

Personalised antimicrobial management in secondary care

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Declaration of originality

I confirm that the work described within this thesis was carried out by myself, unless otherwise stated.

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Abstract

Background: The growing threat of Antimicrobial Resistance (AMR) requires innovative methods to promote the sustainable effectiveness of antimicrobial agents.

Hypothesis: This thesis aimed to explore the hypothesis that personalised decision support interventions have the utility to enhance antimicrobial management across secondary care.

Methods: Different research methods were used to investigate this hypothesis. Individual physician decision making was mapped and patient experiences of engagement with decision making explored using semi-structured interviews. Cross-specialty engagement with antimicrobial management was investigated through cross-sectional analysis of conference abstracts and educational training curricula. Artificial intelligence tools were developed to explore their ability to predict the likelihood of infection and provide individualised prescribing recommendations using routine patient data. Dynamic, individualised dose optimisation was explored through: (i) development of a microneedle based, electrochemical biosensor for minimally invasive monitoring of beta-lactams; and (ii) pharmacokinetic (PK)-pharmacodynamic (PD) modelling of a new PK-PD index using C-Reactive protein (CRP) to predict the pharmacodynamics of vancomycin. Ethics approval was granted for all aspects of work explored within this thesis.

Results: Mapping of individual physician decision making during infection management demonstrated several areas where personalised, technological interventions could enhance antimicrobial management. At specialty level, non-infection specialties have little engagement with antimicrobial management. The importance of engaging surgical specialties, who have relatively high rates of antimicrobial usage and healthcare associated infections, was observed. An individualised information leaflet, co-designed with patients, to provide personalised infection information to in-patients receiving antibiotics significantly improved knowledge and reported engagement with decision making. Artificial intelligence was able to enhance the prediction of infection and the prescribing of antimicrobials using routinely available clinical data. Real-time, continuous penicillin monitoring was demonstrated using a microneedle based electrochemical sensor *in-vivo*. A new PK-PD index, using C-Reactive Protein, was able to predict individual patient response to vancomycin therapy at 96-120 hours of therapy.

Conclusion: Through co-design and the application of specific technologies it is possible to provide personalised antimicrobial management within secondary care.

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Table of contents

Contents

Declaration of originality.....	2
Abstract.....	3
Acknowledgements.....	4
Table of contents	5
List of tables.....	11
List of figures	13
Abbreviations & definitions.....	15
CHAPTER ONE.....	16
1.0 Improving antimicrobial management in secondary care	16
1.1 Evidence-based medicine	16
1.2 Antimicrobial Resistance	18
1.3 Defining overuse / misuse and appropriateness of antimicrobial therapy	23
1.4 Strategies to address Antimicrobial Resistance	25
1.4.1 Antimicrobial Stewardship.....	26
1.5 Hypothesis	30
1.5.1 Aims and Objectives	30
1.6 Project overview.....	32
CHAPTER TWO	33
2.0 A systematic review of clinical decision support systems for antimicrobial prescribing ..	33
2.1 Introduction.....	33
2.2 Chapter objectives.....	35
2.3 Method	36
2.3.1 Study selection	38
2.3.2 Grouping decision support systems and data extraction	39
2.3.3 Quality assessment.....	42
2.3.4 Summary measures.....	43
2.4 Results and discussion	44
2.4.1 Study selection and characteristics	44
2.4.2 Decision support systems reported in the literature.....	47
2.4.3 Analysis of CDSS development and pilot and feasibility testing domains.....	47

2.4.4 Analysis of evidence domain	48
2.4.5 Analysis of implementation and prescriber engagement with systems	50
2.4.6 Reported primary outcome measures of CDSS	51
2.4.7 Limitations	53
2.4 Conclusion and key messages.....	55
CHAPTER THREE.....	57
3.0 How do physicians' make decisions for the management of infections in acute care?... 57	57
3.1 Introduction.....	57
3.2 Chapter Objectives.....	59
3.3 Methods	60
3.3.1 Study design	60
3.3.2 Setting	62
3.3.3 Researcher background	62
3.3.4 Participant recruitment.....	62
3.3.5 Ethics.....	64
3.3.6 Data analysis.....	65
3.4 Results	66
3.4.1 Data analysis.....	66
3.4.2 Mapping the decision making process.....	66
3.5 Discussion.....	81
3.5.1 Physician decision making.....	81
3.5.2 Responsibility for the outcomes of decision making	83
3.5.3 Providing better data to support robust decisions	84
3.5.4 Electronic decision support tools to enhance decision making.....	85
3.5.5 Limitations and future work.....	88
3.6 Conclusion and key messages.....	90
CHAPTER FOUR.....	91
4.0 Are clinicians engaging with antimicrobial resistance and antimicrobial stewardship in different clinical specialties?.....	91
4.1 Introduction	91
4.2 Chapter objectives	94
4.3 Methods	95
4.3.1 Study design	95
4.3.2 Exploring specialty engagement with AMS–AMR using state-of-the-art scientific conference abstracts	97

4.3.3 Exploring specialty engagement with AMS–AMR using postgraduate training curricula	103
4.3.4 Identifying high risk specialties with evidence of low engagement with AMS-AMR	107
4.4 Results	110
4.4.1 Cross-specialty engagement.....	110
4.4.2 Comparison of indicators	124
4.5 Discussion.....	128
4.5.1 Summary of findings	128
4.5.2 Prioritising specialties for engagement	129
4.5.3 Promoting specialty engagement	130
4.5.4 Longitudinal follow up	131
4.5.5 Limitations and future work.....	132
4.6 Conclusions and key messages.....	134
CHAPTER FIVE.....	135
5.0 Investigating patient engagement with antimicrobial decision making in secondary care	135
5.1 Introduction.....	135
5.2 Chapter objectives.....	137
5.3 Method	138
5.3.1 Study setting	138
5.3.2 Patient focus-group workshops.....	138
5.3.3 Pilot study	141
5.3.4 Ethical approval	142
5.4 Results	143
5.4.1 Focus-groups	143
5.4.1.3 Co-development during workshops.....	150
5.4.2 Intervention development.....	154
5.4.3 Pilot study	156
5.5 Discussion.....	161
5.5.1 Summary of participant impressions	161
5.5.2 Opportunities for educating healthcare providers to improve patient engagement	161
5.5.3 Opportunities for improving patient engagement with decision making	162
5.5.4 Co-designed interventions can enhance patient engagement.....	163

5.6 Conclusion and key messages.....	168
CHAPTER SIX.....	169
6.0 Can artificial intelligence support individualised antimicrobial selection in secondary care?.....	169
6.1 Introduction.....	169
6.1.1 Artificial intelligence for infection management	172
6.1.2 Framing the focus of clinical decision support in secondary care	174
6.1.3 Current clinical decision support tool architecture.....	175
6.2 Chapter objectives.....	177
6.3 Methods	179
6.3.1 Study setting	179
6.3.2 Defining variables commonly used during infection management	180
6.3.3 Supervised machine learning tools for the prediction of positive microbiology	180
6.3.4 Case-Based-Reasoning for antimicrobial selection in secondary care.....	184
6.3.6 Ethics.....	190
6.4 Results	191
6.4.1 Identification of variables for inclusion in the system.....	191
6.4.2 Supervised machine learning for prediction of microbiology culture	194
6.4.3 Case-based-reasoning for antimicrobial selection	205
6.5 Discussion.....	209
6.5.1 Summary of findings	209
6.5.2 Supervised machine learning for infection inference.....	210
6.5.3 Case-Based-Reasoning for antimicrobial selection	214
6.5.4 Limitations and future work.....	216
6.6 Conclusion and key messages.....	219
CHAPTER SEVEN:.....	220
7.0 Personalised Antimicrobial Dosing: Development of a minimally invasive biosensor for the continuous monitoring of beta-lactam antibiotics	220
7.1 Introduction.....	220
7.1.1 Pharmacokinetic-pharmacodynamic variation	220
7.1.2 Individualised approaches to antimicrobial dosing.....	223
7.2 Chapter Objectives.....	240
7.3 Methods	242
7.3.1 Study setting and rationale	242
7.3.2 Reagents and equipment.....	251

7.3.3 Biosensor preparation.....	253
7.3.4 Beta-lactam antibiotic calibration	258
7.3.5 Artificial interstitial fluid preparation and calibration.....	259
7.3.6 Rotating disc electrode experiment.....	260
7.3.7 Preliminary in-vivo study	262
7.3.8 Ethical approval	264
7.4 Results	265
7.4.1 Biosensor characterisation.....	265
7.4.2 Beta-lactam biosensor calibration and characterisation.....	267
7.4.2 Pilot test of continuous monitoring of beta-lactam antibiotics in humans	277
7.5 Discussion.....	279
7.5.1 Summary of findings	279
7.5.2 Pilot study	285
7.5.3 Limitations and future applications	287
7.6 Conclusion and key messages.....	290
CHAPTER EIGHT	292
8.0 Personalised antimicrobial dosing: Exploring novel pharmacokinetic – pharmacodynamics targets for antimicrobial therapy.....	292
8.1 Introduction.....	292
8.2 Chapter objectives.....	296
8.3 Methods	297
8.3.1 Study setting	297
8.3.2 Vancomycin bioanalysis	298
8.3.3 Pharmacokinetic modelling software.....	298
8.3.4 Population pharmacokinetic model.....	299
8.3.3 Pharmacokinetic-pharmacodynamic modelling	300
8.3.4 Exposure-response	301
8.3.5 Ethics.....	301
8.4 Results	302
8.4.1 Subjects characteristics.....	302
8.4.2 Pharmacokinetic – pharmacodynamic model	305
8.4.3 Exposure response	309
8.5 Discussion.....	312
8.5.1 Limitations and future work.....	314

8.6 Conclusion and key messages.....	317
CHAPTER NINE	318
9.0 Personalised antimicrobial management in secondary care: Conclusions and recommendations	318
9.1 Conclusion	318
9.2 Identified challenges for the future.....	322
9.3 Recommendations.....	324
9.4 Future work.....	326
REFERENCES	328
APPENDIX.....	384
Appendix 1. Publications from thesis	384
Appendix 2. Supplementary table 1	386
Appendix 3. Topic guide for physician interviews	392
Appendix 4. Outline of behavioural interventions reported per UK specialty.....	393
Appendix 5: Patient workshop topic guides	395
Appendix 6: Patient leaflet pilot survey questions.....	400
Appendix 7. Biosensor fabrication protocols.....	405
Appendix 8. Technical Appendix	411
a8.1 Clinical Decision Support System.....	411
a8.2 Description of closed-loop controllers	413
a8.3 Microneedle fabrication process	414
Appendix 9: Ethics and permissions	415

List of tables

Table	Title	Page
Table 1	<i>Search Criteria used for systematic review of clinical decision support systems for antimicrobial prescribing.</i>	37
Table 2	<i>Analytic framework for the assessment of clinical decision support systems applied to the studies within this review.</i>	41
Table 3.	<i>Summary of clinical decision support systems evaluated.</i>	46
Table 4.	<i>Thematic construction of medical physicians' decision making pathways for the management of acute infections in secondary care.</i>	71
Table 5	<i>Selected quotes surrounding participants' experiences and expectations of prescribing antibiotics.</i>	74
Table 6.	<i>Reported expectations around the review and de-escalation of antimicrobial therapy.</i>	76
Table 7.	<i>Selection of participant quotes surrounding antimicrobial guidelines, clinical microbiology services, and the problems associated with information provided by these sources.</i>	79
Table 8.	<i>Abstract and curriculum search criteria and definitions of antimicrobial stewardship and antimicrobial resistance.</i>	99
Table 9.	<i>Behaviour change taxonomy used for classification of interventions reported in state-of-the-art scientific conference abstracts in 2015.</i>	102
Table 10.	<i>Summary of 2015 UK specialty state of the art scientific conferences included for analysis.</i>	111
Table 11.	<i>Outline of behaviour change functions reported in AMS-AMR abstracts that reported multiple behaviour change interventions at 2015 state-of-the-art scientific conferences.</i>	116
Table 12.	<i>Summary of current UK clinical specialty training curricula included in my analysis of surrogate markers of cross-specialty engagement with antimicrobial stewardship and antimicrobial resistance.</i>	118
Table 13.	<i>Comparison of cross-specialty indicator ranking with antimicrobial usage and healthcare associated infection rates per specialty.</i>	126
Table 14.	<i>An analytical framework developing categories and themes for patients' experiences of infection management in secondary care.</i>	146
Table 15.	<i>Key themes identified during workshops for the development of a patient engagement intervention for promoting enhanced communication and information provision surrounding infection management in secondary care.</i>	152
Table 16.	<i>Summary of participant characteristics and questionnaire results from the pilot evaluation of the patient-focused intervention.</i>	157
Table 17.	<i>Summary of qualitative question responses from participants in the post-intervention survey.</i>	159
Table 18.	<i>Summary of clinical decision support systems for antimicrobial prescribing containing artificial intelligence reported in the literature.</i>	171

Table 19.	<i>Selection of variables identified within the decision mapping process for use within the clinical decision support system for antimicrobial selection.</i>	192
Table 20.	<i>Summary of prospectively collected cases presenting with both infectious and non-infectious symptoms.</i>	201
Table 21.	<i>Summary of Case-Based-Reasoning recommendations made for patients receiving empirical and targeted antimicrobial therapy.</i>	207
Table 22.	<i>Summary of antimicrobial biosensors reported in the literature.</i>	234
Table 23.	<i>Summary of common PK-PD indices with examples.</i>	293
Table 24.	<i>Summary of patient characteristics included in the pharmacokinetic-pharmacodynamic model.</i>	303
Table 25.	<i>Population estimates of the pharmacokinetic – pharmacodynamic parameters for a model linking CRP to vancomycin concentrations in a population of non-critical care patients in secondary care.</i>	308

List of figures

Figure	Title	Page
Figure 1.	<i>Effect of high and low antimicrobial concentration on mutant selection.</i>	21
Figure 2.	<i>Overview of thesis.</i>	32
Figure 3.	<i>PRISMA flow diagram outlining study selection for inclusion within my systematic review of clinical decision support for infection management in primary and secondary care.</i>	45
Figure 4.	<i>Primary outcome measures reported for clinical decision support systems in the literature.</i>	52
Figure 5.	<i>Overview of thesis.</i>	57
Figure 6.	<i>Reported decision making pathway for infection management in secondary care.</i>	68
Figure 7.	<i>Mapping decision support interventions onto the physician decision making pathway in secondary care.</i>	87
Figure 8.	<i>Overview of thesis.</i>	91
Figure 9.	<i>Adaption of Miller's Pyramid for the assessment of clinical competence.</i>	106
Figure 10.	<i>Comparison of antimicrobial stewardship and antimicrobial resistance coverage at state-of-the-art scientific conference in 2015.</i>	113
Figure 11.	<i>Identification of antimicrobial stewardship / antimicrobial resistance curriculum topics and learning points in UK clinical specialty training curricula.</i>	119
Figure 12.	<i>The percentage of UK clinical specialty training curricula related to antimicrobial stewardship and/or antimicrobial resistance.</i>	121
Figure 13.	<i>Frequency of levels of achievement obtained upon completion of individuals antimicrobial stewardship and antimicrobial resistance curriculum learning points.</i>	123
Figure 14.	<i>Antimicrobial usage versus observed rates of healthcare associated infections by clinical specialty.</i>	125
Figure 15.	<i>Overview of thesis.</i>	135
Figure 16.	<i>Summary of identified categories and themes from workshop 1 exploring patient experiences of engagement with decision making surrounding antimicrobial prescribing in secondary care.</i>	145
Figure 17.	<i>Summary of intervention template development and integration into clinical decision support system.</i>	155
Figure 18.	<i>Overview of thesis.</i>	169
Figure 19.	<i>Summary of current electronic health record system architecture and clinical decision support system for investigation within this Chapter.</i>	176
Figure 20.	<i>Distribution of likelihood estimates using a Gaussian Naïve Bayes and Support Vector Machine Algorithm for patients who presented with confirmed blood stream infection and those presenting with non-infectious syndromes.</i>	196
Figure 21.	<i>Receiver-Operator-Characteristic (ROC) for evaluation of likelihood estimates for patients who presented with confirmed blood stream</i>	197

	<i>infection and those presenting with non-infectious syndromes.</i>	
Figure 22.	<i>Distribution of likelihood estimates for individuals with high or low likelihood of infection at presentation analysed with both a Gaussian Naïve Bayesian and Support Vector Machine algorithm.</i>	200
Figure 23.	<i>Receiver-Operator-Characteristics of a Gaussian Naïve Bayesian and Support Vector Machine classifiers for predicting subsequent infection / positive microbiology at the presentation with infection.</i>	204
Figure 24.	<i>Diagrammatic representation of the concept of Support Vector Machines.</i>	211
Figure 25.	<i>Overview of thesis.</i>	220
Figure 26.	<i>Outline of the proposal for closed-loop-control of antimicrobial therapy.</i>	226
Figure 27.	<i>Outline of the typical characteristics of biosensors.</i>	230
Figure 28.	<i>Example normalised plot of steady state velocity against normalised concentration of substrate.</i>	244
Figure 29.	<i>Theoretical kinetic model for an enzyme based biosensor.</i>	245
Figure 30.	<i>Example of boundary layer concept that we aim to control using the Rotating Disc Electrode.</i>	249
Figure 31.	<i>Outline of the design of the microneedle enzymatic electrochemical biosensor.</i>	255
Figure 32.	<i>Microneedle fabrication summary.</i>	257
Figure 33.	<i>Rotating disc electrode set up using a Pinewood Instrument rotator.</i>	260
Figure 34.	<i>Hypothetical plot of $[P]_i$ against $1/\delta$.</i>	261
Figure 35.	<i>Summary of findings from initial AEIROF and cellulose acetate based biosensor development.</i>	266
Figure 36.	<i>Calibration of platinum disc electrode based beta-lactam biosensor against different beta lactam antibiotics in phosphate buffer solution.</i>	269
Figure 37.	<i>Summary of RDE experimental data at low and high concentrations of beta-lactam.</i>	272
Figure 38.	<i>Comparison of calibration against penicillin-G in phosphate-buffer solution.</i>	274
Figure 39.	<i>Calibration of two microneedle arrays in artificial interstitial fluid with penicillin-G.</i>	276
Figure 40.	<i>Summary of the pilot evaluation of microneedle based sensing of penicillin-V in-vivo.</i>	278
Figure 41.	<i>Overview of thesis.</i>	292
Figure 42.	<i>Concentration-time profiles for vancomycin drug concentration data and C-reactive protein data for individuals used with the study.</i>	304
Figure 43.	<i>Pharmacokinetic and pharmacodynamic model individual versus predicted plots.</i>	306
Figure 44.	<i>Normalised prediction distribution error plots for the vancomycin pharmacokinetic model used within this study.</i>	307
Figure 45.	<i>Individual AUC:EC₅₀ estimates against CRP at 96-120 hours post commencement of vancomycin therapy.</i>	310
Figure 46.	<i>Overview of thesis.</i>	318

Abbreviations & definitions

Abbreviation	
Ag/AgCl	<i>Silver – Silver Chloride Reference Electrode</i>
ALP	<i>Alkaline Phosphatase</i>
ALT	<i>Alanine Transaminase</i>
AMR	<i>Antimicrobial Resistance</i>
AMS	<i>Antimicrobial Stewardship</i>
ARI	<i>Acute Respiratory Tract Infection</i>
AU	<i>Antimicrobial Usage</i>
AUC	<i>24-hour Area-Under-the-concentration-time-Curve</i>
BIL	<i>Bilirubin</i>
BSI	<i>Blood Stream Infection</i>
CBR	<i>Case-Based-Reasoning</i>
CDSS	<i>Clinical Decision Support Systems</i>
CPOE	<i>Computer Prescriber Order Entry System</i>
CR	<i>Creatinine</i>
CRP	<i>C-Reactive Protein</i>
EBM	<i>Evidence Based Medicine</i>
ED	<i>Emergency Department</i>
EHR	<i>Electronic Health Record</i>
HCAI	<i>Healthcare Associated Infection</i>
HCP	<i>Health Care Professionals</i>
ICHNT	<i>Imperial College Healthcare NHS Trust</i>
IPC	<i>Infection Prevention and Control</i>
ISF	<i>Interstitial Fluid</i>
MIC	<i>Minimum Inhibitory Concentration</i>
NEWS	<i>National Early Warning Score</i>
NHS	<i>National Health Service</i>
NPDE	<i>Normalised Predictive Distribution Error</i>
PD	<i>Pharmacodynamic</i>
PEG	<i>Polyethylene Glycol</i>
PEI	<i>Polyethylenimine</i>
PK	<i>Pharmacokinetic</i>
RDE	<i>Rotating Disc Electrode</i>
ROC	<i>Area Under the Receiver Operator Characteristics Curve</i>
SDM	<i>Shared-Decision-Making</i>
SIRS	<i>Systemic Inflammatory Response Syndrome</i>
UK	<i>United Kingdom</i>
UTI	<i>Urinary Tract Infection</i>
WCC	<i>White Cell Count</i>
WHO	<i>World Health Organisation</i>

CHAPTER ONE

1.0 Improving antimicrobial management in secondary care

1.1 Evidence-based medicine

In 1996, Sackett and colleagues outlined their perspective of evidence-based medicine (EBM) in the *British Medical Journal* [1]. This definition, in conjunction with the work of Eddy and Cochrane, formed a paradigm that has guided empirical practice and clinical decisions for the last 25 years [2–5].

EBM is the process of integrating the best available evidence, individual clinical judgement, and patient values and preferences to make decisions about the care of individual patients [1]. This definition is based on three epistemological principles that were explored by Djulbegovic and Guyatt in 2017 [5].

1. Not all evidence is created equal. Therefore, the practice of medicine must be based on the best available evidence for the particular situation that it is being applied to.
2. In the pursuit of truth, this is best accomplished by evaluating the totality of available evidence, rather than selecting the evidence that favours a particular claim.
3. Finally, evidence alone is not sufficient for effective decision making. It is vital that evidence is considered within the social context that the decision is being made.

Within infection management, which is the focus of this thesis, a number of dynamic processes occur during decision making. These dynamic processes create another level

of complexity to supporting evidence-based practice. Moreover, for many of the aspects of antimicrobial management, there is a paucity of evidence supporting decision making. Therefore, within this thesis I set out to investigate a number of methods to provide better evidence to support decision making during antimicrobial management. This would focus on both prescribers and patients. However, firstly it is important to put the problem of antimicrobial resistance (AMR) into context. This will focus primarily on the hospital setting, which is the scope of this thesis.

1.2 Antimicrobial Resistance

AMR is a global threat to patient safety [6]. Currently in Europe, it is estimated that 25,000 people die every year because of drug-resistant-infections [6,7]. This costs the UK approximately £1 billion per year [6,7]. Worldwide, mortality is estimated to be at least 700,000 people per year [6,7]. By 2050, up to 10 million people per year will die because of drug-resistant-infections, costing the global economy trillions of pounds and threatening the way that we currently practice medicine [6,8].

AMR is not a new phenomenon. In the early 1900's Ehrlich observed an increase in micro-organism resistance to early antimicrobials whilst experimenting with azo dyes, arsenicals, and triphenylmethane derivatives. Shortly after the discovery of penicillin, Fleming famously reported his observation of penicillin resistance developing in organisms where the drug had previously been effective [9,10].

In fact, AMR can occur naturally in the environment in the absence of antimicrobial pressure. This occurs as part of natural selection when it provides a survival advantage to the micro-organism [11,12]. An example of this was when several resistance genes for a newly licenced antibiotic, daptomycin, were observed in the environment before it was used in clinical practice [13–15]. This observation of resistance in the environment is often described as the “*soil resistome*” and can easily be transferred into human pathogens when selective pressure is placed upon them, such as by the use of antimicrobial agents [16]. This is a complex process with exposure to antimicrobials occurring throughout the environment, acting as a major driver of AMR. This process is often exaggerated in areas where antimicrobials are used in concentration, such as the hospital environment [17–19]. These areas of high antimicrobial usage can be thought of as “enrichment zones” for the expansion of drug-resistant populations [17–19].

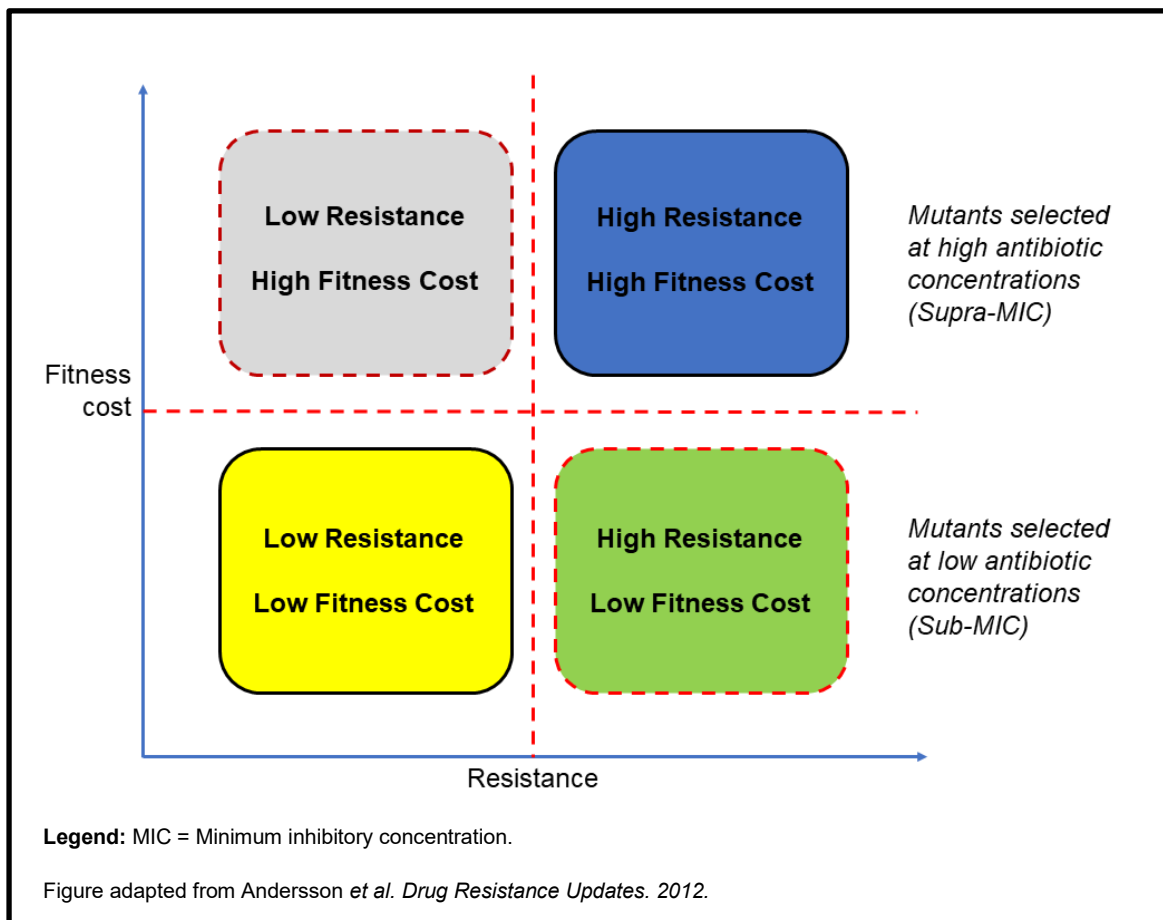
AMR develops through several mechanisms, which can be either intrinsic to that species or acquired [9]. Intrinsic resistance to an antimicrobial refers to a situation when the entire species of organism are resistant to an antimicrobial agent [9]. For example, Gram-negative organisms are resistant to glycopeptide antimicrobials, such as vancomycin, due to their thick lipopolysaccharide cell wall [9]. This prevents the agent penetrating the cell wall and binding to its intra-cellular target [9]. In contrast, acquired resistance occurs when an agent that has been previously effective becomes ineffective within a species [9]. This is often followed by the rapid expansion of resistant strains within the cohort causing a reduction in the therapeutic value of that antimicrobial as more and more of the population become resistant to its action [9,20]. No antimicrobial introduced into human medicine has so far escaped this phenomenon [21].

There are two main mechanisms by which acquired resistance occurs: mutational resistance and transmissible resistance [9,20]. Mutational resistance describes changes that occur within the DNA of a micro-organism by error during DNA synthesis. These variations in DNA may lead to phenotypic variability [22]. This variable phenotype may confer resistance to an antimicrobials action. This can then be selected for when antimicrobial selection pressure is applied to the population [22]. Transmissible resistance describes the most common mechanism by which organisms develop drug resistance. This involves a micro-organism acquiring genetic elements that encode drug-resistance from another organism [23]. Many of these genetic elements tend to be acquired from organisms within the “*soil resistome*” [23]. Both mutational and transmissible methods confer resistance to antimicrobials via three core mechanisms: preventing access to the target site, changing the target site structure, and direct modification (inactivation) of the antimicrobial [16].

Despite resistance occurring in the absence of selective pressure, exposure of organisms to antimicrobials is by far the greatest driver of AMR [20]. With the expanding use of antimicrobial agents, in particular broad spectrum antimicrobials, the rate of selection of drug-resistant organisms will also exponentially grow [24]. In 2014 in the UK, approximately 30% of all hospital in-patients were prescribed an antimicrobial agent [24]. Internationally, large multi-centre studies have suggested that up to 60% of hospital in-patients will receive at least one antimicrobial during their stay [25,26]. Furthermore, many of these prescriptions will be inappropriate in some way, being prescribed for too long, for non-bacterial or non-infectious syndromes, or redundantly in combination [25–27]. This approach to prescribing creates a huge amount of unnecessary exposure of organisms to antimicrobial agents, increasing the potential for resistant mutants to be selected. Therefore, when we consider potentially modifiable drivers of AMR, it is clear that the overuse / misuse of antimicrobials in both humans and agriculture is one of the most significant factors that must urgently be addressed [20][28].

A particularly important consideration when considering the misuse of antimicrobials is the observation of different mutation events that occur at differing concentrations of antimicrobial agent (**Figure 1**) [17–19]. At low concentrations of antibiotics, typically below minimum inhibitory concentration of the organism (MIC), but above the minimum selection concentration (MSC); we observe low level mutations that accumulate [17–19]. These preserve the fitness of the micro-organism in conjunction to promoting resistance to the antimicrobials action. In contrast, selection of mutants at supra-MIC levels often drives single point mutations, which will not lead to the development of a resistant population as there is a significant fitness cost associated with these mutations [17–19] [20].

Figure 1. The effects of antimicrobial concentration on antimicrobial resistance mutant selection.



The observation of low fitness cost – high resistance selection at low concentrations is important to consider for several reasons. Firstly, misuse / overuse of antimicrobials will increase the low-level exposure in the environment (through bodily secretions, contamination, and aerosol formation) to sub-MIC levels of antimicrobial, increasing environmental selective pressures. Secondly, inappropriate dosing (e.g. under dosing) and length of treatment in individuals can also have a similar effect exposing organisms to sub-therapeutic antimicrobial concentrations. These actions will lead to the accumulation of multiple mechanisms or drug-resistance, often to multiple antimicrobials,

whilst preserving the fitness of the organism attaining them [23]. Finally, these types of mutational event make reversing the problem of AMR challenging [23]. This is because reducing the rate of use of a single antimicrobial is unlikely to have an impact on trends in overall resistance to antimicrobials as the mutations tend to confer resistance to more than one agent when low-level mutations occur [17–19,23].

1.3 Defining overuse / misuse and appropriateness of antimicrobial therapy

If I am to consider overuse and misuse of antimicrobials, I must also define “appropriate” antimicrobial usage. During severe infection, which causes sepsis, there is evidence that early and appropriate antimicrobial therapy is a significant determinant of clinical outcome for patients [29,30]. However, the definition of appropriateness of antimicrobial therapy is often heterogeneous and commonly only refers to selection of the most appropriate antimicrobial agent for the organism that is being targeted [31,32]. This fails to account for other factors that are critical to the outcome of antimicrobial therapy (including the development of AMR), such as providing an optimal dose for the individual patient, ensuring an appropriate length of treatment, and providing the narrowest spectrum of agent(s) available for the organism being treated [8,31–33]. It also fails to take into account the other aspects of evidence-based practice, such as clinical judgement and the social context in which prescribing occurs [5].

In the context of antimicrobial stewardship, the Society of Healthcare Epidemiology (SHEA) define appropriate antimicrobial therapy as selection of the optimal drug regimen including: dosing, duration of therapy, and route of administration [33]. Other studies have explored the use of *in-vitro* susceptibility data, adherence to guidelines, expert opinion, and specific scoring systems based on literature such as Micromedex or Clinical Pharmacology departments [32,34,35]. However, wide variability in scoring systems has made it challenging to identify a robust and reproducible measure of appropriateness of antimicrobial therapy [32].

Within this thesis, I have opted to take a pragmatic approach built around the SHEA definition [33] linked with the objective measures described above, where available, to

take a holistic approach to exploring the concept of appropriateness [32,34,35]. This will consider a range of markers for appropriateness of therapy that are specific to the patient, the organism being targeted, the drug being administered, and the context in which the prescribing behaviour is being considered.

By building on these factors I hope to ensure that the principles of EBM have been fully considered during the review of decisions that are made [1,5]. In particular, it is important to determine whether the best available evidence has been applied to the selection of an antimicrobial for the given situation. This includes, not just selecting the antimicrobial based on organism factors, but also taking into consideration the patient's individual factors, preferences, and the wider social context in which the prescribing event has taken place [1,5].

1.4 Strategies to address Antimicrobial Resistance

The work within this thesis must also take into account current strategies that have been deployed to address AMR. To address the growing threat of AMR, a number of core areas for research and development have been proposed. The core strategic areas of focus being used to address AMR are outlined in the Jim O'Neill report on AMR to the UK government, which highlighted 10 areas of urgent action [6,7]. These are:

1. New antimicrobial development
2. Rapid diagnostics
3. Public awareness of the issue of AMR
4. Improvements in sanitation and hygiene
5. A one-health focus including antimicrobial use in agriculture and the environment
6. Development of vaccines and alternatives to antimicrobials
7. Surveillance of AMR
8. Utilising human capital
9. Development of an international coalition for action
10. Development of a global innovation fund to support research and development

Running throughout all of these key areas is the need to better utilise available data and generate more information to support the evidence-based practice of antimicrobial management [6,7]. This often falls under the term of antimicrobial stewardship (AMS), which will be described in more detail below.

It is my belief that the development of techniques to optimise the use of current antimicrobials is of core importance. Not only will this enable us to prolong the life of our current antimicrobials, but also will allow lessons to be learnt and prevent the same mistakes being made with new therapies as they come onto the market [36].

1.4.1 Antimicrobial Stewardship

In 2017, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group for antimicrobial stewardship (ESGAP) reviewed the origins of AMS, citing the terms initial use in 1996 [37,38]. The authors cite that since its inception the definition of AMS has broadened significantly, moving from a locally focused set of interventions relating to the hospital level, to a tiered system that now encompasses national and international policy makers, ethical principles, and the individual prescriber [37].

However, whatever level you evaluate AMS at a commonly acknowledged definition is the one cited by Pope and colleagues on behalf of the Infectious Disease Society of America (IDSA) [39]:

“Optimising the indication, selection, dosing, route of administration and duration of antimicrobial therapy to maximise clinical cure or prevention of infection while limiting the collateral damage of antimicrobial use, including toxicity, selection of pathogenic organisms, and emergence of resistance”

In their review of AMS, the ESCMID ESGAP agree with this definition but also add that the definition has begun to broaden to take into account the societal and cultural context that also govern our approaches to antimicrobial usage [39]. They also focus on the implied responsibility of the steward to make appropriate judgements.

From my own perspective, I see this description given by the ESCMID ESGAP as a mirror or that defined by Sackett and colleagues for the practice of EBM [1]. AMS requires the selection of the most appropriate therapy for the individual situation, based on the best available evidence that the decision maker has available to them, considering the context in which the decision is being made. Furthermore, a problem with the focus on AMS has been that it has often been considered as a different problem to the optimal management of infections, sepsis, or preventative interventions as part of infection prevention and control (IPC) strategy [24,40,41]. This has only recently begun to be addressed by international

organisations such as the United Nations General Assembly, International Coordination Group on Antimicrobial Resistance, and the World Health Organisation (WHO) [42–44]. These three aspects (AMS, sepsis, and IPC) are all in-fact a continuum of “infection management” from the prevention of infection and AMR on one side, and the optimal management of sepsis and critical illness at the other.

1.4.1.1 International focus on antimicrobial stewardship and antimicrobial resistance

Internationally, there has been a significant focus on the problem of AMR and supporting AMS. Notably, in 2016 the United Nations General Assembly (UNGA) held a high level meeting setting out a political declaration aiming to support research into combatting the problem of AMR [45]. Furthermore, the WHO has supported this through the production of a policy package that aimed to support nations to engage with and address the issue of AMR [46,47].

Surveillance has formed a key part of this focus with organisations such as the European Centre for Disease Control (ECDC), the Centre for Disease Control (CDC), and WHO all undertaking international surveillance programmes [48–50]. This has helped to document the rise in AMR and high rates of antimicrobial prescribing globally. It also enables policy makers to begin making decisions on critical areas of focus and drives the allocation of resources to the problem of AMR [42–44,48–50].

Together, the high level meetings and generated evidence describing the rise in AMR has led to commitments from global leaders to address AMR through allocation of resources and setting of targets for the reduction in antimicrobial usage in human health, agriculture, and the environment [42–44].

1.4.1.2 National focus on antimicrobial stewardship and antimicrobial resistance

At national levels, the focus has primarily been on the development of policy to improve the usage of antimicrobials. The UK, USA, and Australia have taken been prominent in the development of national strategy [8,33,51]. In the UK, the department of health issued a five-year strategy to combat AMR in 2013. This focused on seven core areas for future action [8]:

1. Improving IPC
2. Optimising the practice of prescribing antimicrobials
3. Education, training, and public engagement
4. New drug development
5. Enhancing access to and the use of surveillance data
6. Identification and prioritisation of AMR research needs
7. International collaboration

This strategy was led by the department of health, Public Health England (PHE), and the Department for Environment, Food, and Rural Affairs (DEFRA) in collaboration with experts in the field, research councils, and external consultees, such as international Non-Government-Organisations [8].

Examples of how this strategy was implemented in secondary care has been demonstrated through the implementation of:

1. The “start-smart and focus” guidelines for antimicrobial prescribing [52,53]. A national AMS policy for all hospitals in the UK.
2. The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) [24] to monitor and evaluate prescribing and AMR.
3. The introduction of quality premium’s for antimicrobial prescribing in 2017, targeting reduction in important broad-spectrum antibiotics and Gram-negative blood stream infection rates [54,55].

1.4.1.3 Local strategy for antimicrobial stewardship and antimicrobial resistance

A high-level focus on AMR and improving antimicrobial prescribing linked with real-world experience of increasing drug-resistant infections in local hospitals has ensured the response of individual organisations to AMR. Within organisations, there are a wide variety of unique challenges to consider when addressing this issue [56]. At the organisational level, there is the need for strong leadership and the maintenance of visibility of AMR [56]. There is also the need to ensure that policy is implemented at the local level. This has led to interventions such as the creation of Director of Infection Prevention and Control (DIPC) and consultant antimicrobial pharmacists [56,57]. However, within organisations the influence of culture and team dynamics is also a critical barrier to changing behaviours when it comes to antimicrobial therapy [58–61]. This was first described by Charani and colleagues at the hospital Trust where my thesis will be conducted. Within this study, the authors described the significant influence of prescribing etiquette and the culture of non-interference in prescribing practices that are observed within teams and hierarchies [58]. This highlighted the critical importance of addressing cultural and social contexts at the local level when developing interventions to improve antimicrobial prescribing. This includes when considering evidence to support decision making.

1.5 Hypothesis

For this thesis, I have generated the following hypothesis that I wish to investigate:

Personalised decision support interventions have the utility to enhance antimicrobial management across secondary care.

1.5.1 Aims and Objectives

My aim is to investigate personalised decision support approaches to antimicrobial management and determine whether these provide an opportunity to enhance the precision with which we use antimicrobials within secondary care.

In this case, personalisation will be defined as customisation of healthcare where medical decisions, practices, and products are tailored to the individual patient, prescriber, pathogen, or antimicrobial agent [62].

Given the increased use of technologies such as electronic health records and clinical decision support systems (discussed below in *Chapter two*), I aimed to explore the role that technology can play in enhancing the precision of antimicrobial therapy in secondary care.

Personalised approaches will target areas which are currently available for implementation in clinical practice and can help support evidence-based practice of antimicrobial usage:

- Individualisation of antimicrobial selection using decision support technologies.

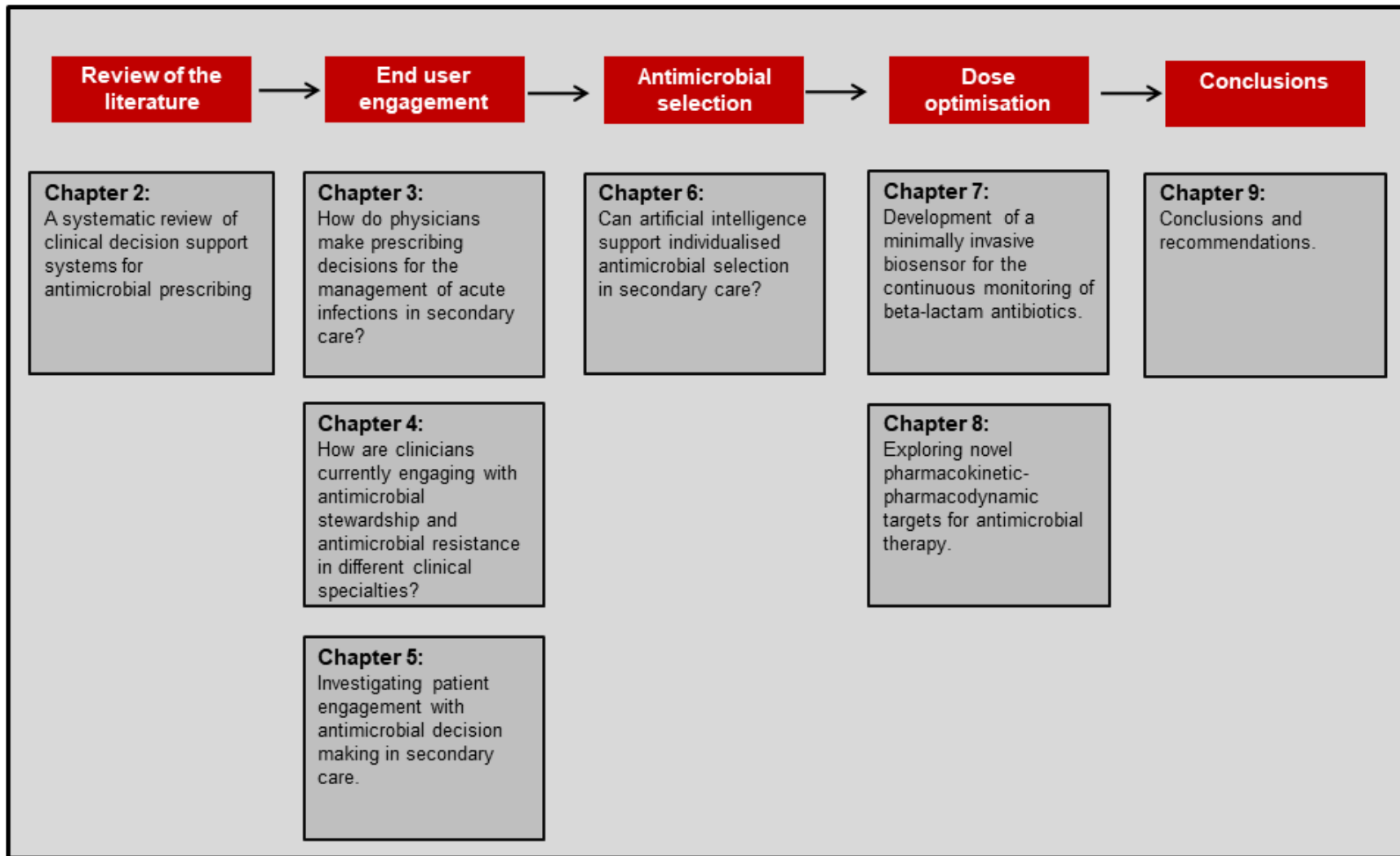
- Optimising the therapeutic outcomes of antimicrobial chemotherapy through mechanisms of precision dosing.
- Enhancing patient engagement in the decision making process.
- Exploring prescriber engagement with antimicrobial stewardship and antimicrobial resistance.

To achieve this, I have set the following objectives:

1. To review current clinical decision support systems for antimicrobial management.
2. To understand the current decision processes prescribers' use in secondary care during infection management.
3. To explore the level that different clinical specialties are currently engaged with AMS and AMR across the UK.
4. To understand patient experiences of engagement with antimicrobial decision making in secondary care and explore the consequences of this.
5. To explore mechanisms of personalising antimicrobial selection through the development of artificial intelligence driven decision support tools.
6. To explore the utility of individualised dosing of antimicrobials across secondary care pathways.

1.6 Project overview

Figure 2. Overview of thesis.



CHAPTER TWO

2.0 A systematic review of clinical decision support systems for antimicrobial prescribing

2.1 Introduction

Given the current focus on improving the accuracy of antimicrobial prescribing, research has turned to investigate whether technology can provide an avenue to achieve this. Globally, there has been a dramatic annual increase in the uptake of electronic health record (EHR) and computerised prescriber order entry (CPOE) systems [63–65]. This means that there is an increasing amount of routinely available electronic health data available to support decision making. In line with the increase in EHR system adoption, there has also been an increase in the reporting of clinical decision support systems (CDSS) for antimicrobial prescribing [66].

CDSS are defined as computerised tools that help healthcare professionals (and patients) make decisions about clinical care. Outside of the field of infection, CDSS have been demonstrated to improve the practice of EBM [67]. Furthermore, they can enhance the efficiency and safety of healthcare [67]. Therefore, it seems logical that CDSS have been explored as a potential avenue for improving the practice of antimicrobial prescribing.

CDSS to support antimicrobial management were first reported in the 1980's. Since then, several systematic reviews of experimental and quasi-experimental studies have explored the potential of CDSS to improve antimicrobial management at different levels of care [68–70]. However, these reviews have only tended to focus on single care pathways, such as the hospital setting or primary care, they have failed to include qualitative studies, and have

focused on outcomes neglecting to evaluate the way that current CDSS are developed, implemented, and evaluated in practice.

2.2 Chapter objectives

To inform the development and direction of my thesis, I decided to perform a systematic review of original literature (qualitative and quantitative) on CDSS. This aimed to understand the current scope of CDSS for antimicrobial management and analyse existing methods used to evaluate and report such systems.

My aim was to use this review to create a pragmatic picture of CDSS for antimicrobial management and produce recommendations for future research and interventions, which may optimise the effectiveness of CDSS within this field. This understanding would form the basis of my subsequent direction taken within this thesis.

2.3 Method

To review the current literature on CDSS for antimicrobial prescribing I performed a literature search. The *Medline*, *EMBASE*, *HMIC Health and Management*, and *Global Health* databases were searched from 1st January 1980 to 31st October 2015 using the search criteria described in **Table 1**. I selected broad based search criteria to capture all information technology products which have been labelled as “clinical decision support systems” for antimicrobial management.

Table 1. Search Criteria used for systematic review of clinical decision support systems for antimicrobial prescribing.

	Searches	Results
1	Antibacterial	136,630
2	Anti-infective	63,354
3	Antimicrobial	258,100
4	Antibiotic	678,831
5	1 OR 2 OR 3 OR 4	963,383
6	Computer*	1,922,886
7	Electronic	314,901
8	6 OR 7	2,188,244
9	Decision support	46,832
10	Decision algorithm	626
11	9 OR 10	47,393
12	5 AND 8 AND 11	559
13	Remove duplicates	400

Legend: * wildcard

2.3.1 Study selection

I included all prospective and retrospective articles in English that reported original research on clinical patient or product outcomes of CDSS for antimicrobial management in primary and secondary care. Study designs included were:

- i. Randomised trials, including cluster randomised.
- ii. Observational studies, including case-control, cross-sectional, cohort, before-after, and interrupted time series.
- iii. Diagnostic tool evaluation.
- iv. Development reports that included the training of systems on real patient data.
- v. Mixed-method evaluations of CDSS.
- vi. Qualitative (survey, semi-structured interview, or ethnographic) studies.

Interventions that focused on critical care were excluded from this review as the CDSS within these studies are implemented differently to primary and secondary care. Within critical care, these tools are used by doctors in conjunction with infection specialist advice, where these close working relationships significantly improve patient outcomes [71–75]. This is in comparison to primary and secondary care where CDSS are often used to supplement the expert support observed in critical care. As well as critical care, CDSS designed specifically for paediatric antimicrobial management were excluded. This was because of the differences in prescribing compared to adult antimicrobial management. Studies that did not present original data were not carried forward.

Myself and another researcher (either Luke Moore [LSPM], Esmita Charani [EC], or Enrique Castro-Sanchez [ECS]) independently screened all of the study titles and abstracts against the inclusion and exclusion criteria described above. Data were extracted and tabulated for comparison (described below). Inter-rater reliability was assessed by calculating Cohen's kappa statistic. Where there was disparity between opinions, we (myself and the other researcher) discussed these to reach a consensus.

2.3.2 Grouping decision support systems and data extraction

Following the selection of studies for inclusion, myself and another researcher (either LSPM, EC, or ECS) independently reviewed each study. We grouped studies describing the same CDSS and extracting data for systems instead of studies. Data recorded included:

- i. The CDSS characteristics, including what decision support was provided, the platform, and system infrastructure.
- ii. The study design(s) used to evaluate the CDSS.
- iii. Any comparator or control used.
- iv. Primary and secondary outcomes were recorded when available with the outcome of these.

Qualitative studies were analysed using a thematic synthesis approach [76]. For this, I used an inductive approach to perform line-by-line coding of the text. This allowed me to draw out descriptive themes from the study. I was then able to work with three of my colleagues (LSPM, EC, and ECS) to re-coded and discuss the studies and agree upon analytical themes that emerged from the text [76].

Finally once data were extracted, the CDSS were evaluated against an analytical framework that I adapted from the Stage Model of Behaviour Intervention Development [77] and the Medical Research Council's Developing and Evaluating complex interventions guidance [78]. The framework is outlined in **Table 2**. CDSS were evaluated as systems, with individual studies reporting the same system pooled.

This framework uses four domains to evaluate CDSS:

- i. Development;
- ii. Feasibility and piloting;
- iii. Evaluation of the system; and
- iv. Implementation.

The description for each domain is outlined in **Table 2**. The aim of this framework was to allow me to evaluate CDSS based on core areas that should be reported. This would allow me to holistically review the evidence presented for a CDSS and provide rationale for why and how the tool was developed and how its effectiveness was evaluated [77,78].

Table 2. Analytic framework for the assessment of clinical decision support systems applied to the studies within this review.

Domain 1: Development	Domain 2: Feasibility & Piloting	Domain 3: Evaluation	Domain 4: Implementation
Literature describing a system should demonstrate:	Literature describing a system should outline:	Literature describing a system should demonstrate:	Literature describing a system should outline:
<i>A definition of stakeholder behaviours that are being targeted and how stakeholders have been engaged with during the development phase</i>	<i>How pilot testing was performed and the findings of this</i>	<i>Efficacy testing in a “real world” setting</i>	<i>How it was tested in the real world with real-world providers</i>
<i>A rationale for how the intervention may influence these behaviours</i>	<i>A understanding of the mechanism of behaviour change witnessed and how the intervention may be having its effect</i>	<i>High levels of control maintained to confirm internal validity of intervention</i>	<i>Strategies for implementation and adoption of intervention that were used and how these may of impacted on observations</i>
<i>An outline of how the system was developed</i>		<i>Confirm how the intervention changes practice and quantify its impact</i>	<i>Plans for (or evidence of) long term surveillance / follow up of the system</i>

Legend: framework adapted from the Stage Model of Behaviour Intervention Development [77] and the Medical Research Council’s Developing and Evaluating complex interventions guidance [78].

2.3.3 Quality assessment

During data extraction, it became clear that there was a wide heterogeneity in the type of studies that were to be included within this review of the literature. Therefore, I opted to use the Integrated quality Criteria for the Review Of Multiple Study designs (ICROMS) criteria [79] to evaluate the quality of studies supporting CDSS development and evaluation.

ICROMS is a quality assessment tool for infectious disease studies focused on behaviour change interventions, such as CDSS. It allows the reviewer to evaluate multiple study designs including Randomised Control Trials (RCT's) (including cluster-RCT's), cohort, before-after, and interrupted time series studies, as well as qualitative studies [79]. However, certain study types are not included in ICROMS, such as cross-sectional and case studies, economic evaluations, diagnostic studies, and development reports containing patient data. For these types of study, I performed quality assessment using other validated frameworks within the literature. These were the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria; [80] the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria [81]; and the Standards for Reporting Diagnostic Accuracy Studies (STARD), respectively [82]. For development reports, I was unable to assign a quality criterion and therefore opted to label these studies as a high risk of bias.

Using my selected quality criteria, studies were scored as advised by ICROMS [79]. To achieve this, a study was awarded 2 points if a specific criterion was met, 0 points if the criterion was not met, and 1 point if it was unclear. The sum of the quality criterion was taken to represent the *global quality score* for each individual study. Within ICROMS scores <60% of the maximum attainable score are recommended to be labelled as high risk of bias / low reliability (referred to as "high risk") [79]. Scores of 60-80% are recommended to be labelled as medium risk of bias / medium reliability ("medium risk"). Studies with >80% of the total score are recommended to be labelled as a low risk of bias / high reliability ("low risk"). Given that my objective was to capture all relevant literature, I decided not to exclude data based on the quality of evidence provided.

2.3.4 Summary measures

Following data extraction and synthesis, I reviewed the CDSS information to identify current barriers and facilitators to success in practice. To achieve this, I classified major primary outcome measures from the studies into patient level, prescriber level, or unit/hospital level outcomes. The level of evidence, determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [83], for the overall achievement of each primary outcome demonstrated within the literature was determined.

2.4 Results and discussion

2.4.1 Study selection and characteristics

Figure 3 describes the process of study identification and extraction that was undertaken. My initial search identified 402 individual titles and abstracts for screening. Of these, 131/402 (33%) abstracts were carried forward for eligibility screening and 58/131 (44%) were included in the review. Cohen's kappa for agreement was 0.88. The 58 studies selected for inclusion described 38 independent CDSS. **Table 3** summarises the CDSS attributes. **Supplementary Table 1 (Appendix 2)** outlines the full findings from the evaluation CDSS. Using ICROMS, risk of bias for studies supporting CDSS were found to be low to medium risk in primary care (7/18;39% and 8/18;44%, respectively). This was in contrast to secondary care, where the majority of studies were medium to high risk (15/40;38% and 22/40;55%, respectively) of bias.

Figure 3. PRISMA flow diagram outlining study selection for inclusion within my systematic review of clinical decision support for infection management in primary and secondary care.

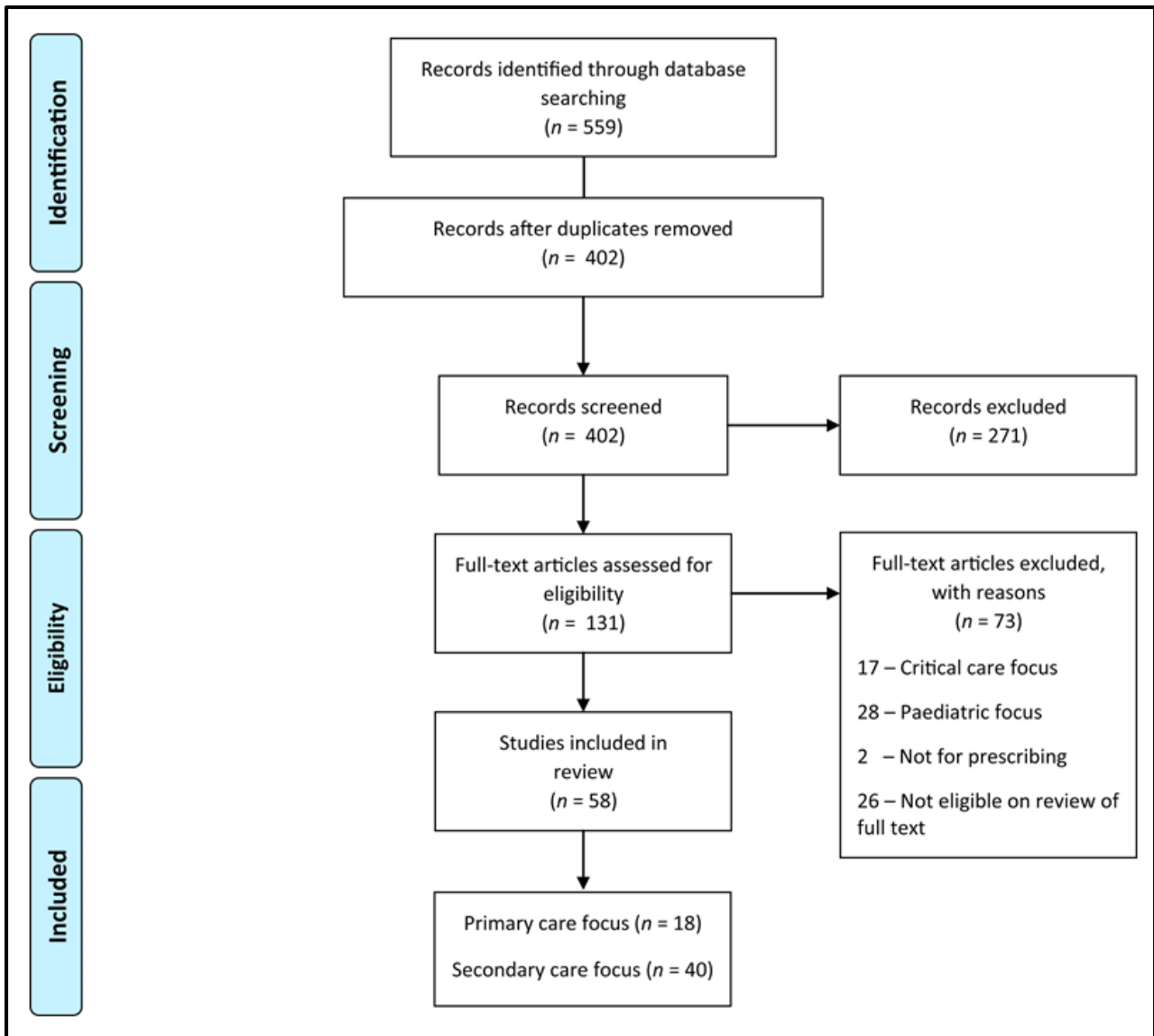


Table 3. Summary of clinical decision support systems evaluated.

CDSS characteristics		n = (%)
System setting		
	Primary care	11 (29)
	Secondary care	27 (71)
Types of decision support		
	Antibiotic prescribing	29 (76)
	Physician feedback	1 (3)
	Alerts / prompts	7 (18)
	Dose optimisation	3 (8)
	De-escalation	2 (5)
	Surveillance	2 (5)
CDSS Platform		
	Integrated into EMR	28 (74)
	On PDA device	3 (8)
	Web-based application	5 (13)
	Standalone software	2 (5)
System Attributes		
	Rule based*	29 (76)
	Causal Probabilistic Networks	1 (3)
	Drug-bug logic	1 (3)
	Pharmacokinetic modelling*	2 (5)
	Fuzzy cognitive mapping	1 (3)
	Guidelines	2 (5)
	Predictive models	1 (3)
	N/A	2 (5)

Legend: CDSS = clinical decision support systems; EMR = electronic medical records; N/A =not available; PDA = personal digital assistant.

* One system had multiple attributes.

2.4.2 Decision support systems reported in the literature

The majority of reported CDSS in the literature targeted antimicrobial prescribing (29/38;76%). All 11 CDSS in primary care focused on antimicrobial prescribing for specific syndromic presentation in adults. The syndromic presentations targeted were acute respiratory tract infections (ARIs) with two CDSS also including urinary tract infections (UTIs) [84–101]. In secondary care, CDSS that targeted antimicrobial prescribing tended to focus on empirical and prophylactic antimicrobial prescribing rather than individual syndromes [102–140]. The exceptions to this included CDSS that focused on prescribing in pneumonia, UTI, MRSA, *Clostridium difficile* infection [102–140]. Other aspects of decision support provided by CDSS included: electronic prompts / alerts (7/38; 18%), optimising antimicrobial dosing (3/38; 8%), supporting antimicrobial de-escalation (2/38; 5%), surveillance (2/38; 5%), and prescriber feedback (1/38; 3%).

Although several different platforms for delivering CDSS were reported, systems that were integrated into hospital EHR (28/38; 74%) were the most prominent. Other approaches included use of web-based platforms (5/38; 13%), personal digital assistants (3/38; 9%), and standalone software (2/38; 5%). The majority of CDSS reported infrastructure that used rules-based approaches to provide decision support (29/38; 76%). There were artificial intelligence approaches reported within secondary care that included the use of neural networks (2/38; 5%), association rule learning algorithms (1/38; 3%) and predictive models (1/38; 3%).

2.4.3 Analysis of CDSS development and pilot and feasibility testing domains

Comparing the observed results for CDSS for the analytical framework proposed in **Table 2**, a paucity of evidence exists to describe stakeholder involvement in the development and piloting of tools (domains 1 & 2). This includes limited evidence demonstrating pre-intervention stakeholder analysis, exploration of end-user decision processes, and an

understanding of how interventions will fit into routine clinical workflows. For example, Andreassen and colleagues describe the development of an intelligent CDSS using Causal Probabilistic Networks (TREAT) for use in secondary care [122]. For this CDSS, the authors place much emphasis on the construction of pathophysiological model for the diagnosis of infection and antimicrobial selection. However, no evidence is provided to describe prescriber's decision pathways and how the system will integrate into this process in clinical practice. In contrast, McDermott and colleagues report during the development of the eCRT study engagement with a small number of stakeholders (n = 33) in the design of the intervention based on behaviour change theories [97]. However, post implementation review of this intervention identified problems with variations in individuals prescribing behaviours, lack of end-user engagement with implementation, and rigidity of the guidelines incorporated limiting the use of the system [95]. These identified aspects of the clinician's decision making process were not explored during the development phase. This observation of the requirement for greater end-user engagement in the development and pilot phases is supported by Zaidi and colleagues. Within their evaluation of CDSS development they highlight significant workflow related issues of their CDSS with junior medical staff during the post-intervention qualitative evaluation of their tool [134].

2.4.4 Analysis of evidence domain

For domain 3 of the framework, examination of experimental design studies in primary care reveals primary outcome measures were heterogeneous. These tended to focus on the overall rate of prescribing of antibiotics either overall or for a defined syndrome. These studies demonstrated zero to minor clinically significant improvements in antimicrobial use [84–86,92,94,96,97]. Failures in demonstrating primary outcome measures were often linked to poor uptake of the CDSS intervention by clinicians [85,96]. For example, Linder and colleagues, reported a cluster-RCT of a rule-based (guideline driven) CDSS embedded in an EHR for antimicrobial prescribing in ARI's [87]. During the intervention period, 21,961 visits

were made by patients with ARI's. 11,954 visits were in primary care clinics where the CDSS was implemented. Of these, the CDSS was accessed and used in 6% of visits [86]. The study did not demonstrate improvement in reducing overall rates of prescribing for ARI visits (43% in control vs 39% in intervention, OR; 0.8, 95%CI;0.6 - 1.2). In experimental interventions where primary outcomes were met, such as the RCT reported by McGinn and colleagues testing the Clinical Prediction Rules (CPR) CDSS, outcomes focused on a rules-based system designed for specific types of ARI. This study demonstrated a 10% reduction in antimicrobial prescribing (adjusted RR: 0.74, 95%CI; 0.60 - 0.92) [94]. However, clinical outcomes and unintended consequences of reducing antimicrobial prescribing for this cohort were not investigated. CDSS adoption rates in this study were reported as 62.8% [94]. Therefore, there is a large variation in uptake of such interventions between studies, which appears to influence the achievement of clinical and statistical outcomes.

In secondary care, three experimental studies were identified evaluating two CDSS. Outcome measures were variable making comparison between interventions difficult. One trial, reported by McGregor and colleagues described an electronic alert system for AMS teams. This CDSS demonstrated a significant financial benefit with the trial stopped early after savings of over \$84,000 were demonstrated over a three month period [135]. During this time, the intervention was used on 359 patients versus 180 controls [135]. The remaining two experimental studies reported were for a CDSS incorporating Causal-Probabilistic Networks (TREAT). These studies did not show significant improvements in primary outcomes following adjustment. Primary outcome measures were the appropriateness of empirical prescribing and 180-day survival following treatment, respectively [124,126]. Analysis of the appropriateness of empirical therapy compared to prescriptions to subsequent organism sensitivity profiles. Within this evaluation, TREAT demonstrated a 9% improvement in appropriateness of prescribing [141]. However, adjustment for medical ward clustering and site, using multivariate regression, the findings did not reach significance (OR: 1.48, 95%CI; 0.95 - 2.29). This may have been partly due to

under powering due to financial and time constraints [141]. The second study of TREAT assessed 180-day survival. Once again, upon intention-to-treat (ITT) TREAT failed to demonstrate significant benefit. However, per-protocol analysis did demonstrate improvements in mortality using the system (6% increase in survival, $p = 0.04$) [126]. This suggests once again that clinical uptake of interventions may be a contributing factor, along with appropriate powering of cluster-RCT's [126].

2.4.5 Analysis of implementation and prescriber engagement with systems

For framework domain 4, I identified that many of the investigated CDSS failed to demonstrate significant results on ITT analysis. This appears to be linked with poor physician adoption of the CDSS. This finding is supported on review of published qualitative studies investigating CDSS implementation in both primary and secondary care. In these studies, a common theme emerges describing barriers to physician engagement with such systems. In primary care, a number of patient, physician, and technical aspects causing a lack of engagement with interventions were identified by McDermott and Litvin [89,95]. For example, both groups cite technical aspects, like usability and work flow of the intervention in normal clinical practice as potential barriers to use [89,95]. This was reported to be exacerbated when end-users felt that using the system would reduce time with or detract from engagement with the patient [89,95]. Furthermore, physician factors such as perceived level of clinical experience and agreement with conventional CDSS were reported as influencing adoption of interventions. Physician engagement was similarly found to be an issue by Zaidi and colleagues, who assessed the implementation of a CDSS in an Australian hospital [133,134]. Finally, a further area of importance was the lack of information available to describe mechanisms to support implementation and adoption of CDSS upon implementation. Furthermore, end-user follow up and long-term surveillance of interventions to support adoptions were also under reported.

2.4.6 Reported primary outcome measures of CDSS

Figure 4 outlines the major primary outcome measures identified. Outcome measures were classified according to whether they demonstrated evidence at the hospital/unit, patient, or prescriber level. Evidence was rated as medium to high at supporting the benefit of CDSS at the hospital and prescriber level. However, there was little evidence to support the impact of CDSS on patient level outcomes, including mortality and experience of complications. Outcome measures tended to be proxy indicators of success, such as appropriateness compared to guidelines or rates of prescribing. They often failed to investigate direct patient outcomes from implementation of CDSS.

Figure 4. Primary outcome measures reported for CDSS in the literature.

	PRIMARY OUTCOME MEASURE	Total number	No achieving outcome	Quality of evidence
UNIT LEVEL	Disease specific antimicrobial prescribing rate (e.g. in total ARI visits)	6	3	H
	Rate of antimicrobial prescribing (drug e.g. DDD/1000 patient bed days)	3	3	M
	Economic benefit of CDSS	3	1	M
PATIENT	Mortality (e.g. 30 & 180 days)	1	1	L
	Patient specific complications (SSI's / ADE's / HCAI)	1	1	L
	Diagnostic accuracy e.g. Infection type (e.g. ARI / UTI), Predicting probability of blood stream infection, or predict causative organism	3	3	L
	Individualised dose optimisation	1	1	L
PRESCRIBER	Appropriate empirical prescribing – against subsequent bug sensitivity	3	3	H
	Individual changes in prescribing behaviour (including de-escalation)	4	4	M
	Adherence to local guidelines	9	7	M
	Appropriate prescribing – duration / timing of therapy	2	2	M
	Acceptance of CDSS	2	1	L
	Compliance with dosing guidance	2	0	-

Legend: DDD = Daily defined doses; ARI = Acute respiratory tract infection; HCAI = Healthcare Associated Infection; CDI = *C. difficile* infection; ADE = Adverse drug event

Overall, the majority of evidence is low to medium in support of improved clinical outcomes. However, there is high quality evidence supporting CDSS at a unit/healthcare organisation level to reduce the cost of antimicrobial therapy. This is supported by the RCT reported by McGregor and colleagues in secondary care [135]. At the prescriber level, high quality evidence is available and suggests that CDSS have the potential to directly influence individual prescribing behaviours. For example, McGinn and colleagues reported a RCT which implemented clinical decision algorithms within a primary care EHR system. This demonstrated significant reductions in antimicrobial prescribing and investigations ordered at the individual physician level [94]. However, there remains a paucity of high quality evidence for patient specific outcome measures, such as mortality or complications of treatment selection, such as adverse drug events (ADE's), healthcare associated infections (HCAI's), and other unintended consequences. This type of evidence is probably not currently available due to the need for longitudinal follow up of individuals across complex care pathways and difficulties with powering such studies.

2.4.7 Limitations

There were several potential limitations associated with this systematic review that I must consider. Firstly, when considering impact of CDSS on different outcomes I was unable to perform meta-analysis of the data. I chose not to explore this option given the heterogenous nature of definitions used between studies for appropriateness of antimicrobial therapy and the fact that use of cluster-RCT design for experimental studies does not allow individualisation of data.

Secondly, many of the CDSS interventions appeared to have been implemented with a number of other AMS-based interventions, such as educational sessions and prescriber feedback [142,143]. In many cases, it was challenging to dissect the individual merits of each facets of the overall intervention, making the direct impact of the CDSS challenging to determine. Furthermore in certain cases, such as with TREAT, although the authors denied that the system was implemented with other supportive measures audit and physician feedback was performed during the study period, which may of influenced the study results [124].

Finally, although broad based search terms were used to try and capture a broad representation of appropriate studies, some may have been missed. This includes commercially developed products that are not reported within the literature and were not within the scope of this review. My review methodology included hand searching of reference lists of identified studies in order to identify missed references where possible.

2.4 Conclusion and key messages

On review and analysis of the literature, I observed that current decision support systems are associated with limited evidence of direct clinical impact on patient outcomes [66]. Furthermore, several key gaps were identified with the development and reporting of CDSS for antimicrobial management. The key gaps identified included:

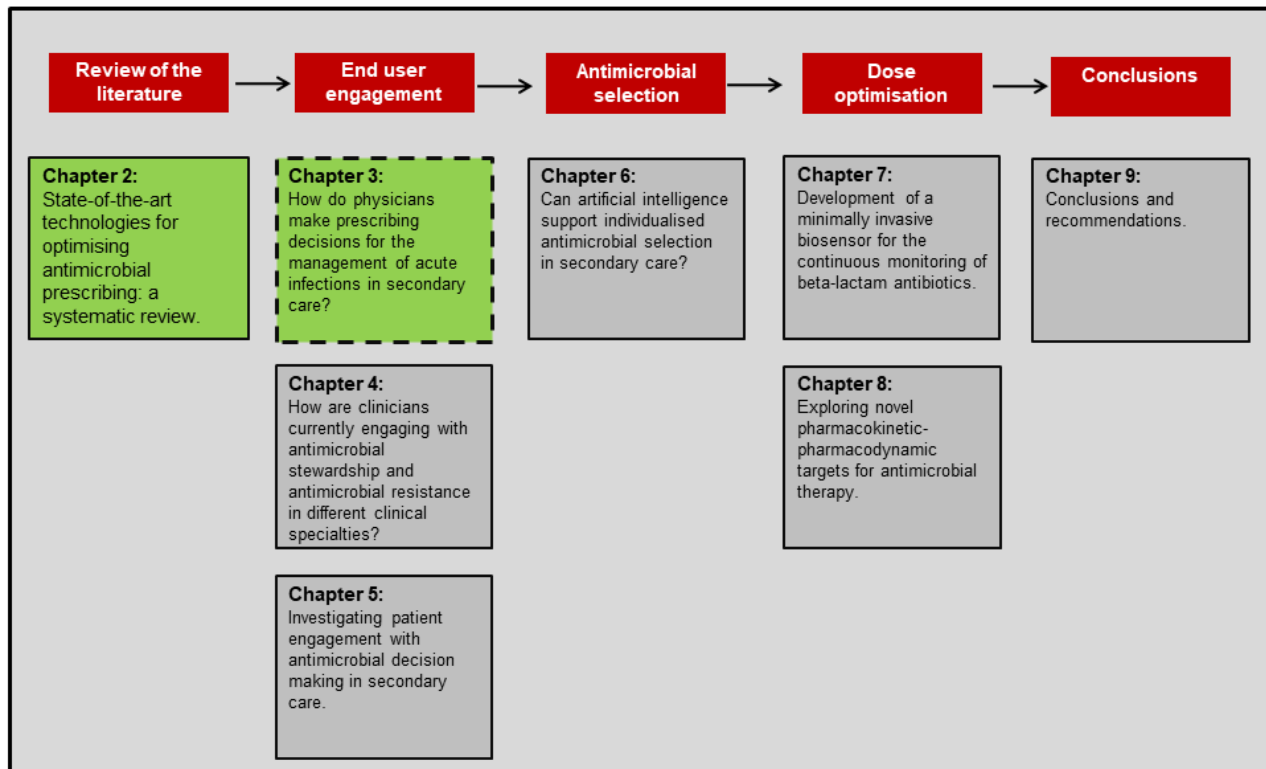
1. **The narrow focus of systems** currently under development, which tend to focus primarily on antimicrobial selection only. In the context of promoting evidence-based practice of antimicrobial management these tools fail to consider other key aspects such as the role of dose optimisation and patient engagement, which could augment this.
2. **A lack of flexibility and personalisation of interventions.** This means that there is limited ability within current systems to adapt decision support to variations that are observed in clinical practice. Therefore, evidence provided tends to not be the best available for the individual clinical situation being considered by the clinician.
3. **Failure to consider the end-users workflow** and needs during the design and implementation of interventions.
4. **Broad failures in the adoption** of decision support interventions for antimicrobial management upon implementation in practice. Furthermore, there was a paucity of reporting of patient-facing interventions associated with the development of CDSS.
5. **A lack of consensus on how to define appropriateness** of antimicrobial therapy makes comparison between interventions challenging.

These gaps have informed the development of my hypothesis, my aims and objectives, and the design of studies to be undertaken within this thesis as I outlined in *Chapter one* (*section 1.5*).

CHAPTER THREE

3.0 How do physicians' make decisions for the management of infections in acute care?

Figure 5. Overview of thesis.



3.1 Introduction

The reasons for the misuse of antimicrobials in humans are complex and multifaceted. However, a number of factors have been described and investigated. At the individual prescriber level, prescribers often prioritise the management of the patient in front of them, paying little regard to the long term consequences (on future patients and generations) of overusing antimicrobials [144]. Moreover, the majority of antimicrobial prescribing is performed by individuals who are not experts in infection management and

may have limited understanding of antimicrobials and AMR [20,145–147]. At the hospital or team level, a number of barriers to the effective use of antimicrobials have been described, including the role of team hierarchies and prescribing etiquette, which can often hinder external interventions to optimise prescribing behaviours [58,60,148]. Finally, patient involvement in the decision making process for antimicrobial prescribing is now recognised to also shape the decisions made by physicians, with patient expectations and their understanding of antimicrobials important in guiding the choices made by physicians during the management of infections [149–151].

It therefore seems appropriate that behaviour change interventions are now thought of as a cornerstone for improving the long term use of antimicrobials [60,61,148]. However, despite evidence describing the knowledge, attitudes, and cultural determinants of antimicrobial prescribing [58,145,152], a paucity of data exists mapping the clinicians decision pathway during infection management within secondary care. This has often been neglected during development, evaluation, and implementation of CDSS [66] as I outlined within *Chapter two*.

When considering mechanisms for personalising approaches for antimicrobial management, such as developing new tools to support clinician decision making, it seems logical to first understand the end-user decision making pathway and what factors influence it. This detailed understanding of decision making may also facilitate a better understanding of areas for further development and customisation beyond the current scope of research within the field.

3.2 Chapter Objectives

The objectives of this chapter are:

1. To investigate and map the decision making process of individual physicians managing acute infections within secondary care.
2. To determine the factors that influence different aspects of physician decision making for infection management.
3. To determine potential target areas for future personalised interventions to enhance decision making for antimicrobial management.

3.3 Methods

3.3.1 Study design

Firstly, it was important to determine the optimal method to explore and understand the decision making process of physicians during the management of acute infections in secondary care.

Within this study, I did not expect there to be a single truth or reality (the ontology) for each situation that would be evaluated. Therefore, this would require interpretation to discover the underlying reasons that drive individual physicians to make the decisions that they do (epistemology). I would therefore need to try to understand the individual's perception of reality in the context that it is described [153–155]. To achieve this, I felt that a qualitative approach would be optimal. This would allow me to interpret and understand the physician decision making process through analysis of in-depth interviews with physicians, which would explore the choices that they make when managing infections. The theoretical perspective that I believed would best allow me to achieve this was by following an interpretive paradigm using Grounded Theory methodology [153–155]. This would be achieved by employing semi-structured interviews.

Briefly, Grounded Theory is a qualitative methodology that was developed in the 1960's with the aim of bringing some of the perceived rigors of positivism based research into the qualitative field [153–155]. It was developed to allow data analysis to begin in advance of any prior assumptions, with theories emerging during the data analysis process, thus allowing theories to be “grounded” in the data [153–155]. As a physician conducting this study, it is important for me not to make prior assumptions or theories about approaches that others take whilst making decisions during infection

management. Therefore, I felt that the Grounded Theory approach would be more appropriate than, for example, trying to act as an observer on the wards and triangulating my findings with interviews (ethnography) [153]. This is because I am very familiar with the setting that I would be investigating. I have previously worked in the hospitals where the study would take place as a doctor managing infections. However, by choosing Grounded Theory I also need to ensure that I address the concerns over reflexivity when using this methodology [155]. By acknowledging this limitation whilst planning my study design; I hoped that this would allow me to be mindful of it during the data analysis process and put steps in place to help increase my awareness during this process.

To ensure that reporting of this study was to a high standard I chose to report it in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist [156]. This is a 32-point checklist developed by Tong and colleagues, through a systematic review of the literature [156]. It provides a comprehensive guide, reporting all checklist items in one of three domains:

(i) **The research team and reflexivity:** Characterised as describing both the research team's personal characteristics as well as the relationship of the interviewer with the participants.

(ii) **Study design:** Including theoretical frameworks, participant selection, the setting that the study was performed in, and how data were collected.

(iii) **Analysis and findings:** Including describing how data were analysed and how it should be reported.

3.3.2 Setting

Recruitment of physicians took place across Imperial College Healthcare NHS Trust (ICHNT), which comprises three main university teaching hospitals in North West London. Interviews were semi-structured face-to-face interviews with individual physicians. No one else was present for the interviews apart from myself (who performed all interviews) and the interviewee.

3.3.3 Researcher background

I personally undertook all interviews within this study. I am a junior doctor, who before commencing my PhD worked for one year at ICHNT. Therefore, I am familiar with the protocols and procedures for infection management within the Trust, particularly in certain clinical specialties (namely acute medicine and haematology). At the time of undertaking the interviews, I was no longer working within the Trust, acting as a full-time research student. I had led several semi-structured interviews prior to undertaking this study as part of other antimicrobial related research projects (not within ICHNT) [157] as well as received formal training in qualitative research methods as part of a two year postgraduate diploma in medical education that I have previously undertaken with Cardiff University.

3.3.4 Participant recruitment

The sampling frame that I selected was medical physicians who were not specialists in infectious disease or microbiology (defined as either; (i) clinical specialties who practiced general internal medicine, such as cardiology, respiratory, and geriatric medicine; or (ii) augmented care specialties, such as haematology and nephrology). Medical physicians

from those in training (i.e. foundation year 1 to specialist trainees) to consultant grade were included.

As most antimicrobials in the UK are prescribed by doctors, I excluded other healthcare professionals involved in infection management (e.g. pharmacists and nurses) from inclusion in this study. Primary care physicians, surgeons, intensive care specialists, and focused specialties such as psychiatry were excluded. This was for two reasons. Firstly, many of these specialist areas tend to engage in a broader range of antimicrobial prescribing activities that are out of the scope of my thesis (e.g. prophylactic therapy in surgery) and often rely on support with infection management through multi-disciplinary (MDT) collaboration with medical and/or infection teams. This MDT approach has been shown to improve patient outcomes of infection within these settings [71–75,158,159]. As the goal of this study was to understand the decision pathways used by potential end-user of CDSS for managing infections, infection specialists were also excluded from this study.

Using purposive sampling, I invited physicians to participate in the study [154,160]. This was facilitated through a single email being circulated to the hospital general medical doctors mailing list, which was then followed up with single targeted emails to identified clinicians, who I felt would be suitable for purposive sampling. All respondents to the emails were contacted a second time to organise a time to participate in the interviews followed by a final email on the day of the interviews confirming their attendance. Participants were purposively sampled at different levels of training (on-rotation, specialist trainee, and consultant) with deliberate selection. This aimed to reflect the diversity of medical specialties within the hospital environment. To achieve this, I sampled physicians in the eleven major medical specialties (excluding infectious diseases) within the hospitals who were responsible for in-patients. Participants were

contacted via email and invited to participate in face to face semi-structured interviews. Two follow up emails were sent if there was no reply from the initial invitation at weekly intervals. I stratified respondents to the email into on-rotation (foundation years to core medical training), specialist trainee, and consultant physicians for interviews.

All participants were consented to participate and be anonymously audio recorded during the interviews. All interviews were conducted between August 2015 and April 2016. I worked with a multidisciplinary team comprising two infection doctors, a pharmacist, a nurse, and a social scientist all of whom worked in the field of AMR. With their support we developed and piloted a 10 question semi-structured interview guide (**Appendix 3**) which would act to structure my initial interviews with participants. This was piloted on a junior doctor, a research pharmacist, and senior infection doctor. Participants from each of the stratifications described were interviewed [154,160,161] and these were continued for each stratified grade and specialty until saturation was reached and no new themes were found to emerge [154,155,160,162]. All data were anonymised with only myself knowing participant identities. The interviews were audio recorded and then transcribed verbatim. I also took notes at certain times during the interviews, often noting aspects that I wanted to return to at a later point in the interview or highlighting key emotions or actions that may not necessarily be reflected in the audio recording. No repeat interviews were performed and transcripts were not returned to participants for comment or correction.

3.3.5 Ethics

The study protocol was submitted and reviewed by the West London Regional Ethics Committee (REC) in August 2015. It was considered to meet criteria for monitoring

under service evaluation governance structures, which were subsequently registered with ICHNT (*REC 15/LO/1269 / ICHNT; Service Evaluation SE113*).

3.3.6 Data analysis

As per Grounded Theory, an iterative approach was applied to data analysis with simultaneous analysis and interviewing undertaken [153–155]. Following rounds of analysis, future interviews were guided by findings and theories as they emerged from the data [154,155,160,162]. NVIVO Pro 11.0 (QSR Software Products) software was used to support data analysis.

The initial analysis was performed by me alone, reviewing all transcripts and performing initial line-by-line coding. Emerging themes and theories were then discussed with the multi-professional team who were described above in *section 3.3.4*. This aimed to increase reflexivity and allow me to be more aware of my own perceptions during the data analysis [163]. I also sought out deviant statements that could contradict emerging themes to improve the rigor of the analysis and ensure that theories and themes were appropriately challenged [155,164]. Thus, this allowed theoretical sampling to be undertaken during subsequent interviews until it was deemed that theoretical saturation was achieved [165]. This was defined as being when all of the concepts within the substantive theory surrounding physician decision making for infection management were felt to be understood and supported by the data [154,165].

3.4 Results

3.4.1 Data analysis

In total, 34 physicians from 10 specialties responded to the invitation email agreeing to participate in the study. However, the study was stopped at 20 participants as saturation was reached. Seven of the participants were on-rotation physicians, four were specialist trainees, and nine were consultants. Of those that participated, the majority were male (12/20, 60%) and the majority of participants were from acute internal medicine (4/20, 20%), haematology (3/20, 15%), care of the elderly (3/20, 15%), and respiratory medicine (3/20, 15%). The remaining participants were from gastroenterology (2/20, 10%), cardiology (1/20, 5%), endocrinology (1/20, 5%), stroke medicine (1/20, 5%), clinical pharmacology and therapeutics (1/20, 5%), and renal medicine (1/20, 5%). The interviews ranged in duration from 12 minutes to 32 minutes, with a median length of 20 minutes.

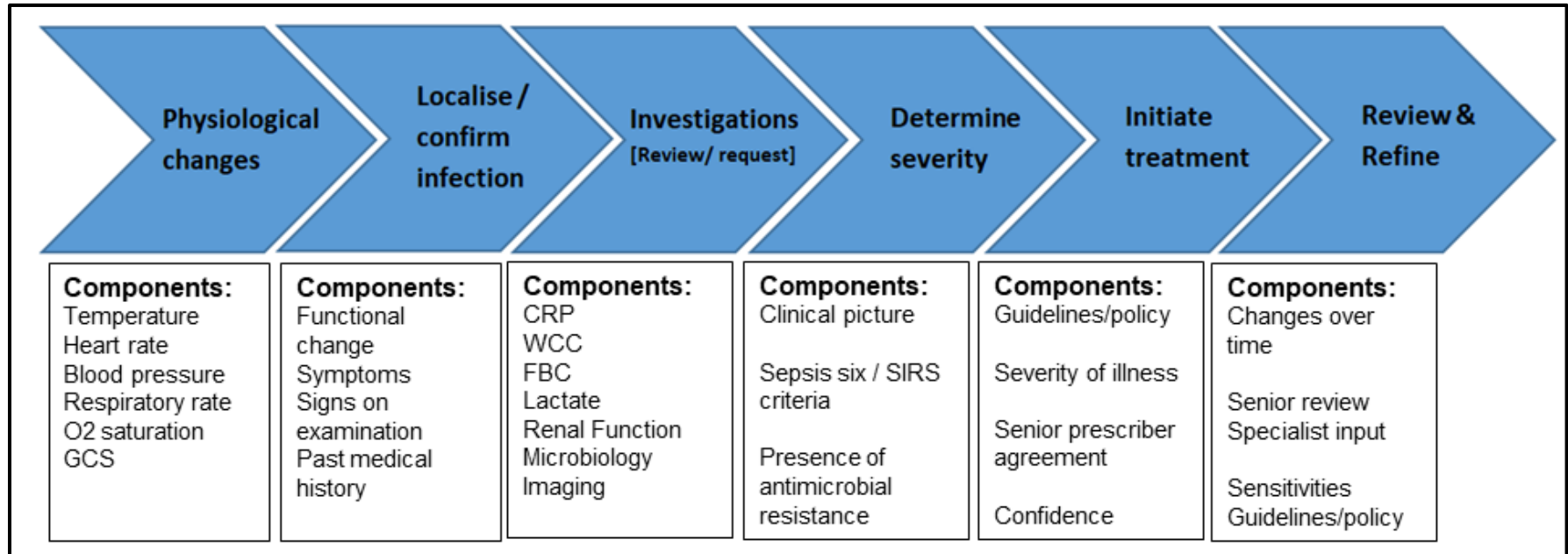
On final analysis of coding performed within this study, a total of 178 initial codes were generated, these were supported by a total of 1094 references from the 20 transcripts.

3.4.2 Mapping the decision making process

Analysis and interpretation of the data identified six themes that describe the stages of reported physician decision making processes during infection management. Physicians reported that they begin decision making by estimating the likely risk of an infection being present in this particular situation. They then systematically add further information in a stepwise process. This allows them to optimise their decisions on diagnosis and management in a dynamic fashion. Although this process could also be viewed as

cyclical and in fact even branching, with physicians returning to step 1 every time they re-assess the patient or hand over care to another physician, the steps and common variables reported as considered within each step have been mapped in a linear fashion for simplicity in **Figure 6**.

Figure 6. Reported decision making pathway for infection management in secondary care.



Legend: O₂ = Oxygen; GCS = Glasgow Coma Scale; CRP = C-Reactive Protein; WCC = White Cell Count; FBC = Full Blood Count; SIRS = Systemic Inflammatory Response Syndrome. Represented in a linear fashion for clarity.

Table 4 provides supporting quotations for the thematic construction of the decision making pathway described in **Figure 6**. Physicians report that the antibiotic decision making process begins by looking for changes in the patient's physiological parameters, with temperature being an important factor at this point. The second reported stage of the decision making process involves attempting to localise and confirm that infection is present in the patient. This was reported to involve searching for symptoms reported by the patient or their carer / family and then backing this up with identification of clinical signs. Thirdly was the review of current and planning of further investigations. C-reactive protein (CRP) was reported as being regarded as a key biological indicator of infection during infection management. Following this step, physicians reported using the information that was present in steps one to three to determine the severity of the infection. Judgement of this was widely reported to be based on the overall "clinical picture" created during steps one to three. Interestingly, more junior physicians reported a higher reliance on the use of diagnostic criteria such as the "septic six" or "Systemic Inflammatory Response Syndrome (SIRS) criteria" during this process compared to senior physicians. These criteria are evidence based scoring systems that have been designed to help physicians determine the severity of an infection, in particular whether it is classified as sepsis [166].

Following determination of the severity of the infection, physicians reported step five as primarily a decision regarding the initiation of antimicrobial therapy. Within this step local microbiology guidance (written or electronic) provided within the hospital was a major factor that determined what therapy would be prescribed. However, it must also be noted that physicians, particularly more senior individuals, reported that therapy would not always be initiated at this point with deferring therapy (or 'watch and wait') also regarded as an option. The final step is the review and refinement stage, which can occur in two

separate and or overlapping routes. The first of these was reported as an internal process, with the individual physician returning to stage one of the decision making pathway and reviewing each stage. This allowed them to revise their decision making based on dynamic changes to individual components over time. The second route was reported to be external review by another physician (often reported as more senior or specialist). By taking this pathway the new reviewer would use stages one to five to review and refine the management decision made by the prescriber in a similar fashion as described above.

Table 4. Thematic construction of medical physicians' decision making pathways for the management of acute infections in secondary care.

No.	Quote	
1	<i>"I think I know when would be an easy enough time as a junior doctor to go, yeah, I think this warrants Tazocin, this warrants cefuroxime IV. So for some drugs I think you have a little bit more of an ease of prescribing because you're not too worried about the downsides"</i>	On-rotation acute medicine [1]
2	<i>"So nights, I think obviously it becomes much more of a zoo doesn't it really, so people tend to start broad spectrum agents without really looking through previous microbes and patients have a tendency to stay on that till it's reviewed in daytime hours"</i>	On-rotation acute medicine [2]
3	<i>"If the patient is septic or something, you have to start antibiotics within your hour, Sepsis Six, but then you're also under pressure to get the right source"</i>	On-rotation acute medicine [2]
4	<i>"Yeah, definitely in terms of how you go but I think anyone who's done hospital medicine now sees that Tazocin is basically the port of call for most things"</i>	On-rotation cardiology
5	<i>"When I look back at years gone past, I think I was probably quite gung-ho with antibiotics because it was the easy option because you didn't want to get in trouble and I'm sure plenty of patients in [region - UK] got BenPen [benzylpenicillin] and Cipro [ciprofloxacin] when they might have lived without it. But this is a situation in which, I think the way I've changed is that I tend to look at what the risks of deferring here versus not"</i>	SpR Cardiology
6	<i>"I've got a bit of a nice cushion from all the senior levels about even if I prescribe the wrong antibiotic, I don't mean of course prescribing penicillin when someone's penicillin allergic, that's not what I mean. I mean prescribing for example flucloxacillin when it's an E.coli bacteria, wrong bacteria, wrong antibiotic of choice or bacteria, but an antibiotic nonetheless."</i>	On-rotation acute medicine [3]
7	<i>"I think a lot of people, myself included, would say if you are admitting the patient to hospital and they have an infection severe enough to come into hospital then you should, and I know this is not what microbiologists would say, but in my mind you like to feel like you are doing something that they couldn't have at home and that's why you give them some intravenous antibiotics when they come into hospital with a view to stepping them down very quickly afterwards, and I think it makes everyone feel better whether it's the patient and more significantly the doctor"</i>	Consultant General Internal Medicine
8	<i>"I would not expect an SHO to decline to give antibiotics"</i>	SpR Geriatrics

3.4.1.2 Factors influencing decision making

In addition to the six themes defining the physician decision making pathway; there were several key themes that emerged from the interviews describing factors that influence the decision making process beyond the components that map onto the pathway in **Figure 6**. Two of these were hierarchical systems in teams and prescribing etiquette, which have previously been reported in the literature and therefore will not be analysed in detail within this chapter [58,59,167]. However, several concepts that had been less widely reported at the time of this study in 2016 were also identified. These themes were associated with stopping/de-escalating therapy, the role of guidelines and microbiology advice, and physician's feelings of responsibility to provide optimal care for the patient in front of them. Many of these factors appeared to mostly influence the latter half of the decision pathway, surrounding initiation and review of antimicrobial therapy and will be explored in detail below.

(i) Physician skills used when assessing the patient

During the interviews, a common theme reported was the feeling of overall responsibility of the team, and in particular the consultant, for the patient under their care (**Table 5**). These feelings of responsibility were reported to lead consultants to make autonomous decisions regarding the management of their own patients. To support this, they reported using previous experiences and accumulated knowledge from years of clinical practice to make subjective assessments of the patient. In contrast were junior team members who whilst often making the initial decision about the management of patients with acute infections, were not considered a final decision maker. This task was reported as remaining with the consultant who perceived their job in antimicrobial management as being to review and refine the decisions of junior colleagues.

This perception of responsibility was also projected down through the medical team hierarchy with specific expectations placed on junior colleagues' actions. For example, during the interviews on-rotation doctors reported how they begin to develop their clinical assessment and decision making skills through clinical practice. They are usually the first individuals to respond to an unwell patient, and during the assessment of the patient tend to rely on objective parameters, such as the patient's heart rate or temperature. These were reported as more highly considered compared to more subjective measures, such as clinical examination and the general impression of the patient. However, these subjective factors were reported to be much more important during consultant and senior registrars' assessment and decision making.

Furthermore, on-rotation doctors report a significant fear of missing the patient with sepsis. It appears that this fear of sepsis, coupled to the expectations that are placed on juniors to prescribe antibiotics, often drives inappropriate views and decision making regarding antimicrobial prescribing. This culminates in there being an overwhelming need to commence antimicrobials as soon as a patient is suspected of having an infection so as not to miss sepsis.

(ii) Antibiotic prescribing is a key component to providing optimal care

A further theme that emerged from analysis of the transcripts was a recurring factor of the physician's view of what was optimal care for the individual patient with an infection in hospital. In particular, when prescribing antibiotics for a patient requiring hospitalisation with infection, intravenous therapy was often felt by the physician to be more optimal than oral. This was regardless of whether the decision was evidence based or not. **Table 5** also provides supporting quotes in for this theme.

Table 5. Selected quotes surrounding participants' experiences and expectations of prescribing antibiotics.

No.	Quote	
1	<i>"I think I know when would be an easy enough time as a junior doctor to go, yeah, I think this warrants Tazocin, this warrants cefuroxime IV. So for some drugs I think you have a little bit more of an ease of prescribing because you're not too worried about the downsides"</i>	On-rotation acute medicine [1]
2	<i>"So nights, I think obviously it becomes much more of a zoo doesn't it really, so people tend to start broad spectrum agents without really looking through previous microbes and patients have a tendency to stay on that till it's reviewed in daytime hours"</i>	On-rotation acute medicine [2]
3	<i>"if the patient is septic or something, you have to start antibiotics within your hour, Sepsis Six, but then you're also under pressure to get the right source"</i>	On-rotation acute medicine [2]
4	<i>"Yeah, definitely in terms of how you go but I think anyone who's done hospital medicine now sees that Tazocin is basically the port of call for most things"</i>	On-rotation cardiology
5	<i>"When I look back at years gone past, I think I was probably quite gung-ho with antibiotics because it was the easy option because you didn't want to get in trouble and I'm sure plenty of patients in [region - UK] got BenPen [benzylpenicillin] and Cipro [ciprofloxacin] when they might have lived without it. But this is a situation in which, I think the way I've changed is that I tend to look at what the risks of deferring here versus not"</i>	SpR Cardiology
6	<i>"I've got a bit of a nice cushion from all the senior levels about even if I prescribe the wrong antibiotic, I don't mean of course prescribing penicillin when someone's penicillin allergic, that's not what I mean. I mean prescribing for example flucloxacillin when it's an E.coli bacteria, wrong bacteria, wrong antibiotic of choice or bacteria, but an antibiotic nonetheless."</i>	On-rotation acute medicine [3]
7	<i>"I think a lot of people, myself included, would say if you are admitting the patient to hospital and they have an infection severe enough to come into hospital then you should, and I know this is not what microbiologists would say, but in my mind you like to feel like you are doing something that they couldn't have at home and that's why you give them some intravenous antibiotics when they come into hospital with a view to stepping them down very quickly afterwards, and I think it makes everyone feel better whether it's the patient and more significantly the doctor"</i>	Consultant General Internal Medicine
8	<i>"I would not expect an SHO to decline to give antibiotics"</i>	SpR Geriatrics

(iii) Ambiguity in stopping / de-escalating antibiotic therapy

Whilst junior physicians report having a huge weight of expectation to start antibiotics as quickly as possible in patients suspected of having an infection, the opposite appears true of them with regards to stopping or de-escalating therapy (**Table 6**). A key factor reported throughout the interviews was that on-rotation doctors are not expected to stop or de-escalate therapy, with this responsibility seen as something only consultants and specialist registrar trainees (SpR) undertake. Furthermore, it was widely reported by junior physicians that there is often variable feedback on the decisions that they have made following review and refinement by an external reviewer. This caused a great deal of frustration with junior prescribers, who often did not fully appreciate why their decisions had been over-ruled or changed. This was reported to leave them feeling that they do not develop a deep understanding of the skill of antimicrobial prescribing, due to a lack of feedback and explanation.

A further area of frustration reported by junior doctors was the heterogeneity in the approaches of senior clinicians to stopping or de-escalating therapy. When this was combined with a paucity of feedback it was reported to often deter trainees from attempting to make or suggest changes to antimicrobial therapy. This is something that was supported by senior participants, who reflected on the current lack of evidence base for many of the decisions they make surrounding length of treatment for example.

Table 6. Reported expectations around the review and de-escalation of antimicrobial therapy.

No.	Quote	
1	<i>"We are responsible for everything on the ward as well as all the decisions and I think we've got these practices in place which make sure that the antibiotics are stopped at a particular time when they needed to be stopped"</i>	Haematology consultant
2	<i>"I'm complete disempowered [to stop antibiotics], completely because they're so complicated and the consultants who know their patients have their own ways of prescribing. It's very unusual that anyone would actually explain to you what they're thinking. I think I've had one explanation which was like a ray of sunshine"</i>	On-rotation renal
3	<i>"In terms of stopping antibiotics yeah, I think stopping antibiotics is a very nebulous thing in itself... it is pretty random and is not really a huge amount of evidence out there.... I feel very happy with making decisions as to whether to stop after three times, seven ten days whatever. I don't think that's a big issue"</i>	Consultant general medicine
4	<i>"So I feel quite, I wouldn't say disempowered, but I feel like the seniors make most of the decisions. So I'm quite reluctant to make any decisions about [de-escalating] antibiotics"</i>	On-rotation gastroenterology
5	<i>"Stopping them is generally, from my experience, has been a senior's [decision]"</i>	On-rotation acute medicine [1]
6	<i>"De-escalating can be a little bit more tricky, it's very much individually based. [For] Some people it's easier but if there's no plan in place, if someone hasn't said for five days, go for IVs and then deescalate to PO I would be hesitant. I would tend to want to get a little bit of reassurance."</i>	On-rotation acute medicine [2]

(iv) The role of guidelines and clinical microbiology advice

Despite reports of senior physicians often acting autonomously and making decisions due to the feeling of overall responsibility for their patients, it was also clearly reported that antimicrobial prescribing guidelines and clinical microbiology services have a large influence on the decision making process. Within this study, on-rotation and registrar physicians reported a rigid adherence to guidelines (**Table 7**). A common point-of-view was that they realise that strict adherence is the expectation placed upon them by more senior colleagues and the hospital. As highlighted above, consultants reported their role was to act as the overseers of management decisions, often reviewing the decisions made against guidelines and then refining either the diagnosis or the prescribing decision made to ensure concordance with guidelines where they see it as appropriate. However, they also retain a level of autonomy over the guidelines driven by their overall responsibility for the individual patient and their desire to provide optimal care for them. This allows them the flexibility to be able to adapt guidelines based on their own experience and feel for the situation.

A similar situation was reported regarding clinical microbiology services provided within the hospital. For on-rotation and registrar physicians, these services and the advice given is seen as valuable and convenient. This is viewed as an easy point of access, being referred to as a safety-net for challenging decisions that are not covered in the local antimicrobial guidelines. Furthermore, they can also be called upon when a junior physician is not confident in the treatment decision that they have made. It is at this point that physicians tend to *“just call microbiology and ask....”*. However, senior physicians tend to view the reliance on this service in a more sceptical fashion when it comes to supporting the making of what is viewed as optimal decisions. Some of the issues considered by senior clinicians include:

- i. Poor communication pathways during microbiology discussions,
- ii. A lack of microbiologist responsibility for the outcome of treatment decisions that they recommend, and
- iii. A lack of continuity in the service provided due to rotation of trainees.

This perceived lack of responsibility led consultants to report that they are often reluctant to change decisions based on the advice of junior microbiology or infection colleagues, such as registrars. This was reported as being driven primarily by concerns that members of the other team may not be fully aware of all the patient factors outlined in the decision process for the reasons outlined above.

Table 7. Selection of participant quotes surrounding their antimicrobial guidelines, clinical microbiology services and some problems associated with information provided by these sources.

Reliance on guidelines	
Quote	
<i>"Does that really change your management? With the majority of cases it hasn't. So you strap them on the standard hospital protocol for CAP/infective exacerbation and you tend to just carry it on"</i>	On-rotation acute medicine [1]
<i>"Well because we're almost held down now by [antibiotic app guidelines] or whatever your Trust uses, so you end up, if you haven't done something by that choice you will go, or normally a pharmacist will go, why haven't you done that?"</i>	On-rotation acute medicine [2]
<i>"I do find antibiotic guidelines very helpful, and actually in the last couple of trusts I've worked in, they've been so comprehensive that I've not really used any other sources at all"</i>	SpR geriatrics
<i>"I think in terms of decision making I have to say I don't keep up to date with the antibiotic formula because I look it up if I need it"</i>	SpR cardiology
<i>"Quite often on a post-take ward round say, why are we giving this, has anyone checked the policy, is this in line with policy because I don't think it is?"</i>	Consultant respiratory
Reliance on microbiology	
<i>"If I think it clearly isn't within guideline or I'm not sure, it doesn't easily fit into the guideline I'm going to say, speak to micro"</i>	Consultant respiratory
<i>"I think when you call the microbiologist the fact that you've made the call has already told them that you're concerned so you're almost saying, I want a change, give me further guidance"</i>	Consultant geriatrics
<i>"If the patient has a lot of allergies for example, then that often makes it more difficult and I often end up speaking to micro if that's the case"</i>	On-rotation respiratory

Problems with guidelines and microbiology		
1	<i>"I mean I'm a complete pedant I hate this idea that microbiologists have just given antibiotics broad spectrum for sepsis of unknown origin because that's not what I'm about as a physician"</i>	Consultant gastroenterology
2	<i>"I think the difficult thing which sometimes arises that microbiology are often the more conservative end of the antibiotic spectrum and say, OK, you've had your course, stop and I may agree with that as a registrar. But the problem is that actually suggesting for me to do it is the wrong person because it's my decision once I've seen the patient on the ward round, but once you've got a consultant [microbiologist] that's come and ratified the decision then that becomes their decision"</i>	SpR cardiology
3	<i>"They tend to give more of a patient specific approach but the difficulty in that is that they haven't seen the patient. So they're sort of just giving you advice over the telephone"</i>	On-rotation gastroenterology
4	<i>"A lot of the time is I would maybe rather wait and speak to someone whose opinion and knowledge seems more valuable, where sometimes maybe the opinion that you get out of hours [from junior microbiologists] is someone who is just answering a question to get it dealt with, and so it's too broad, it's too much"</i>	Consultant respiratory
5	<i>"Well it's not patient specific [local guidelines] so it's quite generalised and it won't always have all the information about the patient"</i>	On-rotation respiratory
6	<i>"I always think that people and especially microbiologists recommend changing antibiotics far too soon. You ring up a micro registrar who just says, oh immediately I want to change from Augmentin to Tazocin. Well why?"</i>	Consultant gastroenterology

3.5 Discussion

As of December 2016 when this study was published [168], this was the first study of its kind to look at describing the decision making pathway of physicians managing acute infections in secondary care in this manner. This has provided an insight into how decision making is perceived by antimicrobial prescribers who are the targets of decision support interventions that I aim to explore within this thesis. Moreover, the understanding generated through analysis of the decision making process has provided me with a structure to explore the potential impact of current decision support tools identified in my review of the literature (*Chapter two*) on the decision making process.

3.5.1 Physician decision making

Physicians reported a common stepwise approach to decision making during acute infection management in secondary care. This followed a Bayesian-like process with new information constantly being considered against prior knowledge or assumptions to constantly review and refine the decisions being made. Despite there being a common overall approach, a number of factors also appeared to be weighed differently depending on the specific situation being described. Many of these factors tended to focus on the later phases of the decision process, and in particular, decisions surrounding antimicrobial management.

Overall, there were four defined spheres of influence that appeared to affect the reported decision making pathway. Thematically, these were identified on analysis and interpretation of the data as acting either consciously or subconsciously. I chose to classify the themes as:

(i) **Implicit factors influencing decision making:** For example, the variables outlined in the decision mapping diagram in **Figure 6** above. These factors are known and acknowledged by both the individual prescriber and the wider medical team and are influences that are commonly incorporated into guidelines and protocols for antimicrobial management. For example, the *start-smart-and-focus* campaign within the UK [53].

(ii) **Explicit factors influencing decision making:** These are often blind spots to the individual prescriber but may be appreciated by others within the team. For example, the influence of team hierarchies and prescribing etiquette on decision making [58,60,148].

(iii) **Internalised rationale (or hidden reasoning) for decision making:** This is known to the individual prescriber making the decision but is often not externalised to others. For example, when senior decision makers alter antimicrobial prescriptions but do not feedback their rationale to other members of the team who made the earlier prescribing decisions. This was reported as causing confusion and frustration when reasons for decisions are not shared beyond the individual who has made them.

(iv) **Subconscious influences on decision making:** These were neither identified by the individual or wider medical team within this study but are likely to have an influence on decision making. This could potentially include the role of other disciplines such as pharmacists and nursing staff who have been demonstrated to have a role in promoting optimal use of antimicrobials in several settings [169,170]. However, within this study, these factors were seldom reported to play a major role in the majority of interviews, even after exploration of this directly with participants during questioning. This finding could have been due to the exclusion of non-prescribing healthcare professionals from this study. However, this may also reflect the local prescriber

hierarchies and systems that exist within the hospitals that participants were recruited through. Either way, this factor warrants further investigation given that the role of the pharmacist in the UK is often described as the corner stone of AMS as well as the expanding realisation of the role of nurses in AMS internationally [169,171–173].

In terms of pharmacist involvement in the decision making process, what was reported was that at the level of seniority and proximity to the ward round appeared to be a major factor in influencing the decision making of the physician caring for the patient.

“And the pharmacists are often good, I think when, we often have the pharmacists on the post-take ward round and it depends a bit on their seniority and confidence, so the ones who will speak up and challenge are excellent.”

[Consultant, respiratory]

This suggests that future interventions may also benefit from aiming to promote multi-professional integration to help normalise the role of the pharmacist and other healthcare professionals within the decision making process. Thus, moving it from a subconscious influencing factor towards an implicit factor that is acknowledged by all as playing a key role in influencing decision making.

3.5.2 Responsibility for the outcomes of decision making

A significant theme that emerged from analysis of the data was that of responsibility for the decisions that are made for your patient. A key example highlighting this was when consultants reported how they consider clinical microbiology advice. Whilst overall clinical microbiology was seen as a great help, physicians reported that they often judge the quality of the advice provided by such services based on the level of seniority that it comes from. Furthermore, a lack of continuity in who provides the advice to a specific

team, and the limited responsibility on that person for the consequences of the choices made also played an important role. When combined with senior clinicians' experience and feelings of autonomy in decision-making, this can cause frustration and lead physicians to consider alternative treatments that may not be evidence based.

I believe that this observation offers an important learning point for those developing personalised decision support interventions, including CDSS. In particular, the requirement for the prescriber to have confidence in the tool developed to follow the guidance that it provides. This triangulates to the need for end-users to be engaged actively in the development of tools and for them to be made specifically to fit into the users workflow, as was highlighted as part of the qualitative synthesis raised in *Chapter two* [66].

3.5.3 Providing better data to support robust decisions

Physicians reported how they develop skills in infection management through an ongoing reflective practice as they progress through training. As junior trainees, they described how they were often scared of sepsis and missing this diagnosis and therefore under treating their patient, causing harm. As a response to this concern, they focus solely on the short-term, preferring to prescribe broad-spectrum agents and seek senior physician support to refine the decisions that they make. This reported caution and tendency towards over prescribe is supported by the availability of local antimicrobial prescribing guidelines that provide junior physicians with justification for making prescribing decisions. Furthermore, they act as a form of protection from judgement by senior team members, even if those decisions are incorrect. This reported fear of sepsis and the need to prescribe on the suspicion of infection is propagated by the expectations

placed upon junior members of the team to prescribe antibiotics for infections by senior doctors. The opposite is true of stopping or de-escalating antimicrobials, which is seen as a more serious decision that could affect the patient negatively and is therefore deferred to the senior decision makers.

To effectively promote improvements in antimicrobial management, these assumptions must firstly be effectively challenged to highlight the negative aspects of antimicrobial therapy and empower individuals to revise decisions when appropriate. A major hindrance to improving optimal decision making in this area is a lack of robust clinical data for many specific infections and antimicrobials [42,174,175] as well as the rigidity of clinical guidelines that are based on population level data. These fail to account for many of the observed variations both between individuals and during the course on an individual's treatment for infection [66,176].

Given these observations, it will be important for me to focus on mechanisms for improving how we use individual and population data that is available to physicians to help optimise the decisions that are made surrounding antimicrobial prescribing. This triangulates with the findings of the qualitative synthesis in *Chapter two*, which identified issues with the rigidity of guidelines within rule-based tools, the ability of decision support tools to educate prescribers in best practice, and the ability of certain tools to guide decision making through data visualisation [66].

3.5.4 Electronic decision support tools to enhance decision making

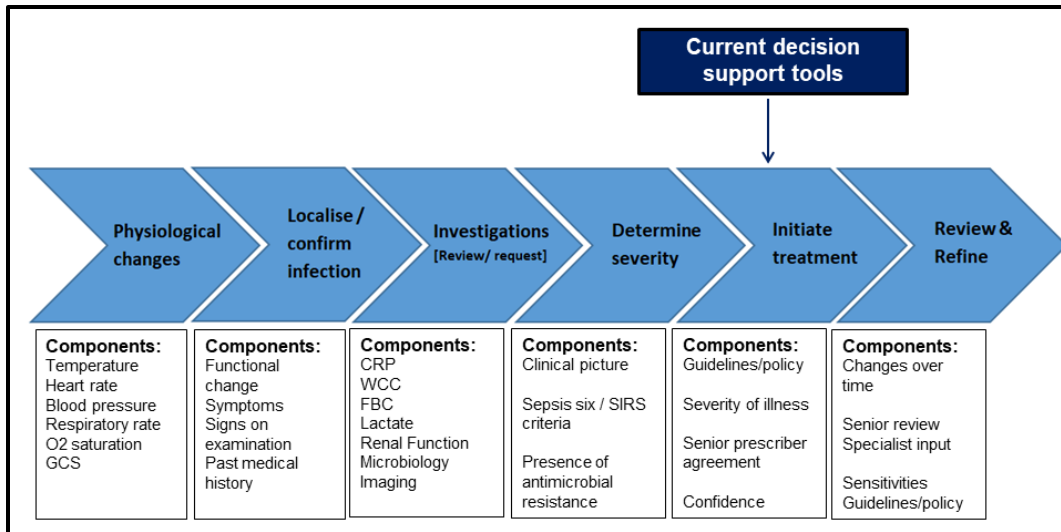
Within *Chapter two*, the narrow focus and rigidity of most CDSS, which utilised rule-based approaches to predominantly influence antimicrobial selection against guidelines was highlighted [66]. On reviewing these observations from *Chapter two* with the

decision making pathway outlined within this *Chapter*, it is possible to map the potential influence of common decision support interventions onto the decision making pathway **(Figure 7)**.

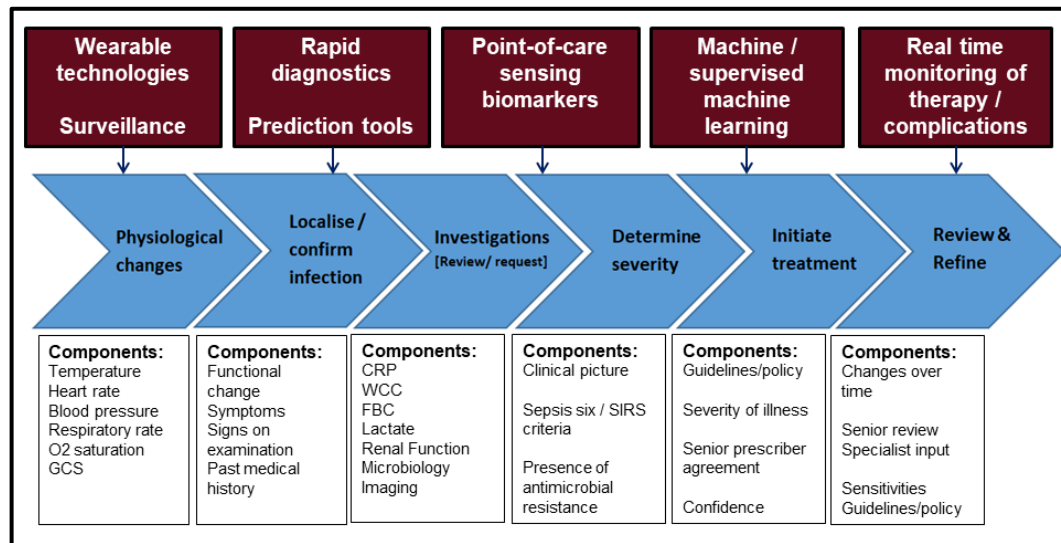
This demonstrates that these types of rules-based system are only likely to influence decision making in a small manner. This is because they are only likely to influence a small number of components, which predominantly focus on antimicrobial selection.

By considering other types of technology and decision support intervention that may be available for development, it is possible to explore whether broader approaches to providing decision support may have a greater influence on decision making overall if implemented either in isolation or as integrated systems.

Figure 7. Mapping decision support interventions onto the physician decision making pathway in secondary care.



Legend: Mapping current rule-based clinical decision support systems onto the individual physician decision pathway indicates that this type of tool only likely to influence one or two components that influence the “initiation of treatment” step in the pathway.



Legend: Mapping other potential technologies reported in the literature to the decision making pathway for infection management. This demonstrates how taking a broader approach to developing decision support tools may in fact influence a greater number of components and steps in the physician decision making pathway.

Therefore, in line with the findings reported in *Chapter two*, I believe that the exploration of a number of different mechanisms for supporting decision making, which can then be integrated into a single decision support tool remains justified [66]. By focusing on personalising the process of antimicrobial management by integrating antimicrobial selection, dosing, patient engagement with decision making, and engagement of users with the tool this may have a broader impact on the decision making process overall. This is because incorporating a wide number of interventions will facilitate a broader influence over the components and steps of the decision making process described within this study [168].

3.5.5 Limitations and future work

There are several limitations that I wish to highlight from this study. Firstly, as I chose to interview only medical physicians from one UK NHS hospital Trust there may be issues over the generalisability of my findings. This may include specialties not included within this study such as surgery, and other hospitals and regions in the world, where infection management and team structures may differ.

Locally, the next steps for this process would be to:

1. Understand the similarities and differences between decision making pathways of other specialties, such as surgery and paediatrics.
2. Compare the reported decision making pathways explored within this study with observed decision making processes, using methods such as ethnography.

This process has been explored by Dr Esmita Charani who led an ethnographic study of surgical and medical antimicrobial decision making during ward rounds in ICHNT [177].

The results of this work will allow further triangulation of my findings and facilitate the

comparison of reported versus observed decision making processes. However, for the focus of this thesis I believe that my decision to focus on medical specialties only is justified and has provided the depth of analysis required to help support the development of further interventions in following *Chapters*.

Another challenge will be exploring the generalisability of these findings outside of the local hospital Trust. This will require further mapping of decision making processes before the implementation of interventions in external sites or other countries. This is something that has been built into future research plans to ensure that we will be able explore and contrast decision making processes within different clinical settings.

Secondly, as a junior medical physician performing the interviews independently this may have introduced a potential source of bias in the responses from interviewees as well as during the data analysis process. As described above, I attempted to increase my awareness of this bias as much as possible through reviewing findings and data with a multi-professional group of researches in our department. This enabled me to consider areas of reflexivity that arose during my analysis.

Finally, although my theoretical sampling methodology followed validated guidelines and I purposefully sought out deviant statements to contradict emerging themes, the reliance on individual responses to invited emails may have introduced selection bias as individuals interested in antimicrobial prescribing and stewardship may have been more likely to respond to invitations [155,164]. However, given that I opted to purposefully sample individuals, this is likely to of had a limited impact on the results of the investigation.

3.6 Conclusion and key messages

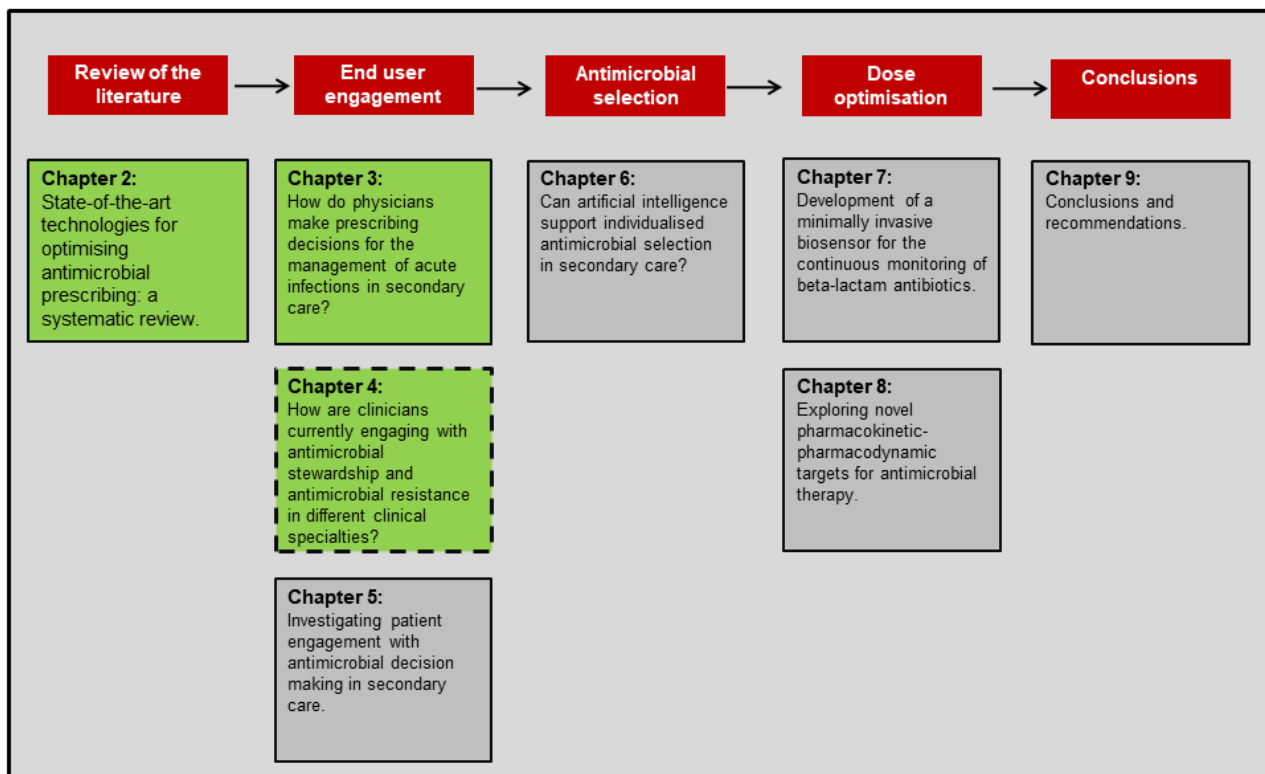
Within *Chapter two* of this thesis, it was outlined that there is a need to better understand the decision making process for infection management employed by end-users who are the target of decision support interventions [66]. Within this *Chapter*, I have described the Bayesian-like process that physicians report using during infection management in secondary care and identified a number of factors that support the further exploration of personalised, decision support interventions for antimicrobial management.

This *Chapter* also highlights several key factors that currently influence physician decision making. Development of specific interventions targeting these areas may enhance the way that antimicrobials are managed. These include addressing concerns around responsibility for the outcomes of prescribing recommendations made by specialists, such as clinical microbiology; addressing the harmful perceptions surrounding junior physicians requirements to urgently prescribe antimicrobials but avoid de-escalating therapy when appropriate; and working on mechanisms of increasing the awareness of the important role that pharmacists and other healthcare professionals play in influencing decision making for infection management.

CHAPTER FOUR

4.0 Are clinicians engaging with antimicrobial resistance and antimicrobial stewardship in different clinical specialties?

Figure 8. Overview of thesis.



4.1 Introduction

The identification of poor end-user engagement with and adoption of CDSS for antimicrobial management, outlined in *Chapter two*, appears to be a major factor in their limited success to improve appropriate antimicrobial usage [66]. In *Chapter three*, I aimed to explore individual end-user decision making pathways during infection management that are targeted by such interventions. This provided new evidence for the

development and deployment of personalised interventions and facilitated an insight into several factors that influence the decision making process [168]. However, despite this study providing insight and evidence into individual decision making and potential areas for intervention, a broader understanding of clinical specialties engagement with antimicrobial management is missing.

Methods for evaluating clinical specialty engagement may be useful for identifying “high risk” specialties who use high amounts of antimicrobials, experience high rates of complications of therapy, but currently appear to have very little engagement with AMS or AMR.

As well as providing recommendations on priority specialties that require targeting, it is also important to understand the current level of behaviour change interventions being explored within those specialties. As described in *Chapter one*, restrictive AMS measures provide adequate short term outcomes for improving prescribing behaviours [60,148]. However, long term success to promote a sustainable change in behaviour towards antimicrobial management requires empowerment of staff [60,148,178]. This includes using innovation and improvement of routine care, such as by developing novel tools to support decision making, to bridge the gap between best and actual practice [60,148,178]. Thus, when considering the development of decision support tools, as I aim to do within this thesis, it is vital to understand the baseline level of engagement with AMS and AMR (AMS-AMR) and focus on behaviour change currently being deployed within the specialties that these interventions targets.

Finally, it also has to be accepted that the development of change in behaviour and culture is likely to involve a multifaceted approach requiring a numerous interventions including; targeted educational, promotion of sustainable behavioural change, and

development of clinical leaders across all specialties [60,148,178]. Whilst each aspect of this may not be addressed within this thesis, the concept of evaluating the level of engagement within clinical specialties may act as a standard from which the impact of further interventions on individual specialties may be evaluated.

4.2 Chapter objectives

The aim of this *Chapter* was to explore the degree to which medical professionals from different disciplines have engaged with the issue of AMS-AMR, and in-particular the promotion of behaviour change.

The objectives of this Chapter were:

1. To investigate surrogate markers for the perceived level of formal engagement of different clinical disciplines with AMS-AMR.
2. To describe clinical disciplines engagement with behaviour change interventions for AMS-AMR.
3. To investigate possible approaches to identifying “high risk” specialties, to allow prioritisation of interventions in specialties with high rates of antimicrobial usage and complications but low engagement with AMS-AMR.

As described in further detail below, I hypothesised that two indicators may provide data that can act as a surrogate marker for the current awareness and attributed importance of AMS-AMR within different clinical disciplines. These were assessment of abstracts at state-of-the-art scientific conferences and assessment of national postgraduate training curricula [179–181].

4.3 Methods

4.3.1 Study design

For this study, I aimed to identify two or more surrogate markers that would allow me to characterise the level of engagement of different specialties with AMS-AMR, whilst also undertaking an assessment of behaviour change techniques currently being employed within specialties.

Within the literature, there is evidence to support the promotion of education and behaviour change toward AMS-AMR through engagement in state-of-the-art scientific conferences [182]. Clinical state-of-the-art conferences offer the individual the opportunity to participate in research and reporting, providing an educational benefit [152,182]. They also provide a platform for key opinion leaders and organisations to promote their current key agendas. Furthermore, state-of-the-art scientific conferences have an advantage over peer-reviewed publications and specialty guidelines that they have broader levels of engagement, which I felt would provide a more representative sample. This is because national leading conferences are often geared for both academic and non-academic clinicians and healthcare professionals, meaning that engagement and attendance is often broader than would be found engaging with the peer-review process. Furthermore, as leading specialty state-of-the-art scientific conferences are often organised by national organisations and for the benefit of their users, it is often easier to identify evidence of local quality improvement projects and other interventions reported at such events, which may never reach peer-reviewed publication.

In a similar fashion, postgraduate training curricula have an important role to promote knowledge and practical skills related to the subject of AMS-AMR [152,180]. This occurs

both at the trainee's current grade, but also in a linear fashion as the trainee progresses to more specialist training pathways and therefore advances through different training curricula. Whilst postgraduate training within infectious disease has been previously explored [183], there is little data describing engagement of clinical specialties with AMS-AMR at the strategic level of postgraduate medical education across other clinical disciplines. In the UK, a trainee will progress through several different training pathways after qualifying from medical school, where AMS-AMR teaching has previously been shown to be variable between medical schools by Castro-Sanchez and colleagues [184].

To briefly describe the pathway taken upon graduation from medical school: all junior doctors initially undertake two years of foundation training. They then normally follow this by undertaking a core training rotation that lasts for a further two years (e.g. core medical or core surgical training). They will then progress onto speciality training. The trainee will remain as a specialist trainee for several years until they attain their certification of completion of training (CCT) [185]. Whilst some specialty training pathways may differ, often missing out core-training (e.g. general practice and obstetrics & gynaecology), these often still contain a core specialty-type pathway within their structure. Therefore, we can expect that all trainees will be exposed to a number of postgraduate training curricula in the years following graduation from medical school as they progress towards CCT over a range of approximately 6 to 10 years for most graduates [185]. As all physicians training in the UK are expected to meet the training requirements set out by these training pathways, I felt that this was an optimal surrogate marker to explore and compare what knowledge, skills, and thus behaviours physicians in different specialties are expected to develop in terms of AMS-AMR during the course of their training.

Finally, it is also important to understand the process of behaviour change and the factors that promote its sustained maintenance being implemented within these disciplines. Whilst there are numerous theoretical perspectives on what drives and maintains behaviour change [186–189], Kok and colleagues outline the importance of ensuring that taxonomies and theories applied are grounding in the context and culture of the intervention [187]. This ensures that techniques employed to change behaviours match the determinants that they desire to change (e.g. education on when to prescribe antibiotics for acute respiratory tract infections), have the desired impact on the behaviour (e.g. reduce prescribing in acute respiratory tract infections), and reinforce a behaviour that is in-fact appropriate (e.g. acute respiratory tract infections are likely to be viral in origin, therefore reducing the use of antibiotics in these cases is appropriate) [187]. This is opposed to other taxonomies that have previously been implemented in AMS-AMR interventions, such as that proposed by Michie and colleagues, which assumes a general structure and range of techniques are applicable across all settings [186]. Therefore, whilst I took into full consideration a number of different taxonomies for assessing behaviour change interventions in the following studies, I also planned to keep a level of flexibility in the framework I used to ensure that they were applicable to the situations being assessed.

4.3.2 Exploring specialty engagement with AMS–AMR using state-of-the-art scientific conference abstracts

In 2015, I led the analysis and publication of the first study exploring cross-specialty engagement with AMS-AMR at scientific conferences both in the UK and internationally [180]. I intended that this study would form the basis of this *Chapter*. However, whilst this study allowed me to demonstrate the ability of this indicator for assessing cross-specialty

engagement and develop the methodology that will be used below; there were also several limitations to my approach when I reflected on this. Firstly, for the analysis I did not include a range of surgical specialties, only focusing on one general surgery conference. Secondly, I did not collect data to allow me to analyse whether abstracts reporting AMS-AMR included behaviour change interventions within this study. Finally, I also felt that one of the major limitations of only analysing data from one year was that this only provided a snap-shot and did not allow for any inference as to whether this marker remained stable from year to year for levels of awareness / engagement. Therefore, using the same methodology this study was repeated, as described below, to address these limitations [181]. Whilst I will report data from both studies, the methodology used for the systematic identification and assessment of abstracts was identical unless otherwise stated below. Assessment of behaviour change reporting was only performed on the new data set.

To identify specialties to include within this analysis I firstly identified all major clinical specialties that are recognised by the Royal College of Physicians, London, UK. I also selected to include major surgical specialties, which were identified by reviewing the intercollegiate surgical curriculum programme website. Furthermore, primary care, psychiatric, paediatrics, and obstetrics and gynaecology specialties were included. To identify leading UK state-of-the-art scientific conferences for each specialty, I contacted one or two specialists (specialist trainees or consultants) in each of the defined fields via email or in person and asked them to provide me with details of the largest clinical scientific/research conference within the UK or run by a UK organisation. For this study, I chose to exclude educational, continuing professional development, and sub-specialty conferences given that these types of conference often contain focused agendas, which may bias the findings and be less representative for the specialty as a whole.

For the study reported in the *Chapter*, conferences held in 2015 were identified, compared to conferences held in 2014 which were published in the initial investigation and was outlined above citing its limitations [180]. The following conference characteristics were collected; location, conference dates, estimated attendance, and total number of abstracts accepted (either as oral, poster, or publication only). Accepted conference abstracts (invited, oral, poster, and publication only) were then identified and interrogated using specified search criteria in **Table 8** to identify all abstracts relating to AMS-AMR.

Table 8. Abstract and curriculum search criteria and definitions of antimicrobial stewardship and antimicrobial resistance.

Abstract search criteria:

- I. Anti* (wildcard search accepting antibiotic, antimicrobial or similar)
- II. Resist* (wildcard search accepting resistant, resistance or similar)
- III. Infect* (wildcard search accepting infection, infective, infected or similar)
- IV. Stewardship

AMS and AMR definitions:

AMS: *“Optimising the indication, selection, dosing, route of administration and duration of antimicrobial therapy to maximise clinical cure or prevention of infection while limiting the collateral damage of antimicrobial use, including toxicity, selection of pathogenic organisms and emergence of resistance”*

AMR: *“Resistance of an organism to an antimicrobial drug that was originally effective for the treatment of infections caused by it”*

AMS = Antimicrobial Stewardship; AMR = Antimicrobial Resistance

The identification and review process was performed in a systematic manner. Abstracts were searched using the broad based criteria in **Table 8** with those identified being reviewed by two researchers independently (one of those was me at all times). Both reviewers were blinded to each person's findings, as well as the specialty conference that the abstract was reported in. Abstracts were included if they were identified as describing an aspect of AMS [39] or AMR [190] that was deemed to have a direct effect on patients. For this reason, *in-vitro* studies with no translational benefit to patients were excluded. Furthermore, as anti-bacterial agents account for more than 93% of all antimicrobials prescribed for systemic use [191] I chose to focus on bacterial resistance and antibiotic stewardship with abstracts describing antiviral, antifungal, antiprotozoal, or antimycobacterial resistance / treatment excluded. Another reason for this choice was that the large variation in prescribing of other antimicrobial classes across different specialties may have caused bias to the results on the analysis. Where there was discrepancy in the findings of the independent reviewers, a third researcher was asked to review the abstracts and to provide their opinion. Once this had taken place, the three reviewers (including myself) met to discuss and agree upon abstract inclusion / exclusion for abstracts where discrepancies occurred.

Once identification of AMS-AMR abstracts at the UK and international conferences was completed, sub-group analysis was performed and proportions of abstracts reporting AMS-AMR for each conference were compared. Abstracts were then re-read by two researchers (one being myself) independently and categorised into types of intervention reported in the abstracts. To categorise the types of interventions reported, I chose to use a modified version of the intervention and policy framework definitions provided by Michie and colleagues, based on the suggestions of Kok and colleagues [187]. The main constructs of Michie and colleagues behaviour change wheel were used (**Table 9**) [186].

However, in the original taxonomy, three layers were described; policy, intervention, and behaviour systems [186]. Within the adapted classification that I chose to develop and use, behaviour systems were not included (capability, opportunity, motivation, and behaviour; COM-B) as the reported interventions in the abstracts were focused on the two levels of the framework above this, which aim to directly influence COM-B [186]. Therefore, on reviewing the abstracts I attempted, where possible, to categorise reported behaviour change interventions into one or more of the sixteen functions (split into policies and interventions) described within this framework. Although the framework was designed to provide flexibility and accommodate multiple interventions / policy combinations, where possible I attempted to strictly categorise reported interventions into the smallest number of categories possible. When there was discrepancy, a third researcher was asked to review the abstract and the group then met to discuss the findings until a consensus was reached.

Table 9. Behaviour change taxonomy used for the classification of interventions reported at state-of-the-art scientific conference abstracts in 2015.

Intervention	Taxonomy	Definition
	<i>Education</i>	Increasing knowledge & understanding
	<i>Persuasion</i>	Communication used to induce positive or negative feelings or drive actions
	<i>Incentivisation</i>	Creating expectation of rewards for actions
	<i>Coercion</i>	Creating expectation of punishment for actions
	<i>Training</i>	Developing new skills
	<i>Restriction</i>	Use of rules to reduce or increase the engagement in a target behaviour (whether positive or negative)
	<i>Environmental restructuring</i>	Changes in the physical or social context
	<i>Modelling</i>	Providing examples for people to aspire to / imitate
	<i>Enablement</i>	Increasing means or reducing barriers to increase capability to achieve a goal or behaviour
Policy	Taxonomy	Definition
	<i>Communication</i>	Using print, electronic, telephonic, or broadcast media
	<i>Guidelines</i>	Creating documents that recommend or mandate practice.
	<i>Fiscal</i>	Taxing actions to reduce or increase a financial cost
	<i>Regulation</i>	Establishing rules or principles of behaviour or practice
	<i>Legislation</i>	Making or changing laws
	<i>Environmental</i>	Designing or controlling the social environment
	<i>Service Provision</i>	Delivering service

Legend: Adapted from Michie et al. Implementation Science 2011, 6:42
<http://www.implementationscience.com/content/6/1/42>

4.3.3 Exploring specialty engagement with AMS–AMR using postgraduate training curricula

In a similar manner as described in *section 4.3.2*, the level of engagement with AMS-AMR in specialty postgraduate training curricula was explored [179]. Briefly, UK clinical specialties were identified and electronic postgraduate training curricula extracted for interrogation. All training curricula were reviewed by two researchers independently, one of those being myself at all times. Initially, all specialties were reviewed with those deemed to have a narrow or low clinical focus excluded from analysis. Curriculum characteristics were described including the date of initial publication, date of the most recent revision, and the total number of curriculum topics and individual learning points within each curriculum.

The search criteria that were employed in **Table 8** were piloted and validated to be used again within this study [180,181]. Curricula were reviewed independently by myself and another researcher who identified (i) all curriculum topics, and (ii) all curriculum learning points, which met the search criteria. Curriculum learning points in the context of UK training curricula were defined as individual learning goals that the trainee is expected to achieve during training. As these points are selected by the specialty education training board, their numbers varied between specialties depending on the number of topics and the depth in which the trainee is expected to demonstrate their knowledge and skills. Two researchers (including myself) then reviewed all electronically identified learning points independently, excluding those not directly related to AMS or AMR based on the definitions in **Table 8**. In keeping with the methodology employed in *Section 4.3.2*, only antibiotic and antibacterial resistance was included. Duplicate learning points within the same curriculum were not counted twice. Where disagreement arose during the

selection of learning points a third researcher was asked to review the learning point and the researchers then met to discuss this and reach a consensus.

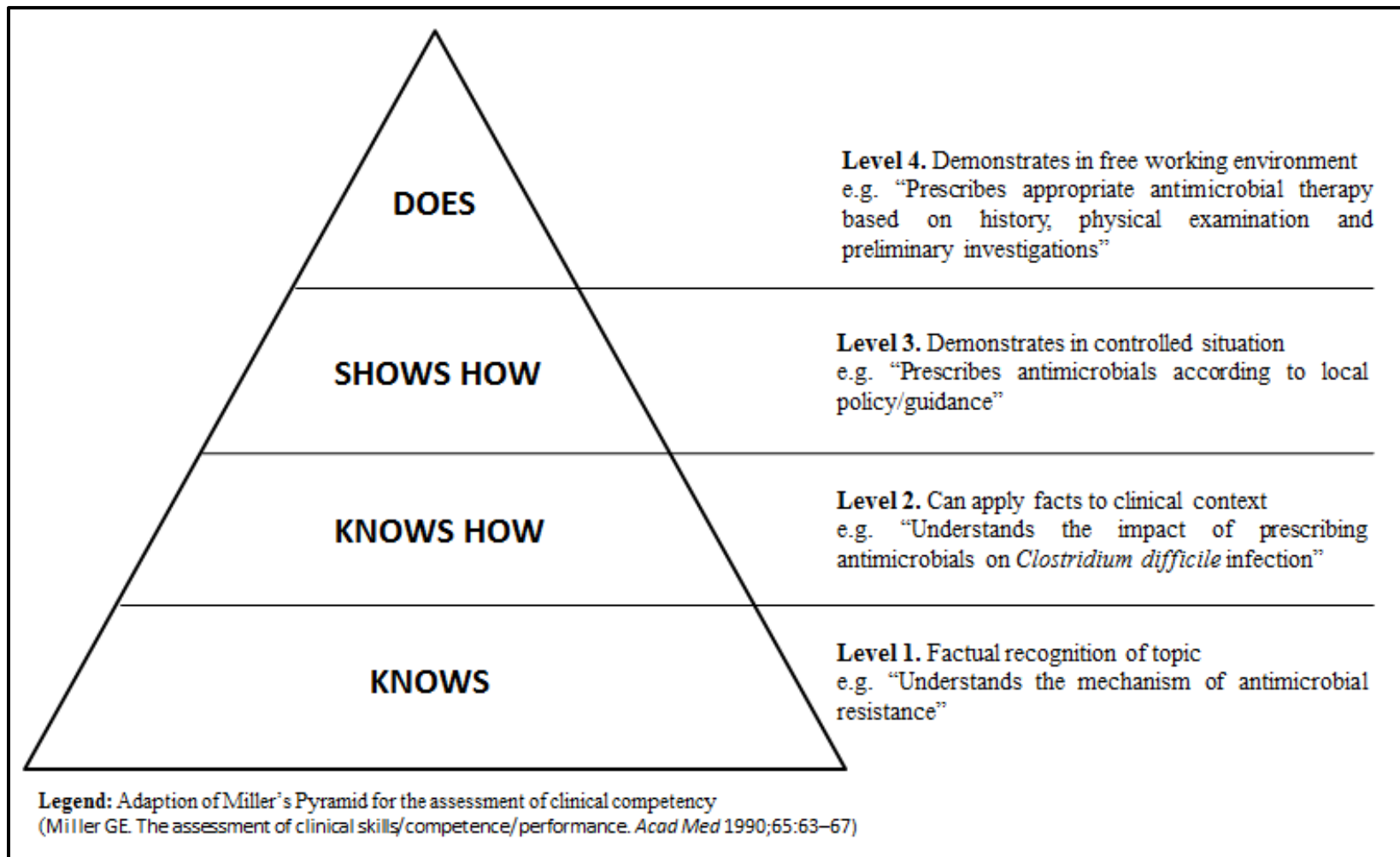
After the identification of curricula topics and learning points for inclusion, inter-specialty variation was assessed in two ways. Firstly, the overall proportions of AMS-AMR dedicated topics and individual learning points were calculated for each specialty using total number of topics or learning points as a denominator, respectively. However, after discussion with colleagues, we agreed that simply assessing and reporting the percentage of AMS-AMR topics or learning points in a curriculum would be difficult to quantify qualitatively in terms of whether or not this is appropriate. Therefore, as a comparator I decided on also collecting data for curricula topics and learning points relating to infection prevention and control (IPC). This data were extracted and analysed in an identical fashion to provide a reference for our observations of AMS-AMR coverage in different clinical specialties.

I chose IPC as the comparator as it is another infection related patient safety issue, which has been a long-term, healthcare priority that has required cross-specialty engagement [192,193]. To achieve cross-specialty engagement, IPC has been promoted through a distributed model [194]. To identify IPC topics and learning points, I explored a number of different search criteria. However, the use of the same search criteria used to identify AMS-AMR learning points was finally selected as the search term “infect” was the most sensitive term for identifying IPC points. Other tested terms (such as, “aseptic”, “control”, and “prevent”) did not appear to add to the sensitivity of the search.

To evaluate the impact of individual learning points in terms of promoting behaviour change within specialty training curricula, I wanted to develop a mechanism of

categorising the level of achievement the learning point was expected to display. To assess the level of achievement, I opted to evaluate and categorise each AMS-AMR learning point against a modified version of Miller's pyramid for the assessment of clinical competence [195]. This allowed learning points to be weighted based on the type of knowledge or skill that the clinician would be deemed to be demonstrated on achievement (**Figure 9**) [195].

Figure 9. Adaption of Miller’s Pyramid that I developed to facilitate the assessment of clinical competence.



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Within the classification there are several levels [195]:

- Level one - demonstration of knowledge (i.e., “*knows*”)
- Level two – demonstration of an ability to understand knowledge in a clinical context (“*knows how*”)
- Level three – demonstration of a behaviour in a controlled environment (“*shows how*”)
- Level four – demonstration of a behaviour in a free working environment (“*does*”).

To rate individual learning points relating to AMS-AMR, I asked a colleague to anonymise the individual points, presenting them in a randomised order to three researchers (including myself). We then independently reviewed each learning point rating the expected level that completion of the learning point would demonstrate. Ratings were then compared, and the mode calculated. When consensus could not be reached using the mode, a fourth researcher reviewed the individual learning point and rated its level in the hierarchy. This rating was then compared against the three researchers’ scores, and discussion held to reach consensus on the appropriate level [179].

4.3.4 Identifying high risk specialties with evidence of low engagement with AMS-AMR

Once data had been collected and behaviour change interventions analysed for both postgraduate training curricula and state-of-the-art scientific conferences, the individual specialties were classified and contrasted according to two measures of “risk”:

- (i) the proportion of patients in each specialty receiving antimicrobials (antimicrobial usage, AU) and;

- (ii) the proportion of patients who acquire healthcare associated infections (HCAI) within each specialty.

This was derived from the European Centre for Disease Prevention and Control (ECDC) point-prevalence survey that was conducted in 2011/12 [196]. At the time of this study, this provided the most up-to-date and complete estimates available to use for the clinical specialties included within this study [196]. For primary care, data were not available to accurately estimate the rate of AU per population and rates of observed HCAI. Therefore, I opted to exclude them from this evaluation. For other clinical specialties not included in the ECDC report, they were given the average AU and HCAI rate for their respected field (i.e. medicine, surgery, critical care, or other). I then ranked each clinical specialty based on their reported proportion of HCAI and proportion of AU per population, respectively. These were ranked in ascending order and the range of HCAI and AU calculated. Based on this range, specialties were then assigned “risks” depending on which third of the range they fell within for HCAI and AU (high, medium, or low). This gave two “risk” scores for each specialty, based on rates of HCAI and one based on AU. The rates were then compared to the surrogate markers for apparent awareness and engagement with AMS-AMR to investigate whether these could be used to identify and prioritise specialties where more urgent interventions were required.

4.3.1.3 Statistical analysis

All statistical analysis was performed using SPSS 22.0 (IBM, Chicargo) software. Descriptive statistics performed included Chi-squared with Yates correction and Fishers exact test where appropriate. Figures were created using R and Igor Pro 7.0.

4.3.1.4 Ethics

Ethics approval was not required for these observational studies of information freely available in the public domain.

4.4 Results

4.4.1 Cross-specialty engagement

4.4.1.1 State-of-the-art scientific conferences

Thirty UK specialty state-of-the-art scientific conferences were identified for inclusion. From these, I identified and extracted electronic abstract booklets for analysis. The 30 conferences ran over more than 110 days with greater than 57,000 delegates estimated to of attended them in total in 2015. **Table 10** outlines the characteristics of individual conferences include within the study.

The median (range) number of days that the reviewed conferences ran for in 2015 were 3 (2 - 4) days. The median (range) number of delegates were 1100 (200 - 8190) accepting a median (range) or 278 (69 - 1945) abstracts. The most common cities where conferences were held were Manchester (6/30; 20%), Glasgow (4/30; 13%), and London (4/30; 13%). Half of the conferences took place between April and June 2015 (15/30; 50%). Thirteen of thirty (43%) conferences were for medical specialties, 11/30 (37%) for surgical specialties, and the remaining 6/30 (20%) other specialties.

Table 10. Summary of 2015 UK specialty state of the art scientific conferences included for analysis.

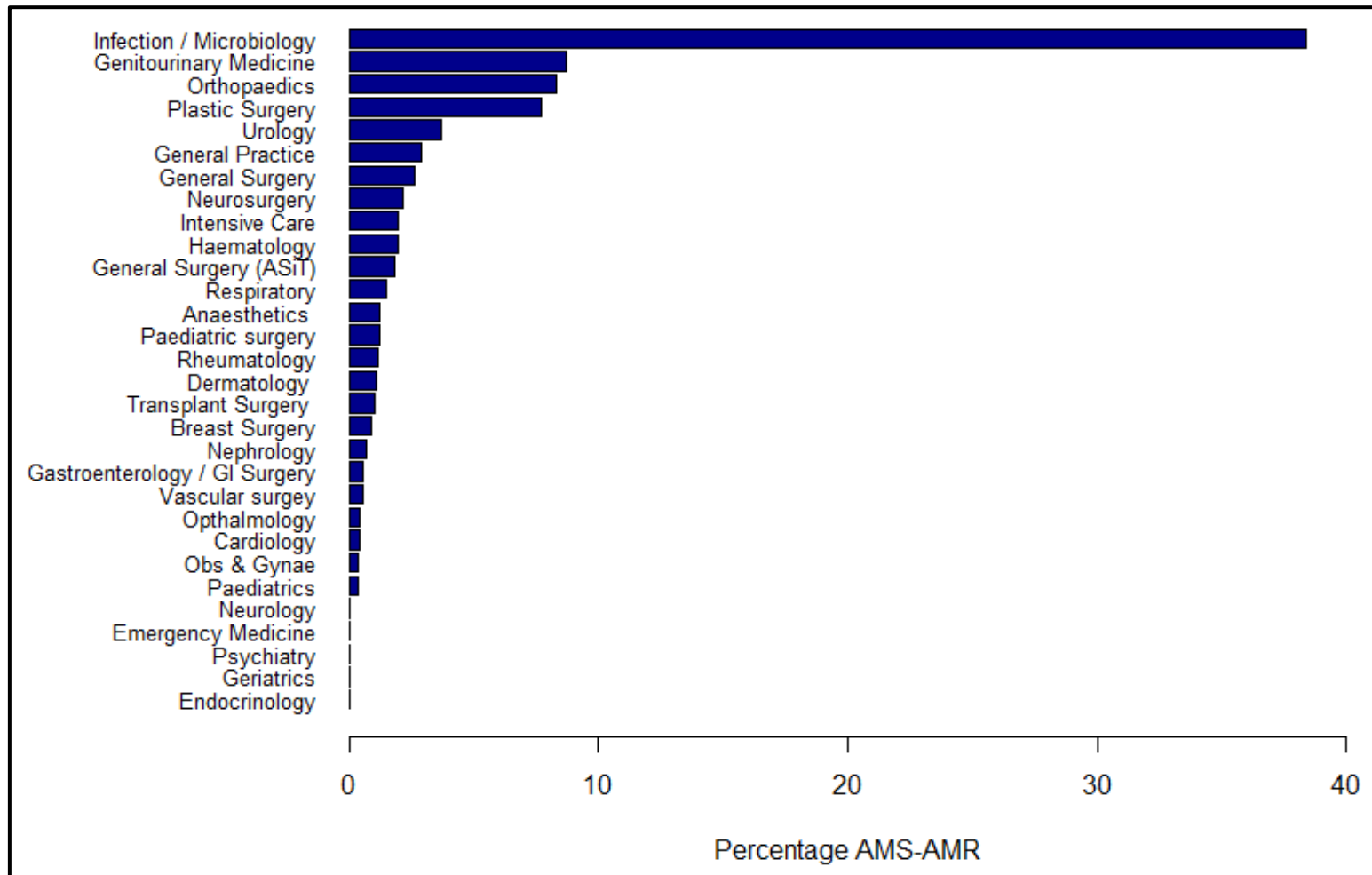
Speciality	City	Date commenced	No Days	No delegates	No abstracts accepted
Anaesthetics[197]	Edinburgh	23/09/2015	3	800	161
Breast Surgery[198]	Bournemouth	15/06/2015	2	870	221
Cardiology[199]	Manchester	08/06/2015	3	2448	235
Dermatology[200]	Manchester	06/07/2015	4	1200	372
Emergency Medicine[201]	Manchester	28/09/2015	3	650	69
Endocrinology[202]	Edinburgh	02/11/2015	3	1000	526
Gastroenterology[203]	London	22/06/2015	4	4500	1240
Primary Care[204]	Glasgow	01/10/2015	3	1600	450
General Surgery[205]	Manchester	22/04/2015	3	1500	1065
Surgery (ASiT)[206]	Glasgow	27/02/2015	3	700	602
Genitourinary Medicine[207]	Glasgow	01/06/2015	3	500	299
Geriatrics[208]	Brighton	14/10/2015	3	500	76
Haematology[209]	Edinburgh	20/04/2015	3	1000	257
Infection / Microbiology[210]	Glasgow	21/11/2015	3	1000	375
Intensive Care[211]	London	07/12/2015	3	1250	154
Nephrology[212]	London	28/05/2015	4	8190	1945
Neuro surgery[213]	York	09/09/2015	3	200	139
Neurology[214]	Harrogate	20/05/2015	3	600	194
Obstetrics & Gynaecology[215]	Brisbane	12/04/2015	4	2300	770
Ophthalmology[216]	Liverpool	18/05/2015	4	1700	228
Orthopaedics[217]	Liverpool	15/09/2015	4	1600	96
Paediatric surgery[218]	Cardiff	22/07/2015	3	346	83
Paediatrics[219]	Birmingham	28/04/2015	3	2000	546
Plastic surgery[220]	Birmingham	25/11/2015	3	400	78
Psychiatry[221]	Birmingham	29/06/2015	4	2500	79
Respiratory[222]	London	02/12/2015	3	2200	460
Rheumatology[223]	Manchester	28/04/2015	3	2000	677
Transplant surgery[224]	Bournemouth	11/03/2015	3	700	382
Urology[225]	Manchester	15/06/2015	4	1200	161
Vascular surgery[226]	Bournemouth	11/11/2015	3	800	373

In total, 12,313 abstracts were extracted for inclusion in the analysis of 2015 UK scientific state-of-the-art conferences. Overall, 311/12,313 (2.5%) were identified as being AMS-AMR focused. Of these, 118/311 (38%) were presented at the UK's infectious diseases/microbiology conference [210]. This made up 38% (144/375) of all the conference abstracts accepted for this conference. Genitourinary medicine [207] had the second greatest coverage of AMS-AMR with 9% (26/299), orthopaedics [217] third and plastic surgery [220] fourth with 8% of abstracts related to AMS-AMR each (8/96 & 6/78, respectively). All other specialties had <5% AMS-AMR coverage (**Figure 10**).

Notably, neurology [214], emergency medicine [201], psychiatry [221], geriatrics [208], and endocrinology [202] did not have any AMS-AMR abstracts in their state-of-the-art scientific conferences in 2015.

On comparison to my previously published study comparing coverage at 2014 specialty scientific state-of-the-art conferences [180], there was no significant difference in the level of AMS-AMR reporting overall (311/12,313, 2.5%, in 2015 & 221/7843, 2.8%, in 2014; $p = 0.22$). Furthermore, on direct specialty comparison the only specialty with a difference in reporting AMS-AMR abstracts between years was Infection/microbiology. In this specialty, the 2014 conference had a significantly larger proportion of AMS-AMR abstracts compared to all other specialties reviewed within this study (80/121; 66% in 2014 versus 143/375; 38% in 2015; $p < 0.01$).

Figure 10. Comparison of antimicrobial stewardship and antimicrobial resistance coverage at state-of-the-art scientific conference in 2015.



4.4.1.1.1 Reported behaviour change interventions for antimicrobial prescribing

Of the AMS-AMR abstracts identified, I found that 56/311 (18%) described behaviour change interventions. **Appendix 4** outlines the classification of these based on the modified taxonomy outlines in *Section 4.3.2* mapping the taxonomy to specialty that it was observed in.

Of the abstracts describing behaviour change, 28/56 (50%) were reported at the infection/microbiology conference. General surgery reported the second largest proportion with 7/56 (13%). In total, behaviour change interventions were reported across 12/30 (40%) specialty state-of-the-art conferences with infection/microbiology reporting a significantly greater amount than all other state-of-the-art scientific conferences ($p < 0.01$). The most frequent abstracts reporting behaviour change interventions were quality improvement projects. These accounted for 44/56 (79%) of all AMS-AMR abstract reporting behaviour change interventions. However, overall this represented a minority the total number of AMS-AMR quality improvement projects identified in 2015 with 80/124 (65%) either not reporting any intervention or not reporting a specific behaviour change intervention. The remaining behaviour change interventions reported in abstract were included within observational studies (12/56; 21%). This also represented a minority of observational AMS-AMR studies across clinical specialties (12/54; 22%).

As outlined in **Appendix 4**, 71 unique behaviour change functions were identified within the 56 abstracts reporting AMS-AMR behaviour change interventions. Eight abstracts were identified as describing more than one behaviour change intervention. Six out of eight were reported at the infectious diseases/microbiology conference [210] and the other two at the primary care conference [204].

Of the policy categories included in the taxonomy used in the study; “guidelines” (16/71) and “service provision” (11/71) were the most frequently reported. For the interventions function included; “education” (6/71), “persuasion” (7/71), “enablement” (9/71), and environmental restructuring (9/71) were also common. For the intervention categories, “incentivisation” and “coercion” were not reported. Similarly, the policy categories “fiscal” and “legislation” were not identified within the abstracts reporting behaviour change interventions.

On analysis, only infection/microbiology and primary care reported multiple behaviour change functions in any one intervention. Furthermore, beyond these two clinical specialties the majority of behaviour change interventions reported in the remaining ten specialties describing AMS-AMR related behaviour change focused primarily on enablement (intervention) and guidelines or service provision (policy). **Table 11** described the types of behaviour change functions reported in abstracts that described multiple behaviour change interventions (8/56; 14%). Within these abstracts, there was a mix of policy and intervention functions with guidelines featuring in 6/8 (75%), environmental restructuring, education and persuasion all featuring in 4/8 (50%), and service provision in 3/8 (38%) of the AMS-AMR related abstracts.

Table 11. Outline of behaviour change functions reported in AMS-AMR abstracts that reported multiple behaviour change interventions at 2015 state-of-the-art scientific conferences.

Primary Care	1. Guideline, persuasion, & modelling
	2. Education, persuasion & environmental restructuring
Infection/Microbiology	3. Guideline, persuasion & environmental
	4. Guideline, persuasion & service provision
	5. Guideline, environmental restructuring, education, communication
	6. Guideline, education, service provision, environmental restructure
	7. Guideline & service provision
	8. Education & environmental restructuring

4.4.1.2 Postgraduate training curricula

For analysis of postgraduate training curricula, I was able to identify 37 UK clinical specialty training curricula for inclusion within this study. **Table 12** outlines the training curricula included and their characteristics. All curricula were initially published between 2009 and 2015; eighteen (49%) had been updated since publication. In total, within the curricula I identified 2,318 curriculum topics and 42,527 individual learning points.

Figure 11 describes the screening and selection process of curriculum topics and learning points, respectively. Overall, 8/2318 (0.3%) curriculum topics were identified relating to AMS-AMR. These were all within the combined infectious diseases training curriculum (8/65; 12%) [227]. In contrast 184/42527 (0.4%) individual AMS-AMR learning points were identified across all specialties included. These were distributed across 33/37 (89%) specialties. The four specialties with no AMS-AMR learning points within their training curricula were psychiatry core training [228], rehabilitation medicine [229], nuclear medicine [230], and hepatology [231].

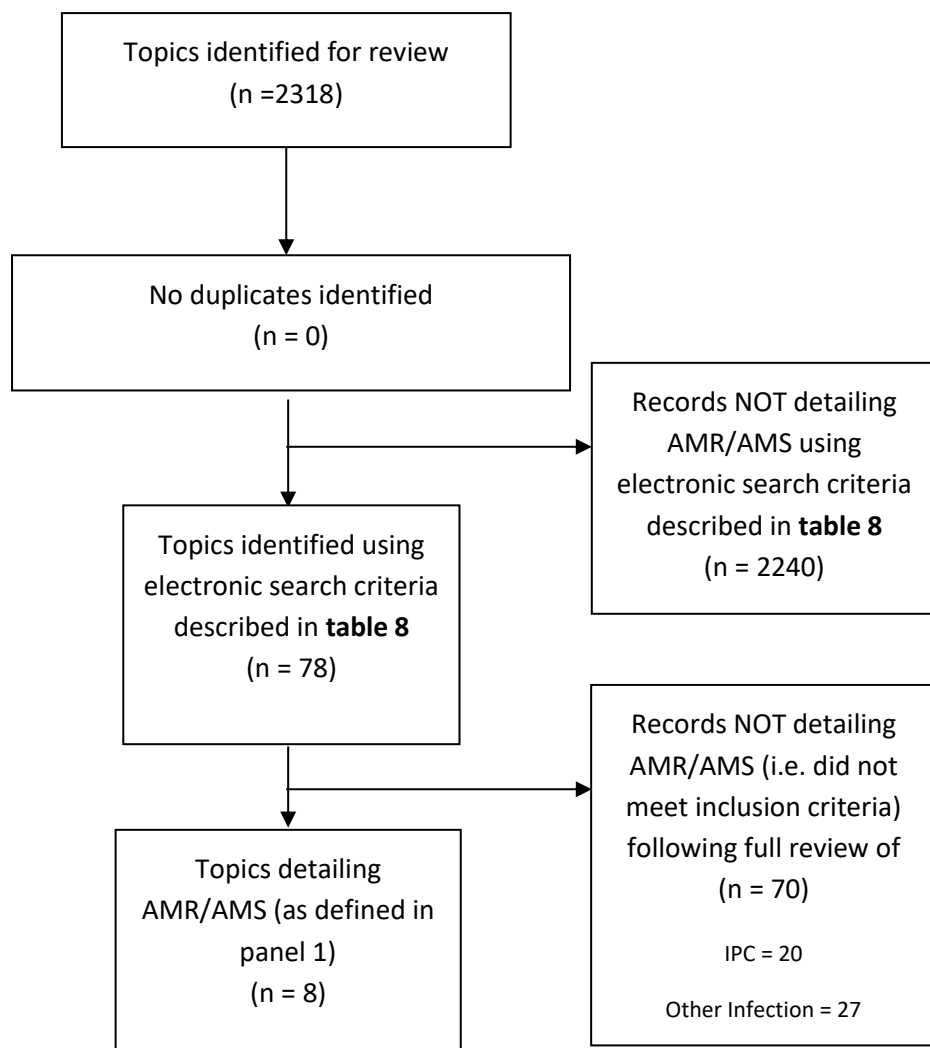
In contrast to AMS-AMR, IPC made up 20/2318 (0.9%) curriculum topics, spread over 20/37 (54%) specialty curricula. Furthermore, 278/42527 (0.7%) individual learning points were identified across the same 33/37 (89%) specialty curricula with the same four specialties not including IPC in their curricula also. Overall, coverage of IPC was significantly greater than coverage of AMS-AMR across specialty curriculum topics ($p = 0.04$) and individual learning points ($p < 0.01$).

Table 12. Summary of current UK clinical specialty training curricula included in my analysis of surrogate markers of cross-specialty engagement with antimicrobial stewardship and antimicrobial resistance.

Specialty curriculum	Date of publication	Date updated	Total number of categories	Total number of individual learning points
Acute internal medicine[232]	Aug-09	Aug-12	121	1680
Cardiology[233]	Aug-10	NA	91	1522
Clinical Pharmacology and Therapeutics[234]	Aug-10	Dec-11	42	870
Core Medical Training[235]	Aug-09	Aug-13	110	1752
Core Surgical Training[236]	Jul-13	NA	35	409
Dermatology[237]	Aug-10	Aug-12	53	789
Endocrinology and Diabetes Mellitus[238]	Aug-10	Aug-12	40	509
Foundation year[239]	Jul-12	Aug-14	42	435
Gastroenterology[240]	Aug-10	Aug-13	11	1290
General Internal Medicine[241]	Aug-09	Aug-12	112	1405
General Surgery[242]	Jul-13	NA	157	3290
Genitourinary Medicine[243]	Aug-10	Aug-12	44	776
Geriatric Medicine[244]	Aug-10	Aug-13	50	917
Haematology[245]	Aug-10	Aug-12	45	767
Hepatology[231]	Aug-10	Aug-13	10	91
Immunology[246]	Aug-10	NA	36	609
Infectious diseases [227]	May-14	NA	65	747
Intensive Care[247–250]	Jan-15	NA	164	3594
Medical Oncology[251]	Aug-10	NA	68	1424
Medical ophthalmology[252]	Aug-10	NA	38	530
Metabolic Medicine[253]	Aug-10	NA	44	707
Neurology[254]	Aug-10	Aug-13	51	289
Nuclear medicine[230]	Aug-14	NA	10	745
Obstetrics & Gynaecology[255]	Aug-13	NA	19	1250
Paediatric surgery[256]	Jan-15	NA	193	2488
Paediatrics[257]	Sep-10	NA	23	1802
Palliative medicine[258]	Jan-10	Oct-14	66	1105
Primary Care[259,260]	Oct-15	NA	37	1368
Psychiatry[228]	Jul-13	Mar-15	44	313
Rehabilitation medicine[229]	Aug-10	NA	36	490
Renal Medicine[261]	Aug-10	Aug-12	114	860
Respiratory Medicine[262]	Aug-10	May-14	81	1538
Rheumatology[263]	Aug-10	NA	58	809
Stroke medicine[264]	Aug-10	Aug-13	18	361
Trauma and Orthopaedics[265]	Aug-15	NA	27	1709
Urology[266]	Jan-15	NA	109	2208
Vascular Surgery[267]	Jul-14	NA	54	1079

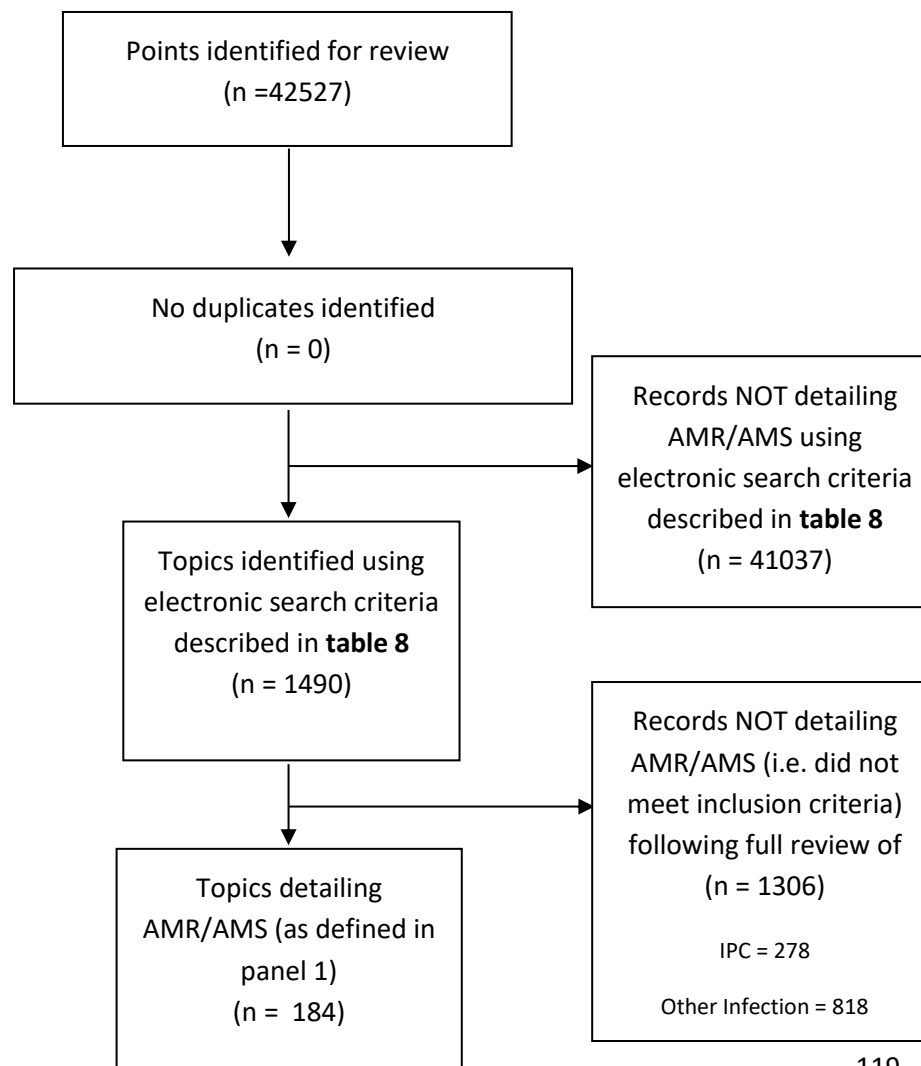
Figure 11. Identification of antimicrobial stewardship / antimicrobial resistance curriculum topics and learning points in UK clinical specialty training curricula.

Figure 11a. Curriculum topics



Legend: IPC = Infection Prevention and Control Point; Other infection = infection related point other than AMS-AMR or IPC

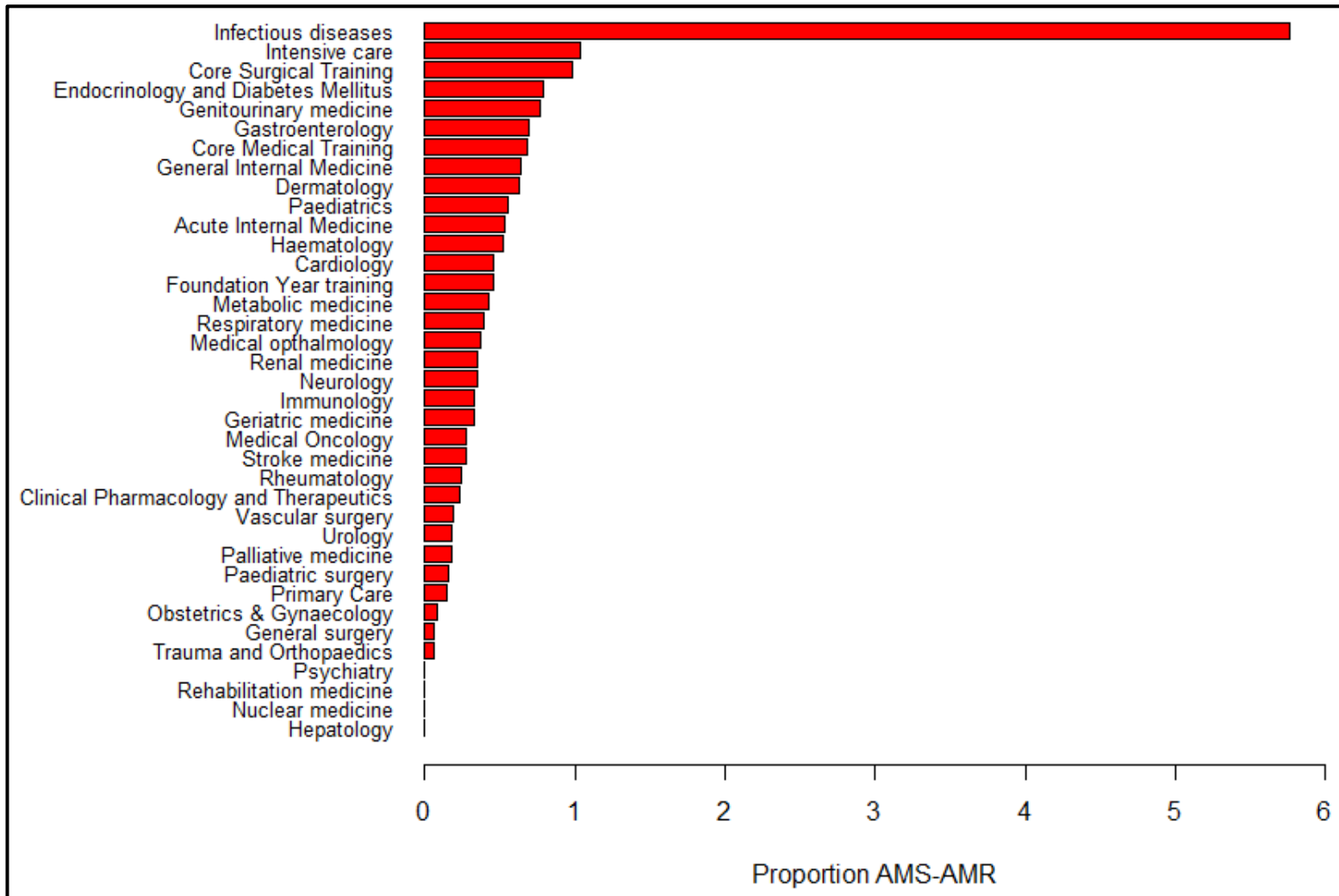
Figure 11b. Curriculum learning points



Legend: IPC = Infection Prevention and Control Point; Other infection = infection related point other than AMS-AMR or IPC

Figure 12 describes the inter-specialty emphasis of AMS-AMR within curricula learning points. Combined infection training had the greatest proportion (43/747, 5.8%); significantly higher than the other clinical specialties ($p < 0.01$ for all). All other clinical specialties had less than 1% coverage. Core surgical training had the second greatest frequency (4/409; 0.98%) [236], endocrinology had the third (4/509; 0.8%) [238], gastroenterology fourth (9/1290; 0.7%) [240], and core medical training had the fifth (12/1752, 0.7%) [235].

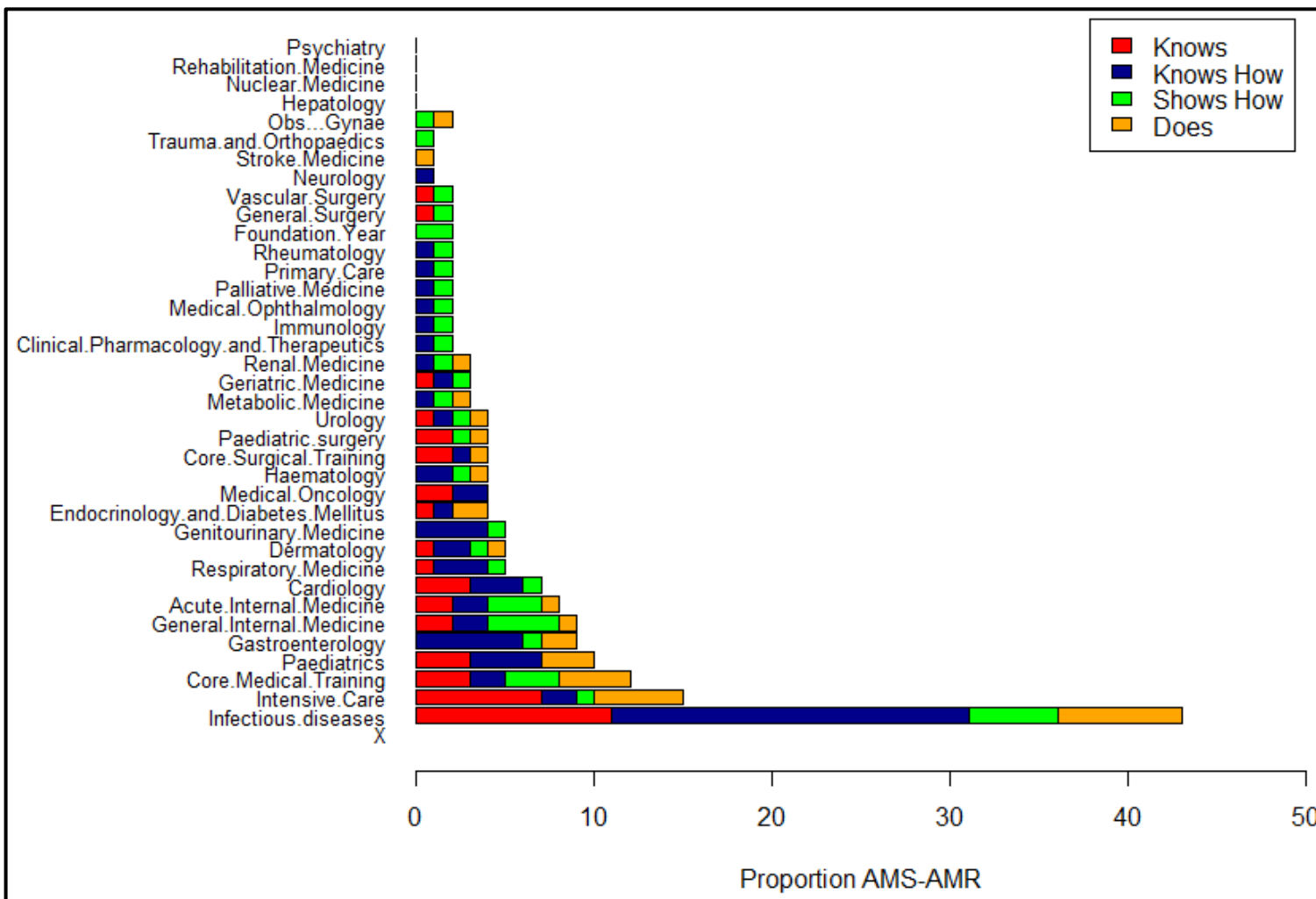
Figure 12. The percentage of UK clinical specialty training curricula related to antimicrobial stewardship and/or antimicrobial resistance.



I then compared the frequency of individual AMS-AMR related learning points per curriculum to the number of learning points that met each level of the adapted version of Millers Pyramid describing the hierarchy of knowledge or skill demonstrated on achievement of each learning point. This is outlined in **Figure 13**. On analysis of the raw number of learning points described, infectious diseases had the greatest frequency related to AMS-AMR (n = 43). Intensive care was second (n = 14) [247,248,250], and core medical training third (n = 12).

On analysis of the expected level of achievement to be demonstrated for each learning point, I observed that the median expectation was "knows how" with 67/184 (36%) expecting the demonstration of "an ability to apply facts to a clinical context" [195]. Of those remaining, 44/184 (24%) were categorised as "knows", 39/184 (21%) as "shows how", and 34/184 as (18%) "does". Therefore, overall within these curricula 60% (111/184) of perceived AMS-AMR learning outcomes do not currently require the demonstration of any behaviour as part of the expected level of achievement. This trend towards learning points focusing on the demonstration of knowledge rather than behaviours was observed across most specialties regardless of the frequency of learning points identified. For example, infectious diseases had the greatest number of individual AMS-AMR learning points, but 31/43 (72%) of them did not require any demonstration of behaviour in clinical practice (11/43 "knows" & 20/43 "knows how"). In contrast general curricula, such as general internal medicine (4/9 "shows how" or 1/9 "does"), acute internal medicine (3/8 "shows how" or 1/8 "does"), and core medical training (3/12 "shows how" or 4/12 "does") demonstrated greater numbers of learning points requiring demonstration of behaviour in clinical practice, despite having low overall frequencies of AMS-AMR learning points.

Figure 13. Frequency of levels of achievement obtained upon completion of individuals antimicrobial stewardship and antimicrobial resistance curriculum learning points.



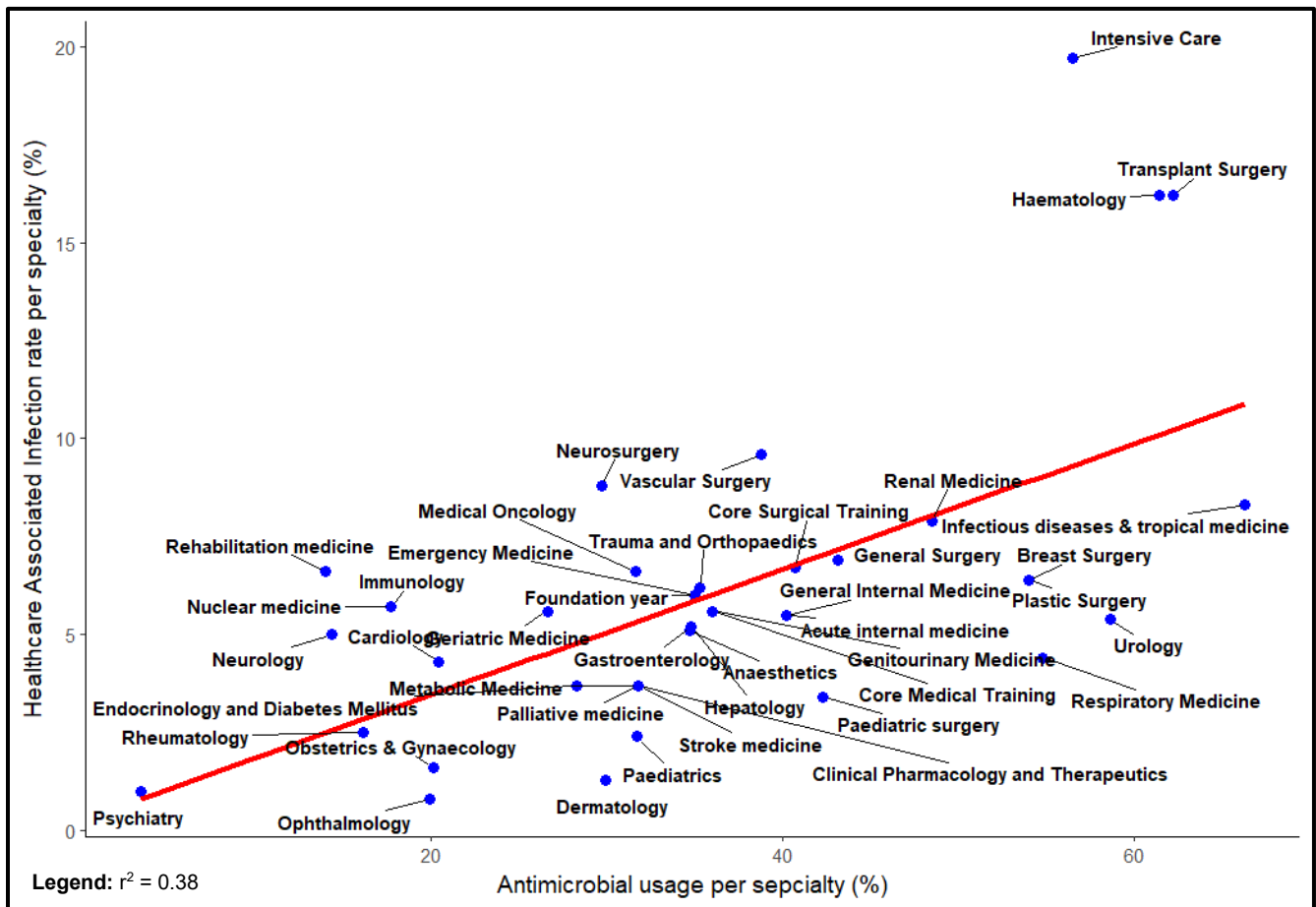
4.4.2 Comparison of indicators

Table 13 summarises the ranking of all specialties described within this *Chapter*. Specialties are ranked for their level of AMS-AMR coverage in postgraduate training curricula and at state-of-the-art scientific conferences in 2015. This is compared to rankings of the rate of observed health-care-associated-infection and antimicrobial usage by specialty.

On interrogation of the ranking data for AU and HCAI in different specialties, several important observations could be made.

- Firstly, there was a moderate association of increasing antimicrobial usage with experience of HCAI within individual patient populations within this data ($r^2 = 0.38$; **Figure 14**)
- Infection and microbiology are assumed to act as a benchmark for all other clinical specialties, which are observed to have significantly lower coverage of AMS-AMR.
- In terms of antimicrobial usage, 11 specialties are ranked in the high rate of antimicrobial usage category with greater than 42% of their population receiving antibiotics.
- Three specialties appear to experience much greater rates of HCAI compared to others. These were haematology, intensive care, and transplant surgery. All three of these specialties have some of the highest rates of antimicrobial usage, with only infection and microbiology having higher rates of antimicrobial prescribing.
- High rate of AU did not always directly correlate with high rates of HCAI. For example, respiratory medicine, plastic surgery, general surgery, and breast surgery all use high amounts of antimicrobials, but had low rates of HCAI.

Figure 14. Antimicrobial usage versus observed rates of healthcare associated infections by clinical specialty.



A further consideration is with regards to Primary Care, who could not be included due to missing data. This should also be taken into consideration given the large volume of antimicrobial prescribing undertaken within this specialty.

Table 13. Comparison of cross-specialty indicator ranking with antimicrobial usage and healthcare associated infection rates per specialty.

Specialty curriculum	AMS-AMR Learning Points %	Rank learning points (High - low)	AMS-AMR abstracts %	Rank	HCAI %	HCAI Rank	AU %	AU Rank
Anaesthetics	N/A	N/A	1.242236025	L	5.1	L	34.7	M
Acute internal medicine	0.535714286	L		L	5.5	L	40.2	M
Breast Surgery	N/A	N/A	0.904977376	L	6.4	L	54	H
Cardiology	0.459921156	L	0.425531915	L	4.3	L	20.4	L
Clinical Pharmacology and Therapeutics	0.229885057	L		N/A	3.7	L	31.8	M
Core Medical Training	0.684931507	L		N/A	5.6	L	36	M
Core Surgical Training	0.97799511	L	1.827242525	L	6.7	L	40.7	M
Dermatology	0.633713561	L	1.075268817	L	1.3	L	29.9	M
Emergency Medicine	N/A	N/A	0	L	6	L	35	M
Endocrinology and Diabetes Mellitus	0.785854617	L	0	L	3.7	L	28.3	M
Foundation year	0.459770115	L		N/A	6	L	35	M
Gastroenterology	0.697674419	L	0.564516129	L	5.2	L	34.8	M
General Internal Medicine	0.640569395	L		N/A	5.5	L	40.2	M
General Surgery	0.060790274	L	2.629107981	L	6.9	L	43.1	H
Genitourinary Medicine	0.773195876	L	8.695652174	L	5.6	L	36	M
Geriatric Medicine	0.327153762	L	0	L	5.6	L	26.6	M
Haematology	0.521512386	L	1.945525292	L	16.2	H	61.4	H
Hepatology	0	L		N/A	5.2	L	34.8	M
Immunology	0.328407225	L		N/A	5.7	L	17.7	L
Infectious diseases & tropical medicine	5.756358768	H	38.4	H	8.3	M	66.3	H
Intensive Care	1.036627505	L	1.948051948	L	19.7	H	56.5	H
Medical Oncology	0.280898876	L		N/A	6.6	L	31.6	M

Ophthalmology	0.377358491	L	0.438596491	L	0.8	L	19.9	M
Metabolic Medicine	0.424328147	L		N/A	3.7	L	31.8	L
Neurology	0.346020761	L	0	L	5	M	14.3	M
Neurosurgery	N/A	N/A	2.158273381	L	8.8	L	29.7	L
Nuclear medicine	0	L		N/A	5.7	L	17.7	L
Obstetrics & Gynaecology	0.08	L	0.38961039	L	1.6	L	20.1	L
Paediatrics	0.554938957	L	0.366300366	L	2.4	L	31.7	H
Paediatric surgery	0.160771704	L	1.204819277	L	3.4	L	42.3	M
Palliative medicine	0.180995475	L		N/A	3.7	L	31.8	M
Primary Care	0.14619883	L	2.888888889	L	N/A	N/A	N/A	N/A
Plastic Surgery		N/A	7.692307692	L	6.4	L	54	H
Psychiatry	0	L	0	L	1	L	3.5	L
Rehabilitation medicine	0	L		N/A	6.6	L	14	L
Renal Medicine	0.348837209	L	0.719794344	L	7.9	M	48.5	H
Respiratory Medicine	0.390117035	L	1.52173913	L	4.4	L	54.8	H
Rheumatology	0.247218789	L	1.1816839	L	2.5	L	16.1	L
Stroke medicine	0.27700831	L		N/A	3.7	L	31.8	M
Transplant Surgery	N/A	N/A	1.047120419	L	16.2	H	62.2	H
Trauma and Orthopaedics	0.058513751	L	8.333333333	L	6.2	L	35.3	M
Urology	0.18115942	L	3.726708075	L	5.4	L	58.6	H
Vascular Surgery	0.185356812	L	0.536193029	L	9.6	M	38.8	M

Legend: AMS = Antimicrobial Stewardship; AMR = Antimicrobial Resistance; HCAI = Healthcare Associated Infection; AU = Antimicrobial Usage; H = "High Risk"; M = "Median Risk"; L = "Low Risk"

4.5 Discussion

4.5.1 Summary of findings

In this study, I have observed that outside of infection/microbiology there is a low rate of engagement with AMS-AMR using two proxy indicators; reporting at state-of-the-art scientific conferences and postgraduate training curricula. Furthermore, where specialties are engaging with AMS-AMR, there is little focus on promoting sustainable behaviour change. Using estimates for specialty rates of AU and HCAI, I have been able to identify specialties with high rates of AU and HCAI to potentially help guide the prioritisation of areas for intervention.

Although infection related specialties may take the lead in AMS-AMR related activities, the failure in adoption of decision support tools outlined in *Chapter two* and the need for integration of interventions into the end-users workflow (*Chapter three*) highlights the need for greater awareness and ownership of AMS-AMR within clinical specialties [66,168]. Given the important role state-of-the-art scientific conferences and postgraduate education play in shaping clinicians knowledge, opinions, and priorities [152,182] these seemed like the most appropriate indicators to evaluate current levels of prioritisation of AMS-AMR for this study.

This study also provides a mechanism for being able to monitor the formal changes in levels of awareness and engagement of different specialties with AMS-AMR over time if used in a longitudinal fashion. This was supported by the demonstration of stable results between 2014 and 2015 state-of-the-art scientific conferences [180,181].

4.5.2 Prioritising specialties for engagement

The findings from this study demonstrate that outside of infection/microbiology, AMS–AMR is generally under represented [179–181]. Therefore, prioritising other specialties to target can be challenging given that compared to other infection related topics, such as IPC, there appears very little formal awareness across the board [179]. By prioritising interventions based on current data describing AU and HCAI rates this offers a potential mechanism to add further justification to prioritisation of interventions. In this case, analysis of AU and HCAI can direct a range of further questions to be explored.

By identifying specialties with high rates of AU, it seems logical that these specialties may benefit most from urgent interventions. This is because improvements in the usage of antimicrobials within these specialties may have the greatest impact on reducing the burden of AMR due to overall selection pressure placed on a population by the volume of agents being used in these settings [17–19]. However, by also comparing groups with high and low rates of HCAI in this cohort, it may allow further identification of factors that drive or prevent complications in those specialties using high amounts of antimicrobials.

Within this study, intensive care, transplant surgery, and haematology had both high rates of AU and HCAI. Respiratory medicine, general surgery, paediatrics, plastic surgery, breast surgery, and urology all had high rates of AU but reported low rates of HCAI. It may simply be the nature of these specialties that drives the differences observed. For example, AU relating to prophylactic antimicrobial prescribing or low HCAI reporting due to high rates of day case surgery. However, these observations do warrant further investigation to confirm the reasons for disparity between AU and HCAI and determine whether these rates of prescribing have effects downstream through the patient care pathway (i.e. in the community, other secondary care specialties, or on the intensive care unit).

A further challenge with prioritisation of current clinical specialties is the fact that primary care could not be included within the analysis of data. This is challenging given the fact that in the UK at the time of this study they were responsible for prescribing 74% of all antimicrobials [24].

Focusing on the data that was available for evaluation, a significant finding was that the majority of specialties identified as “high risk” were surgical. This is a key area for consideration given that the majority of AMS-AMR work that has been implemented tends to focus on medical specialties, including that reported in *Chapters two and three* of this thesis. More recently, the role of surgical engagement with AMS has begun to be considered further, including multi-disciplinary publications aiming to draw surgeons attention to this as a problem [268–271]. This includes the “Global Alliance for Infections in Surgery” which aims to promote evidence based use of antimicrobials in surgical infections, advocating broader engagement with AMS [268,269].

4.5.3 Promoting specialty engagement

Specialty state-of-the-art scientific conferences and postgraduate training curricula offer potential avenues through which greater awareness and engagement can be fostered as well as monitored. As outlined in *section 4.3.1*, conferences provide an opportunity for clinicians to actively participate in research reporting [152,182] whilst also offering a platform for key opinion leaders and organisations to promote important agendas. Greater engagement by these actors within different specialties will offer a mechanism of broadening the reach of AMS and AMR beyond the scope of infection/microbiology [272]. This will help to broaden awareness and participation, promoting self-governance from within individual specialties who are responsible for high rates of antimicrobial

prescribing [8][196]. Likewise, broader engagement of postgraduate training for AMS-AMR with a focus on demonstration of skills in clinical practice, will promote broader awareness of the topic and help change practices through formally mandating the practice of evidence-based prescribing [270,271]. Given the importance of education in promoting behaviour change towards the practice of EBM in other fields, this factor would likely have a significant impact on promoting greater engagement with AMS overall [270,271].

Whilst there are several other methods through which specialty engagement can be fostered, the approaches outlined above are likely to have the broadest reach and provide an appropriate level of coverage of the topic across individual specialties. This is compared to alternative options, such as peer-reviewed publications, which are not always engaged with in as broad a setting as conferences and training curricula [273,274].

4.5.4 Longitudinal follow up

As well as allowing the cross-sectional analysis of formal levels of awareness and engagement with AMS-AMR, the methodology developed within this *Chapter* provides an approach for the longitudinal assessment of AMS-AMR engagement over time. Coupled with a mechanism of mapping specialty AU and HCAI rates, it may also be a mechanism through which temporal relationships between increased engagement and improved usage of antimicrobials can be explored.

Although there are potentially a large number of confounders, such as local policy and agendas that must be considered, this tool may facilitate the assessment of specialty engagement with AMS-AMR following national and international changes in policy and

publicity. This includes interventions such as the UN general assembly declaration on AMR [275] or national strategies, such as the follow on UK Antimicrobial Resistance Strategy, which is due for updated publication in 2018 [8]. Furthermore, within individual specialties, the implementation of policy or focus upon AMS-AMR may also be able to be monitored following similar methodological principles.

4.5.5 Limitations and future work

There are several important limitations that must be considered within this *Chapter*. Firstly, I relied on specialist opinion to confirm relevant conferences (both UK and international), which may have led to selection bias based on individual preferences. To address this, I ensured that where there was disagreement or multiple options provided by specialists, the conference with the largest attendance was selected. The selection of only large state-of-the-art conferences may have also narrowed the range of conferences available for inclusion. However, by selecting high profile national conferences I hoped that this would provide the broadest representation of the attributable importance of AMS-AMR within that specialty. This is because this approach would avoid including narrow agendas often found within sub-specialist, smaller conferences that may have either positively or negatively influenced the observations. In several instances data were not available from conference websites / journals meaning that the conference was excluded from the final analysis. For future investigation I would aim to directly contact the conference organisers to obtain this information.

For evaluation of postgraduate training curricula I used a validated search criteria and quality assessment tool to identify and appraise learning points [180,195]. Inter-rater subjectivity was a potential bias during eligibility screening and quality assessment of

learning points. To account for this, I ensured that points were reviewed by multiple researchers independently. This approach obtained consistent results between reviewers. For example, on assessment of the level of achievement of individual learning points, two or more researchers agreed in 179/184 (97%) of cases. Only 5 learning points requiring review by a fourth researcher.

For both approaches, it is important to acknowledge that these methods only act as proxy indicators for the attributed importance of AMS-AMR within UK clinical specialties. Therefore, it does not account for individual and informal promotion of the topic within different specialties. Furthermore, there is currently no agreed baseline for comparison to determine what an “appropriate level” of AMS-AMR coverage within a specialty is. I attempted to address this through comparison with another infection related topic, IPC, in the training curricula. This was because IPC has been the focus of similar national and international campaigns to AMS-AMR, but over a longer period of time [276]. Future work must explore the validity of IPC as a benchmark and investigate whether other makers are more justifiable within both state-of-the-art scientific conferences and training curricula. This may include the use of non-infection related benchmarks that are deemed to have an equal level of importance across all specialties.

Finally, data in this *Chapter* only focused on UK based specialties. Outside of the UK, specialty training and international conferences must also be explored to give a more global perspective on the issue. However, heterogeneity between countries training pathways must firstly be considered when planning such studies [179,180].

4.6 Conclusions and key messages

With ongoing developments in international frameworks for the implementation and evaluation of AMS, there is a need to be able to encourage and monitor the engagement of clinical leaders across specialties. This will provide an ability to be able to assess the impact of interventions whilst also helping to promote self-governance of AMS within specialties. With the current focus on AMS and AMR from high level organisations, such as the UN General Assembly and government, the ability to demonstrate broad levels of engagement by clinicians will be vital to maintain ongoing support from these policy makers. Furthermore, as education is a critical component for promoting behaviour change in antimicrobial usage, the current lack of educational coverage of AMS-AMR within most specialties must be addressed.

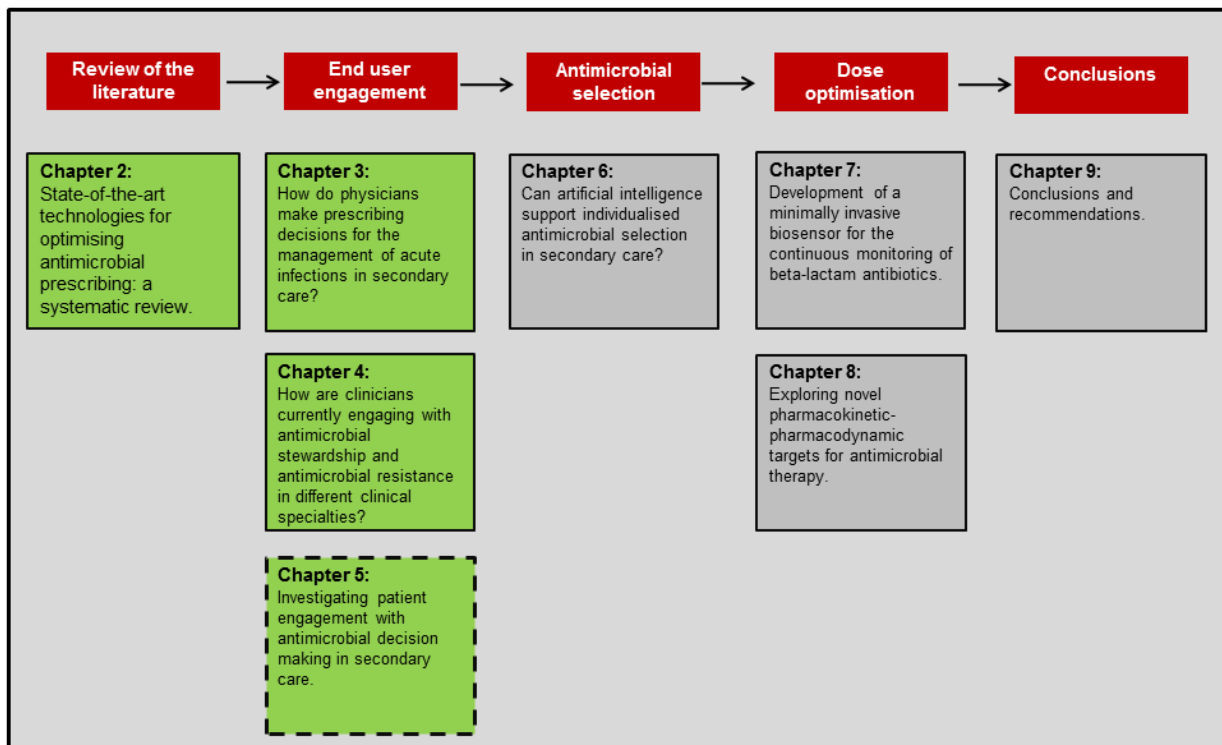
For this thesis, these findings support the critical importance of early engagement with end users in the development of decision support tools. Overall, the low level of engagement across most specialties supports potential reasons for failure in adoption of CDSS upon implementation in clinical practice identified within *Chapter two*. They also provide an insight into potential areas for deployment of such tools. This includes highlighting the need for consideration of surgical specialties, as well as areas beyond the focus of this thesis such as primary and intensive care.

It is now important to consider potential interventions for personalising decision support in keeping with the arguments outlined in *Chapters two to four*. This will need to focus on both patient and prescriber-facing interventions.

CHAPTER FIVE

5.0 Investigating patient engagement with antimicrobial decision making in secondary care

Figure 15. Overview of thesis.



5.1 Introduction

A core aspect of practicing EBM, and thus decision making, is the ability to be able to explore and incorporate patient views and perspectives into the decisions made [1]. To date, interventions to improve antimicrobial prescribing have mainly focused on health care providers. Where patient engagement interventions around AMR and AMS have been explored, these have mainly been via public health interventions, such as media and awareness campaigns, which have difficult to assess for efficacy [60,148,277–286].

Patient-centred interventions have been demonstrated to be vital for ensuring appropriate, effective, safe, and responsive provision of healthcare [287]. Despite a paucity of evidence

to support patient focused interventions within AMS programmes, a growing body of literature is emerging that describes physician and patient desire for increased collaboration in the decision making process surrounding the prescription of medications within secondary care [288]. However, there is currently no specific evidence describing patient experiences of infection management and antimicrobial prescribing within this setting.

Within primary care, the role of shared decision making (SDM), where patients and clinicians come together, acknowledge that there is a decision to be made (i.e., between treatments and including no treatment), and consider the best available evidence with the patient's values, preferences, and context have been demonstrated to reduce the rates of antimicrobial prescribing for respiratory tract infections [150]. However, in secondary care, where infections are often more serious, requiring urgent and highly protocol driven management, the role for the patient in this process remains unclear.

As described in *Chapter two* very few decision support tools reported the incorporation or evaluation of patient engagement interventions within the interventions reviewed. This is despite evidence to support the influence of the patient's role in decision making influencing antimicrobial prescribing decisions [149–151] and the role of engaging patients in decision making surrounding other medications being associated with improved patient reported outcomes in secondary care [288]. Furthermore, a paucity of information is available describing the impact of personalised information provision to patients regarding infections and their management.

5.2 Chapter objectives

Within this *Chapter*, I aimed to explore current patient experiences of engagement with decision making around antimicrobial prescribing in secondary care. I aimed to use this information to develop and test an intervention to address problems identified with current practice.

The objectives of this chapter are:

1. To explore patient experiences of engagement in decision making for acute infection management in secondary care.
2. To work with patients to co-design an intervention to address the current issues identified.
3. To investigate the potential impact of a personalised intervention integrated into a decision support tool on patient engagement with decision making for infection management.

5.3 Method

5.3.1 Study setting

To accomplish the aims and objectives of this study, I opted to use a mixed methods approach. Initially, I undertook focus-group workshops with previous patients who had received antibiotic therapy from secondary care within the preceding 12 months. These participants were recruited through a specialist qualitative research company (*Cherry Picked, London, UK*). The workshops aimed to explore, and subsequently triangulate reported experiences and problems with engagement with infection management in current clinical practice. Subsequently, I aimed to engage participants in the workshops in the co-design of an intervention that could be integrated into a clinical decision support system.

The final objective of this *Chapter* was to pilot test the developed intervention on patients receiving antibiotic therapy in secondary care. This would be performed at ICHNT. I planned to recruit participants from a range of clinical specialties and wards to ensure that the influence of a single team would not bias the investigation. The details of both studies are outlined below.

5.3.2 Patient focus-group workshops

5.3.2.1 Participant recruitment

In total, 30 previous patients who had received antibiotics in hospital during the preceding 12 months (recruited through *Cherry Picked, UK* – a specialist qualitative recruitment company) participated in two separate 1-hour workshops. The first of these was held in September 2015 and the second in May 2016. Citizens were recruited from a sample of 500 people whose data were held within a database of 20,000 individuals from around the UK who had signed up with the recruitment agency previously. An initial email was sent to all individuals in the database advertising the workshops. Respondents were then stratified according to

recruitment criteria and 30 individuals selected for inclusion (10 were selected for the first workshop and 20 for the second). The primary participant recruitment criteria for inclusion was that the patient had received antibiotics in hospital within the preceding 12 months. I also aimed to select an equal spread of age ranges (18-24; 25-49; 50-65; 65+), gender, and ethnicities for the workshops. Following the initial invitation email, two further emails were sent to individuals confirming their participation.

Participants attended focus group interviews at Imperial College London (UK). A small sample size was selected in order to gain an in-depth understanding of individuals' views, thus providing a richness to the data available for analysis [153]. Furthermore, focus groups were selected over individual interviews as these allowed for group exploration of new ideas, point-counterpoint discussion, and resolution of views; allowing identification and consensus on common themes within the groups [153]. All individuals were consented prior to participation. Participants completed a questionnaire collecting demographic data and previous healthcare experiences. For the first workshop in 2015, a validated Single Item Literacy Screener (SILS) screening tool was included to assess the participant's level of health literacy [289]. This was used to allow a baseline estimation of the groups' rate of health literacy and comparison to that of the general population. This was felt to be important for consideration, given that the findings of this study may be used to inform future interventions in clinical practice. A reimbursement of £65 was provided to participants for their time. Participants were consented and the workshops were audio-recorded.

5.3.2.2 Focus groups

For both workshops, the participants were divided into groups of 5-7 with the aim of creating diverse groups based on age categories and gender. Two healthcare professionals (myself with either LSPM or EC), following a pre-determined schedule (**Appendix 5**; developed from a critical analysis of the literature), facilitated a 120-minute focus groups.

These aimed to;

- i) Explore the participants' experiences of engagement with decision making surrounding infection management and antimicrobial use in secondary care pathways; and
- ii) Co-develop an approach to improve experiences to be delivered as part of an integrated decision support tool.

Two independent observers (one non-medical and one healthcare professional; Bernard Hernandez [BH] & ECS) directly observed the sessions and were asked to make notes of key observations. These were used to help triangulation of initial codes during analysis.

5.3.2.3 Data analysis

Focus groups were audio recorded and transcribed verbatim (using anonymous participant identifiers). Data analysis was performed using NVIVO pro 11.0 software. Thematic analysis of transcripts was performed using a mixed deductive and inductive approach [290]. Deductive categories were identified based on review of the literature and findings from previous work exploring the users role in infection control for workshop 1 [291]. For workshop 2, the key themes identified during workshop 1 [292] were used. I initially reviewed all transcripts and data generated during the workshops. For the inductive approach, two researchers (myself and LSPM), reviewed the focus group transcripts independently to allow initial codes to be generated from differing viewpoints by line-by-line coding for first order codes [164,293]. During line-by-line coding, the comments provided by the independent observers' were considered with the aim of complementing areas of reflexivity caused by the analysts' own prior experiences [156]. After familiarisation with the transcripts, the researchers independently coded the data generating a list of emerging categories from the first order codes and those identified deductively, addressing the aims of the study design. After meeting and agreeing on key categories and themes within the text, the two analysts

independently preceded to systematically cross-review the text, coding passages based on these agreed codes and categories, subsequently grouping them into overarching themes. On review, any discrepancies were discussed and consensus reached. Examples of key opinions and ideas from the text for each main theme identified were then charted to allow mapping and interpretation of the results [164].

5.3.3 Pilot study

Following workshops 1 and 2, the co-designed intervention was piloted in ICHNT. Although described in detail below, briefly; the intervention co-designed was a personalisable PDF that was embedded within the CDSS described in detail in *Chapter six* and **technical Appendix 8** (*Section a8.1*). Upon activation of the module, a personalised PDF document with infection and antimicrobial information would be generated, which could then be printed and discussed with the patient.

The pilot involved a pre- and post-intervention questionnaire delivered 12-24 hours either side of the intervention. This was facilitated by two members of the research team (myself and Vivian Alividza [VA]). Participants were identified by clinical members of staff for inclusion from separate clinical wards across three university teaching hospitals making up ICHNT. These wards were staffed by a range of specialties (infectious diseases, care of the elderly, respiratory, gastroenterology, haematology, nephrology, general surgery, urology, and orthopaedics).

Over a four-week period, between 7th August and 1st September 2017, 30 patients were invited to participate in the intervention. Consent was obtained from patients who agreed to participate by members of the research team; they remained enrolled in the study for 3 days. After obtaining consent, participants were asked to complete a 15-point questionnaire on day one (**Appendix 6**). On day two, a member of the research team, following a pre-determined

semi-scripted guide designed to simulate a discussion on infections / antibiotic prescribing during a ward round or brief clinical consultation (lasting less than 5 minutes), delivered the intervention. On day three, the participants were asked to complete a 20-point questionnaire (**Appendix 6**). The questionnaires were designed by the research team and were piloted on two healthcare professionals, four citizens not associated with the research team, and a medical student.

The study was designed to assess:

- (i) Any short-term improvements in patient knowledge and understanding of their infection and antibiotics;
- (ii) What information was still being missed during the intervention; and
- (iii) Evaluate the acceptance and agreement of patients with the intervention.

Where answers were marked as correct/incorrect, members of the research team met and agreed upon correct responses for the individual participant before deployment of the questionnaire. Free text answers were collected and independently analysed inductively by two members of the research team through line-by-line coding and categorisation of answers (myself & LSPM) [164,293].

5.3.4 Ethical approval

The study protocol was initially reviewed by the West London Regional Ethics Committee (REC) in September 2015 and considered to meet criteria for monitoring under service evaluation governance structures (*REC 15/LO/1269 / ICHNT Service Evaluation SE113*). In February 2017, a second ethical review was undertaken by Chelsea-London REC who granted favourable opinion for testing of the developed intervention in clinical practice (*REC 17/LO/0047*).

5.4 Results

5.4.1 Focus-groups

5.4.1.1 Participant characteristics

Within workshop 1, the median age of participants was 52 (21-69) years with an equal gender divide. Seven of the participants were white ethnicity. Six participants had experience of infection management as a hospital in-patient (in the non-critical care setting) with the remaining participants all having received antimicrobials from other secondary care pathways across a variety of South-East England healthcare institutes. These included the Emergency Department (ED), urgent care centres, or consultant led out-patient clinics. Two out of ten participants were identified on screening as potentially having a low health literacy, reporting that they sometimes, often, or always required help with written health information on the SILS screening tool [289]. This indicates that our cohort were likely to be more health literate than the average population, where approximately 43% of individual citizens would require assistance with written health information [289,294].

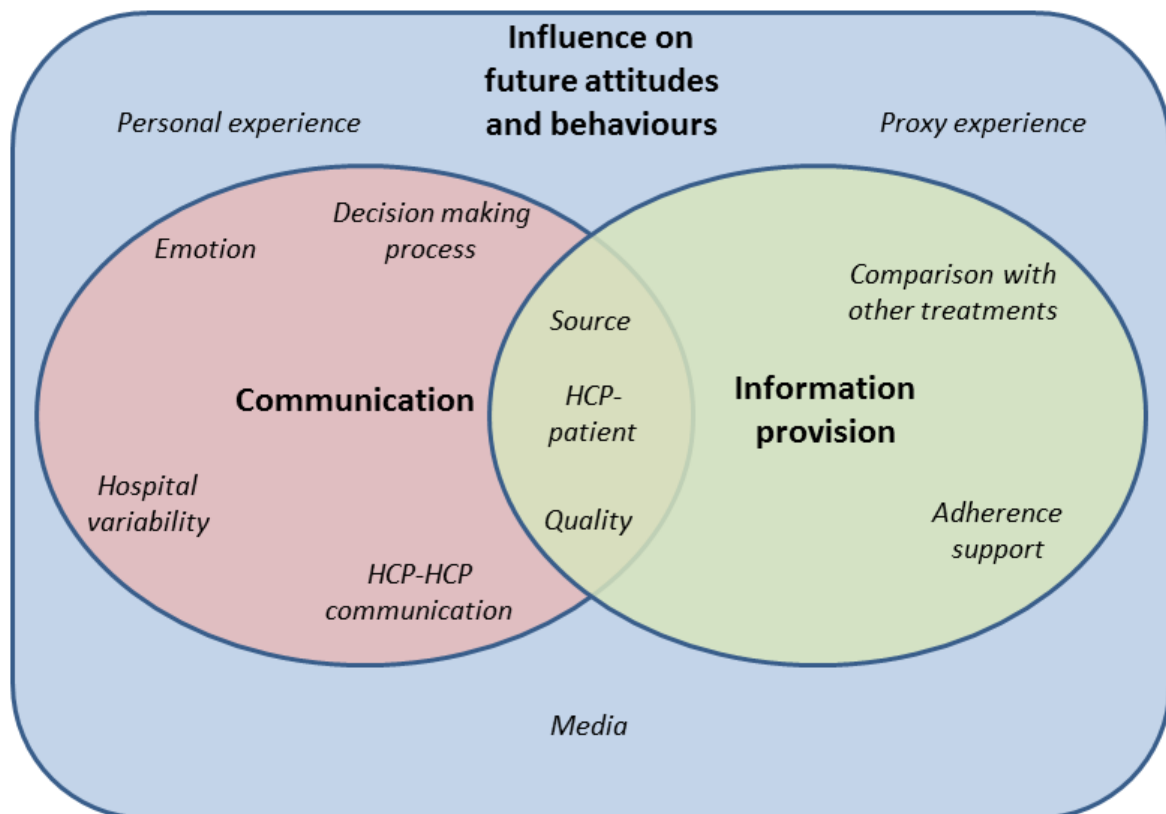
Within workshop 2, only participant age ranges were provided. Five participants were aged 18-25, five 26-40, five 41-64, and five 65+. There was an equal divide of genders. All participants had once again received antibiotics from a secondary care pathway across South-East England in the preceding 12 months. The SILS screening tool was not used during this workshop.

5.4.1.2 Current experiences of engagement with decision making in secondary care

Following thematic analysis of participants current experience of engagement with decision making yielded 92 subcategories that fell into 12 categories. Three interlinking themes were identified (**Figure 16**). **Table 14** summarises key quotes informing the individual categories and themes referred to within the text below. The participants described a failure in

communication and information provision from infection clinicians and support staff in secondary care which subsequently influences the individual's future ideas about infections and their management. This alters the individual's future actions towards infections and antimicrobials and can drive non-adherence to prescribed antimicrobial regimes and loss-to-follow-up after discharge from secondary care.

Figure 16. Summary of identified categories and themes from workshop 1 exploring patient experiences of engagement with decision making surrounding antimicrobial prescribing in secondary care.



Legend: HCP = healthcare professional

Table 14. An analytical framework developing categories and themes for patients' experiences of infection management in secondary care.

Quote	Category	Theme
"I wasn't given any education into what to do [with my antibiotics]. The 5 th day I felt well and so thought I would just stop taking the treatment. I was fortunate that my sister explained to me and made me complete the course" [24 year-old female]	Adherence support	Information provision
"Especially I think that you are often given more information when you are taking other medication... I have allergies to penicillin so always I have to know what kind of antibiotic I have been given. So unless your issues are more complicated, that's when they give you more information, otherwise I feel that they don't provide you with enough" [24 year old female No. 2]	Comparison with other treatments	
"I like to go and see the doctor... Online can't see me [sic]. Infection is a thousand different things and online can't confidently tell you, this is what you have..." [65 year old male] "...you are not an individual to them [corporate pharmacists]. In our case, I think we have the option to be sort of individuals. That is what I find lovely about our current pharmacy!" [69 year old male]	Sources	Information provision / communication
"I think what the problem that I have experienced is, is that they will give you a leaflet to read and I will have to go and research it myself. This is rather than the doctor taking the time to sit down and talk about how it might affect you, what exactly is in it [the antibiotic] – you know a proper consultation. [23 year old female] "Rather than sitting down and taking the time to explain, because they use a lot of medical terminology that I do not know what they're talking about to be honest. I think that they need to take more time to be honest to sit down and make sure that the patient knows exactly what they are putting in your body and exactly what all the side effects were. Because I didn't know what I was reacting to..." [24 year old female]	Quality	
"I think sometimes the doctors normally come and diagnose you they usually tell.... They don't necessarily tell you what they are giving you, they usually prescribe it. Then the nurse just comes along with a pot full of drugs and you just take them. I think, unless you are intrigued and ask for it then the nurse will give you that information." [30 year old female]	HCP - Patient communication of information	
"When you go into hospital, you feel as though the illness is not yours. You go in to hospital and everyone takes over, like 'we do this then we do that later'. You have no ownership in a way. You are going through it but you have no ownership over what is being done for you or what medication you are receiving." [23 year old female]	Decision making process	Communication
"Tell me yes or tell me no... If you can't fix it I don't want to see you again because there will be no point... We've tried this it's not worked so we tried that... it is endless..." [65 year old male]	Emotion	
"You know, the hospitals I have experienced in [region] – I am not really keen based on the lack of information. It is more about; we're doing this operation – get you in, get you out." [23 year old female]	Hospital variability	
"When I went to A&E I visited my GP ... It is more about telling your GP what the symptoms were and what treatment you had rather than exactly what the infection is" [30 year old female] "My GP never knew anything. She had scheduled me in to have the hernia, but the appendix went first. And she was "oh have you..." [53 year old male]	HCP - HCP communication of information	

Legend: HCP = healthcare professional; A&E = accident and emergency; GP = general practitioner

5.4.1.2.1 Failures in communication

Participants described their experiences of being diagnosed with an infection in secondary care as one where they completely lost ownership of their condition. Control of their illness was taken over by a multitude of healthcare professionals (HCPs). Recurring instances were identified where HCP communication with patients became unilateral when antimicrobial decisions were being made, with patients being “*told*” information, often devoid of key aspects such as names of medications, durations of treatment and prospective plans about time courses and potential escalation / de-escalation of therapy. This led to a significant amount of anxiety and frustration as the individual searched for answers.

“I was told ‘you have an allergy [to penicillin], take this instead’ – Tell me what I am taking and exactly what it is going to do for me!” [65 year-old male]

Moreover, in many cases participants did not feel as if they were involved in the decision making process around their infection management with two-way communication with healthcare professionals perceived as absent.

As well as HCP communication with patients, participants reported becoming frustrated by communication between HCPs. This is centred primarily on the way in which information about infections is communicated from secondary care doctors to primary care doctors on discharge from hospital. Whilst patients are provided with a discharge summary of their stay on leaving hospital, it was perceived that this often-neglected information about their infection and the treatment which they received whilst in the hospital. Participants’ reported that they were often forced to communicate this information directly with their primary care physician on follow up visit or were otherwise lost to follow up after discharge due to lack of clear communication pathways.

5.4.1.2.2 Failures in information provision

The current volume and quality of information provided to individuals by HCPs in secondary care causes problems for patients as it is often poorly explained, with medical terminology routinely used. This leads to a feeling of dis-empowerment with individuals frustrated that they then have to “*go away and research it [their condition] themselves*” [23 year-old female]. Fear and anxiety follows when participants see serious side-effects of treatment “*like risk of death [and] no one has mentioned that to me!*” [30 year-old male]. This in-turn causes frustration as participants compare delivery of information on infections and antimicrobials to that provided for operations and medications for chronic disease, such as hypertension. In this example, patients are provided with explanations of their procedure/condition, their management, and potential complications which may arise and how these will be dealt with. In contrast, information on infection management is seen as a “*reactive*” process where information is only often provided once complications have occurred. Furthermore, patients are often unaware of the timeline for their treatment and the potential complications. This lack of clarity drives individuals to stop treatments early or potentially ignore side effects experienced due to false assumptions and misinformation.

Participants reported that this failure in communication about infections and antimicrobials drives them to seek information from a wide range of sources, often with varying degrees of quality. Participants commonly sought information independently due to “*difficulties in accessing [healthcare professionals]*” and the “*[time] pressures of work and children*” [65 year-old male]. A number of avenues were preferred such as the internet, information leaflets provided with medications and local pharmacies. Individuals will seek out recommended or official NHS sources of information which they believe that they can trust to provide them with information on their infection or treatment. Whilst these sources are seen as helpful, patients still prefer to discuss their infection and its management with a HCP as this provides “*individualised*” information compared to the “*standard-reply*” provided by alternative sources [69 year-old male]. This is because the information provided is seen as being based on the

patient's own specific situation and issues. Furthermore, the HCP is a “*trusted*” source being viewed as an “*expert*” [69 year-old male].

5.4.1.2.3 Influences of future attitudes and behaviours

Participants clearly described how these individual experiences of poor communication and information provision influence their future ideas and actions towards infection management both in secondary care and in the community. Influences were described from three sources; personal understanding / experiences, understanding by proxy, and understanding through the media.

For example, one personal experience was described by a participant who was told that he had an allergy to penicillin and told that he would be given a “*weaker*” type of antibiotic for his infection. When this was perceived not to be effective at clearing up the infection after two days, he stopped taking his medication as:

“You know the weaker ones [antibiotics] never seem to clear the infection up. They are not as strong so they don't clear it up. The infection lasts longer” [60 year-old male]

This subsequently led to the participant having to return to secondary care for further treatment of his infection due to the poor information provision and engagement in the decision process surrounding his infection.

The media's role in developing the participants' understanding of infection management arose and was further explored during the focus group. Participants reported that the media's influence occurred through the portrayal of stories about complications of treatment and the dangers of AMR. This created fear and mistrust of medical professionals within our participant group and caused participants to be “*cautious*” when interacting with medical professionals as they are perceived to “*not say the full story*” [21 year-old, female]. This

distrust was reported as driving non-adherence to therapy in the community by several members of the group.

5.4.1.3 Co-development during workshops

On analysis of participants reported views during co-development of the intervention 25 categories were generated. **Table 15** summarises the key themes that emerged from the workshops for the content and structure the participants felt was required from the intervention. There was consistency in identified themes across both workshops. Participants agreed upon the development of a personalised PDF document that could be generated using electronically available data specific to the individual. Participants reported that the PDF was the optimal approach as it allowed the maximum flexibility to either be printed and given to a patient at the bedside or transferred electronically. Other approaches considered included the development of a mobile application, text message services, and written summaries. The ability to be able to print the PDF was considered by participants to address some of the reported concerns about transferring confidential patient information electronically and would also be available for patients without access to electronic devices.

“Couldn’t you have an interactive PDF so people can choose whether or not to include a list of side effects or just the link for further information?” (Female 1, workshop 1)

“I like the idea of getting it electronically and downloading PDFs or something, but I would say an app’s just getting a little bit to gimmicky” (Male 1, workshop 2)

“I feel like that a lot of people prefer forms as they can physically keep track of them [patient information]. I feel more in control of them then. If you are comfortable online then it is good, however with medical records I mean they are quite sensitive, so it might be nice to have them just in their paper form.” (Male 2, workshop 1)

Participants reported that the intervention could act as an important tool for promoting better communication about infections and antibiotic management between patients and healthcare professionals. In particular, participants reported that this may act as a prompt for further questions and support reflection on their infection and its management after the consultation has taken place.

“I usually get home and think ‘oh wait’ I had a really important question which I forgot to ask. I like to be able to process things and then kind of gather my thoughts and find out what I want to know about the issue.” (Male 3, workshop 1)

Table 15. Key themes identified during workshops for the development of a patient engagement intervention for promoting enhanced communication and information provision surrounding infection management in secondary care.

Category	Summary of workshops decision on content	Summary of workshops decision on structure
Platform	<p>Needed to be flexible, to allow use on devices, paper, in and out of hospital, and by all age groups</p> <p>The platform should also be personalisable, to allow the patient and doctor to select relevant information depending on the patient's wishes</p>	<p>A PDF document that can be populated, printed, emailed, or uploaded onto an application was preferred.</p> <p>Mobile applications, websites, automated text systems were also considered but were felt not to have the same level of flexibility.</p>
Individualised	<p>The intervention should provide information about the individual's current condition and treatment.</p>	<p>Information provided should be in summary form.</p> <p>The provision of blood test results, or probabilities was not felt to be appropriate as it could be overwhelming and concerning to some patients.</p>
Health literate	<p>The information must be provided in language that the majority of citizens can understand.</p> <p>The quantity of information provide must be enough to provide key information but not overwhelming to someone who is unwell and in hospital.</p>	<p>Colours and tables were not preferred.</p> <p>Participants opted for the minimum amount of presented information.</p> <p>Basic explanations of conditions with examples of medical terminology sometimes used was felt to be helpful for following discussions and searching for further information after the consultation.</p>
Sign post	<p>Detailed descriptions should not be included, but references for reputable sources of information should be provided to help guide those who want more information.</p>	<p>Links to further information on reputable websites.</p> <p>Blood test results were not preferred on the leaflet.</p>
Practical advice	<p>Advice on common or important side effects of treatments should be included.</p> <p>Practical information, such as whether it is okay to drink alcohol, drive/operate heavy machinery, and interactions with the oral contraceptive pill whilst taking antibiotics should be included.</p> <p>Educational information to promote better understanding of the risks of drug resistant infections could be included.</p> <p>Adherence to therapy should be reinforced.</p>	<p>Minimal numbers of side effects were preferred. The group decided on 3-4 key side effects would be optimal.</p> <p>A short description of antimicrobial resistance and where to find further information was included for reference.</p>
A tool to enhance communication	<p>The intervention should aim to enhance communication between patient and healthcare professionals.</p> <p>It should be designed to be delivered by all types of health care professional.</p> <p>It should provide a prompt to allow the patient to consider whether they have further questions, allowing them to pick this up during future interactions with the healthcare professional.</p>	<p>Diagnosis, causative organism, and treatments (past and present) were included.</p>
Supporting follow up	<p>Information on next appointments</p> <p>Information on who to contact if you have problems or questions on discharge</p>	<p>Removed from the leaflet as participants felt that it overlapped with discharge summaries that are often provided. In this case duplication of information at different times during hospital stay may be unhelpful.</p>

There was agreement across both workshops that the information provided needed to be personalised to the individual patient's current situation and treatment regime. Existing approaches, such as medication information leaflets, were reported to give generic information on infections and treatments that participants felt could be overwhelming and confusing. Participants reported the need to ensure that the quantity and complexity of information provided was at a level that could be understood by the majority of individuals. To address this, the workshops decided that a summary of key points to take away should be presented with links to reputable information sources for patients to seek further information if required.

“Summarise it and then if you want more information you can always go on the internet”
(Female 2, workshop 2)

“Rather than it being ‘here’s all the information in one go’, more of the ‘you have had a positive bacteria reading on your test, click here to read more about it’. And then if you don’t want to [don’t] click there” (Female 3, workshop 2)

Furthermore, the groups focused on providing practical information that they felt was commonly missed during discussions with healthcare professionals regarding their medications in hospital. This included items such as whether it is safe to drink alcohol or drive whilst taking certain antibiotics.

“When I had an infection and they said don’t take it if you have reflux – that stuff I need to know. But stuff like the massive long name of what the drug is really called and stuff like that.... It is irrelevant to me. I just want to know, is it going to make me sick? Can I drive? Can I work with it...” (Male 4, workshop 1)

Participants reported that this information needed to be provided in a health literate format that considered the literacy and language needs of the population who would be utilising this intervention.

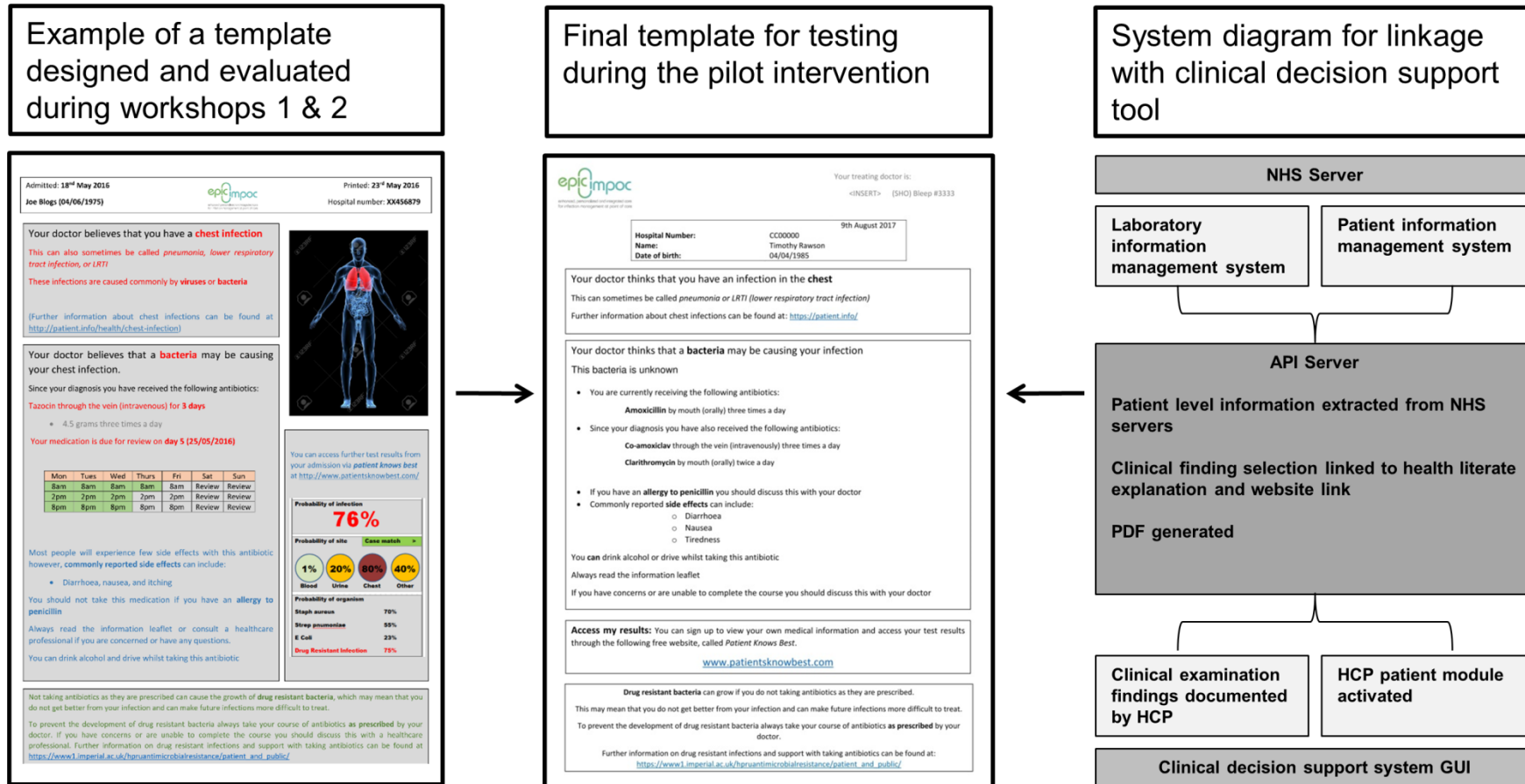
“Yes English as a second language and dyslexia is really common.” (Female 4, workshop 1)

“[It needs to be] easy to understand, easy to just [look down it]. Whereas here, I would look at this and say, well, this doesn't, I don't care because I can't read this, I have no idea what this means” (Female 5, workshop 2)

5.4.2 Intervention development

Figure 17 demonstrates the final template that was agreed upon and co-designed by participants in the workshops. The intervention was embedded in an electronic clinical decision support system that contains several different modules linked to a central server (*Chapter six* and technical **Appendix 8, section a8.1**). This allows individual patient information to be automatically extracted from a number of databases within the hospital. Moreover, the clinician can also input their impression and findings based on the clinical examination. To ensure that individualised information was provided in a health literate format, a number of translations automatically occur upon generation of the personalised information leaflet. For example, if “pneumonia” is recorded by the healthcare professional, it will be coded to display the diagnosis as “chest infection” and a number of alternative names are provided (“pneumonia”, “lower respiratory tract infection”) automatically below on the PDF document. This code also triggers the inclusion of a web address that directly links to an open access patient information leaflet on pneumonia (patient.info). Therefore, on generating the information leaflet through the clinical decision support tool, the clinician is able to provide a personalised information leaflet to the patient, which contains details of their own infection and treatment.

Figure 17. Summary of intervention template development and integration into clinical decision support system.



5.4.3 Pilot study

Eighteen out of thirty (60%) patients invited consented to participate. The 12 who declined to take part did not provide reasons for this. In total, 15/18 (83%) of the enrolled participants completed the study. One patient moved hospital before they could complete the pre-intervention questionnaire, one participant was discharged before completion of the post-intervention questionnaire, and one patient experienced an episode of delirium after completion of the pre-intervention questionnaire leading to him being withdrawn from the study.

Table 16 summarises participant characteristics from the study. Of the 17 participants who completed our pre-intervention questionnaire, the median (range) age was 60 (22 - 85) years, the majority of participants were male (11/17; 65%). Most patients were under the care of medical specialties within the hospital (13/17; 76%). In the pre-intervention questionnaire, 8/17 (47%) reported the correct infection diagnosis and 6/17 (35%) correctly named what antibiotics they were receiving. Participants reported that health care professionals had spent less than 10 minutes discussing their infection with them in 9/17 (53%) cases. Three out of seventeen (18%) did not report healthcare professionals discussing their infection with them at all and 7/17 (41%) reported that healthcare professionals had spent longer the 10 minutes discussing their infections with them. Only 5/17 (29%) reported healthcare professionals discussing their antibiotic therapy with them during this admission.

Table 16. Summary of participant characteristics and questionnaire results from the pilot evaluation of the patient-focused intervention.

Characteristic	Description	Result	p-value
Age ^{&}	Median (range) years	60 (22-85)	
Gender ^{&}	Male (%)	11 (65)	
Reported time spent discussing infection prior to intervention^{&}			
<i>Not discussed</i>	n=(%)	3 (18)	
<i>< 10 minutes</i>	n=(%)	8 (47)	
<i>10-30 minutes</i>	n=(%)	3 (18)	
<i>> 30 minutes</i>	n=(%)	3 (18)	
Antibiotic therapy discussed with patient prior to intervention^{&}			
Yes pre-intervention	n=(%)	5 (29)	
Pre-intervention knowledge and understanding scores			
	Median (IQR)	3 (2-5)	
	Mean (SD)	3.2 (2.2)	
Post-intervention knowledge and understanding scores			
	Median (IQR)	10 (6-11)	$p < 0.01^{\S}$
	Mean (IQR)	8.5 (3.3)	$p < 0.01$ (95%CI: 3.7 - 6.3) [%]
Reported usefulness of intervention			
	Median score (range)	5 (3-6)	
	1 = Not very useful		
	6 = Extremely useful		
Would participants use the intervention again			
	Yes – n=(%)	13 (87)	
Reported optimal time to deploy the intervention			
Initiation of therapy	n=(%)	5 (33)	
On discharge	n=(%)	2 (13)	
Any time during admission	n=(%)	8 (53)	

Legend: All analysis was performed only on participants with both pre- and post-questionnaires (n=15) unless otherwise stated

[§] Wilcoxon Signed Ranks Test

[%] Paired t-test

[&] n=17 who completed pre-intervention questionnaire

Of the 15 patients that completed the study, the pre-intervention questionnaire demonstrated poor knowledge and understanding surrounding participant infections and antimicrobial therapy. Mean (SD) scores out of 13 were 3.2 (2.2). Following the intervention, participants post-intervention questionnaire scores improved significantly to 8.5 (3.3) out of 13 ($p < 0.01$). Feedback on the impact of the questionnaire was positive with participants rating its usefulness a median (range) 5 (3-6) out of 6. Thirteen out of fifteen (87%) participants reported that they would use the intervention again if in hospital with an infection.

Table 17 summarises the questions participants recorded in their pre-intervention questionnaire regarding their infections and subsequent management. It also summarises participant post-intervention written feedback, outstanding questions, and suggestions for further development of the tool.

Table 17. Summary of qualitative question responses from participants in the post-intervention survey.

Questions noted by participants pre-intervention	Frequency
What are the side effects of taking antibiotics?	7
Where to find further information about the diagnosis?	7
Further information about the antibiotics that I am taking	5
Further information about the bacteria causing my infection	3
How long will it take for me to feel better?	2
How can I prevent this happening again in the future?	2
Post-intervention - Why was this useful?	Frequency
It gave information I haven't of been told by the doctor	4
I didn't know the names of the antibiotics I was taking	3
Gave information about side effects	2
It provided information about driving	2
It provided information about drinking alcohol with antibiotics	2
Covered all of the questions that I wanted to ask the doctor	2
Gave information on the infection / bug	1
Clear and understandable information	1
A good reminder of my conversation with the doctor	1
Post-intervention - How could this be improved further?	Frequency
Nothing	3
More information on side effects	2
Would be better with more communication from the healthcare professional	1
Length of treatment	1
A place to write the concerns and questions that I have	1
Provide further information on why I shouldn't drink on this medication	1

Pre-intervention, participants reported requiring more information about their infections and antibiotic therapy than they had been given. Potential side effects were commonly reported questions that patients had. Post-intervention, participants reported that the intervention was useful as it provided information that had not yet been given to them by their treating doctor. This included information about their infection, the antibiotics that they were taking, and general issues around whether it is safe to drink alcohol or drive whilst taking these medications. Feedback provided on improvements to the intervention by participants surrounded, giving further information on specific aspects within the document and also prompting more detailed discussion with the doctor following use of this intervention.

5.5 Discussion

5.5.1 Summary of participant impressions

Within our participant group, individuals reported feeling detached, frustrated, and disempowered from involvement in decision making about their infection management within secondary care. The consequences of the failure of HCP communication and information provision was not limited to the discrete episode they described, reaching beyond secondary care. It appeared that these episodes have a cumulative impact, influencing the ideas and actions towards infections and antimicrobials during future healthcare interactions along a number of different pathways. This was reported as fostering feelings of frustration and anxiety during an individual's journey through complex secondary care pathways and was potentially driving non-adherence to prescribed antimicrobial regimes and loss to follow up after discharge. These findings highlight the need for specialists in secondary care to not view infection management episodes as discrete events, but as cumulative experiences which have the potential to drive future non-adherence to prescribed antimicrobial regimes and thus the promotion of AMR.

5.5.2 Opportunities for educating healthcare providers to improve patient engagement

Importantly, HCPs must appreciate that engagement in the decision process for infection management and antimicrobial prescribing may have an influence on future patient actions towards infections and antimicrobial use. These actions can be influenced by personal experience along with those of friends and family and what is described in the media. The way in which HCP communicate information to patients was reported as the most important aspect in our participants' experience. This was the largest influence on future actions in terms of adherence to prescribed antimicrobial regimes and healthcare seeking behaviours. Participant perception of communication in secondary care infection-related pathways is of a unilateral process which does not invite patient participation. Greater emphasis needs to be

placed on educating HCPs to move away from the decision-maker role [295] into a more bilateral structure. Difficulties such as time pressure on the HCP and the patient is perceived as a key factor by participants and must be taken into account when designing interventions to help facilitate improved communication and patient education during the decision making process. The way that these interventions are designed must be mindful of health literacy, ensuring that the information provided to patients is understandable. Within our small cohort, two of ten participants met screening criteria for health illiteracy. Within the UK, it is estimated that up to 43% of the adults cannot understand currently available health information [289,294]. Therefore, as well as educating healthcare providers in how to improve communication with patients, consideration of the wording and type of health information supporting this is vital to allow patient engagement with the decision making process.

5.5.3 Opportunities for improving patient engagement with decision making

Within our cohort, participants felt strongly that the choice of information provided about their infection and antimicrobial therapy should be dictated by the patient's preference. However, their focus was not primarily on the end decision of whether or not to treat, but on feeling involved and engaged with the process of decision making. This focused on education about their condition and treatment, communicated effectively to them. They described a belief that if a trusted clinician felt they had an infection that required antimicrobial therapy then this was appropriate. Whether this is truly sharing the decision process or not is for consideration, as SDM classically acknowledges that there is a choice to be made, with the patient and clinician coming together to consider available evidence, the patients values and preferences before arriving at a decision [296]. However, Edwards and colleagues, suggest that this can still be classed as sharing the decision (or engaging the patient in the process) where the focus is placed primarily on involving the patient in the decision making process, rather than on who actually makes the final decision on management [297]. Our participants

supported this approach to engagement by describing how they become frustrated and distrusting of the recommended therapy when supporting information about the infection and the proposed management is perceived to be withheld from them.

Participants currently view information provided about infections and antimicrobials as reactive in nature with information only provided after a side effect occurs or the patient fails to respond to a certain type of antimicrobial and therapy is escalated. Individuals want proactive information to help them understand what they are receiving, what to expect, and what the plan is if the treatment doesn't go to plan. This allows them to feel "*prepared*", "*confident*" and invested in the healthcare they are receiving. This is challenging for antimicrobial prescribing in secondary care, which is often an acute event, requiring rapid decision making, and has a short duration of therapy [53]. Moreover, this highlights a key area of misunderstanding surrounding infections and antimicrobial therapy within our participant group that has been driven by poor communication and information provision during previous experiences of infection management within secondary care. Therefore, future tools must aim to promote patient engagement with infection management, considering how they define engaging patients in the decision process. Moreover, these interventions must ensure that identified deficiencies in how HCP communicate and provide information to patients are addressed to facilitate improvements in patient experiences.

5.5.4 Co-designed interventions can enhance patient engagement

Within this study we have demonstrated that a patient-centred intervention, co-designed with patients to promote engagement with infection management in secondary care, improved participant knowledge and understanding of their infections in the short term. Participants responded positively to the intervention, providing data to triangulate findings from previous workshops, and providing feedback on future areas that still require development.

Within secondary care there is evidence to demonstrate that both healthcare professionals and patients desire individuals to have a greater involvement with their medications during their in-patient stay [288]. This can help reduce medication errors and promote greater patient reported outcomes following hospital stay for a wide range of medications [288,298,299]. From previous work published by our group [292], there is evidence to support that healthcare professionals current approaches to engaging patients in their infection management may have a similar outcome to other chronic medications. This study has highlighted the lack of awareness within our population regarding their infection and antibiotic therapy. Recall of infection names and antibiotic therapy were less than 50%. Less than 30% of patients remembered their healthcare professionals discussing their antibiotic therapy with them. There is currently little available data to allow comparison of these findings with other similar studies of in-patients in secondary care. Micallef and colleagues, previously reported on the levels of awareness and understanding of antibiotic resistance and stewardship in a cohort of 1450 citizens attending hospital out-patient clinics and pharmacies in the UK [300]. Within this study, the authors identified broad conceptions about the development of drug-resistant infections and appropriate antibiotic use [300]. These findings have also been reported in community based public awareness surveys that have demonstrated poor awareness and understanding surrounding antibiotics and infection management across a number of different countries [301]. We are now planning to undertake a further cross-sectional analysis of this problem designed to assess the levels of awareness of in-patients both with and without infections.

Within primary care, there is evidence supporting the role of shared decision making for reducing inappropriate antibiotic use [150,151,278,302]. However, in secondary care during acute infection management, the need for antibiotic therapy is often a lot clearer, patients are more unwell, and decisions must be made rapidly, especially in the case of sepsis [168,292,303]. Therefore, when providing information on infections in secondary care interventions may need to adopt a different approach compared to primary care, where there

often is truly a shared approach to making a final decision on the need for therapy. This problem has been addressed by Edwards and colleagues, who argue that engagement of the patient in decision making alone may be sufficient to improve understanding and involvement in the process overall, providing a level of ownership to the problem, whilst not requiring the focus to be on the final decision that is made [297]. This was supported by our findings that participants felt more informed and engaged with the management of their infections following the intervention, regardless of whether they had a final say in the decision that was made. Moreover, feedback on the intervention was overall very positive with the majority of participants happy to use the intervention again in the future. However, a wide variation was observed with the preferred timing of the intervention reported by participants. This triangulates with findings from our development workshops, where there was variation in opinion between participants was observed on this topic.

The main finding from the workshops in this study was the reported focus on providing individualised information to patients that is relevant to their own specific situation. I was able to achieve this through the integration of this tool with a wider electronic clinical decision support tool. This allowed me to utilise available electronic patient data and clinical examination findings recorded by the patient's physician and provided a flexible mechanism of generating a personalised information leaflet for deployment at any point during the patient's hospital stay. There is a wider need to ensure that interventions are joined up during the development of clinical decision support tools, which are often developed with a narrow focus on antimicrobial selection only [66]. Validation of this intervention will now allow it to be tested in tandem with prescriber-focused interventions within the integrated decision support system.

A further aspect that participants in this study wanted to address was ensuring that the intervention was designed so that it could be used by any healthcare professional, not just physicians. The role of healthcare professionals, such as nurses and pharmacists, is critical in infection management and appropriate antibiotic use [57,169,170,172,173]. Therefore,

any tool that is developed must keep this in mind. Within my pilot study researchers of two different backgrounds delivered the intervention. One was a nurse (VA) and the other a junior physician (myself). There were no observed variations in the success of the intervention depending on which researcher delivered it.

5.5.1.4 Limitations and future work

This qualitative analysis aimed to map the current experiences of patients in antimicrobial decision making but it does have limitations. Group facilitation within our study was carried out by two HCPs, which may have influenced socially desirable participant responses to certain questions. To address this dynamic between interviewer and interviewee, two observers' comments were also considered during initial coding to highlight where the interviewer's position may have directly influenced individual responses. For example, during discussion of participants perceptions of doctors' attitudes towards prescribing antimicrobials, one participant apologised after voicing an opinion about doctors simply wanting to

"..sign the prescription and get rid of the patient" (69 year-old male).

The noted anxiety about offending the HCP may have influenced other participants voicing their true opinion on the matter. Secondly, whilst small, this in-depth study provides key themes for future studies to explore the generalizability of and inform the design and evaluation of appropriate interventions. Furthermore, the findings were subsequently tested for validation within an independent group of citizens to search for further categories and themes within our local population. Finally, on comparison of the health literacy of my selected cohort of participants for the workshops, the group appeared to be more health literate than estimates for the general population. Therefore, during subsequent intervention development and exploration, this aspect must be highlighted and considered as this may affect the generalizability of our results across the population.

For the pilot study, this only assessed the impact of the intervention on a small number of participants. To try to reduce bias of outcomes, patients were recruited from a wide number of wards and specialties, so that one clinical team did not heavily influence the outcome of this study. Secondly, the pilot only took place in three West London hospitals. Therefore, it may be difficult to generalise this study to wider populations. However, to address this the development workshops recruited from a large national database, with participants attending from many regions in south England. Thirdly, the questionnaire only aimed to assess short term improvement in knowledge and understanding. It is not possible to determine from this whether there would be any medium to long term impact from the intervention. Furthermore, the reported lengths of discussion with healthcare professionals about infections and antibiotics may not of been accurate given the subjectivity of participant reporting. However, this was felt to be appropriate within this study given that we were assessing the participant perceptions of information provision and communication with healthcare professionals. Finally, this pilot study was not powered to demonstrate statistical significant between pre- and post-intervention questionnaires. I now plan to undertake a larger, controlled study to assess the short, medium, and long-term impact of this intervention of participants receiving antibiotics in secondary care.

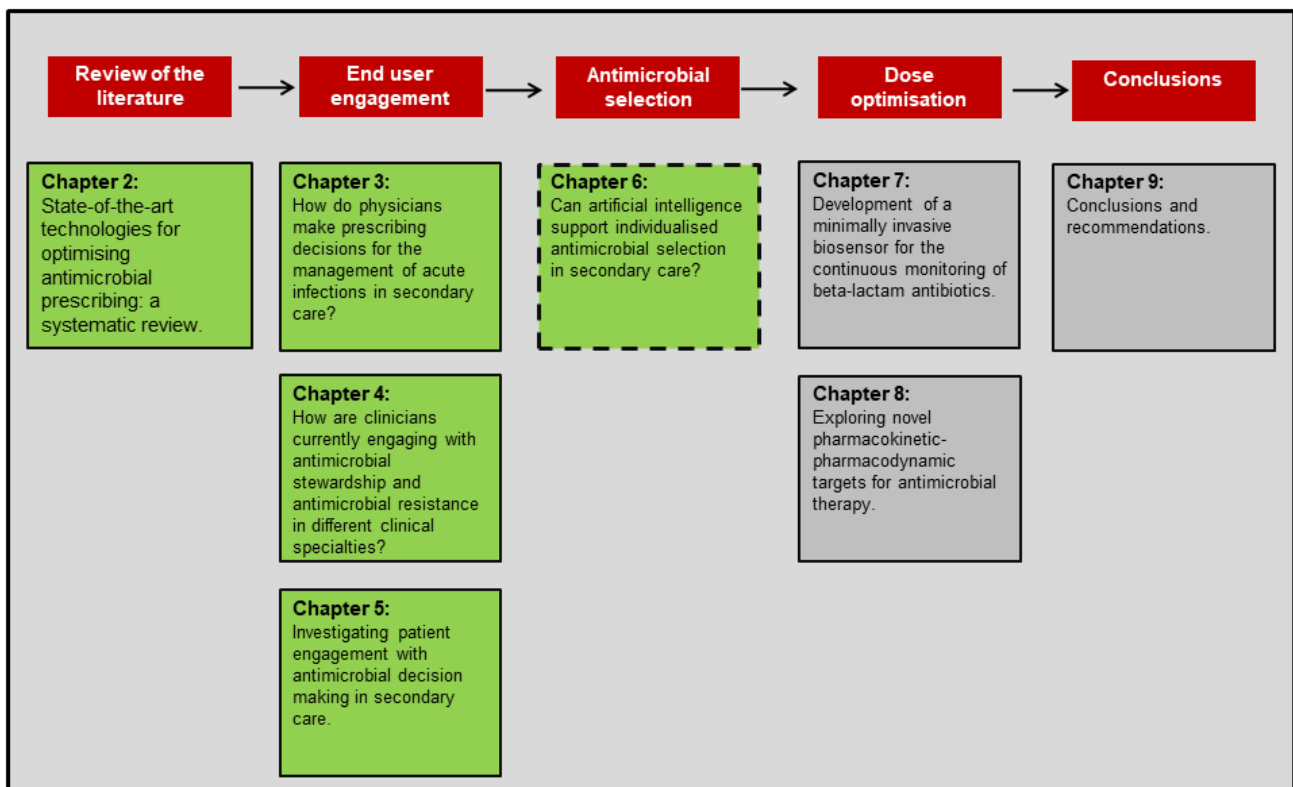
5.6 Conclusion and key messages

Within this study I have observed poor baseline knowledge of antibiotic therapy and infection management amongst in-patients being treated for infections. Patients are accepting of simple, individualised information leaflets that can be delivered during routine clinical interactions. Such an intervention, co-designed by patients and embedded within a clinical decision support system was able to significantly improve short term knowledge and understanding of antibiotic therapy and infection management within patients included in our study. This supports the need for greater emphasis on the development of patient-centred interventions to improve engagement with infections and their management in secondary care. Further work is required to quantify the short, medium, and long-term impacts of such interventions on patient knowledge, understanding, and attitudes towards antibiotic therapy.

CHAPTER SIX

6.0 Can artificial intelligence support individualised antimicrobial selection in secondary care?

Figure 18. Overview of thesis.



6.1 Introduction

With the global increase in uptake of EHR and CPOE systems [63–65], there has been an increased focus on electronic clinical decision support.

Firstly, when looking at promotion of evidence based practice, CDSS have been demonstrated to be enhance knowledge by providing person-specific and population level data to healthcare professionals to support their decision making [67]. This can improve the quality and safety of healthcare provided [67]. It is therefore, no surprise the reporting of CDSS for antimicrobial prescribing have increased in the last 20 years [66]. In line with this,

there have been a number of reviews of CDSS for antimicrobial prescribing, in addition to my systematic review that was published in *Clinical Microbiology and Infection* in 2017 [66]. However, where my review focused on identifying current gaps in the CDSS and the literature reporting them, other reviews have looked at evaluating the efficiency of such interventions [68,69,304,305].

An important consideration of CDSS development is how tools for antimicrobial prescribing can utilise the increasing quantity of routinely available electronic health data being generated by the expansion in development and use of EHR systems. As I outlined in *Chapter two*, the majority of CDSS do not utilise available data to support decision making. They are predominantly rule-based systems that adhere to guidelines and policy [66]. These tend to provide inflexible, population level recommendations to prescribers. However, the development of powerful processing capabilities and artificial intelligence provides an opportunity to utilise available data in a more precise manner, potentially facilitating better decision making around antimicrobial selection, through the delivery of individualised, evidence-based recommendations based on individual patient data.

Within the field of infection management, the role of artificial intelligence has been explored in several clinical areas to date [122–129,306–310] . These are summarised in **Table 18**, which outlines the outlines the current intelligent CDSS reported in the literature to support antimicrobial prescribing.

Table 18. Summary of clinical decision support systems for antimicrobial prescribing containing artificial intelligence reported in the literature.

	Setting	CDSS	Platform	Infrastructure	Study type	Primary outcome	Outcome met
TREAT [122–126,306]	SC, CC	Antibiotic prescribing	Standalone software	Causal Probabilistic Networks	i. DR ii. DE iii. DE iv. CS v. CS/cRCT vi. cRCT	i. – ii. ROC pred. BSI iii. Organism predication iv. Appropriate empirical therapy v. Appropriate empirical therapy vi. 180 day survival rate	i. – ii. Yes - ROC 0.68 (0.63-0.73) iii. Yes - ROC >0.5 for all organisms iv. Yes - Improved by 20% ($p<0.01$) v. Yes - Improved by 13% ($p<0.01$) vi. No - ITT – 3% lower ($p=0.2$)
Mullett [127,128]	SC	Antibiotic prescribing	Standalone software	Drug-bug logic matrix	i. CS ii. CS	i. – ii. Appropriate empirical therapy	i. – ii. Yes - 20% improvement ($p<0.01$)
Papageorgiou [129]	SC	Diagnosis and treatment of UTI	Integrated into EMR	Fuzzy-cognitive map software	i. DR	i. Agreement with guidelines	i. Yes - Predicted treatment appropriate in 87%
Evans [307]	CC	Antibiotic prescribing	Integrated into EMR	Decision-support logic	i. NCBA	i. Antimicrobial usage ii. Cost iii. ADR	i. Improved appropriateness ($p<0.01$) ii. Reduced total cost by \$35,283 and length of stay ($p<0.01$) iii. Reduced ADR (28 vs. 4, $p<0.01$)
ICONS [308–310]	CC	Antibiotic prescribing	Standalone software	Case-based-reasoning	i. DR ii. DR iii. DR	i. – ii. – iii. –	i. – ii. – iii. –

Legend: SC = secondary care; CC = critical care; CDSS = clinical decision support system; EMR = electronic medical record; DR = development report; DE = diagnostic evaluation; CS = cohort study; cRCT = cluster randomised control trial; NCBA = non-controlled before-after study; ROC = receiver-operator-characteristics; ITT = intention-to-treat; ADR = adverse drug reaction

6.1.1 Artificial intelligence for infection management

Artificial intelligence is defined as intelligence that is displayed by a machine [311]. This is compared to natural intelligence, which is displayed by humans and animals. There are a wide range of different approaches to artificial intelligence in healthcare, with machine learning and supervised machine learning being the two most common. Machine learning implies that a system is able to learn without being explicitly programmed or labelled [311,312]. This is compared to supervised machine learning tools that have the ability to infer a solution from data for which we know the potential outcomes (e.g. labelled data with defined outcomes) [311,312].

Within the field of infection, a number of artificial intelligence based CDSS have already been reported for a range of clinical applications. These range from empirical antimicrobial selection to better use of data for surveillance of healthcare associated infections [66,122–129,306–310,313,314].

The most notable example, with high quality data to support it is the TREAT system. TREAT used a CDSS incorporating Causal-Probabilistic Networks. Primary outcome measures were the appropriateness of empirical prescribing and 180-day survival following treatment, respectively [124,126]. Where primary outcome looked at the appropriateness of empirical therapy compared to detected organisms sensitivity, TREAT demonstrated a 9% improvement in appropriateness of prescribing [141]. However, once findings were adjusted for medical ward clustering and site, using multivariate regression, the findings did not reach significance (OR: 1.48, 95%CI; 0.95 - 2.29). This may have been partly due to under powering of the study, due to financial and time constraints, cited by the authors [141]. Furthermore, in the second trial assessing 180-day survival, failures were once again in ITT analysis, with significant benefits identified on per-protocol analysis (6% increase in survival, $p = 0.04$), suggesting that clinical uptake of interventions may once again be a contributing factor, along with appropriate powering of cluster-RCT's [126].

Causal-Probabilistic Networks, or Bayesian networks, are an attractive option for the utilisation of machine learning in medicine. They facilitate the incorporation of qualitative and quantitative variables to model uncertain knowledge [315]. However, a major problem of these types of knowledge-based systems are that they require the construction of hugely complex decision tree's. In the case of TREAT, this comprises over 6000 nodes [312]. This leads to many problems with transferring such tools into clinical practice, given that there is wide heterogeneity in clinical practice and data available [315]. Therefore, these types of tool are often challenging to develop, implement in practice, and require large amounts of information and technical skill to maintain [316].

Case-Based-Reasoning (CBR) is an alternative approach to the use of knowledge-based systems. CBR aims to solve a new problem by adapting a previously successful solution to the current problem encountered [316]. CBR aims to address many of the challenges associated with knowledge-based systems, including:

1. CBR does not require a defined model like Causal-Probabilistic-Networks. Therefore, data collection simply relies on the extraction of case histories.
2. Implementation of CBR requires the identification of significant features within a case, as opposed to creating an explicit model.
3. CBR facilitates large volumes of information to be managed by applying database techniques. Furthermore, it provides greater flexibility when working with sparse or incomplete data sets.
4. CBR learns through cases that it acquires, which makes maintenance of such systems easier than model-based systems.

CBR has been used widely in the field of medical decision making including antibiotic decision making in intensive care [308–310,312], radiology [317,318], psychiatry [319], chronic disease management [320–323], hepatology [324], and cancer [325].

In addition to antimicrobial selection, the use of supervised and unsupervised machine learning tools have also been explored for the prediction of events. This has predominantly focused on predicting the likelihood of infection using clinically available data. For example, TREAT has previously explored the ability of Causal-Probabilistic-Networks to predict the likelihood of blood stream infection and causative organism [123,125]. Other examples include the use of Decision Tree Classifiers using binary classification applied to blood test parameters to predict the diagnosis of *Chlamydia pneumoniae* [326] and hepatitis B/C virus [327]. These approaches have yielded mixed results, demonstrating an overall potential for supporting decision making using these avenues whilst also highlighting that no one technique currently has the ability to replace clinical decision making.

6.1.2 Framing the focus of clinical decision support in secondary care

The role of clinical decision support for antimicrobial prescribing in secondary care must be to augment the decision making of clinicians, who are often not experts in the field of infection, and thus often do not have an appreciation of AMS and AMR [145,196,328,329]. As I identified in *Chapter three*, there is a broad reliance on microbiology and infection specialist opinion for antimicrobial prescribing in clinical practice [168]. In terms of artificial intelligence, there is still much debate across medicine about how these types of tools should be deployed in clinical practice [330]. Given that there is a large reliance on the advice of microbiologists and infection specialities within clinical practice I would like to focus on whether it is possible to transfer “expert” knowledge to computer systems to provide another layer of decision support between this interface. This may create less of a burden from more routine calls on the specialist, whilst providing a more streamlined layer of support for the end-user. This approach will also facilitate the integration of such systems with current rules-based approaches to decision support. An example of this is the Imperial Antimicrobial Prescribing Policy, a mobile based application providing access to the Trusts

antimicrobial policy, which is currently implemented within the hospitals being evaluated within this study [331,332].

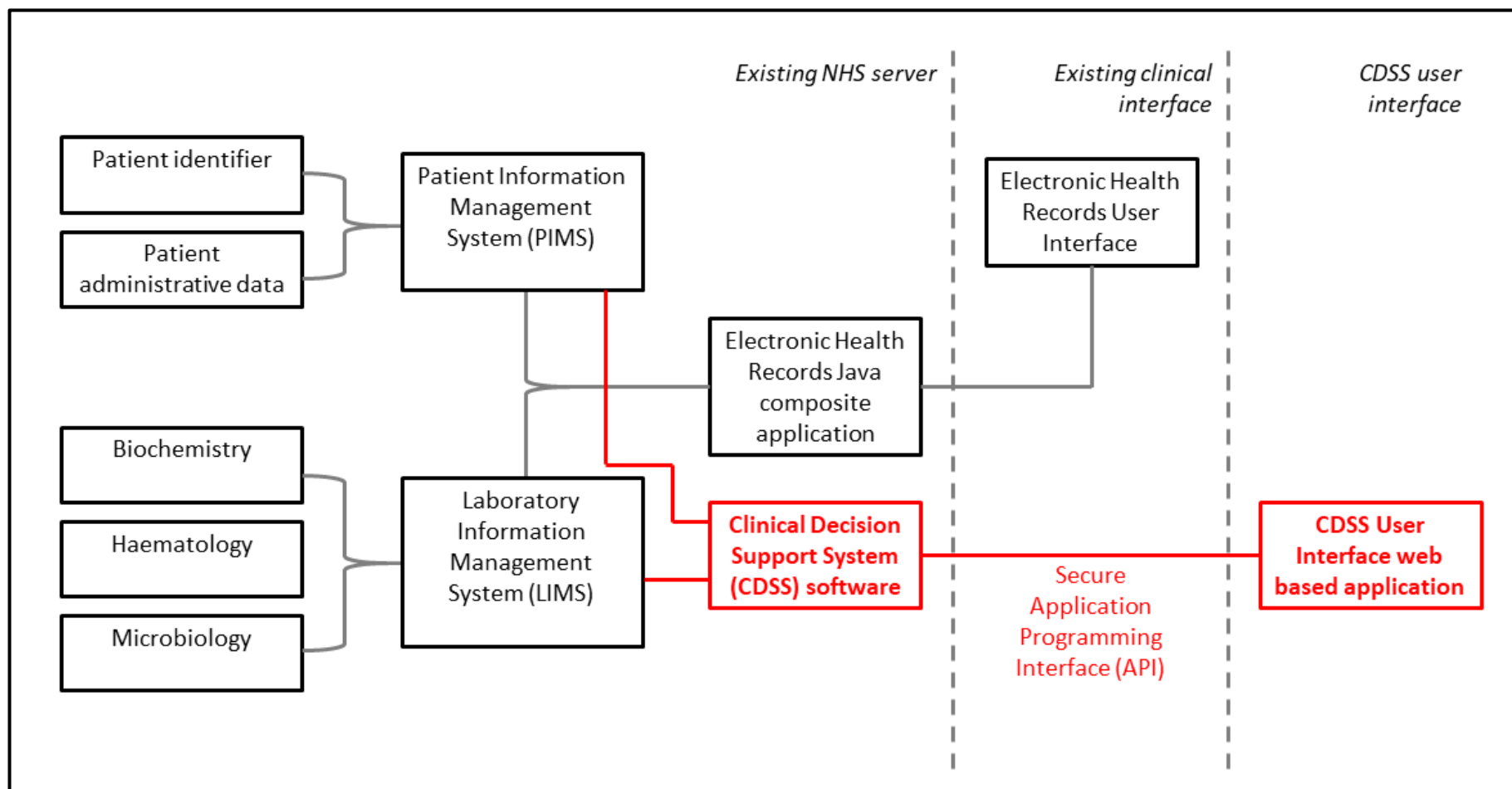
6.1.3 Current clinical decision support tool architecture

Within our research unit, previous work had been undertaken to explore the role of CBR to support antimicrobial prescribing in the intensive care unit [312,313]. This means that an overall system architecture was already available for me to build upon within my research.

Figure 19 summarises the hospitals existing electronic health records system with linkage to individual hospital databases. In red, I have mapped the developed architecture for the clinical decision support system to be investigated within this *Chapter*.

All programming within this study was performed by Mr Bernard Hernandez, a PhD student in the department of Electrical Engineering at Imperial College London, supervised by Dr Pantelis Georgiou. Further technical details outlining the system architecture, security features, and individual modules that make up the CDSS can be found in technical **Appendix 8** (*section a8.1*).

Figure 19. Summary of current electronic health record system architecture and clinical decision support system for investigation within this Chapter.



6.2 Chapter objectives

The aim of this chapter was to investigate whether artificial intelligence can provide enhanced decision support for making personalised decisions during antimicrobial management in secondary care.

Therefore, the modules developed and evaluated would provide intelligent decision support to prescribers, mimicking infection specialist support that is strongly relied upon by prescribers within this setting [168]. Based on the review of decision making processes in *Chapter three*, I chose to focus on providing personalised support in two individual areas;

- (i) Predicting the likelihood / severity of infection, and
- (ii) Individualised antimicrobial selection [168].

The objectives of this Chapter were:

1. To identify key variables to support the development of intelligent decision support tools for antimicrobial selection in secondary care.
2. Explore the potential impact of supervised machine learning tools for providing support in predicting risk of infection using a minimal number of routinely available haematological and biochemical variables.
3. Explore the potential impact of an optimised Case-Based-Reasoning (CBR) algorithm on antimicrobial prescribing in the general medical setting.

This *Chapter* would aim to individually develop and evaluate supervised machine learning tools and a CBR algorithm using routine clinical data. Clinical use of the CDSS interface and end-user engagement was beyond the scope of the *Chapter*.

There are a number of specific desirable characteristics I aimed to achieve during the development and evaluation of the supervised machine learning tools for inferring the likelihood of infection. These are based on the ability of the tool to use routinely available data to make accurate predictions about the likelihood of infection in the individual patient.

This tool aimed to work for the majority of individuals presenting with potential infection (based on available clinical data) and would be accessed based on demonstrating good to excellent predictive capabilities [314,333]. This would be determined by using the receiver-operator-characteristic area-under-the-curve (ROC) [334–336]. I would aim to demonstrate $ROC > 0.80$ during evaluation of the tool in clinical practice.

For the CBR algorithm, the primary aim was to demonstrate the ability of the system to be able to function across the complex, heterogenous case mix that makes up secondary care. I also aimed to achieve a better understanding of the appropriate methods for creating and curating case-bases within this setting [337–339]. This would provide insight into the potential benefits and limitations of deployment of such a system within this clinical setting [340].

6.3 Methods

6.3.1 Study setting

The study utilised routinely available data from ICHNT. Working with colleagues in the department for Electrical and Electronic Engineering at Imperial College London, I aimed to explore a number of core artificial intelligence techniques for replicating “expert thinking” within a computer system. This aimed to provide more intelligent, dynamic decision support than is often provided by guidelines and policy, hence optimising the practice of EBM.

My aims for the study were to refine the system for use across secondary care, characterising its strengths and weaknesses, and validating the approach for deployment in the hospital setting. For accuracy and confidence in the results, I felt that it was initially important to use a defined patient cohort where appropriateness of recommendations could be accurately corroborated. Therefore, for initial testing and validation of the system, I obtained data describing a cohort of 130 patients who had been diagnosed with *Escherichia coli* (*E.coli*) blood stream infections (BSI). This cohort contained prospectively collected microbiology data with *in-vitro* antimicrobial susceptibility results available. This would ensure that the assessment of appropriateness of therapy could be objectively assessed. This meant that expert opinion or guideline recommendations will not be relied upon, as these are often associated with wider heterogeneity in terms of outcome reporting [32].

For real-world evaluation following investigation of the systems using the *E.coli* dataset, all clinical cases were identified and data collected by myself. Dr Luke Moore (consultant in Infectious Disease & Microbiology) and Ms Orla Geoghegan (Antimicrobial Pharmacist) provided support with the assessment of prescribing recommendations and comparison with *in-vitro* susceptibility data and local hospital prescribing policy.

6.3.2 Defining variables commonly used during infection management

For the development and refinement of the artificial intelligence algorithms to be used within this *Chapter*, I utilised data generated during *Chapter three*. Use of this data allowed me to identify key variables that are used during decision making for antimicrobial prescribing by physicians. To map out the factors associated with decision making, individual codes from the transcripts described were ranked and quantified for all interviewees. This allowed comparison and weighting of individual factors that were reported to influence the decision making process. These factors were ranked based on the mode from the order that they were reported by individual physicians describing their approach to decision making. This was used to depict a commonly reported pathway for decision making surrounding infection management in secondary care. Furthermore, all sub-categories emerging within these themes were assessed and given a weighting variable based on the frequency they were mentioned over the course of the interviews. This information was tabulated to allow in-depth comparison of common variables.

Identified variables were then compared to available data that was electronically available at the time of algorithm development to inform the design and architecture of decision support modules that were developed. This formed the basis of data that were available to support the development and evaluation of both types of artificial intelligence tool.

6.3.3 Supervised machine learning tools for the prediction of positive microbiology

6.3.3.1 Data curation, algorithm training, and cross-validation

The focus of this study was to evaluate the clinical potential of a supervised machine learning tool to infer the likelihood of development of a positive microbiological culture and therefore, infection. The detailed method of training and algorithm development is described in *BMC Medical Decision Making* [314]. Briefly, to train the supervised machine learning algorithms clinical microbiology data were extracted from the central microbiology records for

all clinical samples received by North West London Pathology laboratory from 2009 to 2015. Blood test parameters were extracted for all patients within ICHNT during this time period. To select variables for linkage to microbiology records a three-step approach was taken. Firstly, variables reported by physicians as being important during infection management were identified from the ranking of variables reported in *Section 6.4.1*. Secondly, two infection specialists were asked to review these variables and corroborate the findings. Finally, relevant literature was reviewed to provide further evidence in support of these selected variables.

Six variables were eventually selected based on their availability electronically and their use in infection management. These variables were C-reactive protein (CRP), white cell count (WCC), creatinine (Cr), alanine aminotransferase (ALT), bilirubin (BIL), alkaline phosphatase (ALP) [326,327,341–345]. Lactate was also felt to be an important blood marker for inclusion, however, at the time of development this was not routinely available for the majority of patients within the electronic database [346–348]. Furthermore, physiological parameters (heart rate, respiratory rate, temperature, blood pressure, oxygen saturation) were not available electronically [166,349–351]. Following selection of the variables, individual patient profiles were linked to microbiology data.

Linkage was performed in the following way. Initially all individual patient blood test profiles ($n = 1,251,830$) were labelled as “no culture”. For individuals who had a positive microbiology results ($n = >350,000$) within 48-hours of a blood test result, these were then labelled as “positive culture”. If further blood science results for “positive culture” individuals were available before or after the 48-hour window, but in the same admission, these were excluded. This yielded two groups of patient profiles that were labelled either “no culture” or “positive culture”. Moving forwards, although strictly speaking the tools infer the likelihood of positive versus no microbiological culture, we took this as a proxy indicator for the likelihood of infection. Therefore, from here on, these definitions will be used interchangeably.

Curation of the dataset was then performed prior to further processing to remove corrupt data. Corrupt data can be defined as erroneous, imprecise, or missing data [312,352,353]. It has been demonstrated to be important to address these issues within machine learning to ensure that predictions by the system remain robust [354]. This stage focused on:

1. **Removal of outliers:** This has been demonstrated to significantly increase the robustness of machine learning tools [354]. In this study, outliers are likely to be due to human error in data input or erroneous results secondary to technical factors such as diagnostic accuracy or contamination. We defined outliers using the interquartile range (IQR) rule, which takes any variables outside of $1.5 \times \text{IQR}$ to be an outlier removing them from the dataset [354].
2. **Missing data:** Within this study we evaluated the impact of missing blood science variables on the accuracy of the tool during cross validation as outlined below. Of the six variables, the system provided stable results providing that ≥ 4 variables were present [314]. For training however, patient profiles must contain all 6 variables.
3. **Class imbalance:** Invariably, there was likely to be a class imbalance in numbers of individuals between those with “no culture” and “positive culture”. To address this, an approach called Synthetic Minority Over-Sampling Technique was used [354]. This approach combines under sampling of the majority classifier and oversampling the minority classifier group and has been demonstrated to enhance the performance of data that uses this [354].

Following curation of data, several different supervised machine learning tools were developed and evaluated through cross-validation to allow exploration of associations between variables and group classifications [314]. These were:

1. Gaussian Bayes Naïve algorithm
2. Decision Tree Classifier
3. Random Forest Classifier

4. Support Vector Machine with Platt Scaling to allow estimation of probabilities on the binary classifier [354].

The final training dataset consisted of 160,203 patient profiles for use in cross-validation. A 10-fold cross-validation was performed with the sensitivity, specificity, and area-under-the-receiver-operator-curve (ROC) estimated for models [314]. There was also a hold-out set, of cases that had not been seen during training or testing in cross-validation that was used for final testing [314]. Following this evaluation, the Support Vector Machine (SVM) and Gaussian Bayes Naïve (GNB) classifiers were selected as the optimal algorithms for evaluating the clinical utility of this approach [314]. This was because the SVM had the best performance overall with ROC of 0.83 and the GNB algorithm had similar performance with ROC of 0.82, but is a much more simplistic model for implementation than SVM [314]. Comparison of GNB and SVM will be explored further in *Section 6.5*.

6.3.3.2 Evaluation of supervised machine learning using clinical data

Following cross-validation, it was important to evaluate the actual predictive power of the developed tool using real-world data. For this study, I took a two-stage approach.

Stage 1:

Initially, I constructed a dataset using retrospective data. This test set contained blood test parameters for individuals presenting who subsequently went on to be diagnosed with:

- a. **Confirmed blood stream infection:** This data was obtained from randomly sampling half of the patients making up the *E.coli* BSI data set described in *Section 6.3.1*.
- b. **Individuals with non-infective presentations:** Matched for age and gender, identified using the electronic health record system at ICHNT over the same time period and clinical areas as patients in the *E.coli* BSI cohort.

Stage 2:

Following this evaluation, the second stage involved a prospective, longitudinal evaluation. This was undertaken by myself, identifying individuals at their presentation to hospital via the ED. Individuals were grouped into those with high clinical likelihood of infection (n = 20) and those with low clinical likelihood of infection (n = 20) upon presentation. These were admitted on the week of 29th January 2018 – 3rd Feb 2018.

For all individuals included within this study data collected included demographic data, clinical presentation and parameters, microbiology, treatment, and outcome data.

For both stages of the investigation, individuals presenting blood test results were input into the SVM and GNB algorithms to obtain individual estimated likelihood of microbiological culture (and therefore infer the likelihood of infection). Sensitivity and specificity were compared by assessing the ROC for the algorithms. In the retrospective dataset (stage 1), individuals from the *E.coli* BSI cohort were labelled as “infected” and those with no evidence of infection labelled as “non-infected”. For the prospective cohort (stage 2), both high and low likelihood of infection groups were followed throughout the course of their in-patient stay. Labels (“infected” or “non-infected”) were applied on discharge or death.

For statistical analysis, distributions and medians were compared using non-parametric approaches (Mann-Whitney U test). Chi-squared with Yates correction or Fishers Exact test were used to compare cases and controls, when appropriate. Statistical analysis was performed using SPSS software and figures were plotted using R and Igor Pro 7.0.

6.3.4 Case-Based-Reasoning for antimicrobial selection in secondary care

Following adaption of the CDSS for use across secondary care, I wanted to evaluate the prescribing recommendations being made by the CBR module in a robust and objective manner. This would also take a two-stage approach.

- **Stage 1:** Using a pre-defined, narrow dataset with objective outcome measures (*in-vitro* susceptibility data) to compare the recommendations made by the system against.
- **Stage 2:** Undertaking a prospective pilot study, using the CBR algorithm on real-cases encountered by myself over a 4-week period in October-November 2017. Cases would be identified and input by myself during clinical commitments, covering Hammersmith Hospital wards out-of-hours. Data were input at the time (or close to) attending to the patient using the web-based user interface designed for the CDSS. Outcomes of therapy were then updated prospectively. No recommendations made by the system were acted upon in these cases, with the objective being purely observational at this point.

As described in *section 1.3*, the measure of appropriateness of antimicrobial recommendations tends to be heterogenous, making valid appraisal and comparison between studies challenging [32]. Therefore, to ensure that both training and testing datasets for use in this study were representative of each other and allowed for robust evaluation of decisions made; I opted to use a focused approach for evaluating the appropriateness of recommendations being made during stage 1 of the study [353].

This stage would utilise the *E.coli* BSI dataset described above in *section 6.3.1*. Data from this dataset of patients diagnosed with *E.coli* BSI were interrogated. Where required, further information was extracted from individual patient electronic health records. Patient demographics, clinical parameters, treatment history, and outcomes of therapy were extracted.

For the 130 individuals within the *E.coli* BSI dataset, I extracted all variables required by the CBR when available. A test dataset was randomly created extracting 15% of individual cases from the data. The remaining 85% of cases were used to create the CBR case-base (or training set). The training set was made up of parameters available at the individual's

presentation with infection, when empirical antimicrobial therapy was prescribed. These variables were added to the system to create a case library for algorithm training.

The CBR cycle, is dependent on the case-base to provide prior knowledge from which it assesses and adapts previous knowledge to make recommendations for the current, new cases. This was described by Aamodt and Plaza to comprise four key stages [337]:

- i. Retrieval of the most similar cases to the new problem presented to the system.
- ii. Reuse of the case(s) as the system attempts to solve the new problem.
- iii. Revision of the proposed solution if there is no satisfactory resolution of the problem using previous cases only.
- iv. Retention of the new solution as part of a new case within the CBR case base.

Within the CBR algorithm, four types of knowledge must also be considered and defined, as described by Richter [339]. These four knowledge domains are vocabulary, similarity measures, adaption knowledge, and the cases themselves.

Vocabulary describes the types of knowledge that define cases. The vocabulary within the system has the dual function. It must facilitate the retrieval of cases that contain useful solutions to the presented problem. Therefore, it must be discriminative whilst also preventing the retrieval of too few cases. Richter advises that the vocabulary included within case bases must also be chosen in anticipation of the expansion of such a base in the future [339]. This is particularly relevant to my study, where future real-world testing is likely to present a significantly more heterogenous range of cases. Although all possible variables were initially included in the analysis, it was apparent that for this data set several were either redundant or too discriminative within this cohort [312,337,339,355–357]. A sequential least squared programme was used to describe the relative weighting applied to each variable by the CBR algorithm during decision making process for this case base [312,337,339,355–357].

Similarity measures describe the knowledge used by the system to ensure the most appropriate case-retrieval. Within this case, I chose for us to keep a *K-nearest-neighbour* (KNN) approach for similarity matching. KNN, is widely used in CBR and other machine learning [312,337,339,355–357] and has been demonstrated to be highly effective [338,339]. It has the advantage over many other approaches as it is a *non-parametric, lazy learning* algorithm. Therefore, this means that a normal distribution is not assumed, facilitating working with sparser and non-Gaussian datasets. Furthermore, *lazy* implies that this type of algorithm does not need large amounts of training, as the whole dataset is searched upon presentation with a new case. This has the offset, that as the case base grows, retrieval time, required processing speed, and required memory may all increase [338,339].

Adaption knowledge describes the ability of the system to be able understand the differences between similar cases retrieved and the new problem presented in terms of how this effects the end solution (i.e. the outcome). For this system, given the nature of outcome being reported and difficulties in accessing the appropriateness of therapy in real-world situations, I opted to lock the case base and prevent the system from adapting without prior review of new cases and solutions by the research team. This is a common approach taken in situations where case mistakes can have significant consequences (such as inappropriate treatment or death) and may therefore effect the reliability and the end-users confidence in the system [312].

Finally, **cases** contain information about solved problems and thus represent the knowledge that the CBR algorithm has developed during training and testing. Cases are determined mainly by the vocabulary used to describe them and in many cases are carefully selected to balance the need for an adequate number of cases with appropriate coverage of potential possibilities. This is important in terms of reducing retrieval times, memory requirements, and improving the systems performance [312]. Cases are required to have three core characteristics: A description of the problem, the proposed solution, and the outcome [337,339,355]. For this study, cases were entered based on empirical prescribing

recommendations and outcomes were based on a combination of *in-vitro* susceptibility data, whether therapy was amended upon expert review, and mortality whilst receiving therapy.

For stage 1, the test data set was input into the CBR algorithm and recommendations made by the system were provided in two separate formats.

1. Firstly, recommendations were provided for each possible antimicrobial agent based on the similarity to the entire case base, termed “grouped recommendations”.
2. Secondly, individual cases were matched with the treatment from the most similar case recommended, termed “case recommendations”.

For evaluation of the recommendations provided by the CBR algorithm, antimicrobial recommendations were compared to clinical practice, local guidelines for therapy, and *in-vitro* susceptibility data for isolated organisms. The spectrum of the antimicrobial recommended was estimated to allow comparison between clinical practice and CBR. This was estimated by using a validated estimate of the spectrum of agent, the modified Madras-Kelly Score [358,359].

The Madras-Kelly Score was proposed in 2014 as a numerical method of measuring antimicrobial spectrum of antibiotic regimes as part of stewardship intervention evaluation [358]. Each antimicrobial (27 included) is given a spectrum score out of 60 (theoretical maximum) based on the susceptibility profiles of 19 commonly encountered microbial species in clinical practice [358]. This was recently adapted by Gerber and colleagues, with the scoring simplified to a theoretical maximum of 14 [359]. If an individual is on combinations of therapy, then the overall Antibiotic Spectrum Index (ASI) for the combination can be calculated using a scoring table provided by the authors [359]. For example, ceftriaxone, a third-generation cephalosporin, has an ASI of 5. Amikacin, a aminoglycoside, has an ASI of 6. When used in combination, the ASI for ceftriaxone + amikacin is 8, given that there is overlap in the spectrum of organisms covered by these agents [359]. Although

this data is not locally driven and estimations are based on historical susceptibility data, it has been demonstrated as a valid method for assessment of antimicrobial spectrum in the hospital setting, such as evaluating de-escalation of therapy in pneumonia [358–360].

To ensure that local policy and experience was taken into consideration, an infectious disease and microbiology specialist and an antimicrobial pharmacist reviewed the cases and recommendations independently of each other. They were asked to compare the findings to *in-vitro* susceptibility results and rank recommendations and actual practice as either “optimal”, “appropriate but suboptimal”, and “inappropriate”.

After evaluating the CBR using the “real-world prescriptions” within the case-base an “ideal” case base was created for the 85% training dataset using the best-practice recommendations provided by expert review of *in-vitro* susceptibility results. This was based on a prototype case base approach and aimed to prescribe the most appropriate narrow spectrum agent possible for each case (determined by independent review of cases by myself, the infection and microbiology expert, and antimicrobial pharmacist) [309,316,321,353,356]. This case base was then used to test the 15% test set described above and recommendations. Its aim was to investigate whether the use of an optimised case-base would impact on the recommendations made by the system when compared to the original case-base used within this study.

For phase 2, the prospective evaluation on the wards, an alternative approach was taken. Given the potential for slow retrieval times, high memory requirements, poor system performance with large case-bases and the positive results obtained during phase 1 [312]; a “prototype” case base was generated, based on local antimicrobial policy. This was used as the case-base to provide recommendations for prospective cases collected by myself. Analysis was performed in the same manner as phase 1, described above. The desired endpoint was to provide recommendations on how the system could be adapted moving

forwards to improve the accuracy, whilst maintaining oversight of the curation process so that recommendations remained in line with local prescribing policies.

6.3.6 Ethics

Ethical approval for this study was granted by London-Chelsea Regional Ethics Committee (REC: 17/LO/0047). All CDSS features were developed in line with the current directives of the Data Protection Act 1998, The Privacy and Electronic Communications Directive 2003, and the EU Directive 2006/24/EC for data retention [361,362]. Internally, Caldicott approval was granted by ICHNT Information Governance (Ref. 23307 / 726505) for data transfer and informational relationships.

6.4 Results

6.4.1 Identification of variables for inclusion in the system

As described in *Chapter three*, a stepwise process was identified that described individual physician approaches to decision making during infection management. For the identification of core variables to be utilised within the CBR algorithm, data from steps 1 (physiological parameters) to step 4 (determining the severity of infection) were utilised.

For example, during the assessment of physiological parameters temperature (reported by 19/20 [95%] participants) was the most important factor. During stage two, reported symptoms (18/20, 90%) and triangulation with signs found during clinical examination (18/20, 90%) were highly ranked. On review of investigation results a range of blood test results and radiological investigations were considered with C-reactive protein (CRP) reported as the most important results (20/20, 100%). Important in determining the severity of infection included the individual physicians clinical judgement (18/20; 90%) with support from more objective measures such as antimicrobial *in-vitro* susceptibility of current or previous microbiology (15/20; 75%) and criteria such as the “septic six” or “SIRS criteria” (9/20, 45%).

Table 19 outlines the core parameters and reported importance of these by individuals participating in interviews in *Chapter three*. These identified variables were broken down into potential variables that would be available for automatic extraction from electronic health records or manual input by physicians into the CDSS.

Table 19. Selection of variables identified within the decision mapping process for use within the clinical decision support system for antimicrobial selection.

Category	Variable	Data type	Currently available in CDSS	Label / Range	Included
Patient information	Age	Extract	Yes	0-110	Yes
	Gender	Extract	Yes	Male / Female	Yes
	Ethnicity	Extract	Yes	<String>	No
	Name	Extract	Yes	<String>	Yes
	Admission date	Extract	Yes	DD/MM/YYYY	Yes
	Current date	Extract	Yes	DD/MM/YYYY	Yes
	Allergies	Drop down OR Free text	Yes	Antibiotic name <String>	Yes
Physiological parameters	Oxygen saturation	Number	No	0-100	Yes
	Temperature	Number	Yes	25-43	Yes
	Heart Rate	Number	Yes	0-250	Yes
	Blood Pressure	Number	Yes	Systolic / 0-250 Diastolic / 0-150	Yes No
	Respiratory Rate	Number	Yes	0-50	Yes
	Glasgow Coma Scale	Number	No	3-15	No
	Fluid balance	Number	No	-5000 - + 5000	No
Localising infection	Clinical symptoms	Free text	No	<String>	No
	Signs on examination	Drop down for: i) Chest auscultation ii) Abdominal palpation iii) Heart sounds	Yes	i) Crackles / Crepitations / Dull / Clear / Wheeze ii) SNT / Tender / Rigid / Ascites iii) Normal / Murmur (new) / Murmur (old)	Yes Yes No
	Likely infection site	Drop down OR Free text	Yes	<String>	Yes
Investigation results	C-Reactive Protein	Extract	Yes	0-550	Yes
	White Cell Count	Extract	Yes	0-55	Yes
	Full blood count	Extract	Yes	0-210	Yes
	Liver Function	Extract	Yes	ALT: 0-10000 ALP: 0-2000	Yes Yes
	Renal Function	Extract	Yes	Cr: 0-1000	Yes
	Lactate	Number	Yes	0-12	Yes
	Microbiology	Extract	Yes	Organism Susceptibility profile Site of culture	Yes Yes Yes
Radiology	Drop down - CXR	Yes	Clear / Consolidation / Effusion / Oedema	Yes	
Determining severity	SIRS criteria*	Extract	No	0-6	No
	In-vitro susceptibility profiles	Extract	Yes	See above	Yes

Miscellaneous parameters (not identified in chapter two)	Indwelling lines	Tick box	Yes	Urinary catheter	Yes
				CVC line	Yes
	Airway management	Drop down	Yes	Own / Trachy / Intubated / NIV	Yes
	HIV status	Tick box	Yes	HIV positive	Yes
	Diabetes	Tick box	Yes	Diabetic	Yes
	Pregnant	Tick box	Yes	Pregnant	Yes
	Renal support	Drop down	Yes	None / Dialysis / Transplant / CVVH	Yes
	Inotropic support	Tick box	Yes	Yes	No
	Hospital No.	Extract	Yes	<String>	Yes
	NHS No.	Extract	Yes	<String>	Yes
	Ward name	Extract	Yes	<String>	Yes
Outcome	Antibiotic prescription	Drop down	Yes	Antibiotic selection	Yes
	Successful?	Drop down	Yes	No / No – escalated / Yes – completed / Yes – de-escalated / Unknown	No
	Death	Tick box	Yes	Yes	No
	Reason for death	Free text	No	<String>	No

Legend: CXR = chest x-ray; SIRS = systemic inflammatory response syndrome; SNT = soft, non-tender; CVC = central venous catheter; Trachy = tracheostomy; CVVH = continuous veno-venous haemofiltration; NIV = non-invasive ventilation; HIV = human immunodeficiency virus

6.4.2 Supervised machine learning for prediction of microbiology culture

6.4.2.1 Stage 1: Retrospective evaluation with confirmed cases

Firstly, 76 individuals with positive blood cultures (labelled “infected”) were matched to 75 individuals in the control group (labelled “non-infected”); both groups had similar age (66 vs. 63 years, $p = 0.92$) and gender (36/76 male vs. 36/75 male, $p = 0.92$) distributions. Of the six variables used, four had similar distributions between both groups. These were:

- i. ALP with a median (IQR) of 78 (73 - 124) units / L in the infected versus 86 (67 - 111) units / L in the non-infected cohort ($p = 0.49$).
- ii. ALT with a median (IQR) of 21 (19 - 31) units / L in the infected versus 20 (13 - 38) units / L in the non-infected cohort ($p = 0.90$).
- iii. BIL with a median (IQR) of 11 (9 - 20) mg / L in the infected versus 10 (7 - 18) mg / L in the control cohort ($p = 0.24$).
- iv. Cr with a median (IQR) of 98 (70 - 152) mg / L in the infected versus 77 (66 - 125) mg / L in the non-infected cohort ($p = 0.11$).

The remaining variables (CRP and WCC) were observed to be significantly different between the two cohorts. Median (IQR) CRP was 89 (9 - 205) mg / L in the infected and 8 (2.3 - 13.4) mg / L in the non-infected cohort ($p < 0.01$). Median (IQR) WCC was 11.9 (7.4 - 15.5) $\times 10^9$ / L in the infected and 8.4 (6.5 - 10) $\times 10^9$ / L in the non-infected cohort ($p < 0.01$).

Figure 20 demonstrates the distributions of likelihood estimates for both the control and infected groups using both the SVM and GNB algorithms. The estimated likelihood distributions were significantly different for both algorithms. For the GNB algorithm, those with BSI had a median (IQR) likelihood estimate of 1.000 (0.99 - 1.00). The control group had a median (IQR) likelihood estimate of 0.053 (0.02 - 1.00) ($p < 0.01$). Using the SVM algorithm, the infected group had a medium (IQR) estimate of 0.820 (0.82 - 0.83) and the control group 0.49 (0.21 - 0.82) ($p < 0.01$).

The ROC AUC for the GNB and SVM algorithms were 0.82 (95%CI: 0.75 - 0.89) and 0.75 (95%CI: 0.67 - 0.83), respectively (**Figure 21**).

Figure 20. Distribution of likelihood estimates using a Gaussian Naïve Bayes and Support Vector Machine Algorithm for patients who presented with confirmed blood stream infection and those presenting with non-infectious syndromes.

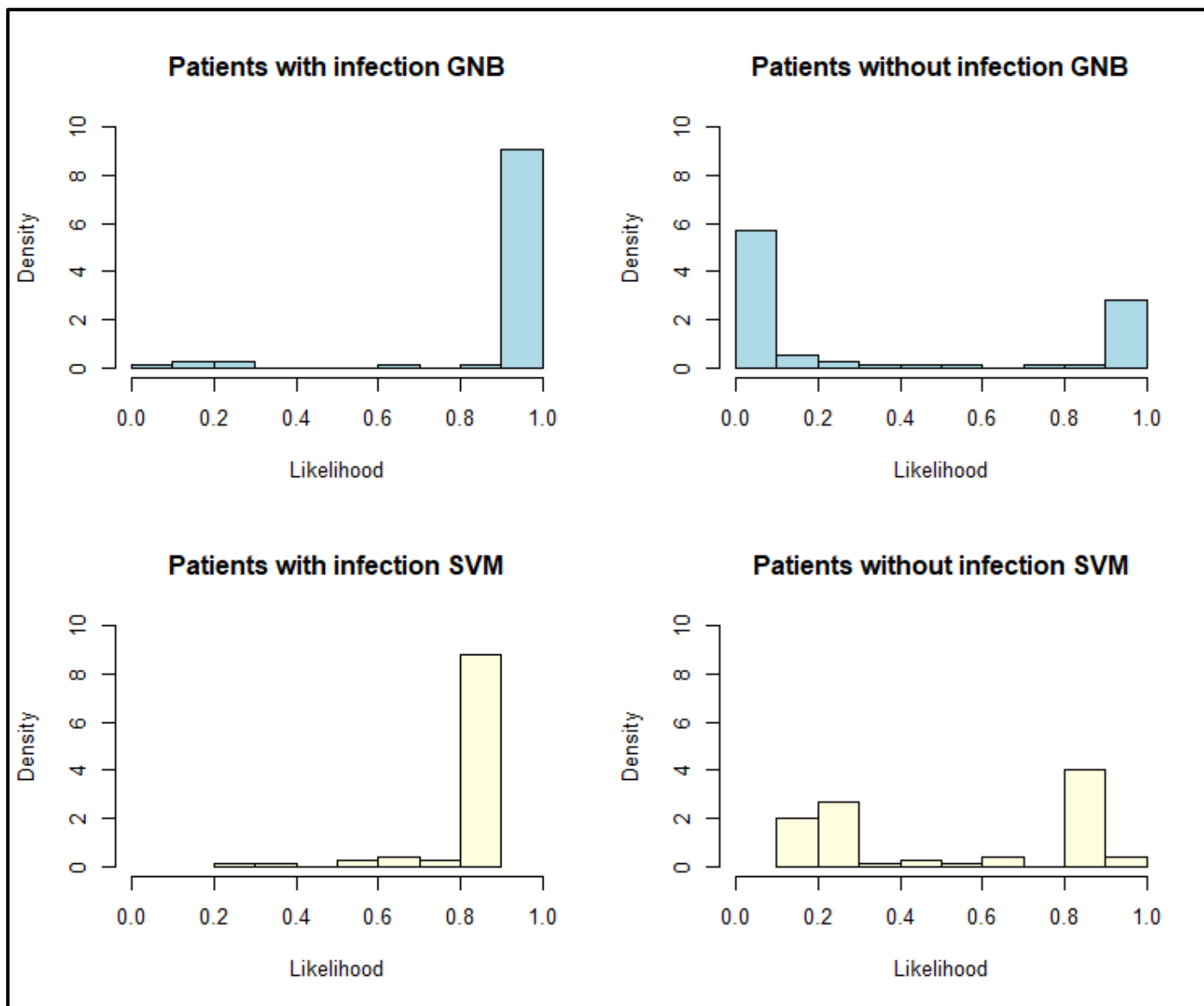
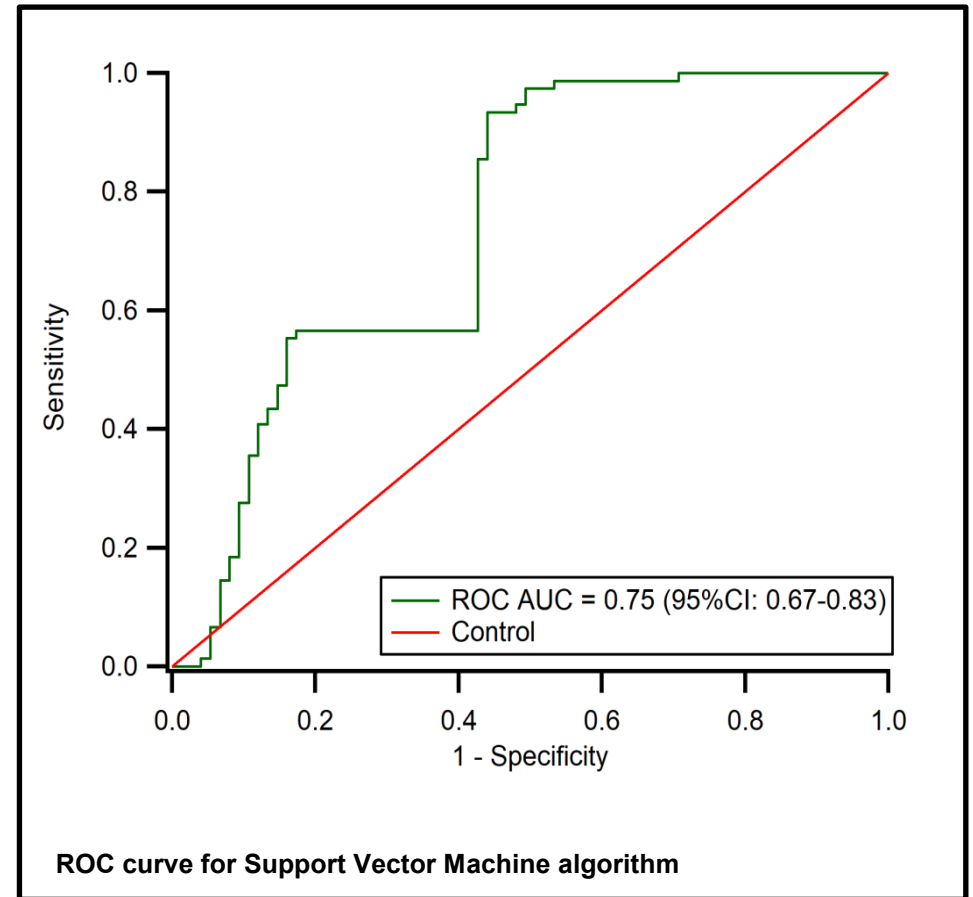
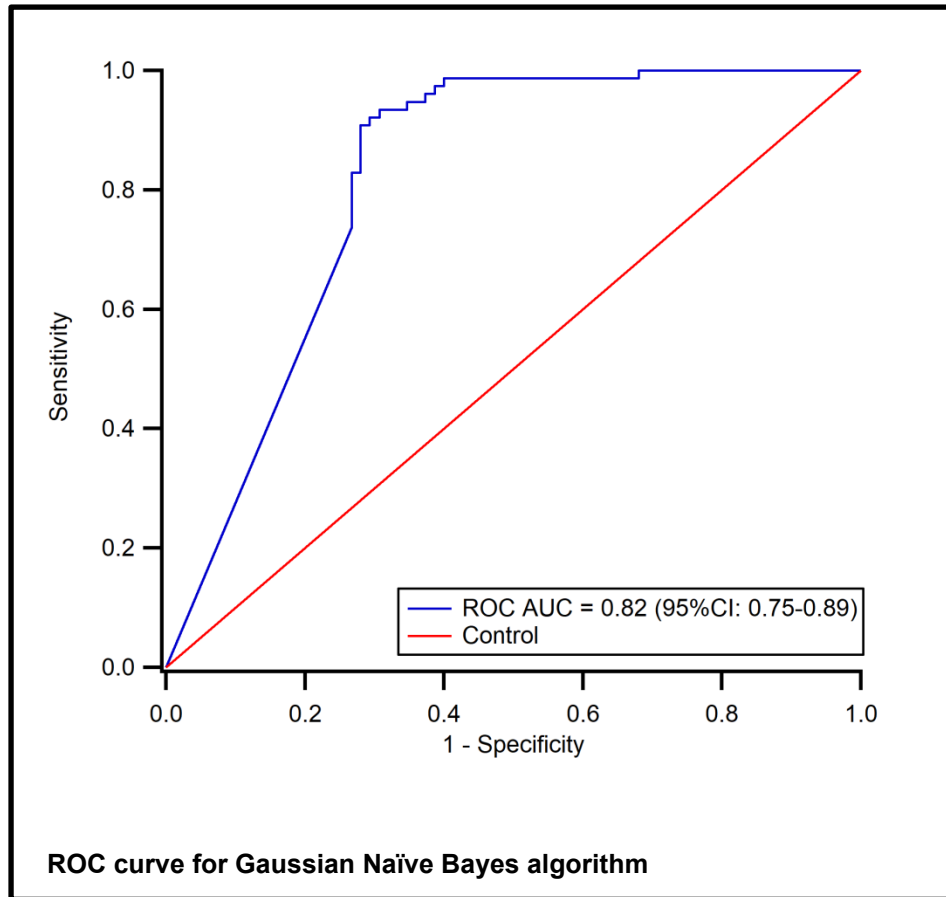


Figure 21. Receiver-Operator-Characteristic (ROC) for evaluation of likelihood estimates for patients who presented with confirmed blood stream infection and those presenting with non-infectious syndromes.



6.4.2.2 Stage 2: Prospective evaluation

On comparison of individuals presenting to the ED with suspected infection versus those with other likely diagnosis; the suspected infection group were slightly older at 78 (65 - 86) years versus 65 (54 - 83) years ($p = 0.81$). Gender distribution was similar with 7/20 males in the suspected infection group and 8/20 males in the control ($p = 0.71$).

Within this cohort four variables had similar distributions (median (IQR)) between groups:

- i. ALT was 18 (10 - 28) units / L in the infection and 24 (12 - 36) units / L in the control group ($p = 0.41$).
- ii. BIL was 9 (7 - 27) mg / L in the infection and 11 (7 - 11) mg / L in the control group ($p = 0.95$).
- iii. Cr was 89 (67 - 163) mg / L in the infection and 92 (73 - 124) mg / L in the control group ($p = 0.88$).
- iv. WCC was 12.5 (7 - 16) $\times 10^9$ / L in the infection and 9 (7 - 11) $\times 10^9$ / L in the control group ($p = 0.13$).

Both CRP and ALP had statistically different distributions on comparison. CRP had a median (IQR) of 111 (51 - 245) mg / L in infected and 8 (2 - 17) mg / L in the control group ($p < 0.01$). ALP was less significant with a median (IQR) of 101 (81 - 146) units / L in the infected and 78 (66 - 115) units / L in the control ($p < 0.05$).

Figure 22 demonstrates the distributions of likelihood estimates for the groups with both high and low clinical likelihood of infection at presentation using both the SVM and GNB algorithms. The median (IQR) estimated likelihood distributions were significantly different for both algorithms. For the GNB algorithm, those with high potential for infection had a likelihood estimate of 1.000 (0.99 - 1.00). The low clinical likelihood group had a likelihood estimate of 0.08 (0.02 - 0.51) ($p < 0.01$). Using the SVM algorithm, the high likelihood group had a medium (IQR) estimate of 0.820 (0.82 - 0.84) and the low likelihood group 0.60 (0.21 - 0.82) ($p = 0.02$).

Table 20 summarises the individual cases likelihood scores, microbiological investigations that were performed (and returned positive within 48 hours of the likelihood estimate). Follow up to discharge or death is also described, including whether individuals were treated for infection. Of the 20 individuals with high likelihood of infection, 20/20 (100%) were treated for infection. One individual (ID 3) was treated as a suspected infective exacerbation of COPD, however, no firm diagnosis was ever confirmed. Furthermore, it transpired that another individual (ID 20) in the high likelihood of diagnosis, already had a diagnosis of osteomyelitis and had been receiving daptomycin from another hospital as an outpatient at presentation.

Of the high likelihood of infection group, 4/20 (20%) did not have any microbiological cultures performed; 13/20 (65%) had blood cultures performed, with 3/13 (23%) growing clinically significant organisms. Of those who had an initial suspicion of respiratory tract infection, 2/9 (20%) individuals had sputum samples received and reported by the laboratory. For suspected urinary tract infections, 3/5 (60%) individuals had cultures sent, and 3/3 (100%) individuals with suspected skin or soft tissue infection had microbiology sent.

Of the 20 individuals with low likelihood of infection, 5/20 (25%) went on to either have a positive microbiological culture (3/20, 15%) or be treated for likely infection (3/20, 15%) within 48 hours of the likelihood estimate. For the remaining 15/20 (75%) individuals, no microbiology was sent and no suspicion or confirmation of infection occurred during their hospital stay.

Analysis of the ROC (**Figure 23**) accounting for the 25/40 individuals who had evidence of infection or positive microbiology versus the 15/40 who did not, demonstrated a ROC of 0.92 (95%CI: 0.82 - 1.00) for the GNB algorithm and 0.77 (95%CI: 0.57 - 0.96) for the SVM algorithm for predicting likelihood of positive microbiological culture / infection.

Figure 22. Distribution of likelihood estimates for individuals with high or low likelihood of infection at presentation analysed with both a Gaussian Naïve Bayesian and Support Vector Machine algorithm.

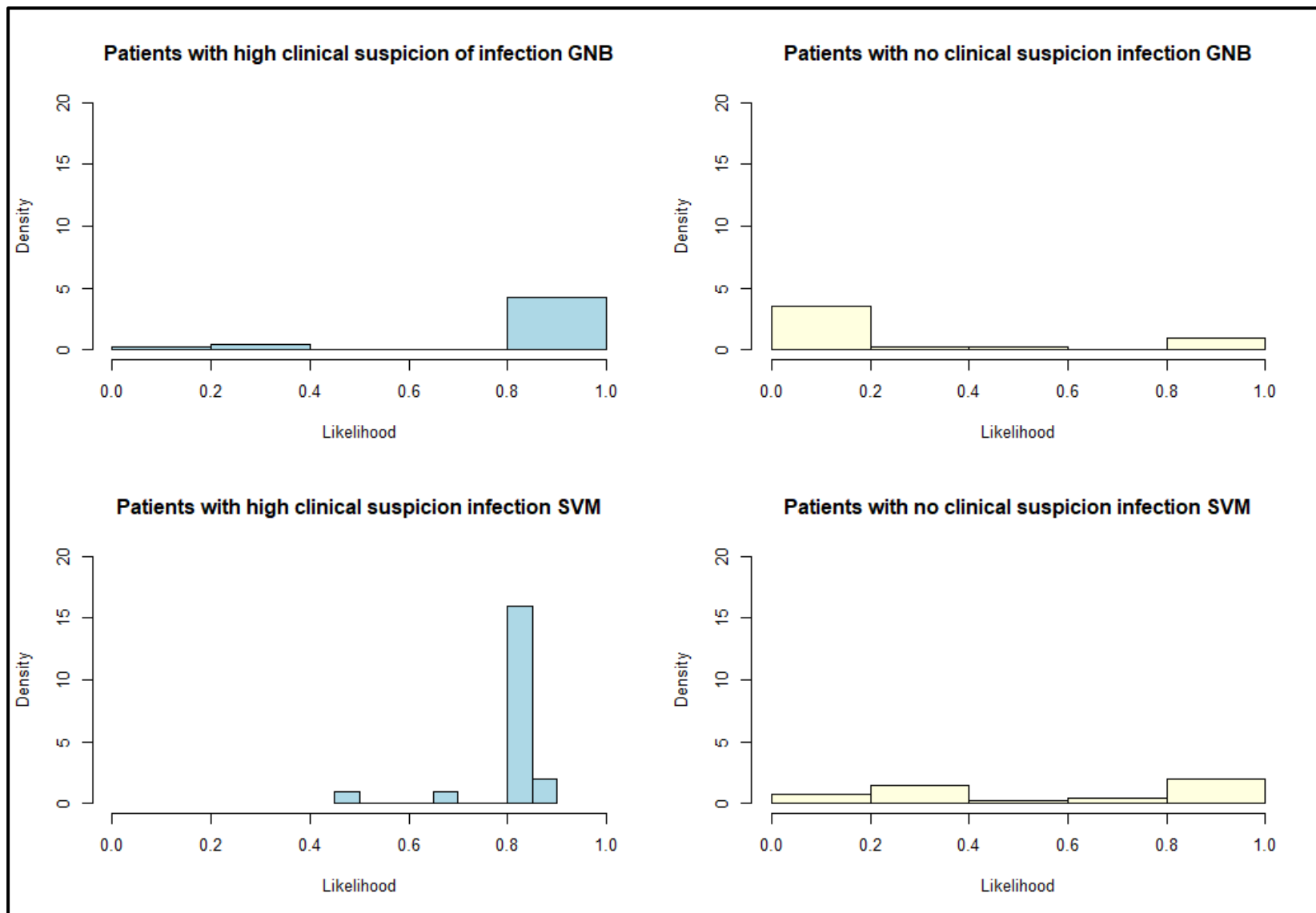


Table 20. Summary of prospectively collected cases presenting with both infectious and non-infectious symptoms.

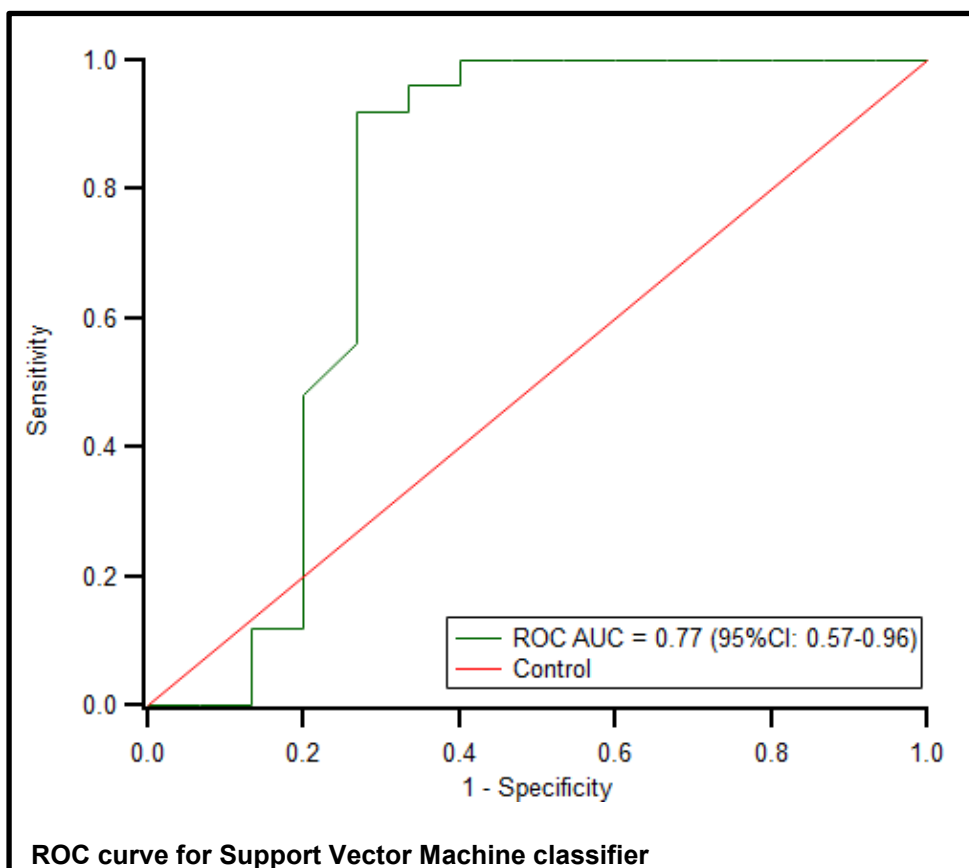
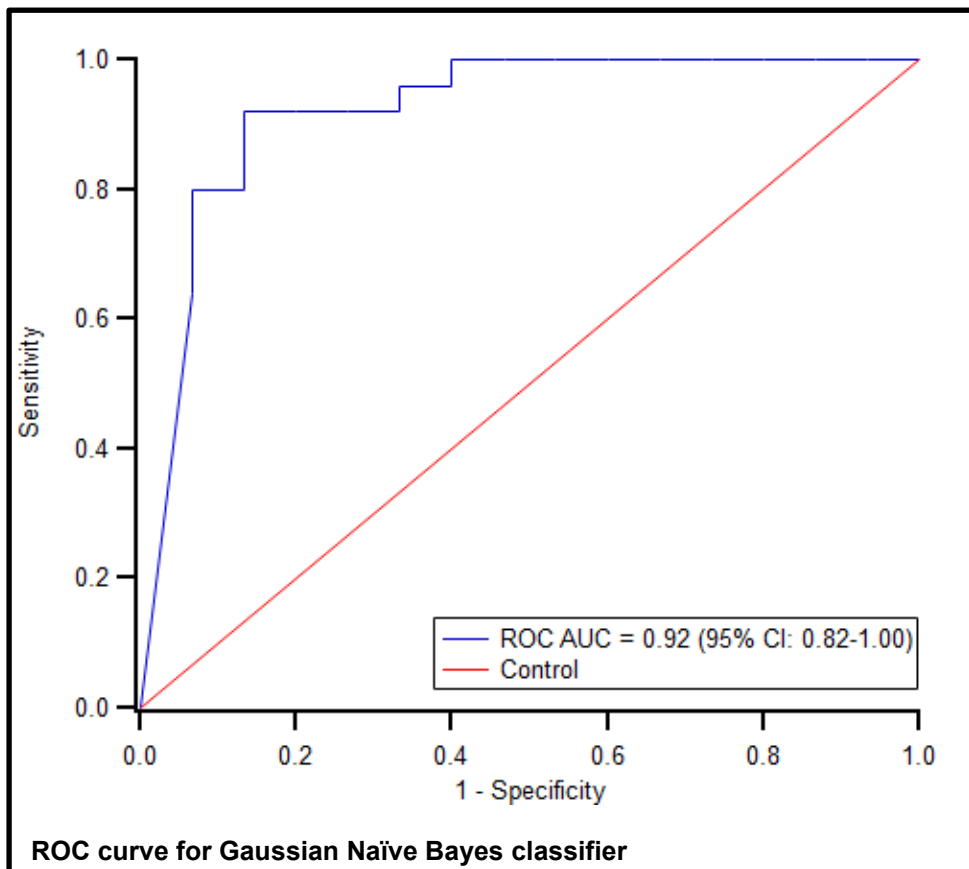
ID No	Clinical Suspicion of infection	Clinical diagnosis on admission	Likelihood estimate GNB	Likelihood estimate SVM	Cultures performed	Treatment / Diagnosis
1	High	LRTI	1	0.817302	No Growth BC	<i>Amoxicillin & Clarithromycin</i> - CAP
2	High	Cellulitis	1	0.817608	<i>Serratia marcescens</i> wound; >100 WCC in urine; No Growth BC	<i>Ceftriaxone & amikacin</i> - Rx severe sepsis secondary to cellulitis
3	High	IE COPD	0.260694	0.855327	No Culture taken	<i>Doxycycline</i> - IE COPD
4	High	LRTI	0.999999	0.838859	No Culture taken	<i>Augmentin & Clarithromycin</i> – LRTI <i>Gentamicin</i> - UTI
5	High	LRTI	0.200088	0.675191	No Growth BC and sputum	<i>Augmentin & Clarithromycin</i> – CAP
6	High	Urosepsis	1	0.817302	No Growth BC	<i>Augmentin & Clarithromycin</i> – Sepsis & Bilateral pneumonia
7	High	IE COPD	1	0.817302	No Growth BC	<i>Doxycycline</i> - IE COPD
8	High	Urosepsis	1	0.823156	Urine mixed growth; No Growth BC	<i>Ceftriaxone & Gentamicin</i> – UTI and spinal infection
9	High	LRTI, Sepsis	1	0.817826	No Growth BC	<i>Doxycycline</i> – LRTI
10	High	Sepsis of unknown origin	0.999999	0.844148	No Growth BC & urine	<i>Ceftriaxone & Metronidazole</i> - Sepsis unknown origin
11	High	Hepatic abscess & BSI	1	0.81735	<i>Bacteroides fragilis</i> BC; & <i>Streptococcus intermedius</i> BC	<i>Tazocin & Metronidazole</i> , on microbiology advice - BSI
12	High	CAP	1	0.832881	No Cultures taken	<i>Augmentin & Clarithromycin</i> – CAP
13	High	Urosepsis	1	0.854771	<i>Salmonella Paratyphi A</i> BC; <i>Escherichia coli</i> urine	<i>Ceftriaxone & Ciprofloxacin</i> – dual infection
14	High	CAP	1	0.817343	No growth BC, urine, sputum	<i>Ceftriaxone</i> - CAP

15	High	Septic arthritis	1	0.817302	<i>Staphylococcus aureus</i> wound swab & joint aspirate	<i>Flucloxacillin & Clindamycin</i> – septic arthritis
16	High	Mitral valve IE	1	0.836123	<i>Streptococcus sanguis</i> BCx3	<i>Benzylpenicillin</i> – IE
17	High	HAP	1	0.833085	No Growth BC	<i>Co-trimoxazole & Ciprofloxacin</i> - <i>escalated to meropenem</i> - HAP
18	High	UTI	1	0.823148	<i>Klebsiella pneumoniae</i> CPE on screen, No Cultures taken	<i>Cefalexin</i> - UTI
19	High	UTI	0.94961	0.839593	<i>Escherichia coli</i> in urine	<i>Cefalexin</i> - UTI
20	High	Osteomyelitis	0.112713	0.452135	No Growth wound swab	Partially treated for <i>MRSA</i> OM already (<i>Daptomycin</i>) – continued
21	Low	Seizures secondary to CNS malignancy	0.555186	0.967045	No Culture	No infection suspected
22	Low	Fall	0.164861	0.917714	No Culture	No infection suspected
23	Low	Dementia	0.040419	0.107216	No Culture	No infection suspected
24	Low	Seizure	1	0.819238	No Culture	Patient self d/c before follow up
25	Low	Diastolic HF	0.024056	0.246871	No Culture	No infection suspected
26	Low	Fast AF	0.042574	0.169934	No Culture	No infection suspected
27	Low	PPM inserted, TAVI	1	0.819662	Mixed bacterial growth urine	No treatment prescribed
28	Low	Syncope post dialysis	1	0.819238	No Culture	<i>Vancomycin & Tazocin</i> - dialysis related infection
29	Low	Hyperparathyroidism	0.011101	0.207284	No Culture	No infection suspected
30	Low	Pulmonary Oedema	0.385616	0.832111	<i>Escherichia coli</i> in sputum	<i>Augmentin</i> - LRTI
31	Low	Syncope	0.088428	0.65672	No Culture	No infection suspected
32	Low	Chest pain	0.009048	0.208489	No Culture	No infection suspected
33	Low	IHD	0.068315	0.643915	<i>Staphylococcus aureus</i> - abdominal wound swab	No treatment required
34	Low	CP & LBBB	0.026876	0.17127	No Culture	No infection suspected
35	Low	PCI with TEE	0.118254	0.561412	No Culture	No infection suspected
36	Low	Lobectomy (Ca)	0.004962	0.204085	No Culture	No infection suspected

37	Low	Acromegaly	0.047108	0.268871	No Culture	No infection suspected
38	Low	RA, on biological therapy	0.00862	0.218441	No Culture	No infection suspected
39	Low	SCC, VoC, Viral URTI	0.188129	0.842654	No Culture	No infection suspected
40	Low	Hernia repair	1	0.819238	No Culture	<i>Augmentin</i> - IAI

Legend: GNB = Gaussian Naïve Bayes; SVM = Support Vector Machine; LRTI = lower respiratory tract infection; IE COPD = infective exacerbation of chronic obstructive pulmonary disease; BSI = blood stream infection; CAP = community acquired pneumonia; IE = infective endocarditis; HAP = hospital acquired pneumonia; CNS = central nervous system; PPM = permanent pacemaker; TAVI = trans-arterial aortic valve insertion; PCI = percutaneous coronary intervention; CP & LBBB = chest pain with left bundle branch block; Ca = cancer; RA = rheumatoid arthritis; SCC, VOC = sickle cell crisis, vaso-occlusive crisis; URTI = upper respiratory tract infection; IAI = intra-abdominal infection.

Figure 23: Receiver-Operator-Characteristics of Gaussian Naïve Bayesian and Support Vector Machine classifiers for predicting subsequent infection / positive microbiology at the presentation with infection.



6.4.3 Case-based-reasoning for antimicrobial selection

6.4.3.1 Stage 1: Evaluation of prescribing recommendations against *in-vitro* susceptibility data

In total, the *E.coli* BSI dataset contained 130 individual cases for extraction. The case-base was constructed of 110/130 (85%) cases with 20/130 (15%) randomly selected cases forming the test set. Three out of the 20 individuals were excluded from the test set due to missing data. No individuals were excluded from the case-base.

The median (range) age of individuals in the training set was 68 (19 - 94) years and 71 (24 - 88) years in the test set ($p = 0.51$). The gender distribution was similar between groups, with females predominating in both (56% in training and 59% in test sets, $p = 0.81$).

Within the training set (case-base), at the time of empirical prescription, the majority of patients were given a clinical diagnosis of either *BSI* / sepsis (44/110, 40%) or urinary tract infection / pyelonephritis (44/110, 40%). In total, 25 antimicrobial agents had been prescribed either individually or in combination. Amoxicillin/clavulanate (47) and piperacillin/tazobactam (41) were the most commonly prescribed antimicrobials in the cohort. Amikacin (37), ciprofloxacin (17), gentamicin (13), ertapenem (10), and meropenem (10) were the next most frequently prescribed agents.

Sequential least-squares analysis demonstrated that only numerical values in the CBR were being used to optimise the system at present. In particular, lactate, blood pressure, and respiratory rate were given the greatest weighting.

On evaluation of the test-set, empirical antimicrobial therapy in clinical practice was deemed to of been appropriate compared to *in-vitro* susceptibility in 11/17 (65%) of cases. On review of prescribing, it was determined that 6/17 (35%) of these prescriptions were optimal or according to guideline. Applying the test-set cases to the CBR yielded appropriate recommendations for therapy in 16/17 (94%) of cases using both the “group” and “individual case” recommendations, respectively. Median (IQR) ASI for therapy prescribed in practice

was 8 (6 - 10) compared to 6 (6 - 8) for both CBR recommendations, respectively. None of these comparisons reach statistical significance.

Re-training of the CBR using “best practice recommendations” for prescribing did not alter the observed results when applying the test cases to the algorithm.

6.4.3.2 Stage 2: Prospective evaluation of Case-Based-Reasoning across secondary care

Over a 4-week period in October-November 2017, 68 patients were reviewed and entered into the CDSS that housed the CBR algorithm during routine clinical out-of-hours practice by myself working as a junior doctor. Retrieval of cases by the system was possible in 47/68 (69%) individuals. A change in the electronic structuring of the hospital wards was found to be responsible for low fidelity of retrieval.

Of the 47 subjects included in the analysis, the median (range) age was 66 (28-93) and the majority of individuals were male (32/47, 68%). Individuals were reviewed on the general medical (39/47, 83%), haematology (6/47, 13%), and general surgery (2/47, 4%) wards at Hammersmith Hospital campus of ICHNT. Empirical therapy was prescribed in 31/47 (66%) cases with the remaining 16/47 (34%) cases requiring targeted therapy. For the targeted therapy cases, 11 organisms were identified as causing infection. *Staphylococcus aureus* (4), *Escherichia coli* (3), and *Enterococcus spp.* (3), were the most commonly identified organisms. Overall, 24 antimicrobials were prescribed either as single or combination therapy. Augmentin (9), vancomycin (9), ceftriaxone (9), and meropenem (8) were the most commonly prescribed agents.

For analysis, individuals with *Clostridium difficile* infection (n = 3) were excluded from the analysis. Cases were then compared according to whether the recommendations made were based on either empirical or targeted treatment of infection. **Table 21** summarises the CBR results for both empirical and targeted therapy groups.

Table 21. Summary of Case-Based-Reasoning recommendations made for patients receiving empirical and targeted antimicrobial therapy.

		Empirically treated n = 31	Targeted therapy n = 13
No. appropriate			
<i>Clinical practice</i>	n = (%)	30 (97)	12 (92)
<i>Optimal (Guideline / ID)</i>	n = (%)	16 (52)	9 (69)
<i>CBR Group</i>	n = (%)	24 (77)	7 (54)
<i>CBR Case</i>	n = (%)	24 (77)	7 (54)
ASI*			
<i>Clinical practice (CP)</i>	Mean (SD)	7.1 (2.9)	7.3 (3.7)
<i>CBR Group Rec (CGR)</i>	Mean (SD)	4.7 (1.8)	5.7 (0.5)
<i>CBR Case Rec (CCR)</i>	Mean (SD)	5.3 (2.4)	6.4 (1.5)
ASI Comparison			
<i>CP vs. CGR</i>	p = (95%CI)	p < 0.01 (0.67 - 3.08)	p = 0.25 (-1.20 - 3.27)
<i>CP vs. CCR</i>	p = (95%CI)	p = 0.06 (-0.08 - 2.75)	p = 0.64 (-2.30 - 3.39)
<i>CGR vs. CCR</i>	p = (95%CI)	p = 0.10 (-0.12 - 1.29)	p = 0.31 (-0.86 - 2.29)
Appropriateness of CBR by system infected			
<i>Intra-abdominal</i>	n/total (%)	2/2 (100)	
<i>Blood / Line / Sepsis</i>	n/total (%)	3/3 (100)	
<i>Skin soft tissue</i>	n/total (%)	2/3 (66)	
<i>Chest</i>	n/total (%)	12/14 (86)	
<i>Neutropaenic Sepsis</i>	n/total (%)	1/5 (20)	
<i>Urine</i>	n/total (%)	4/4 (100)	

Legend: No. = number; CBR = case-based-reasoning; ID = infectious disease specialist; CP = clinical practice; CGR = CBR-grouped recommendation; CCR = CBR-individual case recommendation; 95%CI = 95% confidence interval.

* ASI for individuals where recommendation was appropriate both in practice and with CBR recommendation.

Within the empirically treated group, clinically prescribed therapy was appropriate in 30/31 (97%) cases. This was deemed to be optimal according to guideline, expert opinion, or subsequent *in-vitro* susceptibility in 16/30 (53%) cases. Both CBR grouped and individual case recommendations were appropriate in 24/31 (77%) of cases, respectively.

The CBR recommendations were inappropriate in the majority of situations where individuals had neutropenic sepsis (4/5, 80%), one case where an individual had a skin and soft tissue infection associated with an implantable device, and two cases of pneumonia (both mild). Given the complexity of therapy required in neutropaenic sepsis; I chose to exclude these individuals from the analysis of CBR recommendations. This demonstrated that the CBR made appropriate recommendations for empirical therapy in 23/26 (88%) of cases in non-neutropaenic individuals.

For individuals where appropriate therapy was recommended ($n = 24$), the mean (SD) ASI was significantly smaller for the CBR grouped recommendation compared to clinical practice (4.7 (1.8) vs. 7.1 (2.9), $p < 0.01$; 95%CI: 0.67 – 3.08). In comparison, the CBR individual case recommendations also had a narrower mean (SD) ASI of 5.3 (2.4). However, this was not statistically different to clinical practice ($p = 0.06$, 95%CI: -0.08 – 2.75).

On examination of those individuals receiving targeted antimicrobial therapy, the CBR recommendations were appropriate in 7/13 (54%) of cases. This was compared to 12/13 (92%) receiving appropriate therapy in clinical practice. Of the individuals where the CBR made appropriate recommendations, ASI was reduced from a mean (SD) ASI of 7.3 (3.7) in clinical practice to 5.7 (0.5) in the CBR grouped recommendations and 6.4 (1.5) in the CRB individual cases recommendations.

6.5 Discussion

6.5.1 Summary of findings

Within this *Chapter* I have demonstrated the potential of artificial intelligence as a technology to support health care professionals infer the likelihood of infection and make improved antimicrobial prescribing decisions based on individual patient parameters that are routinely available in clinical practice.

Using large numbers of routinely available microbiology and blood science data, supervised machine learning classifiers were able to infer the likelihood of infection / positive microbiology in individuals with both high and low pre-test probability of infection. Development of these systems have wide potential for improving decision making around infection management, ranging from integration into early warning systems for detection of sepsis, the surveillance of HCAI, and guiding decision making about individual patient management (e.g. collection of microbiological cultures).

In addition, a CBR algorithm demonstrated the ability to provide appropriate empirical antimicrobial recommendations in non-neutropaenic patients, promoting use of narrower spectrum antimicrobials to what was currently being used in practice. The investigation of the tool demonstrated several challenges in ensuring fidelity of data retrieval within large, complex health systems and also provided insight into alternative methods for training and optimising future CBR algorithms.

Whilst these systems help provide individualised recommendations based on the evidence available to them, a number of limitations must also be considered in future work. This includes the lack of available data for certain clinical parameters, such as lactate and physiological parameters, and the importance of evaluating the human decision maker as part of the system.

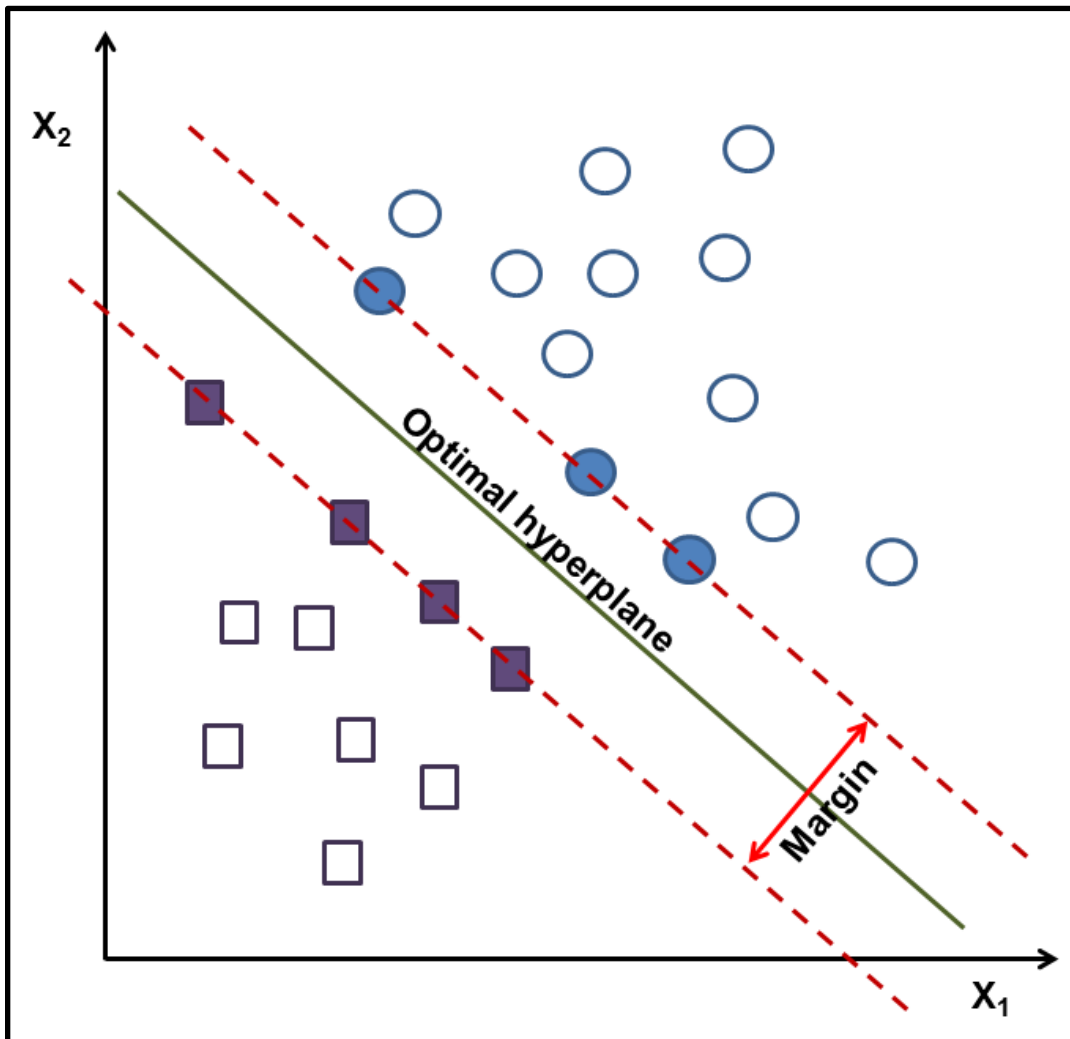
6.5.2 Supervised machine learning for infection inference

Within this study, two supervised machine learning classifiers were selected for evaluation in clinical practice based on their characteristics and performance during cross-validation. These were GNB and SVM classifiers [314].

A GNB classifier is a simple Bayesian network that assumes independence between every pair of features within the network [363,364]. This approach assumes that the likelihood functions for each feature (in this case infection versus no infection) have a normal distribution [363,364]. GNB is attractive for healthcare settings given that they can work with missing values in the dataset, training requires relatively small amounts of data, and processing and computation is relatively fast [363,364].

In contrast, SVM are one of the newest techniques within the field [365–367]. SVM work by trying to maximise the “margin” that sits either side of a hyperplane that separates the two data classes under analysis [365–367]. By maximising the margin, SVM aims to reduce the expected error in estimations made. Once the optimal separating hyperplane is found (**Figure 24**), the data points which lie on its margin, known as the support vector points, are selected and all other data is discarded. These are then used for classification purposes [365–367]. Whilst the improved accuracy of SVM is desirable, there are also limitations. Firstly, it is not always possible to identify a hyperplane between two classifications, this often requires use of a transformed feature space, where a Kernel function is added to the algorithm to map points into the feature space, which facilitates classification [365–367].

Figure 24. Diagrammatic representation of the concept of Support Vector Machines.



Legend: Support Vector Machine classifiers aim to find the hyperplane that separates training examples. This aims to create a maximal margin of the training data sets.

Adapted from Nugroho *et al.* Proceeding of Indonesian Scientific Meeting in Central Japan, 2003.

Within our study, the GNB algorithm performed with a higher degree of precision when challenged with a real-world situation compared to the SVM, such as was described in *Section 6.4.2.2*. This was an unexpected observation given the superiority of the SVM classifier in cross-validation [314]. One explanation is that for 5 of the 40 individual cases, there were missing data in the terms of available variables. Given that GNB classifiers are better able to function with incomplete data sets, this may partly explain the observations made [363,364]. Another explanation for may be under-powering of the study.

The use of supervised machine learning to help with decision making has a wide number of potential applications. In this setting, I have demonstrated the sensitivity of the system for predicting positive microbiology / infection diagnosis in those with typical infective presentations as well as those with low pre-test probability for infection. This may provide a mechanism for augmenting current early warning systems for conditions such as sepsis, which are being implemented widely throughout the NHS [368–376].

Current approaches to early warning scores for conditions such as sepsis have demonstrated variable success to date. In the intensive care setting, the Targeted Real-time Early Warning Score was developed to predict the likelihood of individuals developing septic shock [370]. This scoring system was developed from a database of over 16,000 ICU patients from around the world and demonstrated a high sensitivity (85%) with lower specificity (67%). This could be deployed automatically within a hospital EHR and used to identify those at risk of developing septic shock over one day before the onset of symptoms [370]. However, there are a number of limitations with this work. Firstly, the data from which the model is developed only focuses on patients in the ICU, meaning that generalisability to the rest of the hospital is not clear. Furthermore, the system has not been reported in clinical practice meaning that the adoption of the system by HCP's remains unclear.

A more widely used early warning score in the UK is the National Early Warning Score (NEWS), which was recently revised (NEWS 2) to promote the prompt detection of sepsis in

the hospital setting [368,377,378]. This scoring system is designed as an early warning score, based on physiological parameters that allow the rapid triage and assessment of the patient, inferring the likelihood of clinical deterioration or sepsis. It has demonstrated high sensitivity and specificity in the emergency department for inferring likelihood of sepsis, but has not been reported across the wider healthcare setting despite its ubiquitous use in the NHS [368,377,378].

Currently, the system described within this *Chapter* was unable to evaluate the use of many of the variables used in scoring systems like the NEWS 2, given that physiological parameters were not electronically available. However, using blood parameters only, the GNB demonstrated high sensitivity and specificity (ROC: 0.92, sensitivity 0.85 and specificity 0.80 with cut-off likelihood estimate of 0.752) when using real-world data. However, the current system architecture relies on availability of the blood test parameters, which could still lead to a delay in the detection and therefore management of sepsis. This in turn may potentially not have an impact on initial antimicrobial decision making in certain patient populations, where there is an urgent clinical need to start empirical antimicrobial therapy before blood test results are returned [374].

It must also be noted that this system was not designed with only sepsis in mind. It has been developed to infer the likelihood of infection in general. Therefore, its application for helping individual physicians determine the likelihood of infection in settings where sepsis is not present may be an additional level of decision support that is applicable. This is because there may not be as much urgency to commence antimicrobials in advance of blood test results in non-septic individuals [379,380], suiting the current systems requirement for blood test results. Furthermore, these cases can often being more challenging diagnostically for clinicians, requiring a more individualised approach to rationale decision making [168]. For example, in individuals presenting with urinary or respiratory symptoms not associated with systemic features of sepsis [381–383].

Future work to be undertaken must now explore the other potential avenues for applying this type of technology to the data that we have available. This may include exploring whether it is possible to use the same tools to predict the likely site of infection, causative organism, or even sensitivity profile [125]. Furthermore, with the generation of computerised prescribing data within our hospital Trust, it may also be possible to apply similar algorithms to prescription data to infer the likely optimal length of treatment for the individual patient. However, for these areas to be successful, it is likely that further variables will be required. Further application of this technology and its ability to be linked into the CBR decision tool will be discussed below under future work in *section 6.5.4*.

6.5.3 Case-Based-Reasoning for antimicrobial selection

Within this study, the CBR was able to improve the empirical selection of antimicrobials compared to *in-vitro* susceptibility profiles of subsequent organisms in individual patients presenting with *E.coli* BSI. It also promoted the prescribing of narrower spectrum therapy according to the ASI.

When considering the optimal method for generating a case base for training the system; using “rea-life” prescribing linked to outcomes of therapy and creating “best practice” case bases did not alter the performance of the CBR within stage 1 of its evaluation. This was an important consideration before moving on to test the system in a live fashion (stage 2). Training the system on real cases and experience can lead to large case bases, which can slow the system and potentially introduce error that can be reflected in the recommendations made [321,356,357]. The development of prototype systems can circumvent many of the problems caused by training on large numbers of real cases [321,356,357].

A prototype is a case that is a generalisation from a number of different cases (i.e. from a set of very similar cases) [356]. These can be developed by medical experts, from the literature, or even at times can be computed [356]. The idea is that the prototype contains common

features within its variables that should drive the CBR to place it high in the ranking of cases when a similar new case is presented to it [356]. This shortens the retrieval time and allows control of the case base being used. It has been successfully applied in theory to CBR for antimicrobial decision making in the ICU by Schmidt and colleagues [309].

Within the *E.coli* BSI cohort, I opted to take a hybrid approach to facilitate comparison. I achieved this by working with an antimicrobial pharmacist and an infectious diseases and microbiology colleague to independently work through the cases and retrospectively provide best-practice, empirical prescriptions for cases within the case-base. The hypothesis for this choice was that by training the system in a more optimal manner, the recommendation made by the CBR would also be more optimal. However, within this small cohort, there was no difference between both approaches. This may have been for several reasons, including under-powering, the fact that only numerical variables were optimised within the CBR, or because only positive cases were presented (i.e. by providing best practice recommendations, we assumed that all cases had a positive outcome).

During the prospective analysis of the tool on the wards, the CBR performed to a similar level as was observed in critical care during empirical prescribing for non-neutropaenic patients [384]. However, it struggled in making recommendations for neutropaenic patients and in cases where targeted therapy was required. I believe that the probable explanation for these observations lies in the way the system was currently trained and optimised.

Firstly, the prototypes developed for this study were based on local empirical antimicrobial prescribing policy meaning that targeted therapy was not considered as part of the case base. Secondly, during the optimisation process it became clear that the system was currently only optimising according to numerical values. Therefore, several potentially important string variables, such as site of infection, examination findings, known microbiology, and imaging within the case base were being under-weighted or overlooked entirely. This would likely be significantly more important within the prospective study (stage

2), which comprised a much more heterogeneous population of patients compared to the *E.coli* BSI cohort. Therefore, before further prospective evaluation of the CBR it is important to consider these issues. This may involve the need to translate string variables into numerical ordinal values or ensure that the CBR is able to take account for strings in a more optimal manner.

6.5.4 Limitations and future work

In addition to the limitations and future work already highlight in *sections 6.5.2 & 6.5.3* a further consideration arising from this study is the need for future work to assess the adoption of these tools by end-users upon implementation in clinical practice. Recently there have been growing concerns about the application of artificial intelligence in healthcare [330,385]. However, Verghese and colleagues, recently addressed some of these concerns in their article "*what the computer needs is a physician*" [330]. Within this article the authors bring the focus of using artificial intelligence back towards the concept of EBM. By this they argue that artificial intelligence can provide enhanced evidence to support decision making, but this still must be placed in the context of sound clinical judgement and an understanding of the patients views [330]. To achieve this it requires a skilled physician, as well as a well-designed artificial intelligence tool, which has involved the end-user in its development and evaluation.

For the purpose of this *Chapter*, I decided not to explore end-user feedback of using the device. This was because I felt that it was important to ensure that the underlying artificial intelligence was initially evaluated under optimal conditions to provide a base-line from which I can compare its impact in clinical practice. Now that I have demonstrated the potential ability of these systems to provide enhanced decision support they must be evaluated in the context of clinical practice. I believe that taking this step-wise approach will facilitate the understanding of how to promote adoption of the technology whilst also evaluate its impact

on clinical decision making in practice. This follows observations made during my systematic review of the literature (*Chapter two*), where I highlighted the challenges of determining the impact of the tool in isolation when it is implemented as a multi-modal intervention in clinical practice (e.g. with training, audit & feedback, observation of practice) [66]. Therefore, by providing this base-line, I now have a better understanding of the potential impact I will see from implementation of these tools moving forwards.

During the assessment of supervised machine learning tools, a number of specific limitations were noted. For the initial evaluation set of BSI patients versus those presenting without infection in *section 6.3.3.1*, it is important to note that those without infection at presentation were not followed up throughout the entirety of their hospital stay. Therefore, where false positive results were identified this may of, in some cases, potentially been due to under reporting of infection in the retrospective clinical records. Furthermore, the focus was only to evaluate the predictive ability of the tool. Analysis of prescribing practices was not included within this study. Therefore, it is not possible to infer the direct impact on clinical practice that this type of tool will have until longitudinal, prospective studies in practice comparing the tool to usual practice have been implemented. Work is now underway to explore the integration of this tool into ICHNT EHR system to facilitate this evaluation. This will commence in targeted clinical areas such as the emergency department, haematology, and surgical specialties. Finally, the classifiers used within this study have only been investigated for use using discrete data and at discrete times. Evaluation of the dynamic changes of the system in response to therapy / over time must also be investigated. This may facilitate the application of such tools to other HCAI surveillance which require on more longitudinal assessment [386].

Although many of the limitations of the CBR study have been discussed in *Section 6.5.3* a further comment is required regarding the powering of this study. This was a pilot evaluation, undertaken to explore the feasibility for use of CBR in clinical practice. Therefore, I did not power the study to demonstrate statistical significance. Following further development of the

system (as described above), this will need to be considered before undertaking any further prospective evaluation of the tool. Another key limitation that must be addressed was the fidelity of data retrieval on the wards. This occurred due to changes in the ward allocation system within the hospital Trust and the fact that certain wards have sub-wards within the electronic record system. This meant that often certain bays on wards were not retrieved by the system when patient details were searched. To address this, I have sought support from the ICHNT information technology team, who are exploring the option of allowing us to link the CDSS directly to the hospitals EHR interface. This would mean that there is a direct link between the patient being viewed and the CDSS, so that when the tool is called forward the hospital EHR automatically provides location data to the system.

Finally, further work will now be undertaken to investigate the integration of these different types of decision making aid. For example, the likelihood estimates generated by the supervised machine tools may be able to be linked into the CBR algorithm as a further variable to drive decision making of the system. With the development of new techniques, such as predictions of sensitivity patterns, this may help to increase the knowledge base of the CBR without the requirement for a large increase in the number of variables added.

6.6 Conclusion and key messages

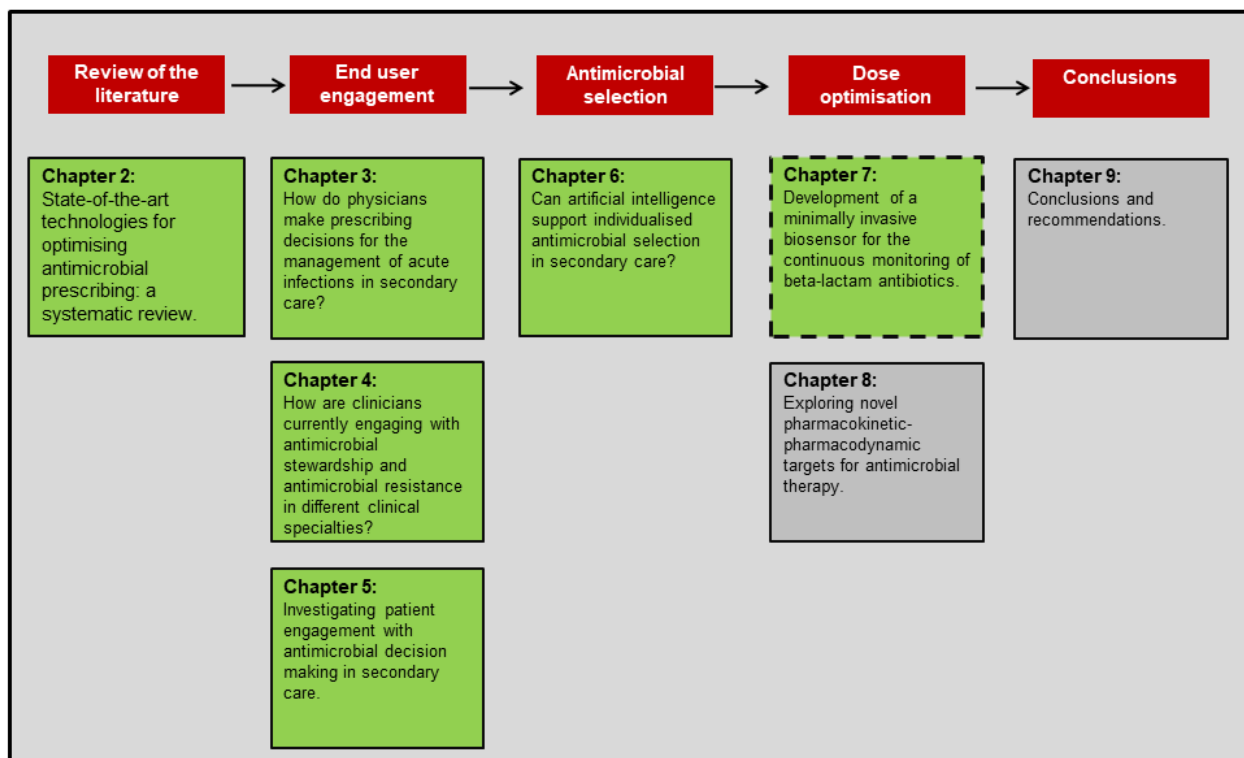
Within this *Chapter*, I have explored the potential of artificial intelligence to help address two core areas of the physician decision making pathways, which was described in *Chapter three*. Supervised machine learning was successfully able to predict individuals who had infections or positive microbiology, using a small number of blood parameters present at their presentation. CBR was able to make empirical antibiotic recommendations that were appropriate for clinical practice and had the potential to reduce selective pressure for antimicrobial resistance by reducing the spectrum of antimicrobials prescribed overall.

Future work must now explore the interaction of the end-user with these tools in clinical practice. It must also explore the integration of these separate approaches to understand whether this can further augment the individualisation of decision making.

CHAPTER SEVEN:

7.0 Personalised Antimicrobial Dosing: Development of a minimally invasive biosensor for the continuous monitoring of beta-lactam antibiotics

Figure 25. Overview of thesis.



7.1 Introduction

7.1.1 Pharmacokinetic-pharmacodynamic variation

When considering the appropriateness of antimicrobial therapy, clinicians will focus on the selection of the most appropriate agent for the organism that they are (or believe they are) treating [32]. However, this focus often neglects to consider the importance of selecting the

most appropriate dose of the antimicrobial agent to maximise bacterial killing, whilst minimising the development of drug resistance and toxicity to the patient.

Whilst much emphasis has been placed upon prudent prescribing, a significantly smaller focus has been the optimisation of the dose of such agents for the individual patient. There is increasing evidence describing the wide variations in antimicrobial PK between individuals across clinical areas, such as critical care, chronic renal disease, obesity, and extremes of age [387–391]. These variations occur for the majority of antimicrobials, not only those that we currently therapeutically monitor like vancomycin, a glycopeptide antibiotic that causes nephrotoxicity [392]. For agents that have smaller risk of toxicity, such as the beta-lactams, PK variation is also observed [393,394].

For example, several studies from critical care units internationally have demonstrated that up to 75% of critically ill patients in intensive care may not be receiving appropriate doses of beta-lactam antibiotics [393]. In the “defining antibiotic levels in intensive care unit patients” (DALI) study, by Roberts and colleagues, the authors demonstrated wide variation in beta-lactam PK-PD target attainment in a cohort of 384 patients [394]. These were recruited from 68 intensive care units in 10 countries. Failures to meet standard PK-PD indices (%time>MIC) were associated with significantly worse patient outcomes [394]. However, it is not just the intensive care setting where optimisation of dosing has evidence of improved outcomes.

Data support individualised dosing for drugs that we already therapeutically drug monitor (TDM), such as vancomycin [392,395–401]. For vancomycin, the 24-hour area-under-the-concentration-time curve (AUC) to MIC ratio of 400 has been associated with optimal clinical outcomes in a range of Gram-positive infections. In more severe infections, such as infective endocarditis caused by *Methicillin-Resistant Staphylococcus aureus* (MRSA), a AUC:MIC of 600 may be required [396,400]. Furthermore, current approaches for TDM of vancomycin currently rely on peak or trough blood samples. In none severe infections, a trough target of

10-15 mg/L is recommended [392]. However, as the commonest MIC of *Staphylococcus aureus* is 1 mg/L [402], this type of therapy is only likely to achieve an AUC:MIC of approximately 250 [392]. Furthermore, with vancomycin's narrow therapeutic window and risk of toxicity, once the AUC of vancomycin rises above 600, physicians are often cautious of increasing the dose of this agent, given increased risk of toxicity at this point [392]. This means that patients often remain sub-therapeutic for much of their treatment. In one retrospective review of non-critical care patients receiving vancomycin therapy, I demonstrated that attainment of an AUC:MIC >400 was only achieved in 63% of patients [397]. Individuals who were obese were significantly more likely to obtain AUC:MIC <400 compared to non-obese individuals [397].

As well as controlling for inter-individual variation in antimicrobial PK, there are a number of intra-individual factors that are likely to influence an individual's pharmacokinetics during the course of infection management [387,389,390,394,403]. These variations can be driven by augmented renal clearance, third spacing secondary to inflammatory response, and the requirement for organ support, which may resolve during the course of infection management [387]. For example, in critically ill patients receiving linezolid therapy for *MRSA*, dose by dose variations have been observed in volume, clearance, and thus plasma and tissue PK [404]. These variations are driven by a multitude of factors, making the forecasting of optimal dosing strategies for the individual patient at an specific time during therapy challenging [404]. This challenge is further enhanced when single time point drug monitoring is performed.

Therefore, to achieve optimal treatment outcomes in the individual we need to explore more personalised methods for monitoring antimicrobials and adapting dosing based on variations both between individual patients and within the individual during the course of infection management.

7.1.2 Individualised approaches to antimicrobial dosing

The argument for more personalised approaches to antimicrobial dosing is gaining increased consensus with the reporting of wide PK variation [405]. There are numerous mechanisms that can be employed to individualise the delivery of antimicrobial therapy. However, this can be simplified into several individual stages. These include:

1. Developing an ability to evaluate antimicrobial concentrations in the individual. This would ideally be at the target site, but if not possible, sampling should be from a compartment that facilitates accurate estimation of target site concentration.

2. Predicting the individual's PK and linking this to an appropriate PD indicator to allow determination of a personalised PK-PD index.

3. Alteration in dosing to optimise the concentration of drug in the individual patient, for the individual organism being treated, at that time during therapy. This will often use the defined PK-PD target selected above.

Several mechanisms for improving the accuracy of antimicrobial dosing now exist. These include closed-loop control and Bayesian forecasting [405–407]. However, these approaches rely on our ability to be able to perform drug monitoring to provide individual patient PK data or develop population models to facilitate Bayesian forecasting. Therefore, the development of novel techniques to improve drug monitoring are highly desirable. Ideally these would be minimally invasive, available at the point-of-care, perform monitoring in real-time, and be available for a broad range of antimicrobial agents [406].

Several studies have explored the role of microfluidics in delivering enhanced drug monitoring [408–410]. However, this approach is hindered by many of the problems associated with routine blood antimicrobial TDM. These problems include:

- The requirement to extract blood / interstitial fluid (ISF), which requires complex techniques, exposure of healthcare workers to potentially harmful material, and does not provide a true *in-vivo* measure of target concentration.
- Transport of samples to a laboratory, which lead to delays in returning results of samples.
- Laboratory analysis, which requires trained technicians, expensive analytical equipment, and the requirement for validated antimicrobial assays to be available, of which there are few commercially.

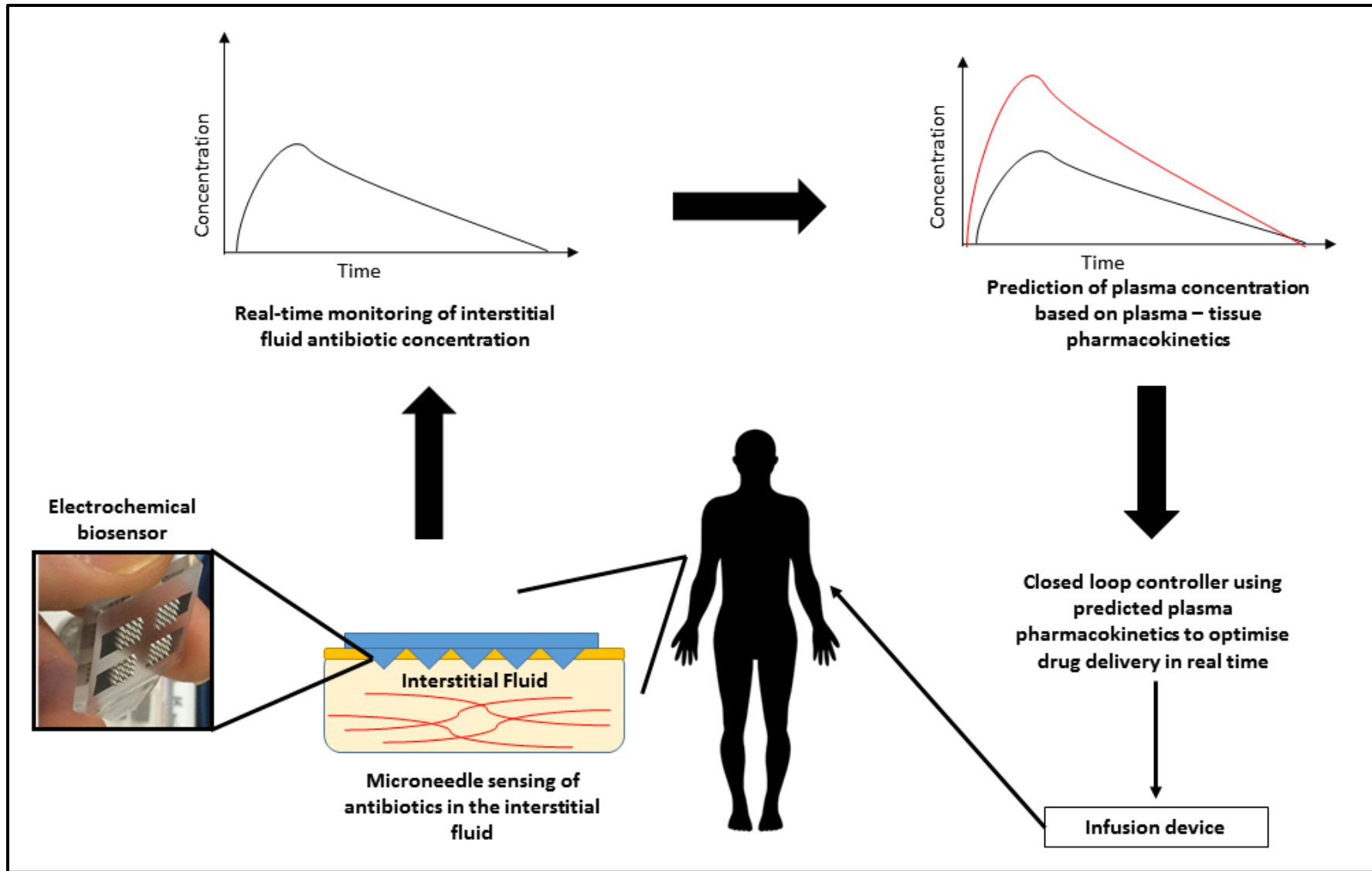
One potential method to avoid these problems is through the development of closed-loop control systems, developed around minimally invasive, microneedle electrochemical sensor technology for drug monitoring [411]. This technology is being applied in other areas of medicine, such as diabetes control through individualised insulin delivery [412–416] and anaesthesia control intra-operatively [417,418]. Closed-loop control offers a potential avenue for enhancing the precision of antimicrobial therapy across a number of settings where invasive monitoring techniques may not be appropriate, including the community and non-critical care hospital settings. In a review of this field, published in *the Journal of Antimicrobial Chemotherapy*, I recently reported the current state-of-the-art for closed-loop control in infection to provide personalised antimicrobial dosing [406]. The core components of a closed-loop system for antimicrobial dose optimisation are outlined below.

7.1.2.1 Components of closed-loop control for individualised antimicrobial therapy

Several key concepts (outlined in **Figure 26**) must be considered for the development of closed-loop controllers for antimicrobial therapy. Ideally monitoring of antimicrobials should be continuous and in a minimally invasive format that does not rely on blood sampling. Microneedle array electrochemical biosensor technology provides an opportunity to achieve this. This facilitates the detection of antimicrobial concentrations in the dermal interstitial fluid

(ISF) [419,420]. Microneedle technology has already been validated in the field of diabetes, demonstrating safety and tolerability in human clinical trials and accuracy in diabetic individuals [411,419,420]. This is despite this cohort of patients tending to have poor tissue perfusion due to underlying diabetic vasculopathy [411,419,420]. As free antimicrobial concentration in the ISF is generally in equilibrium with plasma concentration, this provides an opportunity for using this technology to monitor ISF concentrations as well as estimate plasma free-antimicrobial concentration in near real-time without requiring plasma sampling [421–423]. This may be challenging in certain situations, such as during periods of tissue hypoperfusion in critically ill patients in the intensive care unit (ICU) [424]. However, it may also offer a novel option for supporting the optimisation of antimicrobial dosing in these populations. This is because the majority of infections occur in tissue ISF [424,425]. Therefore, this technology may provide a mechanism for monitoring antimicrobial concentrations in a compartment that is closer to the site where the infection is being treated when compared to plasma [424,425].

Figure 26. Outline of the proposal for closed-loop-control of antimicrobial therapy.



Real-time data, generated by the microneedle sensor, can be linked with machine driven, closed-loop control algorithms. These include Proportional-Integral-Derivative (PID) [426] [427] and Iterative Learning Controllers (ILC) [428]. These controllers facilitate the optimisation of both continuous and bolus (or oral) therapy, respectively. They can achieve individualised target attainment of pre-defined PK-PD indices associated with maximal bacterial killing and/or suppression of the emergence of AMR [429,430]. These may be current gold standard PK-PD targets [431,432] or novel indices, such as AUC:EC₅₀ ratio [433,434].

Each of these concepts will individually be explored and critiqued below.

7.1.2.2 Microneedles for continuous sensing of agents in the dermal interstitial fluid

Microneedle technology was first demonstrated as a suitable mechanism for drug monitoring and delivery over 20 years ago [435]. Development of this technology has progressed rapidly with data supporting the use of microneedles to monitor glucose and lactate concentrations in humans [419,420,436,437]. This replaces previous methods of tissue sampling, such as microdialysis [404,421,438–442]. Microneedles are also being used as delivery systems for drugs and vaccines [415,443]. They work by penetrating the stratum corneum layer of the skin, accessing the dermal interstitial space. This allows access to the ISF, whilst avoiding the nerve fibres and blood vessels that are found within the dermis. Therefore, microneedles are a minimally invasive method for drug or metabolite monitoring [419,420,436,437]. Side effects such as pain, bleeding, skin reactions, and infection risk have all previously been explored and shown to be minimal following application of such devices to the skin [419].

A major step forward in microneedle development has been the ability to directly mount electrochemical sensors onto the exterior surface of the microneedle (developed by

Professor Tony Cass and Dr Sanjiv Sharama, Imperial College London). This type of microneedle will be utilised within the *Chapter*. Until this technique was developed by Sharma and colleagues, microneedles have been hollow, acting as microdialysis needles [444]. This technique is often challenging as it requires transfer of small volumes of ISF to a sensor behind the microneedle structure. This not only presents technical challenges in terms of microfluidic transport, but also causes difficulty in maintaining accuracy of the sensor. Furthermore, the transfer of ISF means that the approach mitigates against their application in real-time control, given delays in fluid transfer and processing [444].

The microneedles described within this *Chapter* have been reported previously by Sharma and colleagues, who claim high reproducibility when using microneedle technology to monitor glucose levels in healthy volunteers compared to capillary blood glucose measurements [413]. They were robust to sterilisation using gamma-irradiation allowing the device to be sterilised and stored over time for use monitoring human glucose concentrations [413]. The simplification of monitoring techniques, mounting the sensor directly on the external surface of the needle, also means that this technology can be reproduced reliably and at low cost through the development of scalable microneedle batch injection moulding, producing up to 300 microneedle bases per hour [436].

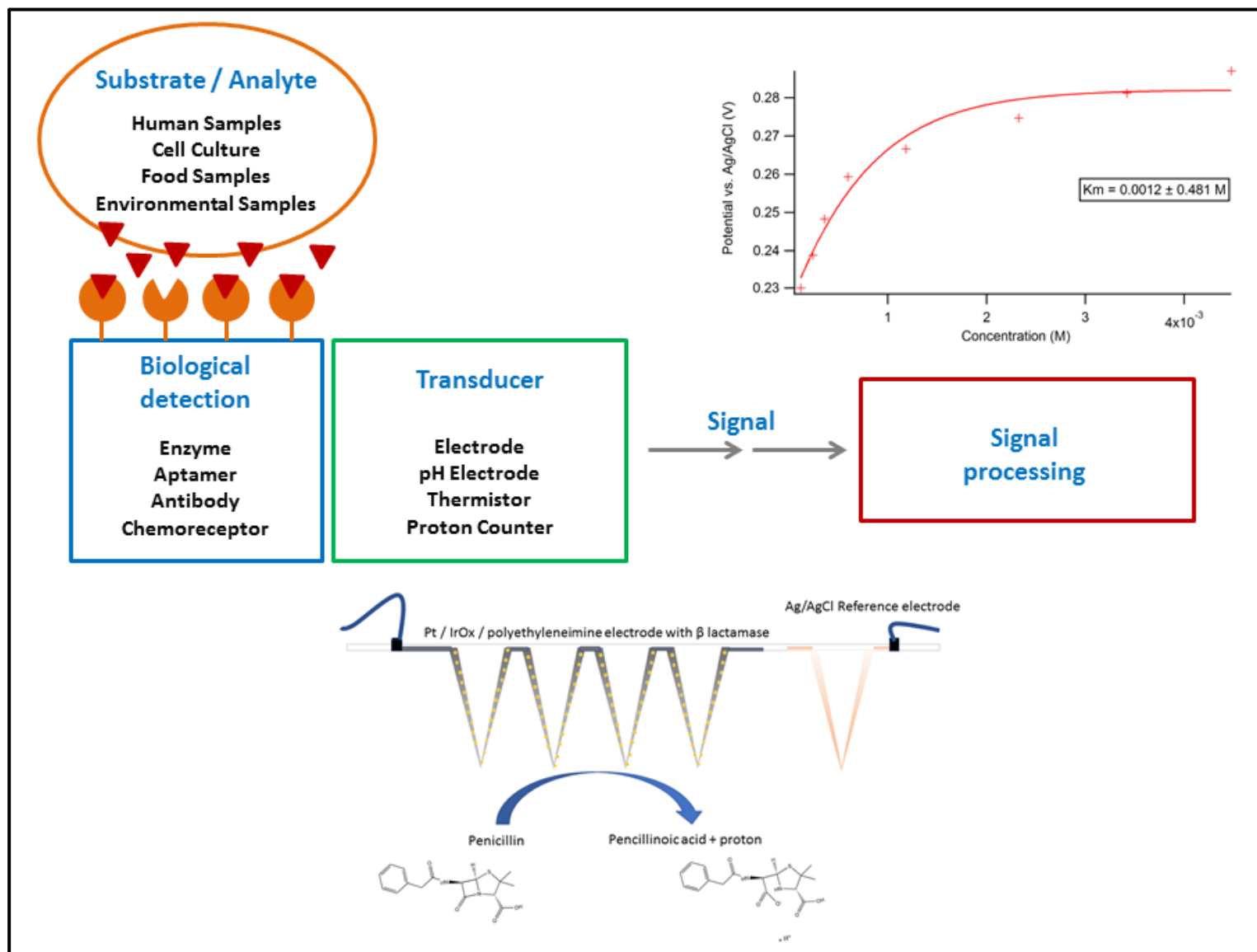
However, there are also challenges that remain in the development of microneedles within this field. In clinical trials for monitoring glucose using glucose oxidase coated microneedles, the sensors appear to occasionally generate artefact. This appears to be caused by movement that leads the needles to be partially removed from the intradermal space [413]. Whilst the observed artefact had a shorter duration than changes in glucose concentration, and thus can be controlled for, this still requires consideration. A further challenge with the current microneedle sensors in humans has been their accuracy at extreme ranges of glucose, especially hypoglycaemic ranges [413]. It is likely therefore that sensor deployment for antimicrobial monitoring will encounter similar barriers for consideration.

In addition to microneedle based sensing, other methods to facilitate continuous monitoring also require consideration. The most developed of these alternatives are attempts to perform real-time monitoring of drug concentrations in ambulatory animals using invasive vascular catheter insertion [445]. In clinical practice, this method would only be acceptable in very specific situations, such as critical care or at the time of surgery. However, this may be acceptable given concerns of the microneedle sensors accuracy when tissue hypo-perfusion may influence the ability of microneedle devices to accurately predict free drug concentrations in blood. However, invasive devices pose their own risks, including thrombosis [445]. Therefore, this type of invasive device would not be acceptable in the vast majority of individuals who receive antimicrobial therapy outside of critical care. A second consideration is the use of none invasive, sweat based monitoring systems. These have once again already been developed for glucose monitoring. However, very little data exists on whether this would be a viable option for monitoring antimicrobial concentrations [446].

7.1.2.3 Antimicrobial electrochemical sensing

Figure 27 outlines the key aspects of an electrochemical biosensor. Biosensors have been reviewed extensively for their use in medical applications [447] [448] [449–451]. They are particularly desirable given that the technology can often be miniaturised, facilitating the development of portable, easy-to-use, point-of-care devices that do not require expensive analytical machinery or technical ability to operate [447] [448].

Figure 27. Outline of the typical characteristics of a biosensor.



Electrochemical biosensors aim to convert a biological response into a quantifiable and processable signal [449–451]. They can be applied to a large variety of samples including, body fluids, cells, food stuff, and environmental material [449–451]. Methods of molecular recognition are varied but can be classified into two broad categories, depending on the nature of the interaction between recognition molecule and substrate. These are:

1. **Bio-catalytic sensors:** These rely on detection of the product of an enzyme catalysed reaction. These are the oldest and best characterised type of biosensor [452]. Enzymatic reactions applied to biosensor technology can be broadly thought of as two subclasses. Firstly, oxido-reductase reactions, such as occurs with the use of Nicotine-Adenine-Dinucleotide (Phosphate) (NADP) enzymes, like glucose oxidase. Upon exposure to glucose this causes a reaction which generates hydrogen peroxide, via the re-oxidation of the of the enzyme by oxygen [447]. The second class occurs through hydrolysis of substrate by the enzyme, such as I will be investigating in this *Chapter* exploring sensing of penicillin, which is hydrolysed by beta-lactamase to penicillinoic acid and a proton [453].
2. **Bio-affinity sensors:** These facilitate detection of a target molecule without conversion of the analyte upon binding. Examples of this type of sensor would involve the use of antibodies or more recently, aptamers, where a substrate binds to a receptor and is detected based on the conformational change in that occurs on binding of the substrate to the aptamer [449,454].

Following molecular recognition, transduction will occur being converted into a signal. Transduction occurs in a variety of ways. However, typically the reaction caused by molecular recognition will generate a measurable change in current (amperometric), a measurable potential or charge accumulation (potentiometric), or will alter the conductive properties of a material between two electrodes (conductometric) [448–452,454]. Alternatively, the binding event may be detected electrochemically through a measure in the

resistance and reactance of the system (impedance) or a transistor may be used to measure the effect on the current as a result of a potentiometric effect at a gate electrode (field-effect) [448–452,454].

Electrochemical sensors for the detection of antimicrobials in the environment, agriculture, and humans have been reported for a wide range of agents used in human medicine (**Table 22**) [406]. Electrochemical sensors for the detection and monitoring of antimicrobials are largely based on aptamer, antibody linked, or enzyme based methods of substrate detection [445,453,455]. However, there is a paucity of data for many antimicrobial agents to accurately support the ability of these devices to predict the PK in both tissue and plasma at present. A major development in the field of biosensors is the development of aptamer based methods of detection.

Aptamers are widely reported to be a potential game changer in the field of small molecule detection [454]. Aptamer sensors are nucleic acid sequences that are highly specific for a target molecule. On binding to their target they are able to produce a signal through the detection of a redox reaction. This is driven by a conformational change in the structure of the aptamer (normally leading to folding), which will move a marker that is attached to the aptamer (e.g. methyl blue) closer or further away from the biosensor surface. Aptamers are engineered using an *in-vitro* selection procedure, called Systematic Evolution of Ligands by EXponential enrichment (SELEX). They have a high sensitivity for detection of molecules down to the range of pico-moles in monitoring of certain environmental contaminants [455].

One such antibiotic aptamer sensor is the MEDIC device, described by Ferguson and colleagues [445]. This device has been reported to be able to monitor a number of different agents, including kanamycin, in real-time in ambulatory rodents. This used a liquid phase filter on a central venous catheter to prevent blood fouling the DNA aptamer sensor interface [445]. Within this study, live rats were injected with increasing doses of kanamycin, an aminoglycoside antibiotic, at hour intervals to demonstrate the ability to monitor the PK

profile in real-time, for both increasing and decreasing blood concentrations, using an aptamer sensor in the blood stream [445]. Aminoglycoside aptamers have also been tested against spiked human serum demonstrating accuracy for determining concentrations of routine, clinically observed targets between 2 to 6 μM .

Table 22. Summary of antimicrobial biosensors reported in the literature.

SENSOR	SETTING TESTED	RANGES OF DETECTION AND REPORTED LIMITS OF DETECTION		REF
Macrolides	<ul style="list-style-type: none"> - Spiked human urine - Water samples - Optimal analytical conditions 	In spiked human urine:	0-2µM (Azithromycin)	[456,457]
Quinolones	<ul style="list-style-type: none"> - Spiked human plasma - Spiked human urine - Milk - Optimal analytical conditions 	<i>In spiked human plasma:</i>	0.05-100 µM (CIP) 0.1-100 µM (OFL) 0.1-40 µM (NOR) 0.06-100 µM (GAT)	[458–463]
Chloramphenicol	<ul style="list-style-type: none"> - Milk - Spiked human urine - Food samples - Optimal analytical conditions 	<i>In food samples:</i>	0.08-1392 µM LLD 0.015 µM	[464–467]
Metronidazole	<ul style="list-style-type: none"> - Spiked human urine - Optimal analytical conditions 	<i>Calibration in lab:</i> <i>In spiked urine samples:</i>	Linear range 0.8 pM – 720 nM Reported recovery at concentrations 87, 96, 110, and 123 µM	[468]
Tetracyclines	<ul style="list-style-type: none"> - Meat / feedstuff samples - Spiked honey - Optimal analytical conditions 	<i>In feedstuff</i>	Linear range 0.3-52.0 µM (tetra) LLD 0.10 µM (tetra)	[469,470]
Rifampicin	<ul style="list-style-type: none"> - Optimal analytical conditions 	<i>Linear detection ranges:</i>	0.006–10.0 mmol L ⁻¹ with a LLD of 4.16 nmol L ⁻¹ And 0.04–10 mmol L ⁻¹ with a LLD of 2.34 nmol L ⁻¹ .	[471]
Penicillin's	<ul style="list-style-type: none"> - Optimal analytical conditions - Food / milk samples 	<i>In spiked milk samples:</i> <i>In optimal conditions:</i>	Linear range 3-283 µM and LLD 0.3 µM (Pen-G) Recovery from spiked samples was 102±6% Km value 67±13 µM reported using Michaelis Menten kinetics equation (Pen-G)	[472–488]

Aminoglycosides	<ul style="list-style-type: none"> - Optimal analytical conditions - Ambulatory animals blood stream - Spiked human serum 	<i>In spiked human serum:</i>	Accurate within therapeutic range of 2-6 μM	[445,479,480,489-497]
Lincomycin	<ul style="list-style-type: none"> - Optimal analytical conditions - Foodstuff - Spiked human urine 	<i>In optimal conditions:</i> <i>In spiked human urine:</i>	Linear detection range up to 1mM and LLD of 0.08 μM Recovery in samples was 96.44% to 103.26%	[498]
Sulfonamides	<ul style="list-style-type: none"> - Optimal analytical conditions - Milk - Spiked human urine 	<i>In optimal conditions:</i> <i>In spiked urine:</i>	Range of 0.1–10.0 mmol L ⁻¹ with LLD of 60 nmol L ⁻¹ (TMP) AND 1.0–10.0 mmol L ⁻¹ with LLD of 38 nmol L ⁻¹ (SMX) Recovery 91.3-101%	[499–501]

Legend: CIP = ciprofloxacin; OFL = ofloxacin; NOR = norfloxacin; GAT = gatifloxacin; LLD = lower limit of detection; tetra = tetracycline; Pen-G = penicillin-G; TMP = trimethoprim; SMX = trimethoprim/sulfamethoxazole.

As well as aptamer based methods for sensing, enzyme based methods are also well described [406]. Enzymatic penicillin-G sensors are some of the oldest antimicrobial sensors reported [453]. These reactions can be detected through electrical, optical, or calorimetric methods [486]. The majority of enzyme based techniques for penicillin sensing detect the hydrolysis of penicillin to penicillinoic acid and a hydrogen ion. One recent example was reported by Ro-Lee and colleagues utilising field-effect devices [476]. The authors described a high sensitivity of their enzyme based device, its stability during storage, and re-usability over a 30 day period [476].

To date, antimicrobial sensing has been demonstrated on microchips, disc electrodes, and nano-tubes. This makes the devices small and highly transportable. Based on current evidence provided by microdialysis of critically ill patients tissue ISF concentrations, microneedle based sensing is a potential avenue for estimation of antimicrobial concentrations and real-time monitoring [421–423]. However, the major gap in the literature supporting translation is a paucity of human, *in-vivo* studies with such biosensors to demonstrate their resistance to bio-fouling from proteins such as albumin and immunoglobulins [447,502]. Furthermore, there remains limited data on the expected concentration of free antibiotic concentrations within the ISF for many antibiotics. This makes it challenging to accurately predict the characteristics of tissue PK for these agents and allow accurate estimates of the linear range of response that such sensors will be required to work in for translation into human studies.

7.1.2.4 Closed-loop control for drug delivery

Closed-loop controllers have a broad application in the field of diabetes, being the cornerstone of novel developments, such as the artificial pancreas system [416,503]. Furthermore, closed-loop control has been demonstrated as effective in controlling delivery of both intravenous and inhaled anaesthetic agents during surgery [417,418]. Working with

colleagues with experience of closed-loop control (led by Dr Pau Herrero and supervised by Dr Pantelis Georgiou), I have already been able to demonstrate the potential of this technology for personalised antimicrobial dose delivery in pre-clinical and *in-silico* studies [445,504]. Two of the most widely used and most robust controllers for continuous and intermittent bolus infusions are the PID and ILC controllers, respectively [429,430]. A detailed explanation of these types of controllers can be found in technical **Appendix 8 section a8.2**.

These controllers are algorithms that optimize the delivery of an agent against a pre-determined set point. The example used for proof-of-concept was vancomycin dosing, using data from 25 individuals who had previously been demonstrated to achieve the target PK-PD index in 63% of cases using routine TDM approaches [397,504,505]. If linked with Bayesian dose optimization software or Case-Based-Reasoning platforms, which can provide individualized initial dose selection, and novel *in-vivo* mechanisms of predicting antimicrobial PD these could offer a powerful approach to reducing the errors that are commonly observed in the practice with current dose optimisation strategies.

In terms of translating these into microneedle sensor driven closed-loop control systems, the biggest challenge that remains is accurately describing individual antimicrobials relationship between tissue and plasma PK. This is especially important to consider during the initial phase of dosing, when the drug is not at steady state. A greater understanding of this concept is required to accurately describe the relationship between free concentrations of drug in both compartments. It will likely require rich plasma and microdialysis PK sampling to support the development of controller algorithms.

7.1.2.5 Additional Pharmacokinetic – Pharmacodynamic indices for individualising therapy

Currently individualised PK-PD indices rely on factors such as the Minimum Inhibitory Concentration (MIC) to form part of time and concentration dependent measures for exposure-response (e.g Area-Under-the-Curve[AUC]:MIC, Time>MIC, or Peak:MIC). MIC as a PD target requires isolation of the causative pathogen and determination of the individual organism's susceptibility. This causes a practical problem in cases where the invading pathogen is not identified, as is observed during the empirical phase of antimicrobial therapy, and in a significant proportion of cases of sepsis that remain culture negative throughout the treatment period [506,507]. Therefore, in the absence of microbiology results, population level assumptions are made about the most likely organism causing the infection and the average MIC of this population. Thus, this does not provide a truly individualised index on which to optimise antimicrobial therapy.

To address this, recent studies have reported the use of the ratio of the AUC to the EC₅₀ in paediatric populations [433,434]. The EC₅₀ is the concentration of a drug (mg/L) that is estimated to induce a half maximal antibacterial effect (such as reduction in serum CRP or galactomannan, a specific plasma marker in aspergillus infection) for an individual patient. The AUC:EC₅₀ ratio can provide an *in-vivo* estimate of drug response by linking drug exposure with PD [433,434]. Acting as an *in-vivo* measure of potency, AUC:EC₅₀ enables an estimate of the host immune response to the invading organism. This has the potential to circumvent the problems associated with *in-vitro* MIC estimation and may provide data that can drive the development of real-time algorithms for the delivery and control of individualized antimicrobial therapy. This approach will be explored in detail in *Chapter eight*. Therefore, it will not be reviewed further within this *Chapter*.

7.1.2.6 Drug delivery

With the exploration of microneedle based technology as a mechanism of drug delivery, it is also important to consider the optimal method by which delivery could occur within closed-loop control systems. During initial development of this concept, intravenous and oral delivery of agents via infusion pump and personalised dosing alerts is likely to be the initial focus. However, microneedles are now being investigated to provide dual functions of sensing and also drug delivery [443]. In the field of infection, the rate of drug delivery that can be achieved may be hindered by certain drug characteristics (such as hydrophilic versus hydrophobic agents) and the volume of agent required to be delivered. However, drug delivery by microneedle may provide an interesting avenue for certain challenging cohorts, such as paediatric patients, as well as for local antimicrobial therapy delivery, such as skin and soft tissue infections or penetration of collections.

7.2 Chapter Objectives

Given the current state-of-the-art in the literature and the importance placed upon finding better methods for both drug monitoring and defining PK-PD indices, I have chosen to focus upon these aspects within *Chapters seven and eight*. Therefore, within these two *Chapters* I aim to investigate two of the core concepts outlined in sections 7.1.2.2 and 7.1.2.5, respectively.

The objectives of this *Chapter* are:

1. Investigate whether it is possible to develop a microneedle biosensor for the continuous monitoring of beta-lactam antibiotics.
2. Characterise the *in-vitro* response of such a biosensor and explore its fundamental characteristics.
3. Demonstrate proof-of-concept for *in-vivo* microneedle based continuous monitoring of beta-lactam antibiotics.

Sensor targets to be achieved:

This *Chapter* aims to describe the preliminary exploration and development of a microneedle biosensor to facilitate proof-of concept for this technology in humans. Within this work, I would be required to undertake multiple iterations of design and testing. Therefore, on commencing this project, I felt that it was important to have clear targets to aspire to and maintain the focus of development. In setting these targets for my sensor, I built on the suggestions of O'Hare and Greishaber who both outline the ideal characteristics for biosensors in their respective reviews of this subject matter [447,449].

The targets for the device that I hoped to achieve by the end of this *Chapter* were:

1. The device should have an appropriate dynamic range for sensing beta-lactam antibiotics in human tissue ISF. This should include characterising the lower limit of detection (LLD), linear operating range, and maximum operating concentration (V_{max}).

2. The sensor must be stable for use *in-vivo*. This would ideally facilitate *in-vivo* monitoring for at least 24 hours continuously and be stable for up to 28 days in storage.

3. The output from the sensor must therefore be reproducible over time.

4. Ideally the response would be logarithmic, with a large enough change in potential per decade change to facilitate a linear operating range.

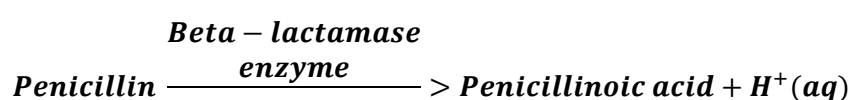
5. The device must be biocompatible and acceptable for use in humans (including passing an ethics board for provisional studies).

6. The device should be small, portable, and be capable of being used by non-technicians.

7.3 Methods

7.3.1 Study setting and rationale

This study took place at Imperial College London, Department for Biomedical Engineering, where I was supervised by Dr Danny O'Hare (Bioengineering) and Professor Tony Cass (Chemistry). For the initial development of an antimicrobial biosensor I opted to explore a mechanism of detection that follows a well described and natural biological reaction; the hydrolysis of beta-lactam antibiotic by a beta-lactamase enzyme.

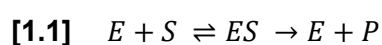


This reaction can be detected using a number of different approaches that rely on the change in pH that occurs as the rate of hydrolysis of penicillin is altered (i.e. by changes in penicillin concentration)[508]. Before proceeding, it is helpful to outline a number of key principles that underpin the development of enzymatic biosensors.

7.3.1.1 Enzyme kinetics

Michaelis and Menten provide a simplistic description of enzyme kinetics at steady state. An understanding of the Michaelis-Menten equation derived through this description is important for the subsequent evaluation of enzyme based biosensors [509].

Michaelis and Menten use a simplified model to describe enzyme reactions in terms of an enzyme (E) and substrate (S) that can form a complex (ES) in a reversible, rapid equilibrium. Furthermore, irreversible breakdown of ES leads to a product (P) as the rate determining step.



The equilibrium reaction can be described with the rate constants k^1 and k^{-1} for the forward and backward reactions, respectively. The irreversible breakdown of ES to P can be described using the rate constant k_{cat} [510,511]. When e_{tot} describes the total enzyme concentration and e_{ES} describes the concentration of enzyme-substrate, the concentration of uncomplexed enzyme can be determined using $(e_{tot} - e_{ES})$. Given the concentration of substrate is normally much greater than the enzyme concentration at steady state, we can assume that the initial concentration of substrate, s , is equal to the concentration of uncomplexed substrate [509]. This allows the expression of [1.1] as a differential equation.

$$[1.2] \quad \frac{de_{ES}}{dt} = k_1 (e_{tot} - e_{ES}) s - k_{-1}e_{ES} - k_{cat}e_{ES}$$

During steady-state, $\frac{de_{ES}}{dt}$ is likely to be small compared to the reaction flux, which can be described using $k_1e_{tot}s$ [509]. This is because [ES] should be constant at steady state, therefore, $\frac{de_{ES}}{dt} = 0$. Therefore, e_{ES} can be described using

$$[1.3] \quad e_{ES} = \frac{k_1e_{tot}s}{k_1s + k_{-1} + k_{cat}}$$

We can describe the rate of the enzyme reaction (V) by the expression

$$[1.4] \quad V = k_{cat}e_{ES}$$

This can then be substituted into [1.3] to give

$$[1.5] \quad V = \frac{k_1e_{tot}s}{k_1s + k_{-1} + k_{cat}}$$

This equation can then be re-written as the Michaelis-Menten equation, given the assumptions that Michaelis and Menten made, treating ES concentration as at steady-state [509]. Here, the reversible equilibrium reaction as described as a single rate constant, K_{MS} .

$$[1.6] \quad V = \frac{k_{cat}e_{tot}s}{K_{MS} + s} = k_{ES}$$

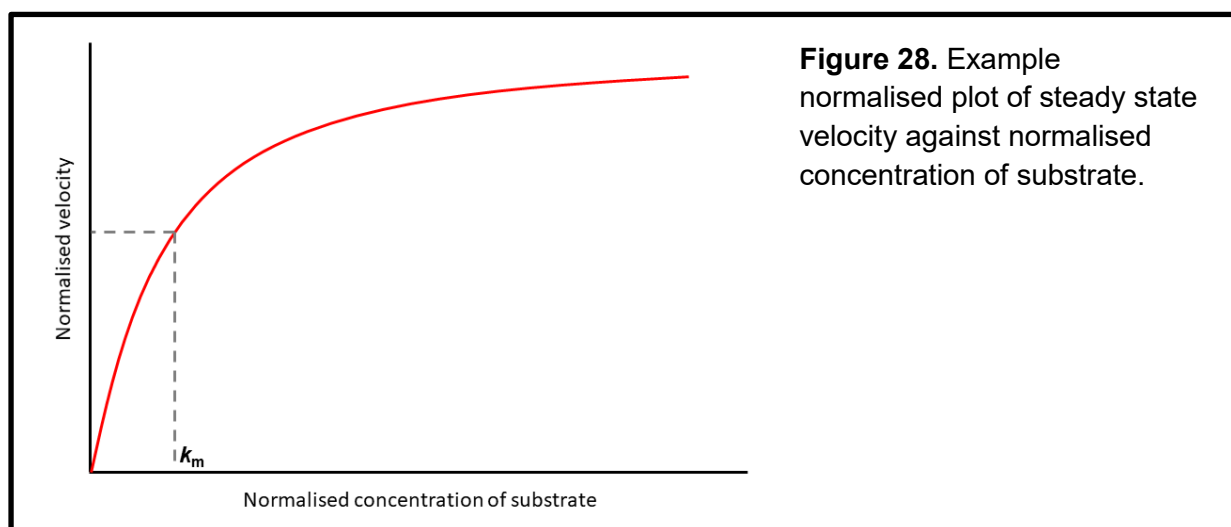
Therefore, k_E can be described as

$$[1.7] \quad k_E = \frac{k_{cat}e_{tot}}{K_{MS}+s}$$

Within this equation, we find that $k_{cat}e_{tot}$ describes the maximum reaction velocity and therefore the K_{MS} is the Michaelis constant, described by

$$[1.8] \quad K_{MS} = \frac{k_{-1} + k_{cat}}{k_1}$$

These concepts, and particularly equation [1.6], describing the Michaelis - Menten equation are vital for developing and evaluating the enzyme based biosensor described within this *Chapter*. **Figure 28** is an example of a normalised plot of steady-state velocity against substrate concentration for an enzyme that follows Michaelis – Menten kinetics.



At low velocity, when substrate concentration (s) is much less than the half maximal velocity of the enzyme reaction (K_{MS}), a linear response is observed. When $s = K_{MS}$ we observe the reaction rate at half its maximal velocity. At large concentrations of s , the reaction velocity becomes independent of substrate concentration, being described by $k_{cat}e_{tot}$ only. This demonstrates the core features of enzyme reactions that obey Michaelis – Menten kinetics. At low substrate concentration, first order, linear response is observed. At high substrate concentration, the reaction becomes zero-order and thus is non-linear [510].

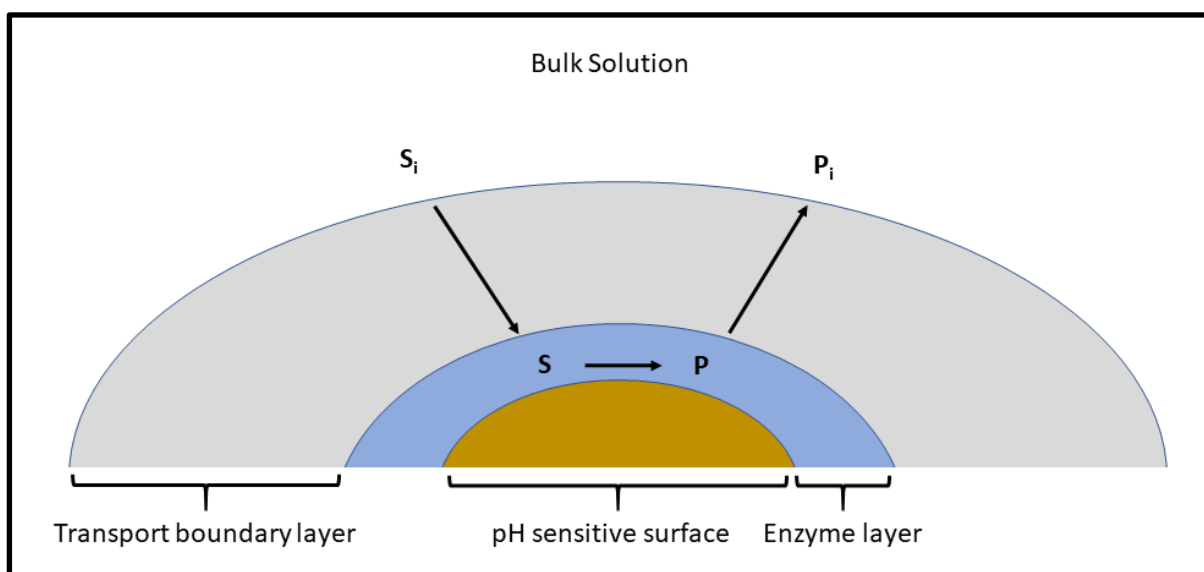
An understanding of Michaelis – Menten is important for considering biosensor applications, given that when $s \gg K_{MS}$, a sensor that has been developed will be limited by enzyme kinetics. Therefore, development of our biosensor must aim to operate at levels where $s < K_{MS}$.

It is also important to link this to an understanding of the effects of mass transport on the enzyme electrode when characterising such devices [512,513]. For my biosensor, the aim is for the enzyme to be immobilised at the sensor interface, with the potentiometric detection of a product of the catalytic reaction. In this case, this will be the detection of hydrogen ion production.

7.3.1.2 Understanding the effects of mass transport on the biosensor

Understanding the enzyme kinetics and effects of mass transport on our biosensor may mean that it is possible to estimate the concentration of penicillin being hydrolysed to penicillinoic acid using the reaction outlined above in *section 7.3.1*. However, the biosensor surface must first be characterised. **Figure 29** depicts the theoretical kinetic model for a biosensor similar to the one being developed within the *Chapter*, including the fluxes involved in the reaction.

Figure 29. Theoretical kinetic model for an enzyme based biosensor.



For estimation of the sensor model, a number of assumptions will be made, based on the work of Eddowes [512,513]. Firstly, in **Figure 29**, we assume that the sensor surface lies at $x = 0$. This is coated with an immobilised enzyme layer of thickness l . Outside of this layer is a transport boundary layer with a characteristic mass transport rate constant, k_D . Beyond this boundary layer the concentration of substrate, S , is taken to be defined by $[S]_i$ and the product of the enzyme reaction, P is zero. The enzyme reaction that occurs within the enzyme layer will be assumed to follow the Michaelis - Menten kinetic equation described in equation [1.6]. This reaction will deplete the substrate in the enzyme layer and produce product. This will generate a diffusion gradient to drive the mass transport process [512]. The product is then detected at the biosensor surface potentiometrically. It is not consumed by this and means that a steady state occurs within the immobilised enzyme layer where the reaction of the enzyme is balanced by mass transport.

For this example, Eddowes assumes that the concentration of enzyme and substrate within the reaction layer are uniform. This will allow approximation based on the thickness of the immobilised enzyme layer, the relative rates of mass transport, and the enzyme reaction [512,513]. These assumptions avoid having to solve the differential of Fick's second law. Instead, using three processes the relationship between bulk solution concentration of the substrate and surface concentration of the product can be described.

Firstly, the transport flux of the substrate towards the surface, j_D , can be described in terms of k_D :

$$\mathbf{[1.9A]} \quad j_D = k_D([S]_i - [S]_l)$$

Secondly, j_R , the enzyme layer reaction flux can be described using the Michaelis-Menten reaction:

$$\mathbf{[1.9B]} \quad j_R = \frac{l k_2 [E][S]_l}{K_M + [S]_l}$$

Finally, the transport flux of the product away from the sensor surface can be described by:

$$\mathbf{[1.9C]} \quad j_D = k_D[P]_l$$

Within these examples, $[S]_l$ and $[P]_l$ are the substrate and product concentration within the enzyme layer. It should be noted that within the example of penicillin-penicillinase, $[P]_l$ can refer to either penicillinoic acid or H^+ , as both are products of the reaction. At steady state, as is assumed here, the fluxes will be equal, which means that [1.9A-C] can be assumed as three simultaneous equations with three unknown parameters; j , $[S]_l$, and $[P]_l$.

Within this study, I am interested in being able to determine $[P]_l$ in terms of H^+ , by eliminating unknowns [512,513]. For example, j can be eliminated by equating [1.9A] and [1.9B] providing an expression for $[S]_l$.

$$\mathbf{[2.0]} \quad k_D([S]_i - [S]_l) = \frac{k_2[E][S]_l}{K_M + [S]_l}$$

Therefore, we can use examples provided by Eddowes to consider the utility of this equation [512,513].

1) Assuming a case where $[S]_l \ll K_m$, we can drop the $[S]_l$ term in the denominator of the equation and simply re-arrange to describe $[S]_l$.

$$\mathbf{[2.1]} \quad [S]_l = \frac{1}{1 + \frac{k_2[E]}{k_D K_M}} [S]_i$$

This equation can then be substituted into [1.9A] and equated to flux equation [1.9C] to provide a description of the relationship between bulk substrate concentration and the surface product concentration.

$$\mathbf{[2.2]} \quad [P]_l = \frac{\frac{k_2[E]}{k_D K_M}}{1 + \frac{k_2[E]}{k_D K_M}} [S]_i$$

2) When $[S]_l \gg K_m$, Eddowes [512,513] describes how K_m can be removed from the denominator of the equation in [2.0]. This describes the surface reaction flux of the product, which in this case is independent of the substrate concentration, given that the reaction is now zero order.

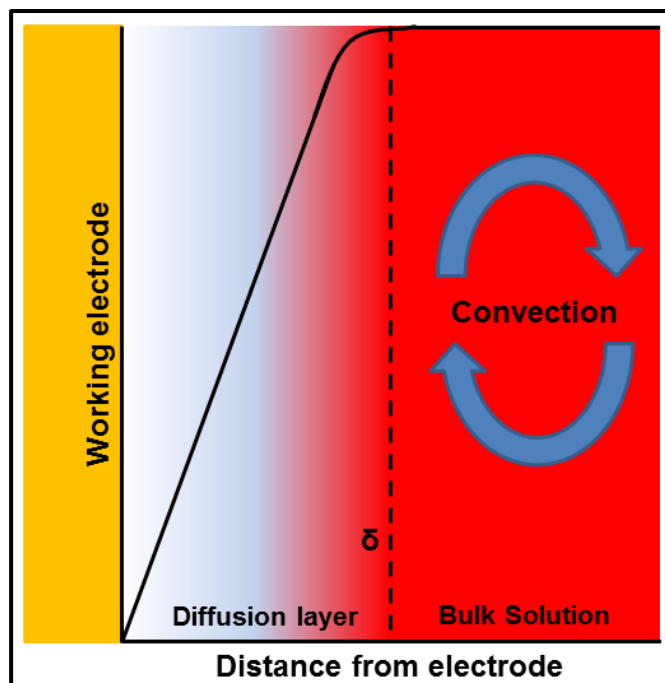
$$\mathbf{[2.3]} [P]_l = \frac{k_2[E]}{k_D}$$

Equations [2.0], [2.2], and [2.3] should theoretically provide the ability to solve cases at both high and low concentrations of substrate.

Another consideration when characterising the biosensor is that the rate of stirring of any external solution may lead to variable rates of convection and thus variable boundary layer thickness [509]. This means that we may never truly reach a steady-state, with the concentration gradient at the electrode surface varying with alterations in the rate of reaction or rate of stirring.

A well defined mechanism of inducing a steady state of delivery of substrate to the electrode surface is through the use of a rotating disc electrode (RDE) [509]. By rotating a disc electrode at a known rate, this generates experimental conditions of forced convection with mass transfer of the substrate to the electrode by both convection and diffusion [509]. This occurs by inducing convection dominated transfer away from the electrode and diffusion dominated transfer close to the surface. Between these two interfaces sits a boundary layer, the thickness of which can be accurately controlled (and calculated) using a RDE approach (**Figure 30**).

Figure 30. Example of boundary layer concept that we aim to control using the Rotating Disc Electrode.



Legend: Figure adapted from Bartlett PN *et al.* Modelling Biosensor Responses. Bioelectrochemistry. Chichester, UK: John Wiley & Sons, Ltd; p. 267–325.

The RDE diffusion layer thickness (δ) can be estimated using the following equation

$$[2.4] \delta = 0.643\nu^{1/6}D^{1/3}\omega^{-1/2}$$

Where ν ($\text{cm}^2 \text{s}^{-1}$) describes kinematic viscosity, D ($\text{cm}^2 \text{s}^{-1}$) is the diffusion coefficient for the electroactive substance being studied, and ω (Hz) is the RDE rotation speed.

When steady state is reached using an RDE (**Figure 30**), convection of substrate on the outside of the boundary layer maintains the concentration of the bulk solution, whilst diffusion from the boundary layer balances the flux of substrate reacting at the electrode surface. Under these conditions using a RDE, the rate limiting step is the diffusion across the stagnant layer around the electrode. J_{ss} , is the steady state flux and can be described by

$$[2.5] J_{ss} = \frac{D s_{bulk}}{\delta}$$

With s_{bulk} describing the bulk concentration of substrate.

7.3.1.3 Iridium Oxide for pH measurements *in-vivo*

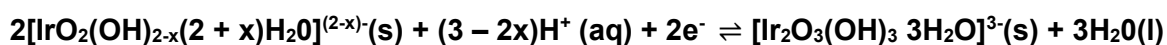
Given that I have chosen to explore the use of an enzymatic biosensor, which utilises a hydrolysis reaction, I will be required to detect changes in pH as the rate of hydrolysis increases and decreases. Several approaches to measurement of pH are well characterised for biosensor development. The hydrogen, glass electrode is probably the most accurate [514,515]. However, it has a number of serious limitations when considering *in-vivo* biosensors [514,515]. This includes, high impedance, slow response times, and being mechanically fragile [514,515]. This makes scaling down the size of such an electrode challenging [514,515]. Metal-metal oxide electrodes have previously been demonstrated to show quick response time, stability, and low impedance making them ideal for *in-vivo* biosensor development [514–516]. Several metal-metal oxides have previously been described including, antimony electrodes [517], iridium-iridium oxide (IrOx) [518], platinum-IrOx [519], gold-IrOx [520], and tungsten-tungsten oxide films [521]. These electrodes are ideal for pH sensors as the potential (E) of the electrode results from the equilibrium between the soluble oxide and saturated solution, changing according to:

$$\text{[2.6]} \quad E = E^{0'} - 2.303 \frac{RT}{nF} pH$$

Here, $E^{0'}$ is the standard potential, including the ionisation product of water and solubility product of the metal oxide, R is a gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$), T is temperature in Kelvin, F is Faraday's constant ($96,485 \text{ C mol}^{-1}$), and n is the number of electrons transferred.

Yamanaka previously demonstrated that anodic deposition of IrOx films can produce smooth, compact films that typically produce a super-Nernstian response (potential change of greater than -0.061 V per pH change) [514,516]. This occurs due to proton to electron

ratios of greater than 1 being achieved by hydrolysis of a hydrated oxide layer overlying a compact anhydrous layer within the film [514,515]. The general equation describing this is:



Where x varies depending on film hydration. Typically, super-Nernstian responses between -0.061 and 0.090 V per pH are observed [447,514,518]. Given the versatility and well documented response of IrOx films and the large change per decade in potential, I opted to explore anodically depositing these on both gold and platinum electrodes.

7.3.1.4 Planned workflow

Given the above theoretical background, I decided to take a stepwise approach to investigating the development of a microneedle biosensor for beta-lactam antibiotics. This would be investigated in a stepwise fashion:

1. Develop a protocol for fabrication of an immobilised beta-lactamase based biosensor for monitoring beta-lactam antibiotics using a disc electrode.
2. Characterise the biosensor using a rotating disc electrode to understand the effects of mass transport at different antimicrobial concentrations.
3. Transfer the final technology onto a microneedle array and evaluate its response in interstitial fluid to detect beta-lactam antibiotics.

7.3.2 Reagents and equipment

The protocols that I developed for this study are described in **Appendix 7**. Several iterations were explored during the development of the protocol for biosensor fabrication. This included membrane formulation, geometry, and size. Agents used within this *Chapter* were purchased from Sigma Aldrich (UK) and used as received unless otherwise stated. I rinsed with and

prepared all aqueous solution using deionised water. This has a resistivity of >15 MΩcm. Phosphate Buffer Solution (PBS, 0.1M phosphate, pH 7.4 at 25 °C) was used unless otherwise stated. Iridium oxide plating solution (100 ml) was prepared as described by Yamanaka [516] using iridium chloride hydrate ($\text{IrCl}_4 \cdot \text{H}_2\text{O}$, 0.15 g), aqueous hydrogen peroxide (H_2O_2 ·30%wt, 1 ml), oxalic acid ($(\text{COOH})_2 \cdot \text{H}_2\text{O}$, 0.5 g), and anhydrous potassium carbonate (K_2CO_3 , 3.9 g), leaving the solution to stabilise for 72 hours before use [516]. IrOx was then stored in the fridge between uses and remade after 90 days storage.

A class B beta-lactamase from *Bacillus cereus* 569/H9 was purchased from Merck Millipore with a mixture of beta-lactamase I & II. For the final enzyme immobilisation used across all sensors, I used 5% aqueous polyethylenimine (PEI). Cellulose acetate also tested initially. Furthermore, I also prepared three further solutions:

- (i) 5 ml 0.1 M phosphate buffer (pH 7.4) with 25 mg / ml beta-lactamase;
- (ii) 5 ml of 0.1 M phosphate buffer (pH 7.4) with 50 mg / ml bovine serum albumin (BSA); and
- (iii) glutaraldehyde solution ($\text{C}_5\text{H}_8\text{O}_2$, 2.5%), used to cross-link the beta-lactamase – BSA to the surface of the biosensor.

Several different approaches were initially tested and validated on standard disc electrode devices.

For calibration of the sensors, penicillin-G, amoxicillin, ceftriaxone, and amoxicillin-clavulanate were obtained from Sigma-Aldrich and stock solutions of each beta-lactam prepared in PBS or artificial interstitial fluid (described below) for dilution. These were made fresh for each calibration run, given the rapid degradation of beta-lactam antibiotics in solution [522].

Cyclic voltammetry, iridium oxide deposition, and open circuit potentials (OCP) were performed using a CHI 650a potentiostat. pH calibration curves were recorded with a Mettler Toledo SevenEasy pH meter.

7.3.2.1 Electrodes used for studies

5 mm diameter platinum and gold disc electrodes were purchased from Alvatek Ltd. The 15 mm gold and platinum RDE and Pine Modulated Speed Rotator (MSR), were from Pine Research.

The base microneedle array for this study was provided by Professor Tony Cass and Dr Sanjiv Sharma [436]. The fabrication process has previously been described in detail [436,523]. An description of this can be found in technical **Appendix 8**, section a8.3.

For preliminary *in-vivo* testing, Torr Scientific Ltd performed metallisation of the microneedle bases with gold and silver sputtering, using a megatron sputter coater. This protocol was developed in collaboration with Torr as a means on providing scalability to the project and improving quality control of the microneedle fabrication process.

7.3.3 Biosensor preparation

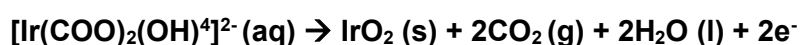
All electrodes were prepared in the same fashion unless otherwise stated. The final protocols for fabrication that I developed can be found in **Appendix 7**. Final protocols used for fabrication were 1.4.2 for disc electrodes and RDE and 1.4.2 and 2.0 for the microneedles.

Disc electrodes were cleaned by polishing with emery paper (P1000, P2500, P4000) and alumina polish (1.0 μM , 0.3 μM , 0.05 μM). Electrodes were cleaned for 3 minutes per step, being polished in a figure of eight motion and rinsed before moving onto the next step. Electrochemical cleaning was then performed using cyclic voltammetry in 1.0 M H_2SO_4 for

50-100 cycles. Disc electrodes were stored in deionised H₂O until used. For the microneedle arrays, cyclic voltammetry was found to destroy the metallised layer on the needles. Therefore, I opted to prepare these by rinsing the surface with ethanol followed by rinsing with deionised H₂O.

For the remainder of the protocol, the process was similar for disc electrodes and microneedles.

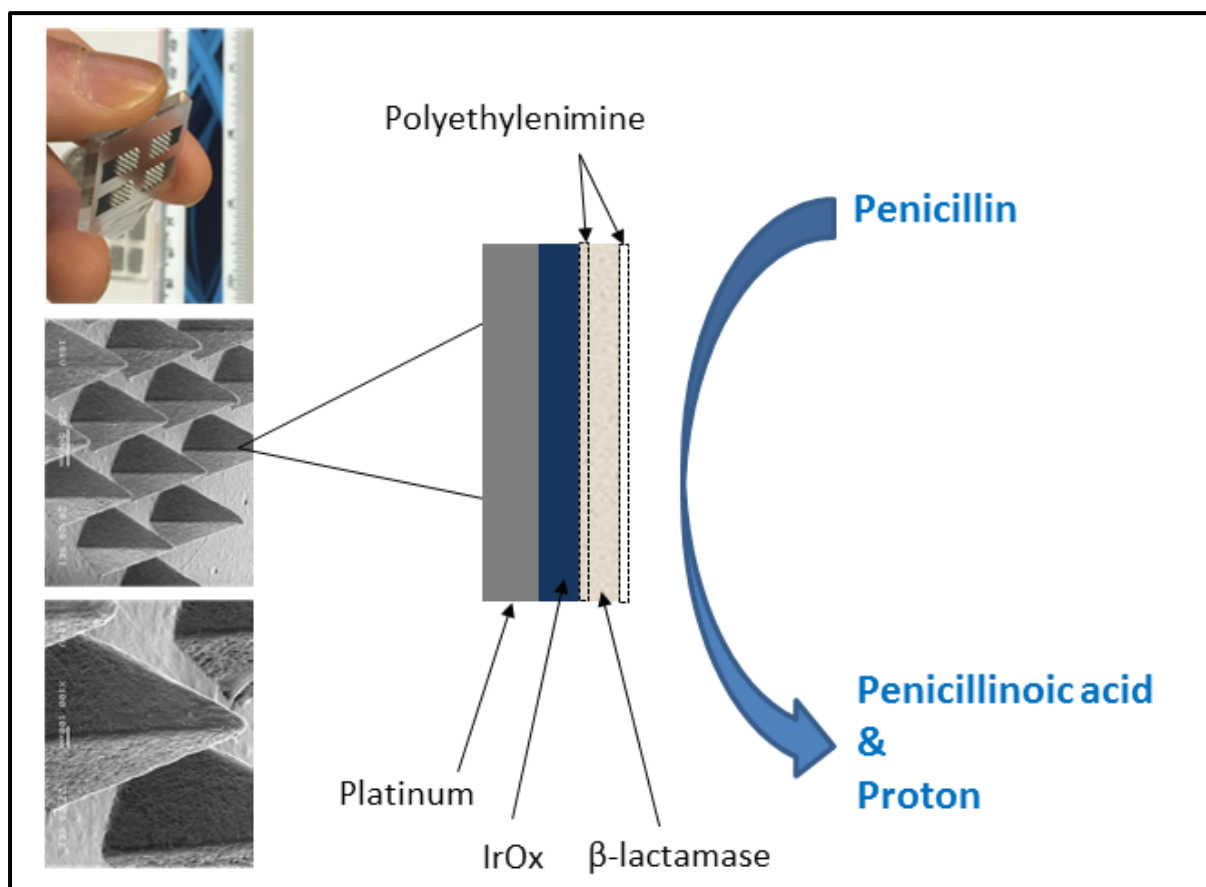
Iridium oxide was electrochemically deposited on the electrodes at a constant potential of 0.95 V for 300 seconds for three cycles with an interval of 10 minutes soaking in the IrOx between cycles. This process of anodic electrodeposition was demonstrated by Yamanaka [516] to produce smooth and compact film when alkaline IrOx was used. On application of a constant potential to the solution, the following reaction occurs:



This causes oxidation of the IrOx ligand liberating carbon dioxide (CO₂) gas and depositing a solid IrOx layer onto the electrode [516]. pH calibration of anodically electrodeposited iridium oxide films (AEIROFs) was performed in PBS with OCP recorded for the pH range 4.0-8.0.

Figure 31 outlines the design of the biosensor. Following AEIROF formation, polyethylenimine (PEI) was layered onto the AEIROFs for mechanical stability. Beta-lactamase was then immobilised onto the electrode surface by depositing beta-lactamase and BSA solution with 2.5% glutaraldehyde solution acting as a fixing agent, cross linking the BSA and beta-lactamase. This was left for 90 minutes and then rinsed. Finally, another layer of beta-lactamase solution alone was deposited onto the outer membrane. After drying a final layer of PEI was added. Sensors were stored in deionised H₂O for at least 24 hours at 4 °C before use.

Figure 31. Outline of the design of the microneedle enzymatic electrochemical biosensor.



Legend: IrOx = iridium oxide

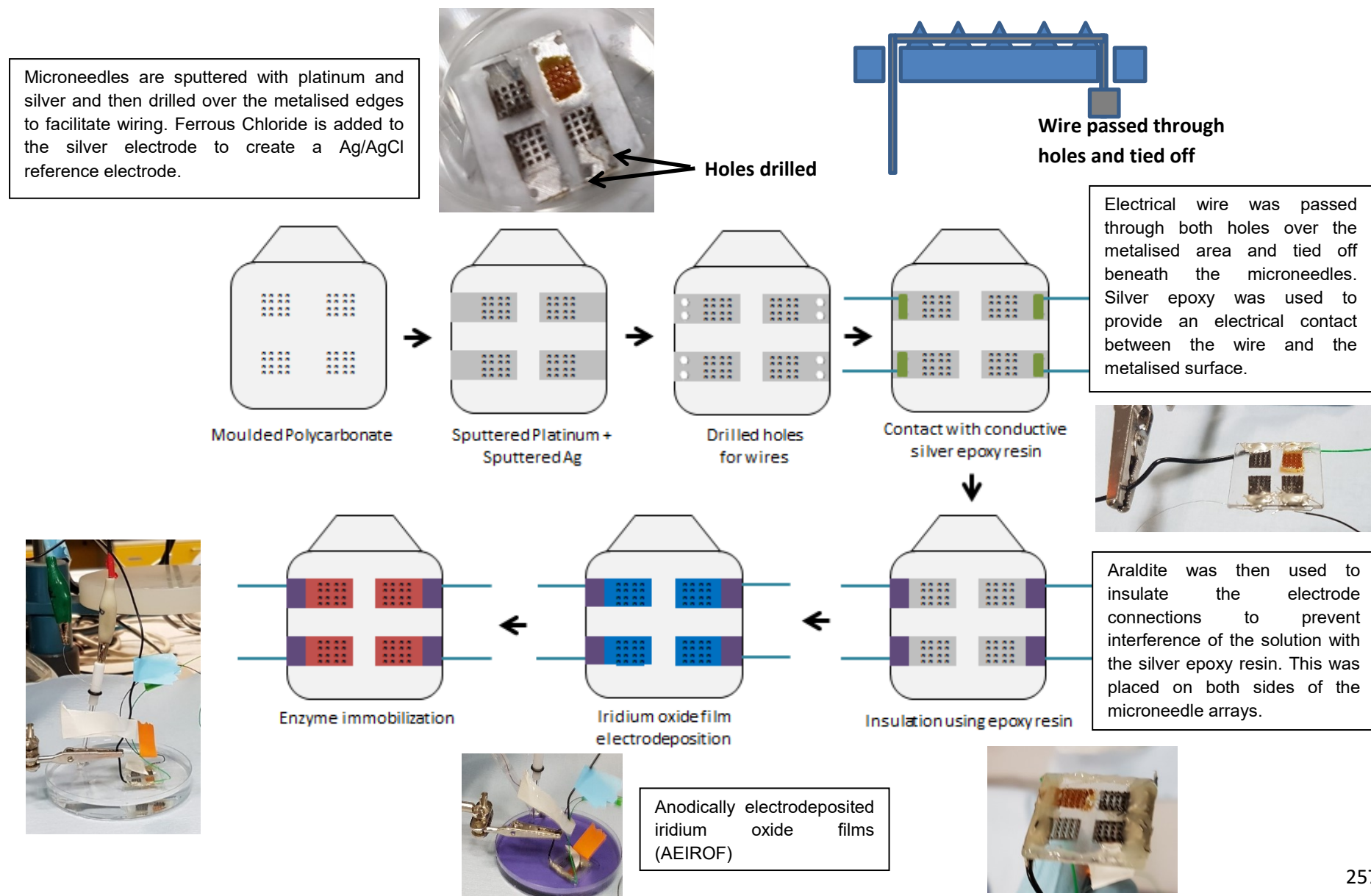
As described below, cellulose acetate was initially used in place of PEI following previous recipes for enzymatic biosensor [524]. However, several challenges were identified, likely due to interference with the AEIROF layer, reducing its response to pH.

7.3.3.1 Microneedle biosensor fabrication process

Figure 32 summarised the fabrication process for the microneedle biosensors. The final protocol for fabrication followed that described in *section 7.3.3* and **Appendix 7**. However, several other specific aspects required my consideration during the fabrication process. These included;

- i) Different types of wire were explored from use of fine silver wire through to 1-1.5mm single strand copper annealed wire. No difference was observed in the response of the sensor between these and electrical connections were similar between all. Therefore, for *in-vitro* work I opted to use the thicker wire, as this added an extra element of stability to the sensor when it was mounted within the test solution.
- ii) Araldite was selected over epoxy resin as the sealant to protect the silver-epoxy used to make the conductive electrical connection between the metallised surface of the sensor and the wire. This was because Araldite dries within four hours, compared to the epoxy, which takes up to 72 hours. Furthermore, the epoxy tended to lose some of its integrity when left in solution, potentially contaminating the calibration solution and exposing the silver epoxy connections.
- iii) For enzyme immobilization a number of different volumes of PEI, and beta-lactamase solution were tested. The aim was to maintain a response rate that stabilised within 300 seconds of calibration in pH solution, whilst also providing a robust enzyme layer to ensure sensitivity of the device. The final volumes described in the sensor fabrication protocol in **Appendix 7** were identified to be the optimal amounts to achieve this.

Figure 32. Microneedle fabrication summary.



7.3.4 Beta-lactam antibiotic calibration

Initial calibration with beta-lactam antibiotics was performed using the disc electrodes to facilitate the characterisation of the sensors response to different beta-lactam antibiotics. A range of beta-lactams were selected based on their relative resistance to hydrolysis by beta-lactamase enzyme. The agents selected were:

- i. **Penicillin-G:** The standard used to describe hydrolysis by the selected beta-lactamase enzyme. One unit of the enzyme will hydrolyse 1 μmol of penicillin-G every minute at 25°C. In this case our enzyme concentration was ~ 250 units/ml [522].
- ii. **Amoxicillin:** a beta-lactam with increased stability to hydrolysis by beta-lactamase compared to penicillin-G [525,526].
- iii. **Ceftriaxone:** A third-generation cephalosporin with greater resistance to hydrolysis in clinical practice compared to amoxicillin [525,527–529].
- iv. **Amoxicillin-clavulanate:** Clavulanic acid is a beta-lactamase inhibitor which would be expected to inhibit the hydrolysis of beta-lactams by beta-lactamase enzyme. This reaction is initially reversible, progressing over time to irreversible inactivation [512].

A stock solution of beta-lactam was prepared in PBS. OCP were recorded for increasing concentrations of beta-lactam from 50 - 5000 μM , based on reports of similar concentrations of beta-lactam detected in patients sub-dermal interstitial fluid [421,423]. This was achieved by adding the concentrated stock solution to PBS under gentle stirring. OCP's were recorded over 600 seconds, or until stable potential was reached. Calibration plots were fitted using the Hill equation [2.7] with K_m values and the maximum velocity (V_{max}) estimated from concentration (M) – potential (E) plots.

$$[2.7] V = \frac{V_{\text{max}} [S]}{K_m + [S]}$$

Where V is the velocity of the enzyme reaction ($M s^{-1}$), V_{max} is the maximum velocity of the reaction ($M s^{-1}$), $[S]$ is the substrate concentration (M), and K_m is the half maximal concentration constant for the reaction.

The slope of log-concentration $[M]$ – potential $[E]$ plots of the data was also investigated to allow comparison of the linear response of the sensors. Intra-sensor and inter-sensor reproducibility was assessed by calculating the percentage coefficient of variation (%CV) [530,531]. This %CV is a methods of calculating the ratio of standard deviation to the mean and is often used to assess the reproducibility of an assay [530,531]. Commercially, %CV of <15% are defined as demonstrating accurate precision in readings by the European Medicines Agency and the Federal Drug Administration [530,531]. For this pilot work, I decided that no target for precision would be set in advance.

After calibration, the sensor was then stored at 4 °C for 28 days and the calibration repeated to assess response over time.

7.3.5 Artificial interstitial fluid preparation and calibration

I prepared artificial interstitial fluid by mixing;

- i) standard physiological solution (0.9% NaCl),
- ii) 11 g/L total protein made up of bovine serum albumin and human alpha-globulins (cohn factor IV-1) in a ratio of 60:40, and
- iii) 5 mM dextrose.

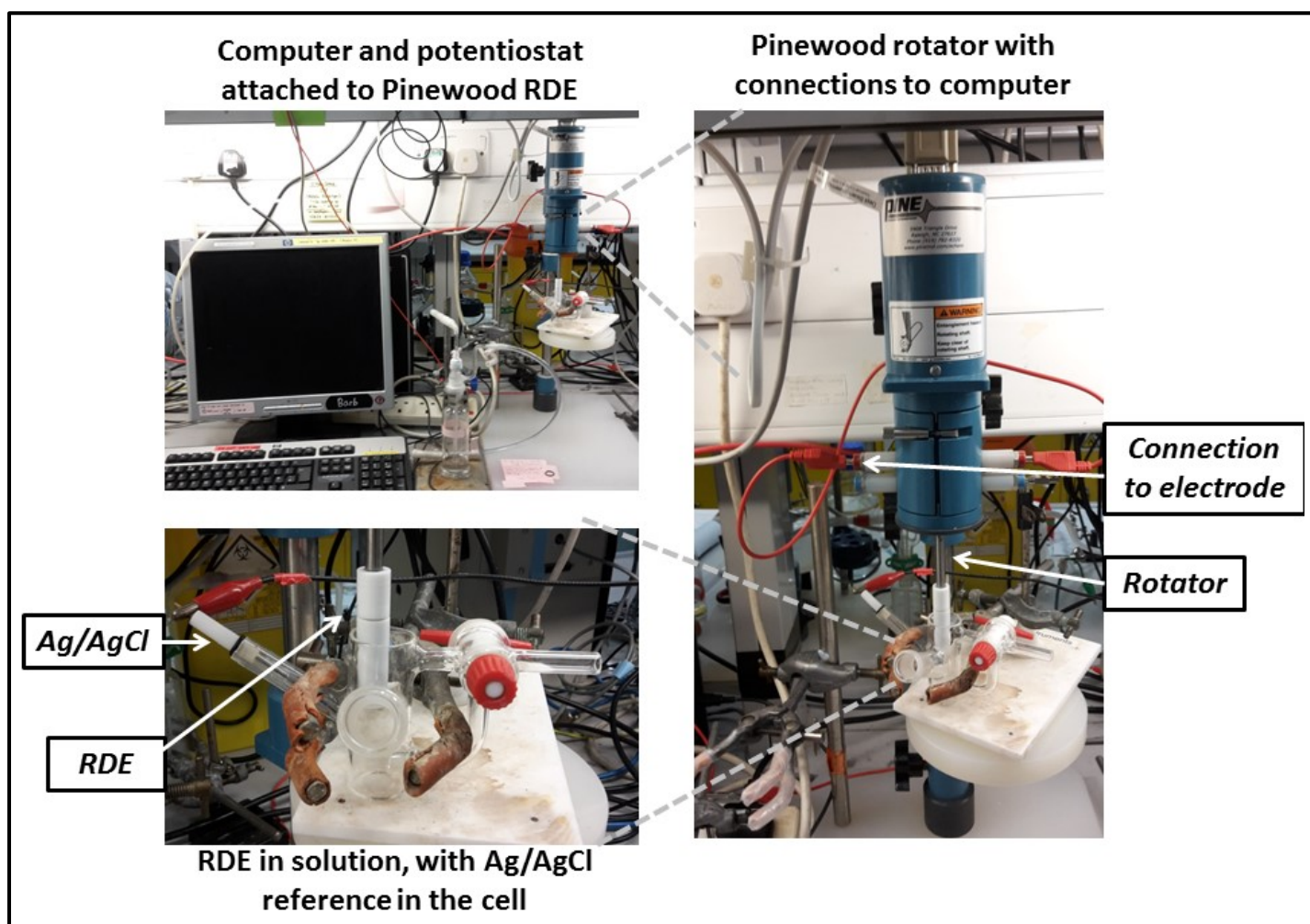
Proclin 150 (6 mg/L) was added as a preservative.

Penicillin-G calibration was then performed and OCP recorded using the methodology described above.

7.3.6 Rotating disc electrode experiment

Rotating disc electrode (RDE) beta-lactam biosensors were fabricated and set up on a Pinewood Instrument rotator (**Figure 33**). This allowed the electrode to be rotated at varying speeds in known concentrations of penicillin-G. By altering the rotation speed of the electrode, this allowed estimation and control of the boundary layer between the biosensor and bulk solution in the experiment, which could be determined using equations [2.4]. Furthermore, the flux through the boundary layer could be estimated using equation [2.5].

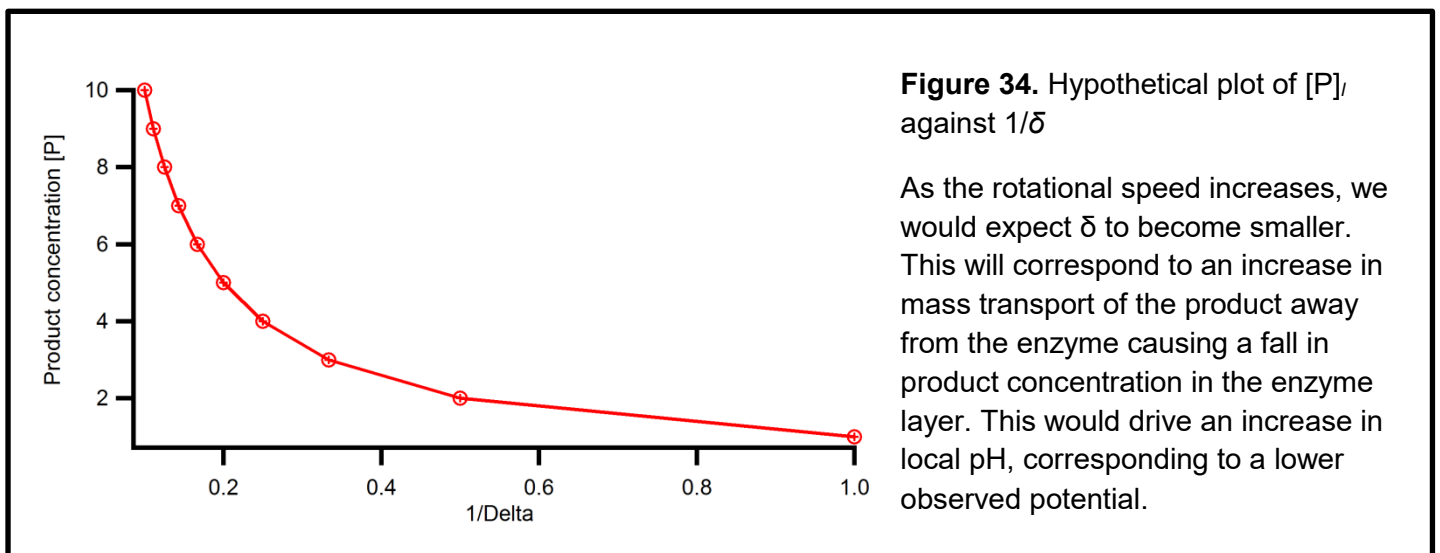
Figure 33. Rotating disc electrode set up using a Pinewood Instrument rotator.



Legend: RDE = rotating disc electrode; Ag/AgCl = silver – silver chloride reference electrode

This allowed me to make predictions about the response of the sensor to increasing and decreasing rotational speed at steady state, based on the assumptions made using equations in *section 7.3.2.1*.

If we take the layer thickness (l), and enzyme concentration ($[E]$) to remain constant within this experiment, we can assume the $lk_2[E]$ is a lumped parameter (K_{lump}) that remains stable. Therefore, considering equation [2.3], during conditions where $S \gg K_m$ we can assume that the product concentration in the enzyme layer, $[P]_l$ is inversely proportional to δ . This can be investigated at steady state by increasing the rotational speed of the electrode. We would expect to observe $[P]_l$ increase (demonstrated by an increase in the observed potential) as δ increases (i.e. at slower rotational speeds).



At low concentration, the response of the system is more difficult to predict. When $S \ll K_m$, we can attempt to make assumptions for the system using equation [2.2]. In this case, we can consider that $\frac{lk_2[E]}{k_d k_m}$ at steady state, using the same biosensor, is a fixed parameter. Therefore, if $\frac{lk_2[E]}{k_d k_m} \ll 1$ I would expect to observe that the system is limited by the surface reaction rate. Conversely, if $\frac{lk_2[E]}{k_d k_m} \gg 1$ then it will be likely that the transport rate constant (δ) is slower than that for the surface reaction. Furthermore, if $[P]_l = [S]_l$ then this will provide

optimal sensitivity as the substrate will be arriving to the surface of the electrode as fast as it is being converted into product. In this case, it is likely that very little change will be observed in the system [512].

Practically, when evaluating the RDE response I can review the expression of δ in equation [2.4]. Within this scenario, the kinematic velocity (v) and diffusion co-efficient (D) will remain constant. Therefore, I can substitute δ for $-\frac{1}{\omega^{\frac{1}{2}}}$ as the remainder of the expression will be constant. For analysis, I aimed to repeat runs with the same RDE at varying rotational speeds at both low and high penicillin-G concentrations. I would then plot the observed potential against $\omega^{\frac{1}{2}}$ as well as $\log(\omega^{\frac{1}{2}})$. This would allow me to visually compare the expected response to varying rotation speeds with my observed results.

7.3.7 Preliminary in-vivo study

Following calibration in artificial ISF, a review of the components of the sensor were reviewed with a view to ensuring safety and acceptability for in-human use. This resulted in the mechanism for cross linking the enzyme within the biosensor being adapted to use PEI – polyethylene glycol (PEG) [531], removing the need for glutaraldehyde for cross linking. This was due to concerns over its potential toxicity in humans [531]. Torr Scientific Ltd. produced fabricated microneedles as described in *section 7.3.2*. This work was led by two post-doctoral students in Bioengineering, Dr Sally Gowers & Dr Michelle Rogers and will not be described in detail within this thesis. Following demonstration of reproducibility with the new design, similar to that demonstrated by my previous work, I developed an initial protocol for the pilot testing the microneedle device.

A narrow spectrum beta-lactam, penicillin-V, was prescribed for two days at a dose of 500mg four times a day, to be taken orally. This was for 7 doses prior to testing to ensure that concentrations were at steady state.

A microneedle array was applied to the non-dominant forearm with firm pressure applied for 60 seconds. The arrays were then secured with micropore tape. Each array was recorded sequentially, using a portable potentiostat (PalmSens, Netherlands) over a 6-hour period. A control array was developed, with a hydrogel containing no enzyme placed on the surface to provide baseline data for comparison. Blood and tissue microdialysis was not available for this pilot study. Potentials were recorded from each array sequentially at intervals of 15-30 minutes over a 6-hour period. The potentiostat sampled once every second when connected to the electrode, being connected to the microneedle array at 10am. An 8th dose of penicillin-V was taken at 12.45, approximately 2 hours 45 minutes after commencing monitoring with the microneedle array.

The same microneedle array was calibrated with penicillin-V solution prior to and after the *in-vivo* study to allow estimation of penicillin-V concentration *in-vivo*. Data were cleaned and plotted for preliminary analysis using Igor Pro, version 7. The aim was to demonstrate the ability of the microneedle array to track expected changes in tissue PK over time.

There is a paucity of PK data in the literature to describe penicillin-V in tissue. However, it is clear that the plasma half life is short at about 0.5 hours with peak serum levels achieved within about 30 - 60 minutes following administration of 500 mg doses [525,532,533]. Absorption from the gastrointestinal tract appears to be variable with ~60% bioavailability quoted [532,533]. Penicillin-V is between 50 to 80 % plasma protein bound [532,533]. Penicillin-V is known to be widely distributed throughout tissues [532,533]. Although tissue concentrations were not identified within the literature, reports of penicillin-V concentrating in breast milk at between and crossing the blood brain barrier are available [532,533].

Given the unknowns within this initial pilot study, I aimed to estimate the maximum observed concentration in the tissue ISF using the microneedles and explore whether the PK response observed correlated to expected response. Given that at steady state penicillin is in

equilibrium, I hoped to demonstrate peak tissue concentration after approximately 30 to 60 minutes following dosing and an observed half-life of approximately 30 minutes.

7.3.8 Ethical approval

Ethics for the study of the microneedle devices described within *section 7.3.7* was granted by London-Harrow Research Ethics Committee (REC 18/LO/0054).

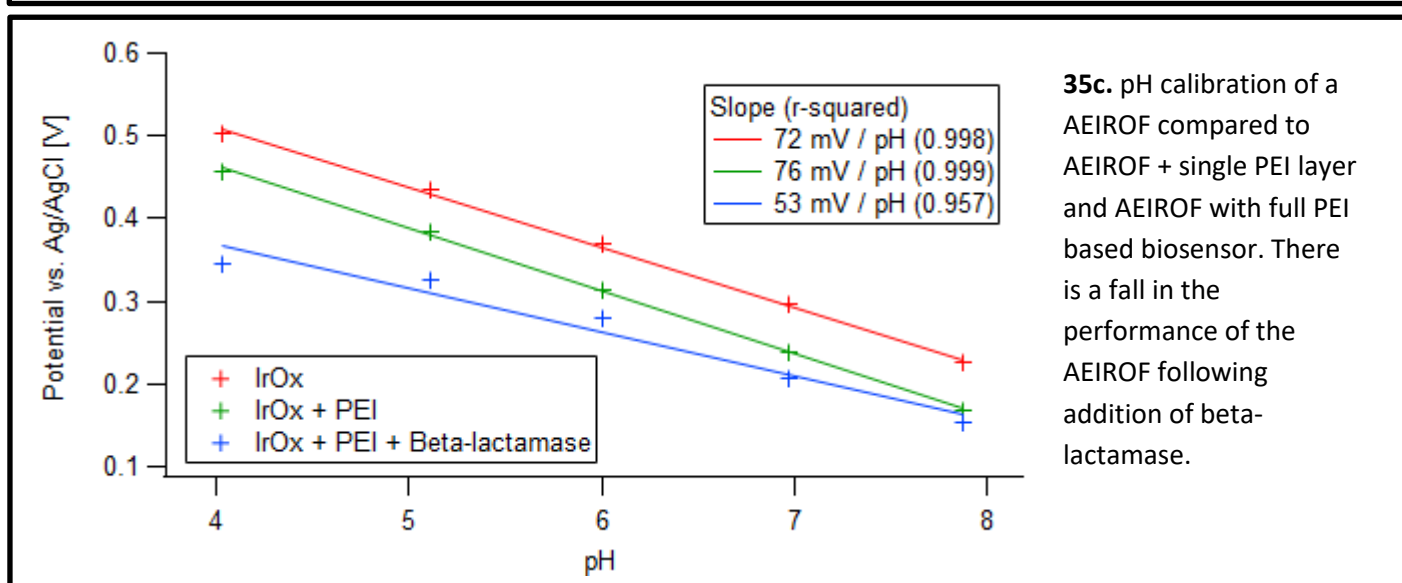
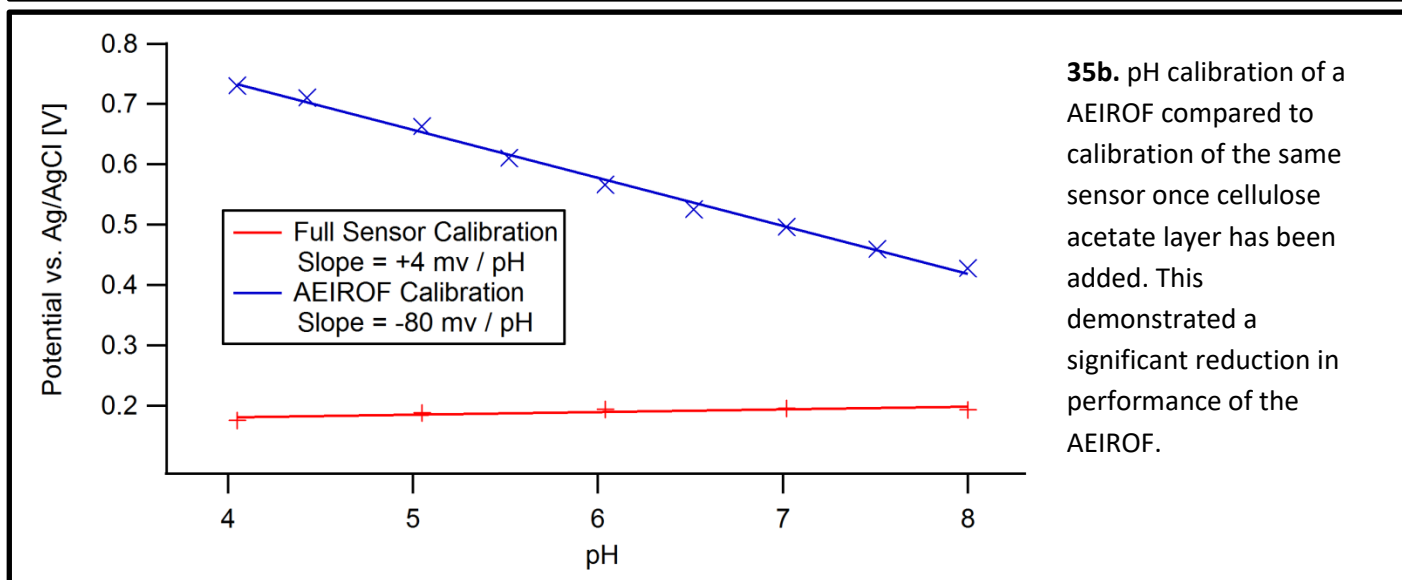
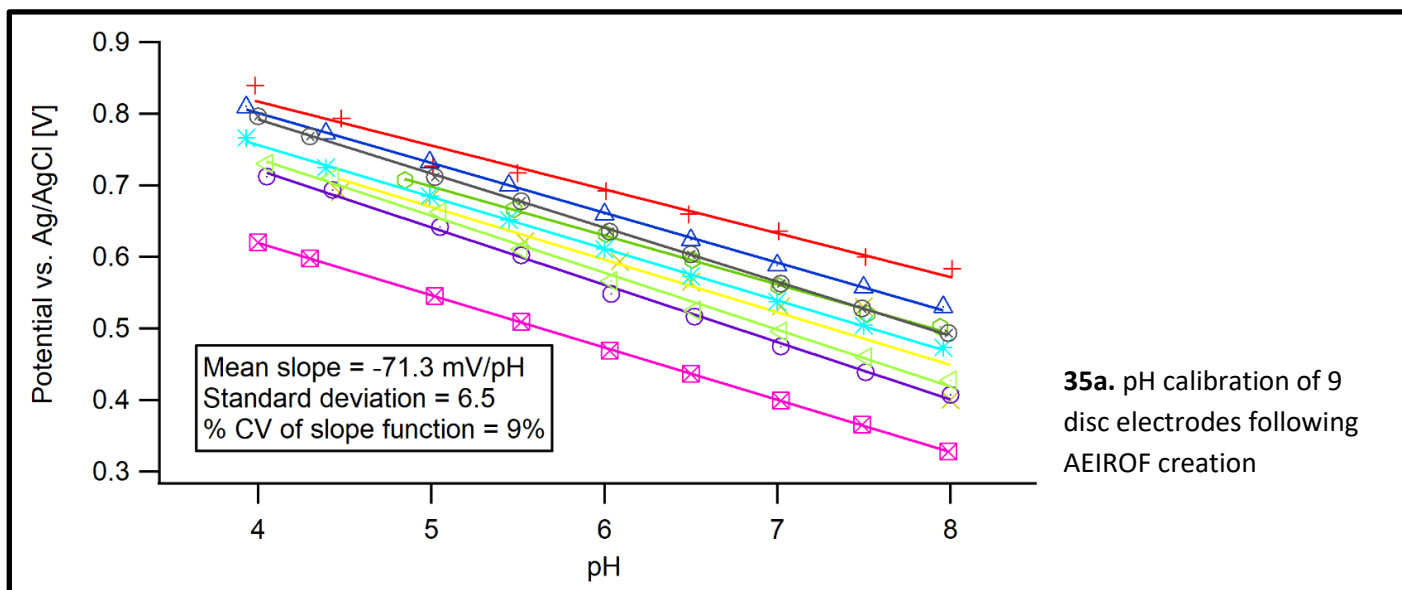
7.4 Results

7.4.1 Biosensor characterisation

Figure 35 outlines evidence from the pH calibration of the AEIROF and subsequent calibration of completed cellulose acetate and PEI based sensors. pH calibration of the disc electrode AEIROF produced a consistent, super-Nernstein slope. Mean (SD) slope ($n = 9$) was $-71.3 (6.5) \text{ mV} / \text{pH}$ (%CV = 9%). However, following application of cellulose acetate and the beta-lactamase enzyme layers, the sensor response did not follow its predicted pathway. For example, during calibration with penicillin-G the sensor did not respond as expected and slope analysis using log-concentration plots demonstrated an inverted slope of $+4 \text{ mV} / \text{decade}$.

To investigate this further, the sensor response to pH change (pH 8.0 – 4.0) was assessed before and after the AEIROF had the cellulose acetate enzyme layer fixed to its surface (**Figure 35b**). This demonstrated similar findings to the initial calibration log-concentration plots of a minimal response of the AEIROF following addition of the cellulose acetate, beta-lactamase layer.

Figure 35. Summary of findings from initial AEIROF and cellulose acetate based biosensor development.



In contrast, PEI based fabrication demonstrated a much improved response from the biosensor (**Figure 35c**). The slope remained similar between the three pH calibration runs with a difference of 19 mV / pH between the AEIROF and the final biosensor (72 mV / pH vs. 53 mV / pH, respectively). The use of the PEI based method also appeared to improve the mechanical stability of the biosensor, which was a problem when cellulose acetate was used.

Finally, as the initial microneedles that I would work with were likely to be platinum coated instead of gold, I repeated the calibration of AEIROF on platinum disc electrodes. The response between platinum and gold electrodes was similar ($p = 0.13$, 95%CI: -13.02 – 1.95). The response remained super-Nernstain for AEIROFs on platinum disc electrodes ($n = 5$) at a mean (SD) slope of -66 (5) mV / pH ($r^2 = 0.997$). The %CV remained low between AEIROFs at 7%.

7.4.2 Beta-lactam biosensor calibration and characterisation

7.4.2.1 Disc electrode calibration

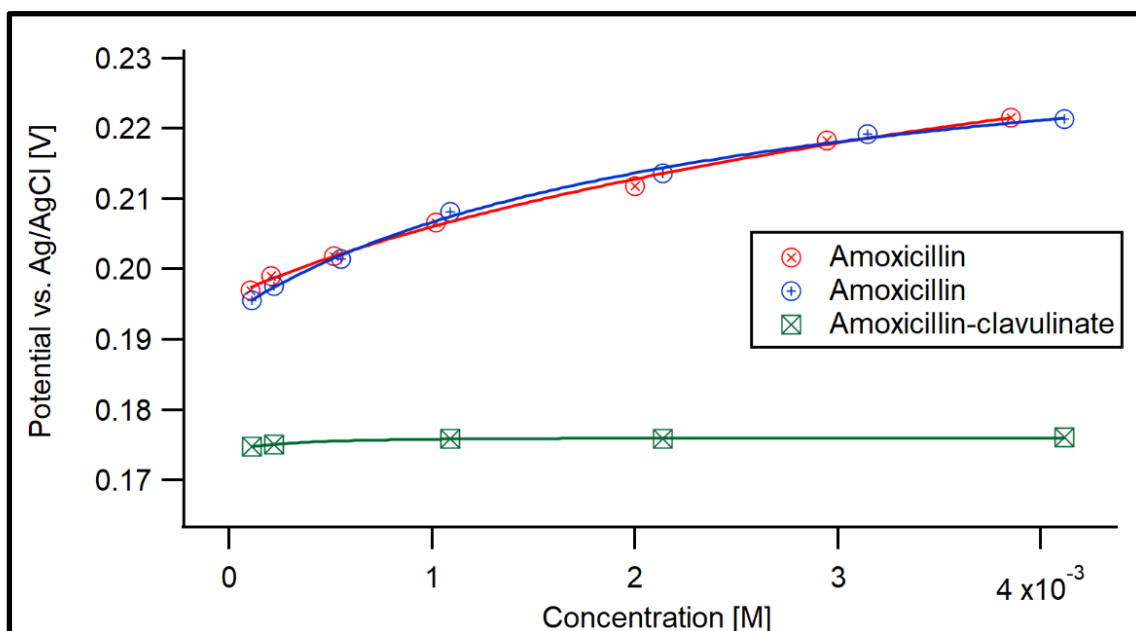
Figure 36 summarises the findings of calibration with a range of beta-lactam antibiotics described in *section 7.3.4*. On comparison of K_m values, V_{max} , and slopes for each antibiotic, penicillin-G was taken as the reference standard, given its known rate of hydrolysis by the enzyme used in this study [534]. No difference was observed in K_m values of the sensor to penicillin-G ($n = 3$) and amoxicillin ($n = 3$) ($p = 0.37$, 95%CI: -0.005 - 0.002). V_{max} was also similar for both agents ($p = 0.27$, 95%CI: -17-43). However, the observed slope function for amoxicillin was observed to be lower ($p < 0.01$, 95%CI: 2.2 - 6.3). For ceftriaxone, no response that could be attributed to enzyme activity was observed during calibration of disc electrode ($n = 6$). However, response was seen following addition of amoxicillin to the solution, demonstrating that the enzyme was still functioning within these cases. Calibration of the biosensor with a beta-lactam – beta-lactamase inhibitor

combination (amoxicillin / clavulanic acid) appeared to inhibit the biosensor response when compared to amoxicillin alone.

Figure 36. Calibration of platinum disc electrode based beta-lactam biosensor against different beta lactam antibiotics in phosphate buffer solution

	Km (SD) [M]	Vmax (SD) [mV]	Slope (SD) [mV / decade]
Penicillin-G	0.0031 (0.0007)	264 (2.5)	20.3 (0.47)
Amoxicillin	0.0046 (0.0021)	251 (17.7)	16 (1)
Ceftriaxone	No response	N/A	N/A
Amoxicillin-clavulanate	0.0003 (0.0002)	176 (18)	8 (1)

Legend: Comparison of mean (SD) Km, Vmax, and Slope values for beta-lactam antibiotic calibrations. M = Moles; mV = millivolts; SD = standard deviation



Legend: Comparison of amoxicillin vs. amoxicillin-clavulanate calibration with a single disc electrode biosensor

7.4.2.2 Rotating disc electrode experiments

Following biosensor protocol development and calibration in PBS, a rotating disc electrode beta-lactam biosensor was fabricated to evaluate the effects of mass transport on the system.

For the RDE biosensors, calibration and slope functions were as follows. The mean (SD) pooled K_m for $n = 4$ RDE, calibrated between concentrations of 10 and 5700 μM penicillin-G, was 123.31 (48.1) μM . The mean (SD) slope for log–concentration plot was 55 (9) mV / decade and mean (SD) V_{max} 247 (11) mV.

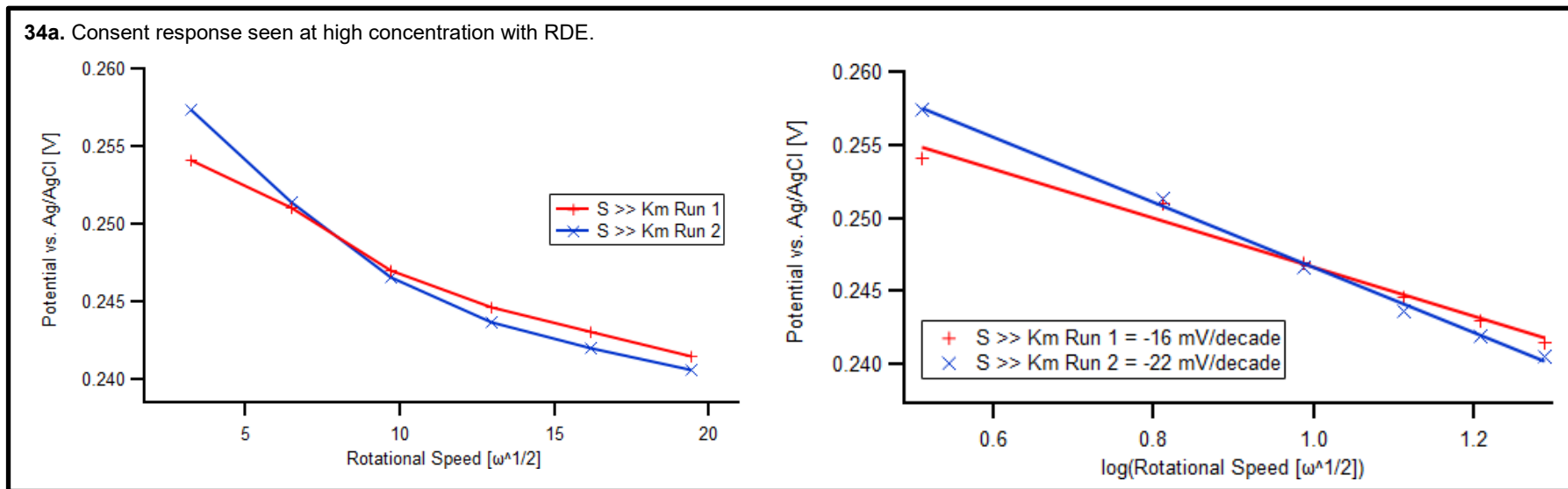
On comparison to the disc electrodes reported above, K_m was significantly smaller for the RDE ($p < 0.01$, 95%CI: -0.0038 - -0.0021). However, V_{max} was similar between electrodes ($p = 0.05$, 95%CI: -0.014-34.01) and the slope function was greater with the RDE ($p < 0.01$: 95%CI: 21 - 48).

Figure 37 demonstrates a typical finding from repeated RDE experiment using the same biosensor. When the system was at steady-state with a high concentration of penicillin-G (i.e. $S \gg K_m$), the system demonstrated mass-transport limitation. As predicted, increasing the electrodes rotational speed caused a fall in the observed potential across the electrode, corresponding with increased transport of the product away from the enzyme layer. In the example RDE experiment below, the potential fell from 254 and 257 mV at rotation speeds of 10 Hz, respectively to 241 mV at 360 Hz rotational speed. The approximate V_{max} for the RDE, estimated as a mean of all four RDE was 247 mV. By plotting the rotational speed logarithmically ($\omega^{\frac{1}{2}}$) against the observed potential, this can be represented as a linear process with a potential change of -16 and -22 mV / decade during runs 1 and 2, respectively. On reduction of rotational speed the potential was observed to recover back to baseline (i.e. back to the estimated V_{max}).

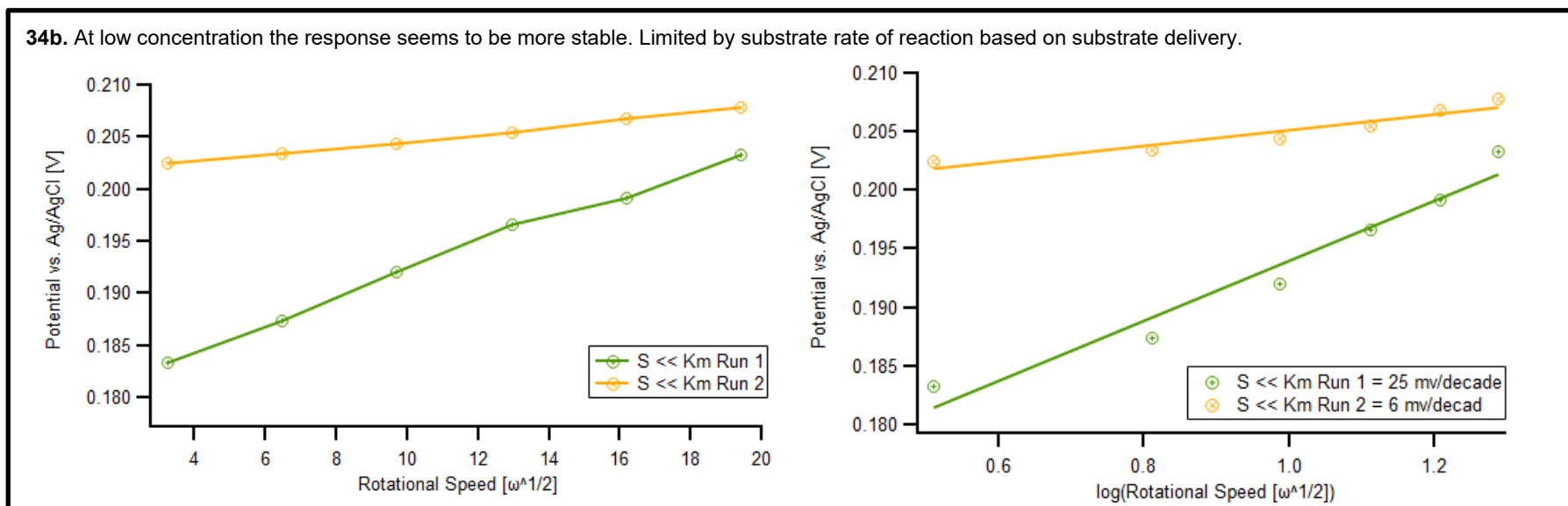
When the system was at steady state for low concentrations of penicillin-G (i.e. $S \ll K_m$) the opposite was observed with increasing rotational speed. For initial runs at low concentration,

an increase in potential was observed with increasing rotational speeds from 183 mV at 10 Hz to 203 mV at 360 Hz. This potential change did not recover after the initial run with the second run, using the same electrode demonstrating a significantly smaller potential change from 203 mV to 208 mV. This was reflected in the log-slope variation between runs 1 and 2 of +25 and +6 mV / decade, respectively.

Figure 37. Summary of RDE experimental data at low and high concentrations of beta-lactam.



Legend: $r^2 = 0.996$ & 0.982 ; Ag/AgCl = silver-silver chloride reference; mV = millivolts; V = volts



Legend: $r^2 = 0.911$ & 0.954 ; Ag/AgCl = silver-silver chloride reference; mV = millivolts; V = volts

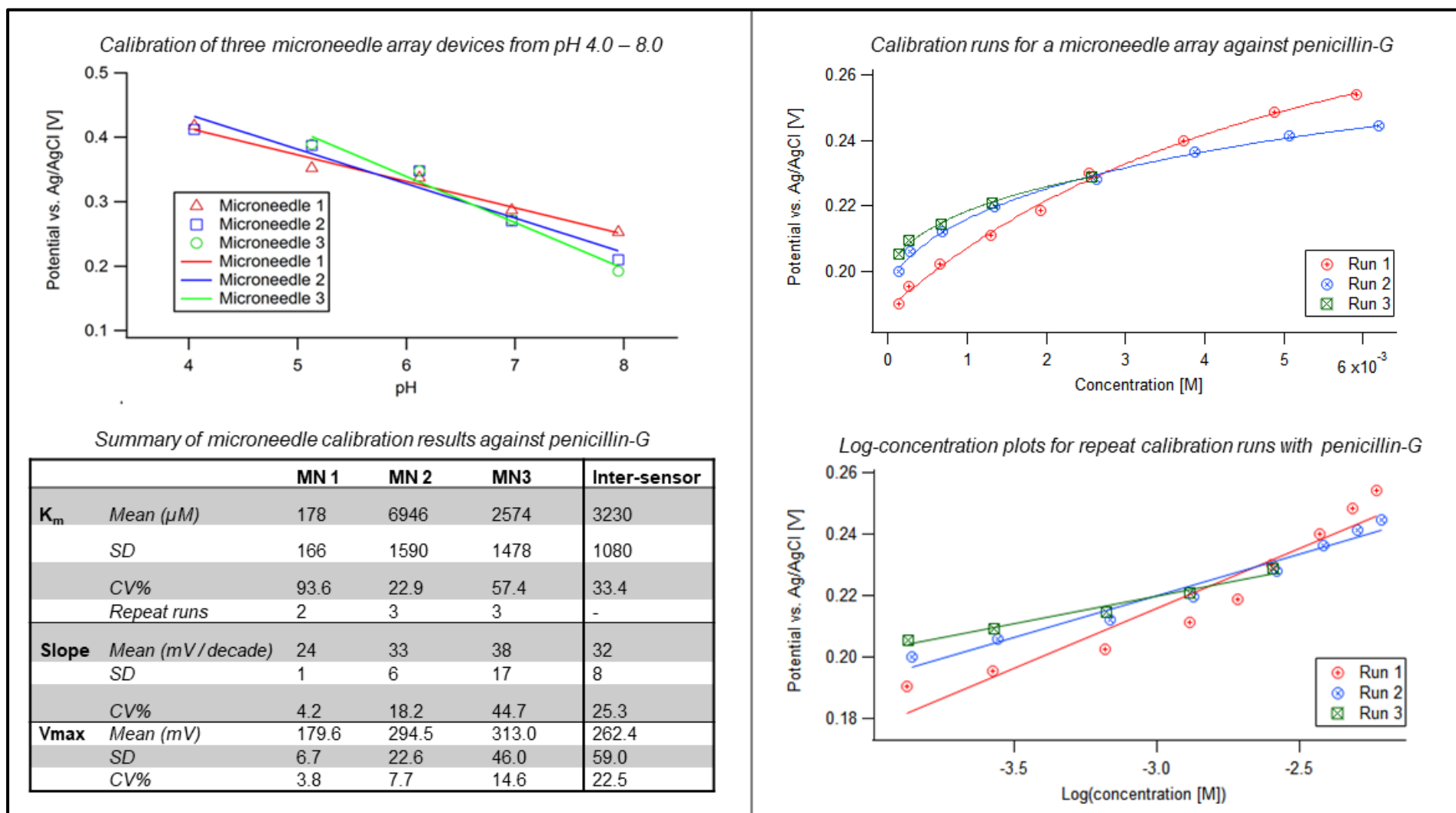
7.4.3 Microneedle beta-lactam calibration

7.4.3.1 Beta-lactam calibration in phosphate buffer solution

Figure 38 demonstrates the pH calibration results for three independent microneedle array's following AEIROF. pH calibration for iridium oxide between 4.0 and 8.0 demonstrated a median (SD) sub-Nernstian response of 48 (11) mV / pH for the microneedle arrays (inter-array %CV = 23%).

Penicillin-G calibration curves were similar on disc electrodes and the microneedle arrays. For the microneedle arrays calibrated, mean K_m (SD) was 0.0032 (0.0011) M. Inter-sensor %CV was 33%. Log-concentration plots demonstrated a mean (SD) slope of 32 (8) mV / decade change with concentration (inter-sensor %CV = 25%). Mean (SD) V_{max} for the sensors was 262 (59) mV (inter-sensor %CV = 22%). The response of the microneedles remained similar after 28 days storage at 4°C with "microneedle 2" demonstrating a K_m value of $K_m = 0.0062$ M, log-concentration slope of 32 mV / decade ($r^2 = 0.933$), and V_{max} 297 mV upon re-calibration.

Figure 38. Comparison of calibration against penicillin-G in phosphate-buffer solution and artificial interstitial fluid.



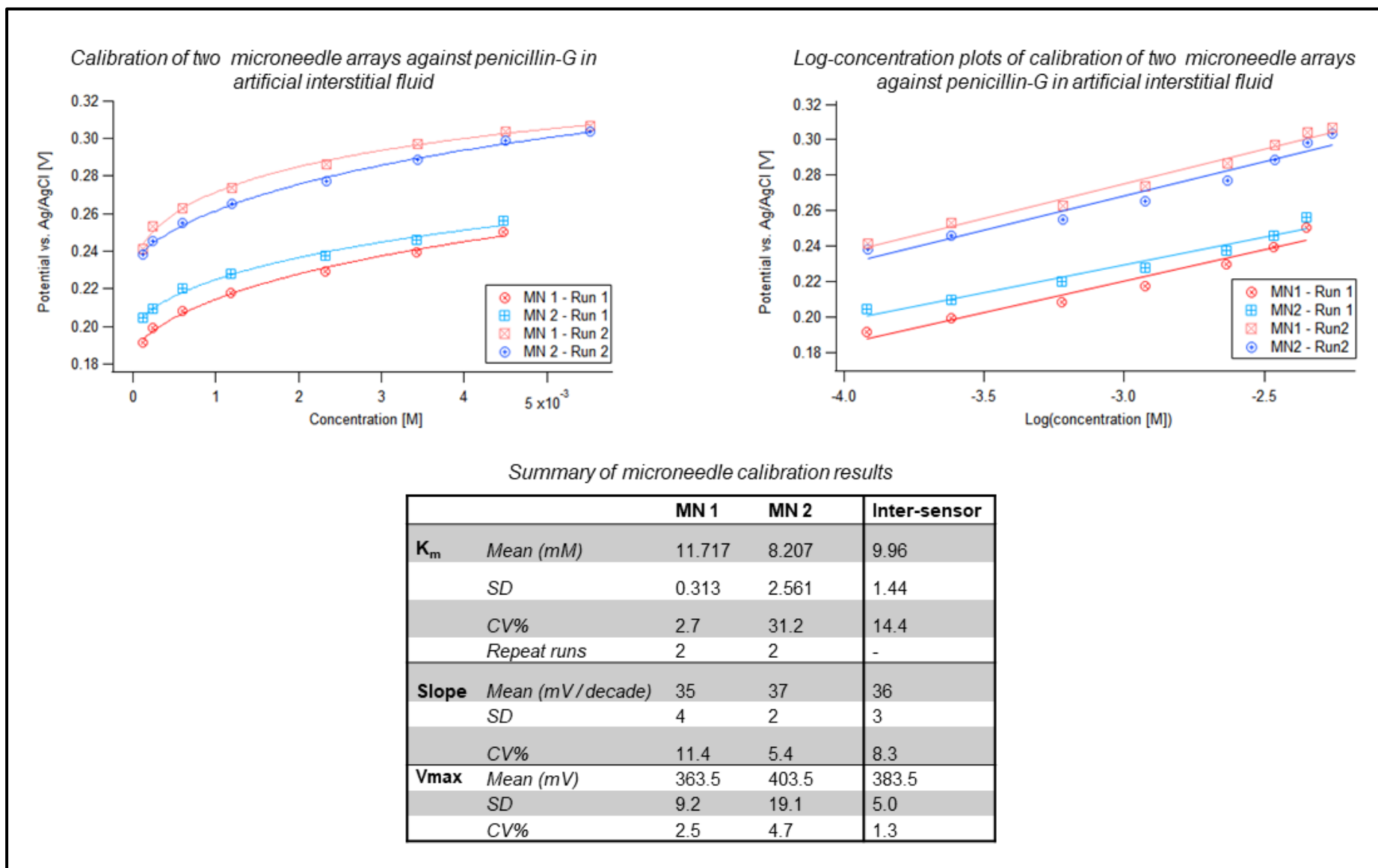
Legend: Ag/AgCl = Silver – silver chloride reference electrode; K_m = concentration required to reach half maximum rate; V_{max} = maximum potential; M = moles; mV = millivolts; SD = standard deviation; CV% = coefficient of variation; MN = microneedle; Inter-sensor = average across all three microneedle sensors

7.4.3.2 Beta-lactam calibration in artificial interstitial fluid

Figure 39 demonstrates the calibration of two new microneedle arrays in artificial interstitial with penicillin-G. The mean (SD) response of the microneedle arrays to penicillin-G calibration in interstitial fluid ($n = 4$) was $K_m = 0.0100$ (0.0014) M, with a slope of 36 (3) mV / decade ($r^2 = 0.966$). V_{max} was a mean (SD) of 384 (5) mV. Inter-sensor %CV was 14%, 8%, and 1% for K_m , slope function, and V_{max} , respectively.

The lower observed %CV were supported by the observation of similar mean K_m ($p = 0.94$; 95%CI: -0.08 – 0.08), log-concentration slopes ($p = 0.59$, 95%CI: -16 – 12), and V_{max} ($p = 0.12$, 95%CI: -103 - 24) values between both microneedle arrays.

Figure 39. Calibration of two microneedle arrays in artificial interstitial fluid with penicillin-G.



Legend: Ag/AgCl = Silver – silver chloride reference electrode; K_m = concentration required to reach half maximum rate; V_{max} = maximum potential; M = moles; mV = millivolts; SD = standard deviation; CV% = coefficient of variation; MN = microneedle; Inter-sensor = average across both microneedle sensors 276

7.4.2 Pilot test of continuous monitoring of beta-lactam antibiotics in humans

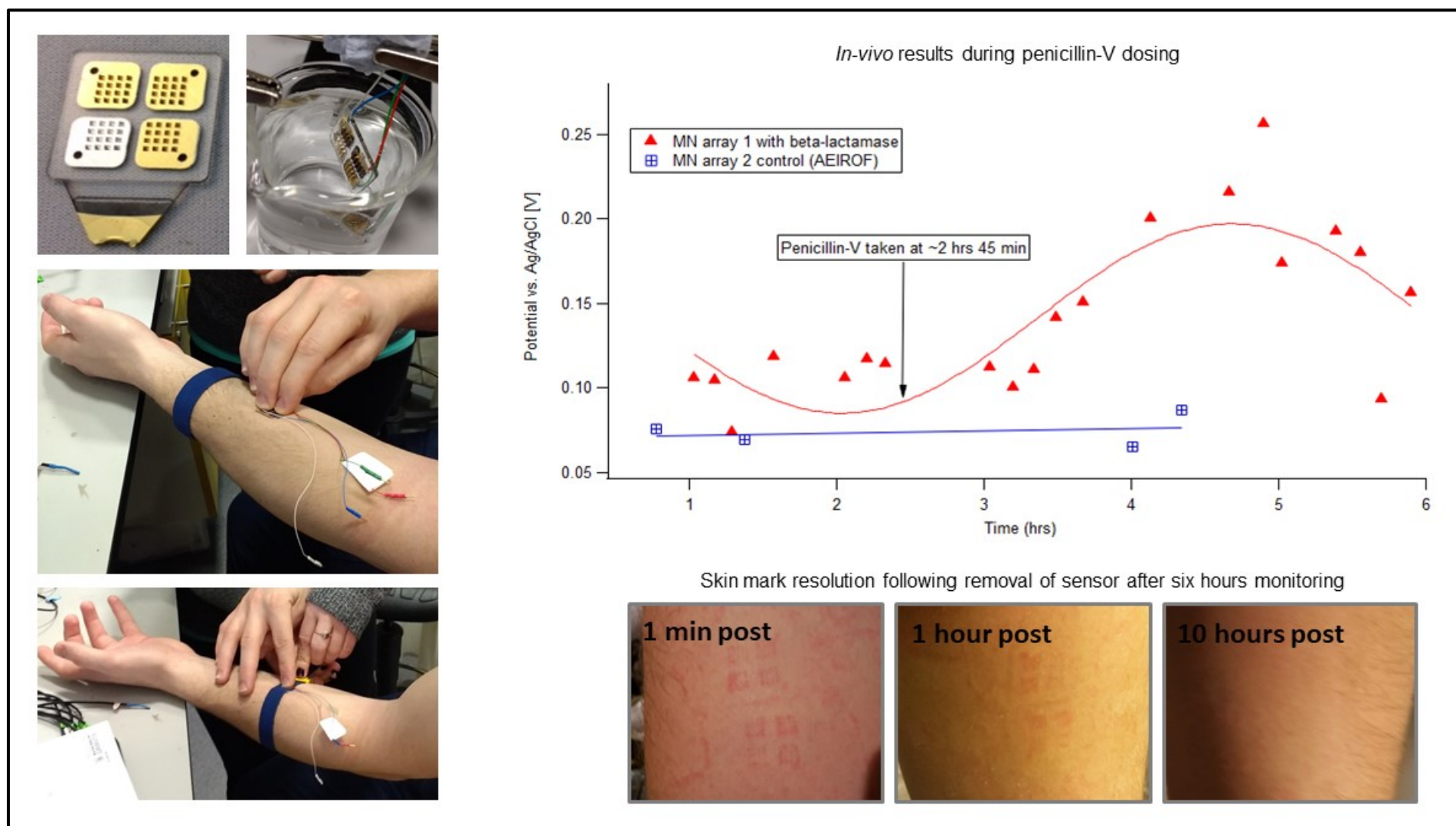
Figure 40 summarises the pilot evaluation of the microneedle array based beta-lactamase sensor for monitoring of interstitial penicillin-V concentrations *in-vivo*.

For the control array, there were four time points where I had documented observations whilst ensuring that the array was appropriately sited. These four recordings were used to approximate the baseline potential of the control sensor throughout the experiment (blue array in **Figure 40**). The beta-lactamase containing array (red) maintained an observed potential above this throughout the experiment.

On estimation of observed PK response from the active sensor, the estimated observed free penicillin-V concentration in ISF over this time period ranged from 0.6 to 12.4 μM . Peak tissue concentration (C_{max}) occurred at approximately two hours post oral bolus. And estimated half-life ($t_{1/2}$) of the observed fall in concentration was approximately 1-hour.

Following wearing of the device for six hours, upon removal red marks were noted in a pattern consistent with the microneedle array spikes on the participants forearm. The redness associated with these had completely resolved within 12 hours of removing the microneedle array.

Figure 40. Summary of the pilot evaluation of microneedle based sensing of penicillin-V *in-vivo*.



Legend: Photos (left) – *Top:* Microneedle array pre-fabrication and undergoing hydration prior to use; *Middle:* Microneedle is held in place with firm pressure for 60 seconds; *Bottom:* microneedle secured with a pressure from a single band around the arm.

Graphic (right): In-vivo data from first test of the microneedle on an individual receiving penicillin-V.

Photos (bottom right): Time series demonstrating resolution of marks left by the microneedle after it had been worn for 6 hours.

7.5 Discussion

7.5.1 Summary of findings

Within this study, I have characterised the response of an enzyme based electrochemical sensor for the detection of beta-lactam antibiotic in human ISF. I have demonstrated that this technology can be translated onto a microneedle array and demonstrated proof-of-concept for microneedle based sensing of penicillin *in-vivo*. The response demonstrated by the sensor was consistent between disc and microneedle based electrodes and the working linear range observed (i.e. when $S < K_m$) was sufficient for the expected range of beta-lactam concentrations that will be monitored *in-vivo*.

As expected, several challenges were also identified during this study that will require further exploration. Although the final microneedles had low inter-sensor %CV, the high %CVs observed at times during preparatory work suggest that the protocol for production of such sensors can be refined to provide more uniform response between sensors. Given the observed inter-sensor variation, the current sensors will require calibration once deployed to be able to accurately convert a potential into a known concentration of penicillin. Furthermore, addition of beta-lactamase inhibitor inhibited the detection of amoxicillin and the use of beta-lactamase resistant beta-lactams (such as ceftriaxone) inhibited detection. Finally, there are several practicalities with deployment *in-vivo* that must be addressed, including determination of optimal site for placement, how to maintain optimal pressure on the sensor to keep the arrays sited, and development of a portable potentiostat that can accurately monitor multiple channels in parallel. These challenges will be explored in more detail below.

Despite this, these results are the first step towards the development of a minimally invasive sensor for the continuous monitoring of antimicrobials in humans. If incorporated into a closed-loop control system, this may provide a method for real-time dose optimisation of antimicrobials based on individual PK or PD variations. Furthermore, this tool may provide

the ability for rich PK data collection during drug development and clinical studies to help provide robust, individualised drug PK data to enhance our understanding of the importance of dose optimisation on the outcome of antimicrobial therapy.

7.5.1.1 pH calibration and polyethylenimine

As reported above, there was inter-sensor variation observed between different AEIROFs within this study (i.e. between disc, RDE, and microneedle). This could be seen during pH calibration as variations in the slope from the AEIROF calibration plot ranging from 48 mV / pH on the microneedles to 71 mV / pH on the gold disc electrodes. This variation occurred in both the apparent E° (pH = 0) value and in slope of calibration.

This is a common observation with IrOx based pH sensors [535] and has been described in detail by Hitchman [515]. Hitchman describes how apparent E° varies depending on the molar ratio of Ir(III) : Ir(IV) within individual AEIROFs [515]. This ratio of Ir(III) : Ir(IV) oxides can be affected by the chemical irreversibility of the interconversion [515]. Since the molar ratio, the charge storage capacity, and the counter ion access will vary with depth and the morphology of the polymeric cross-linked oxyhydroxide film, the precise form of the calibration working curve will depend on underlying substrate properties. Whilst potential scanning can ameliorate this phenomenon for bulk electrodes, the mechanical stability of films on sputtered substrates suffers, and a build-up of relatively non-conductive Ir(III) impairs the sensors performance [514,515]. Furthermore, anodic electrodeposition of such AEIROF makes it challenging to control for the precise level of oxidation that occurs during the deposition process, meaning that variation is always likely to be present in some form [515].

Despite these variations in baseline calibration between sensors, it has been demonstrated elsewhere [514,536] that reproducibility for any given device is good and that the intra-device sensitivity is stable for days, enabling biologically useful pH measurement to be

undertaken [447,514,518]. This was also observed within my work with low inter-sensor %CV for disc electrode based AEIROF. The larger %CV for the microneedles, likely reflects the wider variation in electrode characteristics and human error that can occur during the anodic electrodeposition process. To address this problem for future work, collaboration with Torr Scientific Ltd has been set up. This group have developed a standardised methodology for metallisation of the microneedles, as demonstrated within the pilot study, and are also exploring the possibility of sputtering IrOx onto the needles in place of electrodeposition. These changes in process may provide a much more uniform and reproducible method of standardising the environment and oxidation process, thus reducing the inter-sensor variability that I have observed.

A further challenge during this study was the disruption to the AEIROF following application of the cellulose acetate layer early in the sensors development. This was likely secondary to the interference with the AEIROF by ions such as chloride [514]. Chloride is known to form complexes with the iridium film which causes the AEIROF to decay [514]. This would explain the lack of sensor response observed during initial calibration attempts. I addressed this problem by substituting the cellulose acetate for PEI, which had previously been demonstrated to protect AEIROF from such interactions [514]. I also found that PEI provided much greater structural stability, meaning that it could be substituted for the cellulose acetate entirely. This approach made the biosensors visibly more durable and also enabled me to undertake repeat experiments without a significant decay in the sensors structure and response. Re-calibration of the sensor to pH following final fabrication with PEI demonstrated a slight drop off in potential (72 mV / pH to 53 mV / pH). However, this was within the expected limits and was likely due to the buffer capacity of the PEI and beta-lactamase enzyme on the system and the increased thickness of the biosensor layer [537,538]. Although the disc electrodes were soaked overnight in deionised H₂O to wash away excess PBS in the hydrogel, I must also consider whether the phosphate, contained

within the PBS used to constitute the enzyme-BSA solution played a role in buffering the solution [539].

7.5.1.2 Beta-lactam calibration

The sensor was calibrated against penicillin-G and amoxicillin demonstrating similar responses in terms of K_m and V_{max} values. K_m values ranged between 3100 and 9960 μM within this study and V_{max} ranged from 247 mV to 383 mV.

The identified K_m values suggest that I can be confident detection will be within the linear range of the sensor. This was important as it demonstrates that the working linear range for these sensors is likely to be suitable for the expected beta-lactam tissue concentrations, which have been reported in the literature as $< 300 \mu\text{M}$ for piperacillin and $< 52 \mu\text{M}$ for cefazolin [421,423]. Furthermore, as both reported agents have significantly greater plasma concentrations than the agents tested within this study, it is likely that these are over estimates of the peak tissue concentrations likely to be detected for agents such as penicillin-G and amoxicillin in ISF [525].

The observation of stable V_{max} between runs on the same sensor and between sensors tested in the same environments is helpful in demonstrating that k_{cat} (the rate constant for conversion of ES to P) was similar between runs. This can be assumed given that $V_{max} = k_{cat}e_{tot}$ and the same concentration of enzyme was used as per the protocol outlined in **Appendix 7**. Therefore, the low %CV for V_{max} indicate similar k_{cat} values.

The calibration with penicillin-G in artificial ISF was important for two reasons. Firstly, given previous reports of bio-fouling and reduced sensitivity following the absorption of protein, such as albumin, onto bio-surfaces such as IrOx based pH sensors it demonstrated that this does not appear to be a factor within our system, which is protected by the PEI membrane [447,502]. Secondly, this provided important data to inform future biosensor design as it allowed estimation of the potential working range and potential error of the biosensor on the

microneedle array in near-physiological conditions. By determining the K_m value of the sensor in interstitial fluid (9960 μM), this allows me to ensure that the operating window remained within the linear range required for use in ISF (i.e. when $[S] < K_m$) [509]. This was subsequently validated in the pilot study, where I was able to demonstrate response of the sensor to oral bolus of penicillin-V and estimate free drug ISF concentrations of 0.6 - 12.4 μM . I now plan to validate these observations in human participants who will undergo microdialysis and blood PK analysis whilst wearing the microneedles.

A future challenge that was highlighted by this study was the resistance of ceftriaxone to hydrolysis by the current beta-lactamase compared to penicillin-G [9,540]. Although minimal response was seen in two of the six electrodes tested, this was in the range of several mV. Therefore, it is unclear whether this was simply noise or actual response of fresher enzyme compared to the other four electrodes, which were fabricated towards the end of the beta-lactamase enzymes shelf life. Furthermore, addition of a beta-lactamase inhibitor also inhibited the response of sensor for detecting amoxicillin. In terms of clinical translation this poses a problem, given the broad use of beta-lactamase inhibitors in the clinical setting and high use of third generation cephalosporins. To address these problems, future work will now compare use of extended spectrum beta-lactamase enzyme (acquired from Sekesui diagnostics) versus the enzyme used within this study [541]. The Sekesui extended spectrum enzyme has similar activity against carbapenems and third generation cephalosporins compared to penicillin-G. Therefore, this may facilitate the detection of a broader range of agents [541]. To address the problem of beta-lactamase inhibitors, this is likely to require development of specific aptamers that are selected in the presence of beta-lactamase inhibitor to remove the chance of interference [454].

7.5.1.3 Rotating disc electrode characterisation

The characterisation of the biosensor using RDE is a challenging, but important step in understanding the effects of mass transport and enzyme kinetics on the sensors performance. Whilst this study has confirmed that the sensor is likely not mass transport limited within the expected working range (the key objective of using the RDE within this study), it has also raised several interesting questions for further exploration, which may build on the only previous explanation of RDE with potentiometric studies, described by Eddowes [512].

At steady state at high antimicrobial concentrations (i.e. $S \gg K_m$) the response of the sensor to changing rotational speed was predicted and reproducible, based on the model derived from Eddowes [512]. This demonstrated a mass transport limited system. This was observed by a fall in potential with increasing rotational speed, which immediately recovered upon reduction in the rotational speed. This can be described by the increase in rotation speed, increasing the movement of H^+ (product of the reaction) away from the sensor interface. This leads to an increase in the local pH, leading to a fall in potential across the electrode. The recovery in potential that was observed on reducing the electrode indicates that this is no inhibition of the enzyme is occurring.

At steady state at a low concentration (i.e. $S \ll K_m$) the response is more difficult to predict and characterise. Within this study, I observed different responses between runs with the same RDE. For initial runs, the potential increased with increasing rotational speed. This would then plateau and not recover following reduction in rotational speed. For subsequent runs there appeared to be little effect on the sensor response across a range of rotational speeds at low concentration. These observations would suggest that for the initial runs, response of the sensor was being governed by how quickly substrate was being delivered to the enzyme layer, rather than product being removed. Then, eventually an equilibrium was reached between delivery of substrate and production of product, observed as a stable potential.

Eddowes, describes this type of observation in his work using RDE for potentiometric readings [512]. He suggests that the steady state between substrate and product is the optimal condition for sensors at low concentration, where $S \ll K_m$ [512]. For future work using RDE, it would be of interest to attempt to solve the differential equation describing this low concentration phenomenon (equation [2.2]), using this to further explore the optimal requirements for the components described within $\frac{lk_2[E]}{k_D K_M}$. This could then be potentially applied to the optimisation of the microneedle array based sensors to facilitate optimisation of the sensitivity of the system in physiological conditions.

Despite these further questions, for the purpose of my study, my results are encouraging in suggesting that the system was not mass transport limited at concentrations below K_m with a near steady state between substrate and product observed across changing δ (approximated by changing $\omega^{\frac{1}{2}}$).

7.5.2 Pilot study

Following *in-vitro* testing of the microneedle based sensors, it was important to understand whether this technology has the ability to translate into a plausible method for monitoring of antimicrobial agents before undertaking wider studies on healthy volunteers and patients. For this study, penicillin-V was selected as it could be given orally and was likely to have a small impact on the microbiome of the healthy individual taking the agent. Dosing was selected based on recommendations for the treatment of infections in adults with penicillin-V and seven doses were selected so that the individual would be at steady state by the time they wore the sensor [533].

Encouragingly, although only a pilot experiment on one individual, the results appeared to demonstrate the sensors ability to detect changes in ISF penicillin concentrations. The estimated concentrations were in line with potential tissue PK values and similar to the

observed tissue PK response of other beta-lactams in tissue using microdialysis [421,423]. After removal of the sensor, which was worn for 6-hours, the redness caused by its placement had completely disappeared within 12-hours. This observation is in line with previous reports of safety and tolerability of the microneedle arrays when they have been developed for continuous glucose monitoring [411,419,420].

During the pilot evaluation, several problems were encountered. This included the control sensor (AEIROF with no beta-lactamase) becoming dislodged during the experiment leading to artefact in the response observed. Furthermore, the second microarray with beta-lactamase failed calibration so was not used. Finally, the potentiostat used to record readings at the time could only record one channel, meaning that I was required to rotate the recording between microneedle arrays every 15-30 minutes. Therefore, for the purpose of this experiment I chose to average data from the recordings for every five minutes that the microneedle array was being monitored.

Several other challenges with microneedle based sensing in humans were also highlighted through this pilot period.

- i. The microneedles needed light pressure to be applied to ensure that they remained sited after placement. Movement during the day led to displacement of the control array from the forearm for a period of the experiment, which led to artefact in the observations. To address this, the role of tensioned straps is to be explored as a mechanism of ensuring that a constant pressure is applied across the microneedle to hold it in position. Furthermore, the positioning of the microneedles will be reviewed to explore whether the forearm is the optimal site for placement.
- ii. At present the sensors require calibration before and after use *in-vivo* to allow accurate estimation of tissue drug concentration. This problem will be addressed in the future through exploring methods of reducing the variation in oxidation rates of Ir(III) and Ir(IV) during deposition on the gold electrodes. Furthermore, the

automation of enzyme and hydrogel application may also improve the accuracy and reduce inter-sensor variability, which means that individual sensors require calibration at present.

- iii. This study was explored in individuals at steady state. Very little is known about tissue PK during initial dosing periods to suggest how the sensors may respond and whether their sensitivity will be acceptable for monitoring during the acute phases of management.

7.5.3 Limitations and future applications

Many of the limitations and future applications of such a system have been described within *sections 7.5.1 and 7.5.2*. However, considerations of the future direction of this work must also be considered.

Following proof-of-concept that microneedle based sensors can be used to monitor antimicrobial concentrations in ISF the possibility of moving beyond enzyme based methods of sensing will become plausible. A wide range of aptamers for antimicrobial detection are already commercially available, and translation onto the microneedle structure is highly plausible [406]. The transition from enzymes to aptamers has several key advantages in the mid-to-long term. These are:

- i. The sensitivity of aptamer based technology is significantly greater than enzyme based sensing. In the antimicrobial literature, the lower limit of detection using aptamers is described in the picomole range [406], compared to μM using our enzyme based method [406]. This means that detection of early tissue distribution during the loading phase of initial dosing may be a possibility before the individual reaches steady state.
- ii. Plaxco and colleagues recently reported a potential method for a calibration free aptamer based, electrochemical sensor, utilising what they describe as a “dual

frequency” approach to data analysis [542]. This approach uses square wave voltammetry to monitor binding induced changes that occur during electron transfer kinetics. This would have the benefit of not requiring calibration, meaning that many of the issues associated with inter-sensor variability and need for *in-vitro* calibration would be negated.

Another consideration is whether the use of microneedle technology for monitoring of ISF concentrations will always be appropriate in clinical settings in terms of adapting dosing and estimating target tissue concentration. This question is something that will need to be addressed within formal clinical studies to determine whether the plasma or ISF compartments are more optimal for PK-PD analysis [406]. Although we traditionally have measured plasma drug concentrations, the ISF is a compartment where many infections actually occur throughout the body [424,425]. Therefore, this may offer a potential compartment from which to optimise drug concentrations against. In terms of beta-lactam antibiotics, there is only ISF data for a small number of agents, and this tends to be in critically ill individuals, often on renal replacement therapy [439,440,442,543–548]. These studies suggest that there is wide variability in ISF concentrations depending on the site which they are measured compared to plasma. Therefore, further work will be required to better characterise the relationship between ISF drug concentrations in different compartments against plasma concentrations moving forward.

As well as the development of microneedle based methods for the monitoring of antimicrobial concentrations in ISF, the exploration of applying biosensor technology to the monitoring of plasma drug levels could have been explored. In terms of invasive monitoring, this application has already been demonstrated by Ferguson and colleagues, who used aptamer based technology to monitor aminoglycosides in ambulatory rodents [549]. An interesting alternative application of such technology would be the development of a point-of-care device that allows the monitoring of numerous different compartments, such as capillary blood, urine, and cerebrospinal fluid. This is something that I plan to explore moving

forwards. However, the application of biosensor technology for monitoring capillary blood drug concentrations poses a number of its own challenges, including bio-fouling and interference caused by the presence of red blood cells [275,549].

Finally, how this technology will be applied to the individualisation of antimicrobial dosing must also be considered moving forwards. Although not the focus of the *Chapter*, the role of using closed-loop control to optimise the delivery of continuous and intermittent antimicrobial infusions (and potentially oral dosing) is being explored [504,505]. However, further characterisation of types of biosensor will firstly be required *in-vivo* before being applied to the technology. Further discussion of closed-loop controller systems will be provided in *Chapter eight*. The role of biomarker (e.g. CRP, procalcitonin, creatinine, and lactate) monitoring may also play an important role in facilitating truly individualised therapy, for which this study provides a potential methodology through which similar types of biosensor could be developed and explored. This is supported by the previous demonstration of lactate sensing on the same microneedle bases *in-vitro* [436].

7.6 Conclusion and key messages

In conclusion, I have demonstrated that the development of minimally invasive biosensor for the real-time monitoring of antimicrobials *in-vivo* is a possibility. This is the first time that a biosensor device for monitoring beta-lactam antibiotics has been implemented on a microneedle array *in-vivo* to facilitate the monitoring of drug concentrations. Whilst this study has opened up a wide range of further questions in terms of biosensor development; it also provides an exciting opportunity to better characterise individual patient PK, offering an ability to be able to develop methods for delivering personalised and dynamic dosing through the linkage to platforms such as closed-loop control systems.

On review of the initial targets for my biosensor in *section 7.2* I have:

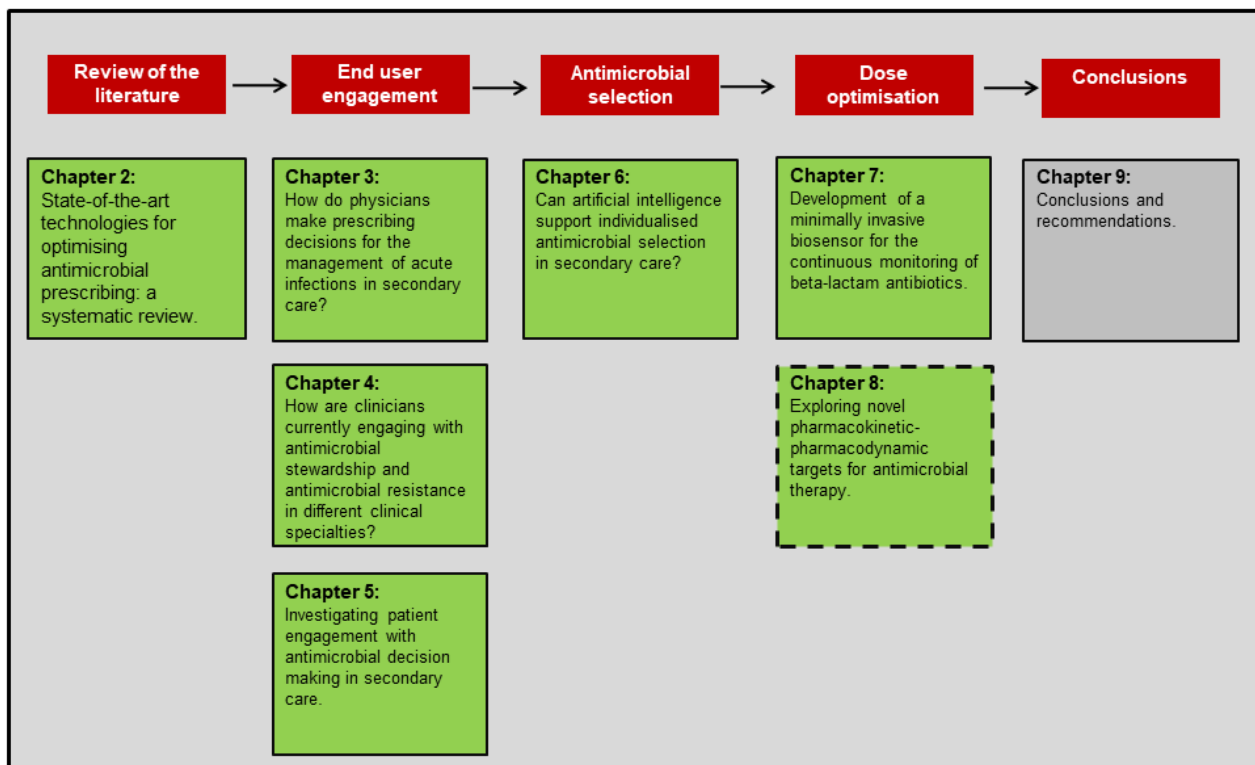
1. Demonstrated an appropriate dynamic range of the device for use *in-vivo*.
2. Demonstrated stability of the device to be stored and re-used after 28 days. I have also demonstrated the stability of the device for continuous monitoring *in-vivo* for up to six hours.
3. Reproducibility of the sensors was achieved with %CV < 15% in artificial ISF runs. However, further work is required to optimise the method of IrOx deposition and enzyme layering to improve the reproducibility of the device.
4. Demonstrated a logarithmic response of the device, with step changes in potential per decade that provide a large enough dynamic range for sensing *in-vivo*.
5. Developed a protocol using biocompatible and acceptable components for use in humans. This was validated by obtaining ethical approval to test the devices in clinical studies.
6. The device is currently portable and small enough to ambulate using our current potentiostat. However, the size and interface between the sensor and potentiostat still have significant room for refinement. This will be further explored as part of future work.

Finally, the development of biosensor technology for drug monitoring is only one area that requires consideration for the development of methods for delivering personalised antimicrobial dosing. A key area that must also be explored further is the development of more individualised PK-PD targets. This will be explored within *Chapter eight*.

CHAPTER EIGHT

8.0 Personalised antimicrobial dosing: Exploring novel pharmacokinetic – pharmacodynamics targets for antimicrobial therapy

Figure 41. Overview of thesis.



8.1 Introduction

The ability to monitor antimicrobials in a continuous manner and link this to closed-loop control systems for the optimisation of antimicrobial therapy may facilitate truly individualised antimicrobial dosing [406]. However, a further gap to be addressed is the exploration of optimal PK-PD targets of antimicrobial therapy.

Current PK-PD indices define exposure and response by using the minimum inhibitory concentration (MIC) of the organism that therapy is targeting. This is compared to a measure

of drug exposure that is either time or concentration dependent [432,550–552]. **Table 23** outlines the common PK-PD targets of a number of antimicrobial agents as described by Ambrose and colleagues in their review of antimicrobial PK-PD [553].

Table 23. Summary of common PK-PD indices with examples.

PK-PD Index	Definition	Examples
Time dependent	<i>Percentage time over MIC (%T>MIC)</i>	Beta-lactams (penicillins, cephalosporins, carbapenems)
Concentration dependent	<i>Peak (C_{max}) to MIC</i>	Aminoglycosides,
Concentration-time dependent	<i>24 hour Area Under the Concentration Curve (AUC) to MIC (AUC:MIC)</i>	Glycopeptides (e.g. vancomycin), clindamycin, macrolides, oxazolidinones

In the UK, only a handful of antimicrobials are routinely therapeutically monitored. These agents do not tend to be optimised according to PK-PD targets. Instead, clinicians adjust doses against single time point, peak or trough blood concentration data. These samples are collected during therapy, often in the preceding 12-24 hours. The use of peak or trough, single time point drug levels requires dose adjustment against estimated peak or trough target values from the population [554]. More optimal methods for dose optimisation would be to use PK-PD targets.

For example, vancomycin is administered as part of empirical therapy when there is a high risk of *methicillin resistant Staphylococcus aureus (MRSA)* infection. Vancomycin is a glycopeptide antibiotic that is used in surgical prophylaxis, for suspected, but undocumented infection, and for treatment of established infection [555]. The PK of vancomycin are highly variable in adult populations [392,395–397,399,400,422,555–568]. The attainment of PD

targets, such as the area-under-the-concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) ratio, is associated with improved clinical outcomes in patients being treated with vancomycin [399]. Vancomycin has a narrow therapeutic index. Therefore, TDM and a range of individualised dosage strategies are required to ensure safe and effective treatment [569–572].

Vancomycin displays concentration-dependent antibacterial activity. The AUC:MIC is the PD index that best links drug exposure with the antibacterial effect. Values >400 are associated with improved clinical outcomes. Higher targets may be required in severe deep infections, such as MRSA infective endocarditis [392,396,398,555,556,565,568,573].

However, the use of AUC:MIC as a PD target requires isolation of the invading pathogen or estimation based on known MIC of common pathogens. Optimisation of antimicrobial dose is a recurring problem in cases where the invading pathogen is not available [506,507]. In these cases, simple measurements of C_{min} , clinical judgement, physiological parameters, and biochemical markers such as C-Reactive Protein (CRP) are used by clinicians to assess response to therapy [168]. CRP is used extensively for infection diagnosis and management in clinical practice [574–576]. However, to date there has been little attempt to use it as a biomarker to estimate the PD of an antimicrobial agent.

Recent studies in paediatric populations have used biomarkers (e.g. CRP and galactomannan) to individualise antimicrobial therapy by enabling the estimation of the AUC:EC₅₀ [433,434]. The EC₅₀ is the concentration of a drug (mg / L) that is required to induce half the maximal antimicrobial effect on a target and is estimated from individual patient data. In cases where EC₅₀ is estimated for CRP, the EC₅₀ provides an *in-vivo* estimate of drug response [433,434] and may integrate many different aspects that govern exposure response relationships (e.g. site of infection, immune status, bacterial load, and *in vitro* susceptibility).

In *Chapters three* and *five*, I demonstrated the frequency with which CRP data is routinely requested and relied upon during infection management in secondary care [168,314]. During the management of infection, CRP is routinely used to evaluate individual response to therapy, including making decisions surrounding escalation, de-escalation, of cessation of therapy [168,314]. CRP is a member of the pentraxin family and an acute phase protein [577–580]. It is produced by the liver in response to interleukin (IL)-6 and is enhanced by IL-1 β [577]. It is a non-specific marker for infection, being raised in response to inflammation and tissue damage. Therefore, raised CRP is observed in a range of infective, allergic, inflammatory, necrotic, neoplastic, and traumatic syndromes [580]. In 99% of healthy adults, CRP will be below 10 mg / L. In response to stimulus from IL-6 (e.g. in response to infection) circulating CRP can increase by up to 10,000-fold. Pepys and colleagues describe the classic response of CRP to a single stimulus in healthy adults [580]. Following a stimulus, *de-novo* hepatic synthesis begins with CRP rising above 5 mg / L after 6-hours. CRP tends to peak by 48-hours. The plasma half-life of CRP is 19-hours and remains constant under all health states [580]. This is desirable as it means that circulating CRP concentration is determined entirely by hepatic synthesis [581]. Therefore, this can be inferred to reflect the intensity of the pathological process stimulating CRP production.

Given the characteristics of CRP and the fact that during infection we wish to correlate response of this maker (that likely reflects the intensity of the infective process) to antimicrobial exposure, the use of a measure such as AUC:EC₅₀ appears to be reasonable method to investigate. Furthermore, for agents such as vancomycin where we already routinely collect TDM data, this may be an avenue that can rapidly be translated into practice given that both CRP and vancomycin TDM data are routinely available.

8.2 Chapter objectives

For this *Chapter*, I aimed to explore whether it is possible to use routinely available data for vancomycin TDM and CRP to estimate individual patient AUC:EC₅₀. This would provide a proof-of-concept for the use of AUC:EC₅₀ in wider studies of anti-infectives in adults if successful. Given the sporadic nature of vancomycin TDM data, a rigorous population PK model would be challenging to achieve. However, individual posterior Bayesian estimates generated from the this data would most likely be rigorous enough for the available PK data to facilitate the estimation of AUC:EC₅₀ [582].

The objectives of this chapter are:

1. Describe the PK of non-critical care patients receiving intravenous vancomycin therapy in secondary care using routinely collected therapeutic drug monitoring data.
2. Explore the development of a linked PK-PD model describing the response of CRP to vancomycin exposure for the individual patient.
3. Explore whether such a PK-PD model can be used to predict the pharmacodynamics of antimicrobial therapy.

8.3 Methods

8.3.1 Study setting

Supervision during this study was provided by Professor William Hope (Liverpool University), who provided support with PK-PD modelling. This study utilised data from non-critically ill patients receiving vancomycin intravenously for the treatment of infections. These patient data were obtained from two audits that occurred in Imperial College Healthcare NHS Trust. The focus of the audit was to review the current standard of vancomycin use within the hospital compared to the local antimicrobial policy. The methodology used for patient identification and data collection was identical in both audits. All patients had undergone routine TDM following local hospital guidelines (which remained stable throughout the two audit periods that spanned 15 months) for treatment of confirmed or suspected infections with vancomycin.

The hospital guidelines recommend routine target trough plasma vancomycin concentrations of 10-15 mg/L, or 15-20 mg/L for more severe or deep-seated infections. Patient characteristics, biochemistry, microbiology data, and treatment history were extracted from electronic health records. CRP data (routinely collected by the patient's clinical team as part of the infection management and clinical care) and estimated glomerular filtration rate (GRF; calculated using Modification of Diet in Renal Disease [MDRD] formula) were retrieved from patient electronic records.

Clinical case histories of all patients treated with vancomycin in the time period were reviewed. Patients were only included if treatment was commenced for suspected or confirmed Gram-positive pathogen(s), for which vancomycin was an appropriate agent. Patients receiving concomitant therapy with other antibacterials overlapping in antimicrobial spectrum were excluded. Patients with a positive culture that was not susceptible to vancomycin (i.e. Gram-negative bacteria, anaerobes, or fungi) were excluded from the analysis.

Patients without TDM data, or on renal replacement therapy were also excluded from the analysis.

All statistical analysis was performed using SPSS 22.0 (IBM, NY, USA). Figures were plotted using R and Igor Pro 7.0.

8.3.2 Vancomycin bioanalysis

Vancomycin concentrations were measured using a commercially available MULTIAGENT assay implemented on an Architect analyser (Abbott diagnostics, CA, USA). The lower limit of quantification was 1.1 µg/L. The linear range of the assay was 1.1 to 100µg/mL.

8.3.3 Pharmacokinetic modelling software

All PK and PD modelling was performed using Pmetrics and ADAPT 5 [583,584]. Pmetrics is an open source programme that runs within R. It was developed by the Laboratory of Applied Pharmacokinetics & Bioinformatics, University of Southern California. It utilises a Non-Parametric Adaptive Grid (NPAG) algorithm which allows the use of sparse data compared to other parametric approaches to antimicrobial PK modelling [583]. As it is non-parametric, a normal distribution of data is not assumed for model parameter values. Therefore, the output from the NPAG is a non-parametric population PK model that consists of discrete support points. Each support point has a set of estimates for each parameter within the defined PK model plus an associated probability for the set of estimates [582].

To perform PK-PD modelling in Pmetrics, two files are required. A data file and a model file. The data file contains dosing and output (drug concentration or CRP) data and the model file describes the PK-PD model to be used. On fitting of a PK-PD model to the data, the user is provided with individual patient, posterior Bayesian estimated values for PK and PD

parameters within the model. This facilitates the estimation of individual AUC and provides the individual EC₅₀.

8.3.4 Population pharmacokinetic model

Data were tabulated for analysis in Pmetrics. One, two, and three compartment pharmacokinetic models were evaluated. Covariate modelling was also investigated using creatinine and GFR, which were the only variables available within this population for all individuals (data shown below in 8.4). As the aim of the PK model was to facilitate individual prior PK estimates, covariate data was not deemed as important as this is commonly used to improve the population fitting of data [582,585,586]. After evaluation, a two-compartment PK model with time-delimited zero-order intravenous input and first order elimination was used.

The structural equations took the form:

$$[1] \quad \frac{dX(1)}{dt} = R(1) + X(2) \cdot K_{pc} - X(1) \cdot \left(\frac{SCL}{V}\right) - X(1) \cdot K_{cp}$$

$$[2] \quad \frac{dX(2)}{dt} = X(1) \cdot K_{cp} - X(2) \cdot K_{pc}$$

X(1) and X(2) represent the amount of vancomycin (mg) in the central (c) and peripheral (p) compartments. R(1) is the rate of infusion of vancomycin into the central compartment (mg / h). V is the volume of the central compartment (L), from which there is clearance of drug (SCL; L / h). The two compartments are connected by first order rate constants K_{cp} and K_{pc} (h⁻¹).

The fit of the model to the data was assessed in the following ways: (i) log-likelihood values, (ii) assessment of coefficients of determination (r²) from a linear regression of the observed-predicted data, (iii) use of the Akaike Information Criterion (AIC) [587]. Furthermore, a predictive check was performed using normalised prediction distribution errors (NPDE) to allow evaluation of the PK model [588,589]. The NPDE tests for differences from a perfect fit of the model to the data using a simulation based approach. It is believed to be more robust

than approaches using residuals and empirical Bayes estimates, which can be misleading when evaluating a population PK model [588,589].

8.3.3 Pharmacokinetic-pharmacodynamic modelling

A two-step approach to fitting PK and PD data was used. The Bayesian posterior estimates for each individual were obtained using the two compartment PK model described in equations [1] and [2]. Posterior Bayesian estimated values (V , Cl , K_{cp} , and K_{pc}) for the individual patients were then fixed as covariates within a PK-PD model made up of equations [1], [2], and [3] to describe the exposure response dynamics of CRP [3]. The model chosen for use in this study was selected based on previous published work investigating the exposure response dynamics of CRP during infection in neonates [434,590] and the described kinetics of CRP as reported by Pepys and colleagues [580].

$$[3] \quad \frac{dX(3)}{dt} = \left(KCRPp \cdot X(3) \cdot \left[1 - \frac{X(3)}{POPmax} \right] \right) - \left(\frac{KCRPi \cdot X(3) \cdot \left[\frac{X(1)}{V} \right]^H}{EC_{50}^H \cdot \left[\frac{X(1)}{V} \right]^H} \right)$$

$KCRPp$ is the maximum rate of CRP production ($mg \cdot h / L$); $POPmax$ is the maximum value of CRP (mg / L). A normal CRP is defined as $<10 \text{ mg / L}$. In the literature, following acute-phase stimulus CRP can be observed to rise to greater than 500 mg / L [580]. Therefore, this was used as an upper limit for the search space used in fitting the model to the data. $KCRPi$ is the rate of maximal CRP inhibition ($mg \cdot h / L$), H is the slope function for CRP inhibition, and EC_{50} is the concentration of vancomycin (mg / L) that produces half maximal effect on CRP reduction.

Whilst previous work exploring CRP response in murine models has often included a mechanism of immune clearance of CRP this was not included in this model [590]. I chose not to opt for this given that there is currently little evidence from natural infection modelling of CRP response to suggest that this mechanism occurs in humans [580].

8.3.4 Exposure-response

The Bayesian posterior estimates for each patient were used to calculate the average AUC (i.e. total vancomycin AUC for the treatment course divided by the number of treatment days). Posterior estimates for individual patient's EC_{50} were also obtained to calculate AUC: EC_{50} . This index was then fitted to patient CRP data 96-120 hours after commencing vancomycin therapy in individuals where Gram-positive infection was microbiologically confirmed. This used an Emax sigmoidal model to identify trends in the data and describe the relationship between CRP and AUC: EC_{50} . The findings from evaluating exposure-response in individuals with microbiology confirmed infections were then compared to individuals with no microbiology who were being treated empirically but had a high suspicion of Gram-positive infection. AUC:MIC estimates were also compared to CRP response in the same manner, with a cut off of 400 used.

8.3.5 Ethics

Ethical approval was not required for this retrospective study using routinely available clinical data. However, this study was approved as part of an ethics application reviewed by London-Chelsea Regional Ethics Committee (REC: 17/LO/0047). This study was also conducted under local service evaluation protocols.

8.4 Results

8.4.1 Subjects characteristics

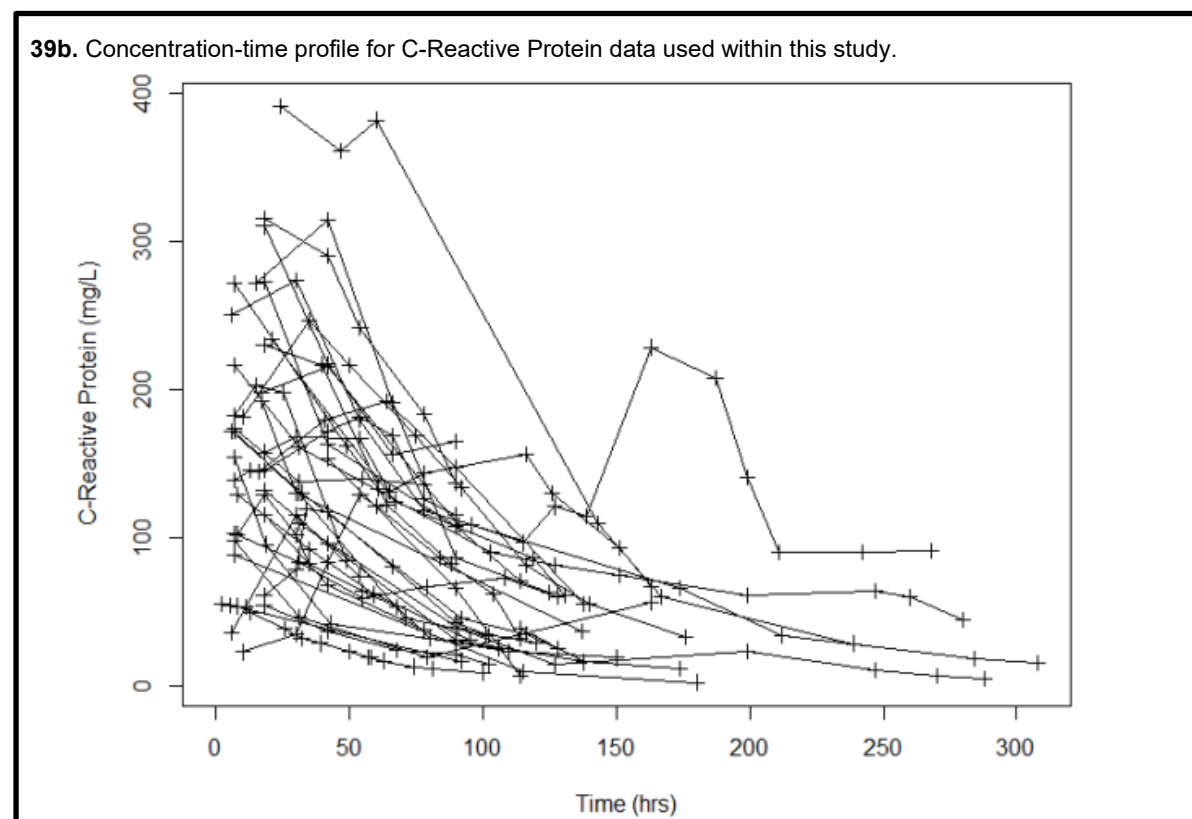
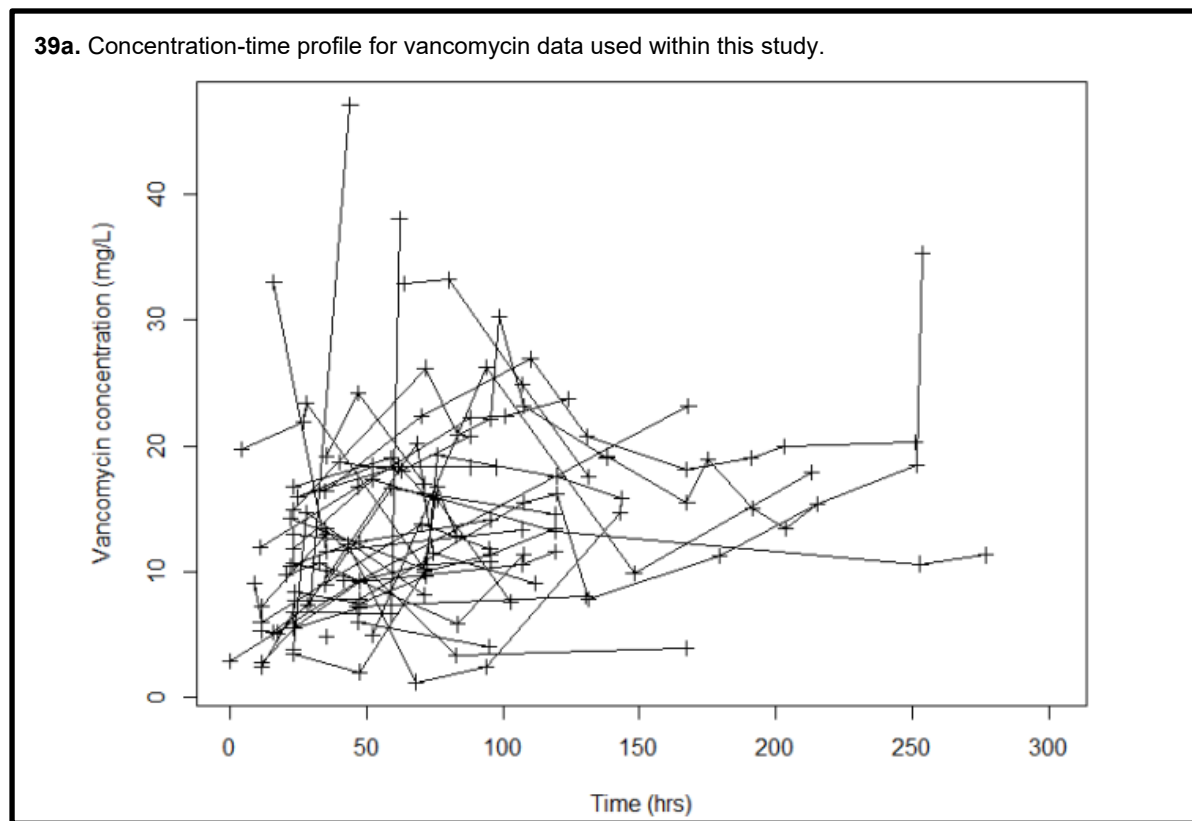
A total of 105 non-critically ill patients receiving vancomycin were identified as potential study subjects. Twenty-nine (37%) patients were eligible for consideration of inclusion in the PK-PD analysis. Of the 76 patients excluded, 20/76 (26%) were on renal replacement therapy, 16/76 (21%) had no TDM data, 8/76 (11%) had other missing data, with the remaining 22/76 (29%) dosed for less than 72 hours or treated for Gram-negative infections / non-infectious syndromes. Vancomycin therapy was used empirically in 48/105 (46%) of patients. All patients had Gram-negative and anaerobic antimicrobial cover administered at the clinician's discretion.

For the 29 subjects included in the PK-PD analysis (**Table 24**), median (range) age was 62 (21-97) years. The majority were female (18/29; 62%) and 15/29 (52%) had microbiology confirmed Gram-positive infection. The mean (SD; range) number of doses of vancomycin received were 10 (4; 4 - 22), with a mean dose (range) of 1000 mg (500 - 2000 mg) per day. Each subject had a mean (SD) of 5 (3) TDM samples taken during therapy. Mean (SD) GFR for the cohort was 82 (37) ml/min/1.73m² and initial mean (SD) CRP on commencement of vancomycin therapy was 154 (110) mg / L. Patients had a median (range) of 5 (2 - 13) CRP measurements during the time period that they were receiving vancomycin therapy. Concentration-time profiles of the raw-data for vancomycin TDM and CRP used for modelling are shown in **Figure 42**.

Table 24. Summary of patient characteristics included in the pharmacokinetic-pharmacodynamic model.

Parameter	Value (%)
<i>Demographics</i>	
Age (range)	62 (21-97)
Female	18 (62)
<i>Infection</i>	
Blood Stream Infection	7 (24)
Pneumonia	2 (7)
Skin and soft tissue	10 (34)
CNS infection	1 (3)
Intra-abdominal infection	2 (7)
Joint (inc. prosthetic)	1 (3)
Line sepsis	1 (3)
Urinary tract infection	2 (7)
Other	3 (10)
<i>Organism</i>	
Empirical therapy (no growth)	14 (49)
Staphylococcus aureus	7 (24)
Coagulase negative	
Staphylococcus	4 (14)
Other Gram-positive	4 (14)

Figure 42. Concentration-time profiles for vancomycin drug concentration data and C-reactive protein data for individuals used with the study.



8.4.2 Pharmacokinetic – pharmacodynamic model

A two-compartment model was found to be optimal. **Figure 43** outlines the individual posterior predicted versus observed plots for the vancomycin and CRP models, as well as a summary of the NPDE for the vancomycin model. The final vancomycin model had an individual posterior observation versus predicted plot r^2 of 0.83 with a bias of 0.37 and imprecision of 0.97 (**Figure 43a**). The CRP PD model was fitted with an individual posterior observation versus predicted plot r^2 of 0.82, a bias of -0.07, and imprecision of 1.05 (**Figure 43b**). As only individual posterior estimates were required for this study, covariate modelling was not explored in detail. However, addition of renal function to the model was not found to improve the accuracy of individual posterior Bayesian estimates during initial model development.

Predictive checking using NPDE demonstrated that the overall model global adjusted p -value was 0.02. This suggests that there was a significant difference between the perfect fit of the model and the data. However, for the purpose of this study (estimating posterior AUC values using routinely available data) this variation was classified as mildly significant ($p > 0.01$) and therefore, the model is therefore likely to be adequate [588,589]. The NPDE also demonstrated that Fisher's variance $p = 0.05$ and the Shapiro-Wilk test of normality $p = 0.24$ suggesting that the data has equal variance and normal distribution compared to the optimal fit of the model [588,589]. This can be observed visually in **Figure 44** with the histogram and Q-Q plots. The means of the data compared to the best fit were significantly different with a t -test value of $p < 0.01$.

A summary of the final population PK-PD parameter estimates are outlined in **Table 25**. Population estimates of vancomycin PK were similar to previously reported observations in the literature [392,591]. There was a substantial variability in the individual Bayesian posterior estimates for EC_{50} values estimated, with mean (SD; range) of 23.40 (13.55; 6.95 - 48.55). Mean (SD; range) AUC: EC_{50} was 31.46 (29.22; 7.30 - 128.41).

Figure 43. Pharmacokinetic and pharmacodynamic model individual observed versus predicted plots.

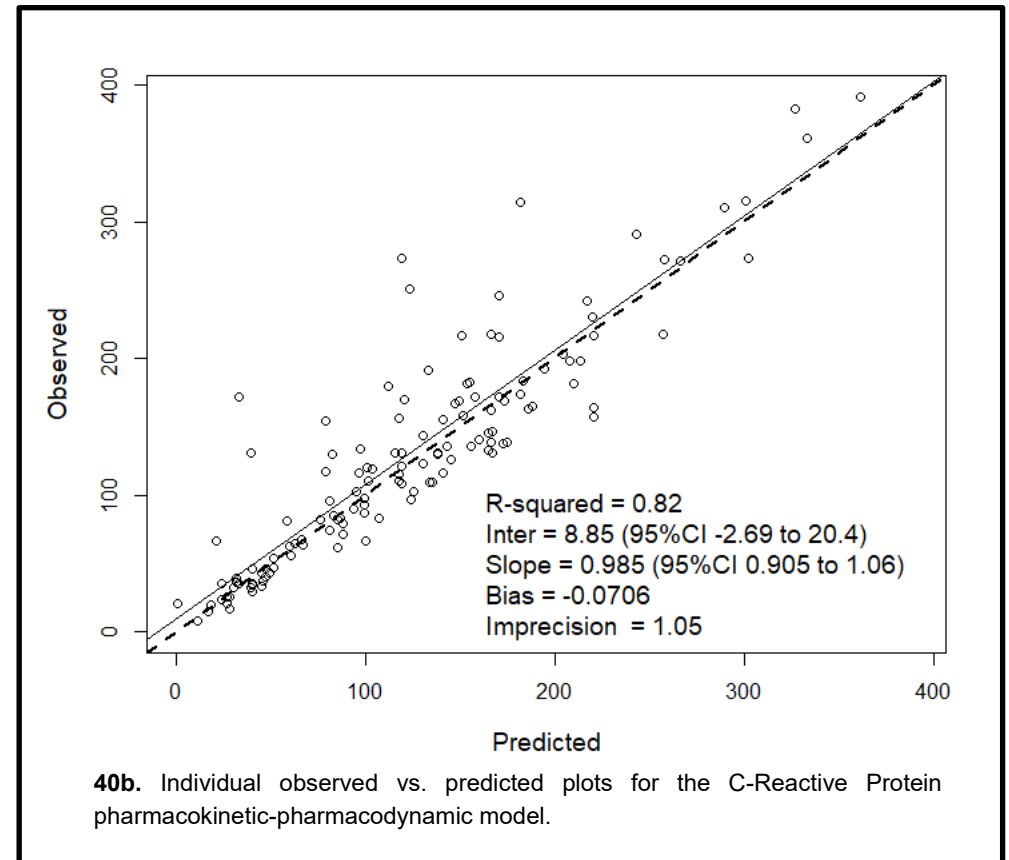
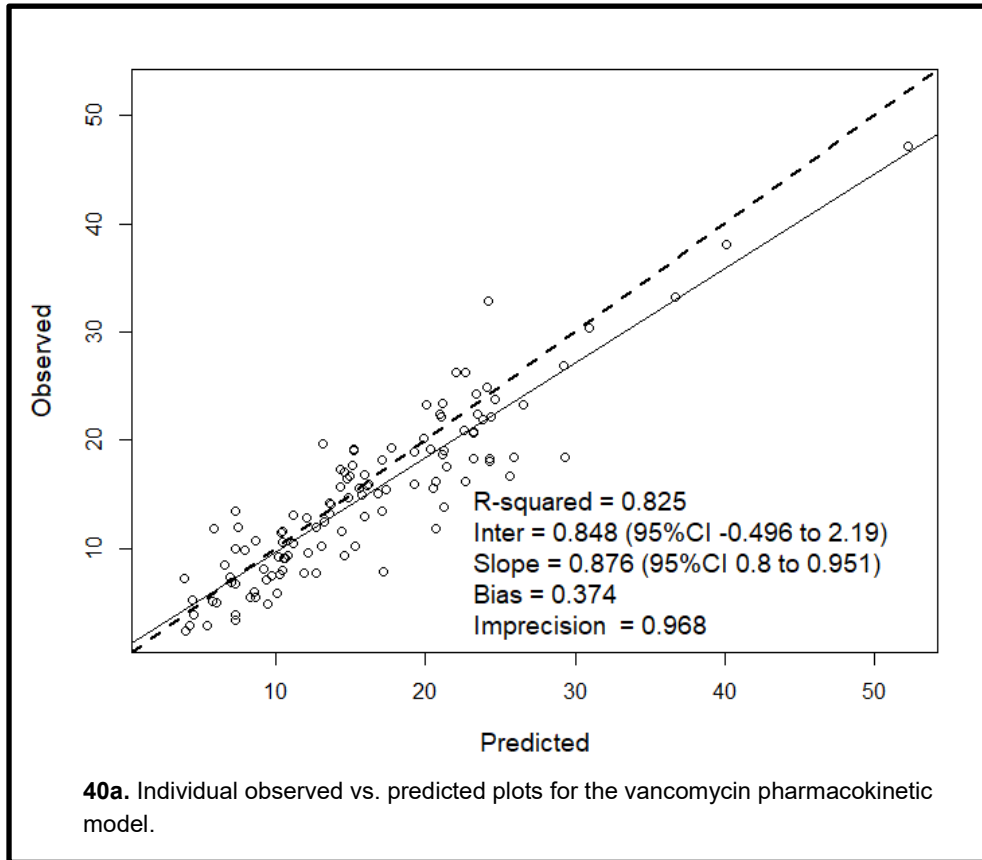


Figure 44. Normalised prediction distribution error plots for the vancomycin pharmacokinetic model used within this study.

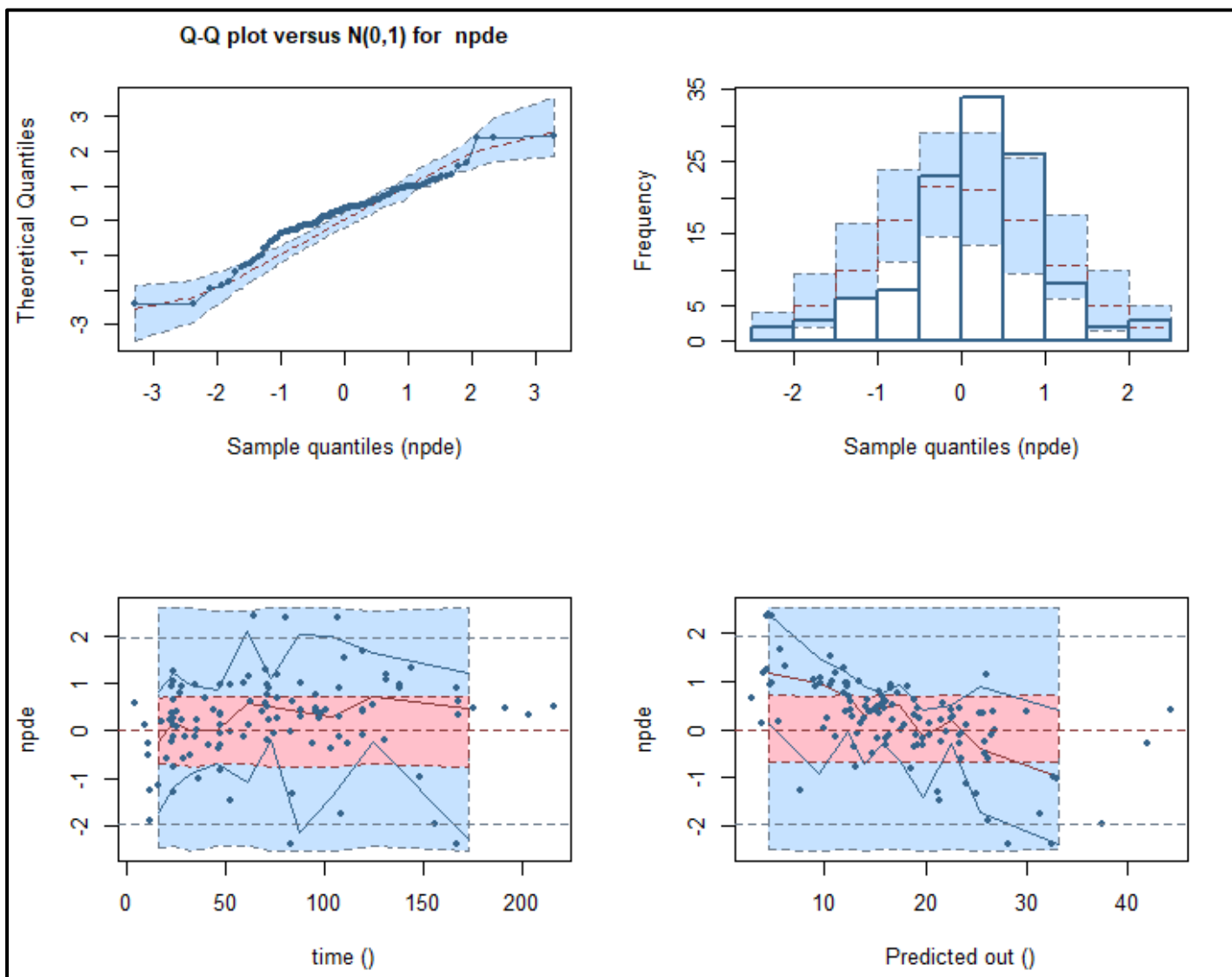


Table 25. Population estimates of the pharmacokinetic – pharmacodynamic parameters for a model linking CRP to vancomycin concentrations in a population of non-critical care patients in secondary care.

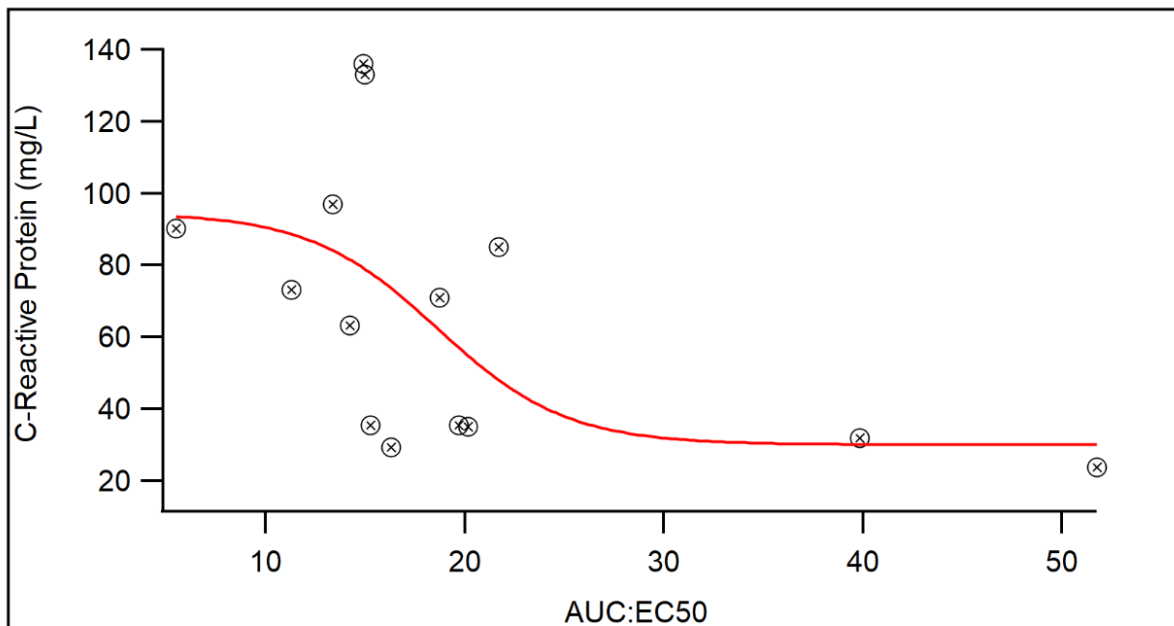
Population parameters		Value
<i>Pharmacokinetic parameters</i>		
Clearance (CL, L/hr)	mean (SD)	3.77(2.23)
Volume (central, L)	mean (SD)	25.89 (12.08)
Kcp (hr ⁻¹)	mean (SD)	3.32 (3.81)
Kpc (hr ⁻¹)	mean (SD)	2.59 (3.17)
<i>Pharmacodynamic parameters</i>		
KCRPp (mg·h/L)	mean (SD)	0.07 (0.07)
POPmax (mg/L)	mean (SD)	494.24 (242.46)
H	mean (SD)	11.14 (8.18)
KCRPi (mg·h/L)	mean (SD)	0.11 (0.07)
EC50 (mg/L)	mean (SD)	23.40 (13.55)
Initial condition of CRP (mg)	mean (SD)	154 (110)
Glomerular filtration rate (ml/min/1.73m ²)	mean (SD)	82 (37)

Legend: L/hr = litres per hour; hr⁻¹ = per hour; mg = milligram; h = hours; min = minute; m² = meters squared; SD = standard deviation; CRP = C-Reactive Protein; KCRPp = maximum rate of CRP production; POPmax = maximum value of CRP; H = slope function for CRP inhibition; KCRPi = maximal rate of CRP inhibition; EC50 = concentration of vancomycin that produces a half maximal effect.

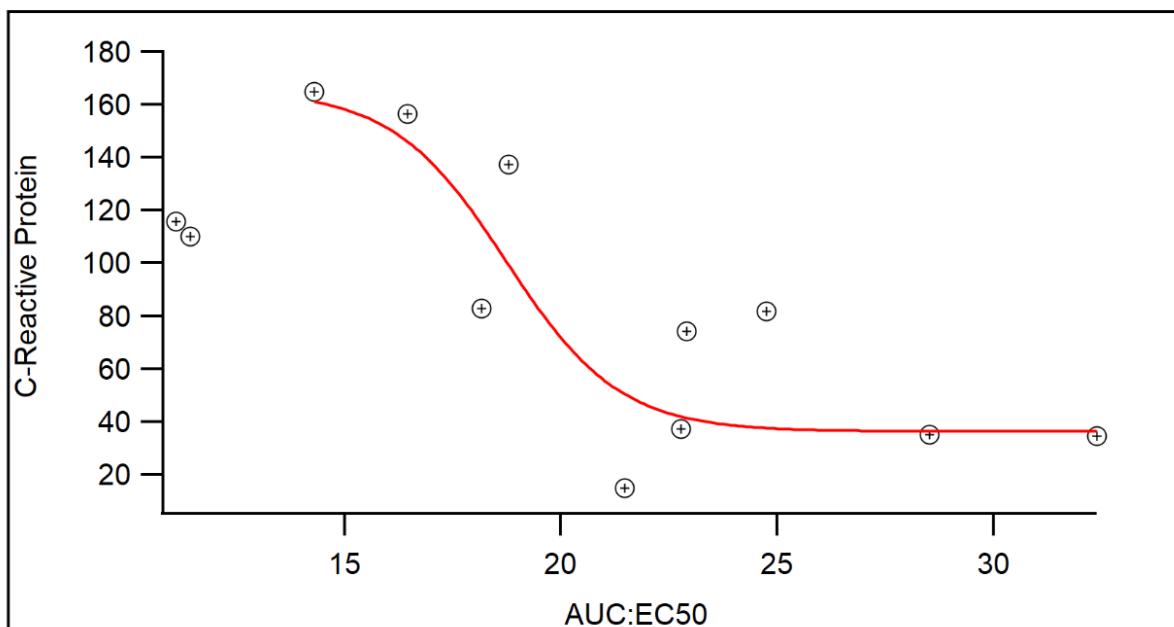
8.4.3 Exposure response

Individual cases were then assessed with Bayesian posterior estimates of individual vancomycin AUC:EC₅₀ fitted to a sigmoid Emax model for Gram-positive confirmed patients and the relationships to CRP values at 96 - 120 hours post initiation of vancomycin therapy assessed (**Figure 45**). This was repeated for those individuals treated empirically. In the microbiology confirmed cohort, one individual was excluded due to being taken back to surgery during the first 120-hours of therapy. Two individuals from the empirically treated group were also excluded as one developed active pancreatitis during the therapy and one was taken back to theatre for further surgery.

Figure 45. Individual AUC:EC₅₀ estimates against CRP at 96 - 120 hours post commencement of vancomycin therapy.



C-Reactive protein prediction at 96-120 hours in patients with microbiological confirmed Gram-positive infections



C-Reactive protein predictions at 96-120 hours for individuals treated empirically with vancomycin

Assuming a mean MIC of 1 mg / L for *Staphylococcus aureus* and other associated organisms treated within this study (only 4/14 microbiology specimens had individual MIC data available), the optimal target vancomycin AUC would be >400 based on previously published clinical outcome data [392,396,398,555,556,565,568,573]. Using AUC:EC₅₀ as a surrogate, values greater than 19 (given a vancomycin AUC of 400 and median EC₅₀ of 21 mg / L) would therefore be expected to correlate to this.

Thus, AUC:EC₅₀ values could potentially be expected to demonstrate a better CRP response to therapy above this. In the Gram-positive confirmed cohort, 5/14 (36%) individuals had AUC:EC₅₀ >19. There was an association with lower CRP values at 96-120 hours with mean (SD) CRP of 42 (24) mg / L in those with AUC:EC₅₀ >19 vs. 81 (38) mg / L for those with AUC:EC₅₀ <19 ($p = 0.06$). For those individuals treated empirically, 6/12 (50%) had AUC:EC₅₀ >19. Once again, an association was observed toward lower CRP at 96 - 120 hours. The mean (SD) for those with AUC:EC₅₀ >19 was 46 (26) vs. 128 (31) ($p < 0.01$).

Pooling of all cases, both microbiologically confirmed and empirical, followed by assessment of AUC:EC₅₀ demonstrated a significant association with AUC:EC₅₀ > 19 and prediction of CRP at 96 - 120 hours. Individuals with AUC:EC₅₀ >19 had mean (SD) CRP of 44 (24) mg / L vs. 100 (41) mg / L in those with AUC:EC₅₀ <19 ($p < 0.01$). Mean (SD) estimated AUC:MIC's for the cohort were then compared, using MIC breakpoint estimates used in clinical practice [402].

Using an estimated MIC of 1 mg / L, CRP response at 96 - 120 hours was compared between individuals with AUC:MIC greater or less than 400. There was no difference between groups with AUC:MIC <400 obtaining a mean (SD) CRP of 65.7 (32) mg / L versus 80.1 (49) mg / L in those with AUC:MIC >400 ($p = 0.45$).

8.5 Discussion

The use of vancomycin in non-critically ill adults is always challenging. There is considerable PK variability. Many patients are culture negative meaning an MIC is not available to guide individualised therapy. Therefore, physicians are often forced to use population level TDM guidelines and organism breakpoints in an attempt to optimise therapy for the individual patient. These approaches are not specific to the individual being treated and fail to consider patient-level factors that drive PK variation. They also fail to consider the individual organism, its response to antimicrobial therapy, and the impact of the host immune system on antimicrobial PD. In an attempt to individually assess physiological response to an infection and subsequent antimicrobial therapy, physicians commonly use non-specific markers such as CRP. To date, there has been very little linkage of this inflammatory marker, and other similar routinely collected bio-markers of infection, to PK-PD parameters [433,434].

The use of AUC:EC₅₀ offers a novel measure to assess individual patients' response to therapy [433,434]. The EC₅₀ value is a measure of the potency of a drug taking into account both the host factors (such as immune response and comorbid status) as well as organisms factors (such as resistance to the therapy being delivered and bacterial load). When linked to the exposure of the drug in question (the AUC), this allows consideration of variables pertaining to both the host and invading pathogen that affect the ultimate exposure-response relationship [433,434]. The use of MIC alone only provides information on the potency of the drug for its microbiological target. Thus, the AUC:EC₅₀ may augment this, acting as a more inclusive estimate of antimicrobial activity. This may be of benefit when MIC data are not available, a common scenario, especially outside of the critical care setting [506,507]. Within this study I have demonstrated a potential of AUC:EC₅₀ estimates obtained through analysis of routinely available data to be able to predict greater response of CRP during therapy. These were in-keeping with current non-individualised AUC:MIC estimates that would routinely be considered during empirical therapy in clinical practice (i.e. target AUC:MIC of

>400). On comparison to estimated AUC:MIC for individual cases within this study, using published MIC breakpoints [402], AUC:MIC >400 did not correlate with lower CRP at 96 - 120 hours. This may support some of the potential benefits of using EC₅₀ to provide more individualised assessment of response to therapy.

However, this study also highlights several challenges that individualised therapy using measures such as the AUC:EC₅₀ face in the future in adult populations. In a previous study performed by Ramos-Martin *et al*, AUC:EC₅₀ values in neonates predicted the likelihood of the normalisation of CRP (defined as <10 mg / L) for infants receiving teicoplanin therapy for the treatment of coagulase negative staphylococcus line infections [434]. In my study population, very few subjects CRP returned to <10 mg / L on cessation of vancomycin therapy. This is, in part, likely to be due to local antimicrobial stewardship policies for adults in the non-critical care setting that means patients are regularly reviewed and therapy is de-escalated before patients biochemical markers have returned to normal limits (usually within 72-120 hours) [53]. It also reflects the co-morbid state of adult patient populations represented within this setting. Therefore, I chose a time point of 96 - 120 hours given that most individuals will be treated for this period of time with vancomycin and the observed response of CRP during therapy.

Given that both AUC and EC₅₀ can be estimated with minimal vancomycin and CRP data, it is possible that future studies could incorporate consideration of AUC:EC₅₀ estimation into medication reviews. This may act as a tool to help inform the likelihood of success of continued empirical therapy when no organism has been identified, providing an individualised estimate of treatment success with the current therapy. A further observation from this study was that a number of individuals appeared to have vancomycin concentrations below recommended targets during therapy. On review of mean dose received by individuals within the study, a mean of 1000 mg / 24 hours may have been lower than is often recommended. However, this is a common problem observed with vancomycin

therapy in similar populations and highlights some of the challenges with conventional approaches to dosing and TDM using trough concentrations [392,554,592].

With the development of continuous monitoring of biomarkers and antimicrobials and translation into closed-loop control systems; the AUC:EC₅₀ may also provide a source for dynamic individualisation of therapy given that changes in the individuals physiological state will also be considered alongside organism response [406,504,505]. Further work is required to explore newer, more specific clinical biomarkers (such as procalcitonin and CD64) that have the ability to improve population PD models for delivering individualised therapy [575]. The model described within this study serves as a framework from which PK-PD models for these biomarkers can be developed and explored.

8.5.1 Limitations and future work

Several limitations with the use of this model within our population were identified during the study.

- i. Given the nature of how our data were collected, PK estimates were made using sparse data, which may have influenced our estimates of vancomycin PK parameters. However, by using a non-parametric approach with the NPAG software this allowed me to work with sparse, routinely collected data. This is because the NPAG does not require a normal distribution of the data, working in a non-parametric fashion.
- ii. Although the population estimates for the data had significant differences in NPDE analysis, the data was likely adequate for the purpose of this study. For future work, using a previous vancomycin PK model, developed using rich PK data may be a suitable method for addressing some of these challenges. Future work must focus on the utility of this technique for predicting the outcomes of therapy with rich PK and PD data for a number of different antimicrobial agents. Ideally this would focus on

monotherapy, to remove any potential overlap in efficacy that could have been caused by other co-prescribed antimicrobials within this study. This is something that I hope to explore in the future, using data from a study of beta-lactam TDM currently being undertaken within ICHNT.

- iii. A large number of individuals identified as receiving vancomycin therapy in were excluded from the analysis as they lacked TDM data, were receiving renal replacement therapy, or were prescribed vancomycin inappropriately (in Gram-negative infections). Therefore, the small and highly selected sample of individuals included means that generalizability of our findings is difficult. This also means that certain aspects may have been underpowered to demonstrate significance statistically. Power calculations were not performed as part of this retrospective analysis, which aimed to explore the development of the concept of AUC:EC₅₀. For future prospective clinical studies of AUC:EC₅₀, appropriate statistical power will be an early consideration that I take.
- iv. Although this study demonstrated that higher AUC:EC₅₀ values appeared to correlate with expected AUC:MIC ratio's for optimal therapy, it did not demonstrate direct improvements in clinical outcome. I know plan to undertake a prospective study to estimate AUC:EC₅₀ within 72-hours of commencement of vancomycin therapy to explore whether this can predict response to therapy as expected. This includes exploration of whether more intensive CRP monitoring can improve the accuracy of EC₅₀ estimates within the PD model.
- v. For estimation of AUC:MIC I had to use estimated organism MIC for the majority of clinical isolates within this study. This reflects the common challenge of using PK-PD indices within this clinical cohort, as reflected upon in *Section 7.1*. For future work I plan to ensure that individual MIC data are available to enable a more individualised comparison of the predictive power of AUC:MIC versus AUC:EC₅₀.
- vi. A final limitation of this study at present is that this technique has not been tested within the concept of closed loop control. Therefore, it is unclear whether the

granularity of data presented within this study would be adequate to influence controller response.

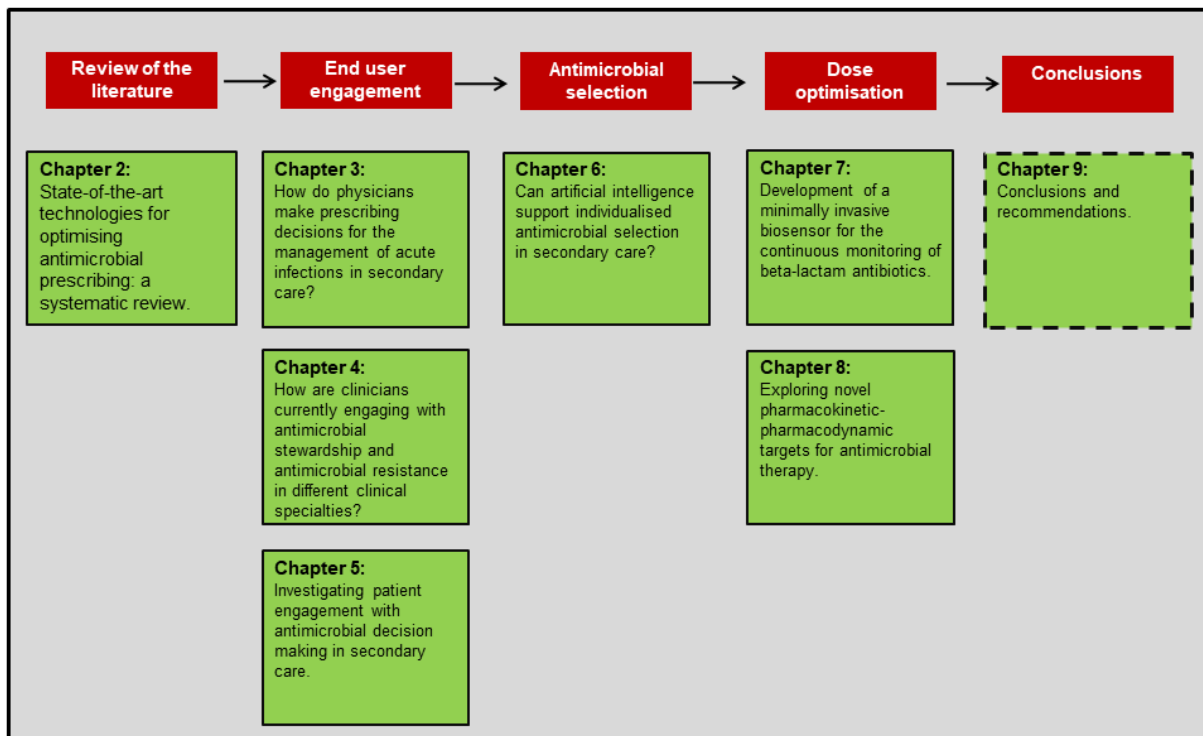
8.6 Conclusion and key messages

Within this *Chapter*, I have demonstrated the proof-of-concept that CPR can be used to predict vancomycin PD through linkage of exposure response using routinely collected patient data. Within this small cohort of patients, AUC:EC₅₀ had greater predictive power for estimating CRP response to therapy at 96-120 hours compared to AUC:MIC. These findings provide evidence to support the development of larger, prospective studies and generation of PK-PD models. It also warrants the exploration of use of other PD markers, such as procalcitonin for therapy response or renal function for risk of toxicity. Finally, these new PK-PD indices must now be explored in the context of continuous biomarker and drug monitoring, using the approach described in *Chapter seven* and linked to techniques for closed-loop control. With this, the AUC:EC₅₀ may augment the truly individualised, precision delivery of antimicrobial therapy by providing an *in-vivo* index of response to antimicrobial therapy.

CHAPTER NINE

9.0 Personalised antimicrobial management in secondary care: Conclusions and recommendations

Figure 46. Outline of thesis.



9.1 Conclusion

Within this thesis I aimed to address the hypothesis:

Personalised decision support interventions have the utility to enhance antimicrobial management across secondary care.

The work described within this thesis addresses this hypothesis by adding a number of new concepts and approaches to personalisation of decision support for antimicrobial management.

Firstly, through the work undertaken in this thesis, it has become clear that current approaches to improving decisions about antimicrobial management are often inflexible, of a narrow focus, and not considerate of the end-user. Personalised medicine does not simply apply to the use of genotypic information in the case of infection management. It must also apply to the customisation of approaches to optimising therapy based on the patient, the prescriber, the antimicrobial in question, and the organism that is being targeted.

During the development of electronic tools, developers must demonstrate an understanding of, and engage with, the end-user throughout development, implementation, and evaluation of any intervention. This will provide clarity on the areas of decision making that require supporting, whilst also promoting greater communication and engagement with the problem of optimising antimicrobial prescribing.

Within my thesis, I have been able to explore decision making of physicians managing acute infections. This has demonstrated how current rule-based decision support tools fail to influence a large part of the decision making process. It has also supported my hypothesis highlighting the potential of using technology to provide better and more individualised data on a wide range of clinical parameters, may help to improve decision making towards antimicrobial management overall.

As well as describing individual decision making, this thesis has explored the need for broader engagement across specialties that are not experts in infection management. Novel mechanism and proxy indicators for monitoring the formal level of awareness and

engagement by individual specialties have been proposed. This includes the evaluation of state-of-the-art scientific conferences and postgraduate training curricula.

Further support of this hypothesis has been through the demonstration that personalised interventions to support decision making should not just be prescriber-focused. Evidence-based practice must also ensure that patient preferences and values form part of the decision making process. Working with patients, I have demonstrated that the development of a simple, personalised, PDF information sheet can improve patient knowledge and understanding in the short term. Interventions like this can potentially foster greater patient involvement in the process of decision making during infection management in secondary care addressing some of the key factors that I have identified as driving negative attitudes and behaviours towards antimicrobial prescribing in the future.

Focusing on the development of tools to support decision making in secondary care, I have reported the development and evaluation of using artificial intelligence to optimise use of routinely available data. These approaches offer methods for providing personalised antimicrobial decision support based on individual clinical parameters. Within this, supervised machine learning can accurately infer the likelihood of patients having an infection using routinely available blood parameters. Furthermore, CBR can be used to provide individualised prescribing recommendations for antimicrobials. The training and curation of such systems have also been explored when considering deployment in complex hospital settings.

However, antimicrobial selection is only one facet of appropriate antimicrobial delivery. This thesis has also demonstrated that the development of electrochemical biosensor technology can be deployed in a minimally invasive fashion. This provides a novel

avenue to explore the real-time monitoring of antimicrobial agents, starting with beta-lactams, such as penicillin-V. By linking microneedle based biosensors to closed-loop control systems and individualised pharmacokinetic-pharmacodynamic indices it may be possible to greatly increase the precision of drug delivery for the individual patient. The parallel development of PK-PD indices, such as the use of CRP and AUC:EC₅₀ ratio, may augment the current reliance of diagnostics and static, *in-vitro* measures of organism susceptibility to an antimicrobial agent, the MIC.

9.2 Identified challenges for the future

Despite the successes described above, I have also identified a number of gaps that remain and future challenges that must be addressed.

Firstly, a major challenge remains in defining what appropriateness of antimicrobial prescribing is when considering different contexts under which this is explored. This has caused a number of challenges during this thesis. This included comparing between different studies reporting the impact of decision support systems in *Chapter two* and assessing the potential impact of artificial intelligence tools on prescribing in *Chapter six*.

Secondly, although numerous artificial intelligence techniques have demonstrated the potential to improve decision support for antimicrobial management, a number of core challenges remain. These include:

- I. Improving the collection of routinely available data within electronic health records to facilitate optimal use of such data.
- II. Ensuring the development of user interfaces and data visualisation tools are appropriate to the end-users that they target.
- III. Defining how such decision support tools will augment the use of prescribing policy and expert opinion.
- IV. Developing systems that are agnostic to different information technology infrastructures and databases between hospitals.
- V. Refining data variables to allow systems to work across numerous care pathways and healthcare settings.

Thirdly, the development of biosensor technology needs to ensure that it is focused on developing scalable and accurate tools, which are developed based on current clinical need. There is currently little evidence to support recommendations on core areas of

focus for the development of such tools in terms of clinical settings, antimicrobial agents, and biomarkers that should be given high priority. Moreover, the role of different methods for biological detection, such as aptamer based technology, must be rapidly assessed for its applicability for use in humans, its scalability, and its cost. Finally, with the development of closed-loop control systems, new methods for drug delivery must be considered and the role of novel PK-PD indices explored across a wide range of contexts, to accurately map and characterise such approaches. The implementation of new PK-PD indices can also be considered independently, outside of this context.

Finally, the development of patient-focused interventions must be better explored across a range of healthcare settings. Despite evidence that simple interventions to promote patient engagement with decision making around infection management can have a positive impact, little work has currently focused upon this, especially in secondary care.

9.3 Recommendations

Given these results and core challenges identified within this thesis, there are several recommendations that can be made for consideration in healthcare practice and research in relation to my hypothesis.

1. For the development of interventions to address the problem of antimicrobial resistance, it is vital for broader engagement with clinical specialties and individual specialists who will be adopting the intervention in question. This will not only facilitate a better understanding of how the intervention fits into the end-user workflow, but will also help to promote awareness, understanding, and generate local leaders and advocates for AMS and AMR within the target population.
2. Engagement must also include our patients. Without patient engagement in the decision making process we will continue to promote negative attitudes and behaviours towards infections and antimicrobials. Therefore, organisations must focus on improving healthcare professional – patient communication surrounding infections and their management. This must focus on delivery of personalised information relevant to the individual.
3. Technology has the potential to facilitate provision of more accurate and individualised data to support antimicrobial decision making. However, this must be considered in integrated packages. Evaluation of such developments must be designed to facilitate the assessment of an individual units impact versus the cumulative impact of the multi-modal intervention that it is delivered as.
4. To support the integration of artificial intelligence in healthcare, we must consider how data is collected and stored to facilitate secondary use as part of decision support systems. This includes streamlining data warehouses and ensuring

standardised approaches to collection and storage of data to help facilitate the implementation of technology across healthcare settings and geographical areas.

5. Artificial intelligence should not be seen as a tool that will take over healthcare decisions, it should be seen as a tool to be used by skilled healthcare professionals to support the evidence-based management of infections.
6. Antimicrobial dose optimisation requires urgent consideration across healthcare settings. This requires a radical re-think of current therapeutic drug monitoring approaches and consideration of investment in the development of new technologies. This should include consideration of biosensor technology, closed loop control, and exploration of novel PK-PD indices for implementing individualised dosing strategies.

9.4 Future work

Whilst I have discussed future work at the end of each *Chapter* for this thesis, there are several core areas that I aim to focus on moving forwards.

Firstly, with mechanisms of monitoring specialty engagement with AMS-AMR it will be important to explore how to utilise this to target individual specialties deemed “high risk”. Locally, I hope to address this by targeting the interventions developed within my work at areas of “high risk”. This includes engaging with critical care, transplant surgery, such as renal transplantation, and haematology within our hospital Trust. Nationally, there is a drive towards the integration of AMS into postgraduate training curricula by Health Education England, in which my work has been cited [593]. Therefore, my developed methodology may serve as a mechanism for tracking impact and success of this intervention in the coming years.

Secondly, as discussed in *Section 6.5*; with the development of artificial intelligence techniques, I must now evaluate the impact of these tools in clinical practice. This will require a quasi-experimental or randomised control study to explore the impact of these interventions, both in isolation and integrated together, on antimicrobial prescribing. Furthermore, with improving availability of data, it will also be possible to expand the predictive capabilities of the algorithms used within *Chapter six*.

Thirdly, now that I have received ethics to evaluate the microneedle electrochemical sensors in healthy volunteers and have successfully piloted the device *in-vivo*; I plan to undertake healthy volunteer studies with concurrent drug sampling from both blood and tissue to allow demonstration of proof-of-concept. Closed-loop control will also be developed to work in conjunction with the sensor devices. In parallel to this, aptamer based technology is under evaluation and I will be applying this to both microneedle based technology as well as point-of-care sensor devices for capillary blood sensing.

Biosensors for clinical biomarkers, such as CRP, lactate, and procalcitonin will also be explored to facilitate rapid diagnosis of bacterial infection and provide rich data to support novel PK-PD indices. The development of these indices follows demonstration of the concept for use of AUC:EC₅₀ using a CRP linked model in *Chapter eight* of the thesis.

Fourthly, given the short-term improvements in knowledge and engagement with antimicrobial decision making reported by patients in my small pilot study in *Chapter five*; I now aim to implement this in a large, controlled trial that will assess medium to long term influence on attitudes and behaviours, post discharge from hospital. This will be achieved by consenting patients for follow up post discharge from hospital to longitudinally assess the impact of this intervention.

Finally, whilst the interventions reported within this thesis have been developed and evaluated largely in isolation, my long-term goal is to implement and evaluate a multifaceted intervention incorporating many of these tools. This would be embedded within a clinical decision support tool, such as the one described in *Chapter six*. This would allow me to evaluate the impact of combining numerous individualised approaches to enhancing decision making at different stages of the decision making process. My hypothesis is that integration of such techniques will demonstrate a significantly greater impact than the sum of the individual interventions implemented in isolation.

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APPENDIX

Appendix 1. Publications from thesis

Chapter 2:

- **Rawson TM**, Moore LSP, Hernandez B, Charani E, Castro-Sanchez E, Herrero P, Hayhoe B, Hope W, Georgiou P, Holmes AH. ***A systematic review of clinical decision support systems for antimicrobial management: are we failing to investigate these interventions appropriately?*** Clin Microbiol Infect. 2017 Aug;23(8):524-532. doi: 10.1016/j.cmi.2017.02.028.

Chapter 3:

- **Rawson TM**, Charani E, Moore LS, Hernandez B, Castro-Sánchez E, Herrero P, Georgiou P, Holmes AH. ***Mapping the decision pathways of acute infection management in secondary care among UK medical physicians: a qualitative study.*** BMC Med. 2016 Dec 12;14(1):208.

Chapter 4:

- **Rawson TM**, Moore LS, Tivey AM, Tsao A, Gilchrist M, Charani E, Holmes AH. ***Behaviour change interventions to influence antimicrobial prescribing: a cross-sectional analysis of reports from UK state-of-the-art scientific conferences.*** Antimicrob Resist Infect Control. 2017 Jan 13;6:11. doi: 10.1186/s13756-017-0170-7.
- **Rawson TM**, Butters TP, Moore LS, Castro-Sánchez E, Cooke FJ, Holmes AH. ***Exploring the coverage of antimicrobial stewardship across UK clinical postgraduate training curricula.*** J Antimicrob Chemother. 2016 Nov;71(11):3284-3292.
- **Rawson TM**, Moore LS, Gilchrist MJ, Holmes AH. ***Antimicrobial stewardship: are we failing in cross-specialty clinical engagement?*** J Antimicrob Chemother. 2016 Feb;71(2):554-9. doi: 10.1093/jac/dkv337.

Chapter 5:

- **Rawson TM**, Moore LS, Hernandez B, Castro-Sanchez E, Charani E, Georgiou P, Ahmad R, Holmes AH. ***Patient engagement with infection management in secondary care: a qualitative investigation of current experiences.*** BMJ Open. 2016 Oct 31;6(10):e011040. doi: 10.1136/bmjopen-2016-011040.
- **Rawson TM**, Moore LSP, Castro-Sanchez E, Charani E, Hernandez B, Alivdza V, Husson F, Toumazou C, Ahmad R, Georgiou P, Holmes A. ***Development of a patient-centred intervention to improve knowledge and understanding of antibiotic therapy in secondary care.*** Antimicrobial Resistance and Infection Control. 2018 [In Press] 10.1186/s13756-018-0333-1

Chapter 6:

- Hernandez B, Herrero P, **Rawson TM**, Moore LSP, Evans B, Toumazou C, Holmes AH, Georgiou P. ***Supervised learning for infection risk inference using pathology data.*** BMC Med Inform Decis Mak. 2017 Dec 8;17(1):168. doi: 10.1186/s12911-017-0550-1.
- Hernandez B, Herrero P, **Rawson TM**, *et al.* **Data-driven Web-based Intelligent Decision Support System for Infection Management at Point-Of-Care: Case-Based Reasoning Benefits and Limitations.** In Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies HEALTHINF, 119-127, 2017; ISBN: 978-989-758-213-4

Chapter 7:

- **Rawson TM**, Sharma S, Georgiou P, Holmes AH, Anthony CE, *et al.* ***Towards a minimally invasive device for beta-lactam monitoring in humans.*** Electrochemistry communications. 2017 July 13.
- **Rawson TM**, O'Hare D, Herrero P, Sharma S, Moore LSP, de Barra E, Roberts JA, Gordon AC, Hope W, Georgiou P, Cass AEG, Holmes AH. ***Delivering precision antimicrobial therapy through closed-loop control systems.*** J Antimicrob Chemother. 2018 1;73(4):835-843 doi: 10.1093/jac/dkx458.

Chapter 8:

- **Rawson TM**, Charani E, Moore LS, Herrero P, Baik JS, Philip A, Gilchrist M, Brannigan ET, Georgiou P, Hope W, Holmes AH. ***Vancomycin therapy in secondary care; investigating factors that impact therapeutic target attainment.*** J Infect. 2017 Mar;74(3):320-324. doi: 10.1016/j.jinf.2016.12.011.
- **Rawson TM**, Charani E, Moore LSP, Gilchrist M, Georgiou P, Hope WW, Holmes A. ***Exploring the use of C-Reactive Protein to predict the pharmacodynamics of vancomycin.*** Therapeutic Drug Monitoring 2018 [Epub ahead of print]. doi: 10.1097/FTD.0000000000000507

Appendix 2. Supplementary table 1

Supplementary table 1. Summary of Clinical Decision Support Systems for antibiotic prescribing and evidence supporting aspects of behavioural intervention development

CDSS Characteristics		CDSS reporting on aspects of system development							Summary of supporting studies			
Setting	CDSS	Platform	Infrastructure	Development	Feasibility & Piloting	Evaluation	Implementation	Study type	Primary outcome	Outcome met	Risk of Bias	
[84] Flottorp	PC	Antibiotic prescribing for ARI & UTI	Software integrated into EMR	Rule based	-	-	<i>Small decrease in prescribing in ARI No effect on UTI</i>	-	cRCT	Rate prescribing	UTI – no ARI – 3% ↓	Low
[99] Rubin	PC	Antibiotic prescribing for ARI	PDA device	Rule based	<i>Algorithms translated from paper to electronic form after demonstration of success</i>	<i>Paper based algorithms proved successful in RCT</i>	<i>High adherence to guidelines</i>	<i>Training provided to providers before deployment & incentives used.</i>	CS	-	76% guideline adherence	Med
[100] Madaras-Kelly	PC	Antibiotic prescribing for ARI	PDA device	Rule based	-	-	-	<i>Failed to gain patient consent for inclusion</i>	NCBA	Average cost of treatment CDSS acceptance	No No	High
[85–87] ARI Smart Form / Quality Dashboard	PC	Antibiotic prescribing for ARI & UTI Physician feedback	Integrated into EMR	Rules based	<i>Based intervention on evidence based guidelines Identified need to improve accuracy of diagnosis of ARI & UTI in practice</i>	<i>Demonstrated high sensitivity & specificity for diagnosing ARI & UTI</i>	<i>No effect observed</i>	<i>Poor engagement with intervention by prescribers</i>	CSS	Accuracy of diagnosis & Prescribing	Yes	Med
									cRCT	Rate of prescribing	No	Low
									cRCT	Rate of prescribing	No	Low
[88] Rattinger	PC	Antibiotic prescribing for ARI	Integrated into EMR	Rules based	<i>Attempted to integrate CDSS into natural workflow of care (stakeholders and methods not identified) Translation of pharmacy processes into CDSS</i>	-	<i>Improvements in adherence to guidelines</i>	-	CBA	Warranted vs. unwarranted AU	Yes – AU improved	Low
[89–91] ABX-TRIP	PC	Antibiotic prescribing for ARI	Integrated into EMR	Rules based	<i>Based on evidence based guidelines for ARI</i>	-	<i>Potential to reduce inappropriate prescribing in ARI</i>	<i>Poor engagement with intervention by prescribers Number of barriers to uptake identified</i>	Qu	No	-	Med
									CS	Appropriate AU	No	High
									CITS	Inappropriate prescribing	Yes	Low

[92] [93] Gonzales & Michaelidis	PC	Antibiotic prescribing for ARI	Integrated into EMR	Rules based	-	-	<i>Reduced rate of antimicrobial prescribing</i>	<i>More expensive to implement than PDSS, which is equally as effective Implementation was supported by implementing with physician training and reinforcement through audit & feedback</i>	CRCT EA	Rate of prescribing Cost of intervention vs PDSS	Yes No	Low Med
[94] CPR tool	PC	Antibiotic prescribing for ARI	Integrated into EMR	Rules based	<i>Based on evidence that CPR improve quality of practice</i>	-	<i>Reduction in individual prescribing rates / changes in prescribing behaviour</i>	-	RCT	Changes in individual prescribing behaviour	Yes – NNT =11	High
[95–97] eCRT	PC	Antibiotic prescribing for ARI Electronic prompts	Integrated into EMR	Rules based	<i>Stakeholders engaged in intervention design for feedback[594] National guidelines followed</i>	-	<i>Small reduction in rate of prescribing for ARI</i>	<i>Poor engagement with intervention by prescribers Reasons preventing engagement identified and explored</i>	CRCT CRCT Qu	Proportion of ARI consultation with antibiotic prescribed	No Yes - ↓1.85%	Med Med Low
[101] Fernández	PC	Antibiotic prescribing	Web-based guideline	Rules based	<i>National guidelines identified</i>	-	<i>Improvement in guideline adherence</i>	-	NCITS	Adherence to guidelines	Yes – 21%↑	Med
[98] McCullough	PC	Antibiotic prescribing for ARI Electronic prompts	Integrated into EMR	Rules based	<i>Designed intervention based on a hypothesis of how CDSS will act to change behaviours. (Stakeholders not engaged)</i>	<i>Reduction in antimicrobial usage</i>	-	-	CS	-	CDSS use reduced AU	Med
[102–105] Antimicrobi al Consultant	SC	Antibiotic prescribing Electronic prompts	Integrated into EMR	Rules based	<i>Based on local guidelines for therapy</i>	<i>Reduction in mortality and reduction in DDD/100 occupied bed days Reduction in pharmacy spending on antimicrobials</i>	<i>Improved timing of prophylactic dosing Improved appropriate selection of therapy in ICU</i>	-	NCBA NCBA CS CS	Improvement in prophylaxis Appropriate selection of therapy Detection of mismatch between abx & organism sensitivity -	Yes - improved timing Yes – 17%↑ Yes -	High Med High Med

[122–126,306]TR EAT	SC	Antibiotic prescribing	Standalone software	Causal Probabilistic Networks	Defining causal probabilistic networks focusing on organism	Ability to predict BSI Ability to predict micro-organism Appropriate empirical therapy recommendations	Appropriate empirical therapy recommendations	-	DR DE DE CS CS/cRCT cRCT	- ROC pred. BSI Organism predication Appropriate empirical therapy Appropriate empirical therapy 180 day survival rate	- Yes - ROC 0.68 (0.63-0.73) Yes - ROC >0.5 for all organisms Yes - Improved by 20% (p<0.01) Yes - Improved by 13% (p<0.01) No - ITT – 3% lower (p=0.2)	High Med High High Low Med
[127,128] Mullett	SC	Antibiotic prescribing	Standalone software	Drug-bug logic matrix	Allows expansion of susceptibility data points	Improved appropriateness of antimicrobial selection	-	-	CS CS	- Appropriate empirical therapy	- Yes - 20% improvement (p<0.01)	Med High
[139] Hwang	SC	Gentamicin dose optimisation	Standalone on PDA	Pharmacokinetic model	PK principles explored to provide rationale PK model constructed	Improved plasma concentration target attainment	-	Found CDSS inconvenient to navigate / use	CCS	Steady state peak and trough target concentration attainment	Yes - Target peak (p=0.04) and trough (p<0.01) targets met more frequently	High
[106] WizOrder	SC	IV to PO switch for quinolones	Integrated into EMR	Rules based	Based on evidence of safety and effectiveness of early iv to oral switch	-	Improvement in oral quinolone ordering	-	NCITS	Proportion of weekly PO orders	Yes - 5.6% (2.8-8.4%) ↑ in weekly orders (p<0.01)	Med
[107] Bernstein	SC	Generic antibiotic prescribing Electronic prompts	Integrated into EMR	Rules based	-	-	Improve prescribing of prescriptions to self-paying patients	Supported with 30 minute didactic lecture	NCBAS	Proportion correct prescriptions to self-paying patients	Yes - 22% improvement (p=0.03)	Med
[108] Webb	SC	Prophylactic antimicrobial prescribing and delivery	Integrated into EMR	Rules based	Based on evidence that appropriate timing of prophylaxis reduces incidence of SSI Paper preoperative order form converted	Improved timely administration of prophylactic antibiotics	-	-	DR	Timing of administration of therapy in relation to surgical site incision	Yes - Timely administration improved from 51 to 95%	High

[135] PharmWatc h	SC	Electronic alerts for patients requiring change in antimicrobial therapy	Web-based application	Rules based	<i>Developed based on evidence in favour of post-prescription review & CDSS for improving efficacy in other fields</i>	-	<i>Economic benefit from use of CDSS</i>	-	RCT	Antimicrobial treatment costs (\$)	Yes - Stopped early – saved \$84,000 in 3 months	Med
[130] Buising	SC	Antibiotic prescribing in CAP	Web-based application	Rules based	-	-	<i>Improved appropriateness of prescribing</i>	<i>Supported with academic detailing with education and advertising campaign in ED</i>	NCITS	Appropriate prescribing for CAP cf. local guidelines	Yes - Improved appropriateness (OR:1.99, 1.07-3.69; p=0.02)	Med
[131–134] iAPPROVE	SC	Prescribing of restricted antibiotics	Web-based application	Rules based	<i>Based on evidence for impact of restrictive policies on antimicrobial prescribing</i>	-	<i>Consumption of cephalosporin's reduced AMR to cephalosporin's & MRSA fell</i>	<i>Detailed that formative evaluation of system use would help promote engagement Barriers to engagement from staff identified</i>	NCBA NCITS Qu Qu	- Change 3/4 th Ceph use -	- Yes - 38.3 DDD/1000 bed days fall in use Formative evaluation may be of benefit Senior staff ID more barrier to uptake	High Med Low Low
[136] Vincent	SC	Electronic pharmacy support with dosing	Integrated within EMR	-	<i>Based on evidence for drug protocol management services and efficacy of CDSS in other clinical areas</i>	<i>Increased time from requests to dosing support being provided</i>	-	-	CCS	Uptake & time from request to dose	No - Time ↑ from 20 to 37 minutes (p=0.03)	High
[109,110] Smart Anaesthesia Messenger (SAM)	SC	Prophylactic antimicrobial prescribing and delivery	Integrated within Anaesthesia information management system (AIMS)	Rules based	<i>Based on evidence surrounding effective timing of prophylactic therapy</i>	<i>Improved compliance with prophylactic antimicrobial administration & re-dosing</i>	-	<i>Roll out with feedback and distributing monthly reports had an additive effect at improving compliance</i>	DR CCS	Guideline compliance Failure of antibiotic re-dosing	Yes - Stepwise improvement to 100% Yes - Improve timely re-dosing from 63%-84% (p<0.01)	High High
[137] Nelson	SC	Detection of SIRS with electronic alerts	Integrated within EMR	Rules based surveillance system	<i>Developed surrounding the need to increase speed of detection & intervention for sepsis</i>	-	<i>Failed to improve speed of intervention for sepsis</i>	-	NCBA	Rate of interventions for sepsis	No – slower than human detection and interventio	High

											n	
[111] Schwann	SC	Prophylactic antimicrobial prescribing and delivery Electronic prompts	Integrated within Anaesthesia information management system (AIMS)	Rules based	Based on evidence surrounding effective timing of prophylactic therapy Developed on evidence that POCEPs may elicit specific behaviour-responses (stakeholders not engaged)	-	Improved timeliness of antimicrobial prophylaxis administration Rate of SSI reduced	-	NCITS	Time to antibiotic dosing Rates of SSI	Yes - 31% ↑ in appropriate timing (p<0.01) SSI ↓ from 1.1 to 0.8% (p<0.01)	Med
[116] Carman	SC	Clinical alerts for detection of MRSA result	Integrated in EMR	-	Based on inconsistent management of MRSA and evidence supporting CDSS for improving adherence to guidelines	-	Improved prescribing and inappropriate culturing for community acquired MRSA	-	NCBA	Appropriate management of MRSA	Yes - ↓ inappropriate cultures (OR 0.69 – p<0.01) ↑ (OR 2.4, p<0.01) Prescribing	High
[115] Haynes	SC	Prescribing surgical prophylaxis	Integrated into EMR	Rules based	Based on evidence surrounding effective timing of prophylactic therapy & for CDSS to reduce adverse events	-	Improvement in timely discontinuation of prophylactic antimicrobials	-	CITS	Timely discontinuation of antibiotic prophylaxis	Yes - ↑ timely discontinuation from 39% - 56% (p<0.01)	Med
[114] Westphal	SC	Antibiotic prescribing for pneumonia	Integrated into EMR	Rules based	Based on evidence that making guidelines available during prescribing can improve practice	-	Improved adherence to guidelines	-	NCITS	Appropriateness of prescriptions	Yes – improved rate or non-conformity to guidelines by 18% (p<0.01)	High
[113] Po	SC	Linezolid prescribing	Integrated into EMR	Rules based	Based on evidence of CPOE reducing errors	-	Reduced the use of linezolid	-	NCITS	DDD/1000 patient bed days of linezolid	Yes - Use ↓ from 44 to 7 DDD/1000 bed days (p<0.01)	High
[112] Rodrigues	SC	Prescribing surgical prophylaxis	Integrated into EMR	Rules based	-	High compliance with antimicrobial prophylaxis guidelines	-	-	CS	Compliance with guidelines	Yes - >90% compliance with guidelines	High

[129] Papageorgiou	SC	Diagnosis and treatment of UTI	Integrated into EMR	Fuzzy-cognitive map software	<i>Probabilistic networks and need to incorporate multiple variables in decision process explored. (Stakeholders not engaged with)</i>	<i>Predict appropriate treatment for UTI's in accordance with guidelines</i>	-	-	DR	Agreement with guidelines	Yes - Predicted treatment appropriate in 87%	High
[117] Beaulieu	SC	Clinical alerts advising on de-escalation / escalation of therapy	Integrated into EMR	Rules based system	<i>Critical needs assessment performed by ASP specialists (MDT).</i>	<i>Generated alert's daily, which tended to prompt de-escalation of therapy</i>	-	<i>System integrated into a closed-loop medication safety process</i>	DR	-	-	High
[138] Cooper	SC	CDI surveillance	Integrated into EMR	Predictive model	<i>Developed due to high risk nature of CDI and requirement for early diagnosis</i>	<i>High sensitivity and specificity of system. Low PPV, high NPV</i>	-	-	DE	-	High sens, spec, & NPV. Low PPV (4%)	High
[118] Antibioarte	SC	Prescribing guidelines and infection management support	Web-based	Rules based	<i>Simple interface type and ease of navigation was preferred</i>	-	-	DR	Acceptance of 2 interfaces evaluated	Simple "at a glance" interface preferred	High	
[119] Filice	SC	Antibiotic prescribing	Integrated into EMR	Electronic guidelines	-	<i>Improved appropriateness of prescribing to guidelines</i>	-	-	CS	Appropriateness of prescriptions 30 day mortality	Yes -11% improvement (p=0.01) No change	Med
[120] Best Practice Alert tool	SC	Antibiotic prescribing	Integrated into EMR	Rules based	<i>Based on local AMS guidelines</i>	<i>Acceptance of best BPA's led to improvements in de-escalation of therapy</i>	-	-	DR	De-escalation according to policy	Yes – significant improvement when engaged with (p<0.01)	High
[121] Demonchy	SC	Antibiotic prescribing in UTI	Integrated into EMR	Electronic guidelines	<i>CDSS integrated into EMR workflow</i> <i>Developed based on previous reported CDSS success</i>	<i>CDSS use appeared to improved antimicrobial prescribing</i>	-	<i>Poor engagement with CDSS by physicians</i>	CBA	Adherence to guidelines	No – poor use. Adherence did improve when CDSS used	Med
[140] Diasinos	SC	Dose & TDM optimisation in aminoglycoside therapy	Integrated into EMR	Bayesian prediction software and Rules based alerts	<i>Based on guidelines for dosing</i>	-	-	<i>Poor uptake of intervention.</i>	MM	Compliance with guidelines	No – poor uptake	Med

Appendix 3. Topic guide for physician interviews

Topic Guide for healthcare professional focus group/ Question areas for follow-up semi-structured interviews (where needed to explore issues further).

Age
Gender
Primary role
Years worked as healthcare professional Years working in primary role
Current grade

1. For a patient with an infection, describe how investigation & management decisions (including prescribing antimicrobials) are made

Prompts:

*what role do physiological parameters have in infection related decision making?
which is most useful/rank their utility? HR, BP, temp.... etc
what role do biomarkers have in infection related decision making?
which is most useful/rank their utility? CRP, PCT, WCC etc
what role do microbiology results have in infection related decision making?
which microbiology result is most useful? Gram stain, bacteria name, sensitivities..etc
how do you make decisions when there are no microbiology results?
What other factors influence choice/dose/frequency of antimicrobial?*

2. If you had to rank (i) patient physiology, (ii) biomarker changes and (iii) microbiology results in their importance in relation to antimicrobial prescribing, how would you do so?

*Prompts: how do these three factors relate to: sending further tests? If so which?
starting antimicrobials/narrowing spectrum of antimicrobials/stopping antimicrobials?*

3. How is the final decision on infection management made?

*Prompts: on consultant ward round, MDT, infection specialist ward round?
How are these decisions made out of hours at night? And at the weekend?*

4. Do you have a vision of an ideal way for infection management decisions to be made? Or what information should be included to make optimal decisions?

5. Are there any barriers to you making what you think are the optimal antimicrobial decisions?

Prompts: what are they?

6. Are there any aids that help with making the optimal antimicrobial decisions

Prompts: what are they? The antimicrobial policy? what are it's good/bad points?

7. How do you access patient data when you are making critical care infection management decisions?

*Prompts: at the end of the bed, in front of a desktop with lab data, in an MDT?
How do you prioritise these data when lab data and patient data are giving mixed messages?*

8. How do you access published medical literature to help make decisions?

Prompts: intranet, internet, apps, paper based guidelines, books, journal subscription?

9. When do you access published medical information to help make decisions?

*Prompts: at point of care, after a consultation, at the end of the day, only for fixed events?
How frequently would you do this?*

10. Do you feel empowered or dis-empowered to make decisions to start, stop or change antimicrobial prescriptions?

Prompts: why?

Appendix 4. Outline of behavioural interventions reported per UK speciality

	Education	Persuasion	Incentivise	Coercion	Training	Restriction	Environmental restructure	Modelling	Enablement	Communication	Guidelines	Fiscal	Regulation	Legislation	Environmental	Service provision
Endocrinology																
Geriatrics																
Psychiatry																
Emergency Medicine																
Neurology																
Cardiology																
Ophthalmology																
Paediatric surgery																
Paediatrics											1					
Anaesthetics																
Breast Surgery																

Vascular surgery																				
Obstetrics & Gynaecology																				
Intensive Care												1								
Neurosurgery										1										
Transplant Surgery																				
Dermatology																				1
Haematology																				
Urology												1								1
Plastic Surgery																				
Gastroenterology												1								
Respiratory																				
Orthopaedics											1									
Rheumatology																				
General Surgery (ASiT)	1									1									1	
Primary Care	2*	2*								1*	1	1								
Nephrology																				1
Genitourinary Medicine																				
General Surgery										2									1	
Infection / Microbiology	3*	5*					1	1		5*									2*	8*

Legend: * Interventions may have been part of a bundle of interventions reported in one abstract

NB. One behaviour change intervention has been excluded as the full nature of the intervention was not clearly defined

Appendix 5: Patient workshop topic guides

WORKSHOP 1:

- Conducting a service evaluation to understand and improve the process of shared decision making during antimicrobial prescribing by clinicians in secondary care (inc. UCC / OP etc)
- We are interested in your own opinions and perceptions of this problem and not what you think others would want you to say
- Everything is kept confidential and no one within the Trust will know what has been said by you. To ensure that confidentiality is maintained you will be assigned a participant number
- We ask you however, NOT to reveal any specific personal information
- Time limit approx. **(as above)** to complete

Topic	Aims	My Questions
1. Introduction	<p>Consent</p> <p>Collect baseline demographic data</p> <p>Collect individual opinions for triangulation against collective group views</p>	<ul style="list-style-type: none"> • Welcome, brief outline of aims of day • Why you have been invited <p>Broad range of people who have been prescribed antibiotics in secondary care (or around) setting</p> <p>Want to improve the information you receive and improve the shared decision making process</p> <ul style="list-style-type: none"> • Consent and baseline questionnaires (confidential). • At end of session may be invited to participate in product evaluation – email address if interested • Split into two groups to begin (delegated before session from participant charter provided by company)
2. Exploration of current issues during consultations	<p>Reflect on current level of information provided to patients by clinicians when prescribing antimicrobials</p> <p>Reflect on how this information is delivered in different settings (on the wards, admission vs. discharge)</p> <p>Explore whether this information is adequate</p> <p>Explore whether the participant feels as if they are involved in the decision making process in these scenarios</p> <p>Explore barriers to “successful” use of antimicrobials (i) in hospital and (ii) on d/c with</p>	<ul style="list-style-type: none"> • Can you describe what kinds of information you were provided about the antibiotics you were prescribed last time you were in hospital (or similar) (i) at the point of prescription (ii) at the point of discharge • How did you receive this information? Prompts for above: <i>prescription? antimicrobial box insert? Printed information from the GP</i> <i>Did you read it?</i> <i>Did it give you the information you were looking for?</i> • Who gave you most of this information? Prompt: Dr / Nurse / Pharmacist? • Was there anything missing that you would like to have been told / had discussed with you? • What are the common questions about your infection/antibiotics do you ask your doctor? Prompt: When do you ask these (during or after reflection)? • Did you feel as though you were a part of the decision making process when you were you and your doctor discussed your infection / treatment? 1. Can you explain why you felt this?

	antimicrobials	<ul style="list-style-type: none"> • What extra information do you seek independently following discussion with the doctor? Prompt: Is this because: <ol style="list-style-type: none"> 1. There is not enough time to have questions addressed 2. The information provided is not clear 3. The patient has a personal view on allopathic meds? 4. Your were embarrassed to ask the question? • What are the day to day challenges (i) in hospital (ii) following discharge with adherence to a course of antibiotics Prompt: Remembering to take the course / timings / monitoring for s/e's Do you complete the course? • What do they think is the major barriers to the above? Prompt: ? Lack of information ? Lack of understanding over importance ? Other • When you visit the GP after a visit to hospital do they know all of the details about the infection & antibiotics that you received during your visit? • How do they receive this information? • Would you be able to explain to the GP which meds you are on and why? Prompt: Do you tell them the majority of this info? If so how do you record it? Clinic letter / discharge summary? (do you feel they get the full picture from it?)
3. Feedback to group	Allow group to understand all issues identified during each groups session	<ul style="list-style-type: none"> • Leads briefly summarise each groups key findings • Allow discussion and consensus on any major points of difference which arise between groups
3. Generating approaches to solving these issues	<p>Explore what further information patients would like to receive</p> <p>Explore what other support with antibiotic use patients feel they require</p> <p>Explore how patients currently acquire this information which they perceive as helpful / whether they receive this support</p> <p>Does this information empower them to take an active role in their infection / antimicrobial therapy</p>	<ul style="list-style-type: none"> • How do you go about finding information about the infection or antibiotics you are given? (a) during your hospital stay (b) once you are discharged with them? • On attaining this information do you feel that it helps you participate more actively in discussions about your infection / antibiotic treatment with the doctors and other HCP's? Prompt: Do you feel as if you are involved in the decision making? Do you feel that your views and ideas are considered? • Is there any difference in the information you require on this (i) when in the hospital c.f. (ii) at the point of discharge on antibiotics Prompts: Do you use your mobile phone to look up things the doctor tells you about your infection / antibiotics? Is this more helpful in or out of hospital?

	<p>Explore approaches that patients would like to be available to attain this information</p> <p>Investigate whether any other support would be helpful</p> <p>Nominal group technique to generate a list of solutions and ranks for their level of importance</p>	<ul style="list-style-type: none"> • Are there any other measures that would be helpful in helping you better understand your infection / support you in taking the course of antibiotics? <p>Prompt:</p> <ul style="list-style-type: none"> (a) Reminders to take medication (b) PMH log / Past infection or abx log for discussion with GP (c) Support networks / chat rooms... (d) Mind map / profiles of health care professionals (e) Recording facilities? (f) Medication passport? <ul style="list-style-type: none"> • Brain storm ideas of how patients could receive / access this information / support - Rank using nominal group tech. <ul style="list-style-type: none"> • Consensus through discussion <p>Prompt:</p> <ul style="list-style-type: none"> (a) Route of info (app / email / text message / interactive / recording / webcast / paper based) (b) What would be provided (c) Level of detail (d) Original info? Reputable source ? individuals own experiences (uncensored) (e) Ideal timing to receive this information <ul style="list-style-type: none"> • If not discussed above: Would you be happy if your doctor communicated with you using a mobile application to support this? • Would you want to receive personalised information about your infection and the treatment of it via your phone? <p>Prompt:</p> <p>What would you find acceptable / not acceptable?</p> <p>What alternative method would you prefer?</p>
<p>4. Triangulate</p>	<p>Confirm results generated through each group</p> <p>Explore whether there are any other comments / observations participants wish to make</p>	<ul style="list-style-type: none"> • Present both groups nominal group exercises • Summarise similarities and differences • Does anyone wish to discuss these?

WORKSHOP 2:

Requirements:

- Abstract from BMJ Open and figures
- Mock ups for discussion
- Current information leaflets
- Observer to take notes
- Split into two groups of 3 (4)

Introduction:

In September 2015 we held a workshop with 10 members of the public to explore their experience of being involved in decision making around management of infections they have been treated for in hospital. This showed us that clinicians and healthcare workers often fail to provide you with the information that you want to know and in a format that allows you to digest it when you are feeling unwell. This appeared to lead to misunderstandings about antibiotics and how to use them during future episodes as well.

The participants have worked with us to develop an idea about how we should deliver this information to help promote your engagement in the decision making process and today we would like you to help us develop this further over the next 30 minutes.

Time	Aim	Question plan
0-5min	Introduction	<p>Introduction and tell us whether you have ever received antibiotics from a hospital or GP (brief statement)</p> <p>Outline of paper findings and figures</p> <ul style="list-style-type: none"> • PDF format – flexible (can be printed / emailed / opened on mobile device) • Allows personalised information so not general like • NOT MEANT TO BE REPLACEMENT FOR PHARMA LEAFLET
10min	Confirm participant agreement with these findings	<ul style="list-style-type: none"> • <i>Do you agree with the groups views from the previous workshop we held?</i> • <i>Would you suggest anything that is different we should focus on / improve?</i>
25min	Hand out of mock ups for consideration	<ul style="list-style-type: none"> • <i>Please imagine that you are in hospital and have just sat down with the doctor. They have told you that you have a chest infection and are going to give you some antibiotics. You are given this information sheet by the doctor who tells you to have a read and let them know if you have any questions.</i>
	Work through hand outs	<ul style="list-style-type: none"> • <i>Explore:</i> <i>Is the wording correct?</i> <i>What information is missing? Is there too much information?</i> <i>Are the links to other sources of information helpful?</i> <i>Is the layout logical and easy to understand?</i> <i>How would you change this?</i>
	Explore whether this is helpful as a standalone information leaflet	<ul style="list-style-type: none"> • <i>Would this help increase your understanding of your treatment?</i> • <i>When would you want to receive this? At the time you are given the antibiotic or on discharge?</i> • <i>Do you feel as if it would help you to question or challenge decisions about your management?</i> • <i>Should a healthcare worker go through this with you or would it be helpful if you were left to consider it by yourself?</i> <i>If so who should / could go through it with you?</i> • <i>Would this add to your understanding of what your</i>

		<i>infection and management?</i>
30min	Confirm findings	<i>Participants confirm the best format for presenting data</i> <i>Participants confirm how this information sheet should be used to promote their engagement in the decision process</i> <i>Participant agreement on what time this should be delivered</i>

Appendix 6: Patient leaflet pilot survey questions

Patient engagement module – pre-intervention survey

Thank you for agreeing to take part in the following survey. At Imperial College, researchers have been working with patient groups to develop a simple intervention to improve the way that healthcare professionals provide information to patients. Please complete the following questions without assistance from any member of staff. If you are unsure please leave the space blank or mark the answer with a cross. Thank you once again for your time and support.

1. What is the name if the infection you are being treated for?

2. What is the name of the organism causing the infection that you are being treated for (e.g. E.coli)

3. I am currently being given the following antibiotic(s) for my infection
 - a. Name(s)

 - b. Doses (amount)

 - c. Length (number of days)

4. Side effects I have been warned about include

5. I could drink alcohol with this (these) antibiotic(s): **True / False / Unsure**
6. I could drive whilst taking this (these) antibiotic(s): **True / False / Unsure**
7. What do you understand by the term “antimicrobial resistance” or “drug resistant infection”

8. How long have the doctors/nurses/pharmacists caring for you spent talking to you about your infection and its treatment:
they haven't / <10 minutes / 10-30 minutes / >30 minutes
9. Has the doctor provided all the information about your infection that you wanted to know?
Yes / No / Unsure
10. What outstanding questions do you have?

11. Has the doctor provided you with information about the medication (antibiotics) you are receiving?

Yes / No / Unsure

12. What outstanding questions do I have?

13. On discharge from the hospital will you have to continue taking antibiotics?

Yes / No / Unsure

14. If so, for how long?

15. When will you have to see a doctor about your infection after being discharged?

16. Will this be your GP or a doctor at the hospital?

Patient engagement module – post-intervention survey

Thank you for agreeing to take part in the following survey. At Imperial College, researchers have been working with patient groups to develop a simple intervention to improve the way that healthcare professionals provide information to patients. Please complete the following questions without assistance from any member of staff. If you are unsure please leave the space blank or mark the answer with a cross. Thank you once again for your time and support.

1. What is the name if the infection you are being treated for?

2. What is the name of the organism causing the infection that you are being treated for (e.g. E.coli)

3. I am currently being given the following antibiotic(s) for my infection

a. **Name(s)**

b. **Doses (amount)**

c. **Length (number of days)**

4. Side effects I have been warned about include

5. I could drink alcohol with this (these) antibiotic(s): **True / False / Unsure**

6. I could drive whilst taking this (these) antibiotic(s): **True / False / Unsure**

7. What do you understand by the term “antimicrobial resistance” or “drug resistant infection”

8. How long have the doctors/nurses/pharmacists caring for you spent talking to you about your infection and its treatment:

they haven't / <10 minutes / 10-30 minutes / >30 minutes

9. Has the doctor provided all the information about your infection that you wanted to know?

Yes / No / Unsure

10. What outstanding questions do you have?

11. Has the doctor provided you with information about the medication (antibiotics) you are receiving?

Yes / No / Unsure

12. What outstanding questions do I have?

13. On discharge from the hospital will you have to continue taking antibiotics?

Yes / No / Unsure

14. If so, for how long?

15. When will you have to see a doctor about your infection after being discharged?

16. Will this be your GP or a doctor at the hospital?

17. Did you find the information leaflet useful?

(Not at all) 1 2 3 4 5 6 (extremely)

18. Why?

19. What can be improved?

20. Would you use this leaflet again?

21. When would the best time to be given this be?

Appendix 7. Biosensor fabrication protocols

Extract of my finalised protocols for biosensor fabrication that I developed during the biosensor development.

1.0 Disc Electrode Fabrication

1.1 Electrode Surface Preparation & Cleaning

1.1.1 Equipment

- Counter (platinum) & reference (Ag/AgCL) electrode
- Gold Electrode
- CH instrument – CHI 650a potentiostat
- Mettler Toledo SevenEasy pH meter
- Sonicator
- Emry paper and Alumina powder
- 0.5M H₂SO₄

1.1.2 Electrode Polishing

Polish with Emry paper

- **P1200** – 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes
- **P2500** – 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes
- **P4000** – 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes

Polish with alumina powder on cloth

- **1µm** alumina powder – 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes
- **0.3 µm** alumina powder – 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes
- **0.05 µm** alumina powder– 3 minutes circle of 8
- Rinse de-ionised water & sonicate for 3 minutes

Voltammetric cycling

- Gold or platinum disc electrode
- Against platinum counter electrode & Ag/AgCl reference electrode
- In 0.5-1.0M H₂SO₄

GOLD DISC ELECTRODE

Setting	Value
E0	0 V
E range	0.4 – 1.6 V
E step (mV)	10 mV
N / Cycles	50-100 scans
Rate	50 mV/sec

PLATINUM DISC ELECTRODE

Setting	Value
E0	0 V
E range	-0.25 – 1.3 V
E step (mV)	10 mV
N / Cycles	50-100 scans
Rate	50 mV/sec

1.2 Iridium Oxide Recipe

1.2.1 Reagents

Based on Yamanaka, K. (1991)

- Iridium chloride hydrate **0.15g**
- **1ml** aqueous hydrogen peroxide (H₂O₂:30wt%)
- Oxalic acid **0.5g**
- Anhydrous potassium carbonate

1.2.2 Equipment required

- Magnetic stirrer with round bottom flask (with lid) and clamp stand
- Mettler Toledo SevenEasy pH meter
- Fume cupboard for hydrogen peroxide addition

1.2.3 Method

1. Weigh out Iridium chloride hydrate (IrCl₄ H₂O) - **0.15g**
2. Dissolve in **100ml** H₂O using magnetic stirring
3. Stir for **30 minutes**
4. Add **1ml** of aqueous hydrogen peroxide solution (H₂O₂:30wt%) with **light swirling**
5. Stir for **10 minutes**
6. Weigh out oxalic acid ((COOH)₂ · 2H₂O) - **0.5g**
7. Add to the solution and **stir for 10 minutes**
8. Weigh out anhydrous potassium carbonate (K₂CO₃) **~4g** powder
9. Calibrate Mettler Toledo SevenEasy pH meter
10. Add small amounts to adjust the solution to **pH to 10.5**
11. Leave standing for at least 2 days to stabilise at room temperature. Once turned violet store at 4°C. Can be used for up to **120 days**.

1.3 Iridium Oxide Electro-deposition & pH Calibration

1.3.1 *Amperometric Deposition of Iridium Oxide*

- Amperometrically deposition against Pt coil & Ag/AgCl reference electrode
- Can be performed using CH instrument – CHI 650a potentiostat or Ivium potentiosta
- Immerse Au or Pt electrode in IrOx solution for **10 minutes**
- **300 seconds** at constant potential of **0.95V**
- Leave immersed for further **5-10 minutes**
- **300 seconds** at constant potential of **0.95V**
- Leave immersed for further **5-10 minutes**
- **300 seconds** at constant potential of **0.95V**
- Stored in DI H₂O at room temperature until ready for calibration.

1.3.2 *pH calibration*

- Performed using CH instrument – CHI 650a potentiostat
 - pH measurements performed with Mettler Toledo SevenEasy pH meter
 - Phosphate buffer mixed of **0.02M Na₂HPO₄** & **0.1M KNO₃**
 - **2.839g** Na₂HPO₄
 - and **10.10g** KNO
 - in **ONE LITRE** H₂O
-
- Calibration solution prepared at 0.5 pH stepwise increments from 4.0 – 8.0 by adding **0.05M H₂SO₄** dropwise to buffer whilst stirring.
 - Measure Open Circuit Potential (OCP) over 300 seconds or until stabilised
 - OCP detected against Ag/AgCl reference electrode for pH range **4.0-8.0**
 - Washed and stored in DI H₂O at room temperature until ready for fabrication.

1.4 Enzyme immobilisation techniques

1.4.1 Cellulose acetate technique

Mix:

- **24g** cyclohexaone
- **24g** acetone
- **1g** cellulose acetate (39.8% acetyl content)
- Stir at room temperature until cellulose acetate **dissolves**
- Layer thin film onto the IrOx coated electrode probe
- **Evaporate** the solvent – leaving the film on the electrode

Prepare

1. 5ml of: 0.1M phosphate buffer (pH 7.4) with 25mg/ml (**approx.**) beta-lactamase enzyme
2. 5ml of: 0.1M phosphate buffer (pH 7.4) with 50mg/ml Bovine Serum Albumin solution
3. 2.5% glutaraldehyde solution

Mix equal amounts of 1 & 2

Place solution onto the cellulose acetate membrane

Then add ½ volume of above of 3

After 1 – 2 hours place beta lactam solution on top of the outer membrane & allow the water to evaporate

Step	Description	Timing
Layer cellulose acetate onto disc electrode	10-40µL tested Pipetted on – forming dome shaped	Left to evaporate solvent for 15-20 minutes
Beta-lactamase – BSA solution (1&2) added	20µL added	Left for 2 minutes
2.5% Glutaraldehyde added	10µL added	Leave for 1-2 hours (mean 1.5)
Add beta-lactamase only (1)	20µL added	Leave to evaporate for 20 minutes
STORE IN EITHER DI H ₂ O or PBS at 4°C		

1.4.2 Polyethylenimine technique (current)

- Polyethylenimine diluted to **5%** in H₂O and added to disc electrode using pipette

Prepare

1. 5ml of: 0.1M phosphate buffer (pH 7.4) with 25mg/ml (**approx.**) beta-lactamase enzyme.

2. 5ml of: 0.1M phosphate buffer (pH 7.4) with 50mg/ml Bovine Serum Albumin solution
3. 2.5% glutaraldehyde solution

Mix equal amounts of 1 & 2

Place solution onto the PEI membrane

Then add ½ volume of above of 3

After 1 – 2 hours place beta lactam solution on top of the outer membrane & allow the water to evaporate

Add a final layer of PEI and allow to dry

Step	Description	Timing
Layer 5% PEI onto electrode	1µL optimal Pipetted on and spread using pipette tip (1-20µL previously tested)	Left to dry for 30 minutes
Beta-lactamase – BSA solution (1&2) added	5µL added (1-20µL previously tested)	Left for 2 minutes
2.5% Glutaraldehyde added	2.5µL added (1-10µL previously tested)	Leave for 1-2 hours (mean 1.5)
Add beta-lactamase only (1)	5µL added (1-20µL previously tested)	Leave to evaporate for 20 minutes
Layer 5% PEI onto electrode	1µL optimal Pipetted on and spread using pipette tip (1-20µL previously tested)	Left to dry for 30 minutes
STORE IN EITHER DI H ₂ O or PBS at 4°C		

1.4.3 Carbomethyl Dextran (CMD) approach

- Polyethylenimine diluted to 5% in H₂O and added to disc electrode using pipette

Prepare:

1. 5ml of: 0.1M phosphate buffer (pH 7.4) with 25mg/ml (**approx.**) beta-lactamase enzyme
2. 5ml of: Carbomethyl Dextran (CMD) dissolved in H₂O [10mg/ml]

Mix equal amounts of 1 & 2

Place solution onto the PEI membrane

After 1 – 2 hours place beta lactam solution on top of the outer membrane & allow the water to evaporate

Add a final layer of PEI and allow to dry

Step	Description	Timing
Layer 5% PEI onto electrode	1 μ L optimal Pipetted on and spread using pipette tip	Left to dry for 30 minutes
Beta-lactamase - CMD solution (1&2) added	3 μ L added	Left for 1.5 hours
Add beta-lactamase only (1)	3 μ L added	Leave to evaporate for 20 minutes
Layer 5% PEI onto electrode	1 μ L optimal Pipetted on and spread using pipette tip (1-20 μ L previously tested)	Left to dry for 30 minutes
STORE IN EITHER DI H ₂ O or PBS at 4°C		

2.0 Microneedle Fabrication checklist

No.	Step	Description	Comment
1	Drill holes x2 per microneedle array	Dentist drill	
2	Thread and tie off wire		
3	Silver epoxy wire to metal	4 hours to set	
4	Seal with araldite / epoxy resin	Araldite sets within 2 hours	Previous issue with epoxy (? Due to out of date tube)
5	Cleaning with ethanol solution		Optional
6	Iridium oxide deposition	1. 10 minutes soaking in IrOx 2. 300 seconds at 0.95V 3. 5-10 minutes soaking 4. 300 seconds at 0.95V 5. 5-10 minutes soaking 6. 300 seconds at 0.95V	10 minute rest at each point appears to work better on these MN's
7	pH calibration	pH 4.0-8.0 OCP's take ~400 seconds to reach steady state	
8	5% PEI layer	5 μ L & leave for 10-20 minutes	Drop wise
9	Add 50:50 mix of beta-lactamase & BSA solution	5 μ L and leave for 2 minutes	Drop wise
10	Add 2.5% glutaraldehyde	3-5 μ L and leave for 1.5-2 hours	Drop wise to get good coverage
11	Add beta-lactamase solution	5 μ L and leave for 20-30 minutes	Drop wise
12	Add 5% PEI layer	5 μ L and leave for 20-30 minutes	Drop wise

Appendix 8. Technical Appendix

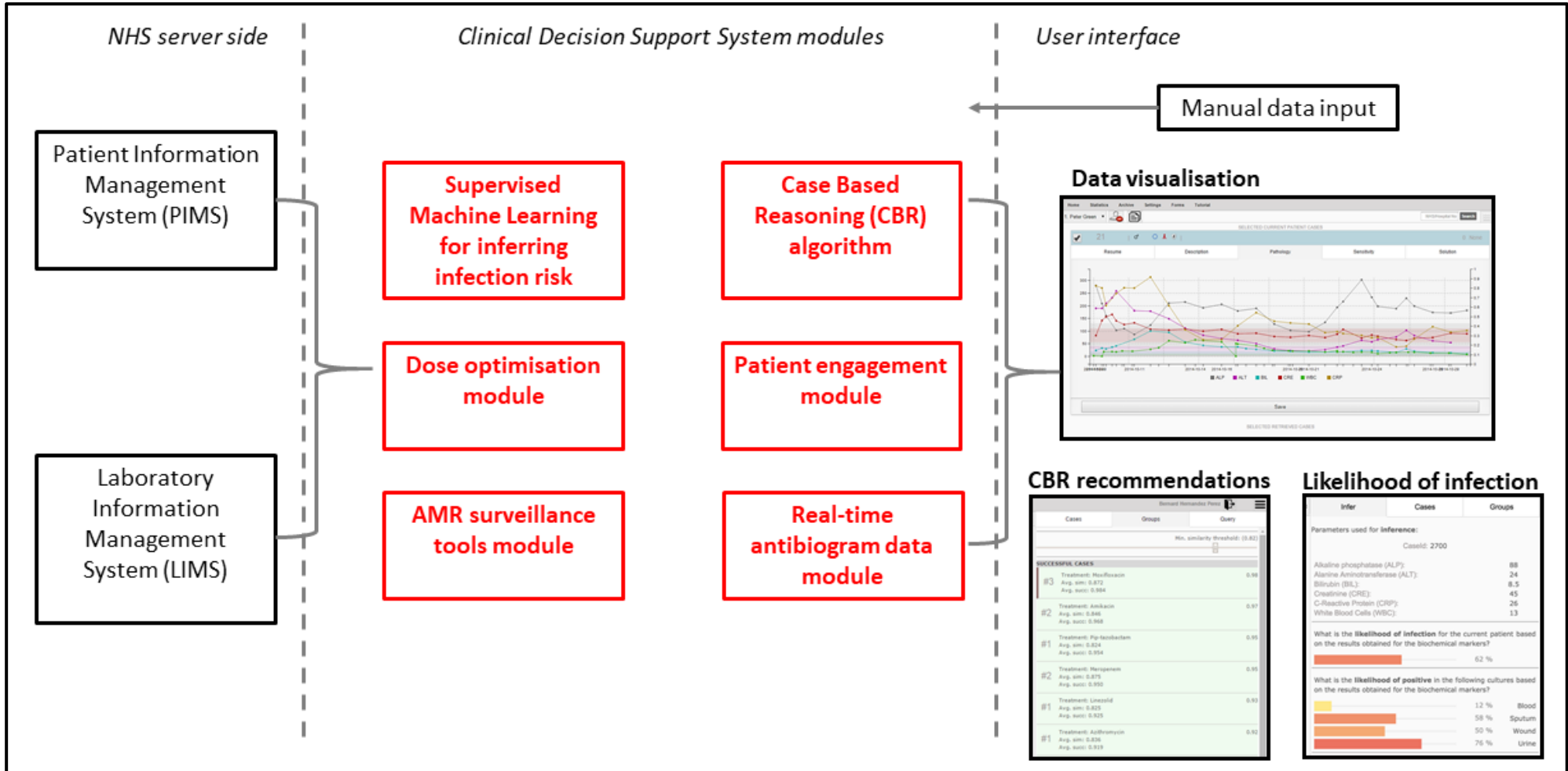
a8.1 Clinical Decision Support System

This additional architecture for the CDSS described in *Chapters four & five* was in place before the commencement of this investigation and was initially developed by an external company (L-shift; <http://www.lshift.net>). This company created the secure application programming interface (API) described to meet the current directives of the Data Protection Act 1998, The Privacy and Electronic Communications Directive 2003, and the EU Directive 2006/24/EC for data retention [361,362].

All programming within this study was performed by Mr Bernard Hernandez, a PhD student in the department of Electrical Engineering at Imperial College London, supervised by Dr Pantelis Georgiou. The server side of the CDSS has been developed using Java with object-relational mapping (Hibernate ORM) of the Java library to the structured-query-language (SQL) databases routinely used within the Trust. A Lightweight Directory Access Protocol (LDAP) facilitates the authorisation of users who have secure access to the NHS server. The user interface for the CDSS is a web-based application with a front-end of HyperText Markup Language (HTML), Cascading Sliding Sheets (CSS), and JavaScript interface. The interface was designed to run across all internet browsers and is responsive to changes in screen size. This means that it adjusts according to whether it is accessed from a computer, tablet, or mobile phone.

Data stored within the CDSS resides only on the server side. Data is stored with patient name and hospital numbers replaced using an SHA#256 pseudo-anonymisation protocol. Within the CDSS server, I was involved in the development of six modules. These are summarised in the **Figure** below.

Summary of clinical decision support system modules developed within the NHS server.



a8.2 Description of closed-loop controllers

Proportional-Integral-Derivative control

PID controllers depend on continuous, or quasi-continuous, monitoring (e.g. every 5 minutes). They are used to control continuous infusions maintaining drug concentrations at a set target (e.g. either target concentration or PK-PD index). As their name suggests, following data input the PID has three coefficients; the proportional, integral, and derivative. It alters these three coefficients to optimize the response against its target. The simplicity and robustness of PID algorithms make them extremely suitable for the range of operating conditions found in healthcare. For antimicrobial management, this may be especially useful in critical-care due to the current drive towards continuous infusions of beta-lactam antimicrobials and nephrotoxic agents, such as vancomycin to optimize the PK exposure and PD properties.[395,423,590,595–599] Furthermore, where current continuous infusion protocols require sporadic plasma TDM, this mechanism offers an opportunity for real-time response to changes in individual patient PK. For example, this would account for intra-individual variations in PK caused by changes in the patients inflammatory response, fluid shifts, augmented renal clearance, and in changing drain outputs that may currently be missed with sporadic TDM sampling [600–603].

Iterative Learning Control in closed-loop control

ILC provides the option for optimization of bolus or oral therapy. This can utilize data from continuous monitoring to optimize the amount, timing, and rate at which a bolus (or oral dose) is delivered. Like PID, ILC algorithms have wide applications but work on the assumption that during repetitive tasks (such as antimicrobial bolus dosing at regular intervals) there will be some error in target attainment (e.g. overshoot or undershoot). The ILC aims to adjust the input, in this case the bolus dose, to reduce the transient

error encountered during routine drug delivery and therefore optimize the accuracy of the system. This type of controller may be more applicable to non-critical care or the community setting (such as out-patient parenteral therapy or oral dosing). It may also be utilized in specialist populations, such as paediatrics, obesity, cystic fibrosis, and pregnancy, where rich data collection will allow for tailored therapy. This could be augmented by linking of real time data generation with previous experience housed within machine learning algorithms, as has been demonstrated by the use of Case-Based-Reasoning in diabetes management [604].

a8.3 Microneedle fabrication process

The microneedles were fabricated in a three-stage process. The solid work designs were transferred to a FANUC ROBOCUT α -Oic (Series 180is-WB) machine for wire erosion. It was set to make three milling passes over the copper-tungsten (Cu-W) (Erodex, UK) block to create master electrodes for spark erosion. The Cu-W master was then used for spark erosion (JOEMARS EDM AZ50DR) of an aluminium block (Erodex, UK) in to obtain the metal inlay. This metal inlay was used for the injection moulding of polycarbonate pellets. The polycarbonate pellets were dried at 110 °C for 24 for hours under vacuum prior to use before injection moulding process at $T_m = 270$ °C (PC melt temperature), $T_w = 80$ °C (tool temperature) at injection speed of $20 \text{ cm}^3 \text{ s}^{-1}$ and shot volume of 4.4 cm^3 and a cooling time (t_c) of 5 seconds. Each polycarbonate microneedle structure ($25 \times 25 \times 2$ mm) comprised of four 4x4 microneedle arrays. They functionalised the needles by taking bare microneedle arrays and sputtering them with chromium (15 nm) / platinum (50 nm) to obtain the working electrodes. One of the microneedle arrays was sputtered with Ag (150 nm), which I modified to form an Ag / AgCl reference electrode by treating with a saturated solution of FeCl_3 [436].

Appendix 9: Ethics and permissions

Ethics favourable opinions:

Study title:	Enhanced, Personalized and Integrated Care for Infection Management at the Point-Of-Care (EPIC IMPOC)
REC reference:	17/LO/0047
IRAS project ID:	204949
Study title:	Microneedle sensing of beta-lactam antibiotic concentrations in human interstitial fluid
REC reference:	18/LO/0054
IRAS project ID:	236047
Study title:	Defining adult beta-lactam antimicrobial pharmacokinetics across the secondary care setting
REC reference:	16/LO/2179
IRAS project ID:	207217

Permissions to reproduce:

Licence Reference: 4316540520329 Rawson TM, Moore LS, Hernandez B, Castro-Sanchez E, Charani E, Georgiou P, Ahmad R, Holmes AH. *Patient engagement with infection management in secondary care: a qualitative investigation of current experiences*. BMJ Open. 2016 Oct 31;6(10):e011040. doi: 10.1136/bmjopen-2016-011040.

Licence Reference: 4316540310976 Rawson TM, Moore LS, Gilchrist MJ, Holmes AH. *Antimicrobial stewardship: are we failing in cross-specialty clinical engagement?* J Antimicrob Chemother. 2016 Feb;71(2):554-9. doi: 10.1093/jac/dkv337.

Licence Reference: 4316540727400 Rawson TM, Butters TP, Moore LS, Castro-Sánchez E, Cooke FJ, Holmes AH. *Exploring the coverage of antimicrobial stewardship across UK clinical postgraduate training curricula*. J Antimicrob Chemother. 2016 Nov;71(11):3284-3292.

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