, no statistical analysis was undertaken. Moreover, Roberts et al (2010) reported an average of 1.38 hits per patient for the CDS tool (which was implemented along with individual educational sessions for clinicians) during the main study period. This rate was reassessed one year later, in which no education activities were conducted, and use was significantly dropped to 0.47 hits per patient (P<0.01). It was estimated that only 25% of doctors who received the CDS educational sessions were still working in the hospital. In response, these educational sessions were made a routine service. Reassessment in the following year identified a significant rise in the use of the tool (1.43 hits per patient, P<0.01). These studies demonstrated the importance of providing education for end-users as an essential measure in tandem with the implementation of new interventions.

Most interventions in this review showed statistically significant improvements in dosing outcomes. However, the lack of power and sample size calculation, poor quality, and high risk of bias in the studies reporting these interventions have limited the reliability of the overall evidence provided.
3.5.2. Clinical outcomes evidence

The clinical outcomes were assessed in only 4 intervention evaluations (2 structural, 1 persuasive, and 1 restrictive). Peak serum levels were assessed with 3 interventions (2 structural and 1 restrictive). All of these showed improvement in the number of desired peak levels. However, only the restrictive intervention was supported by statistical evidence as no statistical analysis was conducted in the other 2 studies. Trough serum levels were also assessed with 3 interventions (one from each type of intervention). Only one (structural) showed improvement in the number of desired trough levels (no statistical evidence) while the other 2 showed no change. The incidence of nephrotoxicity was assessed with 3 interventions (one from each type of intervention). The structural intervention showed a slight improvement (5%, no statistical analysis) while the other 2 showed no change.

In general, the clinical outcomes evidence in this review is poor as only a small number of studies assessed these outcomes and most of these showed no improvement or improvements without statistical evidence.

3.5.3. Which type of intervention to use?

It was not possible in this review to determine the most effective intervention type to improve gentamicin and vancomycin dosing outcomes, given the generally poor quality of the studies. Restrictive interventions were only assessed in two studies, both of which had small populations. Their median effect was not reliable since it was equal to the mean which was highly affected by the results of one study. Evaluations of structural (100%, 8/8) and persuasive (83%, 5/6) interventions showed a high number of dosing improvements. A higher number of statistically significant improvements was observed with persuasive (67%, 4/6) compared to structural interventions (50%, 4/8). Structural interventions were assessed with a higher number of doses/regimens (in total, 1,070 without and 765 with intervention) compared to persuasive interventions (in total, 730 without and 800 with intervention). The quality in the 4 assessed persuasive-intervention studies (without the included conference abstract) was slightly higher (67% average) compared to the 7 structural-intervention studies (61% average). The risk of bias was
similar, as 49% of the criteria items in the 5 persuasive-intervention studies were assessed as low risk compared to 51% in the 7 structural-intervention studies.

All these differences are relatively small and cannot provide an indication of which type of intervention is the most effective in practice. Therefore, combining structural and persuasive interventions would potentially lead to the best results. Based on the current evidence, structural interventions implemented in association with educational activities are probably the best way forward. These educational activities, as discussed above, should be made sustainable and become part of the routine clinical service, especially in the high staff-turnover environment of hospitals.

3.5.4. Limitations

The fact that only one author (AH) assessed the reporting quality and risk of bias in the included studies may have affected the outcomes of these analyses. To minimise this potential effect, these assessments were conducted using widely-accepted criteria (TREND & EPOC). Not all research team members (AH, GC, CW) reviewed all studies in both stages of the study selection process. However, it is unlikely that this has affected the selection process in this review as 2 members independently reviewed all studies in each selection stage and the 3rd member was consulted in case of disagreement.

One of the limitations in this review was the use of median effect to compare the intervention effectiveness. The wide heterogeneity between studies in population sizes, methods, and definitions reduced the reliability of this comparison. In addition, the small number of studies for each design and type of intervention made the median more likely to be affected by the results of a single study. That particularly increased when there were only 2 similar studies (e.g. restrictive-intervention CBAs, structural-intervention OQEs) which made the median equal to the mean and so more unreliable. However, this was the only way to compare between the different interventions and has been used by a recent Cochrane review on antibiotic prescribing interventions (Davey et al, 2013).
3.6. Further work

The various limitations identified in the included studies have demonstrated the need for studies of a higher quality to assess the actual impacts of interventions on gentamicin and vancomycin dosing. This would ideally be a multi-site RCT. However even when an RCT is not possible, other measures can be taken to improve the quality and consequently evidence in future studies of other designs (e.g. CBA). These include, but are not limited to, conducting power and sample size calculations, performing and precisely describing statistical analysis, randomisation where possible, clear reporting and comparison of baseline characteristics, and providing comprehensive information on the intervention, assignment and data collection methods, and participant flow.

This review identified electronic CDS multifaceted with education as the most effective intervention to enhance gentamicin and vancomycin dosing. However, the poor quality of most of the included studies limits the validity of this finding. Electronic dose calculators for gentamicin and vancomycin were recently implemented and promoted at one of the study sites in Chapter 2 (i.e. King’s College Hospital NHS Foundation Trust). A study considering the quality measures above could be conducted to evaluate the impact of these calculators on the dosing accuracy of these drugs.

3.7. Conclusion

This systematic review revealed the lack of reliable evidence on effective interventions to improve gentamicin and vancomycin dosing. The available evidence suggests that structural interventions in tandem with appropriate sustainable education appear to be the most effective. However, further work is still needed to conduct high-quality studies to prove the benefits of such interventions. This review can inform future intervention studies about gentamicin and vancomycin to be conducted and reported in a more robust and transparent manner.
Chapter 4

An Evaluation of the Impact of Dose Calculators on the Accuracy of Gentamicin and Vancomycin Initial Doses
4.1. Introduction

The systematic review in Chapter 3 identified that electronic clinical decision support (CDS) tools allied with appropriate educational activities is potentially the best intervention to improve gentamicin and vancomycin dosing. Online dose calculators were recently implemented at King’s College Hospital NHS Foundation Trust in association with educational activities. The impact of this CDS tool on the accuracy of gentamicin and vancomycin initial doses is evaluated in this chapter.

4.1.1. Clinical decision support

CDS is a wide term that includes different kinds of support from the basic reactive alerts and reminders (e.g. drug allergy and interaction alerts) to the structured order forms that promote correct entries, proactive guideline support (e.g. to prevent omission errors), patient-specific dose checking, and medicines information for prescribers and patients. Essentially, any knowledge-based intervention that can enhance education, communication, workflow, patient safety, or care quality can be considered a type of CDS. (Teich et al, 2005)

Different definitions for CDS have been found in the literature. Wyatt and Spiegelhalter (1992, p.3) defined it as

“Active knowledge systems which use two or more items of patient data to generate case-specific advice”.

Furthermore, Langton et al (1992, p.626) defined CDS as

“Any computer software employing a knowledge base designed for use by a clinician involved in patient care, as a direct aid to clinical decision making”.

In their definition, Perrault and Metzger (1999, p.5) focused on the relationship between knowledge and data. They defined CDS as

“A set of knowledge-based tools that are fully integrated with both the clinician workflow components of a computerized patient record, and a repository of complete and accurate data”.
Based on different definitions, Osheroff et al (2004, p.3) established a more practical definition of CDS which they defined as

“Providing clinicians or patients with clinical knowledge and patient-related information, intelligently filtered and presented at appropriate times, to enhance patient care”.

A review by Wright and Sittig (2008) on the history of CDS formulated a model that divided the development stages of CDS into 4 ‘architectural’ phases. The first phase was the ‘standalone decision support systems’ phase which began in 1959 by Ledley and Lusted through a study in which they expended a probability-based model to aid medical diagnosis. All CDS systems in this phase had a common characteristic; they were independent systems that ran separately from other systems. To use such a system, the clinician has to intentionally look for it, manually enter the data required about the case in question, and then produce and interpret its recommendations. (Wright and Sittig, 2008)

The second phase was the ‘integrated systems’ phase. The first CDS in this phase was the Health Evaluation through Logical Processing (HELP) system which was developed in Utah, USA, in 1967 (Kuperman, 1991). HELP system was first used in the cardiac catheterisation and critical care units to store and manage clinical patient data. Afterwards, it was developed to provide comprehensive CDS to a wide range of clinical specialties. The main characteristic of this phase was that developers started to integrate CDS systems into other clinical systems, such as computerised prescriber order entry (CPOE) and electronic health records. (Wright and Sittig, 2008)

The third phase was called ‘standards-based systems’ and it started in 1989 with Arden Syntax, a language for encoding medical knowledge bases, developed in New York, USA (Hripcsak, 1991). The common feature of all CDS systems in this phase was the ability to standardise the CDS content so it could be encoded, stored, represented, and shared which was not possible in the CDS systems of the second phase. (Wright and Sittig, 2008)

In 2005, the fourth phase ‘service models’ started with a system called Shareable Active Guideline Environment (SAGE) (Ram et al, 2004). The CDS systems in this phase focused on separating and recombining the clinical information and CDS components of ‘integrated’ decision support systems, to allow the usage of a standard application
programming interface. In this way, users are freed from the restrictions of knowledge representation formats (e.g. vocabulary issues) imposed in the phase-3 systems. Since the modules of phase-4 systems are located online, they can be easily shared across a number of hospitals, which makes them more efficient. (Wright and Sittig, 2008)

4.1.2. Benefits of clinical decision support

CDS systems can be used for different purposes including quality and safety, efficiency, and various clinical applications such as diagnosis, monitoring, and therapy. Teich et al (2005) stated that the main benefits of CDS systems are to:

- Reduce different kinds of patient safety incidents
- Improve management of specific diseases
- Provide personalised care for patients
- Enhance evidence-based clinical practices
- Empower appropriate and cost-effective medication use
- Enable effective education about medication use for both professionals and patients
- Facilitate communication and collaboration between different professions
- Aid clinical practice and self-care to be efficient and convenient
- Allow adverse events to be more effectively reported and followed-up
- Facilitate higher compliance with regulatory requirements
- Help disseminating new information by professional firms to clinicians and patients.

A review by Kuperman et al (2007) divided medication-related CDS tools into two main categories; basic and advanced. Basic CDS tools identified in this review provided support for checking drug allergies, drug–drug interactions and duplicated therapy, guiding general drug dosing, and helping in formulary related decisions. Advanced CDS tools provided support for identifying and checking drug-pregnancy and drug-disease contraindications, dosing renally impaired and elderly patients, and guiding laboratory tests with certain medications.
4.1.3. Features of effective clinical decision support

Kawamoto et al (2005) conducted a systematic review of 70 studies to identify the CDS system features that are critical to achieve success. In 68% of studies, CDS systems have significantly improved clinical practice. Four main features were identified as independent predictors of improved clinical practice: providing CDS automatically as part of the clinician workflow (P<0.00001), providing recommendations with CDS rather than just assessments (P=0.0187), providing CDS at the same time and location of decision making (P=0.0263), and providing computer-based CDS (P=0.0294). Thirty-two CDS systems in the review possessed all four features, of which 94% (n=30) demonstrated a significant improvement in clinical practice compared to 46% (n=18) in the other 39 systems. These effective CDS systems included reminders for lab tests and physical examinations, new tools to enhance communication with patients, and treatment guidelines for certain conditions. No study in the review was specific to antibiotics.

A meta-regression on the features of effective CDS systems was conducted by Roshanov (2013). This review showed that among 150 randomised clinical trials, the systems which were more likely to succeed provided advice for patients in addition to practitioners (P=0.03), required practitioners to supply a reason for overriding advice (P<0.001), or were evaluated by their developers (P=0.002).

4.1.4. Effectiveness of clinical decision support

Using information technology and developing CDS tools are essential measures to improve patient safety in the modern complex healthcare systems (Corrigan, et al, 2001). The Agency for Healthcare Research and Quality (AHRQ) proposed a framework to enable conceptualisation and evaluation of efforts made to improve patient safety. This model focuses on structure (the physical and organisational properties of the care setting), process (the treatment or service provided to the patient), and outcomes (the result of the treatment) (Donabedian, 1980). CPOE and CDS systems follow this model and therefore may make important contributions to minimising medication incidents (MIs) and improving patient outcomes. Chang et al, (2011) created a figure of this relationship to show the effect of these interventions in improving the clinical outcomes of nephrology patients (Figure 4.1)
Figure 4.1. Computerised prescriber order entry (CPOE) and clinical decision support systems (CDSS) integrated within the structure–process–outcome framework of Donabedian model of patient safety (from Chang et al, 2011, p.350)

Many CDS intervention studies have been published with most of them showing a positive effect especially on practitioner performance (Jaspers et al, 2011). CDS tools have shown various impacts on improving the safe use of medicines. A systematic review on the effects of CPOE and CDS systems on medication safety was conducted by Kaushal et al (2003). This review included 12 studies; 5 assessed CPOE systems conjugated with CDS and 7 assessed isolated CDS systems. Of the 5 CPOEs, 2 reduced serious MIs (including one insignificant), one improved corollary orders (i.e. test orders triggered by ordering certain treatments such as serum level order following gentamicin prescription or blood glucose level order following insulin prescription), one improved 5 specific prescribing behaviours (e.g. reducing overdoses), and one improved the dose and frequency of nephrotoxic drugs. Of the 7 isolated CDS systems, one improved the choice of antibiotics, one reduced MIs with anti-infectives, one reduced theophylline-associated toxic levels, one reduced aminoglycoside toxicity (insignificant), and one reduced anticoagulation complications (insignificant). The other 2 systems showed no change.

4.1.5. Unintended negative effects of clinical decision support

Some unintended negative effects with CDS interventions were reported in the literature. A group of experts divided the unintended negative consequences of CDS into two main types; consequences related to CDS content and consequences related to CDS

CKD: chronic kidney disease.
Chapter 4: An Evaluation of the Impact of Dose Calculators

presentation. The content-related consequences included issues regarding the elimination or changing roles of clinicians and staff, currency of the CDS content, and wrong or misleading CDS content. The presentation-related consequences included the rigidity of systems, sources of alert fatigue, and sources of potential errors. (Ash et al, 2007)

A study by Koppel et al (2005) assessed a widely used CPOE system at a 750-bed tertiary-care hospital by conducting a survey with 261 doctors in addition to 5 focus groups and 32 interviews with staff from different healthcare professions. They found that this CPOE facilitated 22 new potential sources of medication errors divided into two main types; information errors (i.e. generated by data fragmentation and failure in integrating different information systems at the hospital) and human-machine interface flaws (i.e. machine directions do not correspond with work procedures or common behaviours). The first type included confusion between the displays of pharmacy stock list and dosing guidelines (potential source for wrong doses), antibiotic renewal orders ignored because they are placed on paper charts rather than CPOE (potential source for delays and omissions), and separation of related functions such as cancelling and modifying/reordering (potential source for drug duplication). The second type included fragmented CPOE displays that make it difficult to view all patient medications on one screen (potential source for wrong drugs), medications can be ordered on computers that are not ‘logged out’ by the previous prescriber (potential source for wrong patients and omissions), and CPOE shutdowns when patient is transferred (potential source for wrong patients and delays) or while an order is being entered (potential source for data loss). Three quarters of the hospital staff surveyed observed all of these error sources and indicated that they occurred at least once a week.

In a study by Campbell et al (2006), an expert panel identified nine major types of unintended negative consequences of CPOE systems. These were more/new work for clinicians, unfavourable workflow issues, never-ending system demands, changes in communication patterns and practices, paper persistence (i.e. keep documenting some information on paper instead of CDS which can cause confusion between data sources), negative emotions, new kinds of errors, changes in the institutional power structure, and overdependence on technology.
4.1.6. Challenges in implementing clinical decision support

Users have experienced different challenges in the design and implementation of CDS systems. Substantial efforts and commitment are needed in order to unite the staff from different professions, backgrounds, and cultures to have a common understanding of the overall objectives of the CDS system so they can perform the assigned tasks appropriately (Goldstein et al., 2004). It was also found that failure of the organisation to align the implemented information system with its strategies can lead to missed opportunities, wasted resources, and poor performance (Bush et al., 2009). Furthermore, difficulties in getting the users to accept, adopt and use CDS interventions, as well as obstacles to integrate such interventions into clinical workflow have been reported (Fieschi et al., 2003; Sittig et al., 2008; Moxey et al., 2010).

Implementation of CDS can be a complicated process, especially when it is aimed to deliver the CDS intervention across different healthcare settings, geographical locations, electronic patient records, and for several diseases and services. Translating written guidelines into a code executed by computer can be technically difficult. Efforts to simplify this process are being made, however it still requires specialised skills and expertise in both medicine and informatics. Resolving such difficulties would support the information exchange between CDS and other health information systems (Eichner and Das, 2010). Teich et al. (2005) stated the main barriers to optimal adoption and effectiveness of CDS interventions designed to improve medication use. These included limited functionality, lack of data integration with electronic health records, uneven availability, and high cost. Some solutions were suggested to overcome these barriers such as determining and encouraging core CDS functionality, enhancing the knowledge management infrastructure for CDS interventions, and providing financial, legal and regulatory incentives for implementation and use of such interventions. Table 4.1 describes a list of barriers and solutions.
Table 4.1. Barriers to optimal adoption and effectiveness of clinical decision support systems for medication management and general solutions to overcome them (adapted from Teich et al, 2005)

<table>
<thead>
<tr>
<th>Barriers</th>
<th>General Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDS capabilities of existing eRx products</td>
<td>Determine core capabilities</td>
</tr>
<tr>
<td></td>
<td>Publish practical recommendations and design concepts to reduce vendor rework</td>
</tr>
<tr>
<td>Usability of systems and of CDS modules</td>
<td>Sharing of best practices and lessons learned</td>
</tr>
<tr>
<td></td>
<td>Bibliography/reading list provided by industry thought leadership groups and/or certification organisations</td>
</tr>
<tr>
<td>Access to patient data needed to support CDS</td>
<td>Increased data availability with appropriate protections</td>
</tr>
<tr>
<td></td>
<td>Integration of eRx with EHR</td>
</tr>
<tr>
<td></td>
<td>Clear pathway from eRx to EHR – through same or different vendors</td>
</tr>
<tr>
<td>Access to best CDS knowledge for all products</td>
<td>Accessible published/stored knowledge</td>
</tr>
<tr>
<td></td>
<td>Practical standard representations of knowledge and content</td>
</tr>
<tr>
<td></td>
<td>Knowledge acquisition and execution tools</td>
</tr>
<tr>
<td>Local management and maintenance of knowledge</td>
<td>Practical organisational models for development, selection, and updating of rules, content, and interventions</td>
</tr>
<tr>
<td></td>
<td>Tools to select / extract / customise knowledge</td>
</tr>
<tr>
<td>Lack of standards for dictionaries, data, sigs, etc. increases cost, variability, and error</td>
<td>Creation and acceptance of practical standards</td>
</tr>
<tr>
<td></td>
<td>Endorsement of standards by government agencies and key stakeholder organisations</td>
</tr>
<tr>
<td></td>
<td>Industry collaboration and financial support for standards programmes</td>
</tr>
<tr>
<td>Cost and difficulty of implementation</td>
<td>Financial support programmes</td>
</tr>
<tr>
<td></td>
<td>Revolving loans</td>
</tr>
<tr>
<td></td>
<td>Removing barriers on support programmes</td>
</tr>
<tr>
<td></td>
<td>Development of systems that are easier to implement and configure</td>
</tr>
<tr>
<td></td>
<td>Implementation guides, templates, and toolkits</td>
</tr>
<tr>
<td>Cost of use</td>
<td>Ongoing reimbursement differential</td>
</tr>
<tr>
<td></td>
<td>Pay-for-performance programmes</td>
</tr>
<tr>
<td>Difficulty in recognising value if CDS advice is rejected</td>
<td>Standard classifications and common definitions for CDS elements, to improve generalisability of research on CDS methods</td>
</tr>
<tr>
<td></td>
<td>Educational forums, references, and websites</td>
</tr>
<tr>
<td></td>
<td>Increased publication of results</td>
</tr>
<tr>
<td>Perception of increased liability if CDS advice is rejected</td>
<td>Clearly-stated liability considerations</td>
</tr>
<tr>
<td></td>
<td>Appropriate liability protections and safe harbours</td>
</tr>
<tr>
<td></td>
<td>Education</td>
</tr>
</tbody>
</table>

CDS: Clinical decision support; eRx: electronic prescribing; EHR: Electronic health records.
4.1.7. Impact of clinical decision support on antibiotic use

CDS tools, particularly computer-based, have shown positive impacts on the use of antibiotics. A systematic review by Shebl et al (2007) on CDS systems used to support antibiotic prescribing showed that these systems significantly improved prescribing practice in 8 of the 10 included studies. Eight studies in this review involved computerised CDS systems including 7 which demonstrated significant improvement.

One study conducted at a 425-bed US hospital assessed the effect of a CDS system which provided alerts for potential pharmacist interventions such as intravenous to oral conversion, renal dosing, and vancomycin therapy assessment after 72 hours. A 1-year follow up for each group showed that the number of pharmacist interventions per month increased from an average of 1,986 pre-CDS to 4,065 post-CDS (+105%). The implementation of this CDS was estimated to save the hospital an extra $3 million per year (+96%). (Calloway et al, 2013)

A US study by Pestotnik et al (1996) assessed the effect of embedding local antibiotic guidelines into a computerised CDS tool in a 520-bed US hospital. During the 7-year study, 63,759 hospitalised patients received antibiotics. Preoperative antibiotics received at the appropriate time were increased from 40% in 1988 to 99.1% in 1994. The number of antibiotic surgical prophylaxis doses per patient was reduced from an average of 19 doses to 5.3 doses. Antibiotic-associated adverse drug events (ADEs) were decreased from 26.9% to 18.8%. Mortality rates decreased significantly from 3.65% to 2.65% (P<0.001). Over the same period, this intervention decreased the annual antibiotic acquisition costs from 24.8% ($987,547) to 12.9% ($612,500) of the pharmacy drug expenditure budget.

Evans et al (1998) studied the impact of a CDS tool that provided instant information to clinicians on infection treatment and proper use of anti-infectives. It was linked to the hospital electronic patient records (EPR) to provide patient-specific information for prescribers. This CDS tool has significantly reduced the prescribing of drugs for which patients had documented allergies (35 vs 146, P<0.01), drug overdoses (87 vs 405, P<0.01), antibiotic-susceptibility mismatches (12 vs 206, P<0.01), and anti-infective associated ADEs (4 vs 28, P<0.02). Patients who always received the CDS regimens (n=203), compared to those who did not (n=195) and to the pre-CDS patients (n=766), had significant reductions in the cost of anti-infectives ($102 vs. $427 and $340,
respectively, $P<0.001$), total costs of hospitalisation ($26,315 \text{ vs. } 44,865$ and $35,283, P<0.001$), and length of hospital stay (10.0 vs. 16.7 and 12.9 days, $P<0.001$).

### 4.1.8. Clinical decision support for gentamicin and vancomycin dosing

Narrow-therapeutic-index medications are more likely to cause ADEs and may be more prone to MEs. Dose decision support may therefore be of particular value for these high-risk medications (Vincent et al, 2009). A number of different CDS tools have been shown to be effective in reducing gentamicin/vancomycin dosing errors (DEs). One of these tools, ‘Pharmacist-to-Dose’ where a computerised request is sent by the prescriber to the pharmacist for dosing guidance on vancomycin and aminoglycosides, was evaluated by Vincent et al (2009). This tool significantly reduced MIs with these drugs (from 31.6%, 18/57 to 7.0%, 5/71, $P=0.002$).

Another CDS tool, GFR+, was designed to automatically calculate doses of key drugs based on renal function. As renal function changes the system is updated and doses are recalculated. When evaluated by Roberts et al (2010), this tool showed improvements in dosing conformity for both gentamicin (from 63%, 46/73 to 87%, 33/38, $P=0.01$) and vancomycin (from 47%, 16/34 to 77%, 13/17, $P=0.07$).

Other CDS tools have not been effective in reducing gentamicin and vancomycin DEs. Some were even potentially harmful. One CDS tool was a CPOE system that displayed an initial default dose for gentamicin and tobramycin in the dose box on the electronic prescription. In a large proportion (58%, 227/392) of prescriptions, the suggested default dose had not been amended. This dose was used in 51.6% (132/256) of prescriptions for renal-insufficiency patients and 85.6% (113/132) of these resulted in potential ADEs compared with 53.2% (66/124) for the remaining prescriptions ($p<0.0001$). For patients without renal impairment, use of the CDS to determine doses was not significantly better than dosing where CDS had not been used. The dose was incorrect in 72.7% (165/227) of CDS prescriptions compared to 77.0% (127/165) of prescriptions written without using the default dose ($P=0.4$). Therefore, this tool was a source of potential ADEs especially in patients with renal insufficiency. (Eslami et al, 2006)
4.1.9. Clinical outcomes of improving gentamicin and vancomycin dosing accuracy

Data from the literature show that giving the correct dose of gentamicin or vancomycin improves clinical outcomes. A Scottish study by Buabeng et al (2005) showed that cure rate was significantly higher in patients for whom the gentamicin dose was given according to protocol (95.7%, 22/23) compared to those for whom it was not (75.0%, 24/32), P=0.06. Moreover, less toxicity was observed in patients for whom the doses were adjusted according to protocol (4.3%, 1/23 vs 28.1%, 9/32, P<0.05). Fuller et al (2013) demonstrated that patients who received a vancomycin overdose (>20mg/kg) stayed in hospital longer (P=0.005), were more likely to spend ≥3 days in hospital (OR=1.49, P=0.006), and more likely to die (OR=1.88, P=0.004). They also showed that correct doses were associated with significantly higher numbers of therapeutic serum levels (21.6% vs 14.3%, P=0.004). This study did not assess the independency of the association between these outcomes and vancomycin overdoses.

4.1.10. Local issues with gentamicin and vancomycin dosing

The common incidence of gentamicin and vancomycin DEs in hospital settings was discussed in the previous chapter (section 3.1). Risks with gentamicin and vancomycin were also identified locally (i.e. at the study site) in a number of ways. In Chapter 2, one-third of dose/frequency errors reported (32/96) at the study site, King’s College Hospital, were related to gentamicin (n=16) or vancomycin (n=16). A Failure Modes and Effects Analysis for gentamicin had previously been undertaken internally at the study site to evaluate the usefulness of a new presentation of gentamicin infusions (Cavell et al, 2010). This identified that the risks associated with dose calculation and prescribing, especially in patients with renal impairment or obesity, were greater than the risks associated with the preparation of infusions. The implementation of electronic prescribing across the Trust facilitated the development of computerised dose calculators for gentamicin and vancomycin to address these risks and improve prescribing, which was championed by the Lead Antimicrobial Pharmacist with the support of the Antibiotic Usage Steering Group. This study will evaluate the impact of this new CDS tool on the accuracy of gentamicin and vancomycin dosing.
4.2. Aim and Objectives

4.2.1. Aim of study

The aim of this study was to evaluate the impact of newly implemented electronic dose calculators developed at an NHS Foundation Trust on the accuracy of prescribing of gentamicin and vancomycin initial doses.

4.2.2. Study objectives

- To determine the number of errors related to the calculation of gentamicin or vancomycin initial doses before and after the calculator implementation
- To determine the incident rate of these errors
- To identify the proportion of errors categorised as underdoses and overdoses
- To measure the number of visits to the calculator pages on the intranet.

4.3. Methods

4.3.1. Study design

The study used a pre-post intervention (before-and-after, quasi-experimental) design. The appropriateness of prescriptions for gentamicin initial dose and vancomycin initiation regimen (loading dose and first maintenance dose) written during the 8-month period (01/01/2011–31/08/2011) before implementation of the dose calculators were assessed retrospectively. Throughout the study period, the Trust antimicrobial guidelines (King’s College Hospital NHS Foundation Trust, 2010) were available to help prescribers to select the correct dose. Following implementation of the gentamicin and vancomycin dose calculators, and promotion throughout the Trust, data on the appropriateness of prescriptions for their initial doses were collected prospectively for a 2-month period (01/06/2013-02/08/2013). In addition to loading dose, first maintenance dose was assessed as part of vancomycin initiation regimen. This was considered important as the first maintenance dose is essential in ensuring appropriate serum levels and is reflected in the fact that the new calculator provides support for both loading and first maintenance doses. The detailed study process is shown in Figure 4.2.
It was not possible to randomise prescribers or wards in this study because the intervention was being launched online when the decision to conduct the study was taken (although not promoted nor linked to the hospital system) and so it was theoretically available for everyone to use. Therefore, a pre-post intervention design which is widely used in assessing medical informatics interventions was chosen (Harris et al, 2006). This design allowed the retrospective collection of data from patients treated with gentamicin or vancomycin before the intervention was available.

**Figure 4.2. A step-by-step summary of the data collection, intervention implementation and data analysis stages of the study**
4.3.2. Study setting

The study was conducted at King’s College Hospital NHS Foundation Trust; a 950-bed acute teaching hospital in South East London. It’s one of the UK’s largest teaching hospitals training over 400 doctors, 275 nurses and 750 dentists each year (King’s College Hospital NHS Foundation Trust, 2012A). The Trust cover a variety of secondary and tertiary specialties including many medicine and surgery sub-specialties, haematology/oncology, critical care, women and children, and accident and emergency. The Trust have an Electronic Prescribing and Medicines Administration system (EPMA) as part of its EPR; iSOFT® Clinical Manager 1.4.

4.3.3. Inclusion/exclusion criteria

All adults without severe renal impairment (creatinine clearance -CrCl- ≥20ml/min and not receiving haemo/peritoneal dialysis) who received parenteral gentamicin or vancomycin (loading and at least one maintenance dose) were included in this study. Patients who received gentamicin as antibiotic prophylaxis prior to urinary catheter insertion, and patients receiving gentamicin as part of a twice- or three-times/day endocarditis treatment regimen were excluded. Patients who received vancomycin orally, as a stat intravenous dose, or by continuous intravenous infusion were also excluded. Patients who did not have both height and weight recorded were excluded as well as those with a height less than 152.4cm (5ft) as these criteria are essential for calculating ideal body weight (BW) which is required for dose calculation. Each patient was included once. Patients who received another regimen of gentamicin or vancomycin were not included again.

4.3.4. Research permission

The study was categorised by the Trust Research and Development Department as a clinical audit/service evaluation and so ethical approval was not required. However, the study was registered with the Clinical Effectiveness and Audit Department at the Trust (Project No. 1250).
### 4.3.5. Definitions

The definition of a DE varied across the literature. It was defined in a book published by the American Pharmacists Association (Cohen, 2007, p.22) as

“Any dose given that contains the wrong number of performed dosage units or is, in the judgement of the observer, more than 17% greater or less than the correct dosage”.

The same definition with a narrower range (10%) was used for injectable doses (Cohen, 2007). A DE has also been defined by Koren et al (1983, p.722) as

“Any deviation from the correct dose. It was considered major when the calculation was 10 times higher than or a 10th of the correct answer and minor when it was not more than 20% above or below the correct answer”.

It should be noted that these definitions have not been adopted by any of the leading health organisations such as World Health Organization, National Patient Safety Agency, or Institute for Health Improvement. Different definitions for incorrect doses of gentamicin and vancomycin have been reported in the literature. Roberts et al (2010) considered gentamicin and vancomycin doses to be correct if they were within one-third above or below the intervention-recommended dose. Eslami et al (2006, p.806) defined the incorrect dose of aminoglycosides as

“A dose that exceeded the guideline recommendation by >10% in patients with renal insufficiency”.

One definition used for incorrect gentamicin and vancomycin doses in Vincent et al (2009, p.49) study was

“Discontinuation of an initial medication order and order re-entry of the same medication for a different dosage and/or interval within 24 hours”.

In the lack of a widely accepted definition for a DE and for the purposes of this study, an incorrect dose of gentamicin was defined as any dose more than 10% higher or lower than the recommended dose as specified in the Trust guidelines. The same definition was used for an incorrect dose of vancomycin, but with a wider 20% range. These margins were chosen taking into account that gentamicin and vancomycin have a narrow therapeutic index and that many of the patients taking these drugs have some element of renal
insufficiency. They also consider that doses are usually rounded based on the available dosage forms and the practicalities of dose administration.

4.3.6. Sample size calculation

In order to perform power and sample size calculations, data were collected retrospectively for 49 patients who received (prescribed and administered) gentamicin and for 36 patients who received vancomycin. A power analysis conducted using assumptions of 95% power identified that at each stage, pre- and post-intervention, a minimum sample of 192 patients who received gentamicin and a minimum sample of 141 patients who received vancomycin were required to detect a 30% reduction in error incidence with each drug.

4.3.7. Study intervention

Calculators for gentamicin and vancomycin doses were implemented in the Trust as an Excel® application on the local intranet which can be accessed by users from a menu in the EPMA system within EPR, iSOFT® Clinical Manager. This system gives authorised users access to patient demographics, hospital visit histories, clinical notes, laboratory results, and drug prescribing and administration records. Prescribers are directed to the calculators through a written note within the electronic prescription for each drug. The calculators are not automatically populated from demographic or laboratory data entered elsewhere within EPR. The calculator uses patient information manually entered by the prescriber, including age, actual BW, height, and serum creatinine (SrCr) to provide the appropriate dose and frequency for each patient based on their weight and CrCl. Different calculators are used according to the system of measurement used - there are metric and imperial calculators for male patients and female patients. So, the correct calculator has to be chosen.

Once required data are entered, the calculator automatically determines the appropriate weight to be used (actual, ideal or adjusted), CrCl, recommended dose (loading and first maintenance for vancomycin), recommended dosing interval, and minimum duration of infusion (in case of vancomycin to avoid Red Man Syndrome). The dose given by the calculator is the dose recommended by the Trust antimicrobial guidelines.
The gentamicin calculator is available as one Excel® spreadsheet that includes all the data fields required to be filled, results of the appropriate weight and CrCl calculations, the individualised dose for the patient, and dosing interval (Appendix 4.1). The vancomycin calculator is divided into 2 spreadsheets; the first one includes all the data fields required to be filled and results of the appropriate weight and CrCl calculations while the second one includes results of the individualised loading and maintenance doses, duration of infusion, and dosing interval (Appendix 4.2).

The Trust antimicrobial guidelines developed by the Antibiotic Usage Steering Group at King’s College Hospital NHS Foundation Trust (2010) include instructions for dosing gentamicin and vancomycin. Ideal BW should be used for dosing and CrCl calculation, unless the patient is underweight (below ideal BW) when actual BW is used or overweight (actual BW >20% over ideal BW) when adjusted BW is used. Estimated BW can only be used when other options are not available. The initial gentamicin dose is calculated depending on patient’s appropriate weight and CrCl which is calculated using the Cockcroft-Gault equation (Cockcroft and Gault, 1976). The vancomycin loading dose is calculated based on actual BW. If the patient is ‘unfit’ to be weighed, ideal BW is used, unless the patient looks underweight then estimated BW is used. The vancomycin first maintenance dose is calculated based on patient’s appropriate weight and CrCl. Details of the equations and calculations used in the calculators are described in Table 4.2.
Table 4.2. Equations/calculations used in gentamicin and vancomycin dose calculators

<table>
<thead>
<tr>
<th>Variable</th>
<th>Underlying equation/calculation</th>
</tr>
</thead>
</table>
| Ideal body weight (kg)\(^1\)    | - With height in feet/inches=[male 50kg, female 45.5kg] + 2.3kg for every inch in height over 5 ft  
                                  | - With height in centimetres=[male 50kg, female 45.5kg] + [(2.3 x height in cm above 152.4) / 2.54]           |
| Adjusted body weight (kg)\(^2\) | = ideal body weight (kg) + 0.4 [(actual body weight (kg) – ideal body weight (kg)]                           |
| Creatinine clearance (ml/min)\(^3\) | = \(140 – \text{Age (years)} \times \text{Weight (kg)} \times F\)                                                   |
|                                  | Serum creatinine (micromol/L)                                                                                         |
|                                  | \(F= 1.04\) for females and 1.23 for males                                                                        |
| Gentamicin initial dose\(^4\)   | CrCl (ml/min)                                                                                                        |
|                                  | Dose & dosing interval                                                                                               |
|                                  | > 80                                                                                                                 |
|                                  | 5.0 mg/kg every 24 hours                                                                                            |
|                                  | 60 – 80                                                                                                              |
|                                  | 4.0 mg/kg every 24 hours                                                                                            |
|                                  | 40 – 60                                                                                                              |
|                                  | 3.5 mg/kg every 24 hours                                                                                            |
|                                  | 30 – 40                                                                                                              |
|                                  | 2.5 mg/kg every 24 hours                                                                                            |
|                                  | 20 – 30                                                                                                              |
|                                  | 4.0 mg/kg every 48 hours                                                                                            |
| Vancomycin loading dose\(^4,5\) | Actual body weight (kg)                                                                                              |
|                                  | < 60                                                                                                                 |
|                                  | 600 mg                                                                                                               |
|                                  | 60 – 90                                                                                                              |
|                                  | 1500 mg                                                                                                              |
|                                  | > 90                                                                                                                 |
|                                  | 2000 mg                                                                                                              |
|                                  | Loading dose                                                                                                         |
|                                  | Fluid (NaCl or glucose)                                                                                              |
|                                  | 250 ml                                                                                                               |
|                                  | 500 ml                                                                                                               |
|                                  | 500 ml                                                                                                               |
|                                  | Infusion period                                                                                                       |
|                                  | 120 min                                                                                                              |
|                                  | 180 min                                                                                                              |
|                                  | 240 min                                                                                                              |
|                                  | Pump rate                                                                                                            |
|                                  | 125 ml/hr                                                                                                            |
|                                  | 167 ml/hr                                                                                                            |
|                                  | 125 ml/hr                                                                                                            |
| Vancomycin maintenance dose\(^4,5\) | CrCl (ml/min)                                                                                                       |
|                                  | Dose                                                                                                                 |
|                                  | Dosing interval                                                                                                      |
|                                  | Fluid                                                                                                                |
|                                  | Infusion period                                                                                                       |
|                                  | Pump rate                                                                                                            |
|                                  | > 110                                                                                                                |
|                                  | 1500mg                                                                                                               |
|                                  | 12 hours                                                                                                             |
|                                  | 500 ml                                                                                                               |
|                                  | 180 min                                                                                                              |
|                                  | 167 ml/hr                                                                                                            |
|                                  | 90 – 110                                                                                                             |
|                                  | 1250mg                                                                                                               |
|                                  | 12 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 150 min                                                                                                              |
|                                  | 100 ml/hr                                                                                                            |
|                                  | 75 – 89                                                                                                              |
|                                  | 1000mg                                                                                                               |
|                                  | 12 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 120 min                                                                                                              |
|                                  | 125 ml/hr                                                                                                            |
|                                  | 55 – 74                                                                                                              |
|                                  | 750mg                                                                                                                |
|                                  | 12 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 90 min                                                                                                               |
|                                  | 167 ml/hr                                                                                                            |
|                                  | 40 – 54                                                                                                              |
|                                  | 500mg                                                                                                                |
|                                  | 12 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 60 min                                                                                                               |
|                                  | 250 ml/hr                                                                                                            |
|                                  | 30 – 39                                                                                                              |
|                                  | 750mg                                                                                                                |
|                                  | 24 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 90 min                                                                                                               |
|                                  | 167 ml/hr                                                                                                            |
|                                  | 20 – 29                                                                                                              |
|                                  | 500mg                                                                                                                |
|                                  | 24 hours                                                                                                             |
|                                  | 250 ml                                                                                                               |
|                                  | 60 min                                                                                                               |
|                                  | 250 ml/hr                                                                                                            |

\(^1\)Devine (1974); \(^2\)Schwartz et al (1978); \(^3\)Cockcroft and Gault (1976); \(^4\)King’s College Hospital NHS Foundation Trust (2010); \(^5\)Thomson et al (2009); \(^*\)Also called dose-determining weight.

4.3.8. Calculator implementation

On 1st September 2011, the calculator was made available on the Trust intranet. The calculator was promoted locally by pharmacists in specific clinical areas, particularly in haematology/oncology where once-daily gentamicin is widely prescribed for the treatment of neutropenic sepsis. In February 2013, a link was created between EPMA and the calculators’ page on the intranet enabling prescribers to access the required calculator on the same screen as the EPR. Junior doctors joining the Trust during February 2013 were informed about the calculator as it was included in their induction programmes for safe prescribing. In addition, ward pharmacists started to include information about the existence and use of the calculators at the ward local inductions.

In May 2013, a non-mandatory instruction to use the calculator was added to the gentamicin and vancomycin orders on EPMA. The availability of the calculator was advertised on the intranet news page and via email; the Daily Bulletin email to all Trust
staff and an email sent to all doctors in the Trust. Information about the calculators and how to use them as well as the pre-calculator results were presented to an audience of prescribers at one of the hospital Grand Rounds with the aim of encouraging its use. Detailed information about the materials used for promoting the calculators can be found in Appendix 4.3.

4.3.9. Data collection and processing

4.3.9.1. Data extraction

Data were collected using EPR. Paper notes were also reviewed if necessary to collect data not available within EPR (e.g. missing weight or height, dose and frequency for some pre-calculator doses). A data collection form was developed and piloted before data collection started. Data were collected for 41 patients (21 received gentamicin & 20 received vancomycin) using this form in order to test it and enhance it. The final form used for data collection is shown in Appendix 4.4.

Demographic data collected for each patient included age, gender, weight, height, SrCr, clinical specialty and hospital ward. Patients’ body mass index (BMI) was also calculated. Details collected about antibiotic therapy included the first dose prescribed and administered for gentamicin and the initiation regimen prescribed and administered for vancomycin. Dose frequency was also documented. Drug doses were compared with the Trust antibiotic guidelines valid at the time of prescribing. If patient height was not recorded on electronic or paper notes, patients were asked about their height. If patients were able to self-report their height, this height was used in the study. Estimated weights and heights were used if they were recorded in patient notes (e.g. for critical care patients). Data on number of times the intranet calculator pages were visited was provided by the hospital senior Web Developer.

4.3.9.1.1. Pre-calculator phase

Patients who received gentamicin or vancomycin were identified retrospectively from the Microbiology database of patients for whom a gentamicin or vancomycin serum level had been requested. A random sample of gentamicin initial doses and a random sample of vancomycin initiation regimens that were prescribed during the 8 months prior to implementing the calculators were assessed for eligibility and accuracy.
4.3.9.1.2. Post-calculator phase

Patients were identified prospectively through an electronic filter of all active antimicrobial prescriptions. This filter was checked daily and any patient who was prescribed gentamicin and/or vancomycin was reviewed on EPMA (and paper notes if necessary) for eligibility. During the 2 months following promotion of the calculators, the accuracy of gentamicin initial doses and vancomycin initiation regimens were assessed for all eligible patients. The researcher informed the ward pharmacist whenever an incorrect dose was found.

4.3.9.2. Data cleansing

Data were transferred into SPSS® which was used for analysis. Quality assurance procedures were undertaken to assure the quality and accuracy of the data transferred. Each SPSS® entry was re-checked against the original paper form to ensure that all data were transferred appropriately.

4.3.9.3. Assessment of dose accuracy

The correct dose was calculated for each patient, at both phases, based on the Trust guidelines. Then, the difference between the prescribed dose and the calculated dose was determined. Based on its deviation from the guideline-recommended dose, each dose was categorised as an underdose (>10%– if gentamicin & >20%– if vancomycin), overdose (>10%+ if gentamicin & >20%+ if vancomycin), or correct dose (≤10%± if gentamicin & ≤20%± if vancomycin).

4.3.9.4. Data analysis

Statistical data analysis was performed using SPSS® version 21. Binary logistic regression was used to assess the significance of the difference between the number of correct doses, overdoses and underdoses before and after implementation of the calculators. It was also used to produce odds ratios (OR) for these results. Chi-square analysis and Fisher’s exact test were used to assess the significance of the difference between the patient’s gender, ethnicity, and prescriber specialty before and after
implementation of the calculators. The same tests were also used to measure the significance of the difference between the number of correct doses among different patient groups before and after implementation of the calculators. A two-sample t-test was used to evaluate the difference in the age, BMI, and CrCl of patients before and after the calculators. The level of significance was chosen as 5%.

4.4. Results

4.4.1. Patient demographics

In the pre-calculator phase of the study, a total of 531 patients were assessed for eligibility and 350 of which were included in the final analysis, whereas 482 patients were assessed and 357 were included in the post-calculator phase (Figure 4.3).

4.4.1.1. Gentamicin

In total, 410 patients in this study have received gentamicin; 195 before and 215 after the calculator implementation. Haematology/Oncology was the clinical division at which gentamicin was most frequently prescribed (37.6%, n=154) followed by Medicine (19.8%, n=81) and Critical Care (16.8%, n=69). There was a significant difference in the gender of patients before and after the calculator. Further details in Table 4.3.

4.4.1.2. Vancomycin

In total, 297 patients in this study have received vancomycin; 155 before and 142 after the calculator implementation. Medicine was the specialty in which vancomycin was most frequently prescribed (30.3%, n=90) followed by Haematology/Oncology (18.5%, n=55) and Surgery (16.5%, n=49). The mean CrCl (P=0.001) and BMI (P=0.03) of patients were significantly different before and after the calculator. Further details in Table 4.4.
Pre-calculator phase

Microbiology database of drug serum levels (1/1/2011–31/08/2011) = 1,336 potential patients

498 patients received gentamicin

838 patients received vancomycin

Randomisation

Retrospective data collection = 291 patients

Retrospective data collection = 240 patients

96 patients excluded;
- 31 prophylaxis doses
- 29 renal impairment
- 19 BD*/TDS# doses
- 8 height < 152.4cm
- 6 no height
- 3 no height & weight

195 eligible patients

85 patients excluded;
- 30 single doses
- 20 continuous infusion
- 19 no height & weight
- 11 renal impairment
- 4 no height
- 1 no weight

155 eligible patients

Post-calculator phase

The dose calculators were placed online on 1/9/2011 and promoted throughout the hospital (17/2/2013-23/5/2013)

Electronic antibiotic filter (1/6/2013–2/8/2013) = 482 potential patients

Prospective data collection = 284 patients on gentamicin

Prospective data collection = 198 patients on vancomycin

69 patients excluded;
- 26 prophylaxis doses
- 21 renal impairment
- 13 BD*/TDS# doses
- 5 no height & weight
- 2 height < 152.4cm
- 2 no height

215 eligible patients

56 patients excluded;
- 17 single doses
- 15 no height & weight
- 12 continuous infusion
- 8 renal impairment
- 3 no height
- 1 height < 152.4cm

142 eligible patients

* Twice daily; # Three times daily

Figure 4.3. Study participant flow chart
Table 4.3. Demographic data of gentamicin patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Gentamicin before (%)</th>
<th>Gentamicin after (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=195</td>
<td>n=215</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>117 (60.0)</td>
<td>97 (45.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Female</td>
<td>78 (40.0)</td>
<td>118 (54.9)</td>
<td></td>
</tr>
<tr>
<td>Age ± SD (years)</td>
<td>55.4 ± 17.3</td>
<td>57.6 ± 18.5</td>
<td>0.212</td>
</tr>
<tr>
<td>CrCl ± SD (ml/min)</td>
<td>97.3 ± 51.7</td>
<td>90.6 ± 48.2</td>
<td>0.176</td>
</tr>
<tr>
<td>BMI ± SD (kg/m²)</td>
<td>25.8 ± 6.0</td>
<td>26.2 ± 6.0</td>
<td>0.546</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>133 (68.2)</td>
<td>144 (67.0)</td>
<td>0.833</td>
</tr>
<tr>
<td>Black</td>
<td>37 (19.0)</td>
<td>49 (22.8)</td>
<td>0.396</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (5.1)</td>
<td>13 (6.0)</td>
<td>0.831</td>
</tr>
<tr>
<td>Other</td>
<td>7 (3.6)</td>
<td>4 (1.9)</td>
<td>0.364</td>
</tr>
<tr>
<td>Not specified</td>
<td>8 (4.1)</td>
<td>5 (2.3)</td>
<td>0.400</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemat/Onc</td>
<td>99 (50.8)</td>
<td>55 (25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Critical Care</td>
<td>45 (23.1)</td>
<td>24 (11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Medicine</td>
<td>16 (8.2)</td>
<td>65 (30.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>14 (7.2)</td>
<td>27 (12.6)</td>
<td>0.073</td>
</tr>
<tr>
<td>Liver</td>
<td>8 (4.1)</td>
<td>7 (3.3)</td>
<td>0.794</td>
</tr>
<tr>
<td>Women’s health</td>
<td>6 (3.1)</td>
<td>18 (8.4)</td>
<td>0.033</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (1.5)</td>
<td>1 (0.5)</td>
<td>0.350</td>
</tr>
<tr>
<td>Neuroscience</td>
<td>3 (1.5)</td>
<td>13 (6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Cardiology</td>
<td>1 (0.5)</td>
<td>5 (2.3)</td>
<td>0.219</td>
</tr>
</tbody>
</table>

SD: standard deviation.

Table 4.4. Demographic data of vancomycin patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Vancomycin before (%)</th>
<th>Vancomycin after (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=155</td>
<td>n=142</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87 (56.1)</td>
<td>81 (57.0)</td>
<td>0.907</td>
</tr>
<tr>
<td>Female</td>
<td>68 (43.9)</td>
<td>61 (43.0)</td>
<td></td>
</tr>
<tr>
<td>Age ± SD (years)</td>
<td>60.5 ± 17.3</td>
<td>57.7 ± 16.6</td>
<td>0.159</td>
</tr>
<tr>
<td>CrCl ± SD (ml/min)</td>
<td>84.6 ± 42.4</td>
<td>100.7 ± 43.0</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI ± SD (kg/m²)</td>
<td>26.4 ± 45.9</td>
<td>27.9 ± 6.5</td>
<td>0.030</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100 (64.5)</td>
<td>106 (74.6)</td>
<td>0.060</td>
</tr>
<tr>
<td>Black</td>
<td>30 (19.4)</td>
<td>28 (19.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (3.9)</td>
<td>5 (3.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.2)</td>
<td>2 (1.4)</td>
<td>0.107</td>
</tr>
<tr>
<td>Not specified</td>
<td>11 (7.1)</td>
<td>1 (0.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemat/Onc</td>
<td>39 (25.2)</td>
<td>16 (11.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Critical Care</td>
<td>10 (6.5)</td>
<td>3 (2.1)</td>
<td>0.089</td>
</tr>
<tr>
<td>Medicine</td>
<td>44 (28.4)</td>
<td>46 (32.4)</td>
<td>0.528</td>
</tr>
<tr>
<td>Surgery</td>
<td>22 (14.2)</td>
<td>27 (19.0)</td>
<td>0.277</td>
</tr>
<tr>
<td>Liver</td>
<td>15 (9.7)</td>
<td>13 (9.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Women’s health</td>
<td>1 (0.6)</td>
<td>2 (1.4)</td>
<td>0.608</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Neuroscience</td>
<td>14 (9.0)</td>
<td>25 (17.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>Cardiology</td>
<td>10 (6.5)</td>
<td>10 (7.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

SD: standard deviation
4.4.2. Accuracy of initial doses pre- and post-intervention

4.4.2.1. Gentamicin

The gentamicin calculator page on the Trust intranet was visited 333 times during the 2-month period following implementation of the calculator. Figure 4.4 shows how far pre- and post-calculator doses were from the ideal (i.e. guideline-recommended) dose and whether they were within the correct range of ±10%. Correct gentamicin doses increased from 38.5% (75/195) before to 55.8% (120/215) after the calculator implementation (OR=2.02, P<0.001). (Table 4.5)

<table>
<thead>
<tr>
<th>Category</th>
<th>Before (%)</th>
<th>After (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct dose</td>
<td>75 (38.5)</td>
<td>120 (55.8)</td>
<td>2.02</td>
<td>1.36 - 3.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overdose</td>
<td>83 (42.6)</td>
<td>62 (28.8)</td>
<td>0.55</td>
<td>0.36 - 0.82</td>
<td>0.004</td>
</tr>
<tr>
<td>Underdose</td>
<td>37 (19.0)</td>
<td>33 (15.3)</td>
<td>0.77</td>
<td>0.46 - 1.30</td>
<td>0.331</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Interval.
4.4.2.2. Vancomycin

The vancomycin calculator page on the Trust intranet was visited 388 times in the post-calculator data collection period. Figures 4.5 and 4.6 show how far loading and maintenance doses, respectively, were from the ideal dose before and after the calculator and whether they were within the correct range of ±20%.

Correct vancomycin loading doses increased from 41.9% (65/155) before to 67.6% (96/142) after the calculator implementation, OR=2.89, P<0.001. Correct vancomycin first maintenance doses increased from 44.5% (69/155) to 66.9% (95/142), OR=2.52, P<0.001. The whole vancomycin initiation regimens was correct (both loading and first maintenance doses were correct) in 23.9% (37/155) of patients before and 47.9% (68/142) after the calculator implementation (OR=2.93, P<0.001). (Table 4.6)
Figure 4.5. Distribution of vancomycin loading doses before and after the calculator

Figure 4.6. Distribution of vancomycin maintenance doses before and after the calculator
Table 4.6. Analysis of the accuracy of vancomycin initial doses

<table>
<thead>
<tr>
<th>Category</th>
<th>Before (%)</th>
<th>After (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 155</td>
<td>n=142</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct dose</td>
<td>65 (41.9)</td>
<td>96 (67.6)</td>
<td>2.89</td>
<td>1.80 - 4.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overdose</td>
<td>5 (3.2)</td>
<td>5 (3.5)</td>
<td>1.10</td>
<td>0.31 - 3.86</td>
<td>0.888</td>
</tr>
<tr>
<td>Underdose</td>
<td>85 (54.8)</td>
<td>41 (28.9)</td>
<td>0.33</td>
<td>0.21 - 0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First maintenance dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct dose</td>
<td>69 (44.5)</td>
<td>95 (66.9)</td>
<td>2.52</td>
<td>1.57 - 4.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overdose</td>
<td>56 (36.1)</td>
<td>30 (21.1)</td>
<td>0.47</td>
<td>0.28 - 0.80</td>
<td>0.005</td>
</tr>
<tr>
<td>Underdose</td>
<td>30 (19.4)</td>
<td>17 (12.0)</td>
<td>0.57</td>
<td>0.30 - 1.08</td>
<td>0.084</td>
</tr>
<tr>
<td>Initiation regimen (both loading and first maintenance doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>37 (23.9)</td>
<td>68 (47.9)</td>
<td>2.93</td>
<td>1.79 - 4.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incorrect</td>
<td>118 (76.1)</td>
<td>74 (52.1)</td>
<td>0.34</td>
<td>0.21 - 0.56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Interval.

The vancomycin initiation regimen was considered incorrect in 3 scenarios: loading dose is correct and first maintenance dose is incorrect; 18.1% before (28/155) and 19.7% after (28/142) implementation of the calculator, loading dose is incorrect and first maintenance dose is correct; 20.6% before (32/155) and 19.0% after (27/142) the calculator, or loading dose and first maintenance dose are both incorrect; 37.4% before (58/155) and 13.4% after (19/142) the calculator. (Table 4.7)

Table 4.7. Sub-analysis of the accuracy of vancomycin initiation regimens

<table>
<thead>
<tr>
<th>Category</th>
<th>Before (%)</th>
<th>After (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 155</td>
<td>n=142</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD correct &amp; MD correct</td>
<td>37 (23.9)</td>
<td>68 (47.9)</td>
<td>2.93</td>
<td>1.79 - 4.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LD correct &amp; MD incorrect</td>
<td>28 (18.1)</td>
<td>28 (19.7)</td>
<td>1.11</td>
<td>0.62 - 1.99</td>
<td>0.716</td>
</tr>
<tr>
<td>LD incorrect &amp; MD correct</td>
<td>32 (20.6)</td>
<td>27 (19.0)</td>
<td>0.90</td>
<td>0.51 - 1.60</td>
<td>0.725</td>
</tr>
<tr>
<td>LD incorrect &amp; MD incorrect</td>
<td>58 (37.4)</td>
<td>19 (13.4)</td>
<td>0.26</td>
<td>0.14 - 0.46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Interval; LD: loading dose; MD: first maintenance dose.
4.4.3. Specialty of prescribers

4.4.3.1. Gentamicin

In gentamicin patients, a significant improvement in the rate of correct doses was noticed in 3 clinical specialties; Haematology/Oncology (47.5% to 87.3%, P<0.001), Critical Care (26.7% to 54.2%, P=0.035), and Liver (12.5% to 71.4%, P=0.041). (Table 4.8)

Table 4.8. Accuracy of gentamicin doses based on the specialty of prescribers

<table>
<thead>
<tr>
<th>Specialty</th>
<th>No. of doses before (%)</th>
<th>No. of doses after (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology/Oncology</td>
<td>Correct 99 (50.8)</td>
<td>Correct 55 (25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Incorrect 52 (52.5)</td>
<td>Incorrect 7 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Critical Care</td>
<td>Correct 45 (23.1)</td>
<td>Correct 24 (11.2)</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>Incorrect 12 (26.7)</td>
<td>Incorrect 11 (45.8)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Correct 8 (4.1)</td>
<td>Correct 7 (3.3)</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Incorrect 1 (12.5)</td>
<td>Incorrect 2 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>Correct 16 (8.2)</td>
<td>Correct 65 (30.2)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Incorrect 7 (56.3)</td>
<td>Incorrect 37 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Correct 14 (7.2)</td>
<td>Correct 27 (12.6)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Incorrect 9 (64.3)</td>
<td>Incorrect 18 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Women’s Health</td>
<td>Correct 6 (3.1)</td>
<td>Correct 18 (8.4)</td>
<td>0.649</td>
</tr>
<tr>
<td></td>
<td>Incorrect 4 (66.7)</td>
<td>Incorrect 9 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Correct 3 (1.5)</td>
<td>Correct 1 (0.5)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Incorrect 2 (66.7)</td>
<td>Incorrect 1 (100)</td>
<td></td>
</tr>
<tr>
<td>Neuroscience</td>
<td>Correct 3 (1.5)</td>
<td>Correct 13 (6)</td>
<td>0.529</td>
</tr>
<tr>
<td></td>
<td>Incorrect 3 (100)</td>
<td>Incorrect 4 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>Correct 1 (0.5)</td>
<td>Correct 5 (2.3)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Incorrect 1 (100)</td>
<td>Incorrect 2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>195 (100)</td>
<td>215 (100)</td>
<td></td>
</tr>
</tbody>
</table>
4.4.3.2. Vancomycin

In vancomycin patients, a significant improvement in the rate of correct doses was noticed in 2 clinical specialties; Cardiology (0% to 80%, P=0.001), and Haematology/Oncology (35.9% to 68.8%, P=0.038). A clear improvement occurred in Liver specialty, however it was not statistically significant (6.7% to 38.5%, P=0.069). (Table 4.9)

Table 4.9. Accuracy of vancomycin regimens based on the specialty of prescribers

<table>
<thead>
<tr>
<th>Specialty</th>
<th>No. of doses before (%)</th>
<th>No. of doses after (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology/Oncology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>14 (35.9)</td>
<td>11 (68.8)</td>
<td>0.038</td>
</tr>
<tr>
<td>Incorrect</td>
<td>25 (64.1)</td>
<td>5 (31.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>(0)</td>
<td>8 (80.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Incorrect</td>
<td>10 (100)</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>1 (6.7)</td>
<td>5 (38.5)</td>
<td>0.069</td>
</tr>
<tr>
<td>Incorrect</td>
<td>14 (93.3)</td>
<td>8 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Critical Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0.231</td>
</tr>
<tr>
<td>Incorrect</td>
<td>10 (100)</td>
<td>2 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>11 (25.0)</td>
<td>19 (41.3)</td>
<td>0.121</td>
</tr>
<tr>
<td>Incorrect</td>
<td>33 (75.0)</td>
<td>27 (58.7)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>6 (27.3)</td>
<td>14 (51.9)</td>
<td>0.143</td>
</tr>
<tr>
<td>Incorrect</td>
<td>16 (72.7)</td>
<td>13 (48.1)</td>
<td></td>
</tr>
<tr>
<td>Women’s Health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>0 (0)</td>
<td>1 (50.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1 (100)</td>
<td>1 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Neuroscience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>5 (35.7)</td>
<td>9 (36.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Incorrect</td>
<td>9 (64.3)</td>
<td>16 (64.0)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>155 (100)</td>
<td>142 (100)</td>
<td></td>
</tr>
</tbody>
</table>
4.4.4. High risk patients

Further analysis was undertaken for patients at higher risk including elderly (≥65 years), renally-impaired (CrCl<60 ml/min), and obese (BMI≥30 kg/m²) patients.

4.4.4.1. Gentamicin

No significant differences in the rate of gentamicin correct doses before and after the calculator implementation was found between elderly and non-elderly patients (P=0.248), patients with and without renal impairment (P=0.644), or obese and non-obese patients (P=0.462). (Table 4.10)

<table>
<thead>
<tr>
<th>High-risk group</th>
<th>Total no. of correct doses, n=195</th>
<th>No. of correct doses before (%), n= 75</th>
<th>No. of correct doses after (%), n=120</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (age ≥ 65 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>45</td>
<td>14 (31.1)</td>
<td>31 (68.9)</td>
<td>0.248</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>150</td>
<td>61 (40.7)</td>
<td>89 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Renally-impaired (CrCl &lt; 60 ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 ml/min</td>
<td>37</td>
<td>13 (35.1)</td>
<td>24 (64.9)</td>
<td>0.644</td>
</tr>
<tr>
<td>≥60 ml/min</td>
<td>158</td>
<td>62 (39.2)</td>
<td>96 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI ≥ 30 kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>39</td>
<td>17 (43.6)</td>
<td>22 (56.4)</td>
<td>0.462</td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>156</td>
<td>58 (37.2)</td>
<td>98 (62.8)</td>
<td></td>
</tr>
</tbody>
</table>

CrCl: creatinine clearance; BMI: body mass index.

4.4.4.2. Vancomycin

No significant differences in the rate of vancomycin correct regimens before and after the calculator implementation was found between elderly and non-elderly patients (P=0.247), patients with and without renal impairment (P=0.379), or obese and non-obese patients (P=0.068). Similarly, no significant differences were found with loading and maintenance doses. The only significant difference was in the rate of correct maintenance doses before and after the calculator between obese and non-obese patients (P=0.028). (Table 4.11)
### Table 4.11. The difference in vancomycin dose accuracy between high risk and non-high risk patients

<table>
<thead>
<tr>
<th>High-risk group</th>
<th>Total no. of correct LDs, n=161</th>
<th>No. of correct LDs before (%)</th>
<th>No. of correct LDs after (%), n=96</th>
<th>P-value</th>
<th>Total no. of correct MDs, n=164</th>
<th>No. of correct MDs before (%)</th>
<th>No. of correct MDs after (%), n=95</th>
<th>P-value</th>
<th>Total no. of correct regimens, n=105</th>
<th>No. of correct regimens before (%)</th>
<th>No. of correct regimens after (%), n=68</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (age ≥ 65 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>62</td>
<td>23 (37.1)</td>
<td>39 (62.9)</td>
<td>0.503</td>
<td>47</td>
<td>18 (38.3)</td>
<td>29 (61.7)</td>
<td>0.535</td>
<td>33</td>
<td>9 (38.9)</td>
<td>24 (61.1)</td>
<td>0.247</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>99</td>
<td>42 (42.4)</td>
<td>57 (57.6)</td>
<td></td>
<td>117</td>
<td>51 (43.6)</td>
<td>66 (56.4)</td>
<td></td>
<td>72</td>
<td>28 (27.3)</td>
<td>44 (72.7)</td>
<td></td>
</tr>
</tbody>
</table>

Renally-impaired (CrCl < 60 ml/min)

| ≤60 ml/min     | 31                            | 17 (54.8)                    | 14 (45.2)                        | 0.068   | 24                            | 13 (54.2)                    | 11 (45.8)                        | 0.194   | 13                               | 6 (46.2)                          | 7 (53.8)                           | 0.379   |
| ≥60 ml/min     | 130                           | 48 (36.9)                    | 82 (63.1)                        |         | 140                           | 56 (40.0)                    | 84 (60.0)                        |         | 92                               | 31 (33.7)                         | 61 (66.3)                          |         |

Obese (BMI ≥ 30 kg/m²)

| ≥30 kg/m²      | 35                            | 10 (28.6)                    | 25 (71.4)                        | 0.108   | 43                            | 12 (27.9)                    | 31 (72.1)                        | 0.028   | 25                               | 5 (20.0)                          | 20 (80.0)                          | 0.068   |
| <30 kg/m²      | 126                           | 55 (43.7)                    | 71 (56.3)                        |         | 121                           | 57 (47.1)                    | 64 (52.9)                        |         | 80                               | 32 (40.0)                         | 48 (60.0)                          |         |

LD: loading dose; MD: maintenance dose; CrCl: creatinine clearance; BMI: body mass index.
4.5. Discussion

4.5.1. Accuracy of initial doses pre- and post-intervention

The accuracy of initial doses for both gentamicin and vancomycin have improved significantly at the Trust after implementation of new calculators providing CDS to prescribers. Incorrect initial doses of gentamicin were reduced from 61.5%-44.2% (P<0.001). Incorrect loading doses of vancomycin were reduced from 58.1%-32.4% (P<0.001), while incorrect first maintenance doses were reduced from 55.5%-33.1% (P<0.001). Incorrect vancomycin initiation regimens were reduced from 76.1%-52.1% (P<0.001). The calculator pages on the Trust intranet were frequently accessed during the 2-month period following their implementation (333 times for gentamicin & 388 for vancomycin). It is anticipated that the activities to promote the calculators (i.e. emails, website, induction programmes, and Grand-Round presentation) and make them compatible with the Trust electronic system (i.e. link from EPMA and instructions on electronic prescription form) had a role in such access.

Different CDS tools have shown improvements in gentamicin and vancomycin dosing. A UK study (Qureshi et al, 2012) found that introducing an online gentamicin dose calculator led to a 300% improvement in dosing accuracy (30%, 15/50 pre- to 92%, 46/50 post-calculator) at an NHS hospital. This calculator required the same data needed in the current study (i.e. gender, age, weight, height, and SrCr) to provide the correct dose and prophylactic doses were also excluded from the study. However in comparison to the current study, this study was conducted only on surgical wards, the sample size (50 patients in each phase) was relatively small, and no statistical analysis was conducted. Another study conducted in Taiwan by Chan et al (2006) investigated the impact of an online gentamicin dose calculator incorporated into the hospital CPOE system. This calculator used a pharmacokinetic formula to provide the correct dose. The main outcome measure of the study was the number of gentamicin orders that resulted in undesirable serum levels (low peak or high trough). The calculator reduced the number of undesirable levels from 32.7% (152/465) to 13.5% (40/297). Nevertheless, the fact that this study was conducted only in intensive care units and used a compound pharmacokinetic equation for dose calculation limits the generalisability of its findings compared to the current study. In addition, this study did not perform a statistical analysis.
A US study by Frankel et al (2013) showed an improvement in initial vancomycin dosing in the Emergency Department (ED) after the introduction of a CPOE with vancomycin weight-based orders. The CPOE improved compliance to the recommended initial dosing threshold from 34.9% (82/235) in the pre-CPOE doses to 51.1% (120/235) in the post-CPOE doses (P<0.001). This improvement is comparable to the loading dose improvement achieved in the current study. However, maintenance doses and initiation regimens could not be compared as this CPOE was only valid for loading doses (no dose adjustment for height or CrCl). In addition, it was examined only in ED patients which might limit the generalisability of its findings. The ‘Pharmacist-to-Dose’ intervention in the Vincent et al (2009) study showed significant reduction in aminoglycoside and vancomycin DEs. The study had a relatively small sample size (49 patients pre- & 48 post-intervention). In this study, there were no details for how many correct and incorrect doses were associated with each drug (only combined data were provided) and therefore it was not possible to compare these results with the current study.

The intervention by Roberts et al (2010), like the current study also reduced DEs with gentamicin and vancomycin. However, the reduction of vancomycin errors in this study was not statistically significant (P=0.07), a wide range was used to define the correct doses of both drugs (one-third above or below the ideal dose), and the number of patients in both groups was relatively small and significantly different; 73 pre- & 38 post-GFR+ for gentamicin (P<0.05) and 34 pre- & 17 post-GFR+ for vancomycin (P<0.05). While the current study used the standard equations to calculate the values needed for dose calculation (e.g. ideal BW, CrCl), this study used a modified version of Cockcroft-Gault equation that caps SrCr to a minimum of 60 micromol/L and also a complex gentamicin dosing model derived from local population kinetics, which limits the generalisability of its findings.

### 4.5.2. Vancomycin underdoses

The vast majority of incorrect vancomycin loading doses in the current study were underdoses (92.6%, 126/136). Similarly, 90.8% of 3,461 incorrect vancomycin doses (n=3,143) at an ED in the US were underdoses as per the American Society of Health-System Pharmacists / Infectious Diseases Society of America guidelines (Fuller et al, 2013). Although actual BW is the ideal method for calculating initial vancomycin doses, a fixed dose of 1000mg is commonly used in the ED (Rosini et al, 2013). In a US study...
conducted in an ED, most patients (87.5%, 210/240) were administered an initial vancomycin dose of 1000mg (Rosini et al, 2013). In the current study, 1000mg dose was used in 40.4% of all loading doses (120/297), 75.8% (91/120) of them were underdoses. That suggests that this practice is not only common at EDs, but also across the other hospital departments. The use of 1000mg loading doses was significantly reduced from 52.3% (81/155) before to 27.5% (39/142) after implementation of the calculator (P<0.001). However, the extent of underdosing was relatively unchanged from 79.0% before to 69.2% after the intervention. Similar results were shown in the Frankel et al study where initial doses of 1000mg were reduced from 87.7% (206/235) before, 72.3% of these were underdoses, to 54.5% (128/235) after, 59.4% of these were underdoses, CPOE implementation. The current study was the first to assess first maintenance dose as part of the initial dose of vancomycin in addition to loading dose so no comparison with past studies is possible.

4.5.3. Introduction of CDS tools into healthcare systems

The introduction of CDS tools into healthcare is a complex interaction between people, technology and organisational workflow. In addition to the technology aspect, there should be a focus on changing workflows. In order to achieve benefits from CDS tools, using them should become part of the prescribers’ routine practice rather than an extra task added to their already heavy workload. The automatic provision of CDS tools as part of the prescriber workflow is the most important factor for a successful CDS implementation. Other factors for CDS implementation success include providing support at the time and location of decision-making, recommendations rather than assessments, and information technology support. (Kawamoto et al, 2005; Roberts et al, 2010)

In the current study, efforts were made to incorporate the use of calculators into the prescribing workflow by adding a direct link to them from EPMA and setting an instruction to use them on the electronic prescription forms. However, more work can still be done to fully integrate these calculators into the Trust electronic system (e.g. automatic population with appropriate patient demographic data including age, weight and height, and laboratory results including SrCr and CrCl). Because of the reported advantages of CDS tools in improving drug dosing and therefore patient safety, physicians may overrely on their suggestions (Campbell et al, 2007). However, prescribers should always be careful when using CDS tools, particularly for prescribing
high-risk and narrow-therapeutic-index medications, as some studies have highlighted that these tools may lead to unintended negative results. (Eslami et al, 2006; Ash et al, 2007; Koppel et al, 2005)

4.5.4. Limitations

One of the limitations of this study is that it was not possible, due to technical barriers, to identify whether visitors to the calculator pages actually used the tools to aid prescribing. Therefore, the improvements in gentamicin and vancomycin initial dose accuracy cannot be definitively linked to the calculators. However, the significant improvements in dose accuracy after implementation of the calculators provides an indication that they did play a role in this improvement, especially given that no other proactive initiatives to improve gentamicin and vancomycin dosing took place during the same time period. In addition, the gentamicin and vancomycin dosing guidance was the same pre- and post-intervention.

Another limitation was the use of different sources of data before and after the calculators. The pre-calculator phase of the study was conducted retrospectively because the EPMA system was not available on all Trust wards at that time. So, it was not possible to identify patients from all hospital wards using this system. In addition, the calculators were already available online (although not promoted nor linked with EPMA) when the decision to conduct the study was taken. Thus, the retrospective-review dates were chosen before the date calculators were first available online (i.e. 1/1/2011-31/08/2011). The Microbiology database was the only source available to retrospectively identify patients prescribed gentamicin and vancomycin.

There were some differences in demographic data before and after the calculators including gender in gentamicin patients, BMI and CrCl in vancomycin patients, and some prescriber specialties in both groups (Tables 4.3 & 4.4). These differences are probably due to the different data collection methods used, but it is not anticipated that these affected the overall results. The comparison between high risk and non-high risk patients (Tables 4.10 & 4.11) showed that age, weight, and renal function did not have an effect on the accuracy of gentamicin initial doses or vancomycin initiation regimens.
Moreover, it was deemed that the differences in specialty rates did not affect the overall outcomes because the number of correct doses (for each drug) in the specialty with the highest number of patients was similar or higher in post-calculator patients (Tables 4.8 & 4.9). In gentamicin patients, Haematology/Oncology had the highest accuracy rate among all specialties post-calculator (87.3% compared to 47.5% pre-calculator). The proportion of doses from this specialty reduced from 50.8% of all doses pre-calculator to 25.6% post-calculator. This means that if the proportion of Haematology/Oncology doses remained 50.8%, the number of correct doses post-calculator would have been probably much higher. The proportion of vancomycin doses for Medicine patients pre- and post-calculator was not significantly different and so was the number of correct doses. Most of the other significant differences in specialty occurred between relatively small numbers of patients and therefore was not anticipated to have an impact on the overall outcomes.

4.6. Further Work

With the exception of one study which showed a reduction in undesirable gentamicin serum levels with the intervention (Chan et al, 2006), none of the intervention studies discussed above have assessed patient clinical outcomes. The difference in patient clinical outcomes between pre- and post-calculator doses (e.g. correct serum level, treatment success rate, toxicity incidence) was also not assessed in this study. Thus, further work is still needed to assess the impact of this intervention on patient clinical outcomes.

As it was not possible to identify whether doctors used the calculators to prescribe the assessed gentamicin and vancomycin doses and the doctors’ impression and acceptance of the calculators were not assessed in this study, these areas warrant further work. A qualitative study could be undertaken to explore the views and experiences of doctors in prescribing gentamicin and vancomycin along with the resources and methods they use to calculate the initial dose of these drugs. This would assist in assessing the awareness and usage of the calculators across the Trust.
4.7. Conclusion

The introduction of electronic dose calculators for the initial treatment doses of gentamicin and vancomycin in a large acute teaching NHS Trust with electronic prescribing and patient record systems has led to a significant improvement in their accuracy. However, further work is still needed to demonstrate the clinical benefits of these calculators. Use of these CDS tools can improve clinical care and this study suggests that organisations implementing electronic prescribing systems should consider including such CDS tools in their programmes.
Chapter 5

An Interview-Based Study to Explore Prescribing of Initial Doses of Gentamicin and Vancomycin
5.1. Introduction

Prescribing medicines is a vital skill required by all doctors. Prescribers need to balance potential benefits and risks of any prescribing decision they make. Adequate clinical knowledge and ‘improvisational’ skills of prescribers are essential for providing a high-quality and safe prescribing practice. The emergence of new medicines as well as the large number of ageing and severely-ill patients has increased the challenges and criticality of prescribing (Avery et al., 2012). Prescribing errors (PEs) are one of the most common MI types, particularly with antibiotics (details in section 1.5.1). In the Datix® analysis (Chapter 2), prescribing was the stage at which most antibiotic errors occurred (42.4%, n=407).

The study in Chapter 4 showed that accuracy of gentamicin and vancomycin initial doses was significantly improved following implementation of the dose calculators. Although this improvement was deemed to be mainly due to the calculators, this result could not be considered definite as it was not possible to identify whether doctors have actually used the calculators to prescribe the assessed doses. In addition, the doctors’ impression and acceptance of the calculators was not assessed. Therefore, this chapter comprises a qualitative exploration of doctors’ experiences and views of gentamicin and vancomycin prescribing as well as the resources and methods they use to calculate the initial dose of these drugs.

5.1.1. Dosing errors within prescribing

There is no agreed definition for a dosing error (DE). However, most definitions consider it to be any dose not within a specified range (usually 10-20%) higher or lower than the ideal recommended dose (details in section 4.3.5).

DEs are a common type of PEs. Jayawardena et al (2007) found in a US study that 39.3% (n=1,303) of the 3,321 PEs detected in a teaching hospital were DEs. Another US study in a tertiary-care hospital found that DEs made 48.8% (n=117) of all PEs; 29.2% (n=70) overdoses and 19.6% (n=47) underdoses (Winterstein et al., 2004). Moreover, in another US study, Bobb et al (2004) identified that DEs made 39.2% of 342 clinically significant PEs. An earlier 9-year study identified that DEs accounted for 56.1% (n=6,272) of all PEs and 38.4% (n=804) of potentially fatal, serious, and severe PEs (Lesar et al 1997A).
In the UK, Ashcroft and Cooke (2006) analysed 495 MIs reported to the incident reporting system at a 1000-bed teaching hospital. They found that DEs accounted for 38.6% of all PEs reported (49/127). Dornan et al (2009) conducted the EQUIP study across 19 hospitals in England to investigate PEs committed by junior doctors. DEs was one of the most commonly detected PEs in this study (19.5%, n=2,157). Another study across 9 English hospitals (Seden et al, 2013) found that 20.6% (n=383) of all PEs were DEs. Of the 9 PEs considered fatal in this study, 8 were DEs. The PROTECT study was conducted across 8 Scottish hospitals to explore the outcomes of junior doctors’ prescribing after engagement in a training programme (Ryan et al, 2014). DEs accounted for 12.9% (n=434) of all PEs detected in this study. A systematic review of PEs by Lewis et al (2009) identified that DEs were the most commonly reported type of PEs in 18 out of the 33 studies which provided percentages for PE types.

Antibiotics is one of the drug classes most commonly associated with DEs. Lazarou et al (1998) conducted a meta-analysis on the incidence of adverse drug reactions (ADRs) among hospitalised patients in the US. Eight studies in this meta-analysis included details about the types of ADRs. In these, 76.2% of ADRs were dose-related. Lesar et al (1997A) identified 2,394 antimicrobial DEs in their study which accounted for 38.2% of all DEs and 21.4% of all PEs.

5.1.2. Causes of and factors contributing to prescribing errors

Any step or procedure within the prescribing process can generate errors. PEs can rise from the wrong choice of a drug, wrong dose, wrong frequency, wrong route of administration, or wrong duration of treatment. In addition, PEs may result from failure to take into account patient individual characteristics (e.g. weight, renal function), inaccurate drug history taking, or the presence of concurrent drug therapies. They can also be a result of poor or incomplete handwriting, use of abbreviations, lack of knowledge about the drug, or misjudgements of its potential harm. (Velo and Minuz, 2009).

Some studies have tried to determine the causes and contributory factors of PEs. Lesar et al (1997B) investigated the factors related to PEs by asking 3 expert reviewers to assign a likely contributory factor for each error after providing them with details about the prescription, patient, and response to PE. Error-producing factors were divided into 7
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

main categories related to patient characteristics (e.g. clinical status, medical history), drug therapy (e.g. wrong drug, drug interaction), dosage form (e.g. wrong form for intended use), nomenclature (e.g. sound-like, abbreviation), calculations/unit expression (e.g. calculation error, unit of measure), administrative process (e.g. transcribing), and unclassifiable. Out of 696 PEs detected in this study, errors were primarily related to knowledge of drug therapy (30%, n=209) and patient characteristics (29.2%, n=203) followed by calculation/unit expression errors (17.5%, n=122).

Bobb et al (2004) aimed to investigate the proximal causes of PEs. They classified each error into one of 9 categories based on patient and medication characteristics. These categories included medication knowledge deficiency, patient knowledge deficiency, non-adherence to policies/procedures, slips or memory lapses, nomenclature errors, transcription errors, calculation/unit expression errors, faulty patient-identity checking, and illegible handwriting or faulty prescription form. In this study, clinically significant PEs (n=342) were mostly linked to deficiency in doctors’ knowledge about the medication (64%, n=219) and patient (14.6%, n=50).

Leape et al (1995) took a different approach to investigate the proximal causes of PEs. Instead of basing their classification on external investigation and interpretation, they asked the medical staff who committed the errors about their causes. Classification of error causes emerged from the information gained from the prescribers. Emerged causes were similar to previous studies and included lack of drug knowledge, lack of patient knowledge, slips or memory lapses, rule violations, transcription errors, and inadequate monitoring. The principal cause of PEs was the lack of knowledge about the drug (36.2%, 47/130) and patient (23.8%, 31/130), which were similar to the two previous studies (Lesar et al, 1997B; Bobb et al, 2004).

Error causes in the studies described could be classified according to Reason’s model of human error (1990) into unintended (slips or lapses) or intended (mistakes or violations) actions (see section 1.2.4). Some causes can be clearly classified under one category such as knowledge deficiency under mistakes, faulty patient-identity checking under slips, and rule violations and non-adherence to policies under violations. However, some causes can be classified into more than one category depending on their context. For example, nomenclature errors can be classified as slips (e.g. prescribing sound-alike drugs) or violations (e.g. using abbreviations while knowing it is illegal), and calculation errors/unit
expression can be classified as slips (e.g. failure in performing correct equations, writing other units unintentionally) or mistakes (e.g. not knowing the calculations needed or the correct units).

The causes mentioned above were the direct causes responsible for error incidents and were identified by Reason (2000) as active failures. However, Reason (2000) also identified another way of considering factors contributing to errors, the system approach (latent error-producing conditions) being considered the most important. These are the conditions under which people work and can, where there is a lack of proper defences, facilitate errors (please refer to section 1.2.4 for further details). In the context of PEs, latent conditions can be in the form of insufficient feedback, lack of cooperation among team members, unclear prescribing roles, stressful work settings, tough work environment, heavy workload, poor communication, or bad physical or mental state (Velo and Minuz, 2009).

5.1.3. Qualitative research studies to explore prescribing behaviour and investigate error causes and factors

In the last 20 years, there has been an increase in the use of qualitative methods in clinical research (Al-Busaidi, 2008). Qualitative research can be useful to ask questions about why healthcare professionals behave in a particular way and to focus on participants’ feelings, meanings and experiences. It aims to discover why problems occur in order to identify potential solutions. (Brookes, 2007).

Qualitative studies have been used to understand the doctors prescribing behaviour, especially the factors and causes of poor prescribing practice and adverse events. Dean et al (2002c) interviewed 41 doctors regarding 44 medication errors. This study identified a main active failure in each case. Skill-based slips (n=23) or lapses (n=2) were the most frequent error causes (57%, n=25), followed by rule-based mistakes (39%, n=17) in addition to two violations (4%). All prescribers who made slips or lapses were unable to explain why they happened, however doctors often mentioned that they were busy (70%, n=31) or interrupted during routine tasks (30%, n=13). There were 5 main conditions in the workplace that prescribers identified as error-producing; patient, individual, team, task, and work environment (Figure 5.1).
Figure 5.1. Prescribing error producing conditions identified by Dean et al (2002c, p.3)

Dornan et al (2009) conducted the EQUIP study to investigate the causes of PEs in junior doctors by interviewing 30 doctors from 17 hospitals in North-West England. This study determined that junior doctors relied heavily on pharmacists and nurses to identify and correct errors. They had insufficient support when prescribing, especially while on-call and during ward rounds. PEs were the result of complex mixtures of precursor and contextual factors. For example, violations of routine prescribing procedures were reasonable adaptations to busy and stressful working conditions rather than deviations. Miscommunication was also stated as a reason for errors. Doctors reported some deficiencies in their undergraduate education regarding prescribing skills and error prevention, particularly in linking theory with practice and developing expertise in the complex context of clinical practice. When lack of knowledge was the cause of error, this may have been avoided by better support in the working environment.
Avery et al (2012) studied the causes of PEs in English general practices (PRACtICE study) through 34 interviews with prescribers, 15 root cause analyses, and 6 focus groups involving 46 primary healthcare team members. Seven categories of high-level error-producing conditions were identified: the prescriber (e.g. therapeutic training, drug knowledge and experience, knowing the patient, perception of risk, physical and emotional health), patient (e.g. patient's characteristics, complexity of clinical case), team (i.e. feeling comfortable within the team), working environment (e.g. workload, time pressures, interruptions), task (e.g. signing prescriptions generated by nurses without seeing patients), computer system (e.g. mis-selecting drugs from electronic pick-lists and overriding alerts), and primary-secondary care interface (e.g. ambiguous wording of hospital letters, failure of some GPs to make changes recommended by specialists, lack of automatic update of patients’ computer records promptly with hospital information).

All factors mentioned above can be grouped according to the framework for analysing clinical risk and safety described by Vincent et al (1998) (section 1.2.4) into one of 7 categories that can affect clinical practice and influence patient safety. These categories are institutional context (e.g. primary-secondary care interface), organisational and management factors (e.g. lack of support in working place), work environment (e.g. heavy workload), team factors (e.g. miscommunication), individual (staff) factors (e.g. lack of knowledge, physical/mental state), task factors (e.g. not routine practice), and patient characteristics (e.g. complex disease).

5.1.4. Understanding antimicrobial prescribing practice

Qualitative methods have been used to understand the prescribing process of antimicrobials, its challenges, and influencing factors. A study was conducted in 4 London NHS hospitals to understand the determinants of antimicrobial prescribing (Charani et al, 2013). Semi-structured interviews were conducted with doctors (n=10), pharmacists (n=10), and nurses/midwives (n=19). This study determined that antimicrobial prescribing behaviour of healthcare professionals was dominated by a set of cultural rules. Antibiotic prescribing was performed in an environment where junior doctors’ practice was influenced by senior doctors’ behaviour. In this study, senior doctors considered themselves exempted from following policies and practice and adopted a culture of self-directed decision making which relied on personal knowledge.
and experience rather than guidelines and policies. The junior doctors recognised the prevailing practice within their clinical group and adjusted their prescribing behaviour accordingly. A ‘non-interference’ culture prevented doctors from intervening in antimicrobial prescribing of other colleagues. This culture revealed the presence of what the researchers called a ‘prescribing etiquette’ that dominated the antimicrobial prescribing behaviour of these healthcare professionals. This prescribing etiquette created an environment in which professional hierarchy and clinical groups act as key factors for prescribing behaviour.

A systematic review of 35 qualitative studies was undertaken to explore doctors’ insights about factors influencing antibiotic prescribing (Teixeira Rodrigues et al, 2013). Data collected primarily through interviews, followed by questionnaires and focus groups, were analysed using grounded theory and thematic analysis. Two main groups of factors were identified as having an impact on antibiotic prescribing; intrinsic or extrinsic to the healthcare professional. Doctors’ attitudes (e.g. complacency, ignorance, fear) and socio-demographic factors (e.g. previous experience, education) were rated as the most influential intrinsic factors in antibiotic prescribing. Patient-related factors (e.g. signs and symptoms) or healthcare system-related factors (e.g. time pressure, policies/guidelines) were the extrinsic factors mostly reported. This review concluded that antibiotic prescribing is a complex process influenced by mutually dependent factors which affect all the stakeholders involved including doctors, other healthcare professionals, the healthcare system, patients, and the general public.

A review by Hulscher et al (2010) identified two main types of ‘obstacles’ for appropriate antibiotic use. The first type was the internal obstacles which have a cognitive (knowledge) or affective (attitude) element. The knowledge element included knowledge about the antibiotic, familiarity with available evidence, education, and experience. The attitude element included disagreement with guidelines and lack of outcome expectancy, motivation, or self-efficacy expectations. The second type included the external obstacles which restrict the abilities of healthcare staff. These obstacles can be organisational (e.g. treatment guidelines), social (e.g. junior doctors are not independent prescribers), political (e.g. structural strategies to improve coordination, collaboration, communication, or teamwork), and economical (e.g. use of generics).
A study conducted in the Netherlands by Mol et al (2004) investigated the adherence barriers to antimicrobial treatment guidelines. Fifteen hospital doctors were interviewed. The main barriers identified related to the guidelines themselves, doctors’ characteristics, and social and contextual context. Fourteen out of the fifteen doctors were aware of the guideline, however six had never received a personal copy. It was suggested that more effort was needed to familiarise doctors with the guidelines. All doctors agreed with the basic recommendations of the guidelines and stressed that they need to be concise and up-to-date. While junior doctors were more willing to use the guidelines, senior doctors considered the existence of antibiotic guidelines as a threat to their professional autonomy and as an interference with their daily clinical practice. Junior doctors in most teaching hospitals do not make independent prescribing decisions, they are usually supervised by specialists. Antimicrobial guidelines were perceived by junior doctors as helpful in coping with different practices among different departments. Although an infectious disease specialist was available for advice, junior doctors in this study would primarily seek advice from their consultant, who would always make the final decision.

The studies above identified that antimicrobial prescribing behaviour is mainly affected by internal (prescriber-related) and external (organisation- or patient-related) factors. There was a clear emphasis on the great impact of the predominant culture within a ward or an organisation on doctors’ antimicrobial prescribing decisions. Junior doctors appear to be routinely following their seniors (i.e. specialists, consultants) regardless of organisational policies or treatment guidelines. These studies also emphasised the importance of education, guidelines, and feedback as strategies to improve prescribing practice.

5.1.5. Investigations gentamicin and vancomycin prescribing

Gentamicin and vancomycin are narrow-therapeutic-index drugs known to have high toxicity and are commonly associated with prescribing and particularly dosing errors (see section 3.1). Failure Modes and Effects Analysis (FMEA) can be used to systemically evaluate a process in order to identify the mechanisms and areas of potential failure, which would allow finding and prioritising preventive measures. It was recommended by the US Institute for Safe Medication Practices (ISMP, 2004) and UK National Patient Safety Agency (2004) that FMEA should be used as a strategy to enhance patient safety and improve the quality of care.
FMEA was used by Shebl et al (2009) to explore the gentamicin and vancomycin use process. Two multidisciplinary groups were asked to graphically describe the process of use for these drugs. Both groups agreed on 5 major steps including deciding to start gentamicin/vancomycin, prescribing, administering, monitoring, and finally stopping or continuing treatment. Each group identified 50 failures in the process, however only 17 were common to both. In the prescribing step, the common failures identified included failure to consider renal function, prescribing a wrong dose, and failure to prescribe according to guidelines. The main improvement recommendations made in relation to prescribing were education and training, making guidelines more accessible, increase medical staffing, encourage communication between doctors and nurses, and introduce electronic systems for prescribing and laboratory test results. Due to the variability of failures identified by each group which appeared to be a result of different individual experiences, the authors questioned the reliability of FMEA as these differences did not allow identification and prioritisation of the most risky failures.

Therefore, another study was conducted (Shebl et al, 2012) to assess the validity of FMEA outputs from the first study. They investigated the face validity (researcher’s assessment of the process mapped by FMEA), content validity (judgement of the findings by other healthcare professionals), criterion validity (assessing correlation of findings to similar objective measures), and construct validity (assessing mathematical properties used for scoring scales) of the FMEA findings. Although the face validity was positive as the researcher identified similar processes to those mapped by the FMEA participants, other outputs had poor validity. Other healthcare professionals identified potential failures missed by the FMEA participants. Despite dose omissions being the failure most commonly reported to the incident reporting database, it was not identified by FMEA participants which showed poor criterion validity. Construct validity was also poor as the concept of multiplying ordinal scales to prioritise failures was deemed mathematically inappropriate.

The results of these studies determined that FMEA can be a useful tool for hospitals to understand the process of drug use and identify potential failures. However, the variability of its findings and their questionable validity necessitate the use of other sources besides FMEA to find and prioritise patient safety issues.
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

Although several interventions to improve gentamicin and vancomycin prescribing have been developed, the design of these interventions did not consider the behavioural perspective of the issue. Charani et al (2011) conducted a systematic review of behaviour change strategies used to influence antimicrobial prescribing in acute care. This review included 5 qualitative and 5 quantitative studies. Qualitative studies highlighted the dominating influence of social norms, attitudes, and beliefs on antimicrobial prescribing behaviour. Quantitative studies showed that interventions developed to optimise the prescribing behaviour of antimicrobials did not use theoretical science or primary research to inform the design and choice of these interventions. Thus, this review concluded that the availability of qualitative evidence on the impact of behavioural and social factors on antimicrobial prescribing behaviour did not influence the design and evaluation of interventions developed. Therefore, applying behavioural methods is needed to enhance understanding of the prescribing behaviours of antimicrobials and the effectiveness of interventions designed to improve their prescribing.

Few investigations have been undertaken to understand gentamicin and vancomycin dosing. The studies above showed the importance of understanding the process of using these drugs. The need to assess the knowledge of prescribers about these drugs and the conditions under which they are prescribed was also addressed. This would allow further understanding of the dosing process and identifying potential error-facilitating conditions. Moreover, it was also discussed that using qualitative investigation on interventions to improve antimicrobial prescribing would enhance their quality and usage and address any gaps detected. Using these measures could possibly enhance gentamicin and vancomycin dosing interventions.

5.1.6. Problems with gentamicin and vancomycin dosing

As discussed earlier, gentamicin and vancomycin are commonly associated with DEs. Moreover, risks with gentamicin and vancomycin were identified locally through an analysis of antibiotic-associated medication incidents reported to the centralised incident reporting system of two large acute teaching NHS Foundation Trusts, which included the study site (Chapter 2). One-third of dose/frequency errors reported (32/96) at the study site (i.e. King’s College Hospital NHS Foundation Trust) were related to gentamicin (n=16) or vancomycin (n=16). In addition, a previous internal FMEA (Cavell et al, 2010) to evaluate the usefulness of a new presentation of gentamicin infusions in the study site
identified that the risks of dose calculation and prescribing, especially in renally-impaired or obese patients, were greater than the risks of infusions’ preparation.

Qualitative research methods can investigate how evidence can be translated into practice by understanding the barriers to using evidence-based medicine and the limitations it has in supporting treatment decisions. The value of qualitative methods lies in its ability to thoroughly investigate research questions that cannot be clearly answered using quantitative methods to fill the gap between scientific evidence and clinical practice. (Green and Britten, 1998)

The incident report analysis in this research (Chapter 2) identified that 22.4% (127/407) of the reported antibiotic PEs were DEs. In the calculator study (Chapter 4), it was not possible to identify whether doctors who accessed the calculators have actually used them to prescribe gentamicin and vancomycin. In addition, the doctors’ impressions about and acceptance of the calculators were not investigated. Thus, a qualitative study was required to assess the doctors’ knowledge about gentamicin and vancomycin use, their awareness and usage of the dosing tools available in the Trust, the resources/methods they use to prescribe these drugs, and the factors affecting their dosing decisions. Understanding the process of prescribing initial doses of these drugs and the conditions surrounding this could potentially allow recommendations for improving the quality of initial dose prescribing and identify potential future interventions.

5.2. Aims and objectives

5.2.1 Aim of study

The aim of this study was to explore the views and experiences of doctors in prescribing gentamicin and vancomycin at an NHS Foundation Trust and the resources and methods they used to calculate the initial dose of these drugs.

5.2.2 Study objectives

- To gain an understanding of the current prescribing practice related to gentamicin and vancomycin, the steps employed and common process characteristics
- To identify the resources and methods used by prescribers to calculate gentamicin and vancomycin doses, for both correct and incorrect doses
• To explore the prescribers’ experience and use of resources (e.g. protocols, calculators)
• To assess doctors’ knowledge about gentamicin and vancomycin use
• To detect factors that might led to either correct or incorrect doses
• To explore doctor views of the possible sources of DEs
• To identify doctor recommendations to avoid DEs and improve dose accuracy.

5.3. Methods

5.3.1. Study design

This study used a qualitative interview-based design. Qualitative research is mainly concerned with investigating issues from the social or human perspective. It aims to understand why people behave the way they do, how opinions and attitudes are formed, how people are affected by the events happen around them, and how and why cultures and practices have developed (Hancock et al, 2007). Since the social/human issue of gentamicin and vancomycin dosing has not been sufficiently explored, conducting a survey was inappropriate. Qualitative interviews were chosen for data collection because they combine structure with flexibility which allows topics to be covered in the best order. In addition, the interactive nature of interviews allows the data to be generated through interaction between the interviewer and interviewee. The ability of the interviewer to use different prompts, probes and other techniques to get in-depth answers and fully explore the issue is also another feature of interviews (Ritchie and Lewis, 2003).

Data were collected through a series of semi-structured interviews. Semi-structured (or focused) interviews consist of a group of open-ended questions derived from the research topic under investigation. Although these questions are pre-defined, they still offer opportunities for both the interviewer and interviewee to discuss some topics in further detail (Hancock, 1998). The use of semi-structured interviews in this study enabled the investigation to focus on the research topic of dosing resources, practice, and experience.

5.3.2. Study setting

The study was conducted at King’s College Hospital NHS Foundation Trust; a 950-bed acute teaching hospital in South East London. It is one of the largest UK teaching
hospitals training over 400 doctors, 275 nurses and 750 dentists each year (King’s College Hospital NHS Foundation Trust, 2012A). The Trust covers a variety of secondary and tertiary care specialties including many medicine and surgery sub-specialties, haematology/oncology, critical care, women and children, and accident and emergency (A&E).

The Trust has an Electronic Prescribing and Medicines Administration system (EPMA) as part of its Electronic Patient Records (EPR); iSOFT® Clinical Manager 1.4. The Trust antimicrobial guidelines (King’s College Hospital NHS Foundation Trust, 2012B) are available on the Trust intranet as a PDF document and also as a pocket-sized booklet provided to all foundation doctors at induction and is also distributed by ward pharmacists to prescribers within their clinical specialties. Online dose calculators for gentamicin and vancomycin (see Chapter 4 for details) were implemented and promoted throughout the Trust approximately five months prior to this study.

According to the Trust antimicrobial guidelines (King’s College Hospital NHS Foundation Trust, 2012B), prescribers should contact Medical Microbiology for advice regarding gentamicin or vancomycin treatment in certain conditions (Table 5.1)

<table>
<thead>
<tr>
<th>Prescribers should contact Microbiology if:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin therapy is intended for &gt;48 hours</td>
<td></td>
</tr>
<tr>
<td>&gt;7 days vancomycin for methicillin resistant staphylococcus aureus (MRSA) treatment</td>
<td></td>
</tr>
<tr>
<td>Vancomycin therapy is considered in a dose &gt;1500mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Vancomycin serum level is 10-15mg/L while it is used for serious MRSA infections, osteomyelitis, central nervous system infections, endocarditis, or bacteraemia*</td>
<td></td>
</tr>
<tr>
<td>Vancomycin serum level reaches &gt;30mg/L</td>
<td></td>
</tr>
<tr>
<td>2-3 increases in serum creatinine of &gt;50%/&gt;45micromol/L from baseline after several days of vancomycin</td>
<td></td>
</tr>
<tr>
<td>Considering changing vancomycin to an oral alternative after 48 hours of therapy.</td>
<td></td>
</tr>
</tbody>
</table>

* The target trough level in the Trust is 10-20mg/L. However, levels of 15-20mg/L are recommended in serious MRSA infections, osteomyelitis, central nervous system infections, endocarditis, bacteraemia, and if specifically advised by Medical Microbiology.
5.3.3. Research permission

Ethical approval for this study was acquired from the Biomedical Sciences, Dentistry, Medicine and Natural & Mathematical Sciences Research Ethics Subcommittee (BDM RESC) of the College Research Ethics Committee (CREC) at King’s College London (KCL) on 1st February 2013 (BDM/12/13-26). The Research and Development Department at King’s College Hospital NHS Foundation Trust considered this study as a service evaluation and so no ethical approval was required from the Trust.

5.3.4. Development of data collection tools

5.3.4.1. Pre-study information email

An email including general information about the study was developed to be sent to doctors prior to study conduction. This email explained briefly the aim of the study, eligibility criteria, participant rights, duration of interview, and potential use of the results. The participant information leaflet was attached to this email for further information. This pre-study information email can be found in Appendix 5.1.

5.3.4.2. Interview invitation email and letter

All eligible doctors were sent an email inviting them to participate in the study. The invitation letter and participant information leaflet providing a complete description of the study were attached to this email. The email explained briefly about the study and invited doctors to an interview about the gentamicin/vancomycin prescription they made. It provided specific information about the prescription including patient hospital number, drug prescribed, ward and date of prescribing. The invitation letter (Appendix 5.2) provided information about the study including background, participant rights, duration of interview, and response time window. Both invitation email and letter included researcher contacts in case any further information was needed.

5.3.4.3. Participant information leaflet

A participant information leaflet about the study was developed. This leaflet included detailed information about the study including background, aim of study, eligibility
criteria, interview arrangements in case of agreement, possible risks, possible benefits, anonymity and confidentiality arrangements, and results dissemination plans. This leaflet also included the researcher contacts for any further information that might be needed. A copy of the participant information leaflet is in Appendix 5.3.

5.3.4.4. Consent form

A consent form was developed for the doctors to sign before starting the interview (Appendix 5.4). Without signing this form, doctors could not be included in the study. All consent forms were also signed by the researcher. Participant doctors were required to answer yes or no to some questions on the form regarding their agreement to participate in the study and use of their interview data in research analysis and presentation.

5.3.4.5. Participant rights

Participants were able to withdraw from the study without providing a reason even if they had given consent. Once the interview was completed, participants had 48 hours to inform the research team if they would like to withdraw from the study. In addition, there was no anticipated reason to believe participants would suffer any undue distress, harm or injury. It was clear in the information leaflet that the research team was there to answer any concerns. Any sensitive, embarrassing or upsetting topics were not raised or discussed. All participants’ personal and potential identifiable information (e.g. ward name, date) were anonymised.

5.3.4.6. Interview schedule

The interviews were guided by an interview schedule (Appendix 5.5) which was informed by other studies investigating prescribing practice (Dornan et al. 2009; Mol et al. 2004). The schedule was divided into 4 main sections based on the type of questions asked. The first section of the schedule included questions on the background of the participant including his/her grade, specialty, general experience, and experience at the study hospital. The second section focused on the specific prescribing occasion the doctor was contacted about and it included questions about the process of prescribing this dose, resource/method used for dosing, ward environment, factors that could have influenced the prescribing decision, and whose decision it was to prescribe the drug to the patient. The third section included general questions about prescribing the same drug involved in
the prescribing occasion. These included questions about the number of times the doctor
prescribes this drug, any extra measures or assessments considered when prescribing it,
its toxicity, and how its effects are monitored. The fourth section asked the same questions
in section 3 about the other drug not prescribed in the prescribing occasion and about the
source/method used for dosing this drug. Moreover, it asked about whether the same
resource/method would be used for all patients, resources/methods used by colleague
doctors for dosing gentamicin and vancomycin, possible sources of DEs with these drugs,
and recommendations to solve them.

As guideline recommendations of the initial dose of gentamicin and vancomycin are not
affected by the condition to be treated, doctors were not asked about the indication of
therapy and justification of drug choice. Since semi-structured interviews were used,
some prompt questions were available under the main questions; either to ask the question
in a different way in case it was not clear enough for the participant or to get more
information in case the participant’s answer was not detailed enough.

5.3.4.7. Interview schedule piloting

An interview schedule was developed and approved by the ethical committee. The
schedule was piloted by interviewing five doctors identified through EPMA (between 4th
and 24th September 2014). This pilot led to the addition of some questions (questions
regarding knowledge of drug toxicity and monitoring, awareness of other dosing tools
available in the Trust, and dosing resources used by other doctors) and amendment of
others (e.g. question about factors affecting doctor prescribing decisions) in order to
enhance the coverage of the schedule and improve the quality of its questions. The pilot
also enabled the researcher to practice interviewing and get more familiar with the process
of asking questions and interacting with participants.

5.3.5. Study participants

5.3.5.1. Sampling

The aim was to interview doctors from different divisions in the hospital (e.g.
haematology/oncology, surgery, medicine) to compare their views and responses. In
order to obtain a comprehensive understanding and wide view on the issue of gentamicin
and vancomycin dosing, it was decided that 24 doctors should be interviewed; twelve
doctors who prescribed gentamicin (6 correct and 6 incorrect), and twelve who prescribed vancomycin (6 correct and 6 incorrect). This sample size was deemed to be appropriate for generating relevant codes and achieving data saturation based on different studies from the literature (Guest et al., 2006; Mason, 2010; Baker and Edwards, 2012). Interview invitations were sent randomly to all eligible doctors until each category (of 6 doctors) was filled.

5.3.5.2. Inclusion/exclusion criteria

Doctors who prescribed an initial treatment dose of gentamicin or vancomycin for an adult were invited to participate in the semi-structured interviews regardless of their grade, experience, department, or time of prescribing (i.e. day/night or weekday/weekend). For both drugs, doctors who prescribed a correct dose according to the Trust’s antimicrobial guidelines (King’s College Hospital NHS Foundation Trust, 2012B) as well as those who prescribed an incorrect dose were invited for an interview. Doctors who accepted the invitation within a 72-hour response window, in order to assist recall of the prescribing occasion, and had signed the consent form were interviewed and included in the study.

Doctors who did not respond, replied after more than 72 hours, or declined consent were excluded from the study. Moreover, Critical Care and Paediatric doctors were not included in the study as they had special protocols and different guidelines from those used elsewhere in the Trust (new Critical Care-specific guidelines for dosing gentamicin was implemented in the Trust on 24th September 2013, i.e. after the calculator study - Chapter 4- and before the current study). Doctors were re-invited for an interview, if they did not respond to the first invitation, and prescribed another initial dose of gentamicin or vancomycin. No doctor was interviewed twice, even if he/she prescribed gentamicin/vancomycin for another patient.

5.3.5.3. Participant identification

Potential study participants were identified prospectively from their electronic signature on the prescription on EPMA. Once an initial treatment dose of gentamicin or vancomycin was prescribed, data about the prescription were collected using the form developed for data collection in the calculator study in Chapter 4 (Appendix 4.4).
For each prescription, the dose consistency with the Trust guidelines (King’s College Hospital NHS Foundation Trust, 2012B) was assessed by comparing it to the ideal guideline-recommended dose which was calculated using the patient’s appropriate body weight and creatinine clearance. Based on its deviation from the guideline-recommended dose, each dose was categorised as correct or incorrect. The definitions used to identify incorrect doses of gentamicin and vancomycin in Chapter 4 (section 4.3.5) were also used in this study.

5.3.6. Participant recruitment process

To raise the awareness about the study and to enhance recruitment, the information email was sent to all prescribers in the Trust one week before starting the study. Due to confidentiality issues, the doctors could not be sent this email directly by the researcher. Instead, department coordinators were contacted on 4th August 2013 and asked to forward this email to the doctors in their departments. The researcher was copied into the forwarded emails. The dissemination process took 2 weeks with the last email forwarded to doctors on 18th August. Eight days later (26th August), identification and invitation of eligible doctors started by sending them the invitation email accompanied by the invitation letter and participant information leaflet. These invitation emails were personalised in order to maximise response rates (Oppenheim, 1992). The prescribers were given 72 hours to consider the invitation and to consult with others if they wished. In addition, they were encouraged during this time to contact the research team to discuss any aspect of the study and ask any questions to seek clarification if required.

Once an interview acceptance had been received, participants were contacted to arrange a suitable date and time for the interview. Doctors were asked to read and sign the consent form before the start of the interview. Interviews were arranged at an appropriate and convenient venue and lasted between 15 to 30 minutes. All interviews were audio-recorded using Sony® ICD-PX312 digital voice recorder. Written notes were taken for any information that could not be audio-recorded (e.g. discussion after the interview). The study process is shown in Figure 5.2.
Figure 5.2. A flow diagram of the study process
5.3.7. Data collection and processing

5.3.7.1. Data extraction

Twenty four semi-structured interviews with doctors were conducted between 8th October and 24th December 2013. Most interviews took place in a quiet room on the doctor’s ward or at the KCL medical school library adjoining the research Trust. Before each interview, the researcher was providing the participant with a brief explanation about the study and what to expect during the interview. Participants were asked to verbally confirm that they read the participant information leaflet and signed the consent form.

5.3.7.2. Data storage

All electronic and computer files used during this study were held on encrypted devices including computers, laptops and USB drives. Participants were assigned a unique code which was stored separately from their contact details. Only members of the research team had access to the data. Final copies of the consent forms and interview transcripts were kept in a secure filing cabinet in the Pharmacy Department at KCL. Audio-tape recordings were destroyed at the end of the study.

5.3.7.3. Data transcription

One researcher (AH) transcribed the audio-tape recordings verbatim and cross checked the transcripts against observational notes and audio recordings. To assure the accuracy of the data transcribed, another member of the research team (CW) read the transcripts and cross checked them against the audio recordings and made any needed changes.

5.3.7.4. Data analysis

Each transcript was anonymised and then subjected to thematic analysis. Analysis was supported by NVivo® version 10 and was checked by a second researcher (CW) in order to verify the outcomes. Central to this level of analysis was the process of coding the transcripts by extracting relevant sections of text, such as specific words, phrases and sentences and assigning them into different codes or labels. An example of the coding process is presented in Appendix 5.6. Links between the information and ideas within these codes were then identified and grouped to create common themes and patterns.
5.4.  Results

5.4.1.  Study participants

A total of 140 interview invitations were sent to 102 doctors. Of these, 19 doctors were sent 2 invitations, 8 were sent 3 invitations, and 1 was sent 4 invitations. Seventy-three invitations were regarding vancomycin (52.1%) while 67 were regarding gentamicin (47.9%). There was a response for 34 (24.3%) invitations sent by 32 (31.4%) doctors (2 doctors rejected the first invitation and accepted the second). Twenty-four invitations were accepted (17.1%) and 10 were rejected (7.1%). There was no response for the other 106 (75.7%) invitations. The 24 interviews were conducted with 12 doctors who prescribed an initial gentamicin dose (6 correct & 6 incorrect) and 12 doctors who prescribed an initial vancomycin dose (6 correct & 6 incorrect). The average time of the interview was 20min 59sec; 19min 50sec with gentamicin prescribers (range 16min 11sec – 29min 21sec) and 22min 09sec with vancomycin prescribers (range 18min 40sec – 29min 54sec).

General Medicine (n=6) and Haematology (n=5) were the specialties from which most doctors were interviewed, and it was found they all used the Trust dosing tools. The overall experience of the participants varied from 3 months to 14 years with grades ranging from Foundation Year 1 doctors to Consultants. Eighteen doctors had previous experience at other hospitals, including two who worked overseas (one in New Zealand & one in South Africa). It was noticeable that most doctors interviewed (8 prescribed gentamicin & 10 prescribed vancomycin) were new to King’s College Hospital (i.e. ≤6 months). The rate of doctors’ prescribing of gentamicin and vancomycin varied from their first time to everyday. Tables 5.2 and 5.3 provide detailed information about doctors and their dosing accuracy.

Doctors who used the dosing tools available in the Trust (i.e. antimicrobial guidelines and online dose calculators) were more likely to prescribe a correct dose of gentamicin or vancomycin. Eleven of the 18 doctors who used the Trust dosing tools (61.1%) prescribed a correct doses (5 for gentamicin & 6 for vancomycin) compared to only 1 of the 6 doctors who did not (16.7%). However, seven doctors (3 prescribed gentamicin & 4 prescribed vancomycin) prescribed an incorrect dose despite using the Trust dosing tools. This was due to inaccurate use of these tools (e.g. technical error, lack of knowledge about some features) or using of wrong/inaccurate patient primary data (see section 5.4.6.2).
### Table 5.2. Demographics of the participant doctors and their dosing accuracy

<table>
<thead>
<tr>
<th>Category</th>
<th>Total no. of doctors</th>
<th>Gentamicin correct (n)</th>
<th>Gentamicin incorrect (n)</th>
<th>Vancomycin correct (n)</th>
<th>Vancomycin incorrect (n)</th>
<th>Total correct (n)</th>
<th>Total incorrect (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FY1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>FY2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>CT1</td>
<td>5</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>CT2</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>SHO</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>JCF</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Registrar</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Consultant</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Specialty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haem/Oncology</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>General Medicine</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Acute Medicine</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary Medicine</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>General Surgery</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Trauma &amp; Orthopaedics</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiology</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Obstetrics/Gynaecology</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Neurology</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes &amp; Endocrine</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Overall experience</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>7 months – 2 years</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2 years – 5 years</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Experience at King’s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>18</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>7 months – 2 years</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2 years – 5 years</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

FY: Foundation Year; CT: Core Training; SHO: Senior House Officer; JCF: Junior Clinical Fellow.
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

Table 5.3. Rates of drug prescribing, usage of Trust dosing tools, and dose accuracy by the participant doctors

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of doctors</th>
<th>Correct (n)</th>
<th>Incorrect (n)</th>
<th>Trust tools used (n)</th>
<th>Trust tools not used (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate of gentamicin prescribing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ once a day</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>≥ once a week</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>≥ once a month</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Every 2-3 months</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rarely</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Never</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>Rate of vancomycin prescribing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ once a day</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ once a week</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>≥ once a month</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Every 2-3 months</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Rarely</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Never</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td><strong>Used the Trust dosing tools</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18*</td>
<td>11#</td>
<td>7^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 13 used the calculators & 5 used the guidelines
# 8 used the calculators & 3 used the guidelines
^ 5 used the calculators & 2 used the guidelines

5.4.2. Interview results

Four themes were identified from the analysis of interviews. The first theme consisted of 7 codes and included information on the resources and methods doctors used to prescribe gentamicin and vancomycin initial doses. Doctors’ knowledge of the dose calculation background and dosing tools available in the Trust were also covered in this theme. The second theme involved 4 codes and covered doctors’ knowledge of the drug main toxicities and therapy monitoring. The third theme consisted of 4 codes about the doctors’ working conditions and the factors they consider influenced their dosing decisions. The fourth theme comprised of 4 codes which focused on the doctors’ views about the Trust dosing tools and potential risks and solutions of DEs with gentamicin and vancomycin. Table 5.4 shows how these themes were created from the identified codes.
Table 5.4. The process of creating research themes out of the identified codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource or method used to calculate initial dose</td>
<td>Dose calculation resources</td>
</tr>
<tr>
<td>Knowledge of dose calculation data</td>
<td></td>
</tr>
<tr>
<td>The decision process for drug prescribing</td>
<td></td>
</tr>
<tr>
<td>Knowledge of other dosing resources</td>
<td></td>
</tr>
<tr>
<td>Knowledge about if other doctors use the same resources</td>
<td></td>
</tr>
<tr>
<td>Awareness of the Trust dosing tools</td>
<td></td>
</tr>
<tr>
<td>Reuse of resource/method on future prescribing occasions</td>
<td></td>
</tr>
<tr>
<td>Knowledge of the drug main toxicities</td>
<td>Therapy monitoring</td>
</tr>
<tr>
<td>Drug toxicity monitoring</td>
<td></td>
</tr>
<tr>
<td>Monitoring of therapeutic effect</td>
<td></td>
</tr>
<tr>
<td>Additional measures or assessments undertaken when prescribing</td>
<td></td>
</tr>
<tr>
<td>Work environment</td>
<td>Conditions and factors that might affect dose prescribing decision</td>
</tr>
<tr>
<td>Workload</td>
<td></td>
</tr>
<tr>
<td>Doctor’s feeling upon prescribing</td>
<td></td>
</tr>
<tr>
<td>Factors with potential effect on prescribing decision</td>
<td></td>
</tr>
<tr>
<td>Participant opinions of the Trust dosing tools</td>
<td>Doctor views and opinions about drug dosing</td>
</tr>
<tr>
<td>Explanation for incorrect doses</td>
<td></td>
</tr>
<tr>
<td>Possible sources of dosing errors</td>
<td></td>
</tr>
<tr>
<td>Recommendations to improve dosing</td>
<td></td>
</tr>
</tbody>
</table>

5.4.3. Dose calculation resources

5.4.3.1. Resource or method used to calculate initial dose

Gentamicin and vancomycin have the same prescribing process and require the same data for dose calculation. Doctors were asked to describe the process in which they prescribed the dose discussed. Most doctors used the Trust dosing tools (8 prescribed gentamicin & 10 prescribed vancomycin) to obtain the required dose. These tools included the antimicrobial guidelines, either the online or booklet form (used by 5 doctors who all prescribed vancomycin), and the online dose calculators (used by 13 doctors; 8 prescribed gentamicin & 5 prescribed vancomycin). A doctor who used the online guidelines described the process in which she prescribed a vancomycin dose;

“So I used the antimicrobial guidelines on EPR or Kwiki (Trust internal system). And based on his weight... yes I calculated the loading dose, and then based on his
creatinine clearance, I calculated his maintenance dose.” (Participant 19, vancomycin, correct)

Another doctor who prescribed a vancomycin dose using the guidelines booklet said the following to describe the process he used to obtain the dose:

“So I carry the Trust antimicrobial prescribing policy in my pocket. So I tend to always refer to it if I’ve got started antibiotics and I’m at all unsure about what to prescribe or on what dose. I literally refer to the policy and it said that the vancomycin loading dose is what it should be according to weight. So, I found out the weight of the patient. That’s often is a regular missing step, just getting the nurses to weigh the patient because sometimes it isn’t always very easy to do, and I think that looking at this the patient must have weighed between 60 and 90 kilograms, so I chose that dose, and then based on the age and the weight, that could calculated using that equation, the creatinine clearance and therefore the maintenance dose.” (Participant 3, vancomycin, incorrect)

The online dose calculators was the tool most used by participants to prescribe gentamicin and vancomycin doses. Below are examples of the dosing process described by participants who used the online calculators;

“So uhm I know that we have the calculator that is used on EPR. EPR Well, basically I went to Internet Explorer on King’s Kwiki Web. And if you type in antimicrobial guidelines you go to that section and it has got a calculator uhm for vancomycin (gentamicin) prescribing. And you just type in all the information; so patient’s weight, uhm creatinine, uhm height and age, and it gives you uhm the clearance level and then from that it gives you the dose you need. And then it just goes to the next page on the calculator it told me what dose I need to give for the first dose and the second dose.” (Participant 2, gentamicin, correct)

“Yeah. I don’t know whether you’ve seen it. So on the EPR, there is a section within the intranet, is ah it calculates the creatinine clearance for you and then with the creatinine clearance, it comes up with an Excel spreadsheet. Then on the next tab, it then comes up with the dose that you are supposed to use.” (Participant 11, gentamicin, correct)
“I searched on the intranet for the vancomycin prescribing tool and tried to work out the patient’s creatinine clearance, and then went onto the next tab along which is on the Excel spreadsheet and calculated the dose of vancomycin using that.”

(Participant 9, vancomycin, correct)

Two doctors compared the dose they obtained via the calculator against the Trust guidelines. For example;

“The vancomycin calculator online which I have used a lot before. So I used that and then I just checked it with the pocket guide which is sort of a rough estimation of doses and it matched up. So I thought that must be right. So I prescribed it then.”

(Participant 5, vancomycin, correct)

Four doctors, all of whom had more than 2 years’ experience of prescribing gentamicin (n=3) or vancomycin (n=1) did so without using any dosing resources. They prescribed based on previous experience or routine practice. Only one of these doctors prescribed a correct dose. Examples below;

“It’s a stat dose for the neutropenic sepsis, so it’s like 5 mg per kg. It’s according to her body weight I think, so multiply by 5 her body weight. This is stat dose, so I think it’s 2, I don’t know... 260 mg prescribed.” (Participant 6, gentamicin, correct)

“It was in my head. That was the method. I’m pretty sure, I’m pretty much aware that I think that the starting dose is I think 15 mg per kg, but I opted for 10 mg per kg dose for him or 11, I think it was into it, so something that I have used before.” (Participant 24, vancomycin, incorrect)

In addition, three doctors prescribed incorrect doses based on the dose they reported as being obtained from Microbiology advice;

“I was worried about the patient because she was sick and had a white cell count of 18 so I contacted Microbiology and explained that I thought the source of infection was probably the urine. Uhm they advised me to try and get a urine sample which we were unable to because she had very low urine output so they suggested I prescribe a stat dose of gentamicin followed by trimethoprim 200 mg bd. And he gave me the dosing as 3 mg/kg to use.” (Participant 15, gentamicin, incorrect)
5.4.3.2. Knowledge of dose calculation data

5.4.3.2.1. Primary patient data needed for dose calculation

The primary data needed for dose calculation were the patient gender, age, weight, height, and serum creatinine. Seven doctors (all used the calculators) were familiar with all of these data and used them to prescribe a correct dose;

“It’s essentially creatinine clearance of which you needed height, weight, age. That’s what you enter, what the calculator actually told me to put in. I think those are the ones... and creatinine, serum creatinine.” (Participant 8, vancomycin, correct)

“So whether they’re male or female, their age, their height, their weight, so their body weight, then their creatinine clearance.” (Participant 11, gentamicin, correct)

However, it was identified that although some doctors (n=5) prescribed a correct dose they omitted, during the interview, essential data needed to calculate this dose (e.g. age, height). Three of these doctors used the Trust guidelines without using the height. For example:

“We look at the renal function. If the renal function is normal, just weight, 5 mg per kg.” (Participant 6, gentamicin, correct)

“Weight, creatinine levels, it depends, and uhm age and uh then I don’t know.” (Participant 18, vancomycin, correct)

Four doctors prescribed an incorrect dose, although during the interview they described all the data required for this dose calculation. All of these doctors prescribed using the calculators, but they reported technical issues using them (details in section 5.4.6.2);

“Let me see age, weight, height, creatinine. So that thing worked out your eGFR based on the Cockcroft uh Gault” (Participant 16, gentamicin, incorrect)

“So there was the vancomycin calculator and you had to put in, I don’t know, the age, the height, the weight, all the details of the patient and their creatinine concentration and then it gave you the creatinine clearance and then on EPR when you... Ah you go according to that then.” (Participant 20, vancomycin, incorrect)
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

As illustrated below, other doctors (n=8) were unable to describe the exact data needed and calculated an incorrect dose. Only 3 of these used the Trust dosing tools;

“Oh yeah. You’re prescribing based on weight, based on renal function.” (Participant 7, vancomycin, incorrect)

“No, that was it, just weight and then the value that the microbiologist had already told me.” (Participant 15, gentamicin, incorrect)

5.4.3.2.2. Source of weight and height

As illustrated below, many doctors (10 prescribed gentamicin & 4 prescribed vancomycin) easily retrieved the patient weight from different sources, mainly the bedside medical notes and electronic patient records (EPR). Half of these doctors prescribed a correct dose (n=7);

“So 2 ways sometimes on EPR, but most often it is not recorded on EPR so you have to ring the ward and check because they always do weight for the patient and record it in the notes.” (Participant 2, gentamicin, correct)

“Uh from the admission or um from the paper charts on the patients because patients need to be weighed on admission and all over. Uhm so I take their weight from there.” (Participant 18, vancomycin, correct)

Six doctors, of whom 5 prescribed vancomycin, asked a nurse to weigh the patient at the time of prescribing while 2 others asked the patient for his/her weight;

“I asked the nurse to weigh the patient just before the prescription of gentamicin because she didn’t have any record of her weight since she was admitted. Normally, you can get the weight from the clinical notes of the patient that are at the end of the bed” (Participant 13, gentamicin, correct)

“I get the weight from the ward so there and then. So, I ask the nurse to weigh them in a wheelchair scale. It’s a sitting-down scale.” (Participant 21, vancomycin, incorrect)

“I asked him what his weight was and he was quite clear it was, I believe, 96.2 although I might be wrong. It’s written in the notes, I think. Because he was so
adamant that that was his precise weight and he’s been weighed recently, I believed him. He looked reasonable as well. He did look like over 90 kilos.” (Participant 8, vancomycin, correct)

However, obtaining the patient height appeared to be harder for some doctors including three who believed it is not usually documented. In all cases they prescribed an incorrect dose;

“So he told me his height. I'm not sure if there's a facility to measure height in the ward.” (Participant 1, gentamicin, incorrect)

“We don’t have the height in hospital.” (Participant 10, gentamicin, incorrect)

“I don’t use the calculator because you need the height and I never had the height of the patient.” (Participant 21, vancomycin, incorrect)

However, some doctors (n=4) mentioned they were able to find the height recorded in patient notes or on EPR;

“So I believe I got the height and weight from uhm EPR documentation, from the nurses’ ward round... They document the weight regularly, and I would have taken the height from his uhm initial... booking in... Under Patient Information, there’s a height and weight.” (Participant 12, gentamicin, correct)

“It’s normally on EPR. So on the patient info section, there’s a height and weight bit, and I normally just check the date line, to make sure that it’s relatively recent” (Participant 4, gentamicin, correct)

Estimation of patient weight and height was also used by one doctor who was unable to find recent measurements and needed to give the dose immediately;

“We had to guess her height uhm and sort of guess her weight as well because she didn't have an up-to-date height and weight. And because she was septic, I didn’t want to wait and she was unwell, I didn’t want to wait for the nursing staff to do her height and weight that morning.” (Participant 9, vancomycin, correct)
5.4.3.2.3.Actual or ideal body weight

Doctors were asked whether actual or ideal body weight was used in the dose calculation. In accordance with the Trust guidelines (King’s College Hospital NHS Foundation Trust, 2012B), actual body weight should be used for vancomycin loading doses. Ideal body weight should be used for gentamicin and vancomycin maintenance doses, unless the patient was underweight when actual weight should be used. If there was a greater than 20% difference between actual and ideal then the adjusted weight should be used. As illustrated below, most doctors (8 prescribed gentamicin & 10 prescribed vancomycin), regardless of their dosing accuracy (9 correct & 9 incorrect), did not know or were not sure which weight was or should be used for dosing:

“I used his actual weight, I did think about his ideal body weight but I had no clue how to calculate that.” (Participant 10, gentamicin, incorrect)

“I think on the thing (guidelines) it says the actual body weight, but you can calculate it using the ideal body weight as well.” (Participant 19, vancomycin, correct)

“Ah ha I think it’s the ideal body weight usually but in this case I think I just used the actual, I’m not sure. I think I usually to go with the actual.” (Participant 20, vancomycin, incorrect)

Four doctors, of whom 3 prescribed an incorrect dose, thought that ideal body weight should only be used for underweight or overweight/obese patients;

“I used his actual body weight because he was moderately sized. I didn't feel that he was particularly overweight, so I used his actual body weight.” (Participant 1, gentamicin, incorrect)

“The actual weight, but to me he looked the right weight for his age and height. He didn’t look under or overweight particularly.” (Participant 23, vancomycin, correct)

Six doctors who prescribed a correct dose (3 for gentamicin & 3 for vancomycin) using the calculators explained they used the actual weight without realising that the calculator automatically identifies the appropriate weight (i.e. actual, ideal, or adjusted) to be used;
“Ah to calculate the dose, the actual body weight.” (Participant 13, gentamicin, correct)

“For this chap it was the actual body weight, his actual weight because he’d lost a bit of weight since he had come into the hospital. So what do you mean by ideal weight?” (Participant 5, vancomycin, correct)

“I’ve been going with actual body weight. I’m not sure if that’s correct.” (Participant 8, vancomycin, correct)

“Normally I use the, I think, it’s actual body weight rather than ideal. I don’t use ideal. I think it says actual. Yeah, because there’s no method of calculating the ideal body weight on that tool.” (Participant 9, vancomycin, correct)

However 3 prescribers, all of whom prescribed correct doses of gentamicin, knew which weight should be used for dosing:

“I know it’s meant to be based on ideal body weight, rather than actual body. There, obviously, with very skinny or very obese patients, the ideal body isn’t necessarily accurate for the patients in question… Yeah, it gives you an adjusted weight, which, that seems to be between their ideal body weight and their actual body weight” (Participant 4, gentamicin, correct)

5.4.3.3. The decision process for drug prescribing

It was noted that many doctors (n=15) reported prescribing the drug based on recommendations from Microbiology or other specialist teams. This was reported more by vancomycin prescribers (n=10) compared to gentamicin prescribers (n=5). However, it did not affect the dose accuracy (7 correct & 8 incorrect) as in most cases only the choice but not the dose was recommended (n=12), as illustrated below;

“Okay so basically the gentleman needed uhm gentamicin as a stat dose we've discussed this with Microbiology and they had advised us to give him that on top of the antibiotic that he was already on... Micro just tells you what to give they don't calculate the dose for you.” (Participant 10, gentamicin, incorrect)

“Uhh well yes the fact I prescribed vancomycin was because that was a decision by the diabetic foot consultant and Microbiology... Because it’s complicated for
them to work out (the dose) so they hand that over to the junior doctors to do” (Participant 21, vancomycin, incorrect)

In addition, 5 doctors, all of whom prescribed gentamicin (3 correct & 2 incorrect), based their decision on the Trust guidelines;

“The urine came back as having stuff in it, like when the nurses dipped it had stuff in it. She then had this really high temperature of 39 plus, so I changed it according to the guidelines to Tazocin plus gent.” (Participant 11, gentamicin, correct)

Four doctors took the decision to prescribe gentamicin or vancomycin alone. Two of these doctors were senior doctors (consultant & specialist registrar) and 2 had a number of years of experience (4 years & 3.5 years). However, these characteristics of seniority and experience did not appear to relate to dose accuracy (2 correct & 2 incorrect);

“No it was my decision... She had a UTI and uhm was sick. She had a catheter. Uhm catheter in situ she's at reasonably high risk for becoming quite unwell for it so a single dose of gentamicin followed by an oral course is reasonably standard thing to do in that situation.” (Participant 17, gentamicin, incorrect)

“Yes, so she'd previously grown (bacteria), it was a groin abscess. She'd previously had a recent admission with the same thing on the other side and had temperature that had only settled with vancomycin.” (Participant 9, vancomycin, correct)

5.4.3.4. Knowledge of other dosing resources

Participants were asked whether they knew any resource available to them to assist dosing gentamicin or vancomycin other than the one they had used. Apart from the guidelines and calculators, doctors mentioned primarily two other resources. Of the 19 doctors who identified these resources, 15 used the Trust dosing tools. The first source was the BNF which was identified by 9 doctors, all of whom prescribed a correct dose (5 for gentamicin & 4 for vancomycin);

“Well in case I don’t have obviously the adult pocket guidelines for antibiotic prescription or the website, I’m going on BNF. So I use the BNF.” (Participant 13, gentamicin, correct)
“Yeah I mean there is the eBNF which is on EPMA and the BNF there are usually a few hard copies of the BNF around the wards.” (Participant 5, vancomycin, correct)

The second source identified by 17 doctors (8 prescribed gentamicin & 9 prescribed vancomycin) was other healthcare staff, particularly pharmacists (16/17) and microbiologists (6/17). Of these doctors, 11 prescribed a correct dose (including 7 who also mentioned the BNF) and 6 an incorrect dose;

“Well I ... If I was particularly troubled I could phone pharmacy for advice, but I just go by the calculator.” (Participant 12, gentamicin, correct)

“Apart from the online tools we mentioned already, no I’m not aware of anything else. Well you can call the microbiologist they can give some advice, or the pharmacist.” (Participant 21, vancomycin, incorrect)

However, some doctors cited the unavailability of ward pharmacists during out-of-hours shifts, but commented that they can contact the on-call pharmacist if needed;

“So if it was a day shift uhm I would ask the pharmacist on the ward to help me. I know there is an on-call pharmacist, uhm so if you were really stuck you could contact them.” (Participant 22, vancomycin, incorrect)

5.4.3.5. Knowledge about if other doctors use the same resources

Although a number of doctors stated that they do not know what resources other doctors used and have never spoken about this with their colleagues, most doctors (9 prescribed gentamicin & 9 prescribed vancomycin) commented that the resource or method they used was commonly used across the department or ward where they worked. There was no difference in this view between doctors who prescribed a correct dose (n=10) and those who prescribed an incorrect dose (n=8);

“Yeah I think they do because this calculator exists here; they use it quite a lot.” (Participant 11, gentamicin, correct)

“Yeah. We always use the, for the gentamicin we all use the same checker (calculator)” (Participant 14, gentamicin, incorrect)
“I think everyone would just prescribe 5 mg per kilogram.” (Participant 17, gentamicin, incorrect)

“As far as I’m aware, yes. That’s (the calculator) what we were told to use.” (Participant 20, vancomycin, incorrect)

“Yeah, I think most of them use the guidelines, but they’re probably... A lot of people don’t carry it with them and they use a kind of, you can get a PDF online, so I think most people use that instead.” (Participant 23, vancomycin, correct)

The three most experienced doctors (1 consultant & 2 registrars) were among those who believed the source they used was common across their units;

“Most people would normally do the weight times thing and give the drug, yeah, particularly in the acute setting.” (Participant 10, gentamicin, incorrect)

“I think so. Yes. Certainly because I asked my SHO how to do it before she headed off and that’s what she told me. And certainly (the pharmacist) includes it, has showed us as part of our... when we do the chemotherapy prescribing course, she includes the... shows us where the calculator is as part of the induction and I know the nursing staff double-check it as well using the dose calculator too.” (Participant 9, vancomycin, correct)

5.4.3.6. Awareness of the Trust dosing tools

Doctors who used the Trust dosing tools (i.e. guidelines and calculators) were asked how they knew about these tools. Some doctors were made aware of them during their local or Trust induction programmes;

“When we do the chemotherapy prescribing course, she (the pharmacist) includes the... shows us where the calculator is as part of the induction.” (Participant 9, vancomycin, correct)

“That is part of my (Trust) induction... As an F1, they tell you about the guidelines... They give us the handbook as well. The same pocket guideline that is on the intranet, yeah.” (Participant 19, vancomycin, correct)
“From the pharmacy when we had our (local) induction. The pharmacist, that’s what they advised us to use.” (Participant 20, vancomycin, incorrect)

Other doctors knew about them from other staff such as pharmacists or fellow doctors;

“So the pharmacists are very helpful and do point out the tools.” (Participant 1, gentamicin, incorrect)

While others found the tools themselves by searching the Trust intranet;

“Uhm, when I referred to the King’s guidance on antibiotics before, I’ve seen it below so I knew that it was there.” (Participant 2, gentamicin, correct)

“I just assumed that there would be one there, in my previous Trust there was guidelines on the intranet uhm and so I assumed that there would be one here and there was.” (Participant 22, vancomycin, incorrect)

5.4.3.7. Reuse of resource/method on future prescribing occasions

Most doctors (n=19) stated that they would use the same dosing source for any other patient requiring gentamicin or vancomycin. This included all doctors (n=12) who prescribed a correct dose and 7 who prescribed an incorrect dose. This assertion was the same regardless if the doctor prescribed using the Trust dosing tools (15/18) or not (4/6). Examples;

“Yeah, I think while I was at King’s I’d continue to use the calculator” (Participant 4, gentamicin, correct)

“Uhm yeah that's the method I use, yeah, I would weigh them (and multiply it) and then I'd also check their renal function.” (Participant 10, gentamicin, incorrect)

“I’d use this (pocket guidelines) again.” (Participant 3, vancomycin, incorrect)

“Yeah, so I think... I like the antimicrobial guide (pocket) that we’re given.” (Participant 23, vancomycin, correct)
Nevertheless, five doctors who all prescribed an incorrect dose (of whom 4 prescribed vancomycin) mentioned that they would adjust their prescribing method to avoid similar errors in the future. For example, a doctor who prescribed an incorrect dose based on actual body weight having assumed that patient height was always not available explained;

“Well I’ll probably try and find the height if I overprescribe if that’s important unless I just made a mistake, which I could well have done, because vancomycin is sort of... is quite common one I think we often misprescribe... Well I’ll probably be more active in using the calculator on Kwiki.” (Participant 21, vancomycin, incorrect)

Another doctor who prescribed an incorrect 3mg/kg dose which they explained was on the advice of Microbiology stated;

“No. so I just followed what he said this time because that’s the advice he gave me on the phone. Uhm if I have just been told to start gentamicin I would use the guidelines obviously and try to work out the right dose, but I presumed that the Microbiology registrar would tell me the right dose to give which clearly wasn’t in this case.” (Participant 15, gentamicin, incorrect)

5.4.4. Therapy monitoring

5.4.4.1. Knowledge of the drug main toxicities

During the interviews, doctors were asked about the main toxicities they considered when prescribing gentamicin or vancomycin. Only one doctor, who prescribed a correct dose of vancomycin, did not know about any toxicity for either drug. Several doctors, including all who prescribed gentamicin, identified the two main toxicities of this drug (nephrotoxicity and ototoxicity) as described below;

“Renal toxicity, they can worsen renal function and if you are overdosing a patient, they're at risk of ototoxicity and deafness.” (Participant 1, gentamicin, incorrect)

Many doctors, including 11/12 who prescribed vancomycin, said they would assess vancomycin nephrotoxicity;
“So I just know that it’s very nephrotoxic, and that’s why we have to be so careful about the levels and also dosing it depending on creatinine clearance.” (Participant 23, vancomycin, correct)

Only 3 vancomycin prescribers hesitantly stated that it is ototoxic;

“It’s not ototoxic is it? I’m not sure. I know gentamicin is ototoxic but with vancomycin I’m not sure.” (Participant 20, vancomycin, incorrect)

Four doctors who prescribed vancomycin also mentioned Red Man Syndrome as a toxicity;

“You can obviously get Red Man Syndrome, widespread skin erythema” (Participant 9, vancomycin, correct)

“If you inject it too fast, you get the Red Man Syndrome” (Participant 24, vancomycin, incorrect)

Although a rare side-effect, two vancomycin prescribers also mentioned hepatotoxicity;

“I’m not too sure hepatic. I mean we don’t worry too much about hepatic because you just order some LFTs and if they start being deranged, you stop the drug and you can recover quite easily from that.” (Participant 7, vancomycin, incorrect)

5.4.4.2. Drug toxicity monitoring

The methods used to monitor the toxicities of gentamicin and vancomycin were assessed. Many doctors (5 prescribed gentamicin, which is mostly used as a stat dose in the Trust, and 11 prescribed vancomycin), regardless of their dosing accuracy (8 correct & 8 incorrect), identified that drug serum levels were used to monitor toxicity;

“Clinically I would order the blood test to check that the levels of the drug you are giving are correct” (Participant 2, gentamicin, correct)

“Uhm you have to do levels I think the trough levels prior to the next dose, yeah so they're scheduled.” (Participant 10, gentamicin, incorrect)
“You’re also going to measure levels after every third or fourth dose to ensure that it’s within the normal range so that you’re not underdosing or overdosing.” (Participant 3, vancomycin, incorrect)

“So you do a trough level every, well, before the third dose. Some regimes do it after/ before, but yeah, you do trough levels to make sure that they’re not becoming toxic.” (Participant 19, vancomycin, correct)

All doctors in the study (n=24) explained that they monitored drug nephrotoxicity for these drugs using blood tests (i.e. urea and electrolytes);

“Look at symptoms and check the renal function. If the renal function is going up and that’s the only thing you are giving then it's probably because of that.” (Participant 16, gentamicin, incorrect)

“So the Us&Es looking at the creatinine and the urea.” (Participant 23, vancomycin, correct)

In addition, some doctors (4 prescribed gentamicin & 3 prescribed vancomycin) suggested that gentamicin ototoxicity can be monitored by asking patients to report any hearing problems or by doing hearing tests. Only 2 of these prescribed a correct dose;

“I don’t know how you would routinely go about testing it. In any way, I would’ve been asking the patients to report subjective hearing loss. Then, just to investigate it if they do. So you know kind of performed assessment of hearing loss and if necessary, refer them to ENT to have formal assessments” (Participant 4, gentamicin, correct)

5.4.4.3. Monitoring of therapeutic effect

Doctors described different ways of monitoring the drug therapeutic effect. Nine doctors (4 prescribed gentamicin & 5 prescribed vancomycin) stated checking drug serum levels and making sure they are within the therapeutic range, which is a specific measure with gentamicin and vancomycin treatment, as a method of monitoring the therapeutic effect. Of which, 6 prescribed a correct dose;

“You need to do levels, so between 15 and 20 as a target... So you want to make sure they’re within a therapeutic range and increase or decrease as appropriate to
make sure they've got sufficient levels for it to be therapeutic.” (Participant 9, vancomycin, correct)

“I mean I guess number one, you check that obviously the levels are actually within the therapeutic range, they're not over.” (Participant 10, gentamicin, incorrect)

Doctors mentioned other ways which were specific to antibiotics. One way mentioned by most doctors (9 prescribed gentamicin & 9 prescribed vancomycin) was monitoring inflammatory markers including white cell count and C-reactive protein (CRP). Half of these doctors (n=9) prescribed a correct dose. Some examples:

“I guess clinically if the patient seems to be improving. Uhm I guess if there are inflammatory markers are improving so if CRP is coming down, white cells coming down then they’re probably responding to the antibiotic.” (Participant 15, gentamicin, incorrect)

“So you see the inflammatory markers. You see are they responding to it? If their ESR, CRP, white cell count, those parameters are improving.” (Participant 20, vancomycin, incorrect)

Two doctors mentioned checking bacterial blood cultures;

“Also look for things like fever settling, uhm negative blood cultures, or uhm reducing CRP.” (Participant 9, vancomycin, correct)

“Uhm the other thing is obviously, if you do culture an organism” (Participant 10, gentamicin, incorrect)

Another approach described by most doctors (9 prescribed gentamicin & 10 prescribed vancomycin) was monitoring the patient clinical response. Nine of these doctors prescribed a correct dose. For example;

“If you’re giving it for urosepsis, are their observations getting better? Are their symptoms resolving? Is their urine looking clearer if it was turbid and virulent? So obviously, clinically assessing the patient to see if their infection is improving.” (Participant 4, gentamicin, correct)
“If the patient was clinically septic with an infection, you want to make sure that they haven’t got a temperature anymore, that their observations are stable so their blood pressure is stable uhm and just that they probably will appear and feel more well.” (Participant 23, vancomycin, correct)

5.4.4.4. Additional measures or assessments undertaken when prescribing

Doctors were asked about any extra measures or assessments they undertook which were specific to the prescribing of gentamicin or vancomycin. All doctors (n=24) identified checking patient parameters, especially renal function, as an important measure when prescribing these drugs;

“I try and look at their renal function beforehand and I know I have to do creatinine clearance, uhm so I know how to calculate that and I need to know their age and their weight.” (Participant 15, gentamicin, incorrect)

“Oh yeah I would be pretty clear about their weight and the creatinine clearance. I rarely check those when I'm prescribing other antibiotics or drugs.” (Participant 5, vancomycin, correct)

Eight doctors (3 prescribed gentamicin & 5 prescribed vancomycin) addressed the importance of checking the patient’s previous allergies, although some stated that this is not specific to gentamicin or vancomycin. Only 2 of these doctors prescribed a correct dose;

“Just the renal function and any allergy, that’s it.” (Participant 6, gentamicin, correct)

“Obviously check if they're allergic but that’s not special.” (Participant 21, vancomycin, incorrect)

Some doctors (n=7) explained they had concerns if the patient had any condition which could become worse if they received gentamicin or vancomycin (3 correct & 4 incorrect), e.g. poor renal function or hearing problems;

“You'd think a little bit about their hearing and whether they've got any hearing problems because, obviously you know, they’d be at increased risk of having more ototoxicity.” (Participant 1, gentamicin, incorrect)
“Aside from what their renal function is at the beginning, I’ve had patients with previous gentamicin toxicity who I’ve been wary of giving it to. So ototoxicity, balance induced issues and so we’ve been more wary. So I guess past medical history of the patient your prescribing for.” (Participant 8, vancomycin, correct)

“The only I suppose thing they count for is if they have renal failure or not and if their renal functions are down then... some of the patients are on dialysis and they get vancomycin at dialysis.” (Participant 24, vancomycin, incorrect)

Seven doctors, including 5 who prescribed a correct dose, said that confirming with Microbiology was part of the process they usually undertook before giving these drugs (3 for gentamicin and 2 for vancomycin);

“And uhm normally, honestly I always, before prescribing vancomycin (gentamicin), I always seek advice from Microbiology.” (Participant 13, gentamicin, correct)

“Yeah I might want to speak to Microbiology and consider their renal function.” (Participant 23, vancomycin, correct)

5.4.5. Conditions and factors that might affect dose prescribing decision

5.4.5.1. Working conditions

Doctors were requested to describe the working conditions in which they prescribed gentamicin or vancomycin. First, the ward environment at the time of dose prescribing was investigated. Several doctors described the ward environment as calm, quiet or not busy on the time of prescribing. Some doctors did not prescribe the drugs on the ward. They instead prescribed from their offices (on other wards). Though, they confirmed they saw the patients on the same day during the ward round. A number of doctors prescribed on busy wards. Several doctors linked the ward busyness to the time of the day or week and some linked it to the unit they were working at. However, these differences in ward environment did not appear to affect whether doctors prescribe a correct or incorrect dose.

The workload on the day of prescribing was explored with the doctors. Many doctors, particularly juniors working on weekends or evenings/nights, explained the high load
during their shifts and how many wards/patients they had to cover. Many of them mentioned they were the only doctors on the ward which increased the workload, however they said they could get support (via bleep or phone) from senior doctors if needed. Some doctors who worked during the normal hours seemed to have less workload. However, this did not seem to affect the accuracy of prescribed doses.

The participating doctors were asked about how they felt while prescribing the drug. Many doctors said they felt relaxed and were not stressed when prescribing. Some doctors expressed feeling confident while prescribing because they used the dose calculators. Conversely, other doctors were tired or stressed during prescribing. However, the different feelings upon prescribing described by participants were not related to their dosing accuracy. Table 5.5 includes details about the number of doctors who described each of these conditions with examples of these descriptions.
Table 5.5. The working conditions described by study participants when prescribed gentamicin and vancomycin

<table>
<thead>
<tr>
<th>Category</th>
<th>Doctors (n)</th>
<th>Correct (n)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work environment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calm</td>
<td>11</td>
<td>6</td>
<td>“It was reasonably calm, actually. It wasn’t particularly busy. Uhm, we’ve got quite good office space so you can go into the office and figure things out, away from the patient where it’s a bit calmer and easier to think things through. It wasn’t too busy.” (Participant 1, gentamicin, incorrect)</td>
</tr>
<tr>
<td>Busy</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>linked to time of the day</td>
<td></td>
<td></td>
<td>“It was quite busy because it was uhm the morning and was during the ward round.” (Participant 18, vancomycin, correct)</td>
</tr>
<tr>
<td>linked to day of the week</td>
<td></td>
<td></td>
<td>“Yeah, Monday would be a hectic day. Monday is always catch up for the weekend, which is always a disaster.” (Participant 7, vancomycin, incorrect)</td>
</tr>
<tr>
<td>linked to specialty/department</td>
<td></td>
<td></td>
<td>“The usual it’s a surgical ward so it’s always busy.” (Participant 5, vancomycin, correct)</td>
</tr>
<tr>
<td>Prescribed from an office on an</td>
<td>3</td>
<td>1</td>
<td>“In the ward, I didn’t prescribe it on the ward. I did it on EPR, so I did it from my office… I saw the patient earlier in the morning, and I had to discuss with him first and then I had to come back and discuss with another of my colleagues before starting it.” (Participant 24, vancomycin, incorrect)</td>
</tr>
<tr>
<td>another ward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Workload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td>3</td>
<td>“It was the regular shift, like normal working hours… It wasn’t too busy. There wasn’t a lot going on around me.” (Participant 19, prescribed vancomycin, correct)</td>
</tr>
<tr>
<td>High</td>
<td>17</td>
<td>9</td>
<td>“There’s just one SHO that’s in the hospital for the haematology (during weekends), and there’s one registrar that’s at home but on the phone… here’s about 4 wards, so about 16 patients in each ward, and so it would probably be about 60 patients in total.” (Participant 4, gentamicin, correct)</td>
</tr>
<tr>
<td><strong>Feeling upon prescribing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/relaxed</td>
<td>12</td>
<td>6</td>
<td>I think it was the end of my shift so I was probably feeling a bit more relaxed. So I was about to finish and go home. So yeah” (Participant 21, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Stressed/tired</td>
<td>8</td>
<td>4</td>
<td>“Stressed. Because I’m not used to EPMA, (laughs) I hate EPMA. And because my SHO had been missing from the entire ward round. I’d had to use EPMA quite a lot, so I was quite stressed.” (Participant 9, vancomycin, correct)</td>
</tr>
<tr>
<td>Confident</td>
<td>2</td>
<td>2</td>
<td>“Well I wasn’t stressed and honestly, I was really confident about what I was doing just because I was reassured that I checked the dose with the calculator that it’s provided by the website.” (Participant 13, gentamicin, correct)</td>
</tr>
</tbody>
</table>

EPR: electronic patient records; EPMA: Electronic Prescribing and Medicines Administration system; Senior House Officer.
5.4.5.2. **Factors with potential effect on prescribing decision**

Doctors were asked about any other factors that they thought would influence their gentamicin or vancomycin prescribing. Many doctors (n=11) mentioned patient parameter(s) as an important factor affecting their prescribing. Seven of these prescribed a correct dose. Examples;

“So if I didn’t have access to EPR at the time or I didn’t have access to the Kwiki guidelines or didn’t have access to any of those figures that we discussed, so age, weight, creatinine, etc. that would be one of the factors that would determine my accurate dosing.” (Participant 19, vancomycin, correct)

“So the fact that the patient had poor renal function, uhm that’s what, affected the dose really. I imagine her height and weight would have would alter the dose as I had to put it in the sort of calculation, to work out the creatinine clearance, so there’re different factors which would affect it.” (Participant 22, vancomycin, incorrect)

Several doctors (n=11) identified the Trust dosing tools as the key factor affecting their dosing decisions. However, five of them did not prescribe a correct dose. The calculator recommendations was the main factor considered by 4 doctors (3 prescribed gentamicin & 1 prescribed vancomycin) when deciding the dose to be prescribed (2 correct & 2 incorrect);

“Other than hopefully applying the calculator, there's nothing that will have made me give a different dose to that.” (Participant 12, gentamicin, correct)

“I'm pretty sure I used the dose calculator. I always feel uncomfortable prescribing 300 mg anyway. I'm would've be pretty sure to use the calculator.” (Participant 16, gentamicin, incorrect)

While others (n=7) identified the Trust guidelines as the main factor affecting their dose selection, including 4 who prescribed a correct dose;

“No this is a guideline for the haematology patients. This is the first line for neutropenic sepsis, so we don’t need to think, you know, a lot about that because if the patient is neutropenic, if the patient has a temperature, we have to give it, so everybody know this.” (Participant 6, gentamicin, correct)
“I followed the protocol and that's what I would do. I know that for vancomycin and gentamicin, I'm still not so so familiar that I would just do it like that; I normally will refer to the guideline that I carry in my pocket for that reason.” (Participant 3, vancomycin, incorrect)

Five doctors, of whom 4 prescribed an incorrect dose, considered the Microbiology advice as a key factor influencing their prescribing decisions, again this was primarily regarding the drug choice not dose;

“I didn’t want to start her on anything without consulting Microbiology first because I was worried that she was very sick and could have had sepsis. So I knew I have to call Microbiology before starting on anything.” (Participant 15, gentamicin, incorrect)

“Yeah. Uh aspects. Uh the only aspect is I prescribed based on what Microbiology was suggesting.” (Participant 7, vancomycin, incorrect)

Three interviewees, all senior doctors, described considering the patient clinical condition and history before prescribing these doses;

“I mean this man was septic he was having temperatures of 38, 40, he's now got liver abscesses, we found out. So I mean this was a sick man, I wouldn't want to give him like three hundred milligram of gentamicin or whatever I don’t really think, you know. He'd been on by that time 24 hours of co-amoxiclav and had not did the best, he was a sick gentleman so I was, yes, he's a sick man. CRP was over three hundred, yes and his state stuck despite being on antibiotics.” (Participant 10, gentamicin, incorrect)

“Well I didn't want to overdose her because I know this woman and I know that she has a habit of going... her kidneys are not great. She's heavily pretreated with chemotherapy and so although her creatinine was only 46, so she had... I think probably had an eGFR of over 90. Uhm I know because she's septic, she's on meropenem, she had a stat of gentamicin already, I didn't want to give her renal toxicity... I might underestimated the amount she should have. I don't know.” (Participant 9, vancomycin, correct)
5.4.6. Doctor views and opinions about drug dosing

5.4.6.1. Participant opinions of the Trust dosing tools

A number of doctors expressed their opinion about the gentamicin and vancomycin dosing tools available in the Trust. Six doctors who used the tools (5 used them accurately obtaining a correct dose) were satisfied with them and believed they are user-friendly and easily-accessible. They said these tools made their prescribing experience much easier;

“You can access the antibiotic guidelines and the calculators fairly easily on the computer. So I tend to do it through the King's intranet system and use the tools that they use which are handy and easily accessible... I mean the tools are very available and useful and they tell you exactly what to do. They're very clear. So I think you just have to use them.” (Participant 1, gentamicin, incorrect)

“And also I think it (the calculator) gives you consistency in your dosing so, it avoids kind of human error of giving an erratic dose depending on one’s consideration. You might get one patient, but then not think about the next time you’re dosing it, so it certainly makes it too easier to use.” (Participant 4, gentamicin, correct)

“I like the antimicrobial guide (pocket) that we’re given. It’s pretty self-explain... It’s kind of explain things and it’s quite simple to use... I think the antimicrobial guide is really helpful and really accessible. As I said, you can also just get it up on any computer that you are on, so I don’t think there’s any problem with that.” (Participant 23, vancomycin, correct)

In contrast, five doctors (2 correct & 3 incorrect) did not like the online calculators (4 of whom used them to prescribe). They felt they were impractical, non-accessible, and unclear. Two doctors said the calculators made the prescribing process harder and more complicated;

“Yeah, it (the calculator) can be used, it’s just not very user-friendly. I just want a protocol. I’m used to a chart on the wall which tells you everything you need. These electronic tools are appalling and ‘faffy’ difficult to find things... It’s the drive to make everything electronic because that’s sexy at the moment, but actually, old fashioned tools and cognitive aids are much better. You go into the resource room
in A&E. You’ve got cognitive aids on the wall. You’ve got your A-list guidelines on the wall, on a piece of paper, quickly accessible. It doesn’t fall off. You don’t need to log in. You don’t need to wait for a computer... Yes, it’s accessible, but not in real life, in a busy clinical environment, inaccessible.” (Participant 7, vancomycin, incorrect)

“I think the fact that I’m just not used to using EPMA is difficult...you know I find it much easier to use a calculator duh, duh, duh and then write it on the drug chart rather than have to flip back and forth between three different screens isn’t actually any easier. It actually used to be easier when it was on the thing (paper).” (Participant 9, vancomycin, correct)

The vancomycin calculator was on 2 pages (details in section 4.3.7) which caused confusion for some prescribers. Three doctors had a bad impression of the vancomycin calculator as they considered it lacking specific features which were actually available in the second page, of which they were unaware;

“The vancomycin one (calculator) doesn't work nearly as well. It doesn't end up telling you... or recommending you a dose. It only calculates the creatinine clearance, and so then you got to do another set of measures to calculate it yourself. Unless there's another calculator online I haven't found.” (Participant 12, gentamicin, correct)

“I think so, but it’s with uh with the calculator but it’s not... I don’t think it’s very clear from the way it’s written. Like I said it doesn’t say how many doses you need and for example how you should do each one like it’s not set out very well I don’t think.” (Participant 20, vancomycin, incorrect)

5.4.6.2. Explanation for incorrect doses

Some doctors who prescribed an incorrect dose explained why they thought this had occurred. The most common reason for prescribing an incorrect dose was not considering individual patient parameters. Two doctors prescribed an overdose of gentamicin because they used weight-based dosing (5mg/kg) without considering other patient parameters. They both believed that 5mg/kg was the standard dose for any patient with a normal renal
function. One of them explained the reason for using actual instead of ideal body weight by saying:

“Okay because I have no idea where that calculator is or what your ideal body weight is. I remember thinking about it and I just thought well I'm not sure how... I don't think we know that equation I don't think many medics are given that equation of ideal body weight, we know that that's what we should probably do but we usually just go for the weight and you multiply it (by 5) and then you see what's the maximum and like okay, it's not maximum.” (Participant 10, gentamicin, incorrect)

The other doctor who based renal function assessment on electronic glomerular filtration rate (eGFR) rather than creatinine clearance (CrCl) said;

“She has a normal eGFR. Her eGFR was greater than 90. I don't know any doctor that would dose adjust in a situation where the eGFR was greater than 90 for a stat dose of gentamicin. I think everyone would just prescribe 5 mg per kilogram.” (Participant 17, gentamicin, incorrect)

In addition, two doctors who used the pocket guidelines to prescribe vancomycin prescribed a high maintenance dose after calculating the CrCl using the actual body weight. One justified this by explaining the difficulty in obtaining the patient’s height;

“Yeah I know, but why we need the height. I can’t always find the height. So... Yeah. I think the main thing is usually time because you can’t wait too long to prescribe things. Sometimes you get a weight quite easily, but... the height was there obviously but I didn’t see that.” (Participant 21, vancomycin, incorrect)

The other doctor recognised that they made a mistake when referring to the pocket guidelines during the interview;

“Okay. I kind of made a mistake there. I didn't realise that I meant to be using his ideal body weight. I used his actual body weight.” (Participant 3, vancomycin, incorrect)

Three doctors had problems with the vancomycin loading dose. One doctor who used the calculator prescribed vancomycin based on a weight that was mistakenly transcribed into
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

the nursing notes. They failed to check the operation notes or confirm with the patient and prescribed a high loading dose. When this was explained, the doctor commented;

“Yes but usually when it’s postop the patient is very drowsy, you know, and you don’t really see the patient, you know. They’re not very responsive to you... Maybe I can check to see if the weight is correct but usually you know you do just go by what’s on the bedside and the chart. Uhm so yeah, I could probably clarify that with the patient but you would still want to see the calculator and do it in the same way really because... under the time constraints that you have you can’t always check every weight and height with the patient.” (Participant 20, vancomycin, incorrect)

A doctor who did not prescribe a loading dose justified this by saying that there is no need to load a patient who is clinically stable;

“In a patient who is extensively well with a chronic long-term infection which this patient falls into that category, why would you want to take the risk of overdosing and causing acute kidney injury or ototoxicity?... If somebody was unwell, hypotensive, saggy from an operation, clear source of sepsis and you want to do a bactericidal, yes loading at that point. But in this context, I don’t see how loading falls in. I know protocol is to load, but uh... In terms of pharmacokinetics, by your 3rd dose, you’re going to reach, you’re going to be approaching steady state anyhow which is why you do dose 3 checks, don’t you? (Participant 7, vancomycin, incorrect)

Another senior doctor who prescribed a small loading dose justified this by referring to the medical history of the patient explaining that he previously experienced a neutropenic reaction to a similar antibiotic;

“This’s a private patient. He was very concerned about going back on any medications. I had to be a little careful about how I put him on, so it was a gentle loading... I’ve noticed that sometimes you can have reasonable vancomycin levels, so it’s all about checking the vancomycin level, so that is a rationale for bringing his, or putting him on a slightly suboptimal vancomycin dose because I couldn’t risk him going into a neutropenic event a week or two after. He’s done this before with teicoplanin, and he was just that hesitant to go onto anything. I don’t think
vancomycin is something that I need to start at a low dose. Antibiotics either kill or you achieve sub-therapeutic levels, but with him I’ve been extra cautious.” (Participant 24, vancomycin, incorrect)

One doctor reported prescribing a gentamicin dose based on the Microbiology advice of 3mg/kg. However, the doctor did not consider the patient parameters which made the ideal dose (according to the Trust guidelines) for this patient 3.5mg/kg. The doctor’s response was;

“Well I guess in this instance, the dose was wrong because I was told the wrong dose to give. I think my calculation was clearly correct from based on the 3 mg/kg that Microbiology suggested, but that was clearly the wrong formula. So maybe in the future I should still get this (pocket guideline) out and have a look at it but then I would presume from a specialist in the next XXX (inaudible) will give me the right answer.” (Participant 15, gentamicin, incorrect)

Some doctors (n=4) faced challenges in using the online calculators including two who prescribed an incorrect dose because of that. One doctor was unaware of the second page on the vancomycin calculator and so did not prescribe a loading dose;

“In view of sort of what you’ve brought up about the loading dose I think it would be good if there was something on the guideline (calculator) as well to sort of highlight that a little bit more. Uhm I thought that was quite easy to use.” (Participant 22, vancomycin, incorrect)

The other doctor tried to calculate the dose using the gentamicin calculator which gave ‘invalid’ as a result. After several attempts, the doctor reported consulting with Microbiology who advised a dose of 5mg/kg which resulted in the doctor prescribing an overdose;

“Well oh, I don’t know. In this case, you said that I’ve given this woman an overdose of over a 105 mg, I don’t honestly know what else I could have done because I used the checker. It didn’t give me a dose and then I consulted the microbiologist and she said, gave me a dose. So I don’t know what else could have been done. May be speak to the pharmacist, I don’t know.” (Participant 14, gentamicin, incorrect)
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

It was discovered later that the doctor was doing a technical error by not clicking on the last cell (CrCl field) on the calculator Excel® spreadsheet so it could not be counted (even if filled) and consequently the required calculations were not performed.

Two other doctors, who used the calculator, prescribed an incorrect dose for unknown reason. They both assumed it might be they entered wrong numbers into the calculator;

“Well I mean I put in the weight and everything from that day... So I don't know what could have made it go wrong unless I somehow typed in the numbers wrong or misread the numbers or... I don't know is the answer.” (Participant 16, gentamicin, incorrect)

5.4.6.3. Possible sources of dosing errors

Doctors were asked to state the aspects they thought might lead to DEs with gentamicin or vancomycin (Table 5.6). Several sources of error identified were related to the primary data needed for dosing, particularly weight and renal function. Most doctors (10 prescribed a correct dose & 8 prescribed an incorrect dose) identified the unavailability or use of old data as a possible source of error;

“A couple of things maybe the weight of the patient is not on EPR, so some doctors might not take the effort to look up the weight... and the height of the patient. Uhm maybe bloods aren’t up-to-date.” (Participant 2, gentamicin, correct)

“Uhm I guess if people didn’t have an up-to-date renal function test then you might get the wrong creatinine clearance.” (Participant 15, gentamicin, incorrect)

“Uhm not having a proper weight for the patient, using previous weights from old charts.” (Participant 8, vancomycin, correct)

Confusion between actual and ideal body weight was stated by six doctors as a possible risk factor, of whom 4 prescribed a correct dose;

“I think... if you use the patient’s weight, and you’re unaware of their height, and you’re using a natural body weight, rather than ideal body weight, then you can be over- or underdosing, considerably.” (Participant 4, gentamicin, correct)
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

“So I think the difference between actual weight and ideal weight that can be quite tricky.” (Participant 22, vancomycin, incorrect)

Time constraints was also identified by 8 doctors (of whom 7 prescribed an incorrect dose) as a possible source of error. Three of these talked about estimation of patient weight and height with high workload and lack of time. However, 5 of these doctors mentioned they did not have high workload during the discussed prescribing occasion. Examples;

“If you have a patient that's bed-bound, you know, and they're sick, then you're going to probably estimate their weight and height rather than wait three hours until a nurse can hoist them to weigh them.” (Participant 1, gentamicin, incorrect)

“So I would say if somebody is being overworked and they don't have time to do it properly with the... and they don't check the patient's weight they just 'guesstimate’ everything that would be a big error.” (Participant 5, vancomycin, correct)

Four doctors identified transcribing issues, of whom 3 prescribed an incorrect dose, such as entering wrong numbers into the calculator as a risk for DEs;

“In my experience transcription is the most common... transcription errors are the most common cause of drug error.” (Participant 9, vancomycin, correct)

“Using the calculator wrong. Uhm there's lots of sources; you could type the wrong weight in, you could type the wrong height in, you could type the wrong creatinine in, not double-checking what you’ve done” (Participant 21, vancomycin, incorrect)

Doctors mentioned error sources related to the Trust guidelines. Some doctors (n=2) recognised the difference between different hospital recommendations and the influence previous hospital guidelines may have on current prescribing;

“Uhm one of the big problems is every Trust you go to is different and everyone has different ways of doing it and ah so there's always confusion about it... The difference of dose calculations, the difference of dosing protocols and so on.” (Participant 17, gentamicin, incorrect)
“Just following what you’ve done previously might be different hospital guidelines and not looking them up in accordance with King’s guidelines.” (Participant 8, vancomycin, correct)

Others (n=2) talked about not knowing about the guidelines or the difficulty of accessing them, especially for new doctors, as sources of error;

“So I think if someone’s starting in the Trust newly, they might not know where to look up a particular resource.” (Participant 24, vancomycin, incorrect)

Two vancomycin prescribers considered out-of-hours prescribing as a factor for errors;

“In evening on-calls when people start drugs at odd times they start vancomycin in the middle of the night or a stat dose of gentamicin and don't tell anyone unless somebody checks the prescription chart, calculations get missed or trough levels get missed and blood tests get missed and don't get done.” (Participant 5, vancomycin, correct)

Following the recommendations of senior or specialist colleagues without considering patient individual parameters was identified as a possible source of error by two doctors prescribed vancomycin. One of these doctors has consulted Microbiology on the choice, but did not prescribe a loading dose of vancomycin while the other one prescribed a correct dose;

“...misinformation from Microbiology with regards to loading, not loading.” (Participant 7, vancomycin, incorrect)

“The consultant might say oh I’ll just start him on 1 gram BD, and so you do that, but actually, based on other things, you should be starting them on something else.” (Participant 19, vancomycin, correct)

Although the online calculators were available to use in either imperial or metric units, two of the participants (both used the calculators) stated that the use of different units of weight and height in the Trust and conversion between them could be a potential risk of DEs;

“There's a metric and imperial thing on the calculator which I think it only works in the metric system.” (Participant 5, vancomycin, correct)
“They put the height sometimes in different units, you know, so that could be conversion of the height, it could be a source of error... So if there is just one way, you know sometimes they put it in inches but on the calculator it asks for it in centimetres so calculating it sometimes is not easy.” (Participant 20, vancomycin, incorrect)

5.4.6.4. Recommendations to improve dosing

Doctors were asked for recommendations to improve dosing accuracy and avoid errors with gentamicin and vancomycin (Table 5.7). Most doctors recommended actions related to the Trust dosing tools. For example, 8 doctors (half of them prescribed a correct dose) suggested using the tools as an important measure to avoid errors;

“I guess if it’s shown that the calculator gives you the right dose each time and it’s fairly reliable for most of the adult hospital population, then there should be a way of insisting that it’s used, rather than recommending it’s used for dosing gentamicin.” (Participant 4, gentamicin, correct)

As illustrated below, 9 doctors (of whom 5 prescribed a correct dose) talked about the importance of making the tools more accessible and easier to find;

“They (the guidelines) should be more available, easily accessible, because if I have to prescribe something, I have to find, you know, these stuff in the computer, so sometimes it takes time.” (Participant 6, gentamicin, correct)

“Uhm I did find it quite difficult to find the guidelines, uh so maybe something clearer on Kwiki perhaps.” (Participant 22, vancomycin, incorrect)

Some of these doctors also suggested that a wall chart or nomogram of the guidelines would increase their accessibility;

“Like the easiest way I’ve ever had with gentamicin is using 7 mg per kg and a half of nomogram but obviously you get much more toxicity with that so it's not feasible but if there were such a thing for a 5 mg and a 3 mg per kg dose that would be a lot easier way of doing it.” (Participant 17, gentamicin, incorrect)

“Well, in previous hospitals, they’ve had on the ward, like on a medical ward where you’ve got to be using those drugs more frequently, you have like a plastic sheet
either in the clinical room or near the computers with just, like, reminders of how to dose it and how to do it accurately, because at the moment, although they’re on the computer, there’s nothing obvious on the wards. (Participant 19, vancomycin, correct)

In addition, one suggested a phone application would make the tools more accessible;

“If you can get an app into phone which everybody’s got by the bedside when they’re calculating, like an electronic BNF or electronic dose calculator, that’s useful.” (Participant 7, vancomycin, incorrect)

Eight participants, including 4 who prescribed a correct dose, stated that increasing compatibility between the Trust tools and electronic prescribing system would make the prescribing process safer and easier. Some talked about warning boxes within the electronic prescribing system to ask if the guidelines were used, while others talked about a pop-out box that ‘forces’ the prescriber to enter patient parameters or automatically populating them from electronic patient records (EPR):

“And you could when you type in vancomycin or gentamicin have the box come up and say: have you used this online calculator to calculate this drug dose, yes or no? Just as a warning maybe.” (Participant 2, gentamicin, correct)

“Checks and measures in on the EPR so it perhaps forcing you to state what the renal function is and forcing you to say what the height is and that for ideal body weight, I think that you might slow things down I’m very marginal but it make things quite a bit safer so I think you could easily justify doing that.” (Participant 3, vancomycin, incorrect)

“Yeah, to the actual calculate it into EPR. So you’re doing the calculation where you’re prescribing it... it would be good if that was incorporated into the EPMA automatically because then you wouldn't have transcription errors for age, you know. It could automatically import the most recent height and weight into that, and then it... you could, it would reduce drug errors.” (Participant 9, vancomycin, correct)
However one doctor suggested that this compatibility might bring some risks. After talking about the possibility of data population from EPR and automatic dose calculation, he explained:

“But then again, that would just mean that you turn to one-click prescribing, you don’t actually think about it. So think that the gentamicin calculator is doing it in separate, so you do actually still have to think about the dose you’re giving and you can say if it gives you a funny result, or if the patient’s too short or something, it does telling you that you need to check the dose and speak to somebody else.”

(Participant 4, gentamicin, correct)

Education was also identified by several doctors (n=9) as an important measure to improve dosing, 6 of these prescribed a correct dose. Some doctors talked about educating prescribers on the existence and use of Trust dosing tools;

“Uhm probably some more training for junior doctors on the importance of using the height and using ideal body weight or adjusted body weight because I wasn’t really aware of that... yeah, that’s probably it. Maybe some more online training that would be easy.” (Participant 21, vancomycin, incorrect)

This also included medical school education about the importance of correct dosing;

“I suppose teaching in med school courses is obviously a thing and probably when people first start qualifying, reminding them that it’s really important to make sure you’ve got the correct dose. Uhm and if you don’t know how to do it, look it up because you can always look it up” (Participant 11, gentamicin, correct)

A doctor explained that senior doctors, especially those new to the Trust, needed more training about the tools as juniors were provided with enough training already and followed the guidelines better;

"It’s really raising the awareness of the calculators. I think a lot of the junior staff know about them and read the hospital guidelines and follow them whereas more senior staff they’ve come from other Trusts will just do what they’ve done in their Trusts and it might not be completely in line with the King’s guidelines. So I guess targeted ah education on the more sort of registrar level.” (Participant 8, vancomycin, correct)
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

Five doctors, of whom 3 prescribed a correct dose, emphasised on the need of better documentation and easier access to patient weight and height, mainly by putting it on EPR. Some examples;

“So nurses obviously record weight quite a lot, but if they start to always recording them onto EPR because there is actually, there is a section for patient’s weight and height but no one ever uses it or it’s very rarely used. If nurses used that instead that would be so much more helpful, uhm coz it will tell you when it was last done and it would be accessible wherever you are in the hospital, so you wouldn’t have to go to the ward and check on the chart” (Participant 23, vancomycin, correct)

Two doctors recognised the usefulness of having good communication with pharmacists and microbiologists for dose clarification;

“So if there’s an easy (way) to... prescribe or being in touch with either the pharmacist or microbiologist quickly” (Participant 18, vancomycin, correct)

Two other doctors identified double-checking of calculations either by self-checking or by another member of staff (e.g. nurses) as a measure to avoid DEs;

“I think you just have to be aware of human error and just make sure that you double check everything you do” (Participant 1, gentamicin, incorrect)

Unifying the units used in the Trust for weight and height was also identified by 2 doctors as risk-reduction interference;

“So if there is just one way, you know sometimes they put it in inches but on the calculator it asks for it in centimetres so calculating it sometimes is not easy.” (Participant 20, vancomycin, incorrect)

The last measure to avoid DEs stated by one doctor was to take more time while prescribing;

“Maybe have a bit more time to help prevent mistakes uhm.” (Participant 16, gentamicin, incorrect)
### Table 5.6. The possible sources of dosing errors with gentamicin and vancomycin identified by participants

<table>
<thead>
<tr>
<th>Possible sources of error</th>
<th>No. of doctors</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unavailability of patient primary data or use of inaccurate data</td>
<td>19</td>
<td>“A couple of things maybe the weight of the patient is not on EPR, so some doctors might not take the effort to look up the weight... and the height of the patient. Uhm maybe bloods aren’t up-to-date.” (Participant 2, gentamicin, correct)</td>
</tr>
<tr>
<td>Time constraints</td>
<td>8</td>
<td>“If you have a patient that's bed-bound, you know, and they’re sick, then you’re going to probably estimate their weight and height rather than wait three hours until a nurse can hoist them to weigh them.” (Participant 1, gentamicin, incorrect)</td>
</tr>
<tr>
<td>Confusion between ideal and actual body weight</td>
<td>6</td>
<td>“So I think the difference between actual weight and ideal weight that can be quite tricky.” (Participant 22, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Data transcribing</td>
<td>4</td>
<td>“In my experience transcription is the most common... transcription errors are the most common cause of drug error.” (Participant 9, vancomycin, correct)</td>
</tr>
<tr>
<td>Different protocols in different Trusts</td>
<td>2</td>
<td>“Uhm one of the big problems is every Trust you go to is different and everyone has different ways of doing it and ah so there's always confusion about it... The difference of dose calculations, the difference of dosing protocols and so on.” (Participant 17, gentamicin, incorrect)</td>
</tr>
<tr>
<td>Unawareness or difficulty in accessing guidelines</td>
<td>2</td>
<td>“Difficulty in accessing the guidelines and the protocols. And a lot, most doctors, when they start don’t know what the Trust protocol is and more concerning is, they don’t know how to access it.” (Participant 7, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Out-of-hours prescribing</td>
<td>2</td>
<td>“I’m sure out-of-hours prescribing will probably lead to higher mistakes than during hour prescribing... Because out of hours there you don’t have ward team, you’ve one person managing in the wards, you may not have the ward pharmacist to find out the doses are right and then suggest a correction, so it carries on for a bit longer.” (Participant 24, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Senior/specialist doctors’ influence</td>
<td>2</td>
<td>“The consultant might say oh I’ll just start him on 1g BD, and so you do that, but actually, based on other things, you should be starting them on something else.” (Participant 19, vancomycin, correct)</td>
</tr>
<tr>
<td>Use of different units of weight and height</td>
<td>2</td>
<td>“They put the height sometimes in different units, you know, so that could be conversion of the height, it could be a source of error.” (Participant 20, vancomycin, correct)</td>
</tr>
</tbody>
</table>

EPR: electronic patient records; BD: twice daily.
Table 5.7. The recommendations suggested by participants to avoid dosing errors with gentamicin and vancomycin

<table>
<thead>
<tr>
<th>Recommendations to avoid errors</th>
<th>No. of doctors</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education about the usage of Trust tools</td>
<td>9</td>
<td>“Probably some more training for junior doctors on the importance of using the height and using ideal body weight or adjusted body weight because I wasn’t really aware of that... yeah, that’s probably it. Maybe some more online training that would be easy.” (Participant 21, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Promotion of Trust tools and making them more accessible</td>
<td>9</td>
<td>“They (the guidelines) should be more available, easily accessible, because if I have to prescribe something, I have to find, you know, these stuff in the computer, so sometimes it takes time.” (Participant 6, gentamicin, correct)</td>
</tr>
<tr>
<td>Using the Trust tools</td>
<td>8</td>
<td>“Always make sure it’s done through the intranet and the antimicrobial prescribing guidelines. That probably will get you in the right habit of making sure you don’t make any antimicrobial prescribing mistakes.” (Participant 24, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Increasing compatibility between Trust tools and EPR</td>
<td>8</td>
<td>So you’re doing the calculation where you’re prescribing it... it would be good if that was incorporated into the EPMA automatically because then you wouldn’t have transcription errors for age, you know. It could automatically import the most recent height and weight into that, and then it... you could, it would reduce drug errors.” (Participant 9, vancomycin, correct)</td>
</tr>
<tr>
<td>Improving documentation of patient primary data</td>
<td>5</td>
<td>“On some wards it’s only done on paper, and then you have difficulty finding the accurate weight, and obviously you can’t do it remotely, so I would like regular documenting of weights on EPR.” (Participant 12, gentamicin, correct)</td>
</tr>
<tr>
<td>Enhancing communication between prescribers and microbiologists and pharmacists</td>
<td>2</td>
<td>“So if there’s an easy (way) to... prescribe or being in touch with either the pharmacist or microbiologist quickly” (Participant 18, vancomycin, correct)</td>
</tr>
<tr>
<td>Double-checking calculations</td>
<td>2</td>
<td>“Well, I suppose the nurses could also check the dose with the calculator to make sure that it was correct... I think there should be some sort of way that the dose could be double-checked before it’s given, as you’d with opioid doses or any other potentially dangerous drug to be given in overdose.” (Participant 4, gentamicin, correct)</td>
</tr>
<tr>
<td>Unifying the weight and height units</td>
<td>2</td>
<td>“So if there is just one way, you know sometimes they put it in inches but on the calculator it asks for it in centimetres so calculating it sometimes is not easy.” (Participant 20, vancomycin, incorrect)</td>
</tr>
<tr>
<td>Having more time while prescribing</td>
<td>1</td>
<td>“Maybe have a bit more time to help prevent mistakes uhm.” (Participant 16, gentamicin, correct)</td>
</tr>
</tbody>
</table>

EPR: electronic patient records; EPMA: Electronic Prescribing and Medicines Administration system.
5.4.7. Common patterns for accurate prescribing

The doctors who prescribed correct doses of gentamicin or vancomycin had some common characteristics compared to those who prescribed incorrect doses. They were likely to be Senior House Officers (SHO) or Junior Clinical Fellows (JCF) (7/12 vs 0/12), who prescribed using the Trust dosing tools (11/12 vs 7/12), and were treating non-elderly patients (<65 years) (9/12 vs 5/12) with normal renal function (CrCl≥60 ml/min) (10/12 vs 6/12). The table used to compare the characteristics of correct and incorrect dose prescribers in order to find common patterns can be found in Appendix 5.7.

In addition to the characteristics above, doctors were more likely to prescribe a correct dose of gentamicin when they had better knowledge about the data needed for accurate dosing (5/6 vs 3/6) and about the appropriate weight to be used (actual or ideal) (3/6 vs 1/6). However, doctors who worked in calmer work environments were more likely to prescribe a correct dose of vancomycin (4/6 vs 1/6).

5.5. Discussion

5.5.1. Main findings of the study

A qualitative interview-based study was conducted to explore the views, knowledge, and experiences of doctors in prescribing gentamicin and vancomycin and to investigate the resources and methods they use to calculate the initial dose of these drugs. Although similar studies have been conducted on antimicrobials in general, this was the first study to investigate these issues specifically for gentamicin and vancomycin. In this study, the data collected by interviewing 24 doctors (with different grades, experiences, and specialties) who prescribed gentamicin and vancomycin (including correct and incorrect doses) at one large NHS acute teaching Trust were divided into four themes. These were dose calculation resources, therapy monitoring, conditions and factors that might affect dose prescribing decision, and doctor views and opinions about drug dosing. The main patterns for accurate dosing found in this study were being a SHO or JCF, using the Trust dosing tools, and treating a non-elderly patient with normal renal function.

This study identified that most doctors (n=18, 75%) were unaware of some of the parameters and equations required for dose calculation (e.g. ideal or actual body weight,
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

eGFR or CrCl) and that half of them prescribed an incorrect dose, including some which were directly attributed to this lack of awareness. Although the other doctors prescribed a correct dose mainly by accurate use of the Trust dosing tools, they did not know the basis on which this dose was calculated. This identifies a risk of overreliance on these tools without critical thinking and underpinning knowledge which might lead to DEs in cases where an erroneous value was used with these tools, a technical problem occurred with the tools, or that the tools were unavailable. A qualitative study by Campbell et al (2007) identified three main unintended negative consequences for clinicians’ overdependence on electronic CDS; clinical practice can be interrupted and patient safety can be compromised if the system is unavailable, false expectations of accuracy and processing of data on the system may exist, and a belief that clinicians cannot work effectively in the absence of technology support.

Seven of the 18 participants (39%) who used the Trust dosing tools, either the electronic calculator or the guidelines, in this study prescribed an incorrect dose. Five of these doctors used the calculators and made a technical error while using them (e.g. wrong value entry) or were unaware of some of their features (e.g. second page of the vancomycin calculator). The other 2 doctors who used the guidelines used wrong patient values (i.e. actual rather than ideal weight). Moreover, all 6 participants who did not use the Trust dosing tools were aware of at least one of them, but decided not to use them for different reasons. These findings would suggest that implementation of new interventions and guidelines is not enough to improve dosing quality and safety without providing sustainable support and education on their use and benefits.

Education about the importance of using the Trust dosing tools and how to use them was addressed by many doctors as a recommendation to improve the prescribing practice and avoid DEs with gentamicin and vancomycin. In the Lesar et al (1997A) study, 59.2% (n=412) of PEs occurred due to factors related to knowledge and use of knowledge about the drug or the patient. Lack of knowledge about the drug or the patient, especially the appropriate doses to prescribe, was the most frequent failure leading to PEs in the EQUIP study systematic review (Dornan et al, 2009). Furthermore, lack of knowledge about appropriate drug dosing (38.3%) and failure to consider laboratory test values (18.3%) were the causes most responsible for PEs in the Winterstein et al (2004) study. Deficiency in education was also found by Newham et al (2015) as a barrier to using gentamicin and vancomycin guidelines. The study by Mol et al (2004) suggested that more efforts are
needed to familiarise doctors with hospital antimicrobial guidelines. They proposed education as an intervention to overcome the barrier of insufficient knowledge of doctors about certain areas that prevent them from using the guidelines. In addition, enhancing doctors’ knowledge through education and the use of online support tools were the main interventions recommended by Velo and Minuz (2009) to reduce PEs. Educational interventions regarding antimicrobial dose adjustments have been found to be highly accepted among doctors when compared to interventions about other issues (Calbo et al., 2013).

5.5.2. Dose calculation resources

Like other antibiotics, the prescribing process for gentamicin and vancomycin is complex and involves several factors. As there is no restriction on the prescribing of many commonly used antibiotics, the accuracy of antibiotic prescribing relies on factors that vary between different prescribers including knowledge, training, motivation, and work setting (Calbo et al., 2013). At King’s College Hospital (2012B), vancomycin prescribing is not restricted while gentamicin prescribing is only restricted if intended for more than 48 hours. In most cases, it is prescribed as a once-only dose. This lack of prescribing restriction may have contributed to the development of different prescribing resources for these drugs and possible confusion over the differences in the way the drug doses are calculated.

In the current study, different resources for prescribing gentamicin and vancomycin were used by participating doctors. These included the Trust dosing tools (guidelines and calculators), standard doses, previous experience, and Microbiology advice. The Trust tools were used by 18 participants in this study (75%). However 6 participants (25%) did not use them despite all being aware of their availability. Mol et al (2004) identified characteristics of the guidelines, prescribers, and social/institutional context as the main barriers to the use of antimicrobial guidelines. In this study, the doctors who did not use the Trust dosing tools gave different reasons for not using the tool. Two participants (6 & 17) prescribed a standard dose that they suggested was usually prescribed for all patients with normal renal function in their departments, and one participant (15) reported following a suggestion from Microbiology without considering guideline recommendations (social/institutional context characteristics). One participant (10) did
not know about the recommendation to use ideal body weight and one participant (24) used a suboptimal dose based on clinical judgement (prescribers’ characteristics). One participant (7) found the guidelines not user-friendly and difficult to access (guidelines’ characteristics).

A recent Scottish study by Newham et al (2015) investigated the barriers to safe and effective use of gentamicin and vancomycin in adult patients based on national guidelines (Scottish Antimicrobial Prescribing Group, 2009). These barriers were divided into direct and indirect barriers. The direct barrier identified was the need for experience when using the guidelines. The indirect barriers included lack of awareness of the guidelines, communication issues within hospital sites, unmet educational needs, and staffing issues. All of these issues were identified by the participants in the current study as possible sources of DEs.

Participants in this study recognised the difficulty in finding patients’ weights. They also emphasised that finding a patient’s height was considerably harder. A UK study by Campbell et al (2002) looked at the recording rate of weight and height in the notes of 526 patients. They found that weight was recorded in 67% of notes (n=350) while both weight and height were recorded in only 41% (n=217). An Australian study by Hilmer et al (2007) found that 75.7% (153/202) of patients in medical and orthopaedic wards were not weighed. Participants in the current study also identified estimation as a way of getting patient weight. An Australian study by Evans (2012) showed that although 79% of doctors agreed on the importance of accurate weight in clinical decision making, 24.8% identified that they estimated patient weight.

Many participants in this study identified senior/specialist advice as a major determinant of their gentamicin and vancomycin prescribing practice. The choice of gentamicin and vancomycin in this study was mostly made by doctors other than the participants and was largely influenced by the decisions of senior or specialist doctors. Fifteen participants (62.5%) prescribed gentamicin or vancomycin based on advice from the Microbiology team, other specialists, or their consultants. This is normal in teaching hospital settings where antimicrobial prescribing behaviour is predominantly influenced by the senior doctors (Charani, et al, 2011). In most teaching hospitals, junior doctors do not make independent decisions and their prescribing choices are usually supervised by experienced specialists (Calbo et al, 2013). In addition, the ‘prescribing etiquette’
revealed by Charani et al (2013) also showed that a hierarchy-based culture in which junior doctors prescribing is highly affected by seniors is dominant among teaching hospitals. This culture was also addressed by Hulscher et al (2010). However, most participants in the current study who prescribed based on senior/specialist advice mentioned that they calculated the dose themselves with only the choice of antibiotic being recommended.

5.5.3. Therapy monitoring

The doctors’ knowledge of the main toxicities of gentamicin and vancomycin and monitoring of their toxic and clinical beneficial effects was assessed in this study. Several doctors monitored drug serum levels, blood tests (especially for creatinine clearance and inflammatory markers), and patient adverse (e.g. Red Man Syndrome with vancomycin) and clinical (e.g. fever) reactions as measures of assessing drug toxic and therapeutic effects. Despite the poor awareness of vancomycin ototoxicity, doctors in the current study demonstrated an adequate knowledge of the toxicities and monitoring of gentamicin and vancomycin. This knowledge is important to provide effective treatment while avoiding patient harm. A systematic review by Tully et al (2009) on the causes of and factors contributing to PEs identified inadequate monitoring as a rule-based active failure leading to PEs. In addition, Lazarou et al (1998) stated that many ADRs can be reduced with correct drug monitoring in hospitals. Monitoring of drug actions was also seen by Velo and Minuz (2009) as essential for optimising or adjusting drug regimens or doses. They added that careful evaluation of drug toxic and therapeutic effects, including monitoring of plasma concentrations and biomarkers, is a necessary measure to improve patient safety.

Extra measures or assessments doctors undertake when prescribing gentamicin or vancomycin in comparison to other drugs were also assessed. Half of doctors in the current study mentioned that they routinely checked patient primary data before prescribing these drugs. This is an important quality and safety measure as Lesar et al (1997B) identified patient characteristics (including age, weight, and renal function) as the most common factor (51.1%) for antimicrobial PEs. In addition, adjusting the dose and frequency of antibiotics based on renal function was considered a quality indicator for the antibiotic treatment of community acquired pneumonia (CAP) (Hulscher et al,
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

2010). The PRACtICe study (Avery et al., 2012) also recommended that efforts should be focused on finding context-specific dosing guidance which takes patient factors such as age and renal function into account. The importance of considering the patient’s clinical condition before prescribing gentamicin or vancomycin was also addressed by some doctors in the current study. This is an essential measure for effective and safe prescribing and the failure to take patient-specific factors into account was defined by Dean et al. (2000) as a PE.

5.5.4. Conditions and factors that might affect dose prescribing decision

Working conditions of participants and the factors they considered might influence their prescribing practice for gentamicin and vancomycin were assessed. The ward environment on the day of dose prescribing was described by many participants as busy and hectic. Some doctors linked this busyness to the time of day or week such as on-call or weekend shifts. The EQUIP study (Dornan et al., 2009) showed that busyness and rushing were major error-producing conditions for all types of PEs. It also found that busyness was greater at certain times, such as during on-calls. The review by Tully et al. (2009) showed that busy work conditions were associated with higher PE rates. Moreover, 70% of doctors (31/44) in the Dean et al. (2002c) study said that they were busy at the time of making the PE they were interviewed about.

Participants in this study described the workload they had on the day of prescribing the dose which was the subject of the interview. Many doctors, especially those working out-of-hours, stated that they had a high workload. The study by Dean et al. (2002c) addressed the integration between staffing and heavy workload. In their study, heavy workload was an error-producing condition in 70% (31/44) of PEs while inadequate staffing was a responsible condition in 34% (15/44). High workload was also found by the EQUIP study (Dornan et al., 2009) to be a common error-producing condition in all PE types. Insufficient staffing was one of the five barriers identified by Newham et al. (2015) to using gentamicin and vancomycin guidelines. All foundation doctors across Scotland in 2010 (n=1,564) were invited to participate in a survey about PEs that was conducted within the PROTECT study (Ryan et al., 2014). This survey asked the doctors to suggest causes of PEs. Of 504 responses, heavy workload was the most suggested cause of PEs.
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

(~310 doctors, ~62%). Low staffing levels were also suggested as a cause of PEs by ~180 doctors (~36%).

Doctors’ feeling of tiredness or stress at the time of gentamicin or vancomycin prescribing was assessed. Some doctors expressed that they were tired or stressed upon prescribing, especially out-of-hours or towards the end of their shifts. In the PROTECT study (Ryan et al., 2014) survey, tiredness and stress were the most common individual factors for PEs suggested by participants (230 doctors, 45.6%). Several studies in the Tully et al. (2009) review identified tiredness and stress as conditions facilitating PEs. The EQUIP study (Dornan et al., 2009) also identified fatigue and stress as PE-producing conditions. However, it stated that they were not influencing clinical performance or MI occurrence.

These conditions above did not seem to have affected the dosing accuracy among the participants in this study. This is because several doctors who prescribed incorrect doses were working in a quiet environment, not busy, not tired, and not stressed. Other doctors who were working on a busy ward, had a heavy workload, and expressed their tiredness and stress prescribed correct doses. However, most doctors who suggested time constraints, mainly due to busyness and workload, as a possible source of error prescribed incorrect doses.

5.5.5. Possible sources of dosing errors and recommendations to avoid their occurrence

Doctors participating in this study identified different sources of error and recommendations to avoid such errors (Tables 5.6 & 5.7). The unavailability of up-to-date patient primary data or use of inaccurate data (e.g. old, estimated, actual weight instead of ideal) is a common problem in hospitals (discussed in section 5.5.2) that can have significant negative effects on prescribing decisions. Missing or wrong weight was responsible for 3.7% (23/616) of all MIs found among a paediatric population in the US (Kaushal et al., 2001). DEs are the main type of error that can result from the use of inaccurate weight. A study by the Pennsylvania Patient Safety Authority (2009) found that among 479 MIs reported in relation to the use of wrong weights, 64.7% (n=310) were DEs. Moreover, gentamicin and vancomycin were among the top 10 medications involved in MIs associated with weight-dependent dosing. This inaccurate weight documentation was due to a variety of reasons including confusion between units of weight (i.e. pounds...
& kilograms), unavailability of weights, use of estimated weights, and confusion between ideal and actual body weights; all of which were mentioned by the participants in this study. In addition, Newham et al (2015) stated that the study participants did not consider having an accurate weight and height as an important measure when prescribing gentamicin or vancomycin.

Kahn et al (2007) found that only 33% of 957 weight estimates done for 241 patients were within 5% of the true weight. The risk of getting a wrong estimate was significantly higher (P<0.001) with underweight and overweight patients. Newham et al (2015, p.3) study also addressed the issue of weight estimation with one participant explaining; “…they make up patient weights rather than actually measuring them”.

A study by McCulloch and Kumarasamy (2012) investigated the type, frequency and reasons for prescribing and monitoring errors in adults receiving gentamicin at a Scottish hospital. They found that 11% (15/135) of all errors were due to failure to dose overweight patients using ideal body weight. Different participants in the current study recommended improving weight and height documentation, especially on EPR where it would be more accessible. Evans (2012) suggested that patient weight must become a mandatory measure during the admission process with systems to monitor documentation compliance. She also suggested that a range of actions should be introduced to avoid the need for staff to estimate patient weight such as A&E beds with built-in scales.

Many doctors emphasised on the importance of using the Trust dosing tools to avoid DEs. However, some talked about the difficulty in finding these tools and the need to make them more accessible. In the systematic review by Teixeira Rodrigues et al (2013), participants in 7/12 studies that addressed hospital guidelines described them as a factor influencing their prescribing decisions. A Dutch study of 7,471 antibiotic prescriptions by Mol et al (2005) showed that compliance to antibiotic guidelines was significantly increased (67% to 82.5%, P<0.001) after the introduction of redesigned guidelines. These guidelines were developed after consulting the targeted doctors to enhance ownership. In addition, the accessibility of the guidelines was improved by giving a paperback version to all doctors and developing an indexed and searchable electronic version. The importance of involving social and behavioural factors in designing interventions was also addressed in Charani et al (2011) review. At King’s College Hospital, the guidelines handbook is distributed to all junior doctors during their induction. However, the
electronic version is only a non-indexed PDF copy of this booklet. Some participants in this study found the guidelines unclear and complicated and one of them suggested the development of a phone application to make the guidelines more accessible and easier to search. Taking doctors’ comments and recommendations into consideration in designing and updating dosing tools would increase the ownership of these tools and potentially their use to enhance safe and effective prescribing in accordance with the Trust guidelines.

Study participants also addressed the risk of not being aware of local guidelines or where to find them, especially for doctors new to the Trust. So, they believed that it was important to raise the awareness about the existence and location of these guidelines. A study by Switzer et al (2003) showed that 48% of doctors treating CAP in 7 US hospitals did not know whether local guidelines were available for the treatment of this condition. Newham et al (2015) study also identified the lack of awareness of guidelines as a barrier to their use. Individual prescribing behaviour can be negatively affected by lack of awareness about the guidelines and available evidence on the appropriate use of antibiotics (Hulscher et al, 2010). The participants in Mol et al (2004) study identified the improper dissemination as a barrier to adherence with antimicrobial guidelines. As a solution, the study suggested the development of paper and electronic versions with incorporating departmental policies and updating them regularly. It also recommended organising meetings to introduce the guidelines and creating outreach committees.

As discussed earlier, this study showed that several doctors were confused about using ideal or actual body weight, relied on eGFR rather than CrCl, were unaware of the values and equations needed for dose calculation, or did not know how to use the Trust dosing tools properly. In addition, participants identified the risk that doctors new to the Trust might not know about the guidelines or how to use them and then adhere to the protocols they are familiar with from their previous Trust. The direct barrier to using gentamicin and vancomycin guidelines in Newham et al (2015) study was the lack of experience in using these guidelines and their lack of clarity.

Junior doctors who participated in this study identified the advice of their consultants and other specialist doctors as a major influence on their prescribing decisions. Some participants identified following the recommendations of senior doctors without consideration of patient/clinical factors and Trust guidelines as a possible source of error.
Charani et al (2011) identified that hospital guidelines play a minor role in influencing prescribing behaviour of junior doctors which is mainly affected by the practice of seniors. Dean et al (2002c) identified that junior doctors prescribed what seniors told them to without asking questions, assuming that the suggestion of their senior was correct, which was considered a contributory factor for errors. They also commented that some junior doctors were unaware of who would be responsible in case of any problems with such prescriptions. Tully et al (2009) identified junior doctors’ reluctance to question their seniors as a latent condition facilitating PEs. Therefore, engagement with senior doctors is recommended as a strategy to understand the prevailing prescribing practice and to enhance junior doctors’ adoption and following of hospital antimicrobial guidelines (Charani et al, 2011; Charani et al 2013). Moreover, The EQUIP study (Dornan et al, 2009) suggested encouraging junior doctors to challenge instructions from their seniors as a measure needed to reduce the incidence of PEs.

Some participants in this study identified time constraints as a possible source of error. This was also identified in the EQUIP study in which some interviewees addressed time constraints as a risk factor for PEs (Dornan et al, 2009). The study of Lesar et al (1997A) stated that the short time doctors had to consider drug therapy issues before prescribing the medication was a factor contributing to PEs. Teixeira Rodrigues et al (2013) stated that time pressure had a direct impact on antibiotic prescribing in 11/12 studies in their review that assessed time influence. One of the participants in the current study suggested having more time to spend on prescribing as a way to avoid errors. The PRACtIcE study by Avery et al (2012) indicated that creating more time to thoroughly review the prescriptions can be a good way of tackling PEs.

Out-of-hours prescribing was recognised as a possible risk of DEs by some participants in this study. The main issue identified was that during weekends and evening/night shifts, junior doctors have to primarily take the prescribing decisions in the absence of guidance from specialists and ward pharmacists. The issues of low staffing, higher workload, and lack of support during out-of-hours shifts were also addressed by Newham et al (2015). Franklin et al (2011) investigated the factors contributing to PEs in 3 UK hospitals. Their study addressed the unavailability of clinical information out of hours as a task-related factor of PEs. Doctors interviewed in the PROTECT study (Ryan et al, 2014) also identified poor availability of drug information as the main task-related factor of PEs in out-of-hours admissions. The EQUIP study (Dornan et al, 2009) found that FY1 trainees
received poor prescribing support during on-calls. The current study participants recommended enhancing the communication channels between doctors, especially juniors, and antibiotic experts (i.e. pharmacists and microbiologists). In their review, Hulscher et al (2010) recommended hospitals introduce a phone advice service for doctors to discuss antibiotic prescriptions with pharmacists or microbiologists.

Some doctors in the current study identified transcribing, such as the possibility of using wrong values in dose calculation, as a possible source of error. King’s College Hospital has an electronic prescribing system, which is seen as one of the main interventions preventing transcribing errors (García-Ramos and Baldominos Utrilla, 2011). However, essential information including nursing notes and risk-assessment forms, which were main sources of weight and height in this study, were only available on paper. In addition, some units such as critical care and operating theatres do not use the electronic prescribing system. Therefore, transcription was still required when moving patients between these units and electronic prescribing wards or when entering data into the electronic prescribing tools, e.g. dose calculators. Newham et al (2015) identified poor communication and lack of information transfer as a barrier to the safe and effective use of gentamicin and vancomycin. Out of 40 transcribing errors in Leape et al (1995) study, 29 (73%) were due to slips (misprints). In addition, transcribing was identified as a risk of error by some doctors in the EQUIP study (Dornan et al, 2009).

In the current study, double-checking was suggested as a measure to avoid such errors. The ISMP (2013) addressed the importance of independent double-checking of dose calculations, particularly by nurses or pharmacists. It also stated that independent double-checking is highly effective in avoiding endogenous errors (i.e. due to internal cognitive factors) such as DEs (e.g. miscalculation, transcribing error). Lesar et al (1997B) also mentioned independent double-checking as an effective method of reducing calculation/unit expression errors. However interestingly, Brotto and Rafferty (2012) viewed dose calculation double-checking as a possible risk factor. They explained that the first checker may assume that the second will detect any errors made while the second checker may assume that the first would not make an error, which would lead to a ‘half-check’ rather than double-check.

Some doctors in this study suggested making the electronic dose calculators compatible with EPR so the patient primary data needed for dose calculation would be automatically
Chapter 5: An Interview-Based Study to Explore Prescribing of Initial Doses

populated. This was considered a good solution for both the difficulty in finding primary data and also for avoiding transcribing errors. Marcos et al (2013) stated that clinical decision support (CDS) tools should be integrated with other electronic systems available in the hospital which saves the need for manual re-entering of data already available on any system into CDS tools. This can be achieved by interaction between these tools and EPR to automatically access any clinical data required to enhance the use and effectiveness of CDS tools. However, one doctor in the current study believed that this might introduce a new risk by overreliance on electronic tool recommendations without critical thinking (discussed in section 5.5.1).

5.5.6. Limitations

Few limitations have been identified with this study. In line with all qualitative studies, the results of this study may not be generalisable (Johnson and Christensen, 2003). This issue can be due to the limited representation of the study sample, especially with the relatively small number of participants included in such studies. So, a dominant culture or behaviour across the department or hospital might affect the opinions and views of the participants. As in the EQUIP study (Dornan et al, 2009), doctors may have agreed to participate in this study because they had specific problems with prescribing gentamicin or vancomycin or because they are more reflective about their prescribing. This might limit the representation of the study sample.

However to reduce the influence of these issues on this study, participant doctors were recruited from a wide range of departments, grades, and experiences and included doctors who prescribed correct and incorrect doses. In addition, the fact that several participants in the study had previous experiences at other hospitals in the UK or overseas provided more variation in the participant backgrounds which would have potentially reduced the existence of one dominant culture or behaviour among the participants.
5.6. Further work

A number of participants in this study acknowledged the poor documentation of patient primary data (particularly weight & height) in the hospital which was complicated by the existence of different sources of these data (e.g. admission record, nursing notes). In addition, most participants identified the unavailability of accurate patient primary data as a potential source of DEs with gentamicin and vancomycin. Therefore and as recommended by some study participants, accurate documentation of these data, preferably on one unified easily-accessible source (e.g. EPR), should be promoted. They also suggested this may be further improved by enhancing compatibility between different electronic tools and records/data sets so these data can be automatically populated to the calculators. Further work is needed to assess the feasibility of these proposals and evaluate their potential impact on dosing accuracy and safety.

Another issue identified in the study was that a number of participants had technical issues with the electronic dose calculators which led some of them to prescribe an incorrect dose. In addition, some participants thought the calculators were not user-friendly and they lengthen and complicate the prescribing process. A task analysis for using the calculators would be useful to understand the detailed process of their use, from both manual and mental perspectives (e.g. frequency, duration, assignment, barriers, challenges). This should help identify the best strategies, both technical and educational, to overcome these issues and enhance the adoption and usage of the calculators.

This study identified that many doctors who used the Trust dosing tools to prescribe gentamicin or vancomycin, including correct-dose prescribers, relied on these tools without knowing the values/equations behind the dose calculation, which could be a risk for DEs. Therefore, increasing the knowledge of doctors about these values/equations and enhancing their critical thinking and interpretation of the doses recommended by these tools would be essential to mitigate risks and enhance patient safety while using these drugs. This could ideally involve sustainable education for doctors that is part of their routine practice, especially in environments such as teaching hospitals with a high turnover of doctors. Further work is needed to implement such educational activities and measure their effect on the accuracy and safety of prescribed doses.
5.7. Conclusion

An interview-based study was undertaken to explore the views and experiences of doctors in prescribing gentamicin and vancomycin and the resources and methods they used to calculate the initial dose of these drugs. The main patterns for accurate dosing found in this study were being a SHO or JCF, using the Trust dosing tools, and treating a non-elderly patient with normal renal function. Prescribers who used the calculators or guidelines accurately were more likely to prescribe a correct dose compared to those who used standard doses (e.g. 5mg/kg gentamicin). However, some prescribers could not use the calculators properly which suggested that more support and education on their use is needed. The main factors identified by prescribers as influencing their dose selection were patient parameters (i.e. gender, age, weight, height and renal function), Trust dosing tools (i.e. antimicrobial guidelines and dose calculators), Microbiology advice, and clinical condition of the patient. A number of prescribers who obtained a correct dose using the calculators did not know some of the underlying calculations/values needed for dosing (e.g. creatinine clearance, ideal body weight). This identified that some prescribers may have an overreliance on CDS tools without a sufficient understanding of the parameters required which masks a potential source of error.

Participants identified a number of possible sources of DEs with gentamicin and vancomycin. These included mainly unavailability of patient primary data and use of old or estimated data, confusion between ideal and actual body weight, time constraints, and data transcribing. Participants also recommended some strategies and measures to avoid the occurrence of DEs. These were mainly about improving documentation of patient primary data, using the Trust dosing tools, education about the usage and existence of tools and making them more accessible, and increasing compatibility between the tools and EPR. Understanding the prescribing behaviour of doctors and their thoughts and views about gentamicin and vancomycin use and how to improve it should be employed in developing and updating interventions to enhance the quality and safety of care when using these drugs.
Chapter 6

General Discussion
Chapter 6: General Discussion

6.1. Overview

This thesis investigated the safe use of antibiotics in hospital settings with a particular focus on the high-risk antibiotics gentamicin and vancomycin. In the beginning, the thesis described the global issue of patient safety and healthcare quality and the associated consequences (Kohn et al., 2000; DoH, 2000; Vincent et al., 2011). It also described how the healthcare systems have responded over the last 15 years by establishing dedicated quality and safety bodies such as the UK National Patient Safety Agency (NPSA), US Agency for Healthcare Research and Quality (AHRQ), and World Health Organization (WHO) Patient Safety Programme. The main role of these bodies is to monitor and analyse patient safety incident (PSI) data and disseminate the evidence produced from these data to support the development of preventive strategies and improvement of healthcare quality (DoH, 2001; WHO, 2012; AHRQ, 2012). Different strategies have been recommended by these bodies to enhance patient safety. One of the main strategies was clinical governance which is a comprehensive strategy that involves different approaches integrated together to achieve high quality healthcare. Risk management and safety culture were also identified as effective strategies to enhance patient safety and service quality. These two approaches are essential to improve patient safety and were seen as features characterising the best healthcare organisations (Scally and Donaldson, 1998; DoH, 1998; DoH, 2000; NPSA, 2004; Berwick, 2013). The thesis also discussed Reason’s (1990) model of human error and Vincent et al’s (1998) framework for accidents in healthcare organisations (section 1.2.4).

Medications pass through a complex multi-stage process before reaching the patient, which creates multiple opportunities for several kinds of medication safety incidents (MIs). MIs can be classified according to the stage of medication-use process (MUP) during which they occur (e.g. prescribing), the way in which they occur (e.g. omission), a psychological classification of human errors (e.g. knowledge-based), their severity, preventability/ameliorability, and the staff responsible for them (Morimoto et al., 2004; Ferner and Aronson, 2006; Vogenberg and Benjamin, 2011). Medication safety is a vital area within patient safety especially because MIs are one of the most commonly reported PSIs and they are highly preventable (Wilson et al., 1995; Bates et al., 1995; Barker et al., 2002; Runciman et al., 2003; Otero-Lopez et al., 2006). In 2011, MIs were the second most common PSI reported to the National Reporting and Learning System (NRLS) in England and Wales (NRLS, 2013A).
Antibiotics are widely used in hospitals and commonly associated with MIs (Wilson et al, 1995; Bates et al, 1995; Dean et al, 2002B; Winterstein et al, 2004; Fridkin et al, 2014), especially during prescribing (Lesar et al, 1997A; Jayawardena et al, 2007; Seden et al, 2013) and administration (Valentin et al, 2009; Rodriguez-Gonzalez et al, 2012; Keers et al, 2013) stages of the MUP. Antimicrobial resistance has been recently rising and the Chief Medical Officer for England has described it as a ticking time bomb threatening the whole world. In response, the UK Department of Health (DoH) published a 5-year strategy to tackle resistance and one of its recommendations was to optimise antimicrobial prescribing. Reducing MIs with antibiotics is essential to tackle antimicrobial resistance as it is to provide effective and safe treatment (Davies, 2013; DoH, 2013; Davey et al, 2013).

This thesis described four separate but related studies on antibiotic-related MIs. First, a retrospective analysis was performed to determine the prevalence, incidence and nature of antibiotic MIs reported for inpatients at two large NHS acute teaching hospitals. This study used a novel method for analysing MI data and identified gentamicin and vancomycin as high-risk antibiotics. A systematic review was then conducted to identify the interventions used to improve gentamicin and vancomycin dosing. This review identified electronic clinical decision support (CDS) in association with appropriate education as an effective intervention. Following the literature review, new electronic dose calculators for gentamicin and vancomycin initial doses were implemented and assessed at a large NHS acute teaching hospital. Finally, an interview-based study was undertaken to explore the views and experiences of doctors in prescribing gentamicin and vancomycin at that hospital. The resources and methods they used to calculate the initial dose of these drugs were also explored.

6.2. Evaluating antibiotic-related medication safety incidents

Different methods can be used to detect MIs (e.g. record review, survey) and each of these has its advantages and disadvantages (section 1.3.4). Direct observation is usually seen as one of the best methods to collect accurate and timely incident data. It also allows studying the potential factors of incidents. However, observation is limited by practical and methodological issues. There are confidentiality concerns as staff who committed errors could be identified. This method relies on individual skills and so observers are required to have intensive training. Moreover, there is a possibility of bias if the observers
are not blinded to patient outcomes. Observation is focusing on the providers instead of the entire delivery system. It is also time-consuming, expensive to perform, and may overestimate incidents. Finally, there is the Hawthorne effect which can occur when the observer presence alters the staff normal behaviour (Allan and Barker, 1990; Thomas and Petersen, 2003).

In this thesis, a retrospective analysis was performed to determine the prevalence, incidence and nature of antibiotic MIs reported for inpatients at two large NHS teaching hospitals (Chapter 2). The main limitation of incident reporting is under-reporting which leads to underestimation of incidents and can limit the reliability of this method in measuring incidence and prevalence of MIs (Thomas and Petersen, 2003; Shojania, 2010). Different reasons can lead to staff under-reporting such as cultural issues, busyness, and lack of feedback (section 2.1.6). However, incident reporting has several advantages including providing a broad database of incidents in a specific time period which helps in anticipating potentially harmful incidents, an opportunity for learning from dangerous situations which helps in finding potential solutions, and details about latent failures that lead to MIs (Leape et al, 1997; Staender, 2000; Thomas and Petersen, 2003).

Most studies of MIs report the overall prevalence and do not compare this with drug consumption data. A commonly used drug might be associated with a high number of MI reports and therefore assumed to be of a 'higher risk'. A drug used rarely may be associated with very few MIs and will therefore be assumed to be 'less risky'. In this study, the antibiotic MIs were analysed against defined daily doses (DDDs) which allowed measuring prevalence against consumption and therefore generating an incident rate for each antibiotic. This provided more useful information than the absolute numbers alone (Tables 2.5 & 2.7). When DDDs were taken into account, some rarely used drugs associated with few MIs appeared to be of a 'higher-risk' than other drugs which were commonly used and associated with more MIs. Based on reporting rates alone, trends in incidents with less commonly prescribed antibiotics are unlikely to be investigated. Thus, opportunities to implement preventive strategies may be missed. This analysis identified that the number of MIs associated with each antibiotic does not necessarily reflect the risk of a MI occurring with this antibiotic. Therefore, it highlights the disproportionate risk associated with less commonly prescribed antibiotics not identified using MI reporting rates alone, especially where data might be analysed over shorter time periods.
Hua and Gong (2011) identified terminology/taxonomy/nomenclature as one of the challenges for designing an effective incident reporting system. They stated that the lack of consistent terminology can disrupt the communication between different PSI reporting systems on larger levels. In this study, different categories were used to classify MI stages and types at each Trust. These categories were harmonised to allow comparison between both Trusts. Inconsistency in MI categories across NHS hospitals would make measuring and comparing their prevalence and incidence on NHS level more difficult and less reliable.

The quality of submitted MI reports can be affected by different challenges in relation to design and adoption (Hua and Gong, 2011). In this study, some MI reports had provided poor quality information on the incident. Twenty-eight reports were submitted without documenting the drug involved and identifying it only as an antibiotic. Some reports had a blank ‘drug name’ or ‘error type’ field, though this information was identified from other fields in the report. A reason for this might be that some essential fields in the incident reporting form were not mandatory. It would appear that this issue exists across the NHS as documented in a recent report by NRLS (NHS England, 2014). However, the quality assurance measures applied in this study appear to improve the quality of information yielded from the submitted reports compared to the NHS data (Table 2.10).

Under-reporting may have occurred in this study and therefore the identified incident rates are the lowest possible and true rates are probably higher. However, the rate of MI reporting from both Trusts of this study was higher than the national reporting rate from all acute teaching organisations in England and Wales (Table 2.11) (NRLS, 2013C). This study confirmed that antibiotic MIs are common in UK hospitals and showed that rates can be compared between similar acute Trusts. The results of this study are comparable to other studies showing prescribing and administration as the stages at which most reported MIs occur and wrong dose and omission as the most common types of MIs (Ashcroft and Cooke, 2006; Picone et al, 2008; NPSA, 2009A).

In this incident report analysis, gentamicin and vancomycin were associated with high rates of MI prevalence and incidence, particularly in dosing. Gentamicin and vancomycin are highly-toxic antibiotics known for their narrow therapeutic index and need for continuous therapeutic drug monitoring. The main side effects of these antibiotics are nephrotoxicity and ototoxicity which are dose related. Doses of gentamicin and
vancomycin are individualised according to the patient parameters. Therefore, dose calculations are relatively complex which forms a risk of overdosing (potential toxicity) or underdosing (potential treatment failure) (Martin et al., 2010; Gonçalves-Pereira et al., 2010).

To evaluate the impact of a new intervention on improving gentamicin and vancomycin dosing at one of the study Trusts, this research (Chapter 4) used a pre-post intervention design which is widely used to assess medical informatics interventions. Although randomised controlled trials (RCT) are generally the best method to investigate intervention impacts, randomisation is not always possible/preferable. This can be due to ethical considerations (i.e. if the intervention has proven or questionable efficacy or safety, randomising patients may raise ethical concerns) or the difficulty to randomise by staff/patients (i.e. randomisation reduces the use of intervention and so it may compromise the strength of evidence of its efficacy) or by location (i.e. knowledge learned may be transferred to non-intervention wards and so masking the intervention’s real effect) (Harris et al., 2006). These factors were present in this study as the intervention was based on the Trust guidelines and so assumedly effective (ethical considerations) and it was being launched online when the decision to conduct the study was taken and so theoretically available for everyone to use (difficulty to randomise).

The method used to measure the prevalence of MIs pre- and post-intervention in this study was case note (or patient record) review. Although this method is costly and time-consuming, it allows detection of more MIs and collection of larger amount of information about the incident compared to other methods such as incident reporting and computerised monitoring (Jha et al., 1998; Stanhope et al., 1999; Olsen et al., 2007). Typically this method is limited by the reviewer’s experience and skills, as it relies on the accuracy of documentation in case notes, and provides limited information on drug administration (James, 2009). However, the use of a standard data collection form in this study and an electronic prescribing and medicines administration system (EPMA) in the Trust mitigated the effect of these limitations. In this study, both pre- and post-intervention data were collected from the same sources. These were electronic patient records (EPR), EPMA, paper notes, and bedside folders (i.e. nursing notes).

The majority of incorrect vancomycin loading doses (93%) in the current study were underdoses. In addition, 1000mg standard doses were commonly prescribed in the Trust
and most of them (76%) were also underdoses. Similar results were found in other studies (Fuller et al., 2013; Rosini et al., 2013). This was the first study to assess first maintenance dose as part of the initial dose of vancomycin in addition to loading dose and therefore no comparison with past studies was possible. Evaluating first maintenance doses was deemed important by the research team (including two Infectious Diseases Specialist Pharmacists) as they are essential in achieving appropriate serum levels in a timely manner. This was also reflected in the new guidelines-based vancomycin calculator which provided support for both loading and first maintenance doses.

### 6.3. Understanding prescribing of gentamicin and vancomycin initial doses

Doctors’ prescribing decisions are affected by two main factors. These are internal factors related to the prescriber characteristics and external factors related to the organisation or patient characteristics. Antimicrobial prescribing decisions are greatly affected by the predominant culture, social norms, attitudes, and beliefs within wards or organisations. In addition, junior doctors appear to routinely follow the prescribing choices of their seniors (i.e. specialists, consultants) regardless of organisation policies or treatment guidelines (Mol et al., 2004; Hulscher et al., 2010; Charani et al., 2013; Teixeira Rodrigues et al., 2013). The availability of qualitative evidence on the impact of behavioural and social factors on antimicrobial prescribing behaviour did not influence the design and evaluation of interventions developed to optimise antimicrobial prescribing behaviour. Therefore, applying behavioural strategies, with multidisciplinary support, is needed to enhance the understanding of antimicrobial prescribing behaviours and the effectiveness of interventions designed to improve their prescribing (Charani et al., 2011).

An interview-based study was undertaken to explore the views and experiences of doctors in prescribing gentamicin and vancomycin and the resources and methods they used to calculate the initial dose of these drugs (Chapter 5). Data were collected using semi-structured interviews which consisted of a series of open-ended questions derived from the topic under investigation. Although these questions were pre-defined, they still offered opportunities for both the interviewer and interviewee to discuss some topics in further detail. The ability of the interviewer to use different prompts, probes, and other techniques to obtain in-depth answers and fully explore the issue was another advantage of using semi-structured interviews (Hancock, 1998; Ritchie and Lewis, 2003). Four
themes emerged from analysing the interviews in this study; dose calculation resources, therapy monitoring, conditions and factors that might affect dose prescribing decision, and doctor views and opinions about drug dosing.

This study identified that doctors who used the dose calculators or guidelines accurately were more likely to prescribe a correct dose compared to those who used standard doses (e.g. 5mg/kg gentamicin, 1000mg BD vancomycin). However, a number of doctors who used the Trust dosing tools prescribed an incorrect dose due to technical errors while using them, unawareness of some of their features, or use of wrong patient values (e.g. actual rather than ideal body weight). Moreover, all participants who did not use the Trust dosing tools were aware of at least one of them (i.e. dose calculators or guidelines), however they decided not to use them for different reasons (e.g. not user-friendly, following a suggestion from Microbiology). These findings suggest that implementation of new tools is not sufficient to improve dosing quality and safety without providing sustainable support and education on their use and benefits.

In addition, most doctors were unaware of some values/equations needed for dose calculation (e.g. confusion between ideal and actual body weight). Although half of these doctors prescribed a correct dose mainly by accurate use of the Trust dosing tools, they did not actually know the basis on which this dose was calculated. This identifies a risk of overreliance on these tools without critical thinking and underpinning knowledge which might lead to dosing errors (DEs) if a problem occurred in the system or if the values originally entered on other systems (e.g. EPR) were wrong. Three main themes of unintended negative consequences were identified for clinicians’ overreliance on electronic CDS; clinical practice can be interrupted and patient safety can be compromised if the system is unavailable, false expectations of accuracy and processing of data on the system may exist, and a belief that clinicians cannot work effectively in the absence of technology support. (Campbell et al, 2007)

Participants in this study recognised the poor documentation and difficulty in finding a patient’s primary data, particularly weight and height. The unavailability of up-to-date patient primary data or use of inaccurate data (e.g. old, estimated, actual weight instead of ideal) is a common issue in hospital settings (Campbell et al, 2002; Hilmer et al, 2007; Kahn et al, 2007; Newham et al, 2015). This issue can have significant negative effects on the safety and quality of antimicrobial prescribing, particularly on dosing accuracy.
The choice of gentamicin and vancomycin in this study was usually not made by the participants, particularly junior doctors, and was largely influenced by the decisions of senior or specialist doctors. This hierarchy-based culture is very common in teaching hospitals where antimicrobial prescribing behaviour is predominantly induced by the senior doctors (Hulscher et al, 2010; Charani et al, 2011; Calbo et al, 2013; Charani et al, 2013). However, most of these junior doctors mentioned that they calculated the dose themselves with only the choice being recommended by senior/specialist doctors.

Several doctors in this study monitored drug serum levels, blood tests (e.g. inflammatory markers), and patient adverse (e.g. Red Man Syndrome with vancomycin) and clinical (e.g. fever) reactions as measures of assessing drug toxic and therapeutic effects. Despite the poor awareness of vancomycin ototoxicity, doctors demonstrated an adequate knowledge of the toxicities and monitoring of both gentamicin and vancomycin. This is important to provide effective treatment while avoiding patient harm. Proper monitoring and evaluation of drug toxic and therapeutic effects are essential to optimise/adjust drug doses and improve patient safety (Lazarou et al, 1998; Tully et al, 2009; Velo and Minuz, 2009).

Working conditions of participants and the factors they considered influencing their prescribing decisions for gentamicin and vancomycin were assessed. Busy ward environment, high workload, insufficient staffing, and prescriber tiredness and stress were identified by several studies as prescribing error (PE) producing conditions (Dean et al, 2002c; Dornan et al, 2009; Tully et al, 2009; Ryan et al, 2014; Newham et al, 2015). These conditions did not appear to have affected the dosing accuracy among the participants in this study. However, this was a small exploratory study of 24 doctors so this might limit the association between these factors and DEs. The main factors identified by prescribers as influencing their dose selection were patient parameters (i.e. gender, age, weight, height, and renal function), Trust dosing tools (i.e. antimicrobial guidelines and dose calculators), Microbiology advice, and clinical condition of the patient. These were all identified as important measures for a high-quality and safe prescribing process (Lesar et al, 1997B; Dean et al, 2000; Hulscher et al, 2010; Avery et al, 2012).
In this study, time constraints were identified by a number of doctors as a possible source of error and most of these have prescribed incorrect doses. This was also identified by other studies which stated that the short time doctors had to consider drug therapy issues had a direct impact on their prescribing and was a contributing factor to PEs (Lesar et al., 1997A; Dornan et al., 2009; Teixeira Rodrigues et al., 2013). One doctor suggested having more time while prescribing to thoroughly review the prescriptions can be a measure to avoid errors which was also recommended by Avery et al. (2012).

Some doctors in the current study identified data transcribing as a possible source of error including two who assumed they entered wrong values into the calculator. Transcribing errors due to poor communication, lack of information transfer, and slips (misprints) have been identified as a barrier to the safe and effective use of medicines and a risk for PEs (Leape et al., 1995; Dornan et al., 2009; Newham et al., 2015). The Trust where this study was conducted has an electronic prescribing system, which is seen as one of the primary interventions to avoid transcribing errors (García-Ramos and Baldominos Utrilla, 2011). However, transcribing is still needed in this Trust as some essential information is only available on paper (e.g. nursing notes, a main source of weight and height in this study) and some units do not have electronic prescribing (e.g. critical care).

6.4. Managing dosing errors in gentamicin and vancomycin

The analysis of antibiotic MIs at one of the Trusts in the first study (Chapter 2) identified that one-third of dose/frequency errors reported were related to gentamicin and vancomycin. A local Failure Modes and Effects Analysis (FMEA) for gentamicin (Cavell et al., 2010) had identified that risks with dose calculation and prescribing were greater than risks with preparation of infusions. A systematic review was conducted to identify evidence-based interventions to improve gentamicin and vancomycin dosing in adults (Chapter 3). This review identified computerised clinical decision support (CDS) tools associated with appropriate and sustainable education as the most effective type of intervention. A new CDS tool allied with educational activities was implemented at the Trust to improve the prescribing of gentamicin and vancomycin (Chapter 4).
CDS tools have various benefits which include improving management of specific diseases, providing personalised care, enhancing evidence-based practice, improving compliance with guidelines, guiding laboratory tests, checking interactions and contraindications, providing dosing guidance for specific patients/conditions, and reducing PSIs (Teich et al, 2005; Kuperman et al, 2007). However, CDS tools also have several unintended negative effects including elimination/changing roles of staff, unfavourable workflow issues, currency of the CDS content, wrong or misleading content, rigidity of systems, alert fatigue, confusing and fragmented displays, system shutdowns while a patient is transferred or a command is being entered, separation of related functions such as cancelling and modifying/remaking orders (e.g. prescriptions, tests), paper persistence (i.e. keep documenting some information on paper records), changes in communication patterns, and overdependence on technology (Koppel et al, 2005; Campbell et al, 2006; Eslami et al, 2006; Ash et al, 2007). Therefore, prescribers should always be mindful when using CDS tools, particularly for prescribing high-risk and narrow-therapeutic-index medications such as gentamicin and vancomycin.

The CDS tool in this study composed of two online dose calculators for gentamicin and vancomycin. The introduction of these calculators in the Trust has led to a significant improvement in the prescribing of gentamicin and vancomycin initial doses. Similar interventions have been investigated and showed positive dosing outcomes. However in comparison to the current study, these studies involved small populations (Vincent et al, 2009; Roberts et al, 2010; Qureshi et al, 2012), did not perform statistical analysis (Chan et al, 2006; Qureshi et al, 2012), were conducted at specific departments/units (Chan et al, 2006; Qureshi et al, 2012; Frankel et al, 2013), or used doses based on specific locally-derived formulas/equations (Chan et al, 2006; Roberts et al, 2010). Such factors can reduce the reliability and generalisability of study findings. The use of 1000mg loading doses was significantly reduced after the calculator implementation (P<0.001), however the rate of underdosing was relatively unchanged which was also shown in the study by Frankel et al (2013).

Many doctors in the interview-based study (Chapter 5) emphasised the importance of using the Trust dosing tools (i.e. guidelines and calculators). However, some talked about the difficulty in finding these tools and the necessity of making them more accessible. The Trust tools are an important factor that affects doctors’ prescribing decisions. It is important to involve social and behavioural factors when designing new tools. Consulting
the targeted end-users when developing a dosing tool can enhance ownership and improve the usage of this tool. In addition, the tool accessibility can be improved by promoting it and making it available in different forms such as paperbacks, online, and phone applications. It was also recommended that meetings should be organised to introduce new tools (Mol et al, 2004; Mol et al, 2005; Charani et al, 2011; Teixeira Rodrigues et al, 2013). In the study Trust, the guidelines were available as a handbook distributed to all junior doctors during their induction and as an online PDF version. In addition, the calculators were promoted by recommendations for use and information on how to access them on the electronic prescription forms for gentamicin and vancomycin. Some clinical pharmacists also promoted the tools during specific ward inductions.

The calculator pages on the Trust intranet were frequently accessed during the 2-month study period following their implementation. It is anticipated that the educational activities undertaken had a role in promoting such access. These were a Grand-Round presentation to endorse the importance of using the calculators and to show doctors how to use them, disseminating information about the calculators on the Trust online news page, by an email sent to all doctors in the Trust, and on gentamicin and vancomycin electronic prescription forms. It has been demonstrated that providing educational material(s) in conjunction with dosing interventions can improve their adoption and outcomes. To gain persistent effects, education about such interventions should be sustainable and become part of the clinicians’ routine practice (Manjaly et al, 2010; Roberts et al, 2010).

Education about the importance of using the Trust dosing tools and how to use them was also addressed by many of the interviewed doctors as a recommendation to improve the prescribing practice and avoid DEs with gentamicin and vancomycin. Education is an effective intervention to enhance doctors’ knowledge about the critical areas/features of the Trust dosing tools and to help them become familiar with these tools. Enhancing doctors’ knowledge through education and use of online support tools are measures recommended to reduce PEs. In addition, educational interventions regarding antimicrobial dose adjustments have been found to be highly accepted among doctors (Mol et al, 2004; Velo and Minuz, 2009; Calbo et al, 2013).

Improvements to make the calculators more compatible with the Trust electronic system and as part of the doctors’ workflow were also anticipated to have a role in their frequent
access. These improvements involved adding a direct link to the calculators from EPMA and adding a recommendation to use them and information on how to access them on the electronic prescription forms. The introduction of CDS tools into healthcare is a complex interaction between people, technology and organisational workflow. In addition to the technological aspect, there should also be a focus on changing workflows. The automatic provision of CDS tools as part of the prescribers’ workflow, rather than as an extra task added to their already heavy workload, is the most important factor for a successful CDS implementation. Other factors for CDS implementation success include providing support at the time and location of decision-making, recommendations rather than assessments, and information technology support (Kawamoto et al, 2005; Roberts et al, 2010).

Some measures were suggested in the literature to overcome the issue of using inaccurate/estimated patient primary data (particularly weight and height) in dose calculation such as making documentation of these data mandatory, using A&E beds with built-in scales, and focusing efforts on finding a context-specific dosing guidance which takes patient factors into account (Avery et al, 2012; Evans, 2012). In the current study, some of the doctors interviewed suggested that more compatibility could be introduced so the electronic calculators could populate patient data automatically from the EPR. This was considered a good solution for both the difficulty in finding primary data and transcribing errors. CDS tools can be integrated with other electronic systems available in the hospital to avoid manual re-entering of data already available on other hospital systems. To achieve this, CDS tools should be able to interact with these systems to access required data which would potentially enhance the efficiency and effectiveness of these tools (Marcos et al, 2013). However, some believed this might introduce a new risk by the overreliance on electronic CDS by doctors.

6.5. Implications for policy and practice

Detailed analysis of MI data is essential to understand the incidents and develop strategies to prevent their recurrence. In this thesis, different methods were used to evaluate and understand MIs. Investigating reported incidents can lead to their causes being identified which provides an opportunity for learning from dangerous situations. This can help finding potential solutions and preventive strategies. Incident report analysis provides a stable and reproducible measurement of existing problems within the system which would allow determining the effect of any implemented changes (Leape et al, 1997;
This thesis introduces a new method for evaluating MIs by determining an incident rate for each antibiotic based on its consumption (in DDDs). This analysis showed that interpreting incident data alongside consumption data provides a wider picture than the absolute numbers alone when determining which antibiotics are most ‘risky’ in practice. This method can also be applied when evaluating MIs with other drug classes. Therefore, it is recommended that drug consumption data should be taken into account wherever possible when evaluating MIs.

Unifying MI categories in the incident report analysis was an important aspect of this research and may enable future benchmarking of other incident data. As data could only be compared once categories had been standardised, this highlights the importance of harmonised MI categories for comparison between different hospitals. Therefore, efforts should be made to unify MI categories across all NHS organisations. This can be done either by developing a new taxonomy for MIs or, as suggested by Hua and Gong (2011), using a widely recognised one such as the National Co-ordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy for Medication Errors (2001).

This thesis showed that submitted MI reports may lack essential information about the incident such as the drug name or incident type. The lack of essential information in the submitted MI reports reduces their quality. This makes investigating the incidents and finding their causes more difficult and may affect the whole value of incident report analysis (Hua and Gong, 2011; Thomas et al, 2011; NHS England, 2014). Applying quality assurance measures, by the reporter and/or clinical manager, before reporting MIs can enhance the quality of information yielded from the submitted reports. These measures include reviewing the report and making sure that the incident type, severity, stage of the medication-use process, and drug involved are accurately documented and classified. Some essential fields in the Trust electronic incident reporting form (e.g. drug name) were not mandatory which might be the reason for the poor quality of some reports. Therefore, it is suggested that all essential fields in incident reporting systems should be made mandatory.

Qualitative research is essential to understand the prescribing process. This thesis identified that some doctors may use the Trust dosing tools accurately without knowledge of the dose calculation background, some may use the tools without knowing how to use them or being unaware of their features, and some may know about the tools but decide
not to use them. All of these are risks for PEs, particularly in dosing. These findings demonstrate that appropriate education about the existence of Trust dosing tools, the importance of using them, and how to use them is essential to improve prescribing and avoid DEs. Education is essential to achieve high clinical performance. Doctors in this study can be classified into different levels of the Miller’s (1990) framework for clinical assessment (Figure 6.1). Considering this framework, the Trust dosing tools should not be used before gaining an adequate knowledge about their background and how to use them, and showing competence by demonstrating this knowledge (e.g. in a training course). The doctors described above surpassed some of these steps and used the Trust tools for treating patients without having the required knowledge and competence. The doctors interviewed emphasised that sustainable education is needed to overcome these issues and enhance safe and effective use of the Trust dosing tools in the long term. This education can take place in different forms including online courses, local/general inductions, Grand-Round presentations, and Continuous Medical Education (CME) activities.

![Miller’s framework for clinical assessment](image)

*Figure 6.1. Miller’s framework for clinical assessment (1990, p.S63)*
This thesis demonstrated that the use of electronic CDS tools allied with appropriate education can give rise to improvements in clinical care and it suggests that healthcare organisations implementing electronic prescribing systems should consider including dose calculation tools in their programmes. Considering the end-users’ (doctors in this research) comments and recommendations when designing and updating dosing tools would increase ownership of these tools and potentially their use by end-users to enhance safe and effective prescribing in accordance with the Trust guidelines (Mol et al, 2005; Charani et al, 2011). The qualitative study within this thesis identified suggestions by doctors to enhance the use of the gentamicin and vancomycin dose calculators which can also be applied to other drugs as well as CDS tools. The two most important recommendations were about education and CDS compatibility.

Several doctors in this study suggested making the CDS tools easily accessible and more compatible with the Trust EPR so they could automatically retrieve and import patient data into the tool, especially with the poor documentation and difficulty in finding patient primary data in the Trust. These recommendations suggest that more efforts are needed to make the use of CDS tools part of the doctor’s workflow which would increase their acceptance and effectiveness (Figure 4.1). This can be done by enhancing connection between doctors’ workflow and the CDS tool timing, structure, and design. CDS tools that fit into the workflow are more likely to be used, however integrating them into the workflow may require specific customisation or changes to local processes. The more the CDS tool disrupts the doctors’ workflow, the more likely it is to be ignored (Berner, 2009). As discussed above, doctors should be engaged in the CDS tool design and implementation to enhance integration between their workflow and the usage of the tool. The importance of this engagement was conceptualised by Osheroff (2009, p.175) who stated that “Deploying CDS is done with clinicians and other end users, not to them”.

6.6. Limitations

Each of the methods used in this thesis has limitations. The first study (Chapter 2) was an incident report analysis which is generally limited by potential under-reporting as it depends on the willingness of staff to report incidents and the accuracy of their reporting (Stanhope et al, 1999; Evans et al, 2006; Shojania, 2010). This may have led to underestimation of the prevalence and incidence rates of antibiotic-related MIs in this study and the true rates could be higher. The different sources used to identify patients
pre- and post-intervention in the calculator study (Chapter 4) may have affected the study outcomes. As with other pre-post intervention studies, the internal validity of this study might be affected by threats emerging due to the different time periods in which data were collected such as selection (i.e. systematic differences over conditions in respondent characteristics could cause the observed effect) and maturation (i.e. naturally occurring changes over time could be confused with the intervention effect) (Harris et al, 2006).

The findings of the interview-based study (Chapter 5) may have limited generalisability which is a common issue in qualitative studies (Johnson and Christensen, 2003). This can be due to the small number of study participants (n=24). It can also be because the study was conducted at one hospital and so a dominant culture or behaviour across the hospital may have affected the knowledge and views of the participants. In addition, the accuracy of information collected in interview-based studies is dependent on the subjective reporting of participants and therefore can be affected by hindsight and recall bias (Bowling, 2009).

In the incident report analysis, MIs involving paediatrics were included in the DDD analysis as it was not possible to exclude paediatric data from the Trusts’ antibiotic consumption. As DDDs are applied only to adults, this might have affected the outcomes of the incident rate analysis in this study. In the calculator study, it was not technically possible to identify whether doctors who accessed the dose calculators actually used them to prescribe. Therefore, the significant improvements in gentamicin and vancomycin initial dose accuracy cannot be definitively linked to the calculators. The doctors in the interview-based study may have agreed to participate because they had specific issues with gentamicin/vancomycin prescribing or because they were more reflective about their prescribing (Dornan et al, 2009). This might limit the representativeness of the study sample.

6.7. Further work

This thesis has identified a novel method for evaluating MI data by measuring the incidence against drug consumption to produce an incident rate for each antibiotic which identified new risks and provided a broader view of the issue. However, the MI data used in this analysis were based on incident reports which could have possibly underestimated the true prevalence. In addition, the paediatric data were included in the analysis which might have affected the accuracy of its findings. Therefore in order to increase the
accuracy and benefits of this analysis method, it should be applied in a prospective case note review (the most accurate method in detecting PEs) with only adult data included.

In this thesis, efforts were made to increase the compatibility between the gentamicin and vancomycin dose calculators and the Trust electronic system by making a direct link from EPMA to the calculators and adding a recommendation to use the calculators in the drugs’ electronic prescription forms. However, as discussed above, there is a need to engage doctors when designing/updating such calculators in order to enhance their acceptance and adoption. Some doctors in the interview-based study suggested this compatibility should be enhanced so the patient data could be automatically populated from the Trust electronic system into the calculators. They believed that this might overcome the issues of poor patient data documentation and transcribing errors. Therefore, more work should be undertaken to fully integrate these calculators into the Trust electronic system to automatically populate the patient demographic data required for dosing (i.e. gender, age, weight, height, and serum creatinine). The feasibility of this enhanced compatibility and its potential impact on the safety and accuracy of prescribed doses should be assessed through an experimental study such as a randomised clinical trial or quasi-experiment.

The systematic review undertaken as part of this thesis identified that education is essential to the success of gentamicin and vancomycin dosing interventions. It is anticipated that the educational activities undertaken in the calculator study (i.e. Grand-Round presentation, intranet, emails, and electronic prescription forms) had a role in the frequent access of the calculators. However, interviewing the doctors identified that some education issues were still present regarding awareness of the dose calculation background, importance of using the Trust dosing tools, and how to use them. These issues are potential risks for DEs. Therefore, further work is needed to increase the knowledge of doctors about these aspects in order to mitigate risks and enhance patient safety while prescribing these drugs. In environments such as teaching hospitals with a high turnover of doctors, this could ideally involve sustainable educational activities which form part of doctors’ routine practice (e.g. CME). An experimental study (e.g. randomised clinical trial, quasi-experiment) should be conducted to measure the impact of educational activities on the use of Trust tools and the dosing safety and accuracy.

The online dose calculators assessed in this research have improved the accuracy of gentamicin and vancomycin initial doses. However, the fact that some doctors had
technical difficulties in using these calculators and some thought they are not user-friendly and complicating the prescribing process underscored the need for a better understanding of the detailed process of their use. Ideally, this could be done through a task analysis which would help to comprehensively understand both the manual and mental perspectives (e.g. frequency, duration, assignment, barriers, challenges) of using the calculators. This would allow identifying the best strategies, technical and educational, to overcome such issues and enhance the safe and effective usage of the calculators.

6.8. Summary of findings

A new method for evaluating MIs has been presented in this thesis. An incident rate was determined for each drug based on its consumption (in DDDs) which provided a wider picture than the absolute numbers alone when determining the most ‘risky’ drugs. Accordingly, wherever possible drug consumption data should be taken into consideration when evaluating MIs. MI data could only be compared after incident categories had been standardised, which highlighted the importance of harmonised MI categories for comparison between different hospitals. Therefore, efforts should be made to unify MI categories across all NHS organisations. In both research Trusts, incident reports could be submitted without recording essential information which reduced the quality of some reports analysed in this thesis. This can make incident report investigation more difficult and less valuable. Thus, it is important to routinely apply quality assurance measures before reporting MIs and to make all essential fields in incident reporting systems mandatory.

This thesis identified that some doctors had insufficient knowledge about the dose calculation background, importance of using the Trust dosing tools, and the technique of using them which are potential risks for DEs. These findings showed that implementing new CDS tools is not sufficient to improve dosing quality and safety without providing sustainable support and education on their use and benefits. This thesis demonstrated that using electronic CDS tools in conjugation with appropriate education can improve clinical care. Healthcare organisations implementing electronic prescribing systems should aim to implement dose calculation tools in their systems in association with routine educational activities.
Chapter 6: General Discussion

The measures applied in this thesis to increase the compatibility of CDS tools with the doctor’s workflow have potentially contributed to their frequent access. Still, several doctors recommended that more efforts should be made to integrate the use of CDS tools with the doctor’s workflow by making these tools more compatible with the Trust EPR so they could automatically retrieve and import required data. Considering the end-user’s comments when designing/updating CDS tools is essential to increase their acceptance and usage, which would enhance safe and effective prescribing. Therefore, the Trusts implementing online dose calculators should consider making these calculators compatible with other electronic systems in the Trust.

6.9. Overall conclusion

Comprehensive analysis of MI reports that consider the frequency with which specific drugs are used is useful for evaluating the existing medication-use issues within healthcare organisations as well as identifying and prioritising the possible MI risks in order to develop preventive strategies. One of the most effective strategies to improve the quality and safety of prescribing when using gentamicin and vancomycin is the use of electronic CDS tools in association with appropriate and sustainable education. This could be used to support prescribing of other high-risk drugs. However in order to increase the acceptance and adoption and maximise the benefits of such a strategy, it is essential to consider prescribers’ opinions and suggestions while designing or updating the CDS tools and associated education and promotion programmes.
References
References


Carrington Angela, Leader for secondary care in Northern Ireland Medicines Governance Team. (10:40 on 16th May 2014) Oral communication by phone from Belfast.


References


Franklin BD, Barber N. (2009) *Memorandum by Professor Bryony Dean Franklin and Professor Nick Barber (PS 86): Medication safety: is technology the solution or the problem?*. London: House of Commons, Health Committee Publications.


King’s College Hospital NHS Foundation Trust. (2012A) *All about King’s*. [online] Available at: https://careers.kch.nhs.uk/about/all-about-kings (accessed 14th July 2012).


Olsen S, Neale G, Schwab K, Psaila B, Patel T, Chapman EJ, Vincent C. (2007) Hospital staff should use more than one method to detect adverse events and potential adverse events: incident reporting, pharmacist surveillance and local real-time record review may all have a place. *Quality and Safety in Health Care*, 16(1):40–44.


267


References


References


Appendices
Appendix 2.1. Adverse incident report form at Trust A
Appendix 2.1. (Continued)  Adverse incident report form at Trust B
### Appendix 2.2. The terms used for stage of medication-use process and type of medication incident in each Trust and the agreed terms used in this study

<table>
<thead>
<tr>
<th>Stage in Trust A</th>
<th>Stage in Trust B</th>
<th>Agreed stage term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration or supply</td>
<td>Administration or supply of a medicine from a</td>
<td>Administration</td>
</tr>
<tr>
<td></td>
<td>clinical area</td>
<td></td>
</tr>
<tr>
<td>Dispensing</td>
<td>Dispensing in pharmacy</td>
<td>Dispensing</td>
</tr>
<tr>
<td>Prescribing</td>
<td>Prescribing process</td>
<td>Prescribing</td>
</tr>
<tr>
<td>Medical Information</td>
<td>Advice</td>
<td>Medical Advice</td>
</tr>
<tr>
<td>Medication Other</td>
<td>Other medication error</td>
<td>Other</td>
</tr>
<tr>
<td>-</td>
<td>Monitoring or follow up of medicine use</td>
<td>Monitoring</td>
</tr>
<tr>
<td>-</td>
<td>System for management of drugs</td>
<td>Drug Management System</td>
</tr>
<tr>
<td><strong>Stage in Trust A</strong></td>
<td><strong>Type in Trust A</strong></td>
<td><strong>Agreed type term</strong></td>
</tr>
<tr>
<td>Administration or supply</td>
<td>Contraindication to the use of the medication</td>
<td>Contraindication</td>
</tr>
<tr>
<td>Allergy</td>
<td>Patient allergic to treatment</td>
<td>Allergy</td>
</tr>
<tr>
<td>Delay / failure to monitor</td>
<td>Delay or failure to monitor</td>
<td>Delay / Failure to Monitor</td>
</tr>
<tr>
<td>Documentation</td>
<td>Medication given but not signed for</td>
<td>Documentation</td>
</tr>
<tr>
<td>Expired drug</td>
<td>Wrong/omitted/passed expiry date</td>
<td>Expired Drug</td>
</tr>
<tr>
<td>Inadequate storage</td>
<td>Wrong storage</td>
<td>Inappropriate Storage</td>
</tr>
<tr>
<td>Not indicated / not discontinued</td>
<td>Failure to discontinue treatment</td>
<td>Failure to Discontinue</td>
</tr>
<tr>
<td>Omission</td>
<td>Medicine not prescribed</td>
<td>Omission</td>
</tr>
<tr>
<td>Omission</td>
<td>Omitted medicine or ingredient</td>
<td></td>
</tr>
<tr>
<td>Delay</td>
<td>Medicine prescribed but not provided</td>
<td>Delay (in all stages)</td>
</tr>
<tr>
<td>Wrong drug</td>
<td>Prescribing – Delay</td>
<td>Wrong Drug</td>
</tr>
<tr>
<td>Wrong formulation</td>
<td>Wrong drug / medicine</td>
<td>Wrong Formulation</td>
</tr>
<tr>
<td>Wrong preparation</td>
<td>Wrong method of preparation or supply</td>
<td>Wrong preparation</td>
</tr>
<tr>
<td>Wrong frequency/dosing interval</td>
<td>Wrong frequency</td>
<td>Wrong Frequency</td>
</tr>
<tr>
<td>Wrong patient</td>
<td>Mismatch between patient and medicine</td>
<td>Wrong Patient</td>
</tr>
<tr>
<td>Wrong dose</td>
<td>Wrong/unclear dose or strength</td>
<td>Wrong Dose</td>
</tr>
<tr>
<td>Wrong quantity</td>
<td>Wrong quantity</td>
<td>Wrong Quantity</td>
</tr>
<tr>
<td>Wrong rate</td>
<td>Rate of infusion incorrect</td>
<td>Wrong Rate</td>
</tr>
<tr>
<td>Wrong route</td>
<td>Wrong route</td>
<td>Wrong Route</td>
</tr>
<tr>
<td>Wrong / omitted patient</td>
<td>Wrong / transposed/omitted medicine label</td>
<td></td>
</tr>
<tr>
<td>information leaflet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication - other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration - other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispensing - other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribing - other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug duplication</td>
<td>Repeat prescribing</td>
<td>Drug Duplication</td>
</tr>
<tr>
<td></td>
<td>Inadequate systems or records of medicines and</td>
<td>Inadequate Medicine Systems or Records</td>
</tr>
<tr>
<td></td>
<td>usage</td>
<td>Wrong Time</td>
</tr>
<tr>
<td></td>
<td>Drug Duplication</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Dose Duplication</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Not indicated</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2.3. Risk matrix to grade the severity of adverse incidents
### Appendix 3.1. Strategy used to search databases for relevant articles: Embase

<table>
<thead>
<tr>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin.mp. or exp gentamicin/ or exp gentamicin C/ or gentamycin.mp.</td>
<td>exp harm reduction/ or exp risk reduction/ or reduc*.mp.</td>
<td>exp intervention study/ or intervention*.mp.</td>
<td>exp optimal drug dose/ or exp drug dose/ or exp recommended drug dose/ or exp dose dosages/ or exp dose calculation/ or exp dose response/ or dose*.mp.</td>
<td>exp medical error/ or exp medication error/ or exp therapeutic error/ or exp error/ or error*.mp.</td>
</tr>
<tr>
<td>vancomycin.mp. or exp vancomycin derivative/ or exp vancomycin/ or vancomycin.mp.</td>
<td>quality improvement.mp. or exp total quality management/ or improv*.mp.</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp incident report/ or incident*.mp.</td>
</tr>
<tr>
<td>enchanc*.mp. A AND optimi*.mp. A AND decreas*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp information processing/ or exp decision support system/ or decision support system*.mp. or exp medical decision making/ or decision adj2 support adj2 system</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>quality improvement.mp. or exp total quality management/</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>software*.mp. or exp computer program</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>exp computerized provider order entry/ or computer order entry.mp. or computer*.adj2 order adj2 entry</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>exp computer/ or computer*.mp. or exp computer assisted drug therapy</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>exp drug information/ or exp medical information system/ or exp data processing/</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>exp electronic prescribing</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td>exp nomogram/ or nomogram*.mp.</td>
<td>exp drug dose calculator/ or exp pocket calculator/ or calculator*.mp.</td>
<td>exp hospital policy/ or exp health care policy/ or exp policy/ or polic*.mp.</td>
<td>exp practice guideline/ or exp healthcare quality/ or guideline*.mp.</td>
<td>exp inappropriate prescribing/ or prescribing.mp.</td>
</tr>
</tbody>
</table>
### Appendix 3.1. (Continued) Strategy used to search databases for relevant articles: Medline

<table>
<thead>
<tr>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin.mp. or exp Gentamicins/ or gentamycin.mp.</td>
<td>exp Harm Reduction/ or exp Safety Management/ or reduc*.mp.</td>
<td>exp Guideline Adherence/ or guideline*.mp. or exp Guideline/ or exp Practice Guideline</td>
<td>dose*.mp. or exp Dose-Response Relationship, Drug</td>
<td>exp Medical Errors/ or exp Medication Errors/ or error*.mp.</td>
</tr>
<tr>
<td>vancomycin.mp. or exp Vancomycin/ or vancomicin.mp.</td>
<td>exp Quality Improvement/ or exp Quality Assurance, Health Care/ or improv*.mp.</td>
<td>exp Quality Improvement/ or exp Quality Assurance, Health Care</td>
<td>dosing.mp.</td>
<td>incident*.mp.</td>
</tr>
<tr>
<td>enhanc*.mp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>optimi*.mp.</td>
<td></td>
<td></td>
<td></td>
<td>event*.mp.</td>
</tr>
<tr>
<td>decreases.mp.</td>
<td></td>
<td></td>
<td></td>
<td>exp Adverse Drug Reaction Reporting Systems/ or exp &quot;Drug-Related Side Effects and Adverse Reactions”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>exp Inappropriate Prescribing/ or prescribing.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>accura*.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>incorrect.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wrong.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>exp Clinical Pharmacy Information Systems/ or exp Medication Systems, Hospital/ or exp Drug Therapy, Computer-Assisted/ or computer* order entry.mp. or exp Medical Order Entry Systems/ or exp Medical Records Systems, Computerize/d or computer* adj2 order adj2 entry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>exp Drug Information Services</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>exp Nomograms/ or nomogram*.mp.</td>
</tr>
</tbody>
</table>
### Appendix 3.1. (Continued) Strategy used to search databases for relevant articles: CINAHL

<table>
<thead>
<tr>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;gentamicin&quot; or (MH &quot;Gentamicins&quot;)</td>
<td>(MH &quot;Harm Reduction&quot;) or reduc*</td>
<td>(MH &quot;Crisis Intervention&quot;) or (MH &quot;Nursing Interventions&quot;) or &quot;intervention***&quot;</td>
<td>&quot;dose*&quot; or (MH &quot;Dose-Response Relationship, Drug&quot;) or (MH &quot;Dose-Response Relationship&quot;)</td>
<td>&quot;dosing&quot;</td>
</tr>
<tr>
<td>&quot;gentamycin&quot; or (MH &quot;Quality Assurance+&quot;) or (MH &quot;Quality Management, Organizational&quot;) or (MH &quot;Quality Improvement+&quot;) or (MH &quot;Quality Control (Technology)&quot;) or improv*</td>
<td>(MH &quot;Decision Support Systems, Clinical&quot;) or (MH &quot;Decision Support Techniques+&quot;) or (MH &quot;Clinical Information Systems+&quot;) or decision N2 support* N2 system* or decision N2 support* N2 tool*</td>
<td>(MH &quot;Dosage Calculation+&quot;) or &quot;dosage*&quot;)</td>
<td>&quot;event*&quot;</td>
<td>&quot;incorrect&quot;</td>
</tr>
<tr>
<td>&quot;vancomycin&quot; or &quot;vancomycin&quot;</td>
<td>(MH &quot;Support System Enhancement (Iowa NIC)&quot;) or &quot;enhanc*&quot;</td>
<td>(MH &quot;Therapy, Computer Assisted+&quot;) or (MH &quot;Drug Therapy, Computer Assisted&quot;) or (MH &quot;Computer Systems+&quot;) or computer*</td>
<td>(MH &quot;Practice Guidelines&quot;) or (MH &quot;Guideline Adherence&quot;) or (MH &quot;Clinical Effectiveness&quot;) or guideline*</td>
<td>&quot;incorrect&quot;</td>
</tr>
<tr>
<td>(MH &quot;Vancomycin&quot;) or (MH &quot;Vancomycin&quot;)</td>
<td>optimi*</td>
<td>(MH &quot;Software+&quot;) or software* calculator*</td>
<td>(MH &quot;Program Evaluation&quot;) or (MH &quot;Hospital Programs&quot;) or program*</td>
<td>&quot;incorrect&quot;</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>&quot;wrong&quot;</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>&quot;accura*&quot;</td>
</tr>
</tbody>
</table>

(MH "Inappropriate Prescribing") or (MM "Prescribing Patterns") or (MM "Medication Prescribing (Iowa NIC)") or "prescrib*"
Appendix 3.1. (Continued) Strategy used to search databases for relevant articles: WoS, IPA, Global Health, and HMIC

<table>
<thead>
<tr>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
<th>Linked by OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin or gentamycin</td>
<td>reduc*</td>
<td>intervention*</td>
<td>dose*</td>
<td>error*</td>
</tr>
<tr>
<td>vancomycin or vancomycin</td>
<td>improv*</td>
<td>calculator*</td>
<td>dosing</td>
<td>incident*</td>
</tr>
<tr>
<td>enhanc*</td>
<td>polic*</td>
<td>dosage</td>
<td>event*</td>
<td></td>
</tr>
<tr>
<td>optimi*</td>
<td>guideline*</td>
<td>accuracy</td>
<td>correct</td>
<td></td>
</tr>
<tr>
<td>decreas*</td>
<td>software*</td>
<td>dosing</td>
<td>correct</td>
<td></td>
</tr>
<tr>
<td>quality adj2 assur*</td>
<td>computer*</td>
<td>dosing</td>
<td>correct</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td>safety adj2 manag*</td>
<td>decision support* system* or decision adj2 support* adj2 system* or decision support* tool* or decision adj2 support* adj2 tool*</td>
<td>program*</td>
<td>wrong</td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>quality adj2 assur*</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>safety adj2 manag*</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>decision making</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>computer* adj2 order adj2 entry</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>drug information*</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>electronic adj2 prescri*</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
<td></td>
<td>nomogram</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 3.2. Data extraction form: systematic review

<table>
<thead>
<tr>
<th>Study number:</th>
<th>____________________________________________________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Journal title and year:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Language, if not English:</td>
<td>____________________________________________________________________________</td>
</tr>
</tbody>
</table>

#### Study design:
- [ ] Randomised controlled trial
- [ ] Non-randomised controlled trial
- [ ] Before and after study
- [ ] Interrupted time series

<table>
<thead>
<tr>
<th>Country:</th>
<th>____________________________________________________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Participants:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Data collection process:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Total study period:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Intervention:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Dosing outcomes:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Clinical outcomes:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Financial outcomes:</td>
<td>____________________________________________________________________________</td>
</tr>
<tr>
<td>Comments:</td>
<td>____________________________________________________________________________</td>
</tr>
</tbody>
</table>
Appendix 3.3. PRISMA checklist for assessing the reporting quality of systematic reviews (from PRISMA Statement, 2009)

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td></td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td></td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td></td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td></td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td></td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td></td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td></td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td></td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td></td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td></td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td></td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study; (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see item 15).</td>
<td></td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).</td>
<td></td>
</tr>
<tr>
<td><strong>DISCUSSION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td></td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td></td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td></td>
</tr>
<tr>
<td><strong>FUNDING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3.4. TREND checklist for assessing the quality of non-randomised comparative studies (from CDC, 2010)

<table>
<thead>
<tr>
<th>Paper Section/Topic</th>
<th>Item No</th>
<th>Descriptor</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and Abstract</td>
<td>1</td>
<td>• Information on how units were allocated to interventions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Structured abstract recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Information on target population or study sample</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>2</td>
<td>• Scientific background and explanation of rationale</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Theories used in designing behavioral interventions</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
<td>• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recruitment setting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Settings and locations where the data were collected</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>4</td>
<td>• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Content: what was given?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Delivery method: how was the content given?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Unit of delivery: how were the subjects grouped during delivery?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Deliverer: who delivered the intervention?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Setting: where was the intervention delivered?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Time span: how long was it intended to take to deliver the intervention to each unit?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Activities to increase compliance or adherence (e.g., incentives)</td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>• Specific objectives and hypotheses</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>• Clearly defined primary and secondary outcome measures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Methods used to collect data and any methods used to enhance the quality of measurements</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Information on validated instruments such as psychometric and biometric properties</td>
<td></td>
</tr>
<tr>
<td>Sample Size</td>
<td>7</td>
<td>• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules</td>
<td></td>
</tr>
<tr>
<td>Assignment Method</td>
<td>8</td>
<td>• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3.4. (Continued) TREND checklist for assessing the quality of non-randomised comparative studies (from CDC, 2010)

<table>
<thead>
<tr>
<th>Blinding (masking)</th>
<th>9</th>
<th>• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit of Analysis</td>
<td>10</td>
<td>• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)</td>
</tr>
<tr>
<td>Statistical Methods</td>
<td>11</td>
<td>• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Methods for imputing missing data, if used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistical software or programs used</td>
</tr>
<tr>
<td>Results</td>
<td>12</td>
<td>• Flow of participants through each stage of the study: enrolment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Enrolment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Assignment: the numbers of participants assigned to a study condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Analysis: the number of participants included in or excluded from the main analysis, by study condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Description of protocol deviations from study as planned, along with reasons</td>
</tr>
<tr>
<td>Recruitment</td>
<td>13</td>
<td>• Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td>Baseline Data</td>
<td>14</td>
<td>• Baseline demographic and clinical characteristics of participants in each study condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baseline characteristics for each study condition relevant to specific disease prevention research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Comparison between study population at baseline and target population of interest</td>
</tr>
<tr>
<td>Baseline equivalence</td>
<td>15</td>
<td>• Data on study group equivalence at baseline and statistical methods used to control for baseline differences</td>
</tr>
</tbody>
</table>
Appendix 3.4. (Continued) TREND checklist for assessing the quality of non-randomised comparative studies (from CDC, 2010)

<table>
<thead>
<tr>
<th>Numbers analyzed</th>
<th>16</th>
<th>• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Indication of whether the analysis strategy was &quot;intention to treat&quot; or, if not, description of how non-compliers were treated in the analyses</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17</td>
<td>• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inclusion of null and negative findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory</td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)</td>
</tr>
</tbody>
</table>

DISCUSSION

| Interpretation | 20 | • Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study |
|               |    | • Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations |
|               |    | • Discussion of the success of and barriers to implementing the intervention, fidelity of implementation |
|               |    | • Discussion of research, programmatic, or policy implications |
| Generalizability | 21 | • Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues |
| Overall Evidence | 22 | • General interpretation of the results in the context of current evidence and current theory |
Appendix 3.5. EPOC risk of bias criteria for assessing RCTs, CCTs and CBAs (adapted from EPOC, 2009)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>‘Low risk’ if a random process is described; ‘High risk’ when a non-random method is used; CBA studies should be scored ‘High risk’; ‘Unclear risk’ if not specified.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>‘Low risk’ if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme; CBA studies should be scored ‘High risk’; ‘Unclear risk’ if not specified.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Baseline outcome measures</td>
<td>‘Low risk’ if performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups; ‘High risk’ if important differences were present and not adjusted in analysis; ‘Unclear risk’ if RCTs have no baseline measure of outcome.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>‘Low risk’ if baseline characteristics of the study and control providers are reported and similar; ‘High risk’ if there is no report of characteristics in text or tables or if there are differences between control and intervention providers; ‘Unclear risk’ if it is not clear.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>‘Low risk’ if missing outcome measures were unlikely to bias the results; ‘High risk’ if missing outcome data was likely to bias the results; ‘Unclear risk’ if not specified.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Blinding</td>
<td>‘Low risk’ if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective; ‘High risk’ if the outcomes were not assessed blindly; ‘Unclear risk’ if not specified.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Contamination</td>
<td>‘Low risk’ if allocation was by community, institution or practice and it is unlikely that the control group received the intervention; ‘High risk’ if it is likely that the control group received the intervention; ‘Unclear risk’ if professionals were allocated within a practice and it is possible communication between intervention and control professionals have occurred.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>‘Low risk’ if there is no evidence that outcomes were selectively reported; ‘High risk’ if some important outcomes are subsequently omitted from the results; ‘Unclear risk’ if not specified.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Other bias</td>
<td>‘Low risk’ if there is no evidence of other risk of biases</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; CBA: controlled before-and-after; CCT: non-randomised controlled.
## Appendix 4.1. Gentamicin calculator for males

### Gentamicin Calculator for Male Adults

**STEP 1. CLICK RESET BUTTON FIRST TO CLEAR PAGE**

**STEP 2.** Enter below the patient’s Age, Height, Actual Body Weight, Serum Creatinine and press the Enter/Return key to calculate gentamicin dose and frequency.

<table>
<thead>
<tr>
<th><strong>Male-adult only</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Height in cm</strong> (must be greater than 152.4cm)</td>
</tr>
<tr>
<td><strong>Actual body weight in kg</strong></td>
</tr>
<tr>
<td><strong>Serum creatinine (micromol/L)</strong></td>
</tr>
</tbody>
</table>

- Ideal Body Weight (kg): 70.5
- Appropriate weight to be used (kg): 70.5
- Creatinine clearance (ml/min): 79.6

**Gentamicin dose in mg (rounded):** 280

**Dose Interval:** 24 hours
Appendix 4.2. Vancomycin calculator for females

Creatinine Clearance Calculator for Female Adults

**STEP 1.** CLICK RESET BUTTON FIRST TO CLEAR PAGE

**STEP 2.** Enter below the patient’s Age, Height, Actual Body Weight, Serum Creatinine and press the Enter/Return key to get the Creatinine Clearance value

**Female**

- **Age:** 40.0
- **Height (inches over 5 feet):** 9.0
- **Actual body weight (kg):** 60.0
- **Serum creatinine (micromol/L):** 100.0

**Ideal Body Weight (kg):** 66.2
**Appropriate weight to be used (kg):** 60.0

**Creatinine clearance (ml/min):** 62.4

**STEP 3.** See “Vancomycin Dose Calculator” sheet for vancomycin loading and maintenance doses.

Always use this calculator for calculating doses of vancomycin. Use of eGFR result as available on the EPR system is not applicable.

---

**INTRAVENOUS VANCOMYCIN DOSE CALCULATOR FOR FEMALE ADULT PATIENTS**

Recommended doses and dosage intervals are shown in red

**INITIAL IV LOADING DOSE (based on actual body weight)**

1500 mg over 180 minutes

**REGULAR IV MAINTENANCE DOSE (based on Creatinine Clearance)**

Prescribe an intermittent IV infusion

**Mode of administration**

<table>
<thead>
<tr>
<th>Time after loading to start of maintenance infusion (hours)</th>
<th>Intermittent infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Dose (mg)</td>
<td>750</td>
</tr>
<tr>
<td>Interval (hours)</td>
<td>12</td>
</tr>
<tr>
<td>Duration of infusion (minutes)</td>
<td>90</td>
</tr>
</tbody>
</table>

Creatinine Clearance (ml/min) 72.8

DO NOT USE THIS TOOL IF CREATININE CLEARANCE < 20ml/min OR THE PATIENT IS ON HAEMODIALYSIS/PERITONEAL DIALYSIS – REFER TO THE RENAL TEAM. See Vancomycin intermittent infusion sheet for vancomycin monitoring guidelines.
Appendices

Appendix 4.3. Calculators’ promotion information - the link from the Trust electronic system to the calculators

Antibiotic Treatment And Prophylaxis Guidelines

Gentamicin and Vancomycin Calculators
- Use the following calculators to determine the appropriate dose before reporting GCA (once daily) or Vancomycin:
  - Gentamicin Calculators
  - Vancomycin Calculators
  - Combined Clearance Calculators
Appendix 4.3. (Continued) Calculators’ promotion information - the non-mandatory instruction to use the calculator on the electronic prescribing orders
Appendix 4.3. (Continued) Calculators’ promotion information - the promotion post on the Trust intranet news page

Gentamicin & Vancomycin Dose Calculators for Adult Patients

Gentamicin and Vancomycin dose calculators are available on the Infection Resources section of the Intranet and via the Tools menu on EPMA.

Adult patients receiving gentamicin or vancomycin for the treatment of serious infections, are at risk of toxicity if either of these antibiotics are prescribed and administered without due consideration of the patient's weight and renal function. To support safer prescribing of these antibiotics, the gentamicin and vancomycin orders on EPMA have been simplified.

For IV gentamicin, there are now three choices available:

- 'Gentamicin (IV) Infusion STAT Dose' – to be used when only a single dose is required e.g. catheter change.
- 'Gentamicin (IV) Infusion Every 24 Hours' – to be used when gentamicin is to be continued for at least 2 days. This order set includes a Drug Level Reminder which will prompt for a time to be entered for a trough plasma concentration of gentamicin to be measured the day after the first dose.
- 'Gentamicin (IV) Multiple Daily Dosing Protocol' – to be used for indications including endocarditis, where twice daily dosing is required. This order set also prompts for trough and peak plasma concentrations to be measured.

IV vancomycin options include:

- 'Vancomycin Infusion IV (mg/kg)' – allows individualised dose adjustment based on plasma concentration levels
- 'Vancomycin Infusion Keijser' – this includes both loading and maintenance doses based upon renal function.

Please note that vancomycin also requires monitoring of plasma concentrations, and dose adjustment as necessary.

Calculators to determine the appropriate initial dose of gentamicin (Gentamicin Calculator) and vancomycin (Vancomycin Calculator) for adults are available. The calculators will ask the user to enter patient details including age, height, actual body weight and serum creatinine. Once entered, the calculator will provide the dose of gentamicin or vancomycin to be prescribed and administered, and the interval between doses. Please note that the gentamicin calculator is only for single daily doses, and not for multiple daily dosings for such indications as endocarditis.

The calculators are accessed via EPMA via the Tools menu 'Antimicrobial Guidelines and Calculators'. Alternatively, the calculators may be accessed on the intranet under Infection Resources 'Antimicrobial Treatment and Prophylaxis Guidelines'.

Please contact your ward pharmacist should you require any further support or information, or refer to the Adult Antimicrobial Pocket Guide.

James Hinton
Lead Antimicrobials Pharmacist
jhintongha@kch.nhs.uk
Extension: 5728

293
Appendix 4.3. (Continued) Calculators’ promotion information - the promotion post within the Trust’s Daily Bulletin email

Gentamicin & Vancomycin Dose Calculators for Adult Patients
Gentamicin and Vancomycin dose calculators are available on the Infection Resources section of the intranet and via the Tools menu on EPRIA.

From: Janet Winter

Events and Courses
Appendix 4.3. (Continued) Calculators’ promotion information - the promotion email sent to all Trust doctors

RE: Information to Drs to support Gentamicin and Vancomycin prescribing at KCH

Akintoye Titilayo (KING’S COLLEGE HOSPITAL NHS FOUNDATION TRUST) [akintoye@nhs.net] 29 May 2013

Dear All,

This message was sent with High importance.

Re: Calculators for Adult Paediatrics

Gentamicin and Vancomycin dose calculators are available on the Infection Resources section of the intranet and via the Tools menu on EMPA.

Adult patients receiving gentamicin or vancomycin for the treatment of serious infections, are at risk of toxicity if either of these antibiotics are prescribed and administered without due consideration of the patient’s weight and renal function. To support safer prescribing of these antibiotics, the gentamicin and vancomycin codes on EMPA have been updated.

For Gentamicin, there are now three choices available:

- Gentamicin (IV) lnfusion STAT/Dose - to be used where only a single dose is required e.g. patheter change.
- Gentamicin (IV) lnfusion every 24 hours - to be used where gentamicin is to be continued for at least 3 days. This order set includes a Drug Level Reminder which will prompt for a time to be entered for a trough plasma concentration of gentamicin to be measured the day before the first dose.
- Gentamicin (IV) Multiple Daily Dosing Protocol - to be used for indications including endocarditis, where twice daily dosing is required. This order set also prompts for trough and peak plasma concentrations to be measured.

Vancomycin options include:

- Vancomycin Infusion (mg/kg) - allows individualised dose adjustment based on plasma concentration levels
- Vancomycin Infusion (Regimen) - this includes both loading and maintenance doses based upon renal function.

Please note that vancomycin also requires monitoring of plasma concentrations, and dose adjustment as necessary.

Calculators to determine the appropriate initial dose of gentamicin and vancomycin for adults are available. The calculator will ask the user to enter patient details including age, weight, actual body weight and serum creatinine. Once entered the calculator will provide the dose of gentamicin or vancomycin to be prescribed and administered, and the interval between doses. Please note that the gentamicin calculator is only for single daily doses, and not for multiple daily dosing for such indications are endocarditis.

The calculators are accessed in EMPA/EMPA via the Tools menu. ‘Antimicrobial Guidelines and Calculators’. Alternatively, the calculators may be accessed on the intranet under Infection Resource Antimicrobial Treatment and prophylaxis guidelines.

Please contact your local pharmacist should you require any further support or information or refer to the Adult Antimicrobial Pocket Guide.
Appendix 4.4. Data collection form used in the study

<table>
<thead>
<tr>
<th>Personal Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID number: ...........................................</td>
</tr>
<tr>
<td>Date of Birth: ........................................... Age: ...........................................</td>
</tr>
<tr>
<td>Gender: 1- Male ☐ 2- Female ☐</td>
</tr>
<tr>
<td>Ethnicity: 1- White ☐ 2- Black ☐ 3- E Asian ☐ 4- S Asian ☐ 5- Other Asian ☐</td>
</tr>
<tr>
<td>6- Hispanic ☐ 7- Mixed ☐ 8- Other ☐ 9- NA ☐</td>
</tr>
<tr>
<td>Weight (kg): ........................................... Height (cm): ...........................................</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose-Related Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Prescription: ........................................... Gentamicin ☐ Vancomycin ☐</td>
</tr>
<tr>
<td>Ward: ...........................................</td>
</tr>
<tr>
<td>Specialty: 1- Surgery ☐ 2- Medicine ☐ 3- Renal ☐ 4- Cardiology ☐ 5- Liver ☐</td>
</tr>
<tr>
<td>6- Critical Care ☐ 7- Haematology/Oncology ☐ 8- Neuroscience ☐</td>
</tr>
<tr>
<td>9- Women’s &amp; Children’s ☐ 10- Private Wing ☐</td>
</tr>
<tr>
<td>Loading Dose, if Vancomycin (mg): ...........................................</td>
</tr>
<tr>
<td>Maintenance Dose (mg): ........................................... Dosing Interval: Stat ☐ q12h ☐ q24h ☐</td>
</tr>
<tr>
<td>Serum Level Type: 1- Pre-dose ☐ 2- Post-dose ☐ 3- Random ☐ 4-NA ☐</td>
</tr>
<tr>
<td>1st Serum Level Measurement (mg/L): ........................................... Normal ☐ High ☐ Low ☐</td>
</tr>
<tr>
<td>Serum Creatinine (umol/L): ........................................... e-GFR (ml/min): ...........................................</td>
</tr>
<tr>
<td>Comments: ..........................................................</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calculator Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Clearance (ml/min): ...........................................</td>
</tr>
<tr>
<td>Ideal Body Weight (kg): ........................................... Appropriate Dosing weight (kg): ...........................................</td>
</tr>
<tr>
<td>Correct Loading Dose, if Vancomycin (mg): ...........................................</td>
</tr>
<tr>
<td>Correct Maintenance Dose (mg): ........................................... Correct Dosing Interval: Stat ☐ q12h ☐ q24h ☐</td>
</tr>
<tr>
<td>Loading Dose Accuracy, if Vancomycin: Correct ☐ Overdose ☐ Underdose ☐</td>
</tr>
<tr>
<td>Maintenance Dose Accuracy: Correct ☐ Overdose ☐ Underdose ☐</td>
</tr>
<tr>
<td>Total Accuracy, if Vancomycin: Correct ☐ Incorrect ☐</td>
</tr>
</tbody>
</table>
Appendix 5.1. Pre-study information email sent to all doctors in the Trust

**Email Subject:** An exploratory interview-based study with doctors to determine the methods they use to calculate the initial dose of gentamicin and vancomycin - Circular

*Circular email for use for recruitment of doctors for study reference number BDM/12/13-26, approved by the KCL Research Ethics Committee.*

This qualitative interview-based study which is being conducted for a PhD at King’s College London aims to assess the prescribers’ methods of calculating gentamicin and vancomycin initial doses, their experience and use of resources (e.g. protocols, and calculators) in order to understand and consequently improve the current prescribing practice of these high-risk drugs.

A sample of doctors who have prescribed an initial dose of gentamicin or vancomycin will be invited to participate in the study regardless if this dose was correct or incorrect. If you were selected after prescribing an initial dose of gentamicin or vancomycin, you will be invited to participate in an interview with a member of the research team. If you agree to take part in this interview, it will be arranged at a date, time and venue that are convenient for you and it will take approximately half an hour. With your consent, the interviews will be audio-recorded. All data collected by the research team is strictly CONFIDENTIAL.

There is no anticipated reason to believe any participant will suffer any undue distress, harm or injury from participating in this study. In addition, you will be able to withdraw from the study at any point up to 48 hours after the interview without giving any reason.

Results of this study will be used to further develop interventions to help staff undertake dose calculations which is important to be done safely and effectively to enhance prescribing accuracy and medication safety. If you would like a copy of the results, we will be happy to send you one.

For further information about this study, please refer to the participant information leaflet attached.

Best regards and many thanks for your cooperation,

**Anas Hamad, BPharm MSc**

PhD Candidate

Clinical Practice and Medication Use Group
Appendix 5.2. Invitation letter sent to all eligible doctors who prescribed a treatment
dose of gentamicin or vancomycin

Invitation Letter

BDM RESC Reference: BDM/12/13-26

Dr Catie Whittlesea
Institute of Pharmaceutical Sciences
Room 5.79, 5th Floor
Franklin Wilkins Building
Kings College London
150 Stamford St
London SE1

Participant Name:

Date: .....................

An exploratory interview-based study with doctors to determine the methods they
use to calculate the initial dose of gentamicin and vancomycin

We are writing to invite you to take part in a research study that aims to explore the views,
perceptions and experiences of individuals involved in prescribing initial doses of either gentamicin
or vancomycin. The study will involve participants being interviewed by a member of the research
team for 15 to 30 minutes. This study has been approved by King’s College London Biomedical
Sciences, Dentistry, Medicine and Natural & Mathematical Sciences Research Ethics
Subcommittee.

Background

Gentamicin and vancomycin are narrow-therapeutic-index drugs which are known to have high
toxicity and therefore need more caution and continuous therapeutic drug monitoring (TDM).
Doses of gentamicin and vancomycin are individualised according to patient’s age, body weight,
body composition and renal function. The calculation is relatively complex and doses are not
always appropriately adjusted resulting in potential overdosing (toxicity) or underdosing (treatment
failure).

Many studies in the literature have showed a high incidence of gentamicin/vancomycin adverse
effects due to overdosing leading to toxicity. Moreover, a recent audit conducted at this hospital
(2009-2011) identified that one third of dose/frequency errors (n=95) reported to the hospital risk
management system were related to gentamicin (n=16) and vancomycin (n=16).

This qualitative interview-based study aims to assess the prescribers’ methods of calculating an
initial dose of either gentamicin or vancomycin following a correct or incorrect prescription for a
specific patient. Their experience and use of resources (e.g. protocols, and calculators) will also be
explored.
Appendix 5.2. (Continued) Invitation letter sent to all eligible doctors who prescribed a treatment dose of gentamicin or vancomycin

This will be achieved by obtaining the views, perceptions and experiences of individuals involved in prescribing initial doses of gentamicin and vancomycin. The results of this study will be used to build and extend the current knowledge base in order to potentially develop new policies/interventions to improve current prescribing practice particularly in relation to dose calculation.

We would like you to reply within 72 hours. This is to assist your recall of the specific occasion when you prescribed an initial dose (correct or incorrect) of either vancomycin or gentamicin for a specific patient. If you are interested in taking part in this study, please read the attached participant information leaflet. Then, please confirm your acceptance by email and complete the attached consent form which will be collected at your interview.

If you would like any further information about the study before you make the decision about participating, please contact either Anas Hamad (primary contact) by either e-mail (anas.hamad@kcl.ac.uk) or telephone (020 7848 4853), or Dr Cate Whittlesea via (cate.whittlesea@kcl.ac.uk) or 020 7848 4796.

Thank you for your time and attention.

Yours faithfully,

Anas Hamad  Dr Cate Whittlesea  Gillian Cavell
(Researcher)  (Researcher / PhD supervisor)  (Researcher)

Paul Wade  James Hinton
(Researcher)  (Researcher)
Appendix 5.3. Participant information leaflet sent to all eligible doctors who prescribed a treatment dose of gentamicin or vancomycin

Participant Information Leaflet

REC Reference Number: BDM/12/13-26

YOU WILL BE GIVEN A COPY OF THIS INFORMATION LEAFLET

Study Title:
An exploratory interview-based study with doctors to determine the methods they use to calculate the initial dose of gentamicin and vancomycin

We would like to invite you to participate in this study which is being conducted for a PhD in Clinical Practice and Medication Use at King’s College London. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

- What is the aim of the research and possible benefits?

Doses of gentamicin and vancomycin are individualised according to patient’s age, body weight, body composition and renal function. The calculation is relatively complex and doses are not always appropriately adjusted resulting in potential overdosing (toxicity) or underdosing (treatment failure). Many studies in the literature showed the high incidence of dose calculations errors especially in drugs with a narrow therapeutic index such as gentamicin and vancomycin. This qualitative interview-based study aims to assess the prescribers’ methods of calculating gentamicin and vancomycin initial doses, their experience and use of resources (e.g. protocols, and calculators) in order to understand and consequently improve the current prescribing practice of these high-risk drugs. This study was approved by King’s College London Biomedical Sciences, Dentistry, Medicine and Natural & Mathematical Sciences Research Ethics Subcommittee.

- Who are we recruiting?

A literature review of dose calculation and practice-improvement interventions has formed the basis of this study. This preliminary stage will inform us of key aspects in relation to the vancomycin and gentamicin dose calculations from those individuals that are actively involved within the field (i.e. prescribers). A purposive sample of prescribers who have prescribed an initial dose of gentamicin or vancomycin will be invited to participate in the study. We plan to include participants who prescribed either correct or incorrect dose of gentamicin or vancomycin.

- What will happen if you agree to take part?

You will be invited to participate in a confidential interview with a member of the research team (Anas Hamad). The interviews will take approximately half an hour at a convenient date and time and will discuss the methods you used to calculate an initial dose of either gentamicin or vancomycin following a correct or incorrect prescription for a specific patient. This will be held at a suitable venue which you decide is best for you. With your consent, the interviews will be audio-recorded. All data collected by the research team as part of the study is strictly confidential.

Anas Hamad
Participant information leaflet
Jan 2013 (Version 2)
Appendix 5.3. (Continued) Participant information leaflet sent to all eligible doctors who prescribed a treatment dose of gentamicin or vancomycin

- Are there any possible risks?

There is no anticipated reason to believe any participant will suffer any undue distress, harm or injury. It is not anticipated that any sensitive, embarrassing or upsetting topics will be raised or discussed. In addition, you will be able to withdraw from the study at any point up to 48 hours after the interview without giving any reason.

- What are the possible benefits?

Your input will help and inform future developments in the field of medication safety which will contribute to improving the way patients are treated and managed within the hospital. Results of this study will be used to further develop interventions to help staff undertake dose calculations. It is important that this is done safely and effectively to enhance prescribing accuracy. If you would like a copy of the results, you will be sent one.

- What are the arrangements for ensuring anonymity and confidentiality?

All information collected about you during the course of the research study is kept strictly confidential. The interviews are confidential and the data collected will be anonymised by the researcher. It will NOT be possible to link information used in the research report back to you. Reports and data collected will be stored securely at King’s College London.

- What are the anticipated plans for dissemination/publication?

The findings will be shared across King’s Health Partners. The study will be described in the PhD in Clinical Practice and Medication Use thesis of Anas Hamad. It is anticipated the results of this study will be published and/or presented at a national/international level so all information gained is shared widely.

It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw from the study at any point up to 48 hours after the interview and without giving any reason.

If you have any questions or require more information about this study, please contact the researcher using the following contact details:

Anas Hamad
Tel: 020 7848 4853
Email: anas.hamad@kcl.ac.uk

If this study has harmed you in any way, you can contact King’s College London using the details below for further advice and information:

Dr Cate Whittlesea
King’s College London
Institute of Pharmaceutical Science
Franklin-Wilkins Building
150 Stamford St, London SE1 9NH
Tel: 020 7848 4796
Email: cate.whittlesea@kcl.ac.uk
Appendix 5.4. Consent form signed by all interview participants

Consent Form for Participants in Research Studies

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: An exploratory interview-based study with doctors to determine the methods they use to calculate the initial dose of gentamicin and vancomycin

King's College Research Ethics Committee Ref: BDM/12/13-26

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Please tick or initial

I understand that if I decide at any time during the research that I no longer wish to participate in this project, I can notify the researchers involved and withdraw from it immediately without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to 48 hours after the interview. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.

Participant’s Statement:

I

agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed: Date:

Investigator’s Statement:

I _________Anas Hamad_________

Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed: Date:

Anas Hamad Consent form Jan 2013 (Version 2) 1 | Page
Appendix 5.4. (Continued) Consent form signed by all interview participants

- In case the information you have submitted is published as a report; please indicate whether you would like to receive a copy.

  - Yes
  - No

- I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications.

  - Yes
  - No

- I agree to be contacted in the future by King’s College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature.

  - Yes
  - No

- I agree that what I say during the interviews can be used, anonymously in the presentation of the research.

  - Yes
  - No

- I consent to my interview being audio recorded.

  - Yes
  - No

- I AGREE, and give INFORMED CONSENT to take part in this study

  - Yes
  - No
Appendix 5.5. Final interview schedule used for interviewing participants

**Interview Schedule**

**An exploratory interview-based study with doctors to determine the methods they use to calculate the initial dose of gentamicin and vancomycin**

**Introduction**

Thank you for agreeing to participate in this study which aims to assess prescribers' methods of calculating initial doses of gentamicin and vancomycin, their experience, and use of resources (e.g. protocols, calculators).

In this study, a wrong dose of gentamicin is defined as a dose not within 10% of recommended dose as specified in the Trust guidelines. A wrong dose of vancomycin is defined as a dose not within 20% of the recommended dose as specified in the Trust guidelines.

I would be grateful if you could confirm that you have read the information sheet and that you have read and signed the consent form. During this interview, which will take about 20 minutes, I will be taking written notes but will also be using an audio tape recorder to help me write a transcript. The recording will be destroyed after completion of the study.

Please explain things to me as if I am one of your colleagues. I may ask you for clarification and examples of the topics discussed. Feel free to stop me if you have any questions or need any explanations.

All information collected about you during the course of the research study is kept strictly confidential. The interviews are confidential and the data collected will be anonymised by the researcher. It will NOT be possible to link information used in the research report back to you. Reports and data collected will be stored securely at King's College London.

**Background**

First, I would like to obtain some background information about your experience in the prescribing process generally and particularly when prescribing gentamicin / vancomycin

- Could you please tell me how long have you been prescribing?
- Can I ask you what is your specialty and grade?
- Would you please tell me how long have you been working at this hospital?
Appendix 5.5. (Continued) Final interview schedule used for interviewing participants

**Specific prescribing occasion**

*Interviewer provides information to interviewee on the date and time of prescribing the initial dose of gentamicin / vancomycin (delete as appropriate) to be discussed.*

**Thinking about this occasion you prescribed gentamicin / vancomycin (delete as appropriate)**

<table>
<thead>
<tr>
<th>Can you describe to me the process of how you prescribed this initial dose?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could you explain to me the method and any sources you used to prescribe this dose?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> can you tell me what was it the actual or ideal body weight that you used?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> where do you get the latest weight from?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> what values do you need to calculate the dose?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Please describe what the ward environment was like when you prescribed this dose?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Prompt</strong> can you tell me what was happening on the ward when you were prescribing this dose?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> if weekend/evening shift, how many doctors were available in the ward/service then?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> would you describe what were you feeling at the time of prescribing (e.g. tired/stressed)?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Were there any factors that could have influenced your prescribing decision?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Prompt</strong> could you think of any aspects that have made you prescribe this dose for this particular patient?</td>
</tr>
<tr>
<td>- <strong>Prompt</strong> for junior doctors, whose decision was it to give this drug to the patient?</td>
</tr>
</tbody>
</table>

| Actually, the dose you prescribed for this patient fell within / outside (delete as appropriate) the predefined range of 10% / 20% (delete as appropriate) ± the guidelines recommended dose. |
Appendix 5.5. (Continued) Final interview schedule used for interviewing participants

Gentamicin and vancomycin prescribing

*Interviewer asks general questions about prescribing the drug used in the specific prescribing occasion.*

Now, I would like to discuss in general your experience in prescribing gentamicin / vancomycin (delete as appropriate)

<table>
<thead>
<tr>
<th>Can you please tell me how often do you prescribe an initial dose of this drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there any extra measures or assessments you usually consider or undertake when prescribing this drug in comparison to other drugs?</td>
</tr>
<tr>
<td>• <strong>Prompt</strong> are there any different things you consider when prescribing this drug compared to other drugs?</td>
</tr>
<tr>
<td>• <strong>Prompt</strong> can you tell more about the toxicity of this drug? How do you monitor it?</td>
</tr>
<tr>
<td>• <strong>Prompt</strong> what about monitoring the therapeutic effect of this drug?</td>
</tr>
</tbody>
</table>

Thinking about the factors you considered and the method you used to calculate the dose for the patient we have just discussed, would you use the same method / source for all patients?

| **Prompt if no**, what other factors do you consider and why? |
Appendix 5.5. (Continued) Final interview schedule used for interviewing participants

Interviewer asks general questions about prescribing the drug NOT used in the specific occasion.

Finally, I would like to discuss your experience in prescribing gentamicin / vancomycin (delete as appropriate)

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you prescribe an initial dose of this drug?</td>
<td></td>
</tr>
<tr>
<td>Are there any extra measures or assessments you usually consider when prescribing this drug compared to gentamicin / vancomycin (delete as appropriate) or any other drug?</td>
<td></td>
</tr>
<tr>
<td>Prompt are there any different things you consider when prescribing this drug?</td>
<td></td>
</tr>
<tr>
<td>Prompt can you tell more about the toxicity of this drug? How do you monitor it?</td>
<td></td>
</tr>
<tr>
<td>What method / source do you usually use to calculate an initial dose of this drug?</td>
<td></td>
</tr>
<tr>
<td>In general, would you use the same method / source for all patients?</td>
<td></td>
</tr>
<tr>
<td>Do other doctors in your area use the same method too?</td>
<td></td>
</tr>
<tr>
<td>Prompt if no, what do they do?</td>
<td></td>
</tr>
<tr>
<td>Prompt are you aware of any other tools in the hospital that are available to assist gentamicin and/or vancomycin prescribing?</td>
<td></td>
</tr>
<tr>
<td>Could you please tell me what you think could be done to avoid dose calculation errors with gentamicin / vancomycin (delete as appropriate) from happening?</td>
<td></td>
</tr>
<tr>
<td>Prompt what do you think are the main sources of error that might lead some doctors to prescribe an incorrect dose of gentamicin or vancomycin?</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

Thank you for your time and I am very grateful that you have given me an insight into the process you use to prescribe gentamicin / vancomycin. I would like to remind you that if you wish to withdraw from the study you will need to inform myself or any other member of the research team within 48 hours.
Appendix 5.6. An example of the process used to code the data collected through interviews

<table>
<thead>
<tr>
<th>Researcher:</th>
<th>And is this dose recommended by the trust guidelines?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviewee: Smm per kilogram, yeah.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Mmmmm. And, so can you please tell me is it usually the actual or ideal body weight that you need to calculate the dose or to give the dose?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: If they’re obese then you use ideal body weight, otherwise you just use actual.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Mmmmm.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: And she wasn’t.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Okay. Do you remember, I mean, the weight that you used for her?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Ah, 50 kilos.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Was it documented somewhere or?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Ah, Oh God. I can’t remember whether it was documented it may have been that it was an estimated weight. I can’t remember.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Sometimes it’s quite hard to find the documentation of body weight.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Yeah, actually I was just going to ask where do you usually get the latest weight from?</td>
<td></td>
</tr>
<tr>
<td>Researcher: Usually they’re written in the nursing notes somewhere... I think they’re on EPR somewhere as well but it’s... I normally ask a nurse.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Okay, so you usually just ask the nurse?</td>
<td></td>
</tr>
<tr>
<td>Researcher: Yeah.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: So apart of the weight are there any other values that you need to calculate the dose?</td>
<td></td>
</tr>
<tr>
<td>Researcher: Mmmmm. Can you please describe me what the ward environment was like when you prescribed this dose?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: I mean, like, what was happening on the ward at that time when you prescribed the dose? Was it busy?</td>
<td></td>
</tr>
<tr>
<td>Researcher: Yeah. It was Friday afternoon. It was very busy.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Mmmmm. Did you have - at that time did you have to cover a lot of patients?</td>
<td></td>
</tr>
<tr>
<td>Researcher: Yeah, Yeah.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: So it was a busy day.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Yeah.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Oh okay. It was within the regular hours right? It was around midday.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Yeah.</td>
<td></td>
</tr>
<tr>
<td>Interviewee: And would you describe which way you were feeling at the time of prescribing? I mean were you like tired? Stressed? Anything like that?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Ah. Last Friday, probably maybe slightly stressed. It was quite busy but no more than normal.</td>
<td></td>
</tr>
<tr>
<td>Researcher: Mmm. And were there any factors that could have influenced your prescribing decision? I mean could you think of any aspects that have made you prescribe this dose for this particular patient?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: What do you mean?</td>
<td></td>
</tr>
<tr>
<td>Researcher: I mean is there anything specific in this patient that have led you to prescribe this... to individualize this dose for her?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: No.</td>
<td></td>
</tr>
<tr>
<td>Researcher: So is it just her weight?</td>
<td></td>
</tr>
<tr>
<td>Interviewee: Yeah. Yeah.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5.7. Characteristics of the prescribers of correct and incorrect doses of gentamicin and vancomycin

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>18</th>
<th>19</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug prescribed</strong></td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>FY1</td>
<td>JCF</td>
<td>SHO</td>
<td>JCF</td>
<td>JCF</td>
<td>SHO</td>
<td>FY1</td>
<td>FY1</td>
<td>Registrar</td>
<td>JCF</td>
<td>SHO</td>
<td>FY1</td>
</tr>
<tr>
<td><strong>Overall experience</strong></td>
<td>≤6m</td>
<td>2-5y</td>
<td>7m-2y</td>
<td>2-5y</td>
<td>&gt;5y</td>
<td>≤6m</td>
<td>≤6m</td>
<td>&gt;5y</td>
<td>7m-2y</td>
<td>2-5y</td>
<td>≤6m</td>
<td></td>
</tr>
<tr>
<td><strong>King’s experience</strong></td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>7m-2y</td>
<td>7m-2y</td>
<td>≤6m</td>
<td>≤6m</td>
<td>&gt;5y</td>
<td>≤6m</td>
<td>7m-2y</td>
<td>≤6m</td>
<td></td>
</tr>
<tr>
<td><strong>Rate of prescribing</strong></td>
<td>≥1/w</td>
<td>≥1/d</td>
<td>≥1/w</td>
<td>Every 2-3m</td>
<td>≥1/d</td>
<td>≥1/m</td>
<td>1st time</td>
<td>≥1/m</td>
<td>≥1/w</td>
<td>≥1/w</td>
<td>Every 2-3m</td>
<td></td>
</tr>
<tr>
<td><strong>Trust tool used?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Knowledge of all dosing data?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Actual or ideal wt?</strong></td>
<td>Actual</td>
<td>Ideal</td>
<td>Actual</td>
<td>Ideal</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td></td>
</tr>
<tr>
<td><strong>Knowledge of toxicity?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Work environment</strong></td>
<td>Not on ward</td>
<td>Busy</td>
<td>Calm</td>
<td>Busy</td>
<td>Calm</td>
<td>Busy</td>
<td>Calm</td>
<td>Busy</td>
<td>Calm</td>
<td>Busy</td>
<td>Calm</td>
<td></td>
</tr>
<tr>
<td><strong>Workload</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td><strong>Extra assessments</strong></td>
<td>RF/levels</td>
<td>RF/levels/hearing</td>
<td>RF/allergy</td>
<td>RF/Pt data</td>
<td>RF</td>
<td>RF/hearing</td>
<td>RF/levels/Wt</td>
<td>RF</td>
<td>RF</td>
<td>RF</td>
<td>RF/guideline/Pharmacist/Wt</td>
<td></td>
</tr>
<tr>
<td><strong>Elderly pt (≥65y)</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Renally impaired pt (CrCl&lt;60ml/min)</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Obese pt (BMI≥30kg/m²)</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5.7. (Continued) Characteristics of the prescribers of correct and incorrect doses of gentamicin and vancomycin

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>1</th>
<th>10</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>3</th>
<th>7</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug prescribed</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Gent</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
<td>Vanc</td>
</tr>
<tr>
<td>Grade</td>
<td>CT1</td>
<td>Registrar</td>
<td>CT1</td>
<td>FY1</td>
<td>CT2</td>
<td>CT2</td>
<td>CT1</td>
<td>CT1</td>
<td>FY1</td>
<td>CT1</td>
<td>FY2</td>
<td>Consultant</td>
</tr>
<tr>
<td>Overall experience</td>
<td>2-5y</td>
<td>&gt;5y</td>
<td>7m-2y</td>
<td>≤6m</td>
<td>2-5y</td>
<td>2-5y</td>
<td>&gt;5y</td>
<td>7m-2y</td>
<td>≤6m</td>
<td>2-5y</td>
<td>7m-2y</td>
<td>&gt;5y</td>
</tr>
<tr>
<td>King’s experience</td>
<td>7m-2y</td>
<td>2-5y</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
<td>≤6m</td>
</tr>
<tr>
<td>Rate of prescribing</td>
<td>≥1/w</td>
<td>Rare</td>
<td>≥1/m</td>
<td>Every 2-3m</td>
<td>≥1/d</td>
<td>≥1/m</td>
<td>≥1/m</td>
<td>Every 2-3m</td>
<td>≥1/m</td>
<td>1st time</td>
<td>≥1/w</td>
<td></td>
</tr>
<tr>
<td>Trust tool used?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Knowledge of all</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>dosing data?</td>
<td>Actual or ideal</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Actual</td>
<td>Ideal</td>
<td>Actual</td>
<td>Actual</td>
<td>Ideal</td>
<td>Actual</td>
<td>Actual</td>
<td>Ideal</td>
</tr>
<tr>
<td>wt?</td>
<td>Knowledge of</td>
<td>toxicity?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Work environment</td>
<td>Calm</td>
<td>Calm</td>
<td>Calm</td>
<td>Not on ward</td>
<td>Busy</td>
<td>Busy</td>
<td>Busy</td>
<td>Busy</td>
<td>Busy</td>
<td>Calm</td>
<td>Not on ward</td>
<td></td>
</tr>
<tr>
<td>Workload</td>
<td>Normal</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Extra assessments</td>
<td>RF/levels</td>
<td>RF/wt/Micro advice</td>
<td>RF/allergy/ Micro advice</td>
<td>RF/Wt/age</td>
<td>RF/age&gt;65y/ Recent wt</td>
<td>RF/levels/ Wt</td>
<td>RF/Levels/ Pt data/ guidelines</td>
<td>RF/Wt</td>
<td>RF/Levels/ allergies</td>
<td>RF</td>
<td>RF/Wt</td>
<td>RF/LFT/ WBC</td>
</tr>
<tr>
<td>Elderly pt (≥65y)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Renally impaired pt (CrCl&lt;60ml/min)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Obese pt (BMI≥30kg/m²)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Gent: gentamicin; Vanc: vancomycin; Gen: general; Surg: Surgery; Med: Medicine; Obs/Gyn: Obstetrics and Gynaecology; Cardio: Cardiology; FY: Foundation Year; JCF: Junior Clinical Fellow; SHO: Senior House Officer; CT: Core Training; Y: year; M: month; W: week; D: day; RF: renal function; Pt: patient; Wt: weight; Micro: Microbiology; CrCl: creatinine clearance; BMI: body mass index.
Research Outcomes
Research Papers


Abstracts


Conferences

Oral presentations

Health Services Research and Pharmacy Practice Conference (2012), Cork, Ireland. Incidence of antibiotic adverse drug events among hospitalised patients (data from one hospital).

Poster presentations

Health Services Research Network Symposium (2012), Manchester, UK. Incidence of antibiotic adverse drug events among hospitalised patients (data from two hospitals).

American College of Clinical Pharmacy Annual Meeting (2013), Albuquerque, USA. An evaluation of the impact of a dose calculator on the accuracy of gentamicin and vancomycin initial doses (interim results).