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Evaluating the Effectiveness of Carbapenem and Piperacillin-tazobactam Prescribing Guidelines and Implementation Strategies on Multi-Drug Resistant Gram-negative Bacteria within NHS Scotland

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By

Abdulrhman Ibrahim Mohana, BSC, MSC

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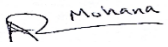
Declaration

‘This thesis is the result of the author’s original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.’

Signed:  Date: 14/11/2018

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Dedication

This thesis is dedicated to my Father (Ibrahim) and my Mother (Norah). Also to my lovely wife Alanoud and the joy of my life Norah, for there endless love, support and encouragement throughout my thesis process.

Abstract

Background: Antimicrobial resistance is one of the most challenging aspects of healthcare worldwide. In 2013 the Scottish Antimicrobial Prescribing Group (SAPG) produced guidance to promote better use of carbapenems and piperacillin-tazobactam as a measure to reduce emergence of Multi-Drug Resistant Gram Negative Bacteria (MDRGNB). The effectiveness of implementation of this national guidance and its impact on the utilisation of these agents in local clinical practice was unknown.

Objectives: To evaluate how SAPG guidance against MDRGNB had been adopted and implemented across NHS Scotland health boards, assess how this translated into clinical practice, and investigate clinicians' views and behaviours about prescribing carbapenems and alternative agents.

Methods: The current research was divided into three parts; online survey, national point prevalence surveillance, and semi-structured interviews. Part one: Local implementation of SAPG MDRGNB guidance was assessed from local AMT committee's responses using an online survey. Part two: A bespoke national point prevalence survey was used to evaluate prescribing of meropenem and piperacillin-tazobactam in clinical practice. Part three: Clinicians' experience of using carbapenems and alternatives was examined through semi-structured interviews within four health boards.

Results: Part one: all 15 health boards responded to the survey. There were greater local restrictions for carbapenems than for piperacillin-tazobactam. Meropenem was

the most common used carbapenem. Laboratory result suppression was inconsistent between health boards and carbapenem-sparing antimicrobials were not widely available. Part two: 13 health boards were included and a total of 12,478 inpatients in 38 hospitals were surveyed. Adherence to local guidelines was good for meropenem but lower for piperacillin-tazobactam. Indication for use was well documented but review/stop dates were poorly documented for both antimicrobials. Part three: 28 interviews were conducted. Decisions to prescribe a carbapenem were influenced by local guidelines and specialist team's advice. Many clinicians lacked confidence to de-escalate treatment. Use of both antimicrobials decreased during the course of the programme.

Conclusions: A multifaceted quality improvement programme was used to gather intelligence, promote behaviour change, and focus interventions on the use of carbapenems and piperacillin-tazobactam. Use of these antimicrobials decreased during the programme, a trend not seen elsewhere in Europe. The programme identified variation in practice and guidance adaptation between health boards, and different approaches had been adopted to encounter MDRGNB. The importance of local guidelines and support of specialised teams were highly influential and much appreciated between participants. The programme could be generalised to other antimicrobials in future.

List of Publications

Peer reviewed Journals

Sian E. Robson, Alison Cockburn, Jacqueline Sneddon, Abdulrhman Mohana, Marion Bennie, Alexander B. Mullen, William Malcolm, Jennifer Armstrong, Andrea Patton and Ronald Andrew Seaton. Optimizing carbapenem use through a national quality Improvement programme. *J Antimicrob Chemother*, 2018 August 1;73(8):2223-2230. (doi:10.1093/jac/dky171)

Conference Presentations

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Abdulrhman Mohana, Alison Cockburn, Jacqueline Sneddon, Sian Robson, William Malcolm, Marion Bennie, Alex Mullen. Evaluating the Effectiveness of Carbapenem and Piperacillin-tazobactam Prescribing Guidelines within NHS Scotland. Federation of Infectious Society, Edinburgh Scotland, 2016. Poster presentation.

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Abdulrhman Mohana. Evaluating the Effectiveness of Carbapenem and Piperacillin-tazobactam Prescribing Guidelines in Scotland. The Scottish Healthcare Associated Infection Prevention institute: future collaboration and capacity building day. Glasgow Scotland, 2017. Poster Presentation.

Abdulrhman Mohana and Alison Cockburn. Carbapenems quality improvement programme - Conclusion of quantitative and qualitative studies. The National Network Event on Improving the quality of antimicrobial prescribing – sharing good practice. Glasgow Scotland, 2017. Oral presentation.

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Glossary

4C's	Cephalosporins, co-amoxiclav, clindamycin and fluoroquinolones
ADTC	Area Drug and Therapeutic Committees
AGREE	Appraisal of Guidelines for Research and Evaluation
AMR	Antimicrobial resistance
AMT	Antimicrobial Management Team
ARDS	Acute respiratory distress syndrome
ASP	Antimicrobial Stewardship Programs
BNF	British National Formulary
BSAC	British Society for Antimicrobial Chemotherapy
BUN	Blood urea nitrogen
CAI	Community Acquired Infection
C. diff	*Clostridium difficile*
CDC	The Centre for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPD	Continuous Professional Development
CPE	Carbapenemase-Producing Enterobacteriaceae
CSAs	Carbapenem-sparing Antimicrobials
DDD	Defined Daily Doses
E. coli	*Escherichia coli*
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ESAC	European Surveillance of Antimicrobial Consumption
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacter* species

ESBL	Extended-spectrum beta-lactamases
ESPAUR	English surveillance programme for antimicrobial utilisation and resistance
EU	European Union
EuSCACPE	European epidemiological survey of carbapenemase-producing *Enterobacteriaceae*
FDA	US Food and Drug Administration
GaV	Gentamicin and Vancomycin Quality Improvement Programme
GGC	Greater Glasgow and Clyde
GI	Gastrointestinal
GP	General Practitioner
HAI	Healthcare-associated infections
HAP	Hospital Acquired Pneumoniae
HMUD	Hospital Medicine Utilisation Database
HPS	Health Protection Scotland
ID	Infectious Disease
ICNARC	UK Intensive Care National Audit and Research Centre
ITU	Intensive Therapy Unit
IV	Intravenous
IVOS	Intravenous oral switch
KPC	*Klebsiella pneumoniae* carbapenemases
MAP	Mean Arterial blood Pressure
MBL	Metallo-beta-lactamases
MDR	Multidrug-resistant
MDRGNB	Multi-Drug Resistant Gram-Negative Bacteria
MRSA	Methicillin-resistant *Staphylococcus aureus*
NAS-PPS	National Antimicrobial Stewardship - Point Prevalence Surveillance studies
NDM	New Delhi Metallo-beta-lactamases

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OBD	Occupied Beds per Day
OPAT	Outpatient Parenteral Antimicrobial Therapy
OR	Odd Ratio
PCR	Polymerase chain reaction
PPS	Point Prevalence Surveillance studies
QI	Quality Indicator
RCT	Randomised controlled trial
REC	Research Ethics Committees
S. aureus	*Staphylococcus aureus*
SAPG	Scottish Antimicrobial Prescribing Group
ScotMARAP	Scottish Management of Antimicrobial Resistance Action Plan
SIGN	Scottish Intercollegiate Guidelines Network
SSC	Surviving Sepsis Campaign
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
VIM	Verona integron-encoded Metallo-beta-lactamases
VRE	Vancomycin-resistant Enterococci
WBC	White blood cell
WHO	The World Health Organisation

Chapter One:

General Introduction

1.1. General Introduction:

1.1.1. Infection:

Infection can be defined as the invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are pathogenic. These infecting organisms can then be found in ordinarily sterile anatomic or non-sterile sites. An infection might be asymptomatic and subclinical, or it may cause symptoms and be clinically apparent. An infection may remain localised, or it may spread through the blood or lymphatic vessels to become systemic [1]. The signs of an infection may vary considerably depending on the causative organism. Some infections affect the whole body generally, causing symptoms such as loss of appetite, weight loss, fatigue, hyperthermia or hypothermia, night sweats, chills, aches and pains. Others are more specific to individual body parts (localised), such as skin rashes, abscesses, coughing, or a runny nose [2].

Infectious diseases are classified to exogenous and virulence based on the source. Exogenous infections may occur as a result of human-to-human transmission, contact with an exogenous infective organism source in the environment, or animal contact. Resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) may colonise hospitalised patients or patients who access the health care system frequently. Virulent infections refer to the pathogenicity or disease severity produced

by an organism. Many bacteria may produce toxins or own growth characteristics that add to their pathogenicity, such as *Clostridium tetani*. Some virulence factors allow the organism to avoid the immune system of the host and cause significant disease [2].

Location of the infection can be used as a classification method; central nervous system (CNS), upper and lower respiratory tract, skin and soft tissue, endocarditis, gastrointestinal, intra-abdominal, urinary tract, bone and joints, and bloodstream (bacteraemia) infections. Each site varies in clinical presentation, pathophysiology, aetiology and laboratory findings [3].

Infections are one of the most common reasons patients seek medical attention, with respiratory tract infections being the most common clinical presentation. The World Health Organisation (WHO), listed that lower respiratory infections have remained the fourth leading cause of death (5.5%) in the world during the past decade[4]. For the year 2004, in the United States, three of the top 20 prescription medicines dispensed were antimicrobials, with total antimicrobial prescriptions exceeding 220 million. Nearly two-thirds of outpatient antimicrobial use is prescribed for respiratory tract infections, and the Centre for Disease Control and Prevention (CDC) estimate that around one-third to one-half of all outpatient antimicrobial are prescribed inappropriately to treat nonbacterial causes. Also, up to one-half of all hospitalised patients receive at least one antimicrobial during their stay [5, 6].

Infectious disease affects all of the Scottish population, at some point in their life, from childhood vaccinations to food poisoning. It is estimated that up to 4,000 Scots die every year from infections. In 2010 – 12, pneumonia was one of the top ten leading causes of death in Scotland, being responsible for 3.9% of deaths/year [7].

Treating infected patient is a complex multi-step process that includes proper diagnosis, stabilisation, treatment and follow-up. Diagnosis aims at establishing the presence of an infection and evaluating its severity, site, and the most likely pathogen(s). Diagnosis starts with physical examination for any signs or symptoms of infection, radiology tests, and microbiological and non-microbiological laboratory tests. After confirming the presence of an infection, treatment begins with an antimicrobial agent, source control, and supportive therapy. The antimicrobial regimen can be either empirical or targeted based on patient-specific factors and site and severity of the infection. Several factors must be considered when choosing an agent; type of pathogen (i.e. bacteria, virus or fungal), the spectrum of activity, local guidelines, and safety profile. Also, the cost, patient underlining diseases, allergies, route of administration, dose, availability of a selected item, and the pharmacokinetics/pharmacodynamics properties of the agent. After isolating and identifying the causative pathogen by an appropriate microbiological test, a narrower spectrum agent should be considered [2, 3].

1.1.2. Infection prevention:

The majority of infectious disease are preventable. Environmental aspects, vaccination, and infection control policies within healthcare systems are all considered contributing factors on infectious disease prevention. Each element has been studied extensively by global and local organisations on national and researcher group's levels. The influence of each component may involve the whole community or impact at an individual level.

1.1.2.1. Environmental aspect:

In 2006, the WHO estimated that 24% of global disease liability and 23% of all deaths could be related to environmental factors. For example, lower respiratory infections are associated with indoor air pollution related mostly to household, solid fuel use and outdoor air pollution. In developed countries, an estimated 20% of such infections are attributable to environmental causes, rising to 42% in developing countries. More than 1.5 million deaths annually worldwide from respiratory infections are attributable to the environment, including at least 42% of lower respiratory infections and 24% of upper respiratory infections in developing countries [8].

Indoor and outdoor air quality are two of the main environmental factors of concern for acute lower respiratory infections. Contributing risk factors include tobacco smoking, solid fuel use [9, 10], housing conditions and possibly hygiene. Previous estimates showed that 36% of lower respiratory infections worldwide were attributable to solid fuel use alone, and 1% of all respiratory infections to outdoor air pollution [11-13]. Overall, environmental factors are a much superior challenge that requires coordination and support on multiple levels locally, nationally, and globally. Also, the collaboration between industry and healthcare sectors besides governments support should be considered and promoted.

1.1.2.2. Vaccination:

Vaccines can be defined as, “A suspension of a pathogenic microorganism, such as virus or bacterium, used to stimulate the body’s immune system and result in defence against the microbe-causing disease” [14].

Vaccination is one of the most significant public health achievements of the twentieth century. Other than safe drinking water, no different modality has had a more considerable influence on reducing mortality from infectious diseases. The first scientific attempt to prevent infection by inoculation was in 1798 by Edward Jenner to prevent infection with smallpox [15]. Since then, vaccines have been developed against more than 28 diseases, with half of these recommended for routine use [16].

The widespread use of vaccines has resulted in the eradication of smallpox worldwide and wild-type poliovirus from the Western hemisphere. Furthermore, there have been dramatic declines in the incidence of diphtheria, pertussis, tetanus, measles, mumps, rubella, and *Haemophilus influenza* type b [17].

Vaccines provide active immunity against bacterial and viral infections. They are designed to prevent acute infections that can be cleared by the immunological system. Immunisation consists of activating antigen presenting cells by processing the antigen via a cytoplasmic or lysosomal pathway. Further activation of T- and B-lymphocytes to replication and differentiation to produce large pools of memory cells to protect against later exposure to the antigen [17].

Vaccines are administered in two- to four-shot series to produce the best protection. Adult and childhood immunisation schedules are revised frequently and published by National Health Service (NHS) for the United Kingdom and CDC Advisory Committee on Immunization Practices for global recommendations [18, 19].

In 1999, following the introduction of a *Neisseria meningitides* serogroup C conjugate vaccine in the United Kingdom, meningitis incidence was reduced by 92% within young children and by 95% in teenagers [20]. Another conjugated vaccine targeting

Salmonella typhi Vi successfully decreased the rate of typhoid fever in two-to-four years old children by more than 90% [21].

1.1.2.3. Infection control:

Infection control is the practical discipline concerned with preventing healthcare-associated infection "nosocomial". The primary goal of infection control is to prevent the spread of infections within the healthcare setting (i.e. patient-to-patient, patients to staff, staff to patients, or among staff). Preventing the spread of nosocomial infections can be achieved by hand decontamination, proper disinfection of daily used items, vaccination recommendations within teams and surveillance organisation. Surveillance, outbreak investigation and management, and monitoring of suspected spread are other goals that infection control targets [22].

Healthcare-associated infections (HAI) can be defined as, "infections occurring during a stay in hospital that was neither present nor incubating at the time of hospital admission". In generally, HAI appears in patients hospitalised for 48 hours or longer, can develop either as a direct result of healthcare intervention (i.e. medical or surgical intervention) or from direct contact with a healthcare setting [23, 24].

The HAI can exacerbate existing or underlying conditions, prolong recovery period and hospital length of stay, and affect the quality of patient life. They are a recognised public health problem worldwide and add significantly to morbidity and mortality in the hospital population [25]. The CDC estimates that 5%-10% of hospitalised patients develop an HAI, resultant to approximately two million HAIs associated with nearly 100,000 deaths each year in US hospitals [26, 27] and estimated to approximately cost $6.65 billion annually [28, 29].

In England, 300,000 patients a year acquire an HAI as a result of care within the NHS. The prevalence of HAI in hospitals for 2011, was 6.4%. Most common types of HAI were respiratory infections; pneumonia and lower respiratory tract; (22.8%), urinary tract infection (UTI) (17.2%) and surgical site infections (15.7%) [30]. Each one of these HAI causes additional pressure on NHS resources, a more significant decrease in patients quality of life and safety [31]. Furthermore, methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections and *Clostridium difficile (C. difficile)* infections were documented as the underlying cause of, or a contributory factor in, approximately 9000 deaths in hospital and primary care across England, 2007 [31].

The first Scottish National HAI Prevalence Survey for 2005/2006, reported that nearly one in ten patients admitted to acute hospitals had an HAI and the inpatient costs of these HAI cases were £183 million. The survey indicated that 9.5% and 7.3% of

patients in acute and non-acute hospitals, respectively, had an HAI at the time of the survey. The most common types of HAI occurring in acute hospital inpatients were UTI (17.9% of all HAI), surgical site infections (15.9%), gastrointestinal (GI) infections (15.4%), and skin and soft tissue infections (11%). At non-acute hospitals, patients with UTI were frequent (28.1% of all HAI), but similar to skin and soft tissue infections (26.8%). The most commonly identified microorganisms in acute and non-acute patients during the survey were *Staphylococcus aureus* (*S. aureus)*, *Escherichia coli (E. coli)* and *C. difficile* [32]. The increasing risk of HAI can be associated with several factors; ageing population [33], widespread use of sophisticated therapeutic interventions and, emerging and re-emerging antimicrobial resistant microorganisms [34].

In 2011, Scotland prevalence of HAI was significantly lower than the initial 2005/2006 survey; 4.9% and 2.5% of patients in acute and non-acute hospitals, respectively. The most common types of HAI occurring in acute hospital inpatients were UTI (22.6% of all HAI); mostly in catheterised patients, with surgical site infections remaining a significant proportion of all HAI (18.6%), particularly in orthopaedic, vascular and gastrointestinal surgery. However, GI infections were lower (6.8%). The percentage of HAI that were skin and soft tissue infection was smaller (4.0%). However, pneumonia prevalence was higher than the last survey (17.5% versus 8.8%) and a quarter of these occurred in patients who had been intubated. In non-acute hospitals, the most common types of HAI were UTI (39.0% of all HAI), mostly in patients

catheterised before onset. Skin and soft tissue (9.8%) and GI infection remained a high proportion of all HAI in this setting (12.2%) [35]. The lower prevalence and changing epidemiology of HAI, from the survey, in acute and non-acute care suggest a sequential relationship with the implementation of the national programme of HAI policy and guidance [35-37].

Infection control policies sub-divided HAI strategies into two divisions, standardised and additional precautions. Healthcare workers should apply standard precautions such as hand hygiene, masks and gloves in all situations. Additional precautions such as patient isolation must be implemented when handling patients that are colonised or infected with specific microorganisms; such as MRSA and *Clostridium difficile* infection (CDI) [38]. HAI prevention guidelines have been developed by local, national, and worldwide organisations such as WHO, CDC, European Centre for Disease Prevention and Control (ECDC), National Institute for Health and Care Excellence (NICE), and Health Protection Scotland (HPS) are all publishing frequently updated guidelines and policies [39-43].

1.1.3. Challenges:

Antimicrobials prescription differ from other medications by the possibility of collateral harm, especially with respect to the generation of antimicrobial resistance,

where both patients and the broader population are at risk. This must be reflected upon in addition to the challenges involved in selecting an appropriate antimicrobial for an individual patient with the correct spectrum of antimicrobial activity that also reaches a sufficient concentration at the site of infection. New antimicrobial development has not kept up with bacterial resistance rates, especially for Gram-negative organisms, and the risk of untreatable infections is rising.

1.1.3.1. Antimicrobials Production:

Sir Alexander Fleming, a Scottish scientist and Nobel laureate, discovered Penicillin in 1928 [44]. Most of the antimicrobials in use nowadays were developed in the 'golden age', 1940 to 1965, of antimicrobial discovery or a modified product from those classes. Since 1970, only two entirely new antimicrobial classes (targeting Gram-positive bacteria specifically) have reached the market: oxazolidinones (linezolid; launched in 2000) and lipopeptides (daptomycin; introduced in 2003) [45]. The absence of new agents, especially against Gram-negative organisms, has caused an increased risk of untreatable infections and compulsory use of older agents, such as fosfomycin and colistin, which may have less desired adverse effect profiles [46].

Today, antimicrobials are the third most profitable class of medications for pharmaceutical companies, outdone only by the central nervous system and cardiovascular medications. The market share for antimicrobials is between $26

billion and $45 billion per year [47]. Despite such large market share, introducing an individual new antimicrobial to the medical field may not be as profitable as other therapeutic classes of chronic medications. For example, the bestselling antibacterial, azithromycin (Zithromax®), made $2.01 billion in 2003. However, an antihyperlipidemic medication, Atorvastatin (Lipitor®), sales by the same company earned $9.23 billion in that same year [46].

1.1.3.2. Antimicrobial Resistance:

One of the most challenging aspects of infectious disease science is antimicrobial resistance. It can be defined microbiologically and clinically. Microbiological resistance can be defined as, “The presence of a genetically determined acquired or mutated resistance mechanism, categorising the microbe as resistant or susceptible depending on the application of a set cut-off in a phenotypic laboratory test” [48].

Clinical resistance can be defined as, “The level of antimicrobial activity that is correlated with a high probability of therapeutic failure; treating a microbe with an antimicrobial to which it has tested susceptible produces a better outcome than that achieved with an antimicrobial to which the microbe has tested resistant” [48]. The test cut-offs for defining clinical resistance may differ with regards to the clinical setting, such as the dosage of the antimicrobial or the site of infection [48].

In general, antimicrobial resistance can be either inherent or acquired. Inherent resistance is a characteristic of all isolates of the entire species, for example, colistin resistance of all Gram-positive organisms due to the absence of lipopolysaccharide contained within an outer envelope. On the other hand, acquired resistance develops when naturally susceptible bacteria gain the encoding genes for a resistance mechanism via either mutation or the transfer of genetic material from other bacteria [49].

Antimicrobial consumption can be correlated with the presence of microorganisms displaying resistance to the antimicrobial at the individual patient and population levels. On an individual patient level, studies have shown persistence of resistance to an antimicrobial up to one year after exposure, in both the urinary tract (caused by *Escherichia coli*) and the respiratory tract (caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*). Furthermore, exposure to a higher number of antimicrobials or for more extended treatment durations was found correlated to the probability of antimicrobial resistance at 12 months [50]. On a population level, there is a correlation between an individual country's antimicrobial consumption and the prevalence of particular multi-resistant bacteria. For example, in Greece, the percentage of *Staphylococcus aureus* bacteraemia from MRSA was 51% vs 1.6% in the Netherlands, and the percentage of *Klebsiella* bacteraemia due to carbapenem-

resistant *Klebsiella spp*. was 38% vs 0.2%, respectively. The antimicrobial consumption in Greece was over three times that of the Netherlands in 2010-11 [51].

There are four main mechanisms by which bacteria develop resistance to antimicrobials [49]:

1. Alteration of the antimicrobial target, such as the alteration of penicillin-binding proteins to PBP2' encoded by the *mecA* gene in MRSA to which β-lactams cannot bind.
2. Inactivating enzymes, such as aminoglycoside modifying enzymes, chloramphenicol acetyltransferase and β-lactamases.
3. Increased efflux of the antimicrobial out of the cell, such as efflux pumps which export tetracycline out of the cell.
4. Decreased permeability to the drug, such as loss of porin channels in *Enterobacteriaceae* causing resistance to β-lactams.

Economically, antimicrobial resistance has a significant impact on health cost. The ECDC estimated in 2009 that around 25,000 people in Europe die every year from HAI caused by resistant pathogens. This results in a cost of about €1.5 billion to the European Union (EU) in additional healthcare spend and lost productivity per year [52].

Different strategies have been implemented to prevent or minimise the spread of multidrug-resistant bacteria and hospital-acquired infections. One dominant approach is improving the efficacy and utilisation of currently available antimicrobial therapy [53]. Guidelines and protocols publications, restricting routine broad-spectrum antimicrobial selection, tailoring antimicrobial use based on cultures and sensitivity reports, and continuous audit of antimicrobial consumption all help to minimise antimicrobial resistance and improve the efficacy and utilisation of antimicrobial agents.

The UK Department of Health released the 'Annual Report of the Chief Medical Officer, 2011', published in March 2013, which addressed the scale of the antimicrobial resistance threat across the UK [54]. In response to it, the 'UK five years antimicrobial resistance strategy 2013 to 2018' sets out actions to address seven key challenges to antimicrobial resistance (AMR) [55]:

1. Improving infection prevention and control practices in human and animal health.
2. Optimising prescribing practice, through the implementation of antimicrobial stewardship programmes.
3. Improving professional education, training and public engagement to improve clinical practice. Moreover, promote a more comprehensive understanding of the need for the more sustainable use of antimicrobials.

4. Developing new drugs, treatments and diagnostics through better collaboration between research councils, academia, industry and others.
5. Better access to and use of surveillance data in human and animal sectors.
6. Better identification and prioritisation of AMR research needs to focus activity and inform our understanding of AMR.
7. Strengthened international collaborations, working with and through a wide range of governmental and non-governmental organisations, international regulatory bodies and others.

Four years before the UK strategy, the Scottish Management of Antimicrobial Resistance Action Plan (ScotMARAP) in 2008 made recommendations for improving the use of antimicrobial agents across all healthcare settings in Scotland as part of the broader Healthcare Associated Infection (HAI) Task Force Delivery Plan [56]. ScotMARAP has primarily been delivered through the establishment of the Scottish Antimicrobial Prescribing Group (SAPG) and collaborative working between national stakeholders and NHS Scotland boards. ScotMARAP has been updated to address key areas 2, 3 and 5 (human sector) of the UK AMR Strategy detailed in bullet points above and ScotMARAP 2 provides an update to the original ScotMARAP document including revised roles and deliverables for SAPG and other stakeholders [57].

The battle against antimicrobial resistance is global and involves multilevel responsibilities by and between professionals. Each country should work based on

local systems and available resources with the collaboration of global organisations. Antimicrobials are the major defence against infections; rational usage is a central pillar of any plan to control resistance. Preserving and controlling antimicrobial usage is essential to ongoing clinical success by minimising resistance.

1.2. Antimicrobial Utilisation:

In the last decade, the spread of multidrug-resistant (MDR) Gram-negative bacteria has become one of the significant risk factors for hospitalised patients. There is a robust relationship between the increased use of antimicrobials and the emergence of antimicrobial resistance [58]. The rate of resistance is highest and correlates with clinical areas where antimicrobial usage is high, such as intensive care units (ITUs) [59].

Improving the efficacy and utilisation of antimicrobial therapy is a significant strategy against MDR and HAI [53]. Applying guidelines and protocols, restricting routine broad-spectrum antimicrobials selection, tailoring antimicrobial use based on cultures and sensitivity reports and continuous audit of antimicrobial consumption all help to improve the efficacy and utilisation of antimicrobial therapy. The importance of efficacy and utilisation improvement were addressed explicitly in the

'UK five year antimicrobial resistance strategy 2013 to 2018' key challenges and in ScotMARAP and ScotMARAP 2 [55].

In Scotland, the report on Antimicrobial Use and Resistance in Humans, 2012, noted that carbapenems and piperacillin-tazobactam use were found to be higher in 2012 by 9.1% and 9.2% respectively compared to 2011. The report suggested that the increase might be influenced by the initiative to reduce CDI risk by reducing the use of the cephalosporins, co-amoxiclav, clindamycin and fluoroquinolones (the 4Cs). Since 2009, there has been a 51.1% increase in the use of piperacillin-tazobactam, which accounted for 1.9% of total antibacterial use in 2012 (compared to 1.4% in 2009). The report recommended closer monitoring of both carbapenems and piperacillin-tazobactam use and improve adherence to the guidelines [60].

To improve efficacy and utilisation of antimicrobial therapy, and to unite the effort, SAPG produced a guidance document to reduce Multi-Drug Resistant Gram-Negative Bacteria (MDRGNB) infections in October 2013 (updated 2016). The guideline aims to support NHS Scotland health boards in managing Gram-negative infections, reducing the emergence of MDRGNB and to promote more judicious use of broad-spectrum antimicrobials [61]. The production of this guidance was a primary action from SAPG against MDRGNB, with close monitoring of consumption, and resistance patterns across Scotland. The guidance will be discussed in detail later on (section 1.2.3).

The researcher performed a rapid survey on 6 of the 14 geographical NHS Scotland health boards in September 2014. The survey aimed to look into local health boards different in guidelines compared to SAPG MDRGNB. The survey has identified that individual health boards have variably differed from the SAPG guidance recommendation, mainly with piperacillin-tazobactam and carbapenem-sparing antimicrobials use (Table 1). Further discussion will follow at sections 1.3.1.1. and 1.3.1.2.

Table 1: NHS Scotland health board adoption of SAPG guideline at Sep 2014 (n=6)

NHS Boards	Sepsis		UTI		Carbapenem-sparing Antimicrobials (CSAs)			
	Unknown source	Neutropenic	Lower UTI	Upper UTI	Aztreonam	Temocillin (Esp. ESBL)	Pivmecillinam (Esp. ESBL)	Fosfomycin (Esp. ESBL)
SAPG	Amoxicillin + aminoglycoside &/or metronidazole	Piperacillin-tazobactam ± gentamicin	Trimethoprim or nitrofurantoin	Co-amoxiclav or co-trimoxazole or Pivmecillinam or fosfomycin	Sepsis Urosepsis (not ESBL) Bacteraemia Pneumonia Intra-abdominal sepsis	UTI (not *Pseudomonas* nor *Acinetobacter*) Septicaemia Urosepsis (Including ESBL) Pneumonia	UTI	UTI
Forth Valley	Co-amoxiclav ± gentamicin	Piperacillin-tazobactam OR Meropenem		Amoxicillin + gentamicin OR ciprofloxacin	Cystic fibrosis	--	--	Uncomplicated lower ESBL UTI, resistant to all other oral agents
GGC	Benzylpenicillin + flucloxacillin + gentamicin	Piperacillin-tazobactam ± gentamicin		Trimethoprim OR Co-amoxiclav or Ciprofloxacin	Neutropenic sepsis HAP Peritonitis Intra-abdominal sepsis cholecystitis	Proven resistant Gram-negative infections	--	--

Grampian	Piperacillin-tazobactam ± gentamicin	Piperacillin-tazobactam + gentamicin		Amoxicillin + gentamicin OR ciprofloxacin	--	--	--	--
Highland	Piperacillin-tazobactam ± gentamicin	Piperacillin-tazobactam ± gentamicin		Co-amoxiclav OR ciprofloxacin	Upper UTI Diabetic foot Neutropenic sepsis	--	--	Intranet
Lanarkshire	Amoxicillin + aminoglycoside + metronidazole	Piperacillin-tazobactam ± gentamicin		Amoxi + gentamicin OR ciprofloxacin	--	--	UTI	UTI's caused by multiple resistant E.coli & Klebsiella with proven resistance to all other agents
Lothian	Co-amoxiclav ± gentamicin	Piperacillin-tazobactam ± gentamicin		Amoxi + gentamicin OR ciprofloxacin	--	Cystic fibrosis Septicaemia UTI Lower respiratory tract infection	UTI	UTI Cystic fibrosis

a (Serious Gram-negative infections)

The report on Antimicrobial Use and Resistance in Humans, 2012, recommended continued consumption monitoring of carbapenems and piperacillin-tazobactam but not a collection of patient-specific consumption data. To date, before this research, no detailed data was available on how effectively carbapenems are utilised in clinical practice or how compliant practitioners are to the published guidance or local guidelines [60].

In the 'UK five year antimicrobial resistance strategy 2013 to 2018' key challenges and in ScotMARAP and ScotMARAP 2, addressed the importance of performing periodic assessments, locally and nationally, of antimicrobials consumption [55, 57] to better understand the relationship between the use of antibacterial drugs and emerging bacterial resistance. The most recommended measurement unit for antimicrobial consumption is defined daily doses (DDD) developed by the WHO [62, 63]. The use of DDDs as an antimicrobial measurement unit is recommended by NHS Scotland [64]. DDD is a metric estimate used by hospitals to aggregate the number of grams of each antimicrobial purchased, dispensed, or administered during a period of interest divided by the WHO-assigned DDD [65]. However, the use of DDD estimates is not appropriate for paediatrics and patients with reduced medication excretion such as renal impairment [62]. Nevertheless, DDDs are a useful measure of progress and improvement when tracked using consistent methodology over time [66-68].

Consumption data from SAPG on carbapenems in 2013 identified that a total of 4.77 (DDDs) per 100,000 population per day were issued compared to 3.79 DDDs in 2008; a 25.8% increase. Furthermore, the data showed that DDD/1000 occupied beds per day (OBD) increased from 7.7 in 2008 to 12.8 in 2013. However, even with the total increase of consumption nationwide, a decrease has been observed in some health boards, especially NHS Ayrshire & Arran, from which we may be able to explore and use to inform further implementation strategies in other health boards. In addition, total piperacillin-tazobactam consumption data also increased from 4.60 DDDs per 100,000 population per day issued in 2008 to 7.39 in 2013; a 60.7% increase.

Ideally, antimicrobial use should be monitored continuously by surveillance programmes. However, surveillance programmes are often resource intensive in the absence of routine electronic data capture. Point prevalence surveillance studies (PPS) can be a reasonable alternative to continuous surveillance programmes and are a good quality indicator for targeted areas of improvement [69]. The ECDC developed and recommended a European Surveillance of Antimicrobial Consumption point prevalence survey (ESAC)-PPS in 2006 [70].

The main three target areas of the ESAC-PPS are the duration of preoperative prophylaxis, having an indication documented in case notes and adherence to local guidelines. The survey also includes patient-related and hospital-related information. And, hospital-related information such as bed capacity, admission rate, speciality

available and regional policy. In the patient part demographic data, admitting speciality/ward, monotherapy or combined, duration of therapy, dose, route of administration, and IV to oral switch is included [70]. The British Society for Antimicrobial Chemotherapy (BSAC) developed a PPS system that is similar to ESAC-PPS system. BSAC plans to introduce the PPS tool in 2015 for NHS Scotland use.

Scotland was one of the European countries that participated in the 2009 ESAC-PPS. SAPG was the responsible group for this collaboration. Data was collected between 1st of May 2009 and 26th of June 2009 involving 31 hospitals with 8732 patients included. The results showed that 27.8% of patients surveyed received antimicrobials (2.6% of the 27.8% were carbapenems; lower than the 2.9% European Union/European Economic Area (EU/EEA) population-weighted mean, 5.6% of the 27.8% were piperacillin-tazobactam; higher than the 0.87% EU/EEA population-weighted mean). Also, 76.1% of the antimicrobials prescriptions had an indication documented, but only 57.9% were compliant with local NHS guidelines [71, 72].

The increasing carbapenem and piperacillin-tazobactam consumption data in Scotland over the last five years, may in part be justified by the increased incidence of *E. coli*, *K. pneumoniae* and *P. aeruginosa* infections [60]. One potential area for further study examination is compliance with local guidelines which in the 2009 PPS was found to be slightly lower in Scotland (57.9%) compared to Europe (62%) [73]. Additionally, early findings from a rapid survey suggest that each health board has

developed their local guideline based on modifications to the SAPG MDRGNB (Table 1). Different implementation methods may influence the use of the specific guidance and the rational utilisation of carbapenems and piperacillin-tazobactam.

1.2.1. Improving antimicrobials prescribing:

Worldwide efforts have been conducted to improve antimicrobials use in healthcare settings. Several in-depth investigations were performed trying to understand antimicrobials prescribing behaviour in hospitals and public settings. Numerous influencing factors can be related to antimicrobial overuse, from patient level to economic impact and all can be informative.

At the patient level, several influencing factors can lead to the inappropriate use of antimicrobials. Lack of knowledge of the difference between bacterial and viral infections, lack of understanding or education about the resistance problem, compliance to antimicrobials choice and duration, and expectations of being issued a prescription are some examples of patient-related factors that might lead to inappropriate antimicrobials use [74, 75]. Solving patient-related factors require detailed programmes of education on the small and large scale where families and parents from the public are targeted and involved to improve awareness [76].

At healthcare professional level, factors such as inadequate knowledge, doubt in diagnosis, the worry of complications and disciplinary cases can lead to inappropriate antimicrobials prescribing. Some healthcare professions find it challenging to differentiate between viral and bacterial infections, which lead to unclear treatment pathways. All may push practitioners toward every day, more familiar pathways of prescribing antimicrobial rather than taking the time and filling the gaps in knowledge [76]. Moreover, practitioners worryingly about complications of not treating, or under-coving if narrow-spectrum antimicrobial selected are noticeable in healthcare providers without taking into consideration the consequences of antimicrobial resistance [76-78]. Interventions to improve antimicrobials prescribing will be discussed in detail later on this research (section 1.2.2.), the current research is focusing on hospital base prescribing.

Another category of factors affecting antimicrobial use is based on the organisation of care. Organisational influences affect coordination and collaboration between different levels of healthcare professionals, transfer and agreement on information required, logistical requirements of the care process and monitoring systems [74]. Switching the decision of prescribing antimicrobials from the Doctor's solo decision to a collaborated team of healthcare professionals or offering a computerised decision support system might all improve appropriate antimicrobial prescribing [79, 80].

In recent years, cultural and socio-economic factors have also played an essential part in influencing and changing prescribing habits. Aggressive marketing by the pharmaceutical industry for an antimicrobial can negatively influence the prescribing of such a product. Furthermore, marketing strategies initiated to target consumers directly, and with the ability of ordering medications from the internet or in another country where antimicrobials are freely available to purchase without a prescription, will all lead to the inappropriate and uncontrolled use of antimicrobials [81].

1.2.2. Interventions to improve antimicrobial prescribing in secondary care:

The majority of antimicrobials prescribing take place at primary care level, 80% in Scotland and 74% in England, rather than secondary care [82]. However, hospitals tend to have higher prescribing rates of broad-spectrum antimicrobials. Broad-spectrum antimicrobials are more likely to drive resistance than narrow-spectrum antimicrobials which are more commonly used at primary care level. In the 2014 antimicrobial consumption data report from NHS Scotland, total antibacterial use at primary care was 1.9% lower in 2014 than in 2013. On the other hand, at secondary care level, total antibacterial use was 5.9% higher in 2014 than in 2013 continuing the incline trend from previous years. Furthermore, there was an 8.2% increase in piperacillin-tazobactam and 2.1% increase in carbapenems use compared to 2013.

Data from the most recent English surveillance programme for antimicrobial utilisation and resistance (ESPAUR), 2010 to 2014, stated that total hospital inpatients prescribing had increased significantly by 11.7% between 2011 and 2014, whereas, consumption remains stable or slightly lower at primary care level. Therefore this data would suggest that secondary care prescribing of antimicrobials are in need of more interventions and attention to further optimise prescribing [83].

Professional interventions toward more appropriate prescribing tend to be persuasive, restrictive or structural and the impact of interventions can be tested by the antimicrobial prescribing process, clinical and microbial outcomes measures, and economical changes [84]. Persuasive interventions can be done by distributing educational materials, educational meetings and events, educational outreach visits, reminders, audit and feedback. On the other hand, selective reporting of laboratory susceptibility, formulary restrictions, prior approval of prescriptions, automatic stop orders, and antimicrobials prescribing policy changes are restrictive interventions. Furthermore, switching to computerised systems, advanced rapid laboratory testing, computerised decision support systems and quality monitoring systems are all structural interventions [84].

1.2.2.1. Persuasive interventions:

Sharing convincing evidence of information to healthcare practitioners and politically forcing them to follow can be reached by different strategies. Actions such as educational material dissemination in printed format or educational sessions, regular audits and feedbacks to the target audience, educational outreach with academic detailing or tailored recommendations, and frequent reminders are all considered as a persuasive type of interventions.

In a study that monitored antimicrobial use and resistance focusing on vancomycin use and vancomycin-resistant Enterococci (VRE) prevalence compared the impact of five different interventions on 20 hospitals with 50 ITU's. Among the five interventions, three were persuasive, and two were restrictive interventions. National guideline on vancomycin use was disseminated by newsletter or emails aiming to decrease the consumption of vancomycin. However, despite this type of intervention, there was an increase in vancomycin use by 2.8%. However, when ITU-specific education in-service sessions disseminated a vancomycin use guideline, vancomycin use decreased by 35% compared to the pre-intervention stage [85]. This highlights the importance and benefit of targeting an intervention.

In a retrospective single-centre study on changes to microbiological characteristics and mortality in patients with sepsis or pneumonia following a reduction in the use

of antimicrobials. The study was conducted in a German 312-bed hospital were special training, standardised algorithms to prevent unnecessary antimicrobial orders, and uniform recommendations were introduced in 2012 and 2013. From January 2010 to the end of December 2011 (n=20954 patients), immediate administration of antimicrobials was conventional and expected course of action. Moreover, from the first of January 2012 to the end of December 2013 (n=22719 patients), antimicrobial prescribing policy changed. The change included algorithms and advice on both the indications for antimicrobial use and the class of drugs to be prescribed if the indications were met. In addition, physicians from all specialities attended training courses on the restrictive use of antimicrobial (covered 61% of all medical staff). Furthermore, pocket algorithms were designed and handed to all physicians. After results comparison, antimicrobial consumption fell from 67.1 to 51.0 DDD per 100 patient days ($p<0.001$) from the period 2010-2011 to 2012-2013. Mortality of patients with sepsis fell from 31% to 19%, from 12% to 6% with pneumonia, and 3% to 2.5% in overall mortality. In addition, the rates of resistance in Gram-negative nosocomial UTI to three or four antimicrobials fell from 11% to 5%. The study concluded that training sessions and clear guidelines on antimicrobials utilisation resulted in a 32% reduction in overall use without negatively affecting mortality rates [86].

In 2015, a cluster-randomised trial investigating two strategies aiming to improve antimicrobial use for patients with complicated UTI held at 19 Dutch hospitals was

published. The study allocates hospitals to either multi-faceted strategies; including feedbacks, educational sessions, reminders and additional/optional improvement list of actions, or similar feedback on the department's appropriateness of antimicrobial use. The study compared the result in a retrospective baseline data pre-intervention (2009) and post-intervention (2012). The sample size included 1964 patients pre-intervention and 2027 patients post-intervention. The researching group sets a principle measure of nine validated guideline-based quality indicators (QIs) which identify appropriate antimicrobial prescribing in patients diagnosed with complicated UTI. The nine QIs are to perform a urine culture, prescribing empirical therapy in accordance with the national guideline, switch from IV to oral therapy within 72 hours on the basis of clinical condition, tailor antimicrobial treatment on the basis of culture results, use of fluoroquinolones selectively, duration of antimicrobial therapy should be at least 10 days, treat UTI in men according to national guideline, replace urinary catheter after initiation of antimicrobial treatment, and adapt antimicrobial dose according to renal function test. The mean patient's QI sum score shows a significant improvement in both strategies group compared to baseline (multifaceted: 61.7% to 65%, p=0.04 and competitive feedback: 62.8% to 66.7%, p=0.01). The study concluded that both strategies were effective and better compliance with the strategies were associated with more improvement. In addition, the study recommends more activities targeted to multidisciplinary teams [87].

1.2.2.2. Restrictive interventions:

Another category of interventions, where organisational higher authorities step in and take action, is a restrictive measure. Changing antimicrobials formulary or policy implementation over an organisation or national level restricting the freedom of antimicrobials prescribing. There are several examples of restrictive interventions; the most common approaches are compulsory order forms, expert approval, restricting access by removal from the formulary or stock, expert team review and action, and financial incentives or penalties.

In the literature, most studies that investigate only the impact of compulsory order forms were before 2000, and more recent studies examine multiple interventions benefits. As an example, a study investigating the impact of implementing an educational program and an antimicrobial order form to optimise the quality of antimicrobial consumption of internal medicine department in a 948-bed hospital. During the one-year study period, a prospective review was performed over a four week period. The second review over six weeks period was performed after the initiation of the intervention, and an identical review was performed after one year. From the first review, 31% of patients were prescribed antimicrobials, and only 40% of these prescriptions were considered appropriate with 13% considered unjustified. After the interventions were applied, 21% of patients were prescribed antimicrobials of which 53% of them were justified, and only 9% were unjustified. However DDD per

100 bed days increased from 59.8 to 72.6 from onset to end of study. The results after one year show that compliance with the order form was 77% and no data available on performance improvement at that stage. The study results support the benefit of having a compulsory order for aiding quality of antimicrobial prescribing [88].

Limiting antimicrobial prescribing to experts or specific specialities is a pervasive restrictive intervention. Several studies investigate the impact of such measure and results were debatable, either agreeing or disagreeing. In a study investigating the impact of vancomycin use restriction targeting all prescribers at a single large hospital (725-beds), over ten years period. The restriction was applied to vancomycin use for >72 hrs during the first two years, after that all use require approval. The study compared results with data from three years pre-intervention. Compared data from the first year against control showed 8.1% decrease in vancomycin use and a 26.9% decrease in the second part. However, at the final period, vancomycin use increased compared to initial period by 15.5%. The author relates the increase of use to decrease in other antimicrobial agent consumption, but however, recommends restriction as a measure of improving consumption in reference to reduction results in first two stages of the study [89].

One of commonly used restrictive intervention is a restriction by limiting access or removal. This type of intervention can be applied to target wards, units or operating

theatres. In the UK, a study was done at elderly care aiming to control *Clostridium difficile* infection by the use of a restrictive antimicrobial policy. The study was conducted in one centre containing 486 patients, recommending antimicrobial treatment to Benzylpenicillin to cover streptococcal infections, gentamicin for Gram-negative resistant bacilli and trimethoprim for urinary tract pathogens and *Haemophilus influenzae* over 16 months. The restriction was applied to cefuroxime IV and removal of oral cefuroxime from pharmacy stock. Data were compared to a seven-month period pre-restriction. Results show that the net effect after one month was a 75.4% reduction in cefuroxime consumption, diminishing to 59.6% after six months. Furthermore, length of stay and mortality were not changed during the study period. However, 37 cases of *C. diff* occurred in the control data compared to only 16 cases after the policy was altered [90].

1.2.2.3. Structural interventions:

In recent years, advanced technological developments have changed the work pattern of the healthcare sector. Recent technologies include improved laboratory testing and turnaround time of microbiology specimens results and reports. Furthermore, applying computerised decisions support systems and switching paper to electronic record, all for the sake of improving antimicrobials prescribing.

In a randomised controlled trial (RCT) among hospitalised patients in the Netherlands, aiming to study the effect of shorter turnaround time of microbiological procedures on clinical outcomes using VITEK 2® system. The 9-month study randomised 1883 patients from a single centre (1100 beds) university hospital. Three study periods were compared; rapid testing but no changes in reporting, rapid testing and same day oral reporting, and the third period was rapid reporting plus same day oral reporting and additional mail delivery of reports. Patients were included in the study if their first sample contained one or more clinically relevant isolates of *Enterobacteriaceae, Pseudomonas aeruginosa, Staphylococcus* species, or *Enterococcus* species. The tested clinical impact was mortality, length of hospital stay, length of ITU stay, number and cost of diagnostic procedures, cost of antimicrobial agents, and additional special care. The study results showed that no significant differences between patient groups regarding mortality, morbidity, cost or additional special care occurred, even though reporting time was significantly lower. However, a 13% increase in the selection of an appropriate antimicrobial treatment (64% intervention vs 51% control) was observed [91].

In a study investigating the effect of measuring procalcitonin biomarker as an assessment of infection on antimicrobial use and outcome in lower respiratory tract infections, the absolute reduction in antimicrobials prescribing was 38.8% and adjusted RR of antimicrobial exposure 0.49. The study design was cluster-randomised, single-blinded intervention trial (n=597 patients) in a single hospital

over four months. Patients included in the study were diagnosed with either pneumonia (36%), acute exacerbation Chronic Obstructive Pulmonary Disease (COPD) (25%), acute bronchitis (24%), asthma (5%), and other respiratory infections (10%). Clinical and laboratory outcome were similar in both groups, conventional care group and procalcitonin-guided treatment group, and favourable in 97% [92].

Polymerase chain reaction (PCR) is an advanced rapid, sensitive, highly specific assay. A multicentre RCT (n=107 patients), used PCR to distinguish between viral and atypical bacterial pathogens causing LRTI. From the 107 patients, 55 were allocated to the intervention group, real-time PCR, as well as conventional diagnostic procedures. Results showed overall antimicrobial use was comparable in the interventional group and control group (median duration of treatment, ten vs nine days). Furthermore, PCR increased treatment and diagnostic costs by €318.17 per patient. Overall, PCR increased the diagnostic yield in LRTI, but it did not reduce antimicrobial use or cost [93].

There are different types and approaches when discussing computerised decision support systems. Some systems are designed to target antimicrobial therapy and some work as a comprehensive therapeutic package. For example, a group developed a computerised decision support system (TREAT) aiming to improve the rate of appropriate antimicrobial treatment, thereby reduce mortality, and to shift antimicrobial use toward ecological and economic choices. To test the improvement

in empirical antimicrobial treatment using TREAT, a multicentre cluster RCT was conducted recruiting 2326 participants. The system is integrated within site workflow and provides advice intended to reduce unnecessary antimicrobial use and promote necessary use. Data were compared to control group (local guideline) prospectively. Results show that the TREAT intervention group prescribed appropriate empirical antimicrobial treatment significantly more frequent than the control group (70% vs 57%) and used less broad-spectrum antimicrobials at half control group antimicrobial cost; OR: 3.70. However, length of stay, cost of related resistance, and total antimicrobials cost were lower in the intervention group but were not statistically significant [94].

1.2.2.4. Mixed strategies interventions:

In the literature, there is a lack of direct comparison that concludes which method of interventions is superior to another. Due to multiple influencing factors, deciding on which intervention to apply may be challenging. The Cochrane Collaboration published a review of interventions to improve antimicrobial prescribing practices for hospital inpatients in 2013. A meta-analysis of persuasive versus restrictive intervention was performed including 52 studies. The included studies in the meta-analysis outcome were prescribing (n=38), microbial (n=14), and cost (n=4). Overall result from the meta-analysis showed a consistency impact on both prescribing and microbial outcome; 25% improvement in the targeted direction. Within one month,

restrictive interventions showed statistically significant improvement (32%) compared to persuasive, however, at the six month stage, the improvement dropped to 10.1%. Furthermore, at 12 and 24 months, persuasive interventions had a greater effect but this was not statistically significant. Restrictive interventions showed statistically more significant effect on microbiology outcome at the six month stage (53%), but this dropped to 16.2% in 12 months, and persuasive interventions gain an advantage at 24 months (0.7%). The authors suggest that restrictive interventions are helpful when the need to try to exert some control on prescribing is urgent but stressed recommending the simultaneous application of both restrictive and persuasive intervention measures as a long-term intervention [84].

The Chinese action plan on antimicrobial consumption is an excellent example of a multiple interventions approach. The study reported a significant reduction in antimicrobial consumption and patient cost after implementation of the China Action Plan, 2010-2014. In this study, pharmacy data from July 2010 to June 2014 were sampled from 65 general public hospitals and divided into three groups; July 2010 to June 2011, preparation period data; July 2011 to June 2012, intervention period data; and from July 2012 to June 2014, assessment period data. Four parameters were targeted; antimicrobial prescribing rates, the intensity of antimicrobial consumption, patients cost, and duration of pre-operative antimicrobials treatment in clean surgeries. Cross-sectional analyses showed a reduction in antimicrobials consumption from 80.1% to 35.3% and 13%, during the assessment period, in

inpatient and outpatient populations respectively, reduction in the intensity of prescribing from 76.6 to 35.9 DDD/100 bed-days, and a statistically significant reduction ($p < 0.001$) in both cost and duration of pre-operative prophylaxis. The study shows that combined managerial and professional actions are effective in reducing frequency and intensity of antimicrobials consumption [95].

In summary, action toward better utilisation of antimicrobials is critical, and several approaches can be made either sequentially or simultaneously to reach this goal. Such actions should involve multiple levels of prescribers and stakeholders. Studies favour multiple intervention strategies to reach the ultimate goal of the appropriate use of antimicrobials.

1.2.2.5. Antimicrobial Stewardship Programmes (ASP):

To make the best use of currently available antimicrobials, Antimicrobial Stewardship Programs (ASP) have been pursuing this goal for decades. The term 'antimicrobial stewardship' is defined as 'an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness' [96]. These programs focus on ensuring the proper use of antimicrobials to provide the best patient outcomes, decrease the risk of adverse effects, promote cost-effectiveness strategies, and reduce or maintain current levels of MDR [97].

In the literature, growing body of evidence demonstrates that healthcare based programs devoted to improving antimicrobials use can both optimise the treatment of infections and reduce adverse events rates associated with antimicrobial consumption [84]. These programs support healthcare providers improve the quality of provided patient care [98] and improve patient safety through increased successful infection cure rates, reduced treatment failure rates, and increased frequency of appropriate prescribing for therapy and prophylaxis [99, 100]. In addition, they can significantly reduce hospital rates of CDI [101, 102] and AMR [103, 104]. Furthermore, these programs often achieve these benefits while reducing healthcare budget [105-107].

However, there is no particular template for a program to optimise antimicrobial prescribing in hospitals. The complexity of medical decision surrounding antimicrobial use and the variability in the size and types of care among healthcare settings require flexibility in implementation. Nevertheless, published literatures demonstrates that ASP can be implemented effectively in a wide variety of healthcare settings and that success is dependent on defined leadership and a coordinated multidisciplinary approach [108, 109].

There are key elements to be included in any designed ASP to insure successful implementation and reaching maximum benefits of such programs. The NICE have published a guideline on designing and implementing ASP [96]. The guideline have identified several key elements to be included when designing ASP; such as: monitoring and evaluating antimicrobial prescribing and how this relates to local resistance patterns, providing regular feedback to individual prescribers in all care settings about their prescribing and patient safety incidence, and provide education and training about ASP [96].

1.2.3. SAPG MDRGNB guideline:

In 1990, the Institute of Medicine (IOM) defined clinical practice guidelines as, "Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [110]. Clinical practice guidelines are usually developed by government agencies, institutions, or expert panels.

To improve efficacy and utilisation of antimicrobial therapy, and to unite the effort, SAPG produced a guidance document to reduce MDRGNB infections in October 2013 (updated 2016). The guideline aims to support NHS Scotland health boards in

managing Gram-negative infections, reduce the emergence of MDRGNB and promote more judicious use of broad-spectrum antimicrobials [61].

SAPG developed the guideline through consultation with clinical speciality teams targeting individual health board Antimicrobial Management Teams (AMTs) and Infection Specialists. Participating patients were those with Gram-negative infections. Surveillance data suggesedt that areas such as critical care, haematology/oncology, and some surgical units are responsible for the increased consumption of carbapenems. Thus, the guideline desired to change the current management of Gram-negative infections, reduce the emergence of MDRGNB, and promote overall the more judicious use of broad-spectrum antimicrobials. However, this was not a definitive guide but aimed to aid the development of local policies. In the guideline, available national and local guidelines were discussed and compared to the present publications. In addition, evidence-based literature was provided to justify recommendations. As a follow-up, surveillance data will be monitored plus updates to follow in light of future national evidence-based guideline. However, no specific date for an update was mentioned and method of implementation and distribution were not investigated.

The guideline adopted persuasive interventions targeting four common Gram-negative infections; sepsis, UTI, direct treatment of Gram-negative sepsis, and infections due to carbapenemase-Producing Enterobacteriaceae (CPE). In addition,

the guidance promoted for five alternatives to carbapenems, with monographs, based on the four targeted infections; aztreonam (IV), temocillin (IV), pivmecillinam (oral), and fosfomycin (oral and IV).

1.3. Gram-Negative infections:

1.3.1. Introduction:

Gram-negative bacteria are classified on the basis of their reaction to Gram's stain. Due to the structural features of the Gram-negative bacteria, they do not retain the crystal violet dye in the Gram staining procedure and as a consequence are stained pink/red with the safranin counter stain when viewed microscopically (Figure 1). A thin peptidoglycan layer between the inner and outer bacteria cell membrane cannot maintain the crystal violet dye upon exposure to organic solvent, which gives the Gram-negative bacteria a red or pink colour following a Gram stain [111]. Two methods can be applied to sub-classify Gram-negative bacteria, based on phenotypic characteristics and growth requirements. Phenotypic classification based on the morphological characteristics divide Gram-negative bacteria to cocci and bacilli (Figure 2). For example, Gram-negative cocci include the *Neisseria* species and Gram-negative bacilli includes *Haemophilus influenzae*, *Klebsiella*

pneumoniae, *Pseudomonas aeruginosa*, and *Escherichia coli* [111].On the other hand, growth requirements classify them aerobic or anaerobic.

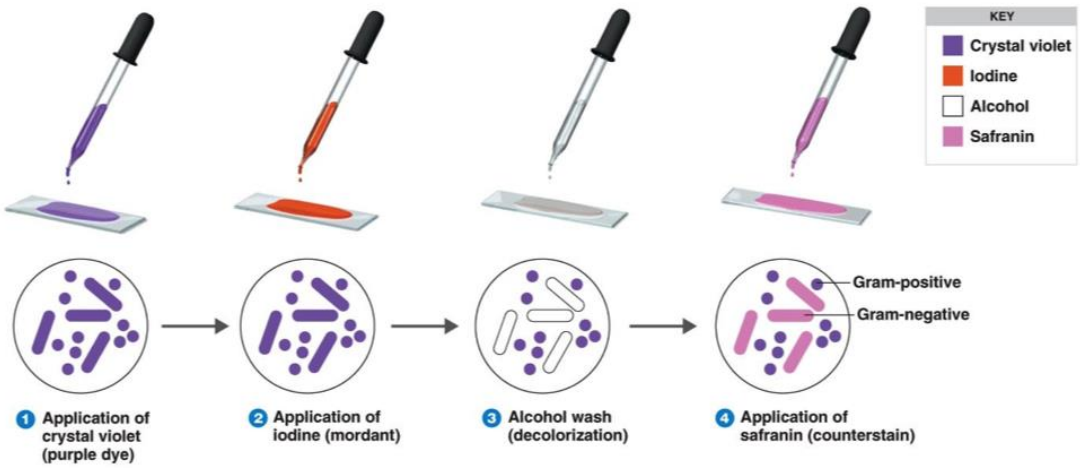


Figure 1.1. Gram staining procedure. Reproduced from Schaum's outline of Microbiology [98]

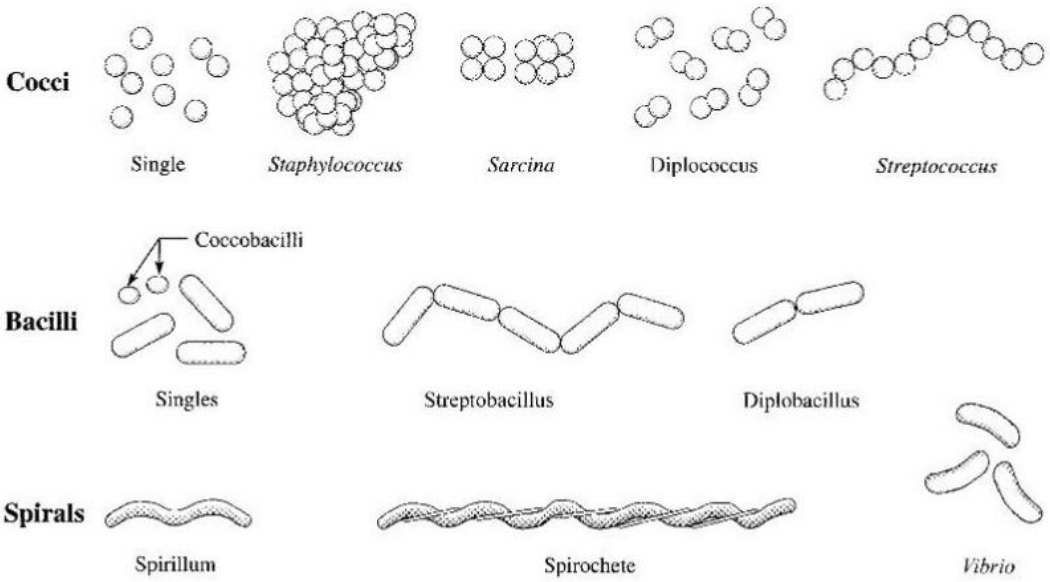


Figure 1.2: The three shapes taken by the great majority of bacterial species. Reproduced from Schaum's outline of Microbiology [112]

In 2008, Rice introduced the "ESKAPE" term referring to; *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacter* species which are recognised as the most important emerging pathogens in this century. Four out of the six pathogens are Gram-negative (*K pneumoniae, Acinetobacter* species, *P aeruginosa*, and *Enterobacter* species) [113]. Worldwide, several highly resistant Gram-negative pathogens; *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa,* carbapenem-resistant *Klebsiella* species and *Escherichia coli*; are emerging as significant pathogens. Currently, limited therapeutic options are available for these pathogens which has forced clinicians to reintroduce older, previously discarded antimicrobials, such as colistin and fosfomycin, which were associated with undesirable significant adverse events and toxicity profiles [114, 115]. Colistin, for example, has been recommended in uncontrolled and small size studies [116], associated with the fear of under-dosing at currently licensed doses [117], and known to be nephron and neurotoxic [118, 119]. Several factors are contributing to the increased risk of antimicrobial resistance. Increased number of immunocompromised patients who are at higher risk of developing MDR Gram-negative infections; the growing number of elderly population, transplantation rates, and patients under chemotherapy treatment [120].

Treating patients with known or suspected infection is currently a therapeutic challenge to clinicians due to increasing rates of MDRGNB worldwide [121]. The rate

of MDRGNB became endemic in some parts of the world such as Greek and India [122, 123]. Scottish levels of MDRGNB are currently stable, but extended-spectrum beta-lactamase (ESBL) producing bacteria are noticeable (7.5% in 2009, decreased to 6.6% in 2012), and carbapenemase-producing (CPE) bacteria have been reported in most NHS board areas [60]. Furthermore, the risk of increasing MDRGNB rates has forced many clinicians to treat patients empirically with multiple broad-spectrum antimicrobials, which can maintain the cycle of growing resistance and lead an economic liability to society [124].

The Health Protection Scotland (HPS) report on antimicrobial use and resistance in humans [60], 2012, reported that *E. coli* and *K. pneumoniae* continued to be the most reported cause of Gram-negative bacteraemia in Scotland. There was a continuing upward trend in the reported numbers of *E. coli* bacteraemias. There were 85 more cases of *E. coli* bacteraemia in 2012 corresponding to a 2.2% increase compared to 2011 report. Also, there was a 3.0% increase in the number of *K. pneumoniae* bacteraemias compared to 2011 report. However, the number of cases reported from *P. aeruginosa* and *A. baumannii* remain stable. SAPG MDRGNB guideline [61] focused on sepsis, UTI and infection caused by carbapenemase-producing *Enterobacteriaceae* (CPE) as the most common infections caused by MDRGNB were medical management can be improved and guided.

1.3.1.1. Sepsis:

The Surviving Sepsis Campaign (SSC) define sepsis (previously known as septicaemia) as, “The presence (probable or documented) of infection together with systemic manifestations of infection.” [125]

Severe sepsis is a condition that can lead to sepsis-induced organ dysfunction or tissue hypoperfusion [126]. Sepsis is a life-threatening situation which requires fast and aggressive medical intervention. Only about 20% of patients diagnosed with sepsis are related to bacteraemia; the remainder are caused secondary to infection at other sites, most often the lower respiratory tract or the abdomen [127].

Bacteraemia is defined as the presence of bacteria in the bloodstream. Gram-negative bacteria account for about 60% of cases and Gram-positive bacteria for 40%. In specific settings, e.g. Intensive Therapeutic Units (ITUs), yeasts such as *Candida spp.* make a significant contribution to overall cases of sepsis. Sepsis and severe sepsis can lead to septic shock, which results in substantial hypotension and organ failure. The presence of shock increases the mortality rate to 60% or more [125].

In the US each year, there are around 750,000 sepsis cases, with more than 215,000 patients dying. Treating those patients costs US hospitals around $17 billion a year

[128]. In the United Kingdom, a secondary analysis of a high-quality clinical database took place between 1996 and 2004 covering England, Wales and Northern Ireland and showed that 25,021 (27%) cases of a total of 92,672 admissions, during the eight years of the analysis, were identified as having sepsis in the first 24 hours after admission. Those identified as having severe sepsis had an average hospital mortality of 46% [129]. In Scotland, a five month study showed that 46% of ITU admissions develop sepsis, equating to a prevalence of 0.77 cases per 1000 population, per annum. Two-thirds of the sepsis cases had more than one organ failure [130].

More recent international estimates of sepsis incidence point to about 300 cases per 100,000 population per year [131]. Reasons are varied but can be explained by the ageing population, increasing use of high-risk interventions, and the development of multidrug resistance and more virulent varieties of pathogens. The mortality rates from sepsis in a European study was 36%, and a typical episode of severe sepsis cost €25,000 [127]. In 2014, it was estimated from the UK Intensive Care National Audit and Research Centre (ICNARC) data that 102,000 cases of sepsis arise annually, with 36,800 deaths and an NHS cost for every 100,000 case of severe sepsis per year estimated at over £2.5 billion [132].

Clinical presentation of sepsis can be divided into two divisions: infection and infection-related, and organs at risk. The signs and symptoms of sepsis are similar to any infection but more severe. The infection affects the heart rate, respiratory rate,

body temperature and white blood cell (WBC) count. Depending on those clinical signs sepsis can be confirmed and severity is determined. The underlying clinical manifestations of sepsis are caused by the inflammatory response of the immune system against the bacteria. Fever and leucocytosis are features of the acute phase reaction, while tachycardia is often the initial sign of haemodynamic compromise [125]. Regular blood pressure monitoring is critical to follow up the hypertensive stage of the patient. Hypotension is a clear sign of deterioration and timely and appropriate clinical intervention is essential. The signs and symptoms of organ dysfunction indicating severe sepsis vary depending on the degree of hypoperfusion and target organ affected. Lung dysfunction is reflected as an acute lung injury or acute respiratory distress syndrome (ARDS). Brain injury results in encephalopathy causing confusion, agitation and coma. Kidney dysfunction presents as oliguria, increased blood urea nitrogen (BUN), increased serum creatinine level, electrolyte abnormality and volume overload. Also, heart dysfunction can be seen in late stages [133].

The SSC recommends five main management steps for sepsis and septic shock [125]. First of all, is the initial resuscitation targeting tissue hypoperfusion; defined as persisting hypotension or blood lactate concentration ≥ 4mmol/L. The goals of the initial resuscitation step are central venous pressure 8-12 mmHg, Mean Arterial blood Pressure (MAP) ≥ 65 mmHg, urine output ≥ 0.5 mL kg/hr, and central venous oxygen saturation of 70%. The second recommendation is inclusion of sepsis screening with

routine clinical assessment, especially in seriously ill patients with potential infections, to allow earlier initiation of therapy. Diagnosis of sepsis is the third recommendation of SSC, cultures as early as possible and imaging studies to confirm a potential source of infection.

The fourth recommendation of SSC is antimicrobial therapy. The goal of therapy is to administer effective intravenous antimicrobials within the first hour (the golden hour) of sepsis recognition. The choice of one or more empiric anti-infective agent which are highly active against all likely pathogens with adequate penetration and concentration into tissues presumed to be the source of infection. Furthermore, a daily assessment of antimicrobial regimen for escalation or de-escalation should be ensured. Combination of empiric antimicrobial therapy is recommended only in neutropenic patients with severe sepsis and for patients with challenging to treat MDR such as *Acinetobacter* and *Pseudomonas spp*. In case of severe sepsis with respiratory failure and septic shock, the recommendation is to treat empirically with an extended spectrum β-lactam and either aminoglycoside or fluoroquinolones to cover *P. aeruginosa* bacteraemia. The guidance also states that duration of therapy should not exceed 7-10 days, 3-5 days for combination therapy unless a patients have a slow clinical response or undrainable foci of infection. Finally, antimicrobials should not be used in patients with severe inflammatory statues caused by non-infectious reasons.

Source control is the fifth recommendation in SSC guideline. Anatomical diagnosis of infection requiring consideration for emergent source control should be pursued and diagnosed or excluded as soon as possible, and intervention is undertaken for source control within the first 12 h after the diagnosis is made, if possible. The final recommendation of SSC is infection prevention. Selective oral and digestive decontamination should be considered to reduce the incidence of ventilator-associated pneumonia (VAP). The risk of VAP can also be reduced by oral chlorhexidine used as an oropharyngeal decontamination in severe sepsis.

The researcher performed a rapid survey on 6 of the 14 geographical NHS Scotland health boards in September 2014 (Table 2). The survey aimed to look into the current local health board's recommendations and different in guidelines compared to SAPG MDRGNB. The survey has suggested that individual health boards have variably differed from the SAPG guidance recommendation, mainly with piperacillin-tazobactam and carbapenem-sparing antimicrobials use. Under sepsis recommendation, four health boards follow SAPG recommendation for sepsis of unknown sources and two added piperacillin-tazobactam to recommendations. On the other hand, the inclusion of CSAs in local guidelines was limited. Aztreonam and temocillin were only future in two health board local guidelines for neutropenic sepsis (aztreonam), and positive sensitivity or septicaemia (temocillin). In chapter 2, detailed investigation of local health boards' guidelines difference compared to SAPG will be discussed.

Table 2: Sepsis treatment recommendations from 6 NHS Scotland Health Boards, Sep 2014

NHS Boards	Sepsis		Carbapenem-sparing Antimicrobials (CSAs)	
	Unknown source	Neutropenic	Aztreonam (Serious Gram-negative infections)	Temocillin (Esp. ESBL)
SAPG	Amoxicillin + aminoglycoside &/or metronidazole	Piperacillin-tazobactam ± gentamicin	Sepsis Urosepsis (not ESBL) Bacteraemia Pneumonia Intra-abdominal sepsis	Urosepsis (Including ESBL) Pneumonia
Forth Valley	Co-amoxiclav ± gentamicin	Piperacillin-tazobactam OR Meropenem	--	--
GGC	Benzylpenicillin + flucloxacillin + gentamicin	Piperacillin-tazobactam ± gentamicin	Neutropenic sepsis Intra-abdominal sepsis	Proven resistant Gram negative infections
Grampian	Piperacillin-tazobactam ± gentamicin	Piperacillin-tazobactam + gentamicin	--	--
Highland	Piperacillin-tazobactam ± gentamicin	Piperacillin-tazobactam ± gentamicin	Neutropenic sepsis	--
Lanarkshire	Amoxicillin + aminoglycoside + metronidazole	Piperacillin-tazobactam ± gentamicin	--	--
Lothian	Co-amoxiclav ± gentamicin	Piperacillin-tazobactam ± gentamicin	--	Septicaemia

1.3.1.2. Urinary Tract Infections:

Urinary tract infection (UTI) is an infection located in any part of the urinary tract system. The infection can be in the bladder (cystitis), kidneys (pyelonephritis), ureters or urethra. It is considered the second most common indication for prescribing antimicrobials in primary and secondary care across the UK including Scotland. Urine samples are the single major category of specimens examined in medical microbiology laboratories [134]. UTIs raise a challenge for healthcare practitioners as diagnosis criteria vary based on the patient, the context and the decision of whether to start antimicrobials or not. Several studies showed evidence of practice variation in the initiation of antimicrobials, reading the signs and symptoms, and use of diagnostic tests [135-137].

Geriatric patients are a major diagnosis challenge in UTI; asymptomatic bacteriuria is more common the older the patient is [138]. The prevalence of bacteriuria in geriatric patients may be so high that urine culture is not a valid diagnostic test [139]. Therefore, geriatrics patients frequently receive unindicated antimicrobial treatment for asymptomatic bacteriuria despite clear evidence of increasing the risk of adverse effects with no compensating clinical benefit [140, 141]. Unindicated antimicrobial treatment of asymptomatic bacteriuria is associated with significantly increased risk of adverse events including *Clostridium difficile* infection (CDI) or methicillin-resistant

Staphylococcus aureus (MRSA) infection, and the development of antimicrobial-resistant UTIs [142-144].

In 2012, the Scottish Intercollegiate Guidelines Network (SIGN) published a guideline on the management of suspected bacterial UTI in the adults [145]. Under the guidance, dysuria, the frequency of urination, suprapubic tenderness, urgency, polyuria and haematuria are considered "classical symptoms" of UTI. Classification of UTI falls into three categories; location (cystitis vs pyelonephritis), severity (mild vs severe), and clinical presentation (asymptomatic bacteriuria vs symptomatic bacteriuria). The primary goal of treatment in patients with symptomatic bacteriuria is to relieve the symptoms. Secondary outcomes are minimising adverse effects of treatment and recurrence of symptoms. For asymptomatic patients, the primary goal of treatment is the prevention of future symptomatic episodes. The guideline recommends that bacteriuria alone cannot be an absolute indication for antimicrobial prescribing unless there is conclusive evidence that eradication of bacteriuria results in meaningful health gain at tolerable risk, such as in pregnancy [146].

The treatment plan for a UTI starts with a successful diagnosis and localisation of the site of infection (pyelonephritis vs cystitis). Following a confirmed diagnosis, the treatment plan should be tailored based on the clinical presentation (acute, chronic or recurrent), patient history, allergies, gender, availability of antimicrobial,

tolerance, local guidelines, and regional resistance pattern. The choice of either nitrofurantoin or trimethoprim is widely recommended to treat patients with uncomplicated cystitis in regional and international guidelines [145, 147]. In addition, fosfomycin and pivmecillinam are suggested as an alternative in case of extended-spectrum beta-lactamase (ESBL) *E. coli* [148, 149]. In the case of pyelonephritis, urine culturing is highly recommended, and an initial empirical treatment should be prescribed based on the infection uropathogenic. Fluoroquinolones and β-lactam antimicrobials are the antimicrobial of choice in case of pyelonephritis and hospital admission might be required if the patient is unable to take oral medication or the symptoms persists after antimicrobials initiation >24hrs [145, 147].

The researcher performed a rapid survey on 6 of the 14 geographical NHS Scotland health boards in September 2014 (Table 3). The survey aimed to look into the current local health board's recommendations and different in guidelines compared to SAPG MDRGNB. The survey has suggested that individual health boards have variably differed from the SAPG guidance recommendation, mainly with piperacillin-tazobactam and carbapenem-sparing antimicrobials use. Under UTI recommendation, all six health boards follow SAPG guideline for lower UTI but varied with upper UTI. On the other hand, the inclusion of CSAs in local guidelines for UTI was limited. Fosfomycin was recommended in three health boards, pivmecillinam in two, and only one health board future temocillin for UTI treatment. In chapter 2,

detailed investigation of local health boards' guidelines difference compared to SAPG will be discussed.

Table 3: UTI treatment recommendations from 6 NHS Scotland Health Boards, Sep 2014

NHS Boards	UTI		CSAs mainly against ESBL		
	Lower UTI	Upper UTI	Temocillin (Esp. ESBL)	Pivmecillinam (Esp. ESBL)	Fosfomycin (Esp. ESBL)
SAPG	Trimethoprim or nitrofurantoin	Co-amoxiclav or co-trimoxazole or pivmecillinam or fosfomycin	UTI (not *Pseudomonas* nor *Acinetobacter*)	UTI	UTI
Forth Valley		Amoxicillin + gentamicin OR ciprofloxacin	--	--	Uncomplicated lower ESBL UTI, resistant to all other oral agents
GGC		Trimethoprim OR Co-amoxiclav or Ciprofloxacin	--	--	--
Grampian		Amoxicillin + gentamicin OR ciprofloxacin	--	--	--
Highland		Co-amoxiclav OR ciprofloxacin	--	--	--
Lanarkshire		Amoxicillin + gentamicin OR ciprofloxacin	--	UTI	UTI's caused by multiple resistant E.coli & Klebsiella with proven resistance to all other agents
Lothian		Amoxicillin + gentamicin OR ciprofloxacin	UTI	UTI	UTI

1.3.1.3. Carbapenemase-producing Enterobacteriaceae (CPE):

Escherichia coli and *Klebsiella pneumoniae* pathogens are members of the larger *Enterobacteriaceae* species that are responsible for a wide range of community and hospital-acquired infections. In general, both pathogens were known to be sensitive to beta-lactams for several decades after their clinical introduction. However, resistant rates were gradually increasing and forced prescribers to start to adopt extensive use of carbapenems to treat resultant ESBL pathogens. The resultant rising use of carbapenems has now led to the selection and spread of carbapenemase-producing pathogens. CPE bacteria are not only resistant to almost all beta-lactams, but also to several other antimicrobials such as quinolones, co-trimoxazole, nitrofurantoin, tetracycline and most aminoglycosides. Moreover, CPE's spread rapidly across healthcare systems around the world via clonal dissemination and spread via plasmid transfer both inside and outside healthcare settings. *Klebsiella pneumoniae* carbapenemases (KPC), Oxacillinase-48 (OXA-48) enzymes and their derivatives, and some metallo-beta-lactamases (MBLs) such as New Delhi MBL (NDM), Verona integron-encoded MBLs (VIMs) and IMP are the most important carbapenemases produced by *Enterobacteriaceae* strains [150, 151]. Carbapenemases are β-lactamases with versatile hydrolytic capacities. They have the ability to hydrolyse penicillin, cephalosporin, monobactams, and carbapenems [152].

The 2013 report from the European epidemiological survey of carbapenemase-producing *Enterobacteriaceae* (EuSCACPE) said that a higher 'state of spread' of CPE was observed in 2013 compared with 2010 in more than half of countries participating in this current survey and two previous surveys [153]. The survey included 35 countries where the stage of spread is sporadic in 21 countries (60%), with regional/national spread in 11 countries (31.4%), and three counties with no reported cases (8.6%). Greece, Malta and Italy were reported as an endemic stage. The UK overall data was reported to be increasing from 'sporadic hospital outbreaks' in 2010 to 'regional spread' in 2012 and 2013. However, Scotland continued to report a 'sporadic' spread.

The choice of treatment against CPE majorly depends largely upon the result of susceptibility tests and site of the infection. Colistin, tigecycline and fosfomycin are the three most used last resort antimicrobial to treat CPE. Colistin in-vitro susceptibility among CPE isolate varies worldwide between 80-100%. However, resistance can be very high due to the clonal spread of resistant strains. Colistin use might be limited due to the dosing and toxicity profile associated with clinical therapy [154]. Fosfomycin inhibits cell wall biosynthesis with in vitro activity against ESBL including KPC [155]. A study tested fosfomycin activity against 68 KPC-producing *K. pneumoniae* isolates, in which 23 isolates were non-susceptible to tigecycline and/or colistin. The result of susceptibility rates were 93% for the overall group, 87% for the

group non-susceptible to tigecycline and/or colistin, and 83% (five out of six isolates) for the exceptionally resistant (i.e. resistant to both tigecycline and colistin) subgroup [156]. Nevertheless, using fosfomycin as a last resort for CPE infection treatment raise the potential for emergence of resistance during therapy [157].

Tigecycline is a glycylcycline which works as a bacteriostatic agent that has a good activity profile in vitro. In 2010, an alert by the US Food and Drug Administration (FDA) [158] encouraged the use of alternative antimicrobials to tigecycline in severe infections. This alert was issued due to a pooled analysis of data from comparative trials for different indications, which showed increased overall mortality with tigecycline treatment. However, a recent large prospective non-interventional study which enrolled 1025 patients, mainly with complicated intra-abdominal infections or complicated skin and soft tissue infections, showed that no excess mortality associated with tigecycline administration. The study also showed clinical success rates in severely ill patients group with a high prevalence of MDR pathogens, reporting even a proper safety and tolerability profile [159].

Since the SAPG MDRGNB guidance targeted piperacillin-tazobactam and carbapenems use and recommended alternatives to their use, the following sections will be a discussion about these agents to provide an overview on their clinical role and importance.

1.3.2. Piperacillin-tazobactam:

Piperacillin-tazobactam is an intravenous antimicrobial classified as an antipseudomonal penicillin in the British National Formulary (BNF). It consists of an 8:1 weight ratio of piperacillin to tazobactam [160]. In 1993, piperacillin-tazobactam was approved by the US FDA for the treatment of severe infections under the trade name of Zosyn® manufactured by Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA (Tazocin® in the UK). Piperacillin is a semisynthetic β-lactam with bactericidal activity achieved by inhibiting septum formation and cell wall synthesis in susceptible bacteria. Tazobactam is a β-lactamase inhibitor derived from the penicillin nucleus which protects piperacillin against Richmond and Sykes class III penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV penicillinases [161, 162].

Piperacillin-tazobactam has broad-spectrum activity against Gram-positive, -negative and anaerobic bacteria. It is active against Gram-positive *Staphylococcus aureus* (methicillin-susceptible isolates only) and *Bacteroides fragilis* group (*B. fragilis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus*) from Gram-negative anaerobic bacteria class. Piperacillin-tazobactam is mostly used for Gram-negative coverage where it is active against *Acinetobacter baumannii, Escherichia coli,*

Haemophilus influenzae (excluding β-lactamase negative, ampicillin-resistant isolates), *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [163, 164].

In the UK [160], piperacillin-tazobactam is licensed to be used for the following indications:

- Hospital-acquired pneumonia (late-onset infection; >5days after admission)
- Severe sepsis “septicaemia” (community or hospital-acquired)
- Complicated intra-abdominal infections (peritonitis)
- Complicated UTI or skin and soft tissues
- Neutropenic sepsis

The recommended dose for piperacillin-tazobactam is 4.5 g every 8 hours IV, increased to 4.5 g every 6 hours in severe case infections and neutropenic sepsis.

Piperacillin-tazobactam is contraindicated in cases of hypersensitivity to any penicillin, cephalosporin, or β-lactamase inhibitors. An anaphylactic reaction is a common adverse event (1-10%) associated with piperacillin-tazobactam use [160]. In addition, the GI tract may experience some disturbance which presents as nausea, vomiting, or diarrhoea. Haematological side effects have been reported such as haemolytic anaemia, leucopoenia, and thrombocytopenia associated with piperacillin-tazobactam use [160]. However, one of the important adverse events

when using piperacillin-tazobactam is the increased risk of *Clostridium difficile* associated diarrhoea and colitis [165].

In Scotland, the report, 'Antimicrobial Use and Resistance in Humans' stated that there was an increase in the consumption of piperacillin-tazobactam by 9.2% in 2012 accounted for 1.9% of total antimicrobial use in Scotland [60]. The report suggested that this increase might be due to restricting broad-spectrum antimicrobials, the '4Cs' (Cephalosporin, co-amoxiclav, clindamycin and fluoroquinolones) associated with *Clostridium difficile* infection (CDI) initiative. Table 4 shows the rise of piperacillin-tazobactam use and the resistant rates for the most targeted pathogen over the period from 2009 to 2012.

Table 4: Piperacillin-tazobactam use and the resistant rates for the most targeted pathogen, 2009-2012 [60]

	2009	2010	2011	2012
	%R (n)	%R (n)	%R (n)	%R (n)
E. Coli	2.9(2169)	7.5(2159)	7.6(2668)	6.2(3109)
K. pneumonia	3.8(426)	7.4(460)	7.9(453)	5.3(617)
P. aeruginosa	9.8(183)	6.6(198)	1.6(190)	5.6(179)
A. baumannii	17.8(45)	19(21)	40(25)	0(17)
Use	4.7%	5.9%	6.5%	7.1%

n: Number of samples

1.3.3. Carbapenems:

The carbapenems are beta-lactam antimicrobials with broad-spectrum activity that includes many Gram-positive, Gram-negative, and anaerobes. Carbapenems inhibit bacterial cell wall synthesis by binding to the penicillin-binding proteins and interfering with cell wall synthesis. They are extremely resistant to beta-lactamase enzymes, giving them a precious advantage in treating bacterial infections where beta-lactamases are expressed that makes other beta-lactam antimicrobials ineffective [166]. Thienamycin was the first carbapenem discovered in *Streptomyces cattleya* in 1976. However, it was not used in clinical practice due to its chemical instability in aqueous solutions and difficulty of chemical synthesis [166, 167]. In 1985, imipenem was the first carbapenem member licenced to be used in clinical practice under the trade name of Primaxin®, Merck & Co., Inc., Rahway, NJ. All clinically available carbapenems have low oral bioavailability and must be administered intravenously or intramuscularly. They are eliminated by renal excretion [166].

In the UK, there are three licensed carbapenems; imipenem, meropenem, and ertapenem. All three antimicrobials have a broad spectrum of antimicrobial activity which exceeds that of most other antimicrobial classes. However, carbapenems lack

activity against *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Stenotrophomonas maltophilia.* Both imipenem and meropenem have excellent activity against *Pseudomonas aeruginosa, but ertapenem lacks anti-pseudomonal activity.* Ertapenem has a longer half-life (4hrs) compared to imipenem and meropenem (1hr) making it suitable for once daily administration [160].

Imipenem and meropenem are approved for the treatment of severe HAIs and multi-microbial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary tract infections. Ertapenem is licensed for treating abdominal, gynaecological infections, community-acquired pneumonia, and foot infections of the skin and soft tissue in patients with diabetes [160].

Carbapenems are contraindicated if the patient has any hypersensitivity to any penicillin, cephalosporin, or β-lactamase inhibitor. Neurotoxicity has been observed at high doses, in severe renal failure, or in patients with CNS disease. Meropenem has less seizure-inducing potential. Thus it is recommended to be used to treat central nervous system infection such as meningitis. In addition, the use of carbapenems can alter the intestinal microflora and lead to CDI [160].

In Scotland, the report 'Antimicrobial Use and Resistance in Humans' states that there was an increase in the use of carbapenems by 9.1% in 2012 accounted for 1.3% of total antimicrobial use in Scotland [60]. Meropenem was the most common carbapenem in use across Scotland accounting for 95.3% of total carbapenem consumption. The 'Antimicrobial Use and Resistance' report suggests that this increase might be due to restricting broad-spectrum antimicrobial associated with CDI initiative. Table 5 shows the rise in carbapenems use and the resistant rates for the most targeted pathogen over the period from 2009 to 2012.

Table 5: Carbapenems use and the resistant rates for the most targeted pathogen, 2009-2012 [60]

	2009	2010	2011	2012
	%R (n)	%R (n)	%R (n)	%R (n)
E. Coli	0.0(2523)	0.0(2845)	0.1(3319)	0.0(3554)
K. pneumonia	0.0(506)	1.0(572)	0.3(597)	0.2(625)
P. aeruginosa	4.7(192)	3.6(249)	4.3(211)	3.7(191)
A. baumannii	0.0(45)	4.2(24)	4.3(23)	5.3(19)
Use	3.9%	4.0%	4.4%	9.1%

n: Number of samples

1.3.4. Carbapenem-sparing antimicrobials (CSA's):

In the SAPG MDRGNB guideline, four infrequently used antimicrobials (aztreonam, temocillin, pivmecillinam, and fosfomycin) were recommended as a substitute for carbapenems and piperacillin-tazobactam for specific indications. Each one has particular indications, dosing, side effects and cautions.

1.3.4.1. Aztreonam

Aztreonam (Azactam®, Bristol-Myers Squibb limited) is a synthetic bactericidal monobactam licensed in 1986 for Gram-negative aerobic infections. Aztreonam works by inhibiting bacterial wall synthesis and has no activity against Gram-positive bacteria. The spectrum of activity includes *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis* [168].

In SAPG MDRGNB guideline, aztreonam is recommended as an alternative to carbapenems and piperacillin-tazobactam in the following:

1- Empirical IV treatment of sepsis; patients with renal impairment and beta-lactam allergic patients. However, consider additional Gram-positive and anaerobic cover since aztreonam works only on Gram-negative bacteria.
2- Direct treatment of Gram-negative sepsis; bacteraemia, urosepsis, pneumonia, and intra-abdominal sepsis.
3- UTI; direct therapy of urosepsis if ESBL infection is excluded.

1.3.4.2. Temocillin

Temocillin (Negaban®, Eumedica pharmaceuticals) is classified under Penicillinase-resistant penicillins first discovered in 1982 [169]. It is active against Gram-negative bacteria and is stable against a wide range of beta-lactamase producing pathogen. However, temocillin lacks activity against *Pseudomonas aeruginosa* and *Acinetobacter* species [160]. The use of temocillin is largely targeted in the treatment of UTI and urosepsis due to its stability against ESBLs [170, 171].

In the SAPG MDRGNB guideline, temocillin is recommended as an alternative to carbapenems and piperacillin-tazobactam in the following:

1- UTI; direct therapy of urosepsis where *Pseudomonas and Acinetobacter* are not suspected.
2- Direct treatment of Gram-negative (especially ESBLs) sepsis; severe sepsis, urosepsis, and pneumonia.

1.3.4.3. Pivmecillinam

Pivmecillinam (Selexide®, LEO pharmaceuticals) is classified under mecillinam penicillins which were first discovered in the 1970s. It is mainly active against Gram-

negatives including *E. coli*, *Klebsiella*, and *Enterobacter* but is not active against *Pseudomonas aeruginosa* or *enterococci*. Pivmecillinam is a prodrug which is hydrolysed to a mecillinam. A significant advantage of pivmecillinam is its bioavailability by the oral route which facilitates its use as a step-down therapy for ESBL UTI [172, 173].

In the SAPG MDRGNB guideline, pivmecillinam is recommended as an alternative to carbapenems and piperacillin-tazobactam. The recommendation mainly relates to the treatment of UTIs as an initial direct therapy or as a step-down agent for patients receiving anti-Gram-negative intravenous treatment.

1.3.4.4. Fosfomycin

Fosfomycin (Fomicyt® IV, Nordic Group) is a phosphonic acid antimicrobial first discovered in 1969 [174]. It is active against Gram-positive and Gram-negatives including *Staphylococcus aureus* and *Enterobacteriaceae*. In the UK, only the IV form of fosfomycin is licensed for the treatment of acute osteomyelitis, complicated urinary tract infections, hospital-acquired lower respiratory tract infections, and bacterial meningitis only when first-line therapies are inappropriate or ineffective. An oral presentation (granules) of fosfomycin is not marketed in the UK. However, it can be requested as an unlicensed medicine. The oral form can be used on the advice of a microbiologist for the treatment of uncomplicated lower UTI caused by multiple-

antibacterial resistant organisms when other antibacterials cannot be used [148, 160].

In the SAPG MDRGNB guideline, fosfomycin oral is recommended as an alternative to carbapenems and piperacillin-tazobactam. The recommendation mainly relates to its use in UTIs as initial direct therapy or as a step-down agent for patients receiving anti-Gram-negative intravenous therapy. In addition, fosfomycin can be a choice in case of CPE infections [175].

1.4. Introduction to the thesis:

The author of this research was working as a clinical pharmacist, ITU, at King Fahad Medical City, Riyadh, Saudi Arabia, for six years. He had a high level of awareness about the importance of the subject as it is a global concern in all realms of healthcare. At the beginning of this research, the author joined in several regular meetings with SAPG members, discussed the topic on one to one basis, and visited multiple hospitals prior to conducting the study. The study then was proposed officially, a brief documentation and protocol were written (Appendix 1 and 2). These were shared with selected members of SAPG and faculties of Strathclyde University for their opinions and support. The proposed project was widely accepted and appreciated by both sides. The SAPG chairperson, Dr Dilip Nathwani, gave full support

of his team and announced the project at SAPG meeting. Following that, a group of experts formed a 'Carbapenems project steering group' to facilitate and authenticate the work.

Although the SAPG MDRGNB guidance was introduced in 2013, there have not been any formal evaluation of its effectiveness and impact on healthcare. Furthermore, consumption data were still showing incline in use of carbapenem and piperacillin-tazobactam. Different implementation methods may influence the use of the specific guideline. The guideline did not discuss the method of implementation and adaptation, which can affect the aim of it.

It is proposed that this study should focus on how individual health boards adopted and implemented the guidance. A second study, conducting a PPS of carbapenem and piperacillin-tazobactam use across NHS Scotland to test how practitioners are using them and how this adheres to local and national MDRGNB guideline was then enacted. Furthermore, a third in-depth case study in selected health boards to explore improvement strategies to support the best use of carbapenems and piperacillin-tazobactam was conducted.

1.4.1. Aim

To examine carbapenem and piperacillin-tazobactam antimicrobials use in NHS Scotland to inform future improvement strategies to promote safe and effective use of this group of antimicrobials

1.4.2. Research questions

1. How are carbapenem antimicrobials being used in NHS Scotland?
2. How are piperacillin-tazobactam being used in NHS Scotland?
3. What are the levers and barriers to the introduction of complex guidelines (MDRGNB) within health boards in NHS Scotland?

1.4.3. Objectives

1. To execute a national survey to establish the extent to which the MDRGNB guideline has been adopted in individual health board therapeutic guidelines and describe and evaluate local implementation strategies within NHS Scotland.
2. To conduct a national point prevalence study using the British Surveillance of Antimicrobial Consumption BSAC-PPS tool to determine the appropriateness of carbapenems and piperacillin-tazobactam use.

3. To perform in-depth qualitative interviews in selected health boards to understand the levers and barriers to guideline adoption and support for frontline clinicians to deliver safe and effective use of carbapenems and piperacillin-tazobactam.

1.4.4. Ethical approval

NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK, is not required as the project will be a part of service evaluation. University ethical approval was also unnecessary because the University of Strathclyde Code of Practice on Investigations Involving Human Beings does not apply to studies of routine practices in professional contexts, service evaluations conducted solely to define or assess a particular service provided or audits of existing services. However, in line with best ethical practice, data was recorded on electronic form with no patient identifiable information, entered and submitted by the lead investigator to the primary research group for analysis [176, 177].

Chapter Two:

Implementation and Adaptation of SAPG MDRGNB Guidance within NHS Scotland Health Boards

2.1. Introduction:

2.1.1. Background

By the second half of 2014, SAPG MDRGNB guidance was fully distributed to local NHS health boards vie AMT's. However, the guidance lacked any feedback or follow-up mechanism to inform SAPG on what should happened next. In fact, following on the survey of six local health boards' guideline, section 1.2., we identified variation in recommendations and different interpretation of the SAPG MDRGNB guidance. Consumption trend of carbapenem and piperacillin-tazobactam was broadly similar with low adaptation and use of CSA's agents (aztreonam, temocillin, pivmecillinam, and fosfomycin). Furthermore, the consumption of targeted antimicrobials was, overall, the same; incline trend of carbapenem and piperacillin-tazobactam use and low consumption of alternatives. As a consequence SAPG was in-need of official baseline evidence on how each health board implemented and adopted the MDRGNB guidance, and detailed information about current practice and policies within individual health boards. This chapter describes how this baseline information was captured and analysed.

2.1.2. Good practice guidance:

To commence this part, we should discuss that there are two terms used that needs to be clarified, “guidance” and “guideline”. Guidance initiatives are considered the seed or starting point of guideline development. They are the act or process of guiding, advising or counselling an individual, group or organisation with the objective of resolving a problem. In contrast, guidelines, which are more common, provide direction to appropriate action or behaviour to be followed [178]. Clinically, practice guidance delivers recommendations for healthcare providers who are involved in governing, regulating, prescribing and commissioning medicines, and those involved in decision-making about medicines. The development of guidance content is performed according to the best available evidence at that time juncture. The guidance should aim to be detailed, useful and suitable to the target audience, with importance on the implications for national, or local, practice emphasised [179].

The use of both terms, guidance and guideline, are overlapping in practice and literature [179, 180]. However, the “guideline” terminology is much popular and extensively used in practice [180, 181]. Guidance is considered as a prior step to guidelines and used internally within departments and organisations.

NICE has published several documents related to guidance writing and integration which can be used to evaluate current SAPG MDRGNB guidance [179]. Based on a NICE publication titled: Good Practice Guidance [179], there are six key activates that the designing team should apply in the production of guidance:

1- Topic selection, relevance and essential to the target audience.
2- Relevant evidence identification and selection stage, using a range of sources.
3- Summary of evidence.
4- Critically reviewing the strength and weakness of the evidence.
5- Combining evidence in the context of guidance.
6- Using selected evidence to formulate recommendations and validated them.

Although SAPG guidance [61] did not explicitly mention if they followed the framework of the NICE publication [2] or not; by examining the guidance and discussing it with members who were part of the writing team (Appendix#3), we can disclose that all of the six key activities mentioned by the NICE publication [2] are covered in the SAPG guidance. In addition to the six key activities that the NICE publication suggested, they recommend a general framework that well-written guidance should have. That framework should include the following: title, date and version, recommendations, introduction, context, legislation and regulatory aspects, methodology, and evidence. The SAPG MDRGNB guidance covers the framework

recommendation from the NICE publication, which assures that the guidance was well written and practical for the purpose of guidance writing.

The current MDRGNB SAPG guidance consisted of eight sections:

1- The aim of the guidance
2- Why is reducing MDRGNB important?
3- National and international guidance available
4- Antimicrobial therapy for treatment of suspected and confirmed Gram-negative infections
5- Advice on antimicrobial treatment review
6- Monographs for suggested alternatives
7- Microbiology laboratory practical advice
8- Advice on surveillance of antimicrobial use and resistance

The SAPG guidance, however, lacked information about implementation and adoption of the document. Also, the guidance did not state a precise feedback mechanism on how local health boards acts towered adaptation and integration of this document into local policies.

2.1.3. Local health boards guidelines:

In Scotland, there are 14 regional NHS health boards which are liable for the protection and the improvement of the country's health and the provision of frontline healthcare services [182]. In addition to the 14 NHS health boards, there is one national hospital, Golden Jubilee National Hospital, providing mainly surgical services. At the time of this research (2014 – 2017), each health board had established their own AMT with a representative member attending all SAPG meetings. Most of the health boards had their local policies and prescribing guidelines based on available resources, needs, and stakeholder's decisions. However, in some small health boards, policies were typically adopted from other, larger, well-established health board guidelines.

There are well-known criteria to apply to achieve a successful guideline. Indeed, there are currently tools to test guideline success from synthesis to implementation to updates. The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument is one of the tools used to assesses the variability in guidelines quality. Six domains AGREE tests, scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence [183]. However, having different guidelines for each individual health board makes the interpretation and comparison of health board performances incomparable since different methods were used to write, implement, and follow-up were applied.

One of the significant issues with guidelines are implementation barriers, which can be internal to the guideline itself or external barriers related to the clinical and local environments. The Scottish Intercollegiate Guidelines Network (SIGN) 50: A guideline developer's handbook discussed implementation barriers and areas to focus on to overcome these barriers [184]. Internal barriers can be resolved by applying the highly respected methodology in developing the guideline and using clear definition, language and format. Further, appropriate guideline presentation, focusing on targeted audience, will help to overcome internal barriers.

To overcome external barriers, SIGN addresses specific implementation strategies consisting of elements from the following four domains:

1- Improving process; robust dissemination process and interactive website
2- Awareness raising and education; activities and training modules linked to Continuous Professional Development (CPD)
3- Networking; professional network and existing projects
4- Implementation support resources; algorithms and care pathways, tools, audits, electronic decision support tools, and documentation templates

Different implementation methods may influence the use of the specific guideline and the utilisation of carbapenems and piperacillin-tazobactam. The SAPG MDRGNB guidance did not suggest a method of implementation or adoption, which can affect the aim and ultimate success of the guideline. It is proposed that this part of the study focus on collecting baseline information on the current local policies of carbapenems, piperacillin-tazobactam, and CSAs prescribing and how individual health boards adopted and implemented the guidance. In addition, to further look into areas that might cause variation between health boards in consumption data of targeted antimicrobials.

2.2. Method:

All fifteen health boards of NHS Scotland were invited to participate in this study. The aim and objectives of the current research were announced and introduced during periodic SAPG meetings; most health boards have a representative attending. The study was supported by former SAPG chairman, Dr Dilip Nathwani, and progress updates were included into SAPG regular meetings agenda. The research brief (Appendix#1) and the study protocol (Appendix#2) were sent to all participant prior to the survey.

2.2.1. Aim

To examine SAPG MDRGNB guidance implementation and adaptation across NHS Scotland and investigate variance in strategies toward such guidance.

2.2.2. Research question

A) What are the current policies, education, monitoring, and alternatives are available in local health boards?
B) How have individual health board adopted and implemented the SAPG MDRGNB guidance?
C) Are there any difference in laboratory reporting toward targeted agents?

2.2.3. Objectives

To execute a national survey (Appendix #4) to establish the extent to which the MDRGNB guideline has been adopted in individual health board therapeutic guidelines and describe and evaluate local implementation strategies within NHS Scotland.

2.2.4. Subjects

Antimicrobial management teams (AMTs) from the participating health board for the national survey.

2.2.5. Setting

The national survey took place in May 2015 over a 2-week period. The target is to involve all geographical health boards, where a full guideline was established and implemented.

2.2.6. Inclusion criteria

All NHS Scotland health boards were included in the study.

2.2.7. Ethical approval

NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK, was not required as the project was part of service

evaluation. University ethical approval was also unnecessary because the University of Strathclyde Code of Practice on Investigations Involving Human Beings does not apply to studies of routine practices in professional contexts, service evaluations conducted solely to define or assess a particular service provided or audits of existing services. However, in line with best ethical practice, data was recorded on an electronic form with no personally identifiable information, and entered and submitted by the lead investigator to the primary research group for analysis [176, 177].

2.2.8. Design

Due to the complexity of the proposed research, a team of experts, a "Steering group", was formed in early January 2015, which includes members from academia, clinical practitioners, and a data analysis specialist. A self-assessment survey was the method of choice to fulfil the aim of this study. Because the study aim to be an explanation and rooted in positive epistemology, the survey methodology is rational to be adopted [185]. The steering group were involved in the synthesis, format, revision, and analysis of data in every step.

2.2.8.1. Survey design

The primary researcher (AM) initially designed the survey on paper, discuss it with the steering group, and the final version was uploaded on to the Survey Monkey© online tool [186]. The survey consisted of 49 questions, tested and was validated by two members, before an electronic link was sent to 15 AMT leaders via email to request that they input data relating to their health board. The AMT leader at targeted health board was allowed two weeks to fulfil input. Questions were structured to allow them to be answered from a drop list, by multiple choice and by population of a free text box. Some questions were asked with a YES/NO response option which depending upon the answer, led to additional questions being populated in the online form.

2.2.9. Data analysis

The number of responses to each question were presented, and frequency of answers will calculated to individual questions. Data analysis and graphs were performed using Microsoft Excel 2010®. In feedback and free text questions, detailed review to individual responses were presented in the results and discussion. Furthermore, data was summarised and presented in an infographic result sheet, where each health board could identify where they compared to other boards on a national basis.

2.3. Results:

Fifteen AMT leaders responded which represented all 15 health boards in NHS Scotland, including the Golden Jubilee National Hospital. All respondents completed the survey during the designated time allowed with no negative issues raised or difficulties.

2.3.1. General questions:

1) **Which health board do you work in?**

Results were obtained from all 14 regional health boards in NHS Scotland and the Golden Jubilee National Hospital.

2) **Before SAPG MDRGNB guidance was available were measures used in your health board to control carbapenems and piperacillin-tazobactam use?**

Thirteen out of fifteen health boards (87%) indicated that measures were used to control the use of carbapenem and piperacillin-tazobactam before SAPG MDRGNB guidance were available. NHS Orkney and NHS Shetland did not use any measures.

3) What were the actions taken by your health board in response to SAPG MDRGNB guidance?

Several different actions were taken in response to SAPG MDRGNB guidance, although no health board used SAPG guidance to produce a local version of MDRGNB guidelines or adopted the SAPG MDRGNB guidance recommendations in their entirety. Fourteen of the fifteen health boards (93%) either updated local clinical guidelines based on the SAPG MDRGNB guidance recommendations or reviewed local clinical guidelines and found them to be in line with SAPG MDRGNB guidance recommendations (Figure 2.1).

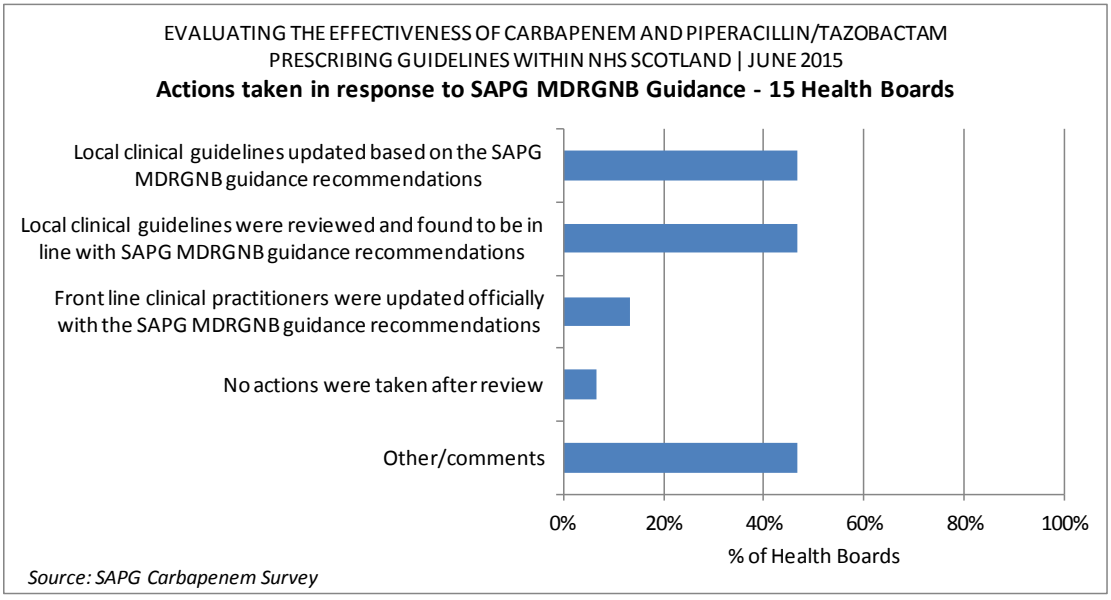


Figure 2.1: Actions taken in response to SAPG MDRGNB guidance - 15 health boards

Several comments were received for this question in the free text box made available. Only NHS Shetland had not taken actions following the release of the guidance, and the free text comment explained why: NHS Shetland AMT was not active at this time and therefore no specific updates were made. However piperacillin-tazobactam and meropenem were already restricted to consultant use only, and no other carbapenems were stocked, so pharmacists were always involved in ensuring requests were appropriate before sourcing.

4) **How were the clinical practitioners informed about SAPG MDRGNB guidance?**

Most health boards (9 out of 15; 60%) informed clinical practitioners about the guidance directly via medical rounds or personal communication with staff. Electronic measures such as emails were used in 6 out of 15 (40%) and hard copies of the guidance were used in 3 out of 15 (20 %). Note that, some health boards adopted multiple approaches.

5) **How training on carbapenems and piperacillin-tazobactam prescribing is is delivered in your health board?**

Twelve out of fifteen health boards (80%) integrated training on carbapenems and piperacillin-tazobactam prescribing into routine training, induction courses and CPD sessions. NHS Highland, noted that piperacillin-tazobactam was not specifically

identified in training. The three (20%) remaining health boards (NHS Orkney, NHS Shetland and NHS Borders) deliver no specific training.

6) **Which of the following staff groups were targeted for this training in your health board?**

Eleven out of fifteen health boards (73%) target FY1-FY2 staff for training on carbapenems and piperacillin-tazobactam prescribing. Pharmacists (67%) and ST/CT (60%) are the next most commonly targeted groups in health boards. Consultants were targeted in 7 (47%) and nurses in 4 (27%) of health boards. No specific training was delivered by NHS Orkney, NHS Shetland and NHS Borders (Figure 2.2).

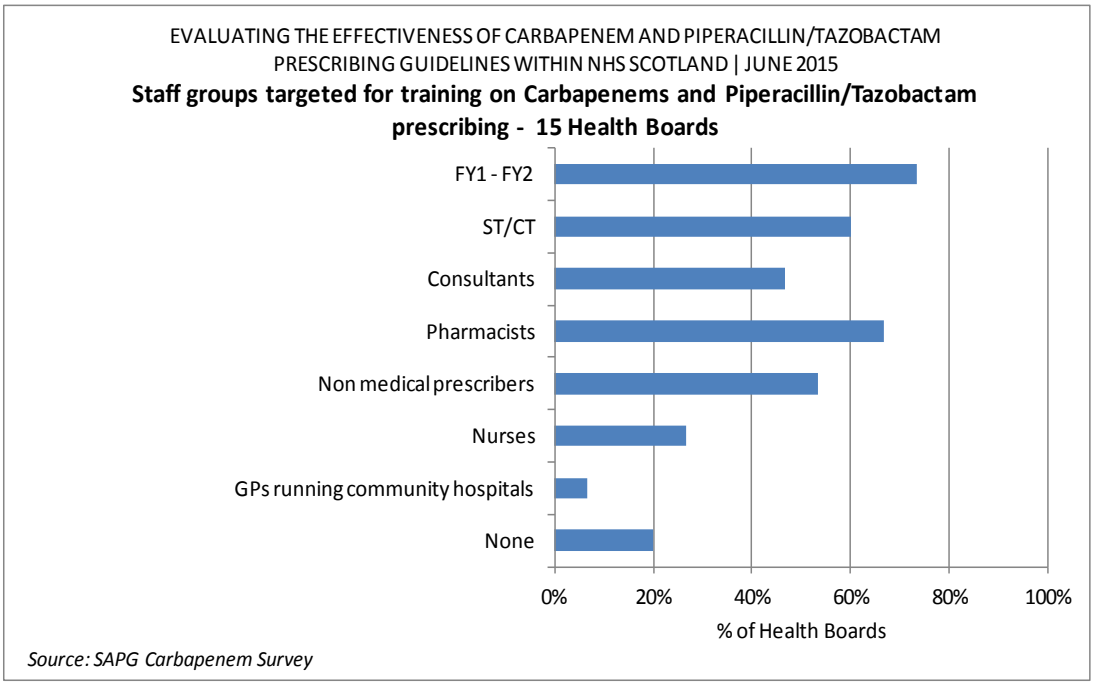


Figure 2.2: Staff groups targeted for training on Carbapenems and Piperacillin-tazobactam prescribing - 15 health boards

7) **Does your health board monitor the consumption of carbapenems and piperacillin-tazobactam?**

Thirteen out of fifteen (87%) health boards monitor the consumption of Carbapenems and Piperacillin-tazobactam. NHS Orkney and NHS Fife did not monitor their consumption.

8) **How frequently do you produce reports on consumption data?**

Of the 13 health boards which monitor consumption of carbapenems and piperacillin-tazobactam, 11 (85%) produced reports every quarter. NHS Highland produced reports every six months and NHS Dumfries & Galloway produced reports annually.

9) **Who are these reports shared with?**

Of the 13 health boards which produce reports on consumption of carbapenems and piperacillin-tazobactam, all 13 (100%) share the reports with the Antimicrobial Management Teams (AMTs). Reports are also shared with 10 out of 13 (77%) Infection Prevention & Control Committees and 8 out of 13 (62%) Area Drug and Therapeutic Committees (ADTCs). The 'others' group is made up of 'consultants' and 'publication on the intranet'. (Figure 2.3).

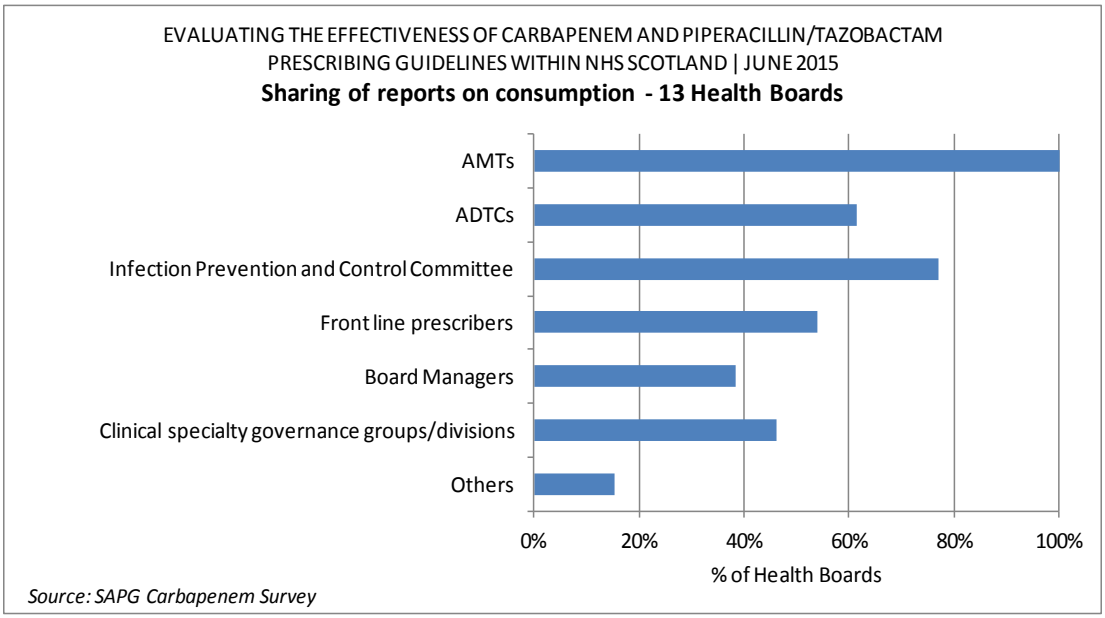


Figure 2.3: Sharing of reports on consumption - 13 health boards

2.3.2. Carbapenems questions:

2.3.2.1. Meropenem

10) Is meropenem formulary approved for use in your health board?

Meropenem is formulary approved for use in all 15 health boards.

11) Who can prescribe meropenem in your health board?

Meropenem can be prescribed by several of the staff groups for most health boards. However, seven (46.6%) health boards commented that there is also the requirement for microbiology advice or there are restrictions as per the alert policy (Figure 2.4).

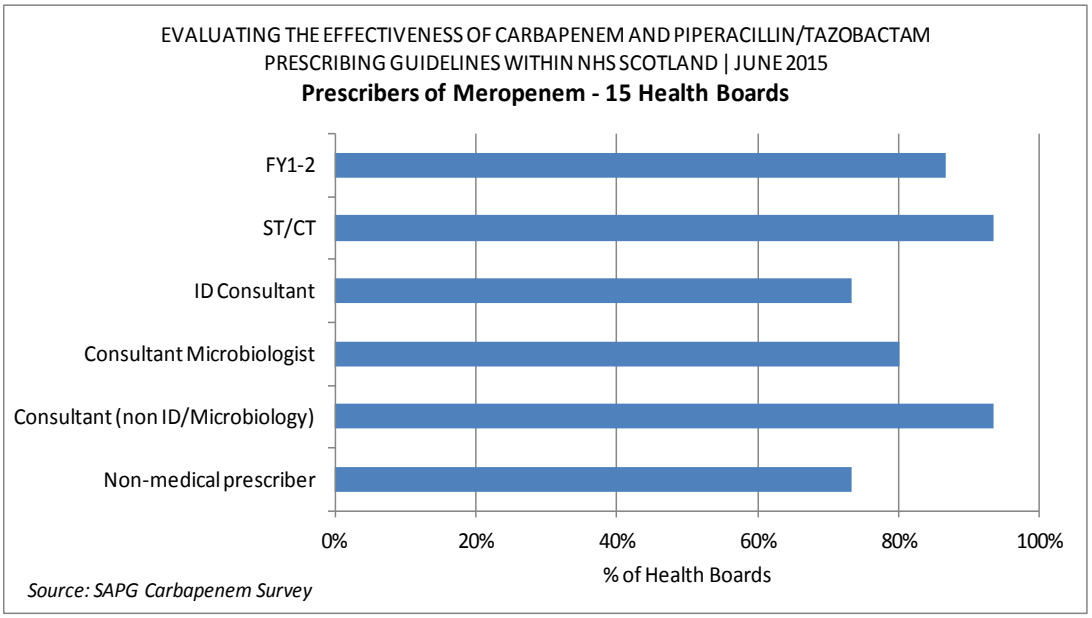


Figure 2.4: Meropenem prescribing - 15 health boards

12) Is meropenem subject to prescribing restrictions in your health board?

Meropenem is subject to prescribing restrictions in 13 out of 15 health boards (87%). NHS Orkney and NHS Borders do not have meropenem prescribing restrictions.

13) Who can authorise meropenem prescribing?

Microbiologist Consultants can authorise meropenem in all 13 health boards that apply prescribing restrictions. Authorisation can be granted by an Infectious Disease (ID) Consultant in 10 out of 13 (77%) boards (Figure 2.5).

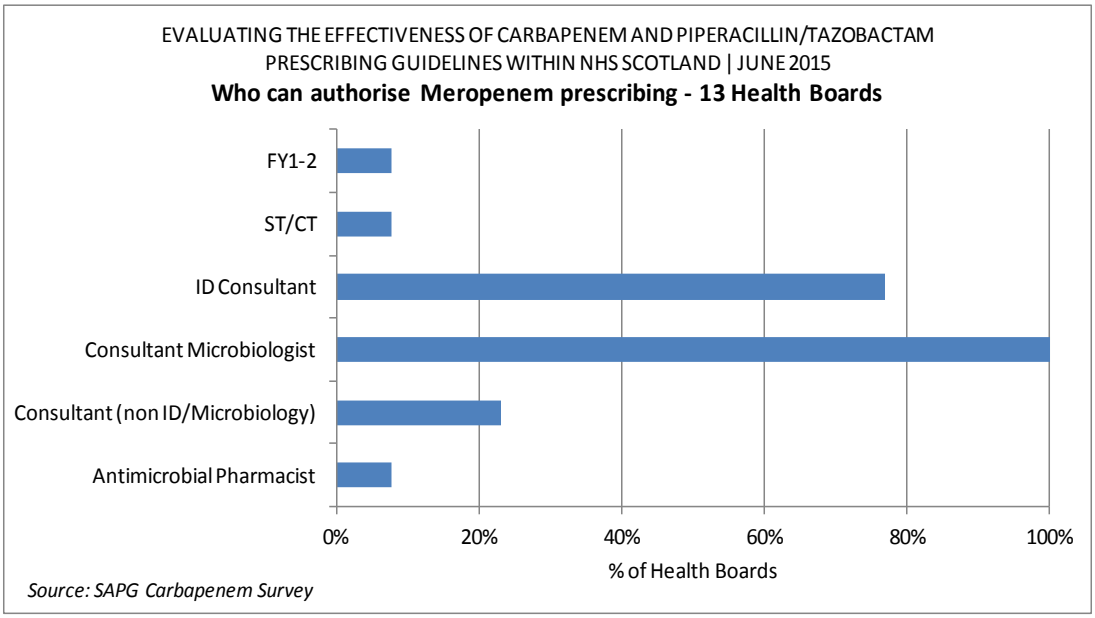


Figure 2.5: Meropenem authorisation - 13 health boards

14) What are the mechanisms for meropenem prescribing authorisation?

Twelve of the thirteen health boards (92%) have an alert policy for meropenem prescribing authorisation. Five of these health boards also have over the phone authorisation. The remaining health board, NHS Ayrshire and Arran, has no formal mechanism, but however undertakes 'continuous monitoring of prescribing feedback into multi-disciplinary ward rounds'. None of the health boards applies the requirement of a senior countersign measure.

15) Which of the following statements applies to meropenem access in your health board?

In 10 out of 15 health boards (67%), meropenem is available for the first 24 hours via an emergency stock cupboard. Meropenem can be obtained from another ward which holds it as stock in 9 out of 15 health bboards (60%). Only two health boards are not covered by these two methods of access and meropenem is freely available for use according to local guidelines or sensitivity tests (Figure 2.6).

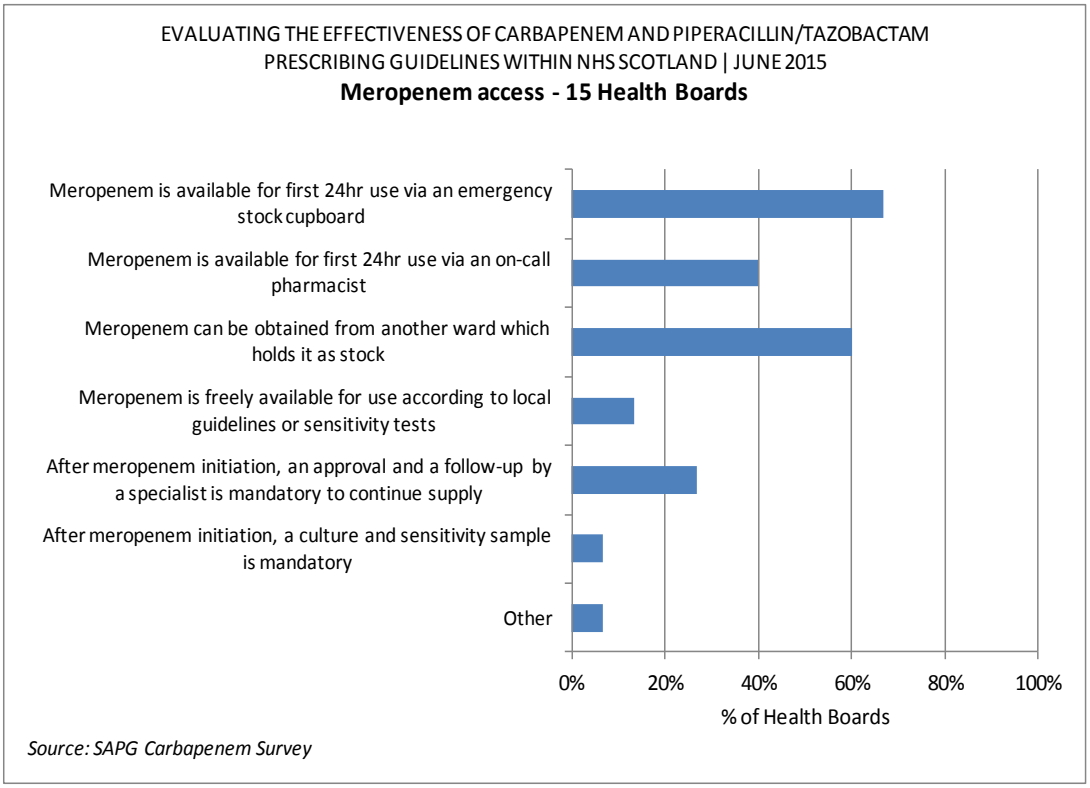


Figure 2.6: Meropenem access - 15 health boards

16) **In which of the following indications is meropenem used in your health board?**

Meropenem is used for '2nd line febrile neutropenia' in 12 out of 15 (80%) health boards Several health boards commented that meropenem is not in empirical guidelines out with 2nd line use in febrile neutropenia. Severe sepsis unresponsive to piperacillin-tazobactam is a common indication in 8 out of 15 (53%) health boards. Figure 2.7 shows most common indications.

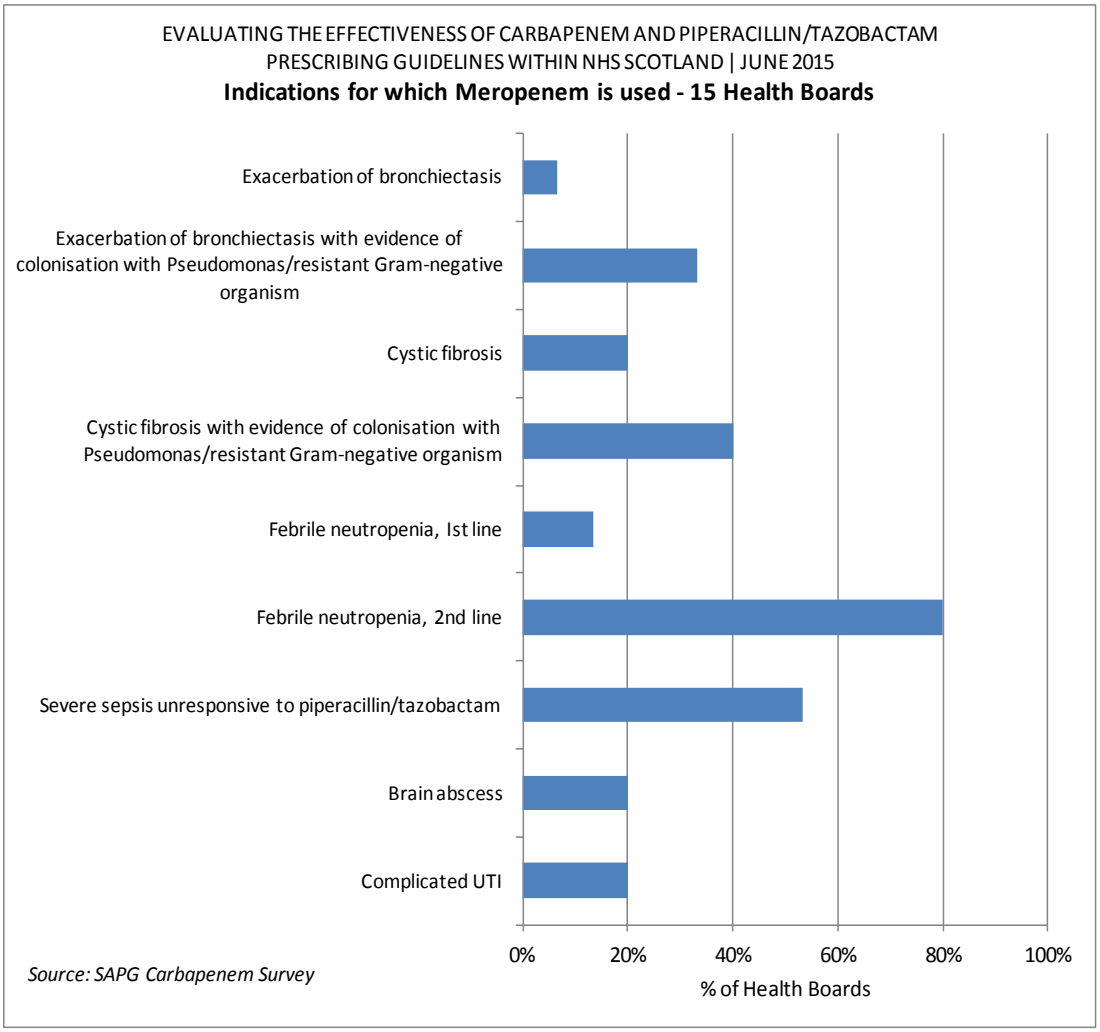


Figure 2.7: Indications for which meropenem is used - 15 health boards

17) Is meropenem sensitivity routinely tested in your laboratory?

Meropenem sensitivity is routinely tested in labs in all 15 health boards (100%).

18) Is meropenem routinely suppressed in your laboratory?

Meropenem is routinely suppressed (including available on request) in 13 out of 15 (87%) labs. It is not routinely suppressed in the labs of NHS Lothian and NHS Tayside. Figure 2.8.

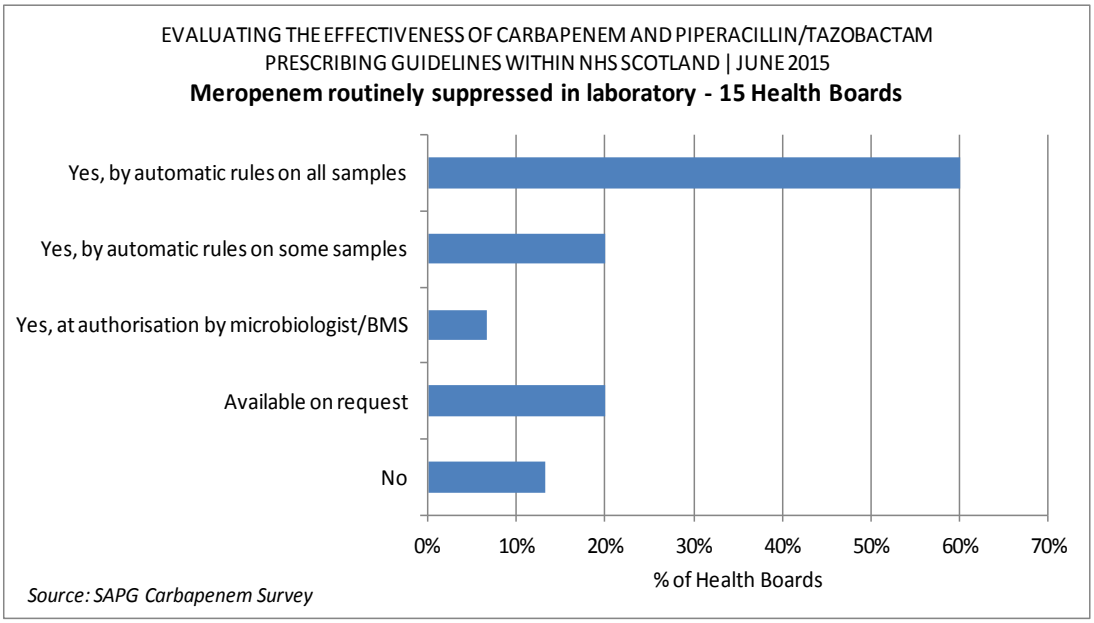


Figure 2.8: Meropenem routinely suppressed in laboratory - 15 health boards

2.3.2.2. Imipenem

19) Is imipenem used in your health board?

Imipenem is used in 3 out of 15 (20%) health boards; NHS Grampian, NHS Lanarkshire and NHS Lothian.

20) Is imipenem subject to prescribing restrictions in your health board and

21) Is imipenem sensitivity tested in your laboratory?

Out of the three health boards where it is used, imipenem is subject to prescribing restrictions in 2 (67%) of these. Imipenem sensitivity is routinely tested in 2 out of 3 (67%) labs and is tested on request in 1 out of 3 (33%) labs.

22) In which of the following indications is imipenem used in your health board?

Two of the three health boards only use imipenem on microbiology advice. The other indicated that they had only used with a couple of patients in the last 4-5 years.

23) Is imipenem routinely suppressed in your laboratory?

Imipenem is routinely suppressed (including available on request) in all three labs (100%).

2.3.2.3. Ertapenem

24) Is ertapenem used in your health board?

Ertapenem is used in 12 out of 15 (80%) health boards.

25) Is ertapenem subject to prescribing restrictions in your health boards and

26) Is ertapenem sensitivity routinely tested in your laboratory?

Out of the 12 health boards where it is used, ertapenem is subject to prescribing restrictions in 9 (75%) of these. Ertapenem sensitivity is routinely tested in 8 out of 12 (67%) labs, is tested on request in 2 out of 12 (17%) labs and is not tested in 2 out of 12 (17%) labs.

27) In which of the following indications is ertapenem used in your health board?

The most common indication for which ertapenem is used is Outpatient Parenteral Antimicrobial Therapy (OPAT), in 9 out of 12 (75%) boards. Other indications for which ertapenem are used are proven extended-spectrum beta-lactamase (ESBL) infections requiring IV therapy, 5 out of 12 (42%), diabetic foot infections, 3 out of 12 (25%), and complicated UTI in 2 out of 12 (17%) health boards, (Figure 2.9).

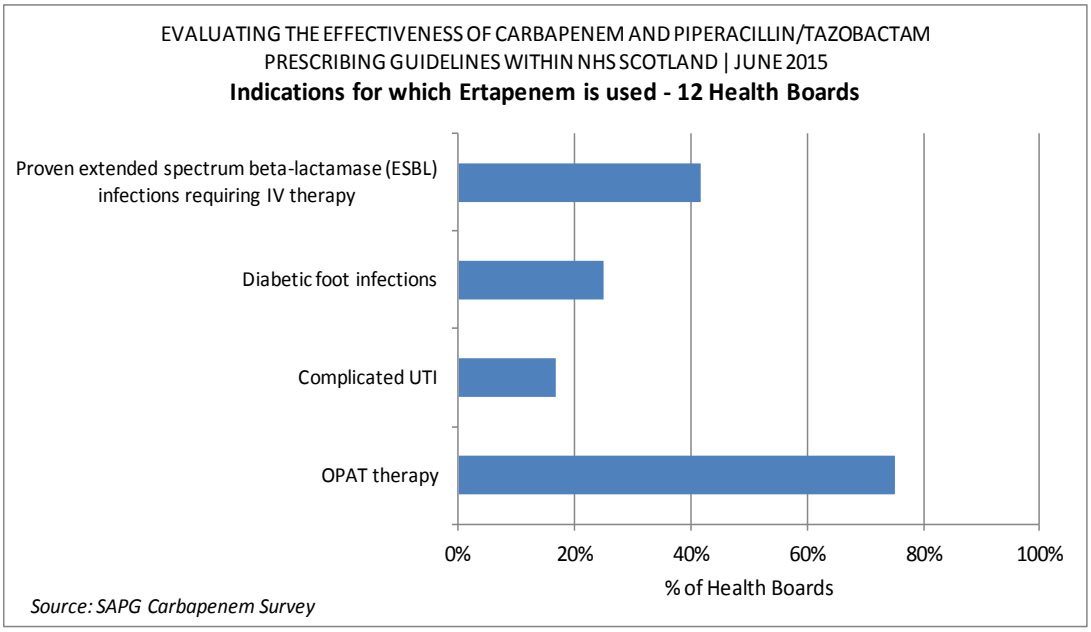


Figure 2.9: Indications for which ertapenem is used - 12 health boards

28) Is ertapenem routinely suppressed in your laboratory?

Ertapenem is routinely suppressed (including available on request) in 11 of the 12 (92%) labs (Figure 2.10).

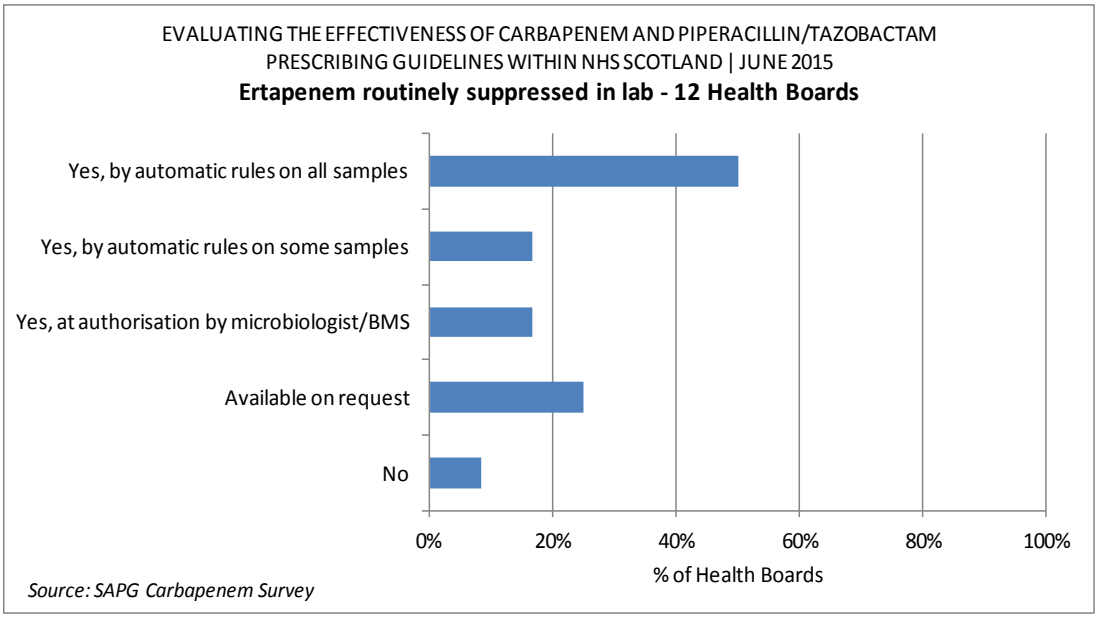


Figure 2.10: Ertapenem routinely suppressed in lab - 12 health boards

2.3.3. Piperacillin-tazobactam questions:

29) Is piperacillin-tazobactam subject to prescribing restrictions in your health board?

Piperacillin-tazobactam is subject to prescribing restrictions in 7 out of 15 (47%) health boards with the remainder of health boards not restricting prescribing.

30) If the answer to the previous question is yes, who can authorise piperacillin-tazobactam prescribing?

Piperacillin-tazobactam can be authorised by a consultant Microbiologist and an ID consultant in all 7 health boards which have prescribing restrictions (Figure 2.11).

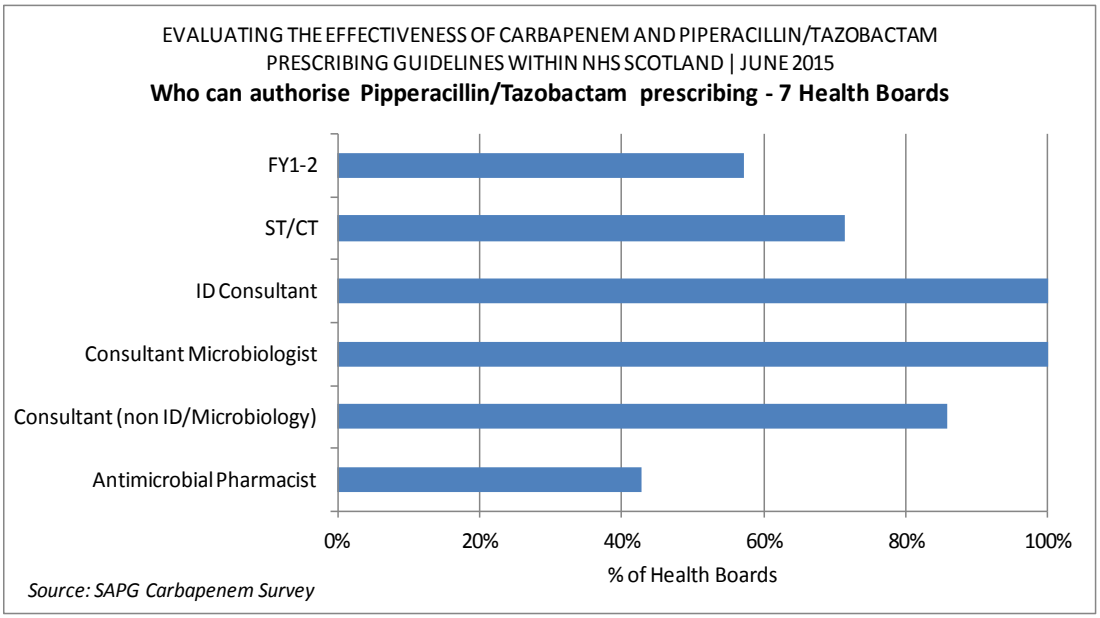


Figure 2.11: Piperacillin-tazobactam authorisation – 7 health boards

31) What are the mechanisms for piperacillin-tazobactam prescribing authorisation?

Six of the seven (86%) health boards have an alert policy for piperacillin-tazobactam prescribing authorisation. Two of these health boards also have over the phone authorisation. The remaining board (NHS Ayrshire and Arran) has no formal mechanism, however, 'continuous monitoring of prescribing fed back into multi-disciplinary ward rounds'. None of the health boards applies the requirement for senior countersign measure.

32) Which of the following statements applies for piperacillin-tazobactam utilisation in your health board?

In 13 out of 15 (87%) health boards, piperacillin-tazobactam is freely available for use according to local guidelines or sensitivity tests. For the remaining two boards piperacillin-tazobactam is available for first 24hr use via an emergency stock cupboard (Figure 2.12).

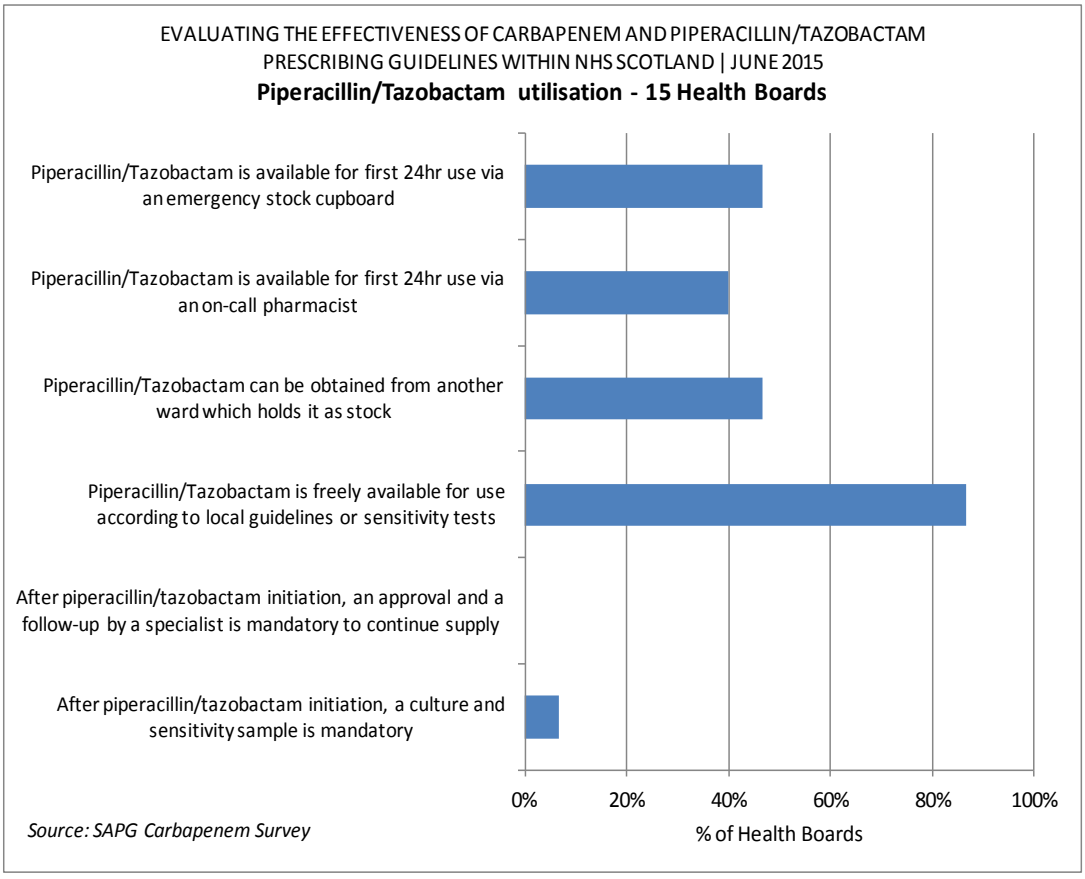


Figure 2.12: Piperacillin-tazobactam utilisation – 15 health boards

33) In which of the following indications is piperacillin-tazobactam used in your health board?

Piperacillin-tazobactam is used for neutropenic sepsis at all 15 health boards (100%). Febrile neutropenia is the 2nd common indication, 12 out of 15 (80%), followed by the complicated intra-abdominal infections 2nd line, nine out 15 (60%) (Figure 2.13).

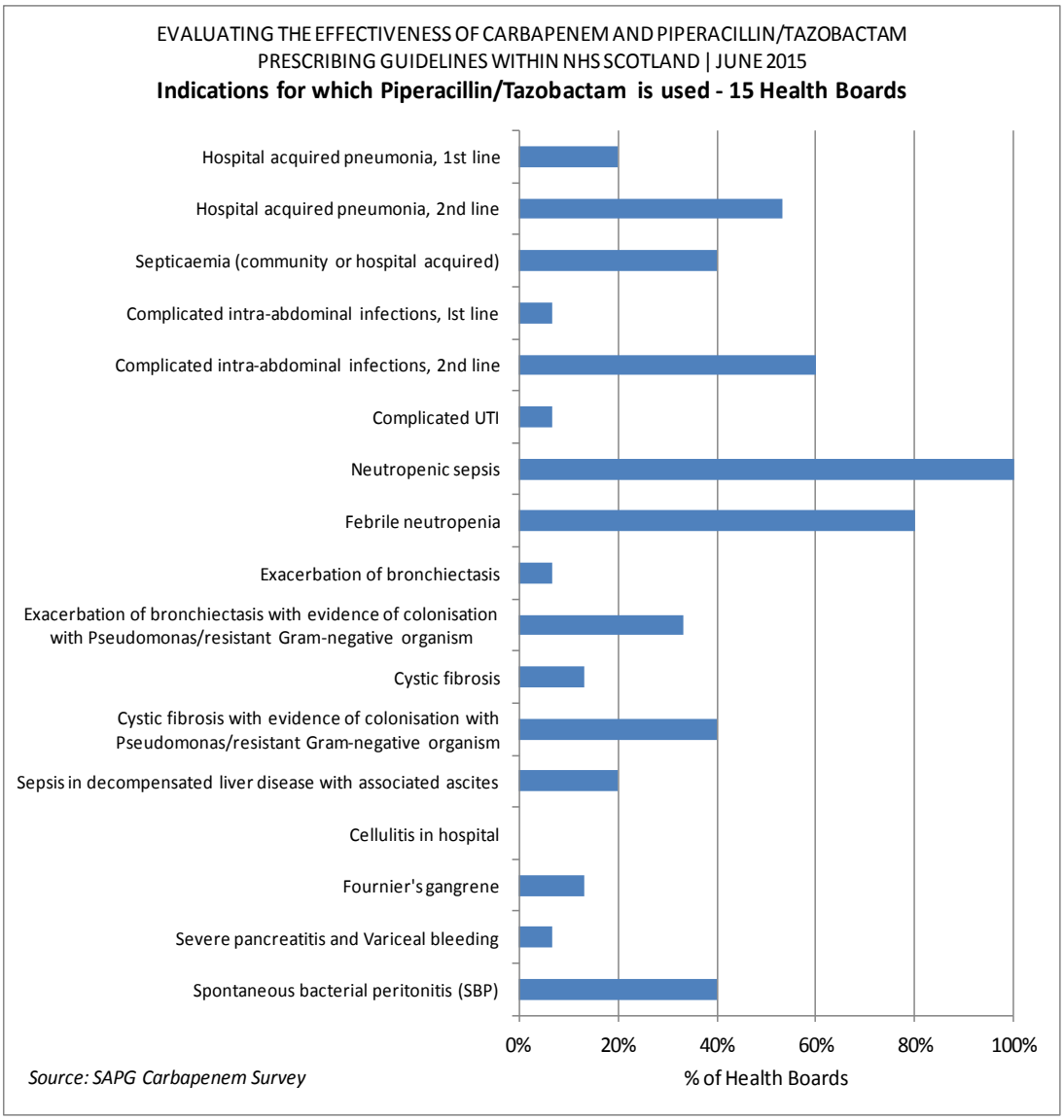


Figure 2.13: Indications for which Piperacillin-tazobactam is used - 15 health boards

34) Is piperacillin-tazobactam sensitivity routinely tested in your laboratory?

Piperacillin-tazobactam sensitivity is routinely tested in the labs of all 15 health boards (100%).

35) Is piperacillin-tazobactam routinely suppressed in your laboratory?

Piperacillin-tazobactam is routinely suppressed (including available on request) in 12 of the 15 (80%) labs. Three health boards (20%) do not routinely suppress piperacillin-tazobactam (Figure 2.14).

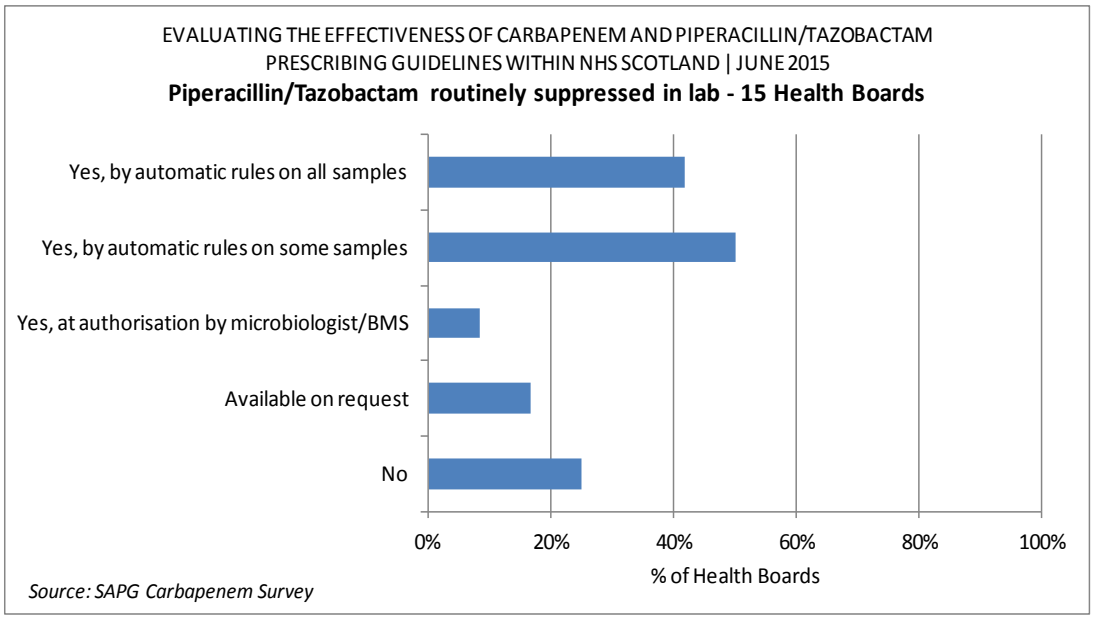


Figure 2.14: Piperacillin-tazobactam routinely suppressed in lab - 15 health boards

2.3.4. Carbapenem sparing agents questions:

36) Which of the following carbapenem sparing antimicrobials are formulary approved for use at your health board?

The carbapenem sparing antimicrobial which was most commonly formulary approved was fosfomycin oral which was approved in 13 out of 15 (87%) health boards. Pivmecillinam was approved in 11 (73%), temocillin in 10 (67%), fosfomycin IV in 9 (60%) and aztreonam in 8 (53%) out of 15 health boards.

37) Are any of carbapenem sparing antimicrobials subject to prescribing restrictions in your health board?

Fosfomycin IV is subject to prescribing restrictions in all 9 (100%) of the health boards in which it was formulary approved. Temocillin was subject to prescribing restrictions in 9 of the 10 (90%) health boards in which it is formulary approved (Figure 2.15).

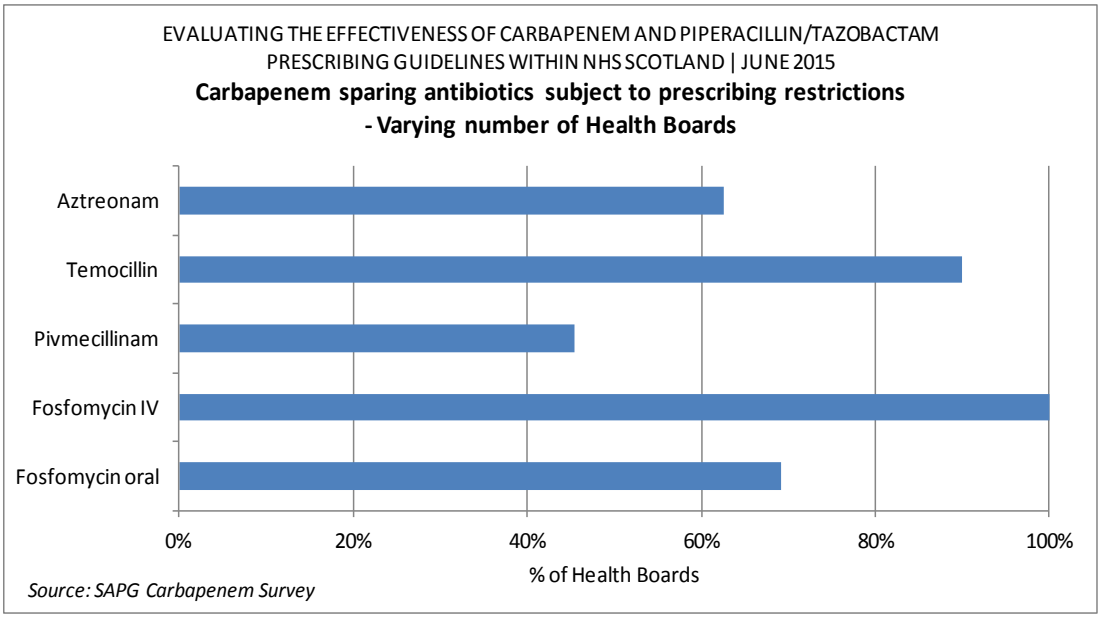


Figure 2.15: Carbapenem sparing antimicrobials prescribing restriction - varying number of health boards

38) Does your health board monitor the consumption of carbapenem sparing agents?

The consumption of carbapenem sparing agents was monitored in 8 out of 15 (53%) health boards.

39) In which of the following indications is aztreonam used in your health board?

For the 8 health boards where it is formulary approved, aztreonam is used for the indications shown in Figure 2.16.

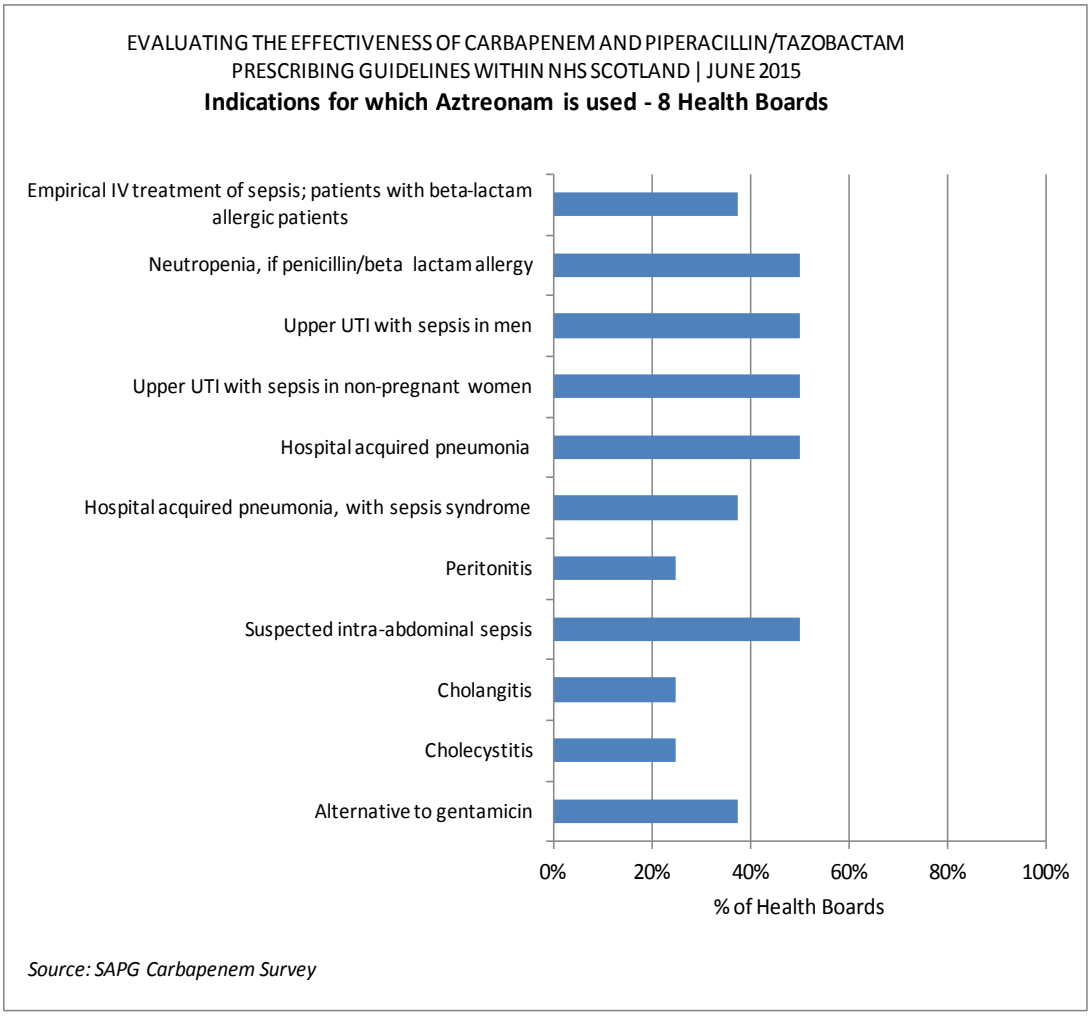


Figure 2.16: Indications for which Aztreonam is used - 8 health boards

40) In which of the following indications is temocillin used in your health board?

For the 10 health boards where it was formulary approved, temocillin was used by 8 health boards (80%) for the indication 'Treatment of Gram-negative (especially ESBLs) sepsis; septicaemia; urosepsis and pneumonia'. Also, indicated in three health boards (30%) for 'UTI; therapy of urosepsis where *Pseudomonas spp.* and *Acinetobacter spp*. are not suspected'.

41) In which of the following indications is pivmecillinam used in your health board?

For the 11 health boards where it is formulary approved, pivmecillinam is used for the indications shown in Figure 2.17.

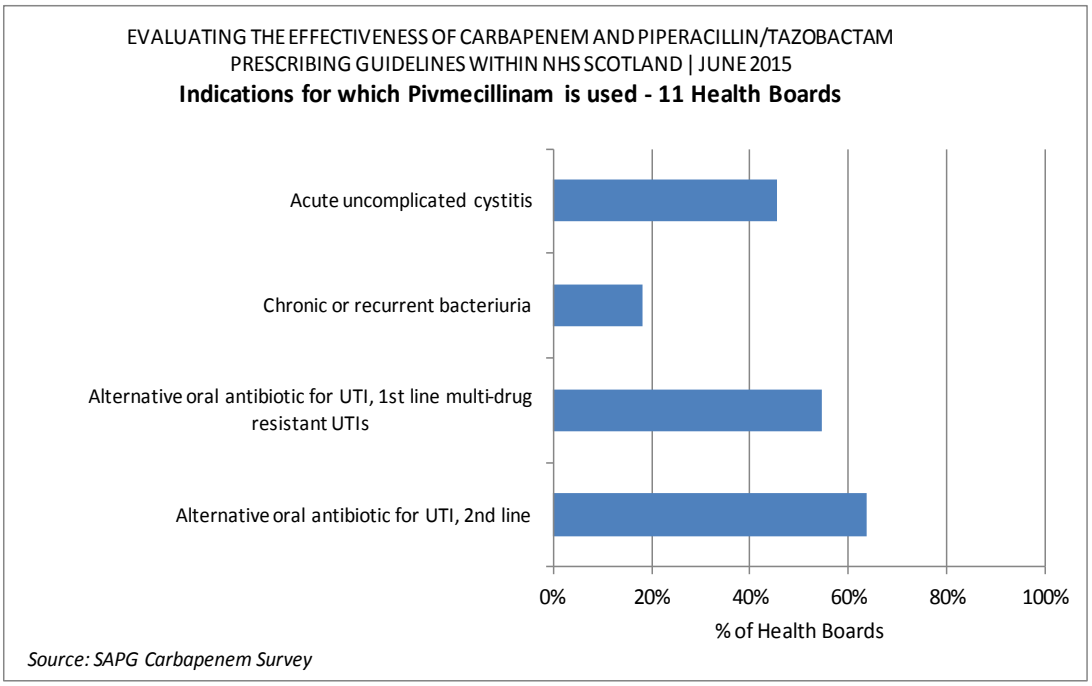


Figure 2.17: Indications for which Pivmecillinam is used - 11 health boards

42) In which of the following indications is fosfomycin IV used in your health board?

For the nine health boards where it was formulary approved, fosfomycin IV was used most often for the indication. 'Complicated UTI, 2nd line (when 1st line treatment was ineffective or inappropriate)', in 5 out of 9 (56%) boards. (Figure 2.18).

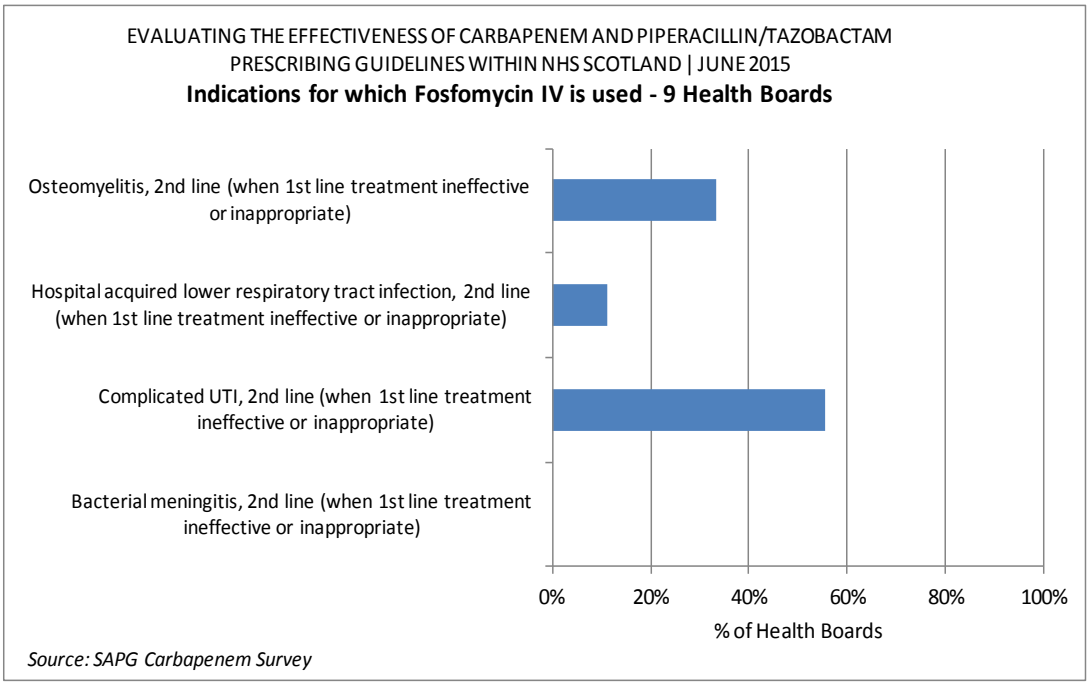


Figure 2.18: Indications for which Fosfomycin IV is used - 9 health boards

43) In which of the following indications is fosfomycin oral used in your health board?

For the 13 health boards where it was formulary approved, fosfomycin oral was used for the indications shown in Figure 2.19.

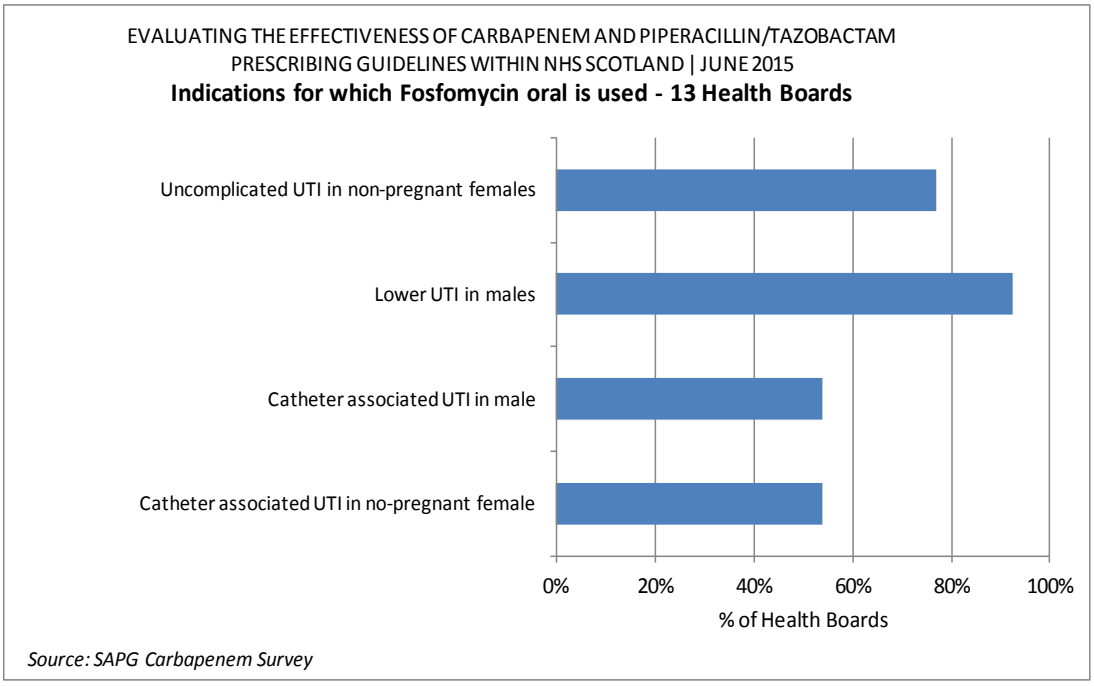


Figure 2.19: Indications for which Fosfomycin oral is used - 13 health boards

2.3.5. Laboratory related questions:

44) What laboratory testing and reporting is available for the carbapenem sparing antimicrobials used in your health board?

A summary of the results are shown in Figure 2.20.

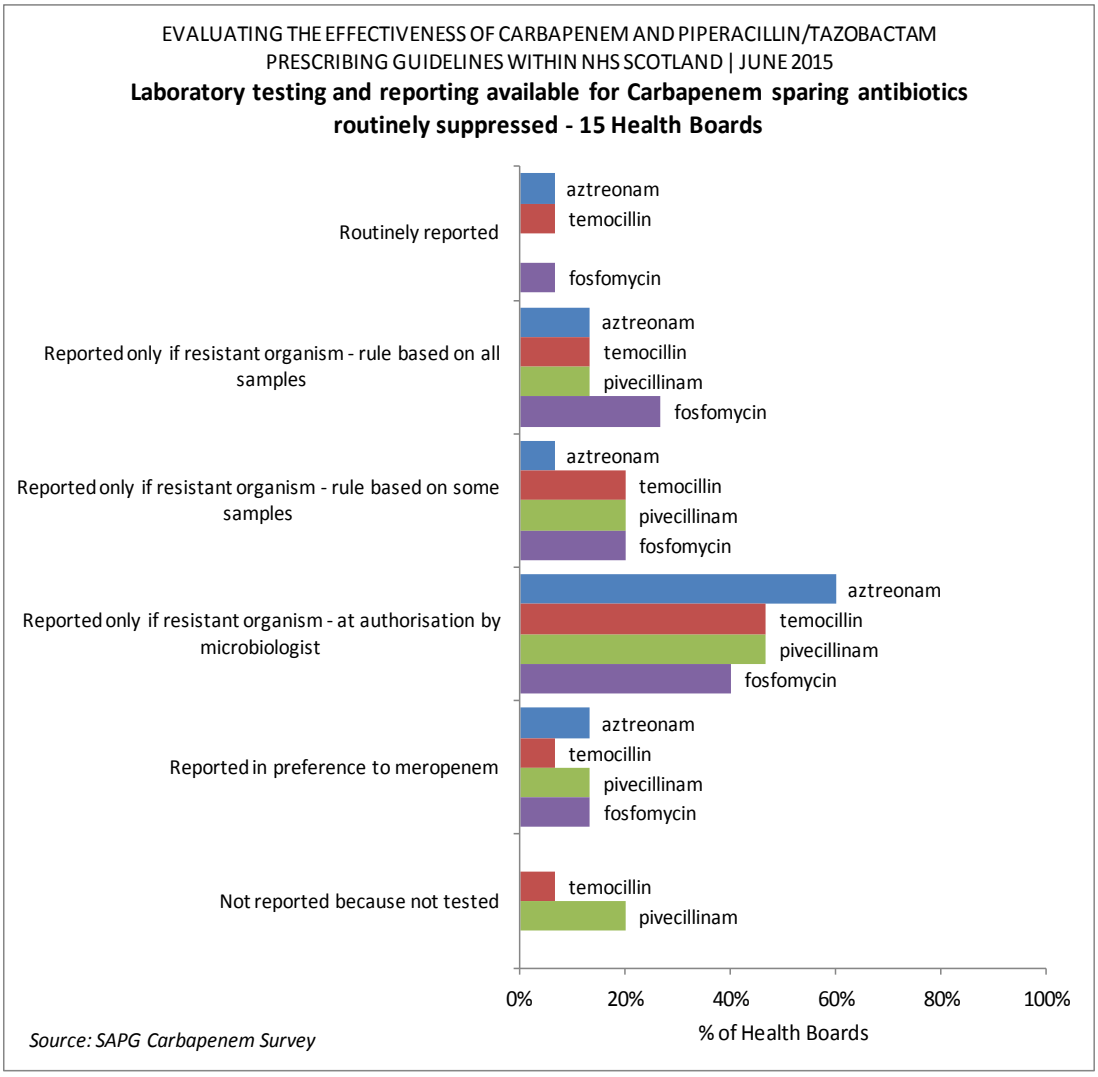


Figure 2.20: Laboratory testing and reporting available for carbapenem sparing antimicrobials routinely suppressed - 15 health boards

45) In your laboratory, which of the following would be reported on an MDR or ESBL E. coli GP urine sample, if found to be susceptible on sensitivity testing?

The antimicrobials which would be reported are shown in Figure 2.21.

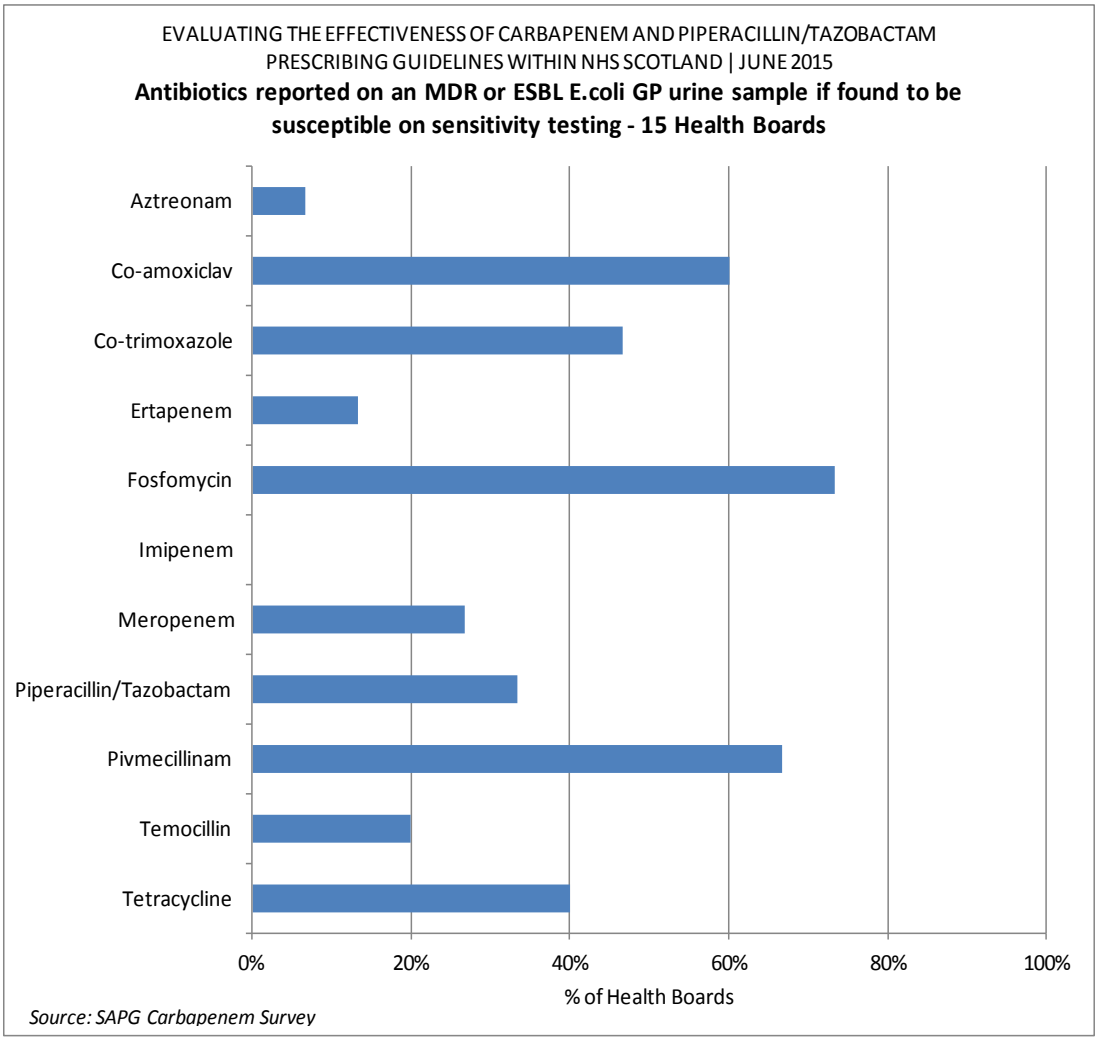


Figure 2.21: Antimicrobials reported on an MDR or ESBL E.coli, GP urine sample if found to be susceptible on sensitivity testing - 15 health boards

46) In your laboratory, which of the following would be reported on an MDR or ESBL *E. coli* hospital urine sample, if found to be susceptible on sensitivity testing?

The antimicrobials which would be reported are shown in Figure 2.22.

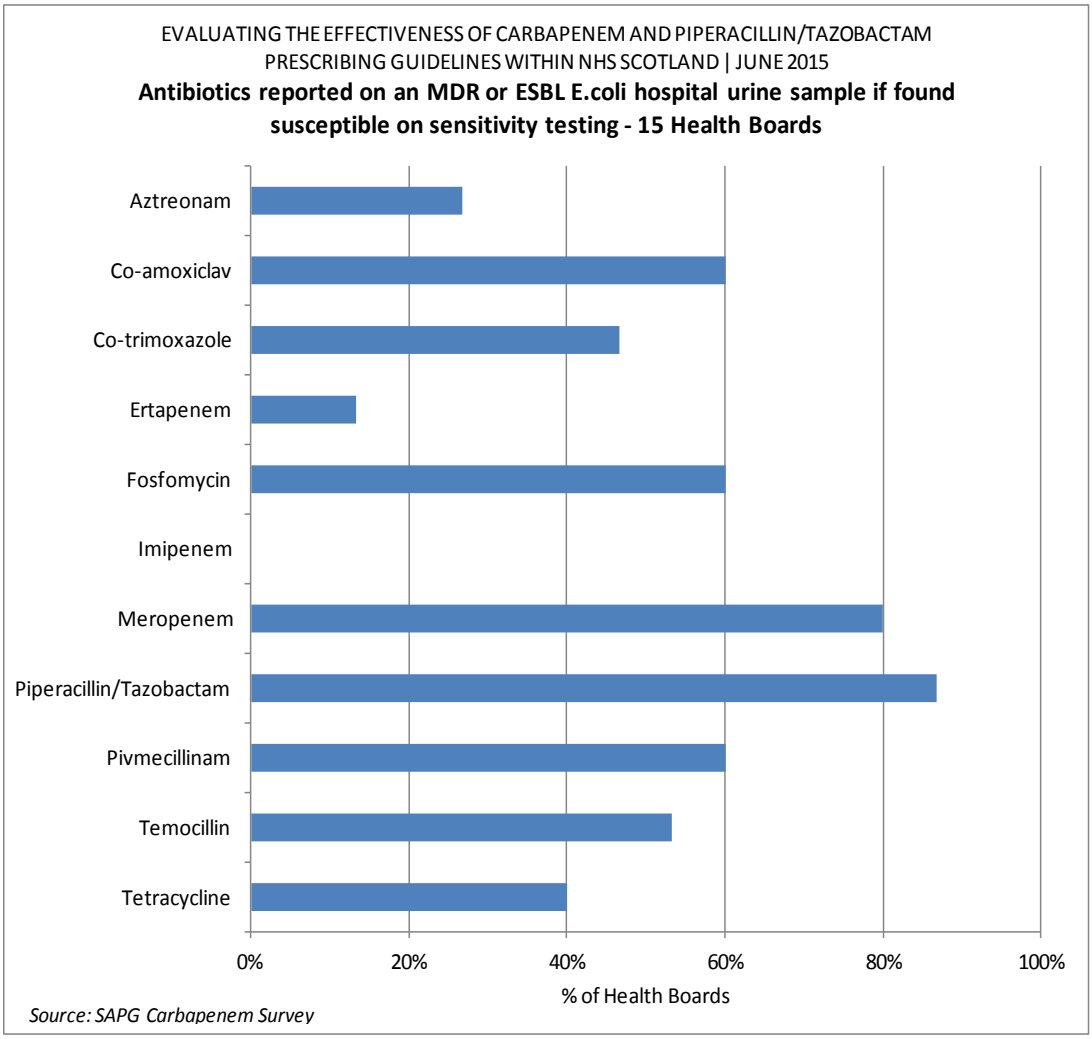


Figure 2.22: Antimicrobials reported on an MDR or ESBL E.coli, hospital urine sample if found susceptible on sensitivity testing - 15 health boards

47) In your laboratory, which of the following would be reported on an MDR or ESBL E. coli blood culture isolate, if found to be susceptible on sensitivity testing?

The antimicrobials which would be reported are shown in Figure 2.23.

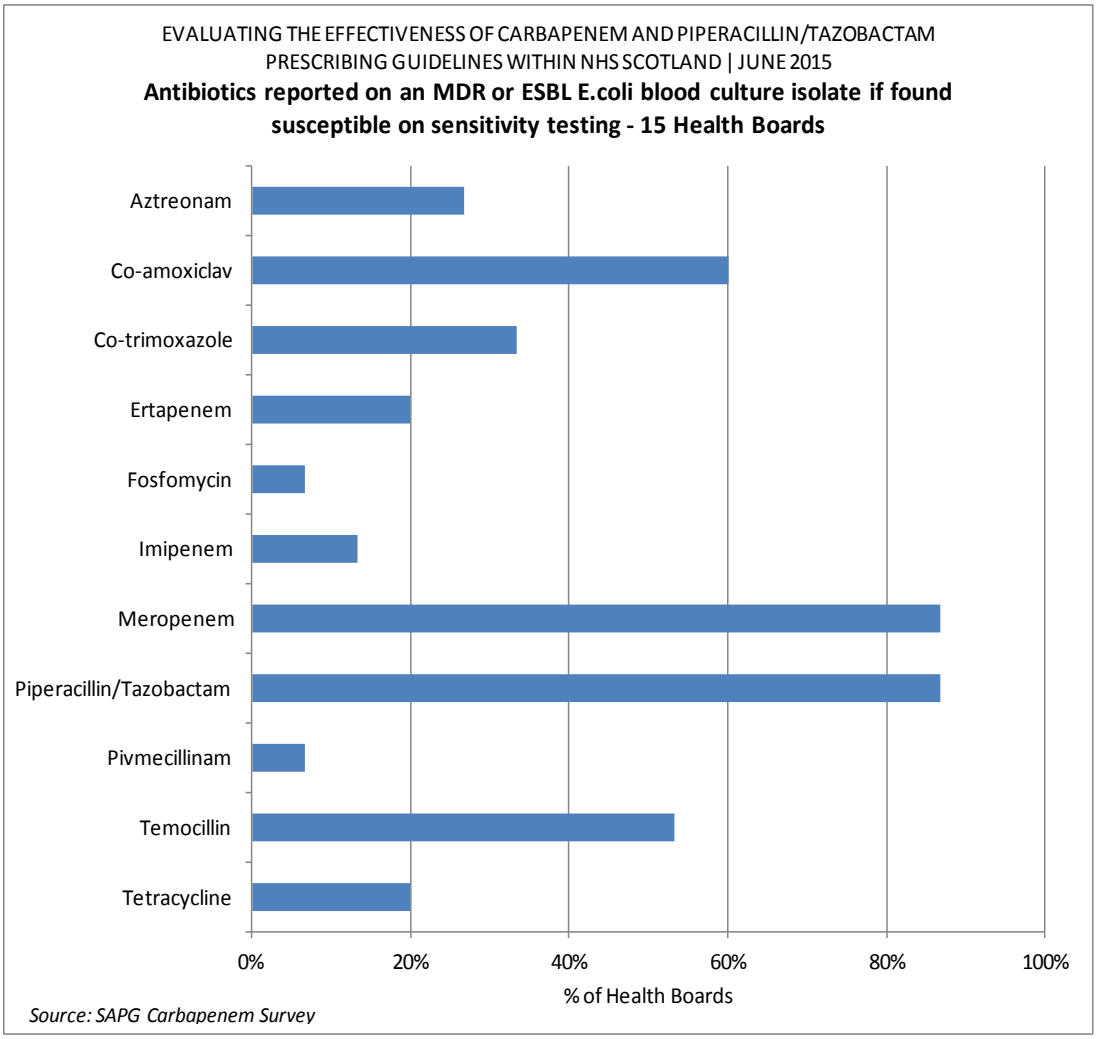


Figure 2.23: Antimicrobials reported on an MDR or ESBL E.coli, blood culture isolate if found susceptible on sensitivity testing - 15 health boards

2.3.6. Additional comments:

48) Please add any additional comments on the prescribing of carbapenems, piperacillin-tazobactam and other agents. Please include any examples of good practice.

In the following, a list of all comments provided by responders:

- *"Our Microbiologists do daily ward rounds and the patients discussed with the clinicians. Therefore the carbapenem prescribing is followed up closely by a microbiologist."*

- *"Until last month, piperacillin-tazobactam was formulary for severe HAP, sepsis unknown origin and aspiration pneumonia. This gave very little leverage in challenging prescriptions for these common indications. The addition of an intermediary option for infection of unknown source will be very useful for reducing piperacillin-tazobactam use. I expect there will be a jump in co-amoxiclav and ciprofloxacin use as an oral step down options so will need to monitor consequences."*

- *"The AMT is currently discussing the wider use of the carbapenem sparing antimicrobials."*

- *"Data on piperacillin-tazobactam use by ad-hoc audits is provided if use is felt to be increasing or increased. This often relates to locum prescribers not adhering to guidelines."*

- *"Impact of Sepsis 6 program on piperacillin-tazobactam prescribing has not been measured, but it is likely to have had an impact. The restricted prescribing protocol has had a significant reduction in carbapenem prescribing since the*

introduction in August 2014 with good buy-in from most clinicians."

- *"Dr G has an increase in piperacillin-tazobactam use after very tight restriction on 4Cs and co-amoxiclav in particular. Now using less piperacillin-tazobactam and more co-amoxiclav and have started to see a couple of CDI cases (having had none for > 1year)."*

- *"Prescribing of meropenem is restricted by the NHS Lothian Alert Antimicrobial Policy although adherence to this policy is variable between specialities."*

- *"Use of piperacillin-tazobactam and meropenem has plateaued as aztreonam use has increased. National referral centre for cystic fibrosis and some concern has been expressed regarding our increasing use of aztreonam in general population (pseudomonal resistance and supply issues are main concern). Aztreonam supply has been an issue in last three months."*

- *"We are trying to increase post-prescription review of carbapenems by ID/Micro. We have an email alert system to the ID/Micro generic mailbox if a pharmacist deems a prescription of a carbapenem inappropriate - this would*

trigger a clinical visit; the pharmacist is our monitor according to ALET guidance."

49) Please add any additional comments on laboratory testing and reporting of carbapenems, piperacillin-tazobactam and other agents. Please include any examples of good practice.

- *"Temocillin, pivmecillinam and fosfomycin are only reported in urine samples."*
- *"All sensitivity patterns are electronically reported to ECOSS for surveillance purposes. We do test aztreonam and temocillin in the laboratory as they are part of the sensitivity card but we always suppress the result."*
- *"A blood culture with an ESBL which is sensitive to piperacillin-tazobactam or co-amoxiclav would have this sensitivity suppressed due to reported treatment failures with these agents."*
- *"Because we do not have a microbiologist on site, everything is rule-based when it comes to reporting. This makes it very easy to suppress certain classes of*

antimicrobials. It also means reporting is very consistent in the board."

- *"Recent change to urine testing protocol (CSU specimens without clinical details not tested, MSU specimens with only dipstick results not tested) yet to realise an impact on resistance patterns but anticipated benefit in reducing prescribing."*

- *"See responses to Q44 whereby we are still promoting antimicrobial stewardship, i.e. not releasing all agents on GP samples, but preferentially reporting carbapenem-sparing agents in the hospital setting. Obviously, not all agents are tested for on all isolates from all sites, but where a carbapenem-sparing agent has been tested, it will be reported for hospital patients."*

- *"VITEK 2 automatic rules designed to restrict the use of these agents."*

- *"Suggestions on how to manage testing and workflow for pivmecillinam would be helpful as this is something we are struggling to resolve locally."*

- *"Suppression of reporting antimicrobials which are tested for in the microbiology labs."*

- *"Low gentamicin resistance locally, therefore, gentamicin often used in these circumstances."*
- *"The previous disconnect between VITEK cards and licensed status of antimicrobials, i.e. fosfomycin and pivmecillinam. Reluctance to introduce temocillin more widely into empirical prescribing as concerns regarding resistance and pricing!"*

2.3.7. Summary of results:

The survey yielded data from antimicrobial management team leaders representing each of the 15 health boards, including Golden Jubilee National Hospital, and found variation in the implementation and adaptation of the SAPG MDRGNB guidance. An infographic was designed to highlight the significant areas of interest, national response, and individual health board input. Each health board was generated an individual infographics, an example is provided in Figure 2.24, with the full list of infographics contained in Appendix #5.

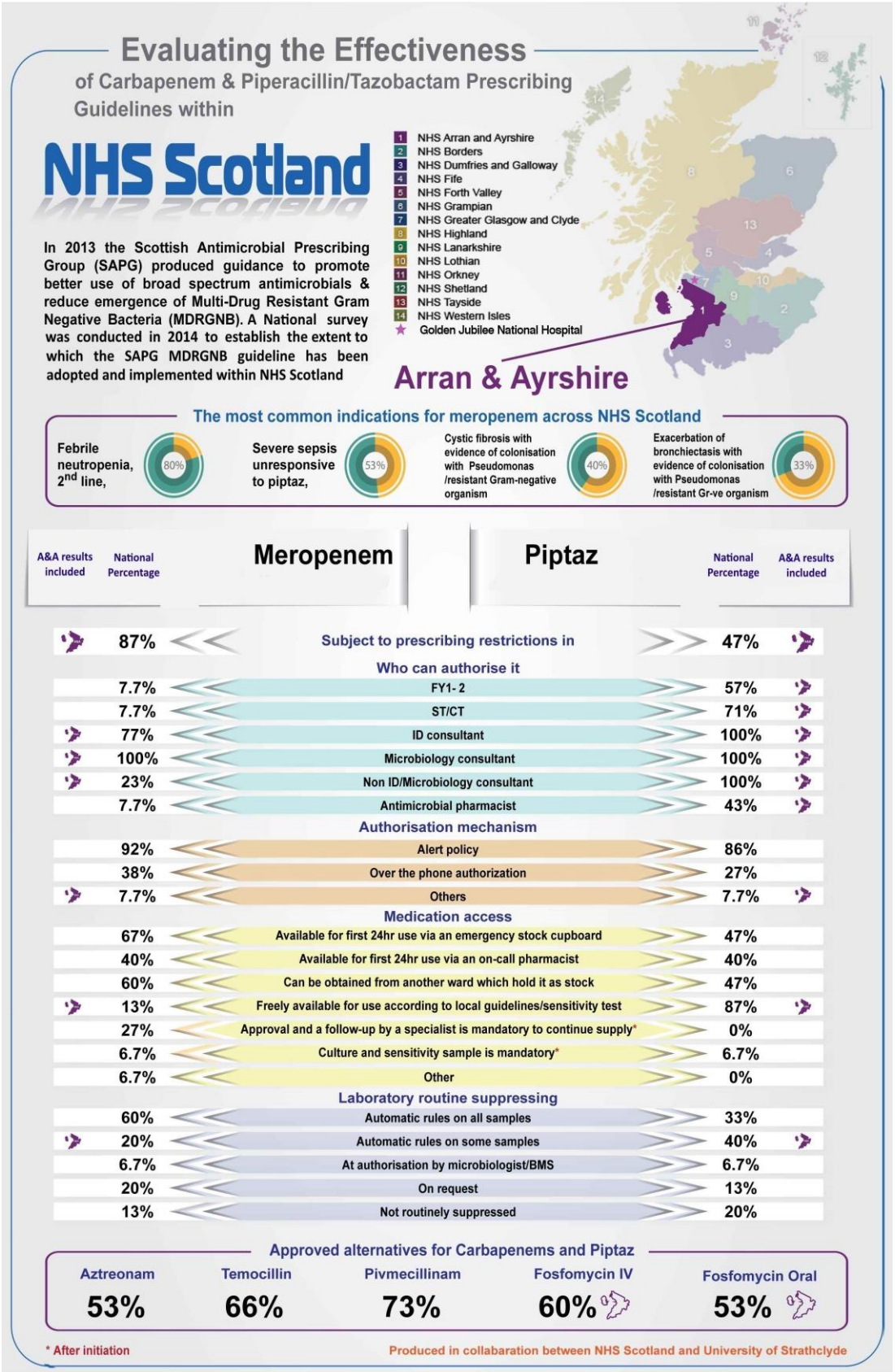


Figure 2.24: Individual Health Board infographics – Ayrshire & Arran Health Board

2.3.7.1. Measures used by health boards to control use of carbapenems and piperacillin-tazobactam

- All 15 health boards in NHS Scotland responded to the survey.
- Fourteen out of fifteen health boards (93%) either updated local clinical guidelines based on the SAPG MDRGNB guidance recommendations or reviewed their local guidelines and found them to be in-line with the SAPG MDRGNB guidance.
- Most health boards (9 out of 15, 60%) informed clinical practitioners about the guidance either directly via verbal means, e.g. during medical education sessions or electronically via email.
- Training on prescribing of carbapenems and piperacillin-tazobactam is integrated into routine training in most health boards (80%), although in 3 health boards no specific training is delivered. In the health boards where training are provided it is mostly targeted to FY1-2 and ST/CT medical staff and pharmacists.
- Thirteen out of fifteen health boards (87%) monitor the consumption of carbapenems and piperacillin-tazobactam.
- Most reports on consumption of carbapenems and piperacillin-tazobactam are produced quarterly (85%), and all health boards (100%) which produce reports on consumption share the reports with the Antimicrobial Management Teams (AMTs). Ten (77%) health boards also share these reports with their Infection Prevention and Control Committees.

2.3.7.2. Use of carbapenems and piperacillin-tazobactam by health boards

Meropenem:

Meropenem was formulary approved for use in all 15 health boards. It was subject to prescribing restrictions in 13 out of 15 (87%) health boards. Most health boards (92%) have an alert policy for authorisation of meropenem prescribing, and most health boards have a stock of meropenem available for the first 24 hours via an emergency cupboard or located on a specific ward. The most common indication for the use of meropenem in 80% of health boards was as a second line agent for febrile neutropenia. Meropenem sensitivity was routinely tested in labs in all 15 health boards and reporting was suppressed in 87% of health boards.

Imipenem:

Imipenem was used in 3 out of 15 (20%) health boards. It was subject to prescribing restrictions and was only used following microbiology advice in two of these (67%). Imipenem was routinely suppressed in all labs in health boards where it is used.

Ertapenem:

Ertapenem ws used in 12 out of 15 (80%) health boards. It was subject to prescribing restrictions in 9 of these (75%) and was used predominantly in an OPAT setting. Ertapenem was routinely suppressed in 11 of 12 (92%) labs.

Piperacillin-tazobactam:

Piperacillin-tazobactam was subject to prescribing restrictions in 7 out of 15 (47%) health boards and in these health boards prescribing can be authorised by a Consultant Microbiologist and an ID Consultant as part of an alert policy for prescribing authorisation. Piperacillin-tazobactam was freely available for use according to local guidelines or sensitivity tests in the majority of health boards (87%).

Piperacillin-tazobactam was used for the treatment of neutropenic sepsis in all 15 health boards with the second most common use being the treatment of febrile neutropenia. This follows the recommendation for empiric treatment of sepsis detailed in the SAPG guidance to reduce MDRGNB. Piperacillin-tazobactam sensitivity testing was routinely performed in all health boards and was routinely suppressed in 80% of them.

2.3.7.3. Use of carbapenem sparing antimicrobials by health boards

- The carbapenem sparing antimicrobial which was most commonly formulary approved was Fosfomycin oral (approved in 87% health boards) followed by pivmecillinam (73%), temocillin (67%), fosfomycin IV (60%), and aztreonam (53%). Fosfomycin IV was subject to prescribing restrictions in all of the 9 health boards where it was formulary approved for use and temocillin was subject to restrictions in 90% of health boards where it was approved. Prescribing restrictions are in place for the other antimicrobials in 45 to 69% of health boards.
- The consumption of carbapenem sparing agents was monitored in 8 out of 15 (53%) health boards.
- In health boards where aztreonam was formulary approved it was indicated for neutropenia if penicillin allergic, upper UTI with sepsis, suspected intra-abdominal sepsis and hospital-acquired pneumonia.
- Temocillin was used for Gram-negative (especially ESBL) sepsis, septicaemia, urosepsis and pneumonia.
- Pivmecillinam was used as an alternative antimicrobial for UTI's in the 11 health boards that approve it.
- Fosfomycin IV was used for complicated UTI's and as a second line treatment for osteomyelitis. Fosfomycin oral was predominantly used for the treatment of lower UTI's in males.

- Most health boards (40 to 60%) report sensitivities to carbapenem sparing antimicrobials for resistant organisms at the authorisation of a microbiologist.
- Recommended indications of carbapenem sparing antimicrobials follow the recommendations in the SAPG MDRGNB guidance.

2.3.7.4. Laboratory reporting

Carbapenem susceptibility testing and reporting

- Meropenem and ertapenem susceptibility testing was performed in all 15 health boards surveyed.
- Meropenem was not routinely suppressed on samples in two health boards.
- Ertapenem was suppressed variably across samples and health boards.
- Imipenem was only used in 3 of 15 health boards and was routinely suppressed in all three health boards.

Piperacillin-tazobactam susceptibility testing and reporting

- Piperacillin-tazobactam susceptibility testing was performed in all 15 health boards surveyed.
- Piperacillin-tazobactam was suppressed variably across samples and health boards.

Carbapenem sparing antimicrobials susceptibility testing and reporting

- Aztreonam, temocillin and fosfomycin are each routinely reported in only one health board.
- Depending on the resistance profile, and sample type an increased number of health boards report these agents variably and also pivmecillinam.
- Only a small number of health boards report these agents in preference to meropenem.

Summary of examples of reporting for resistant organisms

GP urine MDR or ESBL samples:

- The majority of health boards (10 and 11 respectively) would report pivmecillinam and fosfomycin.
- Approximately half of the health boards would variably report the following oral agents if susceptible: co-amoxiclav, co-trimoxazole, and tetracycline.
- Four health boards would report meropenem, and two health boards would report ertapenem if susceptible.
- Five health boards would report piperacillin-tazobactam.
- Three health boards and one health board would report temocillin and aztreonam.

Hospital urine MDR or ESBL samples:

- The majority of health boards (9 each) would report pivmecillinam and fosfomycin.
- Approximately half of the health boards would variably report the following oral agents if susceptible: co-amoxiclav, co-trimoxazole, and tetracycline.
- Twelve health boards would report meropenem, and two health boards would report ertapenem if susceptible.
- Thirteen health boards would report piperacillin-tazobactam.
- Eight health boards and four health boards would report temocillin and aztreonam.

Blood culture MDR or ESBL samples:

- Only one health board each would report pivmecillinam and fosfomycin.
- Slightly less than half of the boards would variably report the following oral agents if susceptible: co-amoxiclav, co-trimoxazole, and tetracycline.
- Thirteen health boards would report meropenem, and three health boards would report ertapenem if susceptible.
- Thirteen health boards would report piperacillin-tazobactam.
- Eight health boards and four health board would report temocillin and aztreonam.

2.4. Discussion:

All 15 health boards of NHS Scotland responded to the survey, providing an insight into the regulatory governance of each board towards implementation of the SAPG MDRGNB guidelines. It was anticipated that the variance between individual health board strategies would identify areas for improvements and identify good practice. Results showed different implementation actions between different health boards on different aspects of the SAPG MDRGNB guidance.

2.4.1. Guideline adaptation and implementation

Before SAPG MDRGNB guidance (October 2013)

The majority of health boards had identified carbapenem, and piperacillin-tazobactam increased consumption as a main area for improvement. Different actions were taken at board level. However, two health boards did not react to the published guidelines. Both of these health boards were small in population size, Orkney (20,000) and Shetland (22,000), and the consumption of targeted antimicrobials was very small. In addition, an AMT for Shetland had not been established until 2014 after the guidance had been published.

After SAPG MDRGNB guidance, October 2013

Almost all health boards acted in response to the SAPG MDRGNB guidance based on its persuasive design and its opportunity to aid development of local guides. Only NHS Shetland had not taken any actions which were explained by having no active AMT at that time. Local guidelines were either updated or already found to be in line with SAPG guidance based on health board need. However, none of the health boards adopted the guidance in its entirety. SAPG did not have any planned reminders or specific educational sessions targeting AMT's. Furthermore, results show that only 60% of health boards informed clinical practitioners about the publication of the SAPG MDRGNB guidance. Sharing the guidelines with different groups of practitioners would have supported the overall goal [187]. Direct communication was the preferred method in most health boards.

The result showed that training of carbapenem and piperacillin-tazobactam prescribing was integrated into routine training in 80% of health boards. This can be helpful time-saving for healthcare professionals but might minimise the impact of the guidance as it is diluted within a broader training package. Three health boards deliver no specific training, and no comments were provided as to why this may be the case. The targeted staff groups were different between health boards. However, the majority focussed on young medical practitioners (FY1/2) and pharmacists. Consultants were updated in less than half of health boards even though they are the major authorising group of the targeted antimicrobials. The nursing staff was

targeted the least (≈ 30%) despite the increased attention on their potential role in targeted antimicrobials consumption and improving prescribing quality [188]. Nurses have a significant role on the importance of avoiding missed doses, maintaining therapeutic levels, and ensuring that all required diagnostics tests are carried out promptly [189-192]. The role of nursing staff could exceed to question and highlight the duration of therapy and choices or prescribing where they do not meet with established local guidelines [189, 193, 194]. Aiming to include most of the clinical specialities would potentially improve antimicrobial consumption [195].

Antimicrobial consumption reports are good indicators of prescribing trends, the frequency of reporting benefits more active health boards for close monitoring and better reactivity to data. Close monitoring of quarterly reports was found in 85% of health boards. However, the benefits of reporting might be limited by the extent of sharing results with relevant personnel who are driving consumption. Reports should be shared with a broader group to increase awareness and support overall goal [196-198].

In a time series analysis study [197], aiming to determine whether feedback on antimicrobial use improves physician compliance with local guidelines. A historical control period was compared with an intervention period, 2,807 orders for antimicrobials placed from first of November, 2002, through the end of April, 2004, were investigated by AMT for compliance with hospital guidelines.

Feedback was given for the second 9-month period in the form of a weekly report to prescribing physicians, a monthly hospital newsletter, and a quarterly report to various hospital committees. Compliance with hospital guidelines before AMT recommendations was 70% during the control period and 74% during the intervention period (P=.02). Compliance after AMT recommendations was 90% during the control period and 93% during the intervention period (P< or =.01). Thus, the use of feedback had a significantly favourable impact on physician compliance with the hospital's guidelines on antimicrobial prescribing.

2.4.2. Carbapenems

Three carbapenems are licenced in the UK; meropenem, imipenem, and ertapenem. All three antimicrobials have a broad spectrum of antimicrobial activity which exceeds that of most other antimicrobial classes. Both imipenem and meropenem have good activity against *Pseudomonas aeruginosa*, but ertapenem lacks activity against this microorganism. Ertapenem has a longer half-life (4hrs) compared to imipenem (1hr) and meropenem (1hr) making it suitable for once daily administration [160]. Meropenem has less seizure-inducing potential. Thus it is recommended to be used to treat central nervous system infection such as meningitis. Meropenem was the most common carbapenem in use across Scotland accounting for 95.3% of total carbapenem consumption. Meropenem was formulary approved for use in all health boards compared to 12 health boards for ertapenem

and only 3 for imipenem. This can be supported by the preferred safety profile of meropenem over imipenem and the total cost even though imipenem is used more worldwide [166, 199, 200].

Meropenem

The survey results showed a high degree of liberty in meropenem prescribing privileges, the act of writing prescribing order, amongst all prescribing groups. However, meropenem prescriptions need to be authorised (approved) in 87% of health boards. Controlling the use of such agents by limiting authorisation privileges are a common intervention in practice, see section (1.2.2.2.). Such action have been seen to decrease resistance trends, cost and consumption of antimicrobials [201-204]. In health boards where restrictions apply, the alert policy was the most common method of authorisation (92%). Authorisation over the phone was offered as an additional method in 5 health boards. Allowing several mechanisms of authorisation might encourage other prescribers to involve specialised teams. Allowing meropenem stock to be available at emergency departments and high-risk wards are crucial for critical cases such as sepsis [125, 131] and 67% of health boards made meropenem stock available for use in the first 24hr by that mechanism

Results showed that meropenem's most common indications were rational and evidence-based. Most health boards were observed to test for meropenem

sensitivity and suppress results. However, two major health boards (Lothian and Tayside) did not routinely suppress results and no explanation was provided for this stance.

Imipenem

The results of the survey are limited since only a small number of health boards (20%) approve imipenem's clinical use. Two of the health boards restrict the use of imipenem to microbiology advice, and the other one commented that they have not had any clinical reason to prescribe imipenem over the last four years.

Ertapenem

The main advantage of ertapenem over the other carbapenems is the extended half-life. Thus, ertapenem is the perfect choice for OPAT therapy. The majority (80%) of health boards use, and restrict (75%) ertapenem prescribing to Microbiologist or ID consultants. Sensitivity testing is performed routinely in 67% of health boards, and on request in 17%. However, two health boards do not test for sensitivity and an explanation was not provided. Even though sensitivity testing is performed in 67% of health boards, results are suppressed in various method and only one health board does not suppress results, no explanation provided. The most common indication (75%) for ertapenem was for OPAT therapy, primarily due to the long half-life of ertapenem. This is in-line with worldwide trends [205, 206].

2.4.3. Piperacillin-tazobactam

Piperacillin-tazobactam was available across all NHS Scotland health boards and its use was less restricted compared to meropenem (47% vs 87% respectively). In clinical use, piperacillin-tazobactam had more approved clinical indications than other broad-spectrum antimicrobials. Furthermore, it was widely recommended to start with piperacillin-tazobactam for empiric therapy in local and national guidelines. In SAPG MDRGNB guidance it is suggested to use piperacillin-tazobactam in suspected neutropenic sepsis and urosepsis as monotherapy and in combination with an aminoglycoside in severe sepsis and septic shock as an alternative choice for meropenem [61, 125]. This may explain why there was limited restrictions and wider authorisation privileges for piperacillin-tazobactam compared to meropenem across individual health boards. Authorisation was permitted by different grades of healthcare prescribers and not limited to Consultant level. In addition, piperacillin-tazobactam was freely available for use in 87% of health boards compared to only 13% for meropenem.

The study results showed that neutropenic sepsis and febrile neutropenia are the most common indications for piperacillin-tazobactam across Scotland, which was comparable to worldwide trends [72]. However, 20% of health boards used

piperacillin-tazobactam as a first line therapy in Hospital Acquired Pneumoniae (HAP) which is not recommended practice [160, 207]. From a laboratory perspective, piperacillin-tazobactam sensitivity was available in the labs of all 15 health boards. However, three health boards do not suppress results to healthcare professionals in any way. One health board explained that unsuppressed results happen when piperacillin-tazobactam was clinically indicated for a given infection, and another health board mentioned that suppression of sensitivity results was provoked predominantly on resistance profile. The third health board did not provide an explanation for their actions in relation to suppressing results.

Overall results showed that piperacillin-tazobactam was less restricted, more commonly used, freely accessed and authorised compared to carbapenems. As a result, the consumption data of piperacillin-tazobactam is higher than carbapenems, and the rate of increase is faster year on year than carbapenems.

2.4.4. Carbapenem sparing antimicrobials

The SAPG MDRGNB guidance recommended five alternatives to carbapenems and included monographs for each one in the guidance to help direct selection and use for particular clinical indications. However, individual health boards promoted the use of these alternatives in extent variable manner, and this can limit their

subsequent utilisation. The registration and approval status of targeted antimicrobial was a common limitation worldwide and not only in Scotland [72]. Furthermore, restrictions on the use of the alternative agents in health boards that approve their use was tighter compared to restrictions on piperacillin-tazobactam, except for pivmecillinam (where 45% of health boards apply restrictions). Survey results also highlighted that consumption monitoring for these agents was only performed by 53% of health boards which may lead to loss of opportunities to optimise knowledge in their use in specific infectious indications.

In SAPG MDRGNB guidance, aztreonam is recommended in patients with renal impairment and for empirical treatment of sepsis in patients with a beta-lactam allergy, direct treatment of Gram-negative sepsis bacteraemia, urosepsis, pneumonia and intra-abdominal sepsis. However, these indications were approved in less than 50% of health boards that added aztreonam to their formulary (53%) and were only reported in preference to meropenem in two health boards. Sensitivity testing and reporting were generated in all health boards only in resistant organisms and at the authorisation of a microbiologist.

Temocillin was approved to be used in 67% of health boards across NHS Scotland. Based on SAPG MDRGNB guidance, temocillin was suggested for UTI's and severe infections due to Gram-negative bacteria including ESBL-producing organisms.

Survey results showed that these indications were applied in 30% and 80% of health boards that added temocillin to their formulary respectively.

Oral pivmecillinam was approved in 73% health board, the second highest agent approved among the alternatives, and recommended to be used as an initial direct oral therapy for UTI or as a step-down agent for those receiving IV therapy against Gram-negative bacteria for a urinary tract infection according to SAPG guidance. The survey results showed that for the health boards where pivmecillinam was formulary approved, 64% approved it as a 2nd line alternative for the treatment of UTIs or as a first line in the case of multi-drug resistant microorganisms (55%). However, testing and reporting results for pivmecillinam were only made available if the organism was resistant and at the authorisation of a microbiologist and not reported nor tested in three health boards.

Fosfomycin is available in both oral and IV presentations, the oral formulation was the most common approved alternative (87%), with the IV form having 60% approval. The SAPG MDRGNB guidance recommends fosfomycin IV only in CPE infections, and health boards also use it as a 2nd line agent for the treatment of osteomyelitis, complicated UTIs and hospital-acquired lower RTI. This could be a potential area for improvement in the SAPG MDRGNB guidance to consider expanding indications and recommendations of fosfomycin IV. On the other hand, fosfomycin oral was found to be more accepted as an alternative based on the high approval status (87%). Both

dosage forms of fosfomycin, IV and oral, sensitivity are tested and suppressed routinely, at local health boards, in case of detected resistant organism, by microbiologists' authorisation.

2.4.5. Laboratory reporting

The culture and sensitivity reporting of an antimicrobial agent is a key factor in informing and directing a patient's treatment plan [208]. It can be helpful in preventing overtreatment or undertreatment of a patient. The study results show that all health boards routinely test the sensitivity of microbial isolates against meropenem and piperacillin-tazobactam. However, suppressing the results of these sensitivity reports were not performed for meropenem in two, and for piperacillin-tazobactam, in three health boards. When it comes to carbapenem sparing agents, the laboratory reporting of sensitivity profiles vary between health boards, and are mostly only reported only if a resistant organism is identified and under the authorisation of a microbiologist. Such an approach may limit the aim of the SAPG MDRGNB guideline to control the overuse of carbapenems and promote the use of the alternative agents [209].

The current survey included three questions targeting microbiology samples in an attempt to explore how NHS Scotland health board laboratories procedure of testing

to different samples origin and source. The questions were about MDR and *E.coli* suspicions which are the most common indication for targeted antimicrobials in this study. By investigating urine samples, results showed that fosfomycin, pivmecillinam, and co-amoxiclav are tested against over 60% of GP urine samples. In contrast, 80% of urine samples from hospitals were tested against meropenem and piperacillin-tazobactam, which is higher than that undertaken for the suggested alternative agents. Furthermore, these results perhaps suggest that microbiologists tend to focus on oral antimicrobial options for GP samples, but not to a greater extent. On the other hand, laboratory reporting focuses more on sensitivity of isolates to meropenem and piperacillin-tazobactam of hospital isolates in higher trend than other suggested alternatives which may affect the use and promotion of such agents.

Furthermore, only one health board would report the sensitivity of blood cultures to pivmecillinam and fosfomycin, and less than half the boards report the sensitivity of other oral agents; co-amoxiclav, co-trimoxazole, and tetracycline. Results showed that meropenem and piperacillin-tazobactam reporting were high for blood cultures [209].

2.5. Summary and introduction to the next chapter:

In summary, the majority of health boards have either updated local clinical policies based on the SAPG MDRGNB guidance recommendations or reviewed their local guidelines and found them to be in-line with the SAPG MDRGNB guidance. Training on prescribing of carbapenems and piperacillin-tazobactam are integrated into routine training in most health boards, and all health boards produce reports on consumption of these antimicrobials.

Meropenem is the most commonly used carbapenem in most health boards. It is formulary approved by all health boards, highly restricted, and prescribing is authorised via an alert antimicrobial policy. On the other hand, piperacillin-tazobactam is subject to prescribing restrictions in only 47% of health hoards whereby prescribing is authorised via an alert antimicrobial policy. It is used for the treatment of neutropenic sepsis in all health boards in accordance with the recommendation for empiric treatment of sepsis detailed in the SAPG guidance to reduce MDRGNB.

The most commonly used carbapenem sparing antimicrobials are fosfomycin and temocillin both of which are subject to prescribing restrictions within health boards. However, the other carbapenem sparing agents in use, namely pivmecillinam and aztreonam are infrequently used by health boards. The use of the carbapenem sparing agents is also in accordance with the SAPG MDRGNB guidance recommendations.

Meropenem, piperacillin-tazobactam and co-amoxiclav are the most frequently reported antimicrobials in MDR or ESBL *E. coli* urine and blood samples found to be sensitive. There is inconsistency in the approach of individual laboratories towards antimicrobial reporting nationally. Suppression and release of antimicrobials occur via a variety of mechanisms. The most common is by automatic rules on all samples. Other less commonly used methods include automatic rules on some samples or authorisation of lab reports by the microbiologist. There are differences between the reporting of antimicrobials depending on the origin of the samples (community vs acute services), though this is not consistent across the boards. Although tested in the laboratory, some carbapenem sparing agents are not routinely reported, and few are reported in preference to meropenem.

The results of this element of the study were shared with each health board AMT and discussed within the project steering group and SAPG regular meetings. From the results, we identified that most of the health boards have been acting to control both meropenem and piperacillin-tazobactam use. However, the consumption of meropenem and piperacillin-tazobactam are not improving, and consumption is on the increase. The result of this study was reported by the AMT's of each health board to their peers and stakeholders. However, the results from this research might not reflect real practice, data from this section of the project adds evidence on what stakeholders and regulators applied and implemented in their local health boards

[210]. Real practice situations need to explored and compared with this section result to investigate how adhered local practitioners are to local regulations and policies. This encourages the researcher to take the next chapter to the field and investigate how clinicians are prescribing targeted agents. In the next chapter, research will go to the field and look into practice at front-line stage focusing on targeted antimicrobials by this project. Thus, comparing what do leaders think and aim to happen at their local health boards with what is the situation in reality.

Chapter Three:

National Point Prevalence Surveillance Study within Acute NHS Scotland Hospitals

3.1. Introduction:

3.1.1. Background

By the second half of 2014, SAPG MDRGNB guidance was fully distributed to local NHS health boards via AMT's. However, no formal communication mechanism had been designed to allow health boards to feedback to SAPG on what actions had been organisationally implemented in response to the MDRGNB guidance and its downstream impact on clinical practice. In fact, when analysed, the consumption of carbapenem and piperacillin-tazobactam trend were fluctuating; Figure 3.1. Monthly carbapenem and piperacillin-tazobactam DDDs per 1000 population were plotted over the study period (Figure 3.1). Before SAPG MDRGNB guidance (intervention 1) carbapenems were increasing by 0.001 DDD per 1000 population each month (*P=0.006*) from a baseline of 1.287 DDDs per 1000 population. Intervention 1 was associated with an immediate decrease of 0.213 DDDs per 1000 population (*P=0.001*) and a change in the trend of 0.0058 DDDs per 1000 population (*P=0.28*). Before intervention 1, piperacillin-tazobactam was increasing by 0.014 DDDs per 1000 population each month (*P<0.001*) from a baseline of 1.888 DDDs per 1000 population. Intervention 1 was associated with an immediate increase of 0.149 DDDs per 1000 population (*P=0.02*) and a change in the trend of -0.015 DDDs per 1000 population (*P=0.002*). In May 2015, the researcher (AM) conducted a self-assessment

survey (Chapter 2) to have official baseline information regarding how health boards responded to the MDRGNB guidance. From the results in Chapter 2, it was identified that different health boards had been acting in a variety of ways to control meropenem, and to a lesser extent, piperacillin-tazobactam use. However, the consumption of these agents was not improving, which suggested that other contributing factors may also be driving usage of these antimicrobial agents. Base on the trend in the consumption data it was decided to undertake additional field work at targeted sites to understand better how these antimicrobial agents were getting used in clinical practice.

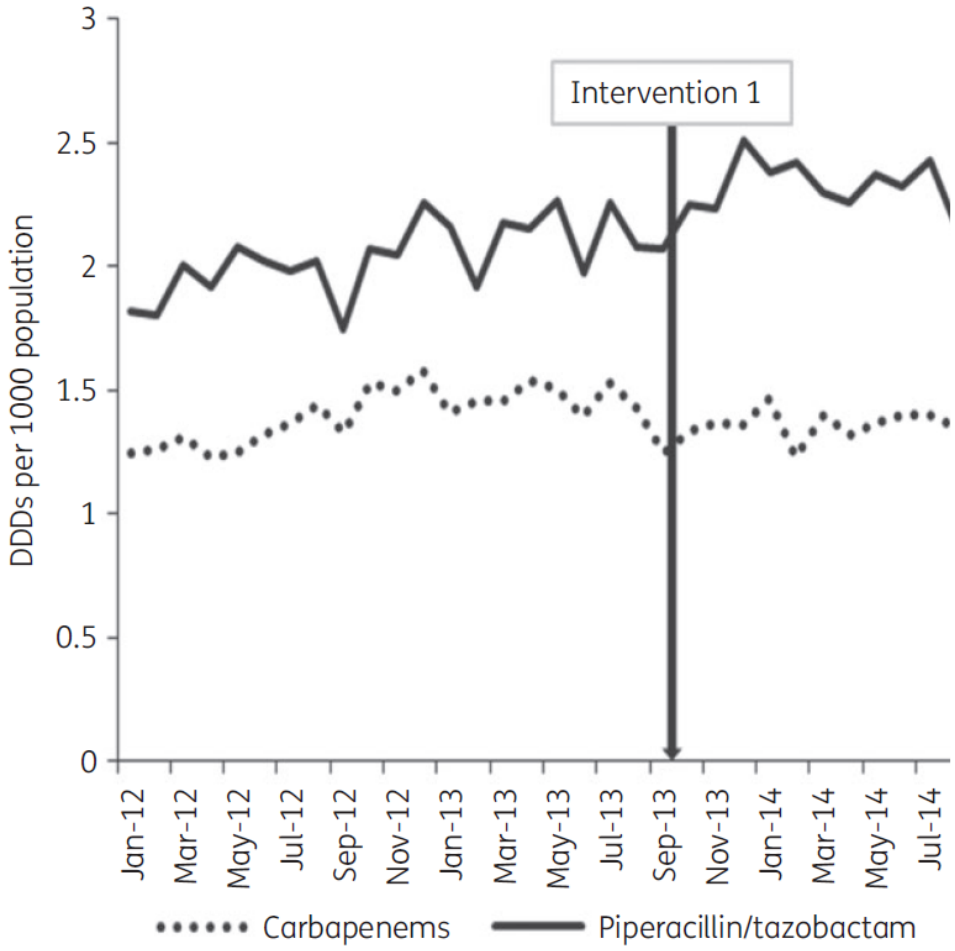


Figure 3.1: NHS Scotland: Meropenem and piperacillin-tazobactam national use (DDDs) from January 2012 to July 2014. Intervention 1: SAPG guidance on MDRGNB (October 2013)

3.1.2. Compliance with guidelines:

Antimicrobial prescribing is a multifaceted process incorporating numerous influencing factors. For example, within the same healthcare practice team, there is great variability in individual attitudes, the level of training, motivation, workload, patient interaction, accessibility to specialised support teams (e.g. infectious disease

and microbiology specialists), and diagnostic techniques. The multifactorial nature of antimicrobial prescribing often means that there is a high risk of inappropriate or sub-optimal antimicrobial prescribing. Ideally, good adherence to prescribing guidelines would enhance the quality and appropriateness of antimicrobial prescribing. However, real-life decisions and initiation of antimicrobial prescribing are most frequently not based on definitive clinical diagnoses, but on initial clinical presentation of the potential system(s) affected and the severity of the infection. Many antimicrobial prescribing errors occur around the choice and duration of treatment [211, 212]. Antimicrobial management policies should be developed to "improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration" [213]. Effective clinical practice guidelines appear to be fundamental to realising this objective [214, 215].

However, clinical practice guidelines become irrelevant and worthless if prescribers are unaware of their existence, and, consequently, fail to adapt and reduce them to practice. A number of studies have revealed that 30-40% of patients do not receive health care that is embedded in evidence-based medicine, and 20-25% of all healthcare provided is unnecessary [216-218]. The findings for antimicrobial prescribing are similar to some assessments suggesting that up to 50% of all hospital antimicrobial use is inappropriate [219, 220].

3.1.3. Antimicrobial prescribing evaluation:

There has been numerous research undertaken to define an accepted and standardised criteria of antimicrobial prescribing for auditing purposes. In 1973, Kunin et al. [221] published a simple classification of usage to "*appropriate, probably appropriate, inappropriate due to alternatives being less expensive or less toxic, or needing modification of the dose, or unjustified*". The classification was broad and nonspecific which led researchers to develop and refine classifications. The criteria were extended to include dose, dosage interval, route, serum concentration requests, duration of therapy, cost, allergies, the broadness of antimicrobial spectrum, therapy update after culture results, and keeping good patients record [218, 222]. Gyseens [222] modified and summarised the well-established factors that influence appropriate antimicrobial prescribing.

The criteria consist of six major areas:

1. Sufficient data in the records for evaluation, as a lack of sufficient data will affect any attempt to evaluate prescribing
2. Indication for antimicrobial therapy - is it justified?
3. Appropriate choice of antimicrobial
4. Duration
5. Appropriate pharmacokinetics; dose, interval, and route

6. Timing - too early or too late?

In recent years, both Public Health England and SAPG have promoted a “Start Smart – Then Focus” technique for a better antimicrobial prescribing [188]. The treatment algorithm can be observed in Table 6

Table 6 Start Smart then Focus treatment algorithm [188]

Treatment Algorithm	
Start Smart	→ **Then Focus**
Start with clinical evidence of bacterial infection	Clinical review after 48-72 hrs, document plan and microbiology results
1. **Allergy history** 2. **Therapy within one hour of diagnosis** 3. **Comply with local prescribing guideline** 4. **Document indication, dose and route** 5. **Include review/stop date or duration** 6. **Obtain cultures prior to initiating therapy when possible**	1. STOP 2. IVOS 3. De-escalation 4. Continue 5. OPAT Document all decisions and next review date

In 2016 SAPG published a document entitled, “Good Practice Recommendations for Hospital Antimicrobial Stewardship in NHS Scotland” [223] which supplemented the UK “Start Smart then Focus” document. For example, when selecting an antimicrobial, the SAPG document highlighted significant drug interactions which were absent in the “Start Smart then Focus” document. In addition, the SAPG document promoted daily review of antimicrobial prescribing with modifications made in light of any updates from microbiology test results or based on clinical signs. Furthermore, the SAPG document stressed the importance of documenting each decision made so that robust clinical governance was maintained. Both documents were up to date with the UK five years antimicrobial resistance strategy [55]. Therefore both documents help as a guide and a recommendation toolkit to audit the use of antimicrobial agents and improve patient safety.

3.1.4. Methods for evaluating the quality of antimicrobial prescribing:

Antimicrobial prescribing quality is conventionally measured by an in-depth review of patients’ medical records, charts or audits. An audit of antimicrobial use can be defined as “the analysis of the appropriateness of individual prescriptions” [224]. In-depth audits are time and labour-intensive. However, they are a comprehensive method to evaluate all aspects of therapy. In addition, feedback on the results of an

audit can be applied as an intervention to optimise antimicrobial use and define quality improvement targets [88, 225]. With new technology, computer software and health informatics systems are able to link clinical information with pharmacy and laboratory databases for the evaluation of antimicrobial prescribing quality. For example, the susceptibility of the causative pathogen can be directly linked to the empirically chosen antimicrobial in an ITU setting [226, 227]. This can facilitate extensive audits and reduce time and labour-intensity.

Another method for auditing and evaluating the quality of antimicrobial prescribing are prevalence studies. Prevalence survey studies are a useful and reliable method for estimating the use and quality of antimicrobial prescribing within a hospital setting. In addition, prevalence studies can be performed rapidly and less expensively. Furthermore, the trend of use and efficacy of intervention over time can be observed with a repeated prevalence study [228].

In Scotland, there are 14 regional NHS health boards and one national hospital, the Golden Jubilee National Hospital, providing mainly surgical services. At the time of this research project, all health boards had been involved in the first element of this research, outlined in chapter 2.

From Chapter 2 results, we identified variations regarding prescribing regulations and policies applied to the targeted antimicrobials. Different implementation methods may influence the use or interpretation of the SAPG MDRGNB guideline and subsequent utilisation of carbapenems and piperacillin-tazobactam. The SAPG MDRGNB guidance did not suggest a method of usage audit or feedback and simply encouraged close audit and monitoring. Despite the effort from stakeholders and decision makers at health boards, real-life practice cases can tell a different story. It was proposed that this part of the study focus on exploring how prescribers were adhering to policies. In addition to investigating how compliant prescribers were with good practice recommendations and the general quality of carbapenem and piperacillin-tazobactam prescribing, research also attempted to identify health boards that were considered to adopt best practices.

3.2. Method:

In this part of the research, all NHS Scotland health boards were invited to participate in evaluation meropenem and piperacillin-tazobactam prescribing quality in real-life clinical practice. The project was announced and publicised during regular SAPG meetings, with progress updates.

3.2.1. Aim

To examine the prescribing quality of meropenem and piperacillin-tazobactam across NHS Scotland and investigate variance in clinical use of these agents.

3.2.2. Research questions

D) How is meropenem used and prescribed in NHS Scotland?

E) How is piperacillin-tazobactam used and prescribed in NHS Scotland?

F) Are there any differences between health board's utilisation of meropenem, piperacillin-tazobactam, and CSAs?

3.2.3. Objective

To conduct a national point prevalence study using the British Surveillance of Antimicrobial Consumption (BSAC) National Antimicrobial Stewardship (NAS) PPS tool to determine the appropriateness of meropenem, piperacillin-tazobactam use, and CSAs.

3.2.4. Subjects

All patients within participating health boards prescribed meropenem or piperacillin-tazobactam, or CSA's during the survey period.

3.2.5. Setting

The project took place between September-November 2015 over a two-week period. The target was to involve all geographical health boards, where a full guideline is established and implemented.

3.2.6. Inclusion/exclusion criteria

All NHS Scotland health boards were invited to participate in this study. The following hospitals, wards, and patients were included:

- Hospitals: All acute care and paediatric hospitals, identified by the lead antimicrobial pharmacists.
- Wards: All wards, with the exception of day care units, and out-patient departments.

- Patients: All patients admitted to the ward/present on the ward on the morning of the survey, with the exception of day care patients.

The CSAs were excluded after discussions within the project steering group and feedback from SAPG meetings. The dissuasion was made based on the health board's CSAs approval status variation. From chapter two results, CSAs were not available in some health boards and implemented limitedly in others. Therefore, results will be influenced by multiple uncontrolled factors which support the dissuasion of excluding them at the current stage.

3.2.7. Ethical approval

NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK, was not required. The proposed project was designed to evaluate current prescribing of meropenem and piperacillin-tazobactam without any interference with ongoing therapeutic plans or violating patients' confidentialities. Furthermore, the researcher (AM) applied and granted a Caldicott Guardian approval prior to conducting the research (Appendix#6) which ensure the research follows ethical obligations. University ethical approval was also unnecessary because the University of Strathclyde Code of Practice on Investigations Involving Human Beings does not apply to studies of routine practices in professional contexts,

service evaluations conducted solely to define or assess a particular service provided or audits of existing services. However, in line with best ethical practice, data were recorded and stored in an electronic form (and NAS-PPS encrypted server) with no personally identifiable information, entered and submitted by health boards leader investigators and reviewed by research lead investigator for feedback to research steering group for analysis [176, 177].

3.2.8. Design

The point prevalence surveillance study was the method of choice selected to fulfil the aim of the study. Following discussion with the project steering group, electronic surveillance software (BSAC-PPS; [229]) was recommended to coordinate and collate data collection across NHS Scotland. This software for PPS studies was a development of previously used ESAC-PPS software [70]. The NAS-PPS software was used in the pilot phase of software development. During the project, BSAC gave the PPS software free of charge and provided full technical support.

3.2.8.1. Setup Phase

There were three phases of project delivery with an agreed deadline date for completion of the PPS (30th of October, 2015). Phase one: the responsibility of the

Survey Administrator (project lead) managing and directing the survey, and set up all "Organisation Supervisors" within each health boards. Phase two: once each organisation was set up by the survey director; all organisation supervisors received an email with their login details. Each organisation supervisor needed then to register all hospitals which were to be included in the survey. In parallel, organisation supervisors assigned users to each hospital (defined as the Hospital Supervisor). Phase three: once set up by the organisation supervisors, all hospital supervisors received an email with their login details. Each hospital supervisor needed to set up all wards to be included in the survey and inform individual ward nurse in-charge about the project. At the same time, hospital supervisors must assign users to each ward (defined the Ward Officer). By the deadline date, any health board that failed to finish setting up as described were excluded from the study.

3.2.8.2. Education and training

Once the setup phase was performed, names of participants from each health boards were known. Each individual received a confirmation letter, project protocol, concise guide for using the NAS-PPS (Appendix#7) and had to participate in a webinar education session conducted by the survey director and primary researcher (AM) on three separate dates.

3.2.8.3. Data Entry Phase

The survey opened for data input from 21st of September to the 30th of October, 2015. Any data entered before or after these dates were excluded from the study. There were four phases of data entry. Phase one: ward officers were responsible for collecting and entering data into the system for review and approval. Phase two: Once data entry was complete for each ward this was submitted to the hospital level (hospital supervisor) for approval. Hospital supervisors were responsible for checking data-entry from each ward, reviewing submitted patients, approving submitted patients, or rejecting submitted patients if needed. Phase three: once all the data was complete for the hospital, the hospital supervisor submitted the data to the organisation supervisor (board/trust level). Organisation supervisors were responsible for checking data-entry for each hospital, reviewing approved patients, and publishing hospital data. Phase four: once all of the data completed and approved by the organisation supervisor for the board/trust, the data was submitted to the survey director. There were different roles and responsibilities for running surveys, and these were defined within the database during the setup phase, each is outlined in Table 7.

Table 7 Roles and responsibilities of each surveyor

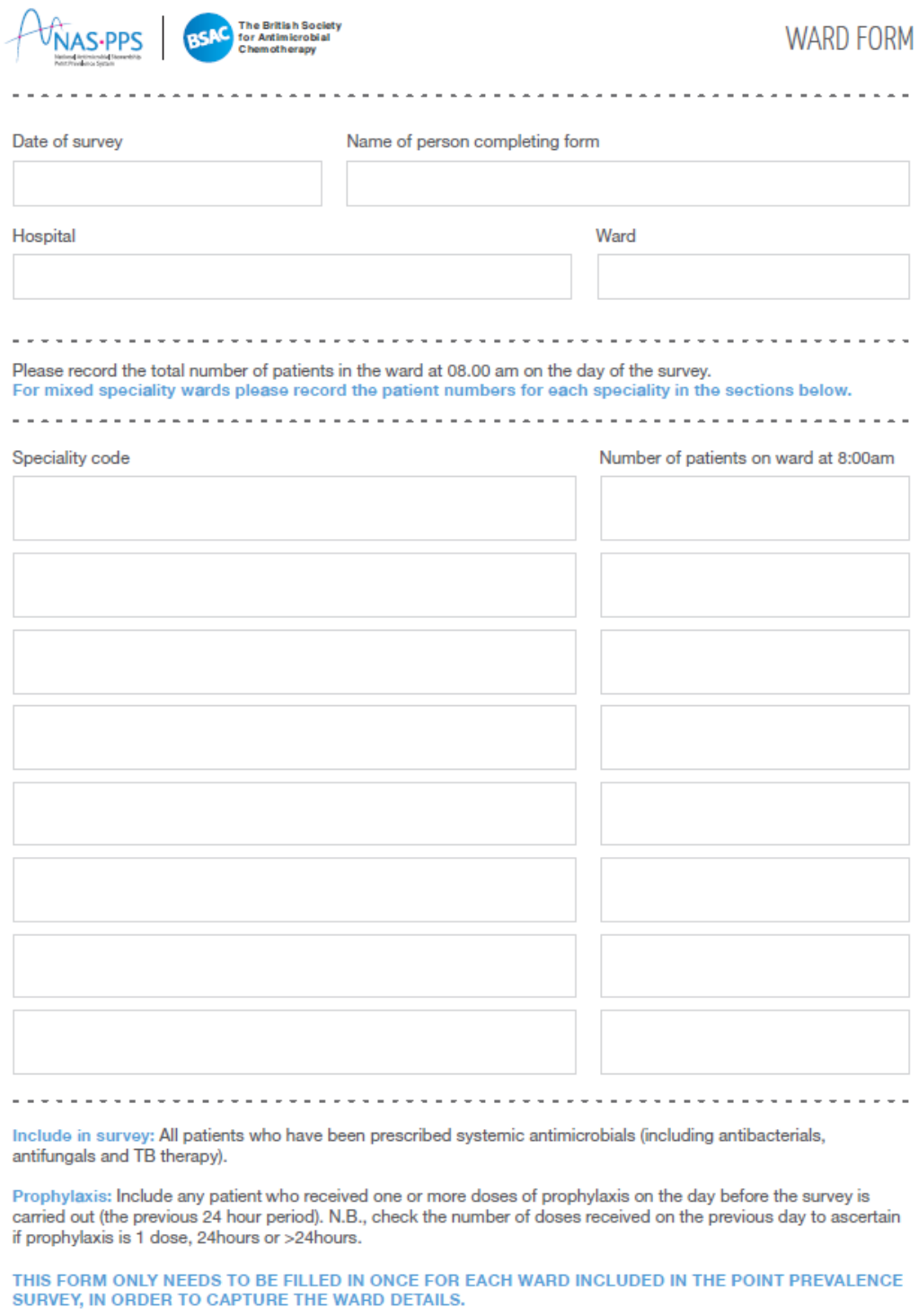
Role	Description	Responsibilities
Survey Director	Survey Lead / Manager	• Creating Organisations (at the board/trust level) • Creating Organisation Supervisors for each organisation (board/trust) • Creating National Surveys
Organisation Supervisor	Trust / Board user	• Creating hospital organisation records • Creating Hospital Supervisors / Users • Allocating a hospital supervisor to each hospital in the survey • Publishing hospital data
Hospital Supervisor	Hospital user	• Creating Ward records • Creating Ward Officer users • Allocating an Officer to each ward in a survey • Reviewing and approving patient data
Ward Data Manager	Ward user	• Capturing ward specialities • Capturing data for patients • Reviewing and submitting patient data for approval to Supervisors

3.2.8.4. Data collection

Prior to the day of data collection, a letter was sent to each ward outlining the background to the survey and how data would be collected on the day of the survey, Appendix #7. The nurse(s) in charge of each ward was notified in advance of the date of the visit to collect data. On the day of the survey data, collection staff introduced themselves to the staff on the ward and started to populate the ward form, Figure 3.2. The ward form only needed to be completed once for each ward included in the survey day and all admitted patients were reviewd for targeted antimicrobials. The form contained the date of data collection in a particular ward, the name of the data

collector, the name of the hospital, and the ward speciality code (appendix#8). Also, the total number of patients in the ward at 0800 on the day of data collection was recorded.

Each patient identified (on targeted antimicrobials) and included in the study had a patient form completed, Figure 3.3, one form per patient. There were three types of patient forms: adult, paediatrics, and neonatal. In each patient form hospital name, ward number or name and speciality code were written. In addition, CHI number of the patient, date of birth, and gender was included in the patient's demographic information. Drug information followed by entering the name of the medication, meropenem or piperacillin-tazobactam, dose in grams per administration, frequency, and indication using the code list provided (Appendix#8) which can be found in the medical notes or the Kardex. Also, the starting date, reason or rational of antimicrobial use (if available from notes), the day of therapy, review/stop date documentation in medical note or Kardex, and whether the indication of the antimicrobial used followed local guidelines or not.



NAS·PPS | BSAC The British Society for Antimicrobial Chemotherapy

WARD FORM

Date of survey

Name of person completing form

Hospital

Ward

Please record the total number of patients in the ward at 08.00 am on the day of the survey.
For mixed speciality wards please record the patient numbers for each speciality in the sections below.

Speciality code	Number of patients on ward at 8:00am

Include in survey: All patients who have been prescribed systemic antimicrobials (including antibacterials, antifungals and TB therapy).

Prophylaxis: Include any patient who received one or more doses of prophylaxis on the day before the survey is carried out (the previous 24 hour period). N.B., check the number of doses received on the previous day to ascertain if prophylaxis is 1 dose, 24hours or >24hours.

THIS FORM ONLY NEEDS TO BE FILLED IN ONCE FOR EACH WARD INCLUDED IN THE POINT PREVALENCE SURVEY, IN ORDER TO CAPTURE THE WARD DETAILS.

Figure 3.2: NAS-PPS Ward information collection form. Each surveyed ward had a dedicated form filled by the data collector, including speciality and a total number of all patients on the day of the survey.

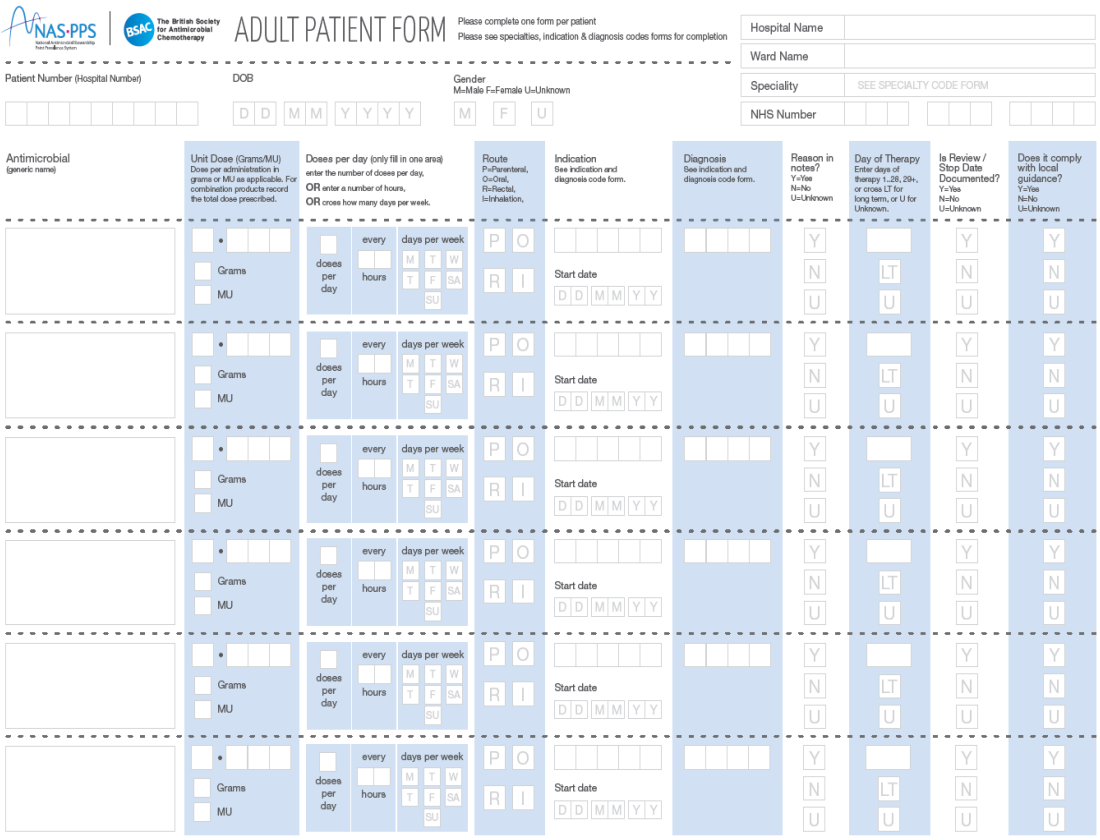


Figure 3.3: NAS-PPS Adult patient collection form. Each identified patient with meropenem or piperacillin-tazobactam was recorded in an individual form. All information was collected by the data collector from medical notes and KARDEX.

3.2.8.5. Prescribing rate during the PPS study:

Comparison of the prescribing rates for meropenem and piperacillin-tazobactam during the period when the boards undertook the PPS, and their annual prescription rates were conducted. The annual rate of prescribing was obtained through the Hospital Medicine Utilisation Database (HMUD).

3.2.9. Result reports

The NAS-PPS database had a built-in report generator. This feature was flexible and specific reports could be requested prior to conducting the PPS. The project steering group agreed on the following reports: demographics, treatment duration, number of prescriptions per speciality, diagnosis, the source of infection, compliance with policy, documentation of review/stop orders, and indication documentation. The reports were generated through NAS-PPS software stating the number of occurrences. Data were then exported to Microsoft Excel 2010® for further analysis and graphical illustration. Data analysis was carried on by the primary researcher (AM). Results from these reports fulfilled the objectives of this element of the study. Furthermore, data were presented; by the main researcher, in an infographic format, allowing each health board to identify where they stood compared to the national average.

3.3. Results:

All 15 health boards responded to the PPS. However, two smaller health boards, Orkney and Shetland, were excluded because of having no AMT lead-in post (Orkney health board) or administrative delays (Shetland health board). Both health boards

combined account for less than 0.8% of the Scottish population, so the impact of their omission from the PPS was limited.

3.3.1. Survey Characteristics:

A total of 12,478 inpatients in 38 hospitals were included in the survey, representing 13 out of 15 NHS Scotland health boards. From the 12,478 patients surveyed, 466 patients were eligible (3.7%) for study inclusion. Meropenem was observed in 129 patients (27.7% of eligible patients) and piperacillin-tazobactam in 337 patients (72.3% of eligible patients). The number of prescriptions from each health board were normalised to prescriptions per 100 sampled patients, Figure 3.4.

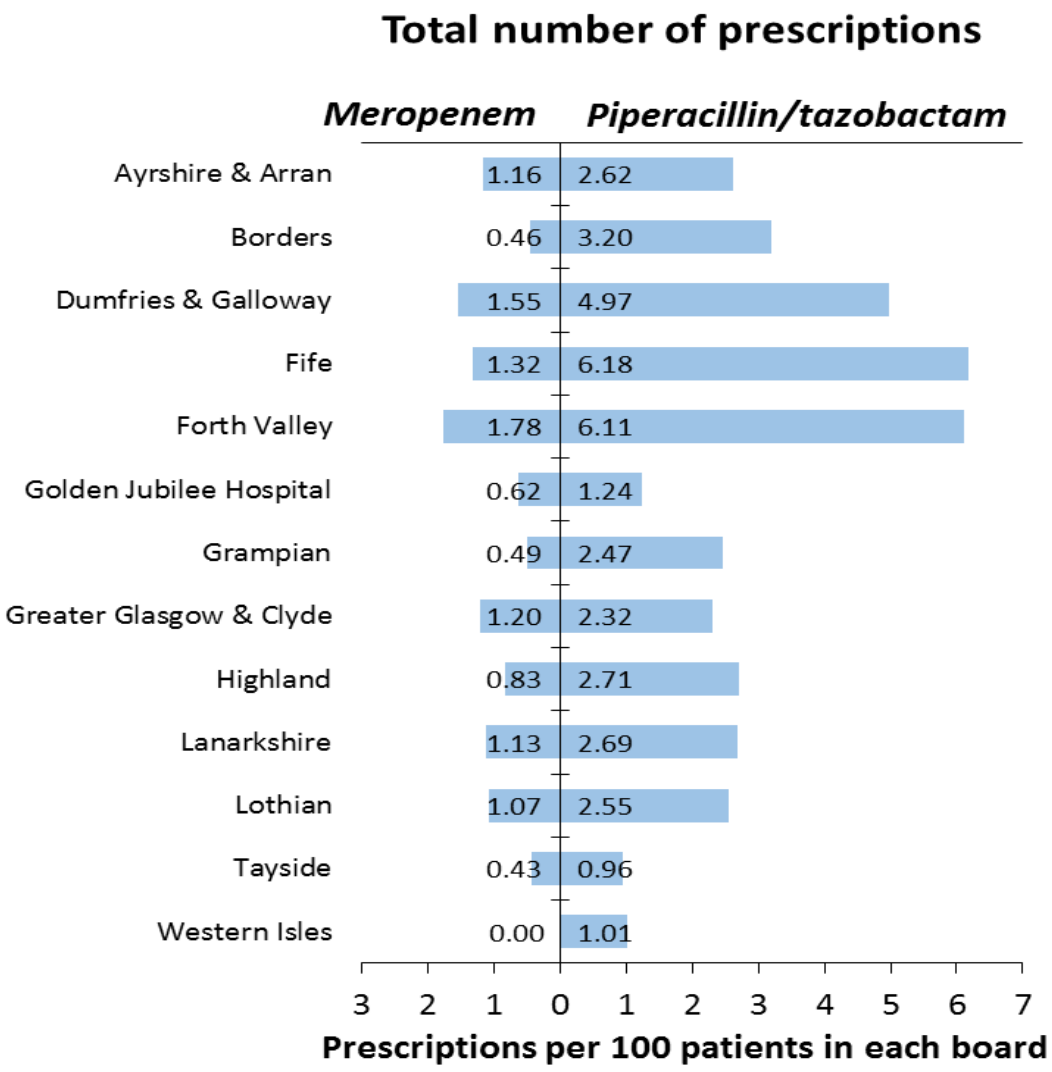


Figure 3.4: Prescriptions for meropenem and piperacillin-tazobactam normalised to per 100 sampled patients in each health board. Dumfries & Galloway, Fife, and Forth Valley were the top three health boards in prescribing both meropenem and piperacillin-tazobactam per 100 patients. Western Isles, Tayside, and Borders health boards were the meropenem less prescribing per 100 patients. Western Isles, Tayside, and Golden Jubilee health boards were the piperacillin-tazobactam less prescribing per 100 patients.

3.3.2. Description of the survey population:

The age range and gender distribution of the included patients, classified based on each targeted antimicrobial, is described in Figure 3.5. Overall, the study included 262

males (56%) and 204 females (44%). The highest age range of patients on meropenem surveyed was 65-79 years old (34%), where 58% of patients were male (n=75), and 42% female (n=54). The highest age range of patients on piperacillin-tazobactam surveyed was also 65-79 years old (38%), where 55% of patients were male (n=187), and 45% female (n=150).

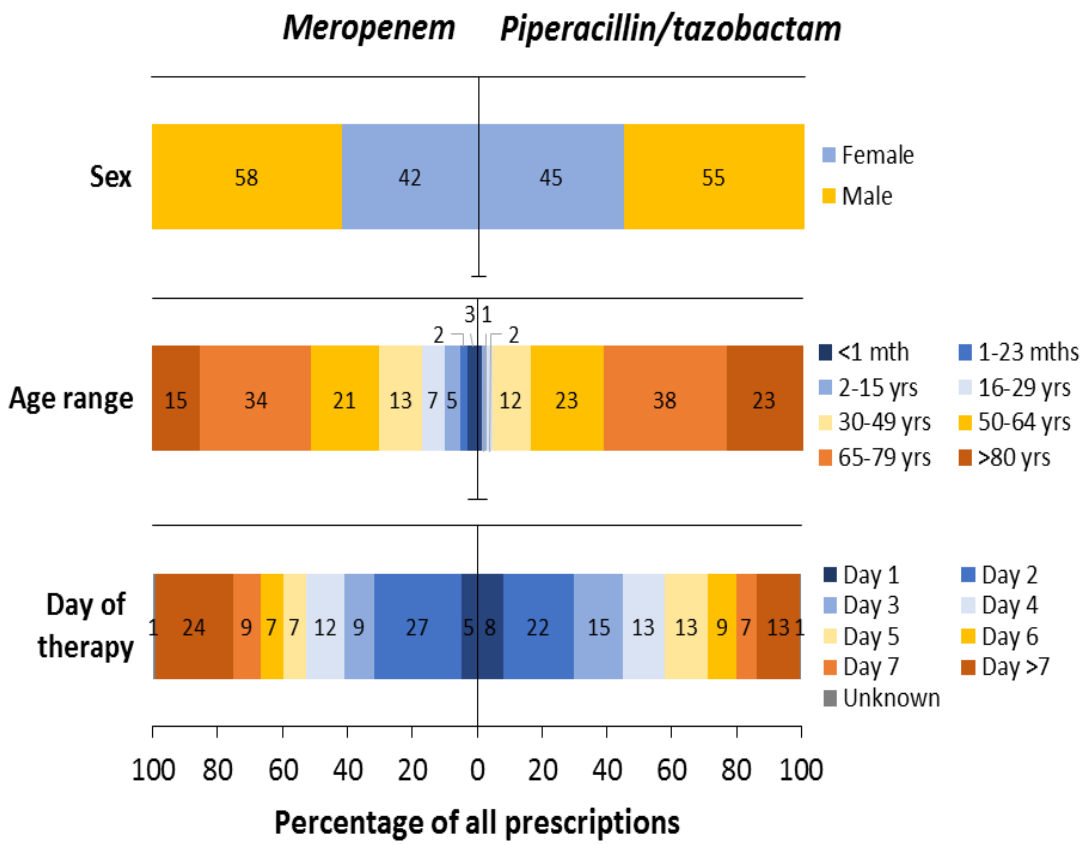


Figure 3.5: Demographics results of the population (gender and age range), and day of therapy for both targeted antimicrobials in percentage. Male>female, 65-79 years age range was the most common, and day 2 in therapy was more frequent.

3.3.3. Antimicrobial therapy characteristics:

In this section, results relating to the therapeutic plan of included patients are presented. This includes days of therapy, diagnosis, the source of infection (hospital vs community), and the clinical speciality to which the patient was admitted.

3.3.3.1. Days of therapy

With both antimicrobials, the majority of patients were in their second day of therapy, meropenem (27%) and piperacillin-tazobactam (22%), however, around 60% of prescriptions were prescribed for four or more days. Patients on meropenem over seven days were the next common group (24%), followed by patients on the fourth day of therapy (12%). On the other hand, piperacillin-tazobactam patients on day three of therapy were the second most common group (15%). Only one patient on meropenem and two patients on piperacillin-tazobactam had an unknown day of therapy (Figure 3.5).

3.3.3.2. Speciality

The ward speciality where patients were admitted was included in the data collection phase. However the results may not clearly represent who initiated the targeted

antimicrobials, but it at least indicates the primary speciality team of each patient. Figure 3.6 illustrates the most common specialities where patients were admitted. Both antimicrobial agents were prescribed by different specialities. General medicine wards accounted for (13%) of meropenem and (20%) of piperacillin-tazobactam prescribing. Intensive care units were the second most common prescribers of meropenem (10%), followed by general surgery (9%). General surgery wards accounted for (16%) of piperacillin-tazobactam prescribing, followed by geriatrics (9%).

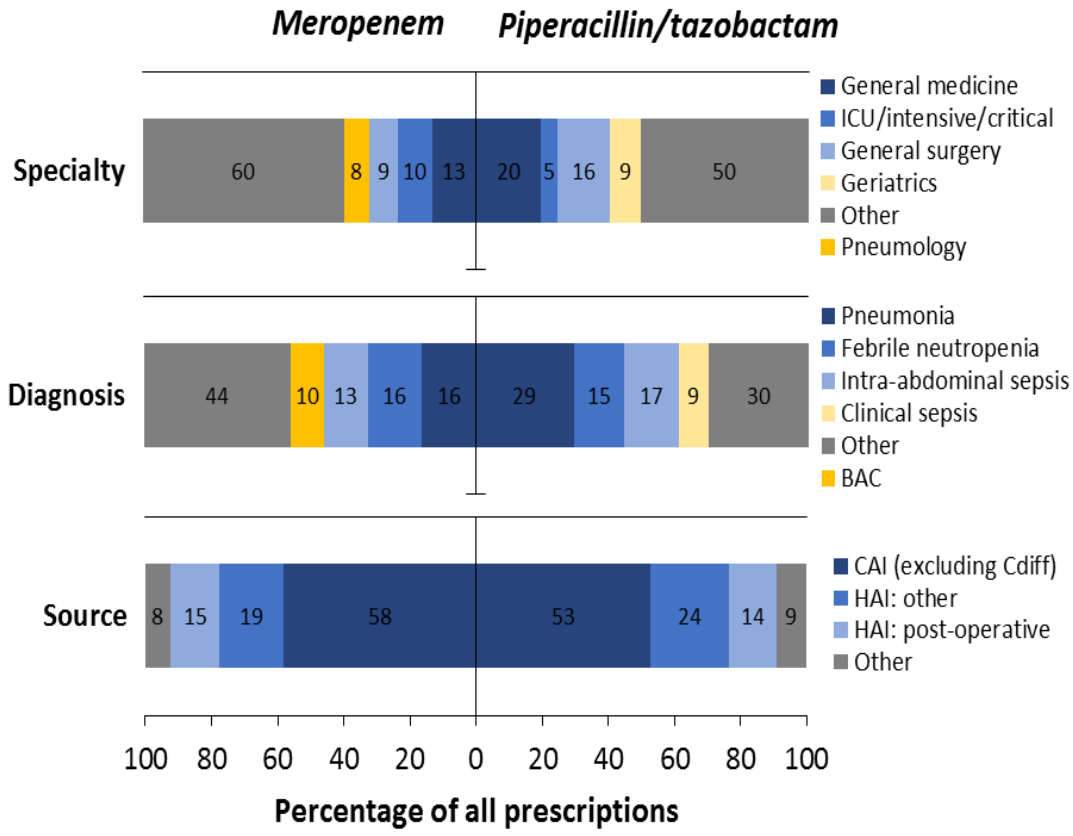


Figure 3.6: Antimicrobials therapy characteristics result in percentage. General medicine (20%, 13%) was the major prescribing speciality for both agents. Pneumonia (29%) was the main reason for prescribing piperacillin-tazobactam, febrile neutropenia (16%) and pneumonia (16%) were the main prescribing reason for meropenem. Community-acquired infections (53%, 58%) was the predominant Source of infection in collected data.

BAC: Laboratory Confirmed Bacteraemia

CAI: Community-Acquired Infection

HAI: Hospital Acquired Infection

3.3.3.3. Diagnosis

The diagnosis was identified and classified based on the BSAC NAS-PPS definitions (Appendix#8). The presented results are based on the diagnosed infection recorded by the treating teams (Figure 3.6). Non-infectious diagnoses were not included in this

study. The most common clinical indications for meropenem prescribing were pneumonia, intra-abdominal sepsis, febrile neutropenia or clinical sepsis, which accounted for 66% of all prescriptions. For piperacillin-tazobactam, 70% of prescriptions were for pneumonia, intra-abdominal sepsis, and febrile neutropenia or bacteraemia indications.

For meropenem prescribing, pneumonia and febrile neutropenia were the top two diagnosed infections (both 16%), followed by intraabdominal sepsis (13%). Laboratory confirmed infection came in third (10%) and only one patient prescribed meropenem have an unknown diagnosis.

Piperacillin-tazobactam was prescribed in patients diagnosed with pneumonia (29%), intraabdominal sepsis (17%), and febrile neutropenia (15%). Clinical sepsis diagnosis included suspected bloodstream infection without laboratory confirmation and/or results were not available, no blood cultures collected or negative blood culture, excluding febrile neutropenia. This accounted for 9% of prescriptions. There were 13 patients prescribed piperacillin-tazobactam (3.8%) who had an unknown diagnosis.

3.3.3.4. Source of infection

The source of infection, based on the BSAC NAS-PPS collection guide, was classified as either community-acquired (excluding *C. difficile*) or hospital-acquired. Hospital-acquired infection was further classified to into either post-operative infection (within 30 days after surgery or one year after implant), hospital-acquired intervention related infections, "other" hospital-acquired infection, and hospital-acquired infection present on admission from another hospital or care/nursing home.

Both antimicrobial agents were mostly prescribed for community-acquired infections, meropenem (58%) and piperacillin-tazobactam (53%), Figure 3.6. Other hospital-acquired infections; i.e. not associated with post-operative, intervention-related, and cases presented from other facilities with an ongoing hospital infection; accounted for 19% of meropenem and 24% of piperacillin-tazobactam prescribing. All patients prescribed meropenem have an identified source of infection. However, nine patients (2.6%) prescribed piperacillin-tazobactam had an unknown source of infection.

3.3.4. Antimicrobial prescribing quality indicators:

Three quality parameters evaluated the prescribing quality of targeted antimicrobials. All three were agreed on by the project steering group as they fulfilled the study objectives and could be collected in a time efficient manner. All three indicators were recommended and available in the BSAC NAS-PPS data collection sheet. Compliance with local policy, indication documentation in medical notes or Kardex, and a review/stop date documentation were the three chosen indicators.

3.3.4.1. Overall result

The reason for the antimicrobial prescription was documented in 97% of meropenem prescriptions and 88% of piperacillin-tazobactam prescriptions. Compliance with local policy was 88% for meropenem and 70% for piperacillin-tazobactam. Documentation of a review or stop date for antimicrobial prescriptions was 31% for both antimicrobials (Figure 3.7).

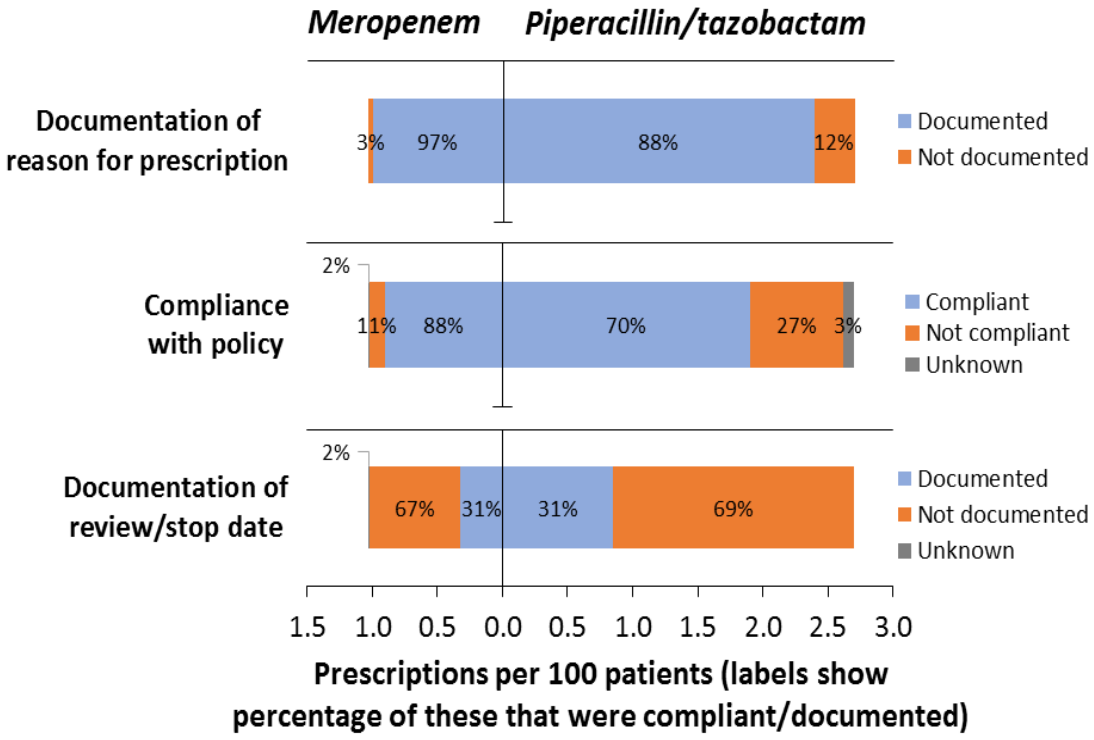


Figure 3.7: Overall results in percentage per 100 patients of prescribing quality indicators. Results show a high level of reason for prescribing documentation and compliance with policy for both agents. Documentation of review/stop date was low for both agents (69% piperacillin-tazobactam, 67% meropenem).

3.3.4.2. Prescriptions compliant with local policy

Although the top quartile level was calculated, it was not possible to directly compare compliance with policy between the health boards as they all follow different antimicrobial prescribing policies (see Chapter 2, sections 2.3). However, the top quartile values provide an indicator for the health boards of good practice to aspire towards (Figure 3.8).

Meropenem in six health boards achieved 100% compliance with local policy although the number of prescriptions for meropenem was small, varying from one (0.46 per 100 sampled patients, Borders health board) to nine prescriptions (1.78 per 100 sampled patients, Forth Valley health board). The remaining health boards achieved 80% to 90% compliance with the numbers of meropenem prescribing varying between 5 (1.55 per 100 sampled patients, Dumfries and Galloway health board) to 44 (1.2 per 100 sampled patients, Greater Glasgow and Clyde health board).

Piperacillin-tazobactam compliance with local prescribing policies was much lower than meropenem, varying from 44 - 93% in 10 health boards. Only Borders, Western Isles, and the Golden Jubilee achieved 100% compliance, and the numbers of prescriptions were minimal (seven (3.2 per 100 sampled patients), one (1.01 per 100 sampled patients) and two (1.24 per 100 sampled patients) prescription respectively). Four health boards achieved the top quartile level of 89% prescriptions compliant with policy. Again there was a considerable variation in the numbers of prescriptions assessed, ranging from 84 (2.32 per 100 sampled patients) in GGC to 1 (1.01 per 100 sampled patients) prescriptions in the Western Isles.

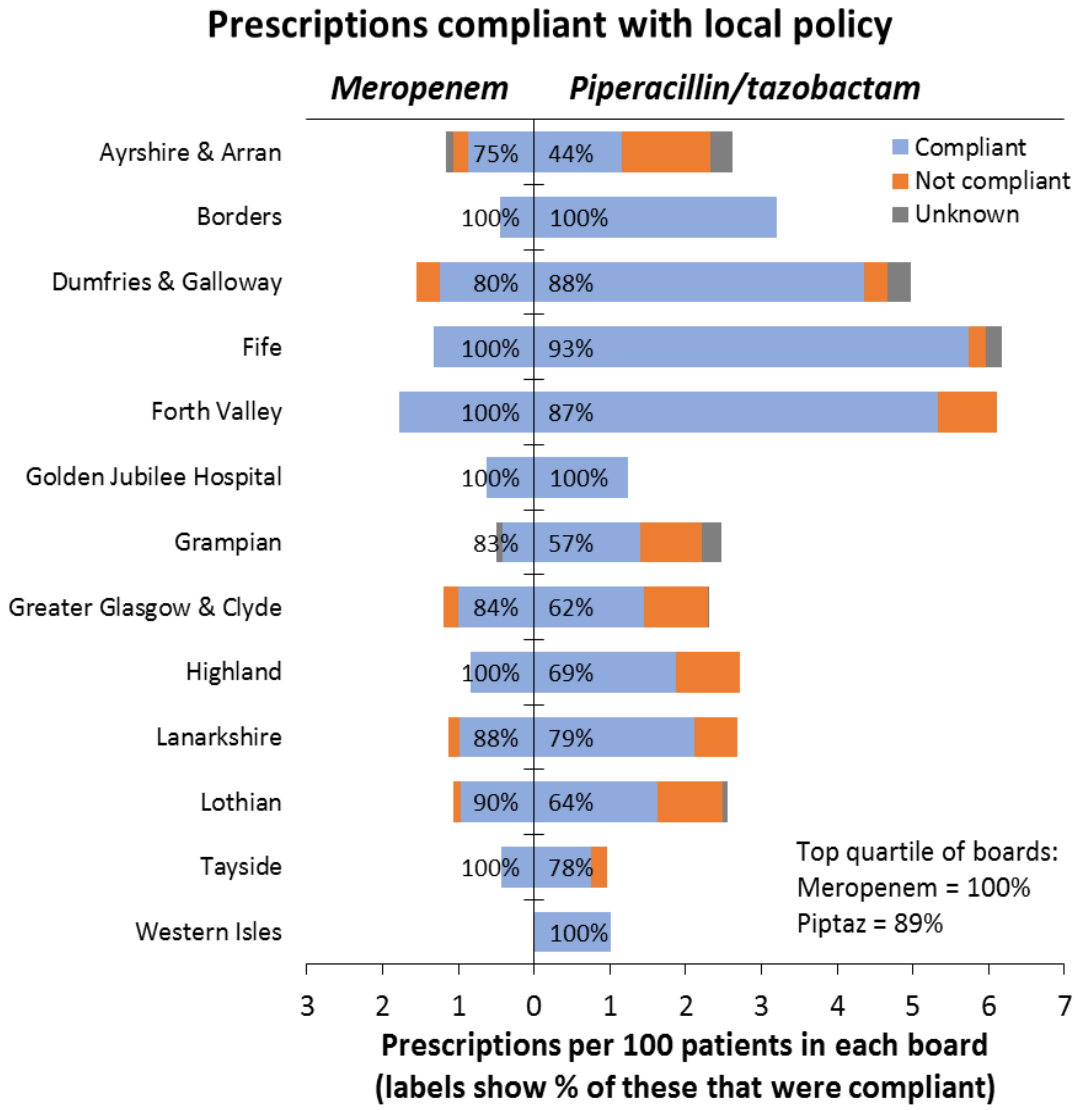


Figure 3.8: Individual health board prescriptions compliant with local policy in prescriptions per 100 patients. Meropenem: higher rates of compliance to local policy, top quartile 100%. Piperacillin-tazobactam: top quartile 89%. The Western Isles had no prescribed meropenem during collection stage.

3.3.4.3. Prescriptions with a documented indication

For meropenem prescribing, most health boards achieved greater than 92% documentation of the clinical indication, with numbers of meropenem prescriptions

ranging from 1 to 44 prescriptions. Nine health boards out of 13 achieved the top quartile level of 100% documentation of indication (Figure 3.9).

With piperacillin-tazobactam prescribing, documentation of clinical indication was much less frequent compared to meropenem and ranged from 50% in the Golden Jubilee to 100% in Tayside and the Western Isles. Five health boards achieved greater than 95% documentation of indication (the prescribing indicator target level and top quartile level) for piperacillin-tazobactam. The numbers of prescriptions analysed varied considerably from 2 in the Golden Jubilee to 85 in GGC (Figure 3.9).

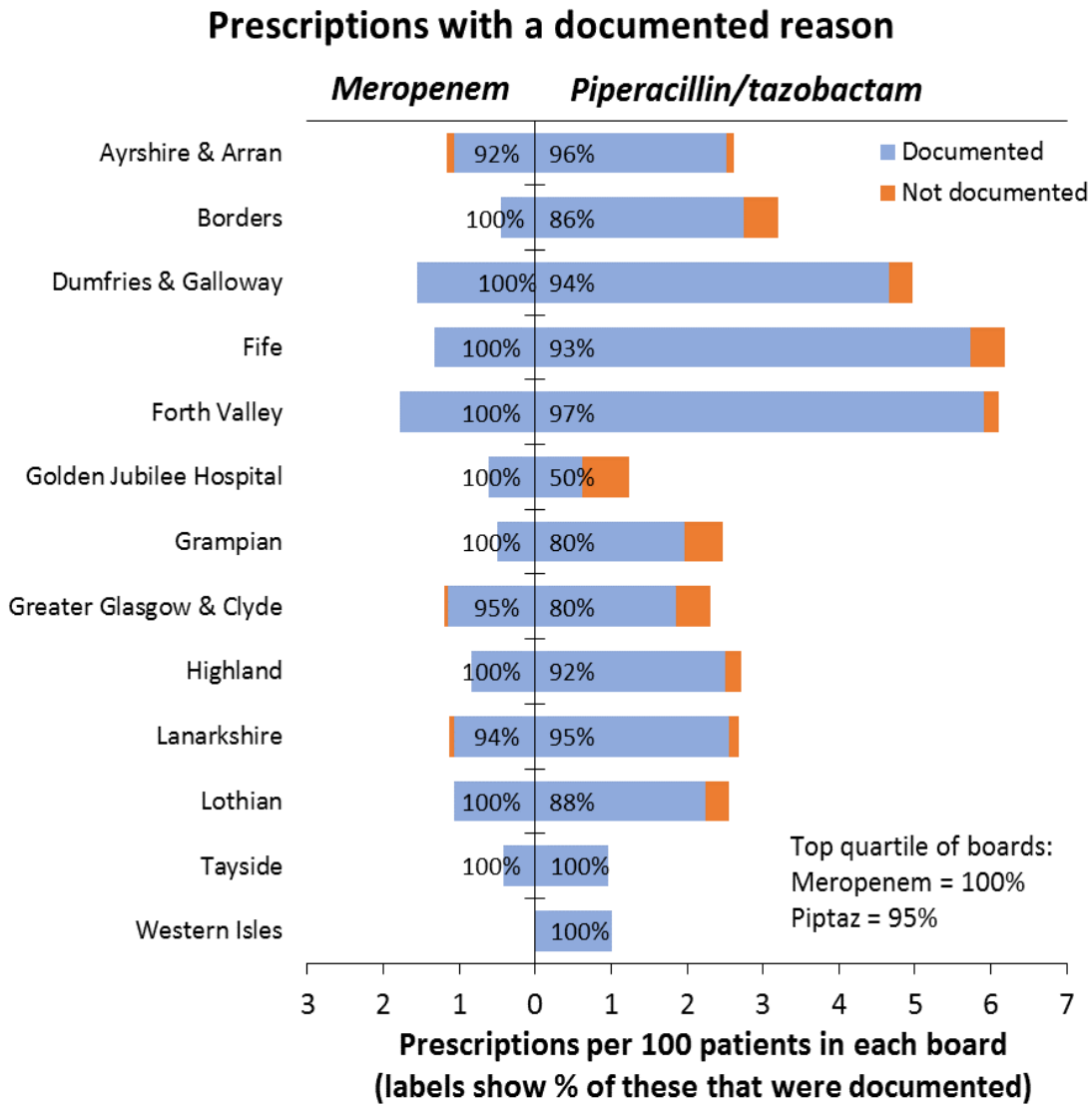


Figure 3.9: Individual health board prescriptions with a documented indication in medical notes or KARDEX in prescriptions per 100 patients. Meropenem: higher rates of compliance to indication documentation, top quartile 100%. Piperacillin-tazobactam: top quartile 95%. The Western Isles had no prescribed meropenem during collection stage.

3.3.4.4. Prescriptions with a documented review/stop date

For meropenem prescribing, there was considerable variation between the health boards with results ranging from 0% (Dumfries and Galloway, Western Isles and

Borders) to 100% (Highland and Golden Jubilee) prescriptions with a review/stop date. Numbers of prescriptions again varied considerably between the health boards and ranged from zero in the Western Isles to 45 in GGC. Only three health boards achieved the top quartile level of 69% (Tayside, Highlands and Golden Jubilee; Figure 3.10).

With piperacillin-tazobactam, prescriptions with a review/stop date also varied considerably between health boards ranging from 0% in Dumfries and Galloway to 100% in the Western Isles. Eight health boards achieved from 20% to 67% prescriptions review/stop date documentation. Only four health boards achieved the top quartile level of 54% prescriptions of review/stop documentation. Again, the number of prescriptions assessed varied considerably from one in the Western Isles to 87 prescriptions in GGC (Figure 3.10).

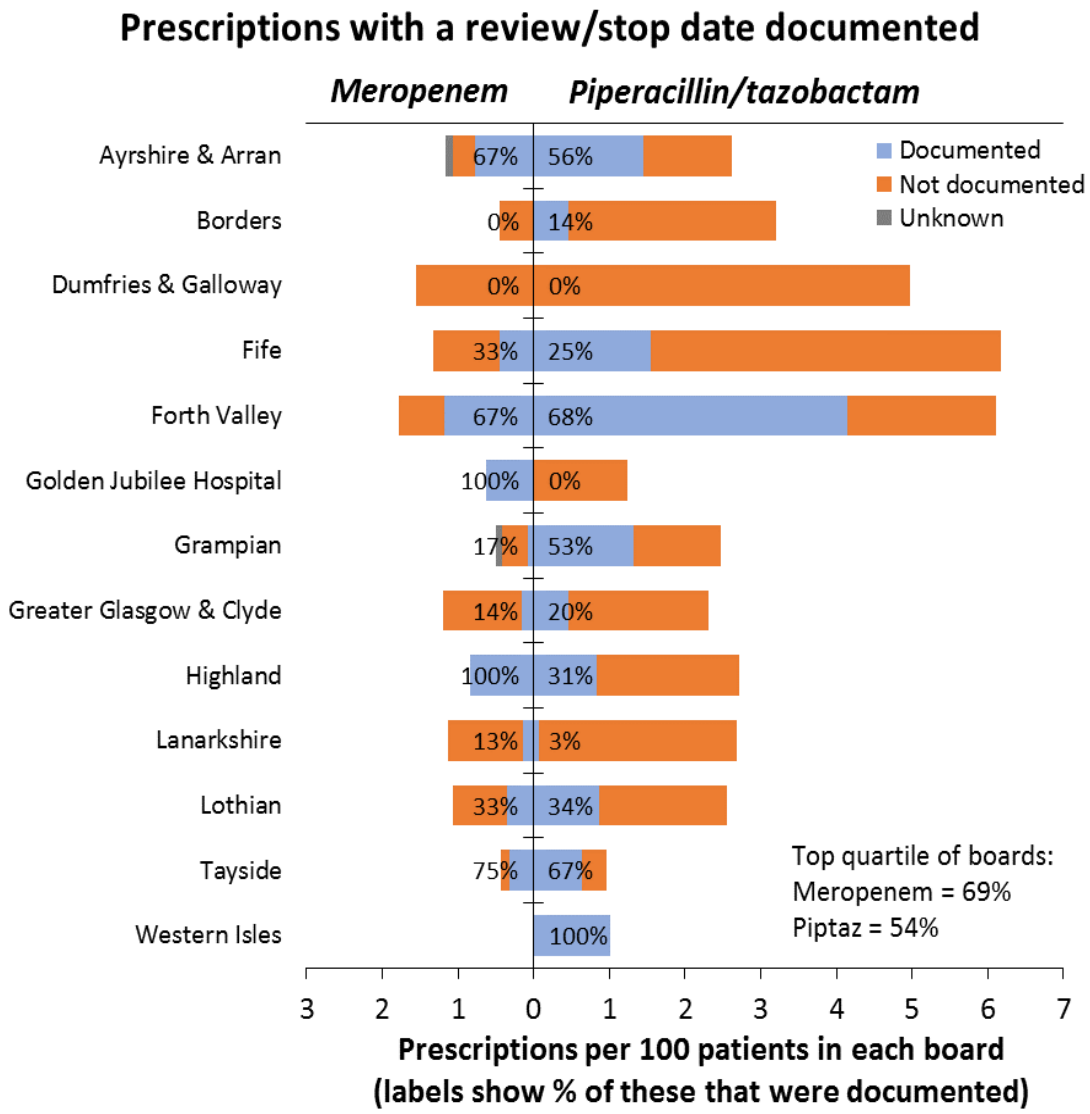


Figure 3.10: Individual health board prescriptions with documented review/stop recorded date in medical notes or KARDEX in prescriptions per 100 patients. Overall, compliance was low, meropenem: higher rates of compliance compared to piperacillin-tazobactam, top quartile 69%. Piperacillin-tazobactam: top quartile 54%. The Western Isles had no prescribed meropenem during collection stage. Borders and Dumfries & Galloway health boards showed no documentation for targeted antimicrobials.

3.3.5. Prescribing rate during the NAS-PPS study period

To confirm that use of meropenem and piperacillin-tazobactam on the day of the PPS was typical, data were compared with the previous year's annual use of the antimicrobials in each health board, measured in defined daily doses, using HMUD database. Comparison of the prescription rates for the period when the boards undertook the PPS and their annual prescription rates for both meropenem and piperacillin-tazobactam showed that the prescription rates during the PPS were comparable to the annual prescribing rates (Figure 3.11).

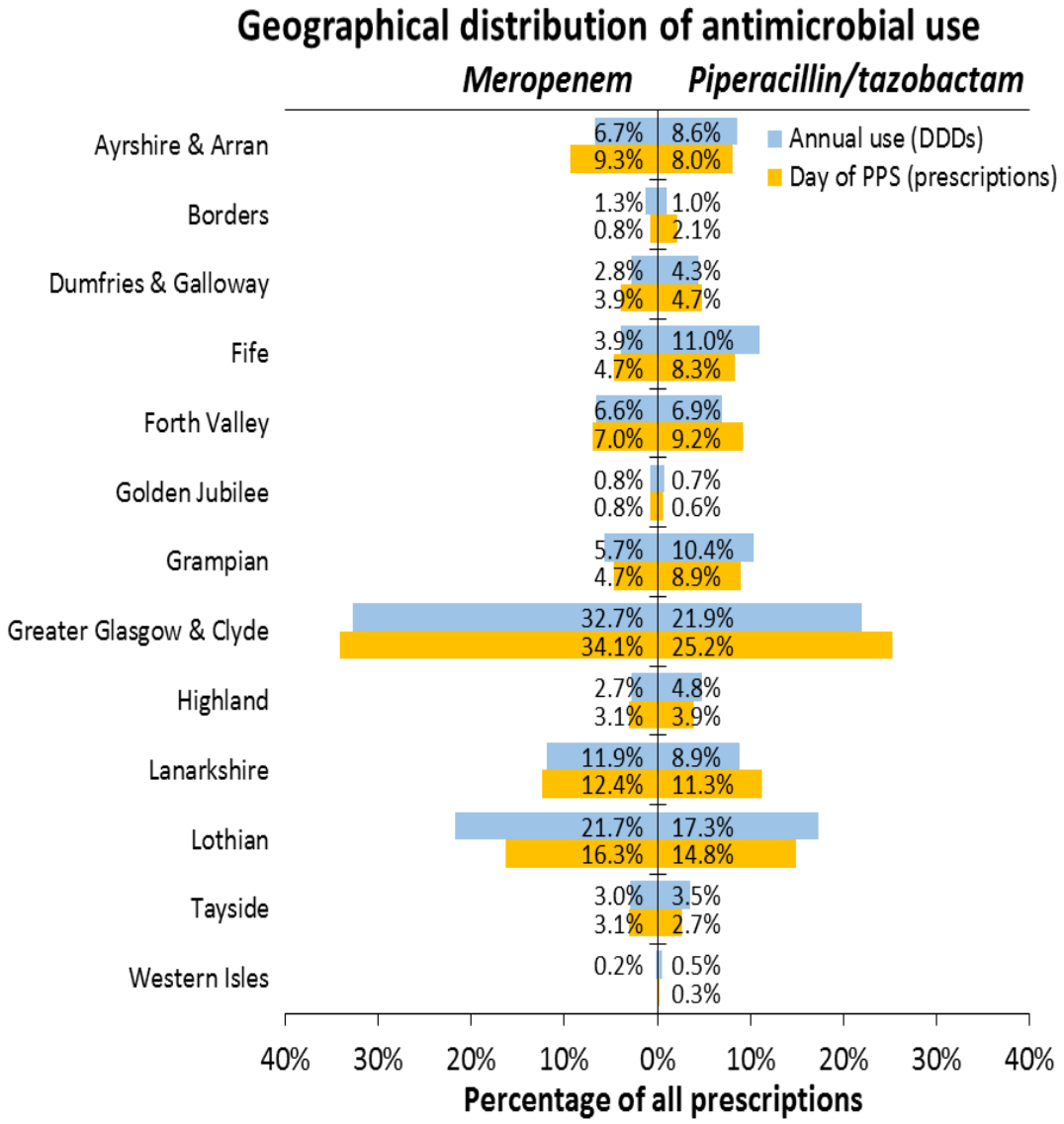


Figure 3.11: Geographical distribution of meropenem and piperacillin-tazobactam prescribing rates in per cent during the PPS study period compared to annual use rate. Prescribing rates during PPS study period were comparable to annual use rate. Source: HMUD

Each health board received an individualised report including both survey and PPS results. The report shows national results and where is the individual health board stand in comparison to the national report. An example of the report in Appendix#9.

3.4. Discussion:

In this part of the research, all NHS Scotland health boards were invited to participate in the PPS study; all health boards were included, with the exception of Orkney and Shetland, for the reasons previously provided. Thirteen health boards successfully enrolled in the PPS, providing a unique insight into meropenem and piperacillin-tazobactam prescribing habits. Comparison of the prescription rates for the PPS period and annual prescription rates for both meropenem and piperacillin-tazobactam demonstrated that the prescribing rates were comparable.

The result of the PPS, therefore, provides valid insight into prescribing practices within individual health boards. This will allow identification of areas of good practice that can be shared to improve overall prescribing quality with these antimicrobial agents. The results from the PPS, therefore, provide a basis for a coordinated quality improvement initiative at a national and local level.

NHS Scotland has been involved in several PPS studies at national and international levels. The best known was the ESAC-PPS undertaken in 2008 and 2011 evaluating hospital-acquired infections [70, 72]. In the majority of health boards, local PPS studies are conducted based on individual health board needs, on a small scale, and are rarely published [230]. To date, there has not been a PPS that has specifically

focussed on carbapenem or piperacillin-tazobactam use either locally or internationally. The present PPS is therefore unique for attempting to quantify and understand the use of both antimicrobial agents.

The proportion of the Scottish population to be aged 65 years old and over is expected to increase by more than 20% from 2014 to 2024 [231]. This patient population accounted for approximately 90% of acute hospital admissions in 2018 [232]. In the PPS undertaken, both antimicrobial agents were most frequently administered to the 65-79 age range, reflecting their high proportion of admissions.

3.4.1. Antimicrobial therapy:

The PPS results presented three parameters related to antimicrobial choice: prescriber speciality, diagnosis, and source of infection. Most of the included patients (60%) in the surveillance are in day 4 or more of therapy. This ensures most patients passed the first 48hrs where a high uncertainty level of diagnosis or source of infection might accrue.

3.4.1.1. Speciality

The 2016 Scottish national PPS of HAI and antimicrobial prescribing had identified that the highest prevalence of patients receiving one or more antimicrobials was reported in intensive care patients (56%), followed by general medicine patients (40%), and in (40%) of surgery units patients [82]. Overall antimicrobial use in Scotland, based on speciality, is similar to European consumption [72], China [233], and others [234] where intensive care is the dominant prescribing site. In the current PPS, both meropenem and piperacillin-tazobactam were prescribed across a wide range of specialities. General Medicine accounted for 13% of meropenem and 20% piperacillin-tazobactam prescribing. Intensive care units come in second, accounting for 10% of meropenem and 5% of piperacillin-tazobactam prescribing [82]. This highlights the importance of intensive care units as a primary area of prescribing meropenem.

Based on the 2016 national PPS, geriatric medicine wards are responsible for 26.7% of all antimicrobials. In our study, we found that 9% of piperacillin-tazobactam and 7% of meropenem were prescribed under the geriatric department. In literature, there is increased attention on the overall use of antimicrobials in geriatrics, especially UTI cases [235, 236], however, limited focus on meropenem or piperacillin-tazobactam use [237, 238]. Furthermore, there is a minimum focus on geriatric speciality as a major prescribing group from SAPG, i.e. SAPG MDRGNB guidance.

Thus, more focus on geriatric prescribing would influence targeted agents prescribing.

Further investigation of the collected data from the PPS revealed that haematology/oncology wards if aggregated, were responsible for a significant share of meropenem (15.5%) and piperacillin-tazobactam (7.4%) prescribing. This can be explained by the relatively common incidence of febrile neutropenia in haemato-oncology as a side effect of chemotherapy regimens [61, 160].

Results also highlighted that 8% of all meropenem prescribing was observed in pneumology (pulmonology) departments, mostly within GGC and Lothian health boards, where they host national referral centres for cystic fibrosis. In addition, pneumonia was one of the most common indications for the use of either antimicrobial agent [61, 160].

3.4.1.2. Diagnosis and source of infection

From the results, pneumonia was the most frequently stated indication for piperacillin-tazobactam (29%). However, piperacillin-tazobactam was recommended for pneumonia in (53%) of the health board's local guidelines, (Section 2.3.3), which rank pneumonia as the fourth common indication. Thus, results from the PPS

suggests that piperacillin-tazobactam might be overused in pneumonia cases at health boards' that approves the use of piperacillin-tazobactam in pneumonia. Furthermore, health boards that do not approve piperacillin-tazobactam for pneumonia need to assess the possibility of prescribers overpassing restrictions on piperacillin-tazobactam in such cases.

After analysing the data, clinical sepsis and intraabdominal sepsis were combined to one category for more rational evaluation and comparison to chapter 2 method. From the results, sepsis diagnosis predominates meropenem identified diagnosis (20%) and comes second for piperacillin-tazobactam (26%). From the self-assessment survey, Section 2.3.2.1, meropenem was only approved in half of the health boards for sepsis indication. Having sepsis as the major prescribing indication, from the PPS results, raise attention to overuse possibility of meropenem in sepsis cases at health boards that approves meropenem for sepsis. Furthermore, the possibility of overpassing the local guidelines recommendations at health boards that do not approve meropenem for sepsis indication.

From the PPS results, meropenem and piperacillin-tazobactam were used for the diagnosis of laboratory-confirmed bacteraemia in 10% and <4%. These results were expected to be higher, as prescribing of such agents should be supported by laboratory-confirmed results. However, a future study should look into the real reason aiming to identify if there is a gap between laboratory results and diagnosis

decision because of prescribers habits and communication or diagnosis based on microbiological evidence is limited by negative results. The results also show that ≈4% of piperacillin-tazobactam prescriptions were for an unknown indication. In contrast, only one case of meropenem was for an unknown indication, which supports the need for investigating the link between laboratory results and prescribers.

Six per cent of piperacillin-tazobactam prescribing was for the diagnosis of cellulitis, wounds or deep soft tissues not involving bone. However, when cross-referencing to approved indications in chapter 2 (section 2.3.3), no health boards listed these as approved indications in their local policies, with only two approving it for the treatment of Fournier's gangrene. These results highlighted a gap between approved health board policy indications (section 2.3.7) and actual clinical usage of meropenem and piperacillin-tazobactam.

From local and national data, it is known that antimicrobials (in general) are more prescribed for the community-acquired source of infections than for hospital-acquired [82, 233, 239]. This study shows that our targeted antimicrobials were no exception from other antimicrobials and gave results similar to previous 2011 and 2016 national PPS [82]. All cases, included in our study, of meropenem prescriptions were known the source of infection, and only <2% of piperacillin-tazobactam were unknown.

By looking to latest reports from SAPG (2016) on resistance data in Scotland [82], *E. coli* (22.7%) and *Klebsiella pneumoniae* (3.5%) were in the top reported microbiological isolate in acute adult inpatients care. *E. coli* resistance rates to co-amoxiclav increased 6.1% between 2012 and 2015 ($p<0.001$) and resistance rate to piperacillin-tazobactam increased 8.6% between 2012 and 2015 ($p=0.002$). On the other hand, *Klebsiella pneumoniae* overall susceptibility trends between 2012 and 2015 were unchanged with the exception of co-amoxiclav and piperacillin-tazobactam demonstrating a 14.8% ($p=0.01$) and 28.7% ($p<0.001$) [240]. The lack of effective therapy and the worrying increase in resistance rates might influence the NHS Scotland prescribers to overuse broader-spectrum antimicrobials, such as meropenem [241, 242]. Continuous reporting and sharing of such data and promoting alternatives will ensure prescribers and guide them toward the more efficient use of targeted antimicrobials.

3.4.2. Antimicrobial prescribing quality indicators:

The quality of meropenem and piperacillin-tazobactam prescribing was evaluated by three quality indicators; prescriptions compliance with local policies, indication documentation, and review/stop date documentation.

NHS Scotland was involved in the 2009 European PPS (ESAC-PPS), which identified areas of improvement in documentation of prescribing reason and compliance to policy [70]. In consultation with clinicians, SAPG agreed late 2009, on the national prescribing indicator to drive improvements in the quality of hospital prescribing. This was disseminated to NHS boards as part of a revised national surveillance framework from Scottish Government [243]. The indicator was targeting hospital-based empirical prescribing: whether the choice of antimicrobial prescribed is compliant with the local antimicrobial policy (policy compliant) and the rationale for treatment is recorded in the clinical case note (indication documented) in ≥95% of sampled cases. This was implemented and evaluated regularly in subsequent years, and overall improvement in antimicrobials prescribing were reported in the 2011 ESAC-PPS [73, 234] and the 2016 national PPS [82].

Although the top quartile level for the present PPS was calculated it was not possible to directly compare indicators between health boards since they had slightly different antimicrobial prescribing policies. However, the top quartile provides an indication for the health boards of a target level of good practice to aspire to and overall areas of improvement in targeted antimicrobials prescribing quality nationally.

3.4.2.1. Prescriptions compliant with local policy

In the 2009 ESAC-PPS, 81% of all prescribed antimicrobials in NHS Scotland were compliant with local policy, compared to 82.5% in Europe [70]. After the implementation of prescribing indicators in 2009, results improved to 82.8% in 2011 [35] and up to 87.2% in 2016 [82]. The 87.2% compliance reported in 2016 was promising, especially when compared to other published data. In the Netherlands, reports from local PPS demonstrate compliance rates of up to 84% for all prescribed antimicrobials [244]. In the Republic of Ireland, local PPS where restriction policies are applied indicated variability in compliance rates between hospitals with an average of 70% [234]. In a multiple PPS study, conducted in Croatia at a university hospital, assessing adherence to printed guidelines between 2008 and 2011 method; the level of policy adherence varied between 35% and 50%. The study authors noted that the highest level of non-compliance with the guidelines was observed when a broad-spectrum antimicrobial such as ceftriaxone was prescribed [245]. Therefore a high level of prescribing compliance with local policies although challenging, is achievable.

In the present PPS, national data shows that compliance with local policy was 88% for meropenem and 70% for piperacillin-tazobactam meaning that both agents fall behind overall 87% compliance rate for antimicrobial prescribing, in Scotland [82]. However, 100% compliance in prescribing meropenem with local policy was achieved

in six health boards although this may have been facilitated by the low levels of prescribing for meropenem (1 – 9 prescriptions (0.46 - 1.79 prescription/100 patients)). The remaining health boards achieved 80% to 90% compliance in meropenem prescribing with a prescribing rate of 0.43 - 1.55 prescription/100 patients. Piperacillin-tazobactam compliance with local prescribing policies was much lower than meropenem, varying between 44 - 93% in 10 health boards. Only Borders, Western Isles, and the Golden Jubilee achieved 100% compliance, although prescribing levels were low (seven (3.2 per 100 sampled patients), one (1.01 per 100 sampled patients) and two (1.24 per 100 sampled patients) prescription respectively). Four health boards achieved the top quartile level of 89% piperacillin-tazobactam prescriptions compliant with policy.

Further data analysis revealed that the treatment of pneumonia and intra-abdominal sepsis with piperacillin-tazobactam were the two indications when prescribers did not adhere to policies. This might be highlight prescriber uncertainty in diagnosis or a gap within the local guideline. Again, there was considerable variation in the numbers of prescriptions observed within the PPS period, ranging from 84 prescriptions in GGC to one prescription in the Western Isles. Nevertheless, piperacillin-tazobactam showed less compliance to guidelines which could be related to factors proposed in section 2.4.3.

3.4.2.2. Prescriptions with a documented indication

In 2009 ESAC-PPS, 76% of prescribed antimicrobials in NHS Scotland had a documented indication for prescribing, which was similar to European 75.7% rate [70]. Following the implementation of prescribing indicators in 2009, results improved to 89% in 2011 [35] and further increased to 94.8% in the 2016 survey [82]. A PPS conducted in Ireland where restriction policies are applied showed that indication documentation varies between 70% and 88% within different hospital sites [234]. Very low rates of 27% have been reported from German PPS [70] reports from local PPS shows that 27% of prescribed antimicrobials lacks indication documentation and suggests that it is a major area of improvement. From the current results, NHS Scotland antimicrobial prescription indication was documented in 97% of meropenem prescriptions and 88% of piperacillin-tazobactam prescriptions.

It was encouraging to observe that meropenem had an overall 97% prescribing indication rate, higher than the previous PPS undertaken, with most health boards achieving greater than 92% documentation of indication for the use of meropenem. Nine health boards achieved the top quartile level of 100% prescriptions which reflects the overall success of implementing this quality indicator. However, this may partly have been achieved or influenced by the high level of restrictions and authorisation for meropenem prescribing.

Piperacillin-tazobactam documentation of indication rate was much less than for meropenem and ranged from ≈ 50% in Golden Jubilee to 100% in Tayside and the Western Isles. Five health boards achieved greater than 95% documentation of indication (the prescribing indicator target level and top quartile level) for piperacillin-tazobactam. The numbers of prescriptions analysed varied considerably from two (Golden Jubilee) to 85 (GGC). The observed piperacillin-tazobactam scores were lower than the overall score for antimicrobials reported in the 2016 PPS [82]. This may be attributable to piperacillin-tazobactam having fewer restrictions placed upon its clinical use, with relatively easy access to stocks (section 2.3.3).

3.4.2.3. Prescriptions with a documented review/stop date

To improve antimicrobials prescribing, one of the recently acknowledge indicators has a clear plan after initiation, with regular review of continuing need or appropriateness and anticipated stop date. Although having a documented review/stop date was documented by the "Start Smart then Focus" campaign, the recording of a documented review/stop date has not been reported in previous national or European PPS studies. The results from the current PPS show that documentation of a review or stop date for antimicrobial prescribing was 31% for both piperacillin-tazobactam and meropenem (Figure 3.7). Therefore, this could be a significant area for quality improvement at a national level and could dramatically contribute to reducing antimicrobial consumption levels. In fact, this parameter post-

PPS results was immediately adopted by SAPG as an additional quality indicator for antimicrobial prescribing in hospitals.

The documented review/stop date for meropenem prescribing varied considerably from 0% (Dumfries & Galloway, Borders and the Western Isles) to 100% (Highlands and Golden Jubilee), with the number of prescriptions also varying widely from zero to 45 prescriptions. Only three health boards achieved the top quartile level of 69% prescriptions with indication documented. There was also a substantial variation for a documented review/stop date for piperacillin-tazobactam between health boards (0% to 100% prescriptions). Twelve health boards had a review date documented in less than 68% prescriptions. Only four health boards achieved the top quartile level of 54% prescriptions with indication documented.

3.4.3. Summary of results and introduction to the next chapter:

In the bespoke PPS, lack of proper documentation for piperacillin-tazobactam use may reflect its place as the 'go to' antimicrobial for a severe infection. Further analysis of the PPS data showed that carbapenem use was <2% of all antimicrobials in all health boards and <1% in many. Piperacillin-tazobactam usage varied from 1% to 6% of all antimicrobials used, possibly reflecting overuse due to a lack of different control measures implemented rather than absolute clinical justification. Another key finding

from the PPS was that over half of the patients had received antimicrobials for >72 h, and about one-third of these patients had an undocumented review or stop date recorded in their medical notes. These findings were used to underpin SAPG's work on antimicrobial documented review/stop date to support clinical teams through education and quality improvement tools to further optimise prescribing practices.

The PPS results show that compliance with prescribing policies for the use of meropenem is high within health boards but varies considerably for piperacillin-tazobactam. Documentation of indication for use was recorded in greater than 92% of meropenem prescriptions but was poorly documented for piperacillin-tazobactam use. Prescriptions documentation of a review/stop date for both meropenem and piperacillin-tazobactam varied considerably between the health boards but was generally low.

Although NHS Scotland current PPS results shows areas of improvements, results stand high compared to other countries. In a recent global-PPS conducted in 53 countries measuring antimicrobial consumption and resistance rates, overall, the reason for treatment was recorded in (76.9%) of antimicrobial prescriptions, a stop/review date in (38.3%), and guideline compliance was 77.4% [246].

The results of this part of the study were shared with each health board AMT and their implications discussed within the project steering group and regular SAPG meetings. From the results, we identified variation in the quality of antimicrobial prescribing between health boards. This variability, when viewed in conjunction with the results from the self-assessment survey (chapter 2) identified that some health boards could be considered as models of good clinical practice, where invaluable lessons could be learned by the wider clinical community. However, it was apparent from the results of these two work packages that direct input from front-line practitioners was also required. The experiences of these front-line practitioners in their clinical decision making processes to prescribe antimicrobials would supplement the macroscopic data collected at the institution level and better inform the project about what contributes to good antimicrobial prescribing practices. From this granular data, a more targeted national policy could be constructed and applied using support tools that are better aligned to aid practitioners in their daily clinical activities. The following chapter qualitatively explores at a practitioner level their drivers to prescribe within the existing clinical frameworks.

Chapter Four:

In-depth Qualitative Interviews with Front-line NHS Scotland Physicians

4.1. Introduction:

At the beginning of the research, approximately mid-2014, the research group was aware that each health board adopted and implement guidelines based on their local clinical governance processes and available resources. The SAPG guidance against multidrug-resistant Gram-negative bacteria (MDRGNB) was anticipated to be advisory guidance to supplement local guidelines. However, it was unclear about how each health board respond to the MDRGNB guidance. Therefore, at the first stage, a self-assessment survey (chapter 2) was performed and answered by each health board antimicrobial team leader. That survey identified major information regarding carbapenems, piperacillin-tazobactam, and carbapenem-sparing antimicrobials (CSA's) prescribing policies, availability, access, and microbiology testing. In addition, the survey explored each health board method of guidance adaptation, implementation, and related educational resources. Results highlighted that meropenem use was strongly restricted and access was limited in most health boards compared to piperacillin-tazobactam. Furthermore, results from self-assessment survey (chapter 2) explored carbapenem-sparing agent's variation among health boards in approval status and stock availability. Also, results from chapter 2 showed that microbiology lab result reporting did not always suppress or release targeted antimicrobials results.

Following the survey, a point prevalence surveillance study (PPS) was performed on meropenem and piperacillin-tazobactam use across NHS Scotland, aiming to reflect the routine clinical prescribing of these antimicrobial agents (chapter 3). Data collected showed that compliance with local prescribing policies for meropenem use was high within health boards but varied considerably for piperacillin-tazobactam. Indication documentation was recorded in most meropenem prescriptions, but piperacillin-tazobactam indications were poorly documented. In addition, follow-up and prescription review for both agents were found to be generally poor.

From both parts of this research, results showed variations between individual health board's strategies in reducing the use of meropenem and in the treatment of Gram-negative bacterial infections. Furthermore, when connecting these two elements of research, the results suggested that there were differences between what health board strategic leadership planned to happen and what actually happened at the front-line implementation level. It was therefore judged to be valuable to qualitatively explore the reasons which may underpin the different behaviours of clinical staff within health boards to try to identify the drivers for their behaviours in relation to prescribing carbapenems and/or piperacillin-tazobactam. In doing so, it may allow better mechanisms for enhancing national quality prescribing standards for these antimicrobial agents.

Qualitative studies offer excellent opportunity to investigate and explore why the impact of the SAPG MDRGNB guidance on local guidelines were variable across health boards. Such studies will also enhance our knowledge of front-line clinician's opinions and factors influencing daily prescribing, which may ultimately identify relevant areas that could be targeted for improvement. Qualitative interviews are considered one of the most successful methods of understanding the opinions of people and provides authentic insights into the perspectives of the study participants [247] by learning what people think of a particular topic, expressing their experiences and understanding why they act in the way they do, and their thoughts on a given subject [185, 248]. However, qualitative interviews only deliver information about what interviewee's say they are doing but not what they are necessarily doing in routine practice [185]. For example, the interviewee may tend to give responses that sound to be socially and logically acceptable behaviours and practice in an attempt to reduce the extent to which their behaviour could be judged negatively by the researcher, or in an attempt to satisfy the researcher, which does not reflect their real views. Nevertheless, qualitative interviews are considered a valuable information resource in the healthcare field.

Qualitative interviews can be classified to three types based to what extent the researcher drives the interview process; based on the topics covered and how they are discussed. The types are structured, informal, and semi-structured interviews. Structured interviews are mostly used in survey design and aim to produce narrow,

specific data. The interviewer must follow a specific set of questions, in a specified order, for each interview to produce comparable responses from each participant. In contrast, informal interviews are more like natural discussions that happen casually in the field, in which data is gathered opportunistically. Semi-structured interviews sits in the middle between these extremes. The researcher sets the agenda of the topic covered, but keeps an open mind to any information disclosed by the respondents and responds to the information based upon the importance of each element of information [185, 247].

In semi-structured interviews, the researcher will follow a pre-set interview schedule, which consists mostly of open-ended questions where the order of asking questions is changeable based upon participants' responses. This technique allows the researcher to explore further details of any issues raised by respondents. Even though the researcher sets the interview agenda about research topics discussed, it is the interviewee's response that generates the information collected about the desired topics and this flexibility assures that almost the same range of topics are covered within each conducted interview [185, 249-251].

Healthcare providers and stakeholders were aware of the overall SAPG goals of controlling carbapenems consumption rates over the last five years and supporting the introduction of carbapenem-sparing agent's use. This was apparent from the self-assessment survey. However, PPS results showed that in real clinical practice,

there was a noticeable gap between guidance and practice in some critical areas of daily prescribing that might impact on prescribing quality and possibly patient care. Therefore a comprehensive and detailed understanding of what levers and barriers affecting front-line practitioners would help to understand and identify quality improvement areas that contributed to the variation between health boards, and improve carbapenems quality of use in the future.

To understand why the variation between health boards from the survey and the PPS results, it was imperative to explore in-depth the views and opinions of the professionals who are directly involved in regulating carbapenems, piperacillin-tazobactam, and carbapenem-sparing agents prescribing. Therefore, a semi-structured interview approach was adopted to include different types of specialities and different levels of healthcare staff who are known to prescribe such agents. This qualitative part of the project was built and designed based on the results of the self-assessment survey (chapter 2), national PPS (chapter 3), and continuous discussion between this project steering team of experts to answer predetermined questions regarding the impending reasons for target agents prescribing variation amongst health boards. In addition, trying to identify best practice measures that make a different in daily practice and applicable to amplified to other health boards across NHS Scotland. The qualitative interviews would evaluate how fit for purpose the local guidance and policies are in supporting prescription authorising and front-line clinicians to deliver safe and effective patient care.

4.2. Aims and objectives:

Aim:

To assess how adaptation and implementation across NHS Scotland of the current SAPG guidance for MDRGNB and local guidelines changed prescribing behaviour and understanding levers and barriers at front-line clinicians level to deliver safe and effective prescribing.

Objective:

To perform in-depth qualitative interviews in selected health boards to understand the levers and barriers to guideline adoption and support front-line clinicians to deliver safe and effective use of carbapenems, piperacillin-tazobactam, and carbapenems sparing agents.

4.3. Method:

4.3.1. Study design:

Since the 1990s, qualitative research methods have gained an increased appreciation for healthcare and pharmacy practice research [252]. Such methods are used to provide rationalisation and in-depth data on complex topics [253]. Qualitative research methods are considered the acceptable approach for the questions about "how?" and "why?'' phenomena develop. Results generated from such method are valuable in exploring and understanding the ways and patterns in which people think and act. Furthermore, qualitative methods are more flexible and open to respondents' viewpoints; unlike quantitative methods, which are governed by the researcher's viewpoint and based on a standardised approach [252, 253].

Interviews are the most commonly used qualitative approach in research of healthcare and pharmacy practice [252]. They are very interactive which allows for the generation of rich data which can be collected through the interaction between the researcher and respondents. Prompts and probes are allowed to be used when conducting interviews, which help in raising detailed answers about the target topics. Focus groups are another commonly used qualitative method, although it is more time efficient as many people can interview at once, it is more useful in documenting

public view on a target topic rather than individuals opinions [254]. Also, some participants may not interview well in groups [255]. Based on the proposed research target population that we wish to interview, it will be very difficult to accommodate a single suitable time for multiple numbers of busy healthcare professionals recruited from multiple sites, so this qualitative method will be discounted as a viable option.

Semi-structured interviews are a half-way approach for generating data about the issues of interests to the researcher and providing an opportunity for the interviewees to express their point views [252]. It was therefore decided to conduct one-to-one, semi-structured, interview-based research to meet the aim and objectives of this research element. This method allows understanding and insight into the perceptions of front-line healthcare staff and their views about causes and contributing factors for variations in carbapenems, piperacillin-tazobactam, and carbapenem-sparing antimicrobial prescribing.

The project steering group had identified two key areas to focus on to succesfully answer the aim and objectives of this research:

a. Challenges to antimicrobial prescribing and monitoring, including laboratory reporting and suppression of meropenem, piperacillin-tazobactam, and carbapenem sparing antimicrobials.

b. Levers applied locally or considered useful for future for improving the prescribing of meropenem, piperacillin-tazobactam, and carbapenem sparing antimicrobials at a national level.

4.3.2. Study settings:

4.3.2.1. Health board selection:

It was proposed that up to four health boards would be selected based on outputs from the national self-assessment survey and the PPS (Chapters 2 & 3 respectively). Due to the complexity of variables analysed in the national survey, deciding on which health board to recruit was difficult. However, the Carbapenem Steering group agreed that Tayside represented a good model of practice; both carbapenems and piperacillin-tazobactam prescribing was restricted, with variance in prescribing privileges amongst healthcare providers, with different methods of authorisation, and all recommended carbapenem-sparing antimicrobials approved for local use where appropriate. For this reason it was included as one of the research sites.

The project steering group continued searching for a representative candidate health board, using the PPS results. Examination of PPS variables suggested that Fife, Forth

Valley and Tayside were in the top quartile of antimicrobial prescribing quality indicators (section 3.3.4) results (Table 8).

The decision was made based on the results of PPS, one point for each top quartile scored, Tayside and Forth Valley scored the highest, 5 and 4 out of 6 points (Table 9). Borders, Highland, and Fife; scored 3 out of 6. Highland health board include five general hospitals whereas both Borders and Fife have only one. However, the selection of Fife to be included over Highland and Borders was made due to a higher number of patients were found to be on meropenem or piperacillin-tazobactam during the PPS stage, the total number of patients on meropenem and piperacillin-tazobactam was 34 in Fife, 17 in Highland, and eight patients in Borders.

Table 8 Top quartile antimicrobial prescribing quality indicators PPS results

Parameter	Top quartile		Fife		Forth Valley		Tayside		GGC	
	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam
Compliance with policy	100%	89%	100%	93%	100%	87%	100%	78%	84%	62%
Review / stop date documented	69%	54%	33%	25%	67%	68%	75%	67%	14%	20%
Indication documented	100%	95%	100%	93%	100%	97%	100%	100%	95%	80%

Furthermore, the consumption of meropenem at Fife health board was higher than Highland and Borders in the period between 2008 and 2014, Table 3. This support the selection of Fife over Highland and Borders where they are in need of improvement and targeted population for the interviews are more exposed to meropenem use.

The choice of Fife, Forth Valley and Tayside health boards is also supported by meropenem consumption data (table 10). Both Forth Valley and Fife are in the top five consumers, whereas Tayside consumption is in the average range of national data but consistent over the period from 2008 to 2014. Furthermore, the consumption data of carbapenem-sparing antimicrobials was investigated (Table 10). The results indicated that both GGC and Tayside health boards are amongst the top consumers. Also, Tayside and GGC were the top consumers of carbapenem-sparing agents between July-September 2015 (Figure 4.1). Therefore, the steering group decided to add GGC as the fourth health board aiming to explore good practice and methods of improvement implemented to support the choice of alternatives at the front-line practitioner level.

Table 9 Summary of PPS results in the top quartile antimicrobial prescribing quality indicators

Health Board	Antimicrobial prescribing qualitative measures						Total Score (Out of 6)
	Compliant with local policy		Review/Stop date documentation		Indication documentation		
Antimicrobial	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam	Meropenem	Piperacillin-tazobactam	
Top Quartile	100%	89%	69%	54%	100%	95%	
Lothian					√		1
Ayrshire and Arran				√		√	2
Forth Valley	√			√	√	√	4
Grampian					√		1
Fife	√	√			√		3
D & G					√		1
GGC							0
Highland	√		√		√		3
Tayside	√		√	√	√	√	5
Borders	√	√			√		3
Lanarkshire						√	1

Table 10 Meropenem and alternatives consumption. Source: SAPG

Health Board	Consumption 2008-2014 (Average DDD per 1000 occupied bed)	Carbapenem sparing antimicrobials Average DDDs dispensed from 2010 to Q2-2015			
	Meropenem	Aztreonam	Temocillin	Fosfomycin	Pivmecillinam
Lothian	31.8	214	30	33	54
Ayrshire and Arran	23.6	21	14	23	73
Forth Valley	19.4	18	NA	15	100
Grampian	17.56	16	136	72	54
Fife	15.46	2	92	4	NA
Dumfries & Galloway	14.98	17	7	6	9
GGC	14.12	853	287	97	327
Highland	12.2	32	21	14	46
Tayside	10.5	726	617	44	1173
Borders	9.1	NA	11	3	19
Lanarkshire	8.43	9	65	118	126
Western Isles	5.6	10	NA	NA	NA
Orkney	2.2	NA	NA	1	NA
Shetland	1.83	NA	NA	NA	NA

NA: Not approved at health board

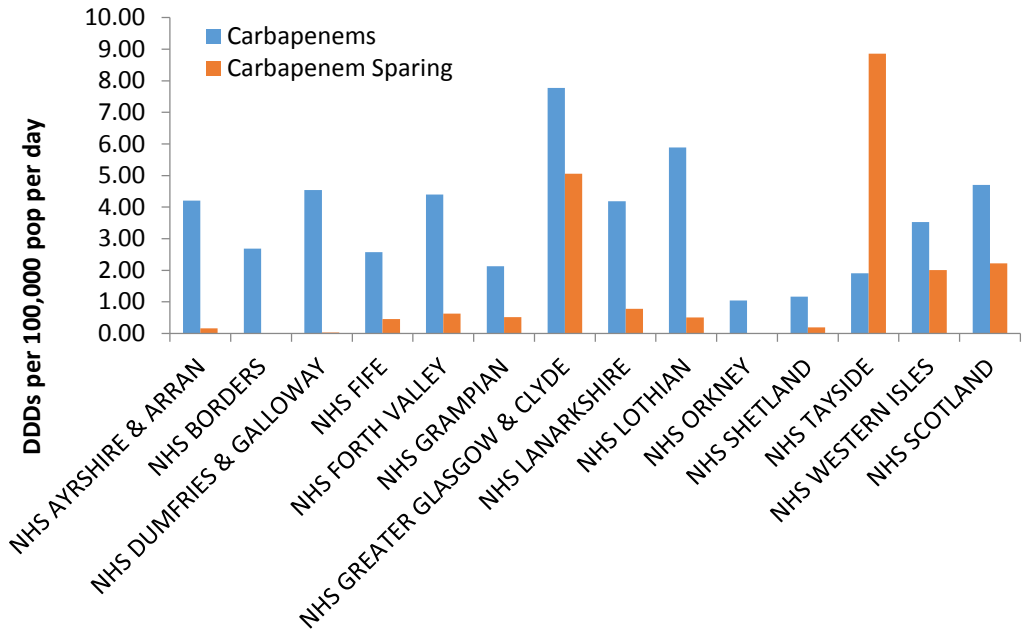


Figure 4.1: Carbapenem vs carbapenems-sparing agents use in 2015 Jul-Sept. Source: SAPG

4.3.2.2. Development of data collection tools:

To ensure that the research areas of interest were covered, a topic guide was developed through discussion within the steering group. The initial topic guide could be altered, if appropriate, after piloting at the first stage, in Fife and Tayside health board interviews, to include any emergent practice themes for stage two interviews in GGC and Forth Valley (Figure 4.2).

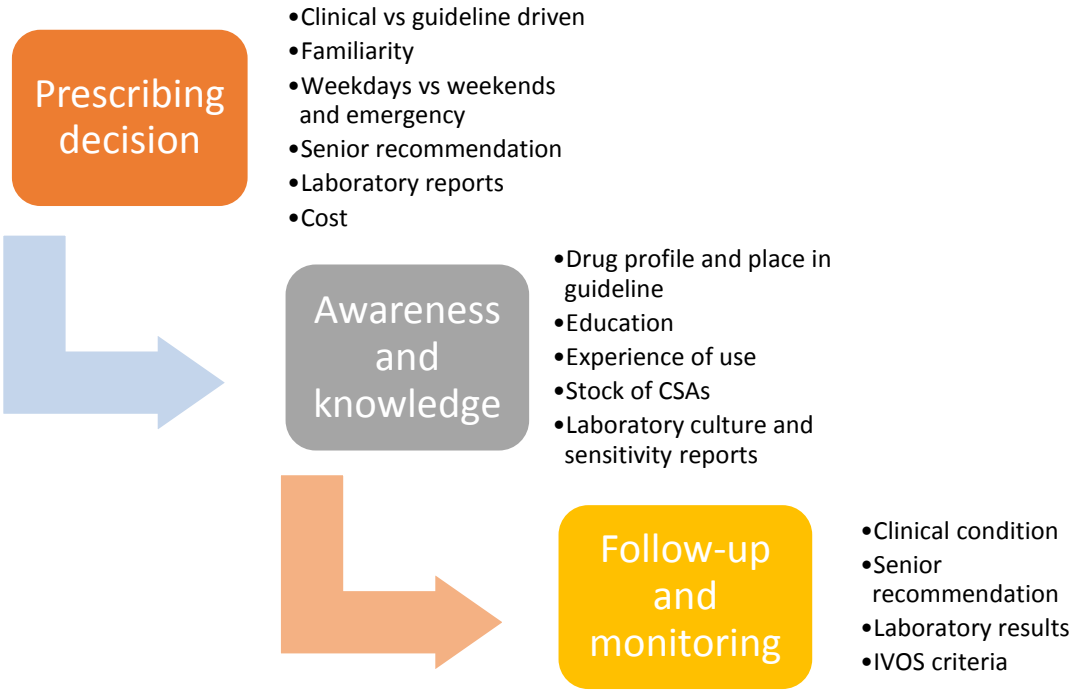


Figure 4.2: Meropenem and carbapenem-sparing antimicrobials initial interview topic guide

4.3.2.3. Participant information sheet

A participant information sheet was developed (Appendix#10). Information provided in the leaflet included the research background, aims and objectives, participation process, potential benefits from the research, anonymity and confidentiality, organisers and funding, participant's rights, and contact details of the research team in case the participant required any further information about the study.

4.3.2.4. Study invitation letter

The invitation letter (Appendix#11) was attached to the study invitation email and also provided information about the study including the aim, background, what participation involves, and what outcomes and benefits will be gained. The letter was sent on behave of the research group by the SAPG chairman, Dr Dilip Nathwani, and co-signed by the Project Lead, Dr Jacqueline Sneddon.

4.3.2.5. Consent forms

A consent form was developed to be read and signed by the respondent, at the location, before conducting the interview (Appendix#12). Agreeing to sign and give consent was essential before conducting the interview. The consent form consisted of questions requiring a yes or no answer about the participant's agreement to participate, recording the interview using audio recording devices, and potentially using the interview data anonymously in research publications. At the end of the form, demographic information was asked about participant age, gender, current position, speciality, years of qualification, and if they had any designated role in their health board's antimicrobial management team.

4.3.2.6. Interview schedule

The interview schedule (Appendix #13) used to guide the interview, was developed to ensure that the pre-identified areas of interest emerging from the PPS were covered and that the interviews were standardised as far as possible [256]. The topic guide was developed through discussions within the project steering group, comprising pharmacists, physicians, and information analyst and further reviewed by social science and psychology experts from the University of Strathclyde.

During the development of the first two topic guide drafts, meropenem, piperacillin-tazobactam, and carbapenem-sparing antimicrobials were included in the questioning. However, in the final version, the group decided to omit piperacillin-tazobactam from the interview schedule to keep the interview time below 30 minutes.

The interview schedule was divided into three main sections around meropenem, carbapenem-sparing antimicrobials, and general discussion. In the first section, participants were asked to think specifically about meropenem prescribing, and questions focussed on meropenem initiation, follow-up and monitoring. The second section, focussed on carbapenem-sparing agents - had they ever prescribed carbapenem-sparing agents instead of meropenem and if so, which one? If the respondent answer yes, then additional questions about prescribing circumstances,

levers and barriers of prescribing were explored. However, if the respondent had never prescribed CSAs, what supportive needs that might encourage them to do so in the future were explored. Finally, the third section consisted of one general question about factors and issues that they would like to share specifically relating to meropenem or carbapenem-sparing antimicrobials prescribing. Under each section, a prompt was used to ask for more clarification and explanations if required. Also, any issues raised by the interviewee during the interview was challenged and discussed by the interviewer for further clarification from interviewee, if required. It was found after the first round of initial interviews conducted in Fife and Tayside health boards that no additional modifications were required.

4.3.2.7. Appreciation letter

For those whom we interviewed, a letter of gratitude was sent directly on behalf of the research group, issued by the SAPG chairman and the project lead, for the personal participant's record.

4.3.3. Study participants:

Within the participating health boards, a representative number of key prescribers; consultants, middle grade, and juniors were recruited.

Recruitment strategies

Antimicrobial management team (AMT) leads of targeted health boards were asked by the project lead to identify one or two clinical locations where targeted agents are used frequently and then nominate willing participants for further communication. Each AMT leader provided names and contact details of candidates to be reached by the primary researcher (AM) via email. Once the list of nominee's contacts were available, a personalised invitation email inviting them to participate in a 20–30 minutes semi-structured interview was sent to confirm participation, before each health board scheduled time slot 14 days in advance. Candidates, who did not reply within seven days, were sent a reminder email (Appendix #14) with the AMT leader copied in the email. Any contacted participant that did not subsequently respond to the reminder email within seven days was excluded from the study. The study planned to recruit at least five respondents from each health board.

4.3.4. Permissions:

NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (REC) in the UK, was not required as the project was considered a service evaluation. University ethical approval was also unnecessary because the

University of Strathclyde Code of Practice on Investigations Involving Human Beings did not apply to studies of routine professional practices, service evaluations conducted solely to define or assess a particular service provided or audits of existing services. However, in line with best ethical practice, data was recorded on a secure electronic form with no participant identifiable information, entered and submitted by the lead investigator to the primary research group for analysis [176, 177].

4.3.5. Piloting data collection tool:

The initial interview schedule was piloted on an ID registrar on May 2016 after first obtaining consent. As previously discussed, the pilot aimed to assess the clarity and validity of questions in the interview schedule, layout, order of questions, and to ensure that key details were collected clearly without any risk of confusion. The pilot interview also allowed the interviewer (AM) to practice and test his interviewing skills while asking questions and interacting with the respondent.

4.3.6. Data collection process:

Interviews in all four health boards were conducted between June and November 2016. Each health board was assigned a designated period of two to three weeks,

based on the stage and suitable recommended dates from the AMT lead. After date confirmation, the researcher created a dedicated Doodle® poll link (Google Inc.), for each health board, showing days and time slots available for willing participants to select most suitable availability. The link included in the personalised email and names were kept anonymous and only seen by the primary researcher.

4.3.6.1. Conducting interviews

The interviews were conducted at the most convenient time and venue. All interviews were conducted by the primary researcher. However, the first four interviews were observed by a member of the project steering group to provide additional feedback on the research's interview skills. At the beginning of each interview, the participants were given a summary of the project, the flow and nature of the interview questions, and an indication that the interview would last for 20–30 minutes. All study participants were assured of confidentiality and anonymity, and were asked for their permission for an audio recording of the interviews to be allowed. Two devices were used to ensure voice capture/to have a back up device in the event of failure of one of the recording devices. Consent was signed just before the start of the interview.

4.3.6.2. Data Storage

To ensure confidentiality, and data security of all study information, electronic data files were saved on a Strathclyde University online drive, password protected and encrypted. Audiotape recordings were destroyed at the end of the study. Each participant was given a reference code which was used throughout the study and stored separately from their contact details. Only the primary researcher had access to this data which were kept in a locked cabinet in a locked room.

4.3.7. Qualitative data analysis:

All anonymised interviews were subjected to the framework analysis method, which sits within a qualitative analysis method named “thematic analysis approach” [257, 258]. Thematic analysis approach usually involves identifying, analysing and reporting of themes inductively; themes are grounded in the data and obtained from it data gradually [259]. However, it also contains the identification of new themes deductively [254]; themes that are pre-set and anticipated based on previous discussion and literature; as well as those obtained from the data inductively [260]. In summary, the thematic analysis method includes coding data, distributing the text data into small segments, assigning a label to each segment and then grouping the codes into themes.

The application of such qualitative descriptive analysis is considered appropriate for this research which requires a relatively low level of interpretation, in comparison to grounded theory where a higher level of interpretive complexity is needed [258]. It was described as “a method for identifying, analysing and reporting patterns (themes) within data” [261]. The pilot interview was not included in the analysis.

4.3.7.1. Transcribing

All audio recordings were transcribed verbatim and cross-checked against the recording multiple times by the primary researcher. The first four transcripts were read and cross-checked against the recordings by one of the supervisors (ABM) and a social science researcher (EC) who made any required changes to the written transcripts to ensure that transcribing techniques and recordings were accurately transcribed. Any personal identifiers or locations were removed and replaced by a study ID known only to the primary researcher.

4.3.7.2. Familiarisation with the data

Familiarisation with the data was achieved by listening and re-listening several times, at least twice, to the audio recording and reading the transcripts line by line and generating initial ideas.

4.3.7.3. Generating initial codes

Transcripts of the first few interviews were analysed into different codes, and each segment of the text was assigned to a relevant code. These codes were used as a primary starting point and refined by analysing the rest of the interviews. To avoid ignoring any data, we added an 'other' code and 'stories of success'; when relevant; under each theme for any data that did not fit with any code.

4.3.7.4. Identifying themes

Coded data organised into sections under the topics covered by the interview schedule; meropenem, carbapenem-sparing agents, and overall areas of improvement; were coded to identify connections and over-arching themes to answer and achieve the study aims and objectives. This involved labelling and grouping ideas to reflect broader perspectives and this process was the core feature for analysing the qualitative data [262]. Similar codes were grouped and organised into coherent categories and themes that summarised them and made the text meaningful.

Since the study aimed to investigate the understanding and perspectives of front-line participants, the analysis was not limited to those topics or headings related to study aims. Topics or issues that emerged from the interview were also included. Arranging the data in this way allowed linking the front-line participants' response to each question and specific topic individually and made it easier to identify themes and subthemes.

4.3.7.5. Reviewing themes

Generated themes were reviewed and discussed with the project steering group to assess whether they were appropriate in relation to coded texts and also the whole dataset. The developed thematic map was refined if necessary by either merging or gathering codes.

4.3.7.6. Software used

The computer software NVivo® (version 11), QSR NVIVO Project, was used during analysis. The software supports qualitative and mixed methods research and organises, analyses and finds insights in unstructured, or qualitative data.

4.3.7.7. Validation

Before producing the report, the analysis was validated from two different parts; the transcribing accuracy and the coding and themes identifications [254]. One third of the audio-recorded interviews with their written transcripts were checked by a colleague (NA), PhD candidate, to validate the accuracy of transcribed interviews.

Also, about one third of the interviews transcripts were given to a member of the project steering group (SR), an information analyst, to code and identify themes based on the research method. Then both the validator and the main researcher compared codes, identified themes, verified the outcomes, and any disagreements were discussed and resolved. In both parts, confidentiality and anonymity of respondents were maintained.

4.4. Results:

4.4.1. Characteristics of study participants:

Of the four selected health boards, AMT leaders nominated 44 physicians after a verbal agreement with them. Out of the 44 invited clinicians, 28 were able to be

interviewed (64% response rate). The major reasons for non-recruitment of the remainders were either not responding or unavailability at a given period. The mean age of the interviewed participants was 39±9.6 years. Interviewed clinicians had a range of characteristics in terms of age, gender, rank, years since qualified, specialities, and role in AMT. Over 60% were consultants, and specialities were mostly general medicine (28.6%), infectious diseases (21.4%) and microbiology (10.7%). Details of participants' characteristics can be found in Table 11. Interviews duration ranged between 16 to 30 minutes.

Table 11 Demographics of the participants (N=28)

Participants' characters	N (%)
Site	
NHS Fife	8 (28.5)
NHS Tayside	6 (21.5)
NHS Forth Valley	6 (21.5)
NHS GGC	8 (28.5)
Rank	
Consultants	18 (64.3)
Registrars	6 (21.4)
FY doctors	4 (14.3)
Speciality	
General Medicine	8 (28.6)
Infectious diseases	6 (21.4)
Microbiology	3 (10.7)
Surgery	2 (7.1)
Haematology/Oncology	2 (7.1)
Respiratory	2 (7.1)
Intensive care/Anaesthesia	2 (7.1)
Acute care	1 (3.6)
Care of the elderly	1 (3.6)
Diabetic and Endocrine	1 (3.6)
Years since qualification	
Less than two years	2 (7.1)
2-5 years	4 (14.3)
>5-10 years	4 (14.3)
>10-15 years	5 (17.9)
More than 15 Years	13 (46.4)
Gender	
Male	17 (60)
Female	11 (40)
Member of AMT team	
Yes	10 (36)
No	18 (64)
Age	
Under 25	2 (7.1)
25 – less than 35	8 (28.6)
35 – less than 45	11 (39.3)
45 – less than 55	5 (17.9)
55 – less than 65	2 (7.1)

4.4.2. Interview results:

The interview schedule covered questions and themes about front-line clinicians' views around meropenem and carbapenem-sparing antimicrobials prescribing decisions, including meropenem follow-up and monitoring. Then they were asked about their opinions about supportive measures to improve review and documentation of meropenem prescriptions. Experience with previous use of carbapenem-sparing antimicrobials were explored to identify the most commonly used alternatives, to understand prescribing rates, and what levers and barriers they encounter in daily practice. Finally, interviewees were given a chance to discuss what could improve the overall prescribing of meropenem and carbapenem-sparing antimicrobials and share any success stories from their practice. Table 12 summaries the topics and themes covered by the interview schedule and Appendix #15 shows additional supporting quotes under each code.

Table 12 Summary of covered topics and themes by the interview schedule

Topics and themes identified
Prescribing decision of meropenem and carbapenem-sparing antimicrobials
Organisational influenced
Recommendation by others
Patient-related specialities causes
Meropenem follow-up and monitoring
Prescription review
Documentation
De-escalation
Meropenem review support and improvement
Local policies and regulations
Education
Limitation for a better review
Communication
Good practice examples
Experience of using carbapenem-sparing antimicrobials
Previous experience
Common agent in use
Levers of prescribing carbapenem-sparing antimicrobials
Local system
Knowledge
Stories of success
Barriers to prescribing carbapenem-sparing antimicrobials
Local system
Knowledge
Reasons for never prescribing carbapenem-sparing antimicrobials
Local system
Knowledge
Overall use improvement for meropenem and carbapenem-sparing antimicrobials
Limitations
Responsibilities
Organisational level
Education

4.4.3. Prescribing decision of meropenem and carbapenem-sparing antimicrobials

All interviewees had experiences of meropenem prescribing. In contrast, experience of carbapenem-sparing antimicrobial prescribing varied between health boards (see section 4.4.6 for detail).

Identified themes and codes of prescribing decision were found to be very similar between meropenem and carbapenem-sparing antimicrobials. Three major themes identified in relation to prescribing were categorised as organisational, recommendations, and patient-related factors. Table 13.

Table 13 Summary of meropenem and carbapenem-sparing antimicrobials

Codes	Subthemes	Themes
Local guidelines *Empirical guidelines* *Carbapenem-sparing substituting other antimicrobials*	Guidelines	Organisational influenced
Restriction policies *Authorisation process*	Prescribing policies and restriction	
Discussions and meetings *Direct recommendation or advice* *Consultation base* *Agreement between ID/Micro and teams*	Advice from Micro/ID	Recommendation by others
Testing and suppressing *History of resistant* *Multidrug resistance*	Microbiology reports	
Senior recommendation		
Febrile Neutropenia *Penicillin allergy* *Failure of current therapy* *Oral/IV switch* *Last resort choices*	Special Indications	Patient-related specialities factors
Ward related factors		
Patient clinical condition		

4.4.3.1. Organisational Influenced decisions

Organisational influenced prescribing decision was discussed by all participants and mentioned over 35 times during interview. The organisation directly influence prescribing by the availability and promotion of local guidelines and prescribing policies. In addition, by also applying restrictions and authorisation mechanisms. Under the organisational influence theme, two subthemes emerged; guidelines, and prescribing policies and restrictions. Appendix #15 shows additional supporting quotes.

Guidelines:

Organisational guidelines were a major discussion topic and was recognised as an important prescribing tool. Meropenem was generally omitted from empirical guidelines and only listed for highly specific indications e.g. febrile neutropenia. In these cases, referral to a specialised team or individual e.g. AMT, ID or microbiologist consultant for advice on meropenem prescribing was advised.

> *"I do not think I have seen Meropenem on the [name of health board] Therapeutic Handbook"* (C5, FY1 Medicine)

> *"The guidelines [local guideline] that we should seek consultant microbiology advice before prescribing Meropenem"* (B7, FY2 Medicine)

> *"No! Meropenem is not anywhere in our guidance"* (C7, Microbiology Consultant)

On the other hand, having CSA's included in the guidelines was beneficial in providing confidence in prescribing decisions and promoting such agents. Having such agents

in local guidelines and policies was a key factor in supporting/facilitating their prescribing. In addition, aztreonam and temocillin were listed as a drug of choice in some empirical guidelines for specific indications.

> *"I was not aware of any of those antimicrobials [CSAs] till maybe 2015. They appeared on our guidelines of the hospital antimicrobial guidelines. So I have used, certainly, aztreonam quite a lot, temocillin I would say maybe weekly or fortnightly, the other two [pivmencilinam and fosfomycin] not so much"* (C4, Senior Registrar Medicine)

> *"Yeah. It is in our NHS [name of health board] policy."* (B1, Microbiology Consultant)

Prescribing policies and restrictions:

Meropenem prescribing is typically restricted with a policy for authorisation, e.g. code system. The decision to prescribe meropenem was noted by some interviewees to influenced their actions.

"We have a policy that meropenem and tazocin are restricted items" (A9, Senior Registrar ID)

"Only prescribed with a code!" (A5, Microbiology Consultant)

4.4.3.2. Recommendation by others

Prescribing of both meropenem and CSA's by non-microbiology/non-infectious specialities was heavily reliant on a recommendation from either specialised infection teams or by appropriate microbiology evidence. Even with the availability of prescribing guidelines, most clinicians recommend seeking the advice from a specialised team before initiation of meropenem or CSA prescribing. Appendix #15 shows additional supporting quotes.

Advice from Microbiologist/Infectious disease:

In the case of meropenem prescribing, the decision usually comes from the attending team, especially consult-led recommendations. In fact, in some health board guidelines, the advice is to directly contact a microbiologist. In other cases the type of advice sought varied from official consultation, ground rounds, direct recommendation, and agreement between specialised and attending teams in high-risk wards such as ITU's and Haematology. In addition, results showed that even some

infection team members would seek advice from a microbiologist before initiating meropenem prescribing.

> "*I probably wouldn't be prescribing meropenem off my own bat. I would discuss with a consultant who would probably want micro advice*" (B6, CT Medicine)

> *"We use meropenem on advice from either ID or microbiology. Microbiology or infectious diseases will recommend, in failure of current antimicrobials and escalation to meropenem. Either empirical treatment or based on sensitivities that we have."* (C3, Senior Registrar Medicine)

> *"I would only use meropenem after discussing with the duty microbiologist"* (B8, Acute care Consultant)

> *"It says explicitly in the guidelines that we should seek consultant microbiology advice before prescribing meropenem."* (B7, FY2 Medicine)

"So, basically we use both techniques, guideline and microbiology recommendation." (A9, Senior Registrar ID)

Specialised teams advice and recommendations on prescribing CSA's were significant and very influential because local guidelines and policies are, in some health boards, excludes CSA's. In fact, the role of specialised teams in prescribing CSA's predominated prescribing decision with non-specialised teams.

"Based on advice by the consultant microbiologist" (A3, Intensive care Consultant)

"We use temocillin a few weeks ago as a meropenem sparing agent, specifically on advice of a microbiologist" (B9, Care of Elderly Consultant)

Microbiology reports:

Having microbiological evidence supports the prescribing decision of meropenem and CSA's. Thus, decision to prescribe meropenem and CSA's becomes evidence-based. Prescribers from non-specialised teams become more confident in making the decision to use these agents. Microbiology laboratory reports include more than

specific patients' culture and sensitivity reports; they provide prescribers with overall multidrug resistance rates and any history of the resistant organism which are tools to be used in prescribing decision, especially with specialised teams.

> *"Meropenem, generally guided by culture result"… "Based on culture and sensitivity … Pivmecillinam and fosfomycin we have used in multi-resistant E. coli urinary tract infections"* (B9, Care of Elderly Consultant)

> *"Usually in complex, Gram-negative infections which have built up resistance to other agents would be the kind of primary area that we would prescribe meropenem"* (C8, Senior Registrar ID)

> *"We have greater confidence in the use of aztreonam where susceptibility is laboratory confirmed"* (B4, ID Consultant)

4.4.3.3. Patient-related factors

Prescribing decision was influenced by other factors that are mainly patient-related, such as allergies, specific indications, failure of current therapy, and the need for an

oral agent. Patients with known penicillin allergy influenced the prescribing decision towards the prescribing of meropenem or CSA's. Appendix #15 shows additional supporting quotes.

> *"The only times I would routinely prescribe meropenem would probably be in febrile neutropenia with penicillin allergy, and in patients who have got ESBL-producing organisms, normally confirmed"* (A9, Senior Registrar ID)

> *"We would use meropenem as a first-line antimicrobial for somebody who is neutropenic or considered to be highly immuno-suppressed due to previous therapy and who is allergic to penicillin"…"We have used aztreonam in a few folks, and it is tended to be people who are both carbapenem and penicillin-allergic"* (C9, Haematology Consultant)

In cases of treatment failure with current therapy or patients with rare indications, prescribing decision was most commonly discussed with specialist infection teams.

"Microbiology or infectious diseases will recommend, failure of current antimicrobials and escalation to meropenem. Either empirical treatment or based on sensitivities that we have" (C3, Senior Registrar Medicine)

"I used meropenem in patients who have deteriorated despite other antimicrobial therapy and only on advice of microbiologists or an infectious diseases team." (C4, ST Medicine)

"There are some patients for whom you have run out of options. Particularly patients who've had a lot of antimicrobials, like on intensive care, and they are not respondent." (B1, Microbiology Consultant)

The need for oral agents that covers Gram-negative infection was a factor in prescribing CSA's. The availability of oral dosage forms of pivmecillinam and fosfomycin aid prescribers in deciding to choose them.

"Pivmecillinam and fosfomycin are almost exclusively in patients who are clinically well and have, for example, a urinary tract

infection and they are not unwell, but they do have a UTI, but it is not sensitive to any oral antimicrobials except them" (B8, Acute Care Consultant)

"Actually you can give them pivmecillinam, fosfomycin orally and get them home" (C2, Medicine Consultant)

4.4.4. Meropenem follow-up and monitoring

In this section, the interviewees were asked about meropenem prescribing review, documentation, and de-escalation decision making in order to have an insight into daily practice scenarios. All interviewees provided commentary in this section of the interview which resulted in multi-level information on prescribing habits. The meropenem prescription review theme was divided into two subthemes; the frequency and mechanism of reviewing. Documentation of prescribing was also divided into two sub-themes; where and what is documented and what other documentation sources have been used. Finally, the de-escalation from meropenem was majorly discussed under two sub-themes; de-escalation decision recommendation and decision limitations. Each theme, sub-theme, and code is summarised in table 14. Appendix #15 shows additional supporting quotes.

Table 14 Summary of meropenem follow-up and monitoring themes and codes

Code	Subtheme	Theme
Routinely *Once only* *Guideline/microbiological evidence*	Review frequency	Prescription review
Pharmacist follow-up *Code based review* *Emails follow-up* *Embedded in daily practice*	Review mechanism	
Medical notes and KARDEX *Duration plan* *What is documented*	Where and what	Documentation
Lab records and system *Electronic prescription* *E-mails* *Antimicrobials chart/book/sticker* *Admission referral letter*	Other sources	
Micro/ID *Senior* *Microbiology evidence*	Recommendation by others	De-escalation
Patient clinical condition		
Lack of confidence/knowledge *Patient stable/deteriorating*	Limitations	
Guideline/IVOS policy		

4.4.4.1. Meropenem prescribing review:

Review frequency:

In most cases, meropenem prescribing does not have a specific review policy or recommended frequency of review. In general, all patients are seen by attending teams once daily in current practice and twice in some cases, e.g. critical care patients. However, the authoriser of meropenem prescribing e.g. Micro/ID teams, would typically only see the patient at initiation of therapy and then rely on the attending team to follow-up with them only if needed.

> *"Every patient usually gets a daily review by medic staff. Not necessarily consulted, but one of us will see them"* (B6, CT Medicine)

> *"We would advocate reviewing the prescription on a daily basis, but if meropenem is prescribed for a patient on the surgical or medical floors it would be flagged up by the pharmacist for review within 48 or 72 hours so that the prescription can be reviewed…prescription should be reviewed within 48 to 72 hours, and rationalisation of therapy should occur"* (A9, Senior Registrar ID)

"In microbiology, we advise the consultant to prescribe it. We would not necessarily see the patient again…If you have any concerns about the patient at that point, call us back. If you are not happy to stop it, call us back" (C7, Microbiology Consultant)

Review Mechanism:

From the results, there were several attempts used by health boards to encourage or facilitate the reviewing process. The involvement of pharmacists in the review and follow-up process, by emails or rounds, was a common practice.

"The prescription will be flagged via a pharmacist to a shared inbox that micro/ID have to say, "Are you aware of this patient? Somebody go and review this patient to see why they are they on meropenem." (B3, Consultant ID)

In addition, one health board that uses the code system limits the validation of the code to force the attending team into communicating with Micro/ID and review prescription.

"The code…valid for three days and then they have to phone us back" (A5, Microbiology Consultant)

4.4.4.2. Meropenem prescribing documentation:

Discussion with interviewee resulted that all meropenem documentation takes place in the medical notes and-or KARDEX. However, there are some who reported using a separated sheet for antimicrobials in intensive care units.

"We use separate green antimicrobial chart which records all the culture results and blood cultures, and within each antimicrobial prescription you need to write the indication...i.e. chest sepsis or abdominal sepsis and then also there's a stop review date which we aspire to fill in with discussion with the microbiologists" (A3, ITU Consultant)

Duration:

Overall, there is an agreement between interviewees, especially non-Micro/ID, that duration is the least documented parameter in meropenem prescribing. The reasons behind the lack of duration documentation vary, and potential ways of improving this process will be discussed later.

"We use electronic prescribing now, so there is the option of putting an end date as well. But, it is optional, so you do not have to." (B6, Medicine CT)

"I think it is not very well documented as duration of treatment. It gets started on recommendation, but the review to stop is not made at the beginning" (C3, Senior Registrar Medicine)

"We are not as good as putting a duration as we should be" (B1, Microbiology Consultant)

"If its empiric and you are waiting for culture results to come back, your total duration's going to be seven days, but you would flag that you need to come back in three days or two days, when the cultures are back" (B3, ID Consultant)

Some few interviewees reported that meropenem prescribing documentation is held in other sources.

"We start our documentation as held in the lab computer system"

(B1, Microbiology Consultant)

4.4.4.3. Meropenem de-escalation:

The majority of interviewee leave the decision of de-escalation to others e.g. Micro/ID for non-Micro/ID teams, and Microbiological supporting evidence for Micro/ID specialists. However, recommendations of de-escalation can be neglected in unstable patients and where the prescriber may lack sufficient confidence and knowledge.

"Depends on the severity. If someone has failed on quite a lot of different antimicrobials before they reached meropenem, then sometimes we will ask infectious diseases or microbiology for an appropriate step-down option" (C3, Senior Registrar Medicine)

"It depends on what the clinical condition is and what the microbiologist advises. Usually, they advise us to complete the course once we have started it. If the patient is well, has a good clinical response then sometimes we stop the antimicrobial, or

sometimes it is another alternative, depending on the patient" (C1, General Surgery Consultant)

"To de-escalate it depends. If the patient is getting better, and usually what we will do is if a patient is successful on an antimicrobial, we usually continue the course" (C1, Consultant General Surgery)

Microbiological evidence to support possible de-escalation is essential for the specialised team.

"What the organism is that you are supposed to be treating, what the condition is the patient is being treated for and whether they can handle alternative antimicrobials. So, yes we would try to de-escalate them if there is an obvious alternative. But often you do not know what you are actually treating" (B1, Microbiology Consultant)

"The thing about de-escalation is confidence in the use of oral alternatives to meropenem" (B4, ID Consultant)

In a few health boards, there is an IV-Oral switch (IVOS) policy implemented to facilitate switching to oral agents. However, in the few interviews that discussed policy, there was very limited applicable meropenem oral options to use.

4.4.5. Meropenem review support and improvement

All interviewees were asked an open-end question regarding review process aiming to share their thoughts and having an insight opinion of daily practice. All participants were happy to share what do they thought and what might support the review process, especially when they were informed about the NAS-PSS result (Chapter 3).

Thematic analysis of this transcribed data revealed four major themes. Local policies and regulations can influence the review process and support prescribers by policies, review techniques, and involvement of a specialised team. The second major theme was education about the reviewing process and the importance of it by increasing awareness and knowledge about the issue. Thirdly, communication was discussed by interviewees as an area of improvement and support. Finally, a fourth theme was grouped to include any limitations or difficulties that influence meropenem prescribing review. Each theme, sub-theme, and code is summarised in table 15. A fifth theme was created to group any shared practice examples, positive or negative,

that influence reviewing prescriptions. Appendix #15 shows additional supporting quotes.

Table 15 Summary of meropenem review support and improvement themes and codes

Code	Subtheme	Theme
Prescribing restrictions *Formalised review policy* *Mandatory sampling and cultures* *Attention to high-risk wards*	Prescribing Policies	Local policies and regulations
Electronic system/emails *Definite review date/automatic stop orders* *Embedded in daily practice* *Review decision at initiation* *Antimicrobial prescribing sheet*	Review process techniques	
Active AMT-Micro-ID teams *Multidisciplinary teams*	Leadership and Stewardship	
Meropenem overuse risk *Review importance* *Availability of alternatives*	Awareness	Education
Review process and policy *De-escalation policy and option*	Knowledge	
Documentation		
Sampling errors *Multidrug resistance* *Release of alternatives sensitivity*	Microbiology samples and reports	Limitation for a better review
Behaviour and attitude		
Patient and ward factors		
Seniors vs Juniors *Between Micro/ID and treating teams*		Communication
		Good practice examples

4.4.5.1. Local policies and regulations

The role of local policies and regulation was discussed and mentioned as a key influence in supporting meropenem review by all interviewee, from both specialist and non-specialist clinical areas. There was a general agreement from all interviewee that reviewing not only meropenem but all antimicrobials prescriptions should be promoted by stakeholders and decision makers locally and nationally. In this part, thematic analysis resulted in three subthemes.

Prescribing policies:

Interviewees agreed on having a prescribing policy or updating current policies to include and highlight the importance of meropenem review. Current restrictions policies on meropenem were mentioned as a supportive measure in the reviewing process.

> *"When you were given a code for meropenem you are given a list of things to document and feedback at the end of five days as a closure to the prescription"* (A7, Respiratory Consultant)

There were suggestions from the interviewees to have a mandatory formalised review policy to improve the quality of prescribing.

"I think that mandatory review…within three days, the prescription is specifically reviewed" (A9, Senior Registrar ID)

"If there was a way that you force doctors to review antimicrobials, I think it would be done better" (C3, Senior Registrar Medicine)

"That could be built in for meropenem and tazocin prescribing as an automatic prompt to review the prescription. Not to just to review the prescription but to check for culture, microbiology culture results. Perhaps at 42 hours and then again at another 72 hours. That would be the most reliable way of doing it" (B8, Acute Care Consultant)

In one of the included health boards, sampling for culture and sensitivity was mandatory upon meropenem initiation. However, the policy was only mentioned once and with negative feedback in term of adherence.

"It is mandatory but the problem is just because it is mandatory doesn't mean it always happens" (B8, Acute Care Consultant)

From the results, patients with critical conditions and patients in high-risk units, i.e. ITU or Haematology units, were said by interviewee to be challenging in term of reviewing and a clear policy would be helpful and supportive.

"The problem comes that because of the nature of the patients that we treat and we only grow bugs in under 30 per cent of our population; it is very difficult to know what you are dealing with" (C9, Haematology Consultant)

"I suppose the ones that are less likely to be reviewed are the neutropenic sepsis patients that end up on meropenem because they have not responded to tazocin. We tend to just leave that to the haematologist to stop the antimicrobials when appropriate." (B1, Microbiology Consultant)

Reviewing process techniques:

Overall, there were lots of suggestions and good stories of how to improve reviewing process techniques in daily practice. Most of the suggestions were around how to use advanced technology for reviewing benefit and promotion. Suggestions and experience vary from a simple email to a complex health informatics system.

> *"We use electronic prescribing like I said. So maybe if something flashed up on the E-prescribing, to say this patient is on meropenem. Do you want to review this? Or, something like that…rather than having an optional end date that should be compulsory when you are prescribing it"* (B6, CT Medicine)

> *"I think electronic prescribing would be really helpful. If there was some flag to me"* (A5, Microbiology Consultant)

Another technique that has been mentioned is having a definitive review/stop date for meropenem prescription, enforced by policies or by team agreement.

> *"Mandatory review…within three days, the prescription is specifically reviewed"* (A9, Senior Registrar ID)

"Maybe we should have a defined review period… to put in a defined date of review" (B7, FY-2 Medicine)

"Perhaps at 48 hours and then again at another 72 hours. That would be the most reliable way of doing it." (B8, Acute Care Medicine Consultant)

There was a commonly shared perspective between interviewees that reviewing prescriptions should become embedded in daily practice. The mechanisms described varied considerably and included, having a checklist of things to do during the ward round including a review of antimicrobials, discussing antimicrobials in daily ward safety meetings, clear reminders or stickers on-top of patients medical notes, and prompts on the KARDEX.

"You have to ingrain a review of antimicrobials into the daily ordering process rather than being just, carry on, carry on… needs to be part of a daily process…Got ward round checklists, on some wards, in which that is part of the process, to review antimicrobials" (B9, Care of Elderly Consultant)

"We had stickers, or some kind of page in the notes that said basically this patient is on meropenem, or whatever, and it gets reviewed every day" (B6, CT Medicine)

"Having prompts on the KARDEX" (B8, Acute Care Medicine Consultant)

"…draw a little box, showing the bit on the drug prescription chart where the dose, when you definitely want it reviewed by, and just put next to it, "Review date." The nurses then, when they are about to give it, they would contact the medical staff and say, "This is up for review. Are you continuing?" (B5, ID Consultant)

Another technique mentioned by the specialised team is to have a definitive stop date if possible or a review date upon initiation of meropenem.

"We really do suggest meropenem infrequently, but we would give them a plan on duration" (C7, Microbiology Consultant)

"Try and make the decision right at the start of treatment, how long you want to give treatment for" (C3, Senior Registrar Medicine)

Only a small number of interviewees suggested having a dedicated prescribing sheet for meropenem prescriptions in each patient's medical notes.

"I think an antimicrobial specific prescription chart" (B3, ID Consultant)

"Prescribed on a separate form… the gentamicin is much better done now than when I first started because it is a separate form, you have to prescribe it actively every day" (C3, Senior Registrar Medicine)

Leadership and Stewardship:

In this subtheme, two main codes were identified from interviews. Having an active AMT team and/or a Micro/ID teams within hospitals and easily contactable was particularly popular with non-specialised teams as a supportive measure in prescribing and reviewing. This suggestion was also popular with specialised teams.

This commentary may give the impression that non-specialised attending teams were trying to avoid the responsibility of reviewing meropenem prescription and shift ownership on to a specialised team.

> *"Proactive microbiologists…daily input from a microbiologist…leads to healthy cross-fertilisation of knowledge"* (A3, ITU Consultant)

> *"One thing that's quite good in this particular hospital is that we have got an ID team that is clinical based. Once or twice a week, the ID team here goes round the different wards. If we have got complicated patients with complicated infections, or who are on antimicrobials that we are not particularly using regularly, they are easily accessible for advice regarding duration, escalation, de-escalation of treatment."* (C3, Senior Registrar Medicine)

> *"I think that can only be led by the microbiologists. If they have closed records, who is on meropenem, they then need to initiate the follow-up and the de-escalation plan for that"* (B2, Anaesthesia/ITU Consultant)

"I guess us visiting on a consult service during the week might prompt a discussion about could de-escalate this to an alternative agent or actually are at the stage where they could move to orals, and prompting that discussion" (C8, Senior Registrar ID)

There is also a sense from a specialised team member that they should be responsible for such antimicrobials;

"Having a proactive microbiologist or I should say a proactive infection specialists…many doctors know their knowledge on antimicrobials and infection is not as good as it has been in the past and that is partially the responsibility of microbiologist; we have sort of taken that role and responsibility away from them and taking it on our shoulders" (A5, Microbiology Consultant)

From the results, not all interviewees pass the responsibility of reviewing to the specialised team, although it was popular. There were few suggestions of having a multidisciplinary team involved in such activities. This was suggested more commonly by specialised teams, incorporating pharmacists and trained nurses, who were thought to be helpful in the reviewing support.

“I think that the antimicrobial management team as a whole, and it could be the appropriate trained nursing or pharmacy staff, or it could be one of the physicians, or ID infection trainees” (A9, Senior Registrar ID)

“It is useful to have the antimicrobial pharmacist to bring it to their attention that someone has been started on meropenem and I think that does help it does prompt them to be reviewed.” (B1, Microbiology Consultant)

“Junior members or also nurses could flag that up and highlight to the consultant that there needs to be a decision made about de-escalation or even stopping that particular drug” (B2, Anaesthesia/ITU Consultant)

“I think empowering the nurses to ask, to feel that they're able to ask the junior doctor, "Do they still need intravenous antimicrobials or can we switch to oral?" (B9, Care of Elderly Consultant)

4.4.5.2. Education

In this theme, any discussed information related to educational needs were analysed. Two major subthemes and one minor resulted from the analysis. Awareness related to meropenem overuse, the importance of reviewing antimicrobials and the availability of alternatives were all grouped. The other major subtheme was knowledge about the reviewing process and policies and the options of de-escalation. Finally, a small subtheme that focuses on the importance of documentation was included as it was mentioned on a number of occasions during interviews. Appendix #15 shows additional supporting quotes.

Awareness:

Overall, there was an agreement between the interviewees that meropenem was overused in some areas, especially by specialised teams. However, there was a lack of awareness in non-specialised teams about the importance of meropenem review and what other alternatives available. The practice of continuing on the same antimicrobial, because the patient was clinically responding remains common;

> *"I think that antimicrobials across the board, meropenem or otherwise, they are not looked at very well, as to should they*

continue, should they stop…the attitude is, if someone's getting better on a broad spectrum antimicrobial like meropenem, even if they have got sensitivities, why change that if they are already getting better?" (C3, Senior Registrar Medicine)

"Trying to improve people's awareness of their responsibilities"…
"The awareness of alternatives like aztreonam and temocillin and their familiarity with using them is probably not that great…Trying to improve people's awareness of their responsibilities" (D1, Respiratory Consultant)

"…many doctors know their knowledge on antimicrobials and infection is not as good as it has been in the past and that is partially the responsibility of microbiologist…the ease of use side effect profile and also what other alternatives are there" (A5, Microbiology Consultant)

There were some suggestions and examples of having a written manual regarding prescribing or dedicated to a speciality which includes antimicrobials, and this can be used to incorporate the importance of review and increase awareness.

"Induction manual that I as a faculty tutor have written alongside my colleagues which include guidance on antimicrobial prescription we have…promote that on induction and throughout trainees' placements…e-learning resource too" (A3, ITU Consultant)

"…there are policies where meropenem is allowed in neutropenic sepsis. So, maybe it would be helpful to do a bit of improvement... there will be pharmacists involved in these units and maybe a bit more cooperation and education with pharmacists involved in these units." (B1, Microbiology Consultant)

"…staff educated to a certain standard that review, follow up, and de-escalation will happen appropriately" (B2, Anaesthesia/ITU Consultant)

There was some concern from senior level interviewee toward junior staff practice and method of support;

"…educating the junior doctors and put it in induction and all these things" (B8, Acute Care consultant)

However, the junior staff level was keen towards having more education and increase in awareness of reviewing prescriptions;

"…being reminded and educated from day one, that with antimicrobials, when you are prescribing them, or you are seeing a patient that's on antimicrobials, to know what the duration is, what you are treating them for" (C5, FY-1 Medicine)

"it is about supporting junior staff as well and educating them to know when it is appropriate to change things and where you can go for advice if your seniors are not there." (C6, FY-2 Medicine)

Knowledge:

There were very limited responses about available reviewing policies, mostly comments about single or group effort or consensus. Interviewee's lacked confidence in how to de-escalate from meropenem which affected the reviewing process and impacted upon overall quality of practice.

"I think better guidance on ... where to go following meropenem would benefit ... because it is something I would not feel comfortable" (B7, FY-2 Medicine)

"…being reminded and educated from day one, that with antimicrobials, when you are prescribing them, or you are seeing a patient that's on antimicrobials, to know what the duration is, what you are treating them for" (C5, FY-1 Medicine)

"It is probably something that they may not feel confident doing on their own, but I guess encouraging juniors to come and ask seniors about it" (C8, Senior Registrar ID)

Documentation:

Few interviewees had referenced the importance of documenting the prescription, duration, and reason of initiation to facilitate and support better reviewing process.

"Basic data on duration and what is documented in the notes, and trying to improve on that…Better documentation would help in

reviewing later on"… "Patient's notes they are absolutely massive" (C4, ST Medicine)

"Our practice is to go see patients regularly. We all document that. If it is documented and everything is reviewed, but it has to be on close line with microbiology and those pharmacist's advice, in terms of type of antimicrobials and dose and everything…The pharmacists always document in the notes, advise us about the antimicrobials" (C1, General Surgery Consultant)

4.4.5.3. Communication

One of the themes developed was relating to communication. This theme includes both horizontal communication between teams and vertical communication between different levels of staff rank or administration. The majority of responses can be grouped into senior vs junior communication and between specialised teams and attending primary team. Appendix #15 shows additional supporting quotes.

Senior vs Junior:

In clinical practice, it is usually the junior doctors who physically write the orders and follow-up patients closely on their daily workflow. From junior medic feedback during

interview, some think that it is not their decision to change or raise the question of why are we using this item or when are we going to stop it. Such action might affect the workflow and quality of prescribing.

> *"It's such a team decision usually, with antimicrobials like meropenem which are another IV antimicrobials that I wouldn't necessarily make these decisions on my own…because obviously the consultant's advising me, and then I figure out would write it, but I'm not really the one who's making that decision to get this patient on it"* (C5, FY-1 Medicine)

> *"I think I would assume a lot of stuff comes from junior medical staff doing ward rounds. So people like myself, are probably more scared to change therapy that's prescribed by a senior and prescribed by a consultant…it's about supporting junior staff"* (C6, FY-2 Medicine)

To add, some senior also noticed that juniors tens to avoid changing;

"…you should be reviewing that daily, but especially with probably your more junior staff, the assumption is, you know, it is not their job…I guess encouraging juniors to come and ask seniors about it." (C8, Senior Registrar ID)

In addition, it was mentioned that good communication between teams at the end of shift handover could support reviewing and continuity of treatment.

"…handover process between shifts, between different colleagues…" (A1, FY-1 Medicine)

Between Micro/ID and treating teams:

In this group of opinions, all agree that having open communication channels between specialised and attending teams is a must to support the review process. The type of communication varies based on available resources in each health board, from electronic to face-to-face approaches. This not only improves the quality of prescribing but also upskills the knowledge and expertise of the attending teams.

"Healthy cross-fertilisation of knowledge of us presenting the clinical picture and our keenness on adequate antimicrobial

therapy for our patients alongside the laboratory results and opinion of the microbiologists" (A3, ITU Consultant)

"I guess us visiting on a consult service during the week might prompt a discussion about it" (C8, Senior Registrar ID)

"We have a meeting every morning for all of us, and we will say that, "I think those antimicrobials should stop today", or if it is the weekend, then we will usually put in the notes on a Friday that we think these antimicrobials should stop on Monday or whenever" (C9, Haematology Consultant)

"Involving microbiologist in the ward more often…stronger interaction with microbiologist and the clinical team" (A8, Surgery Consultant)

4.4.5.4. Limitation for a better review

Further to the thematic analysis, limitations and difficulties that face interviewees to have a better review of meropenem prescription were analysed. The results mostly

were covered in previous sections of this chapter (section 4.4.2). However, new thoughts or different from previous section was grouped under this theme and yield in a major subtheme and two minor subthemes. Microbiological samples and reports were found to be a common limitation in some cases which were grouped to a major subtheme. The other two minor subthemes are the behaviour and attitude of prescribers and patient factors. Appendix #15 shows additional supporting quotes.

Microbiology samples and reports:

In this limitation, mainly consultants were discussing that it is difficult to tailor and review a meropenem prescription if there were not enough clinical samples sent to the lab before initiation of therapy. This may happen due to a wrong sampling technique or timing.

> *"Not sending off an adequate numbers of sets of blood cultures before you start antimicrobial therapy at all…before antimicrobial therapy is initiated increases the likelihood that you will treat without knowing what the infection is and then results in downstream decisions that become inevitable"* (A4, ID Consultant)

Another limitation related to the microbiology report, not having a prompt response or a sensitivity report available to guide the attending team limits their ability to review and make a decision.

> *"The lab needs to tell me what I am dealing with"* (C9, Haematology Consultant)

Furthermore, having a report with the alternative antimicrobial sensitivity data included might help in the decision of reviewing and tailoring therapy. This issue was discussed in details later in the interviews.

> *"Unless you have got in the front of you…then the motivation to use, an alternative agent is slightly less"* (D1, Respiratory Consultant)

In addition, from a specialised team point of view, having patients with MDR limits options and reviewing process.

"Unless we have a resolution of the patient's symptoms or new microbiology results and sensitivities, you are almost committed to those antimicrobial." (C7, Microbiology Consultant)

Behaviour and attitude:

In this minor subtheme, discussion leads to exploring limitations that are related to the behaviour and attitude of prescribers. One topic discussed was whether a stable patient on a certain antimicrobial should be kept on it even with a positive culture result available that supported an antimicrobial de-escalation/switch. This topic was not mentioned frequently among the interviewees.

"Sometimes I think the attitude is, if someone's getting better on a broad spectrum antimicrobial like meropenem, even if they have got sensitivities, why change that if they are already getting better?" (C3, Senior Registrar Medicine)

Few interviewees reported that they are not able to review an individual patient's files in detail due to time pressures or other commitments. This can be included under behavioural practice limitations and was only reported by consultants.

"You might not be able to specifically read through all the different drugs that are on the drug chart" (B2, Anaesthesia/ITU Consultant)

Patient and ward factors:

Few of the limitations were related to the patient status, i.e. unknown history or very critical, and ward speciality, i.e. haematology or ITU. Unstable patients that are unresponsive to therapy can be clinically challenging. On the other hand, patients admitted to high-risk wards such as haematology are seen to be complex cases where it is difficult to have a clear review of therapy due to contributing multifactorial condition.

"There are cases where there's a very unwell patient that started on broad-spectrum treatment, often including meropenem, and it is not documented what we are treating" (C4, ST Medicine)

"I suppose the ones that are less likely to be reviewed are the neutropenic sepsis patients that end up on meropenem because they have not responded to tazocin." (B1, Microbiology Consultant)

"The problem comes that because of the nature of the patients that we treat and we only grow bugs in under 30 per cent of our population, it is very difficult to know what you are dealing with." (C9, Haematology Consultant)

4.4.5.5. Good practice examples:

This theme was developed later in the analysis to include any good practice examples that were shared during the interviews by the interviewee, who thought that it could have an impact on the meropenem review process. Almost all interviewee had a positive story to tell, with most examples discussed under other themes. The most common good practice enacted included an engaging, supportive Micro/ID team with antimicrobial pharmacist involvement. Appendix #15 shows additional supporting quotes.

"One of the things we use, the pharmacists, where meropenem has been dispensed, and it is checked whether or not, has it been approved, we are then contacted to check whether or not approve" (A9, Senior Registrar ID)

“One thing that's quite good in this particular hospital is that we have got an infectious diseases team that is clinical based” (C3, Senior Registrar Medicine)

“In intensive care unit patient, we are reviewing them every day anyway. And we are reviewing patients in the subject high dependency every day” (B1, Microbiology Consultant)

“Ward base pharmacists flagged to antimicrobial pharmacist use of meropenem. That is then forwarded to the microbiologist or infectious diseases teams to ask, "Has this been discussed?"” (B4, ID Consultant)

A code system for meropenem approval was applied in one of the health boards included in this study. The use of a code system improved the antimicrobial reviewing process based on the feedback of the interviewees from that health board.

“Prescribed with a code…microbiologist or a specialist infection doctor is more likely to be involved” (A4, ID Consultant)

"When you were given a code for meropenem you are given a list of things to document and feedback at the end of five days as a closure to the prescription" (A7, Respiratory Consultant)

Another good practice story mentioned was the use of a sticker on the patient medical notes to work as a reminder of reviewing patient antimicrobials. However, there was mixed opinion expressed about their use;

"We try looking at the KARDEX, the drug prescribing KARDEX and putting stickers in there. That did not really seem to work." (B8, Acute care consultant)

"Stickers or some kind of page in the notes that said basically this patient is on meropenem, or whatever, and it gets reviewed every day. It has why they are on it and for how long they should be on it" (B6, CT Medicine)

In one interview, an attempt to include antimicrobial review in the daily round was conducted by listing antimicrobial usage in the ward round checklist. This was mentioned only in one interview, and the feedback was positive.

"Got ward round checklists, on some wards, in which that is part of the process, to review antimicrobials" (B9, Care of Elderly Consultant)

Finally, a daily-base meeting between attending team members and discussing each patient therapy, including antimicrobials, were found to be helpful and improved reviewing of antimicrobials in general from both the senior and junior medics point of view.

"Daily safety meeting which we discuss anyone who's on IV antimicrobials" (A1, FY-1 Medicine)

"We have a meeting every morning for all of us, and I will say that day, "I think those antimicrobials should stop today" or whatever" (C9, Haematology Consultant)

"We sit down and review all the patients all medication in the morning" (A8, Surgery Consultant)

4.4.6. Experience with Carbapenem-Sparing Antimicrobials (CSA's)

From the 28 interviewees included in the study, only three (10%) had not prescribed any of the CSA's. The three interviewees were from the same health board, and only one of them was a consultant. On the other hand, eleven interviewees (39%) have experienced prescribing all of the CSA's. Aztreonam was the most common CSA's with 22 interviewees (78.5%) prescribing it, followed by temocillin prescribed by 20 interviewees (71%). Fosfomycin was the third most common CSA's prescribed with 17 interviewees (60%) having clinically used it. Pivmecillinam was the least commonly prescribed (15 interviewees, 53.5%).

Based upon an individual interviewee's response to CSA prescribing experiences, the interview diverted to two sections aiming to further explore what the interviewee had earlier confirmed. The decision behind initiation or selection of CSA's over meropenem was discussed previously, section 4.3.1.

4.4.7. Levers of prescribing CSA's

From interviewees that had prescribed CSA's, two follow-up questions were asked to explore levers and barriers that they encounter with prescribing CSA's. Thematic analysis of levers resulted in two major themes identified: local system and knowledge, and one minor theme, stories of success. All interviewees that prescribed CSA's before answered and discussed this topic. Table 16 lists a summary of themes and codes yielded from thematic analysis of prescribing levers. Appendix #15 shows additional supporting quotes.

Table 16 Summary of CSA's prescribing levers themes and codes

Code	Subtheme	Theme
Micro/ID advice *Microbiology reports*	Recommendation of prescribing	Local system
Guidelines *Communication* *Leader/Senior reinforcement*	Organisational influenced prescribing	
Patient factors		
Drugs profile *Experience of use*	Confidence	Knowledge
Educational activities *References, posters and handbook* *Meropenem overuse*	Education	
		Stories of success

4.4.7.1. Local system:

In this theme, the local system influenced prescribing CSA's from different approaches. Two subthemes were developed under local system influence; recommendation of prescribing and the influence of organisational prescribing. Further, a minor subtheme included patient related factors that influenced the prescribing of CSA's.

Recommendation of CSA prescribing

From the results, help and support from specialised teams and microbiological evidence were a significant lever for prescribing CSA's. In fact, most of the interviewees prescribe CSA's only if advised by Micro/ID teams.

> *"We rely on microbiologist coming around"* (A3, ITU Consultant)

> *"…speaking to colleagues in microbiology is another prompt to using them"* (C4, ST Medicine)

> *"Think where we might have an alternative. Then speak to the microbiologist about what they feel the best alternative to it. I*

think we are well supported by the microbiologist" (B9, Care of Elderly Consultant)

"I think microbiology are advising these agents as well" (C8, Senior Registrar ID)

"We have been advised by microbiology…the ID ward rounds" (D1, Respiratory Consultant)

Another lever for prescribing is the availability of positive sensitivity to CSA's in microbiological reports. This supported some interviewees in prescribing alternatives with more confidence.

"I am being told by microbiology they have got a bug that's that sensitive to... then I will happily go with that" (C9, Haematology Consultant)

"As far as levers go, I suppose having sensitivities for those agents reported" (C2, Medicine Consultant)

Furthermore, microbiologists agreed that culture and sensitivity reports were levers in prescribing CSA's once they included and suppressed them in reports.

> *"The antimicrobials we report"*…*"These are in the antimicrobial prescribing policy that determines what we report for our sensitivity patterns in microbiology."* (B1, Microbiology Consultant)

The importance of having CSA's included in culture and sensitivity reports was helpful for specialised prescribers, such as ID;

> *"Close working relationships with the laboratory staff, the microbiology staff"* (B4, ID Consultant)

> *"…they are now reporting, certainly much, they have incorporated it into their reporting more certainly"* (C8, Senior Registrar ID)

Organisational influenced prescribing

Promoting CSA's in local guidelines was considered an important supportive lever in prescribing. Two health boards feature CSA's in local guidelines and the feedback from interviewees, specialised and non-specialised, of both boards was very positive. Featuring CSA's in local guidelines not only supported prescribing but also elevated knowledge of their clinical usage.

> *"…they are placed in the guidelines"* (A9, Senior Registrar ID)

> *"…we follow the guidelines, and we just go with that…and it has made its way on to the empirical guidance"* (C3, Senior Registrar Medicine)

> *"Aztreonam in the guidelines. That is a lever you described"* (C5, FY-1 Medicine)

> *"They are placed in guidelines…people are very guideline compliant here."* (B3, ID Consultant)

"Having them embedded in the empirical guidelines is very helpful…having them on the guidelines, having the dosages there and the regimes there, is very helpful" (C8, Senior Registrar ID)

Another organisational related factor reported by interviewees was the level of communication between attending and specialised teams, and between seniors and juniors. Having an open channel of communication between specialised teams and non-specialised was seen as a lever in prescribing CSA's by both sides.

"I think close working relationships with the laboratory staff, the microbiology staff" (B4, ID Consultant)

"…very close communication with microbiology" (A2, Medical Registrar)

"I find helpful and helpful when speaking to clinicians is to be able to quote our local resistant rates. In comparison to our antimicrobials that they are really familiar with… it is just trying to give them that reinforcement for them" (C7, Microbiology Consultant)

One interviewee hinted at the importance of open communication between senior and junior doctors;

> *"Good communication with the senior doctors, and one-to-one if anyone asks for it"* (B5, ID Consultant)

Active leaders with strong leadership skills have some influence in supporting CSA's prescribing. Reinforcement of CSA's role and importance by leaders or local committees were seen as a fruitful effort.

> *"That was from the AMT level because there was that kind of drive from SAPG about restricting Piptaz and meropenem use. These were things that we implemented at a local level"* (A9, Senior Registrar ID)

> *"…it kind of comes down from the antimicrobial management team"* (A5, Microbiology Consultant)

"One of the consultants here is very averse, doesn't like using meropenem unless it is the last option" (C5, FY-1 Medicine)

"The chair of the antimicrobial group being a driver of change, and someone who has great clinical experience, and their confidence of recommending particular alternatives, probably lends a huge weight to not only clinicians within the infection group but clinicians out with the infection group." (B4, ID Consultant)

Patient-related factors

Only a few interviewees discussed an individual patient clinical condition as a lever for prescribing CSA's. Three interviewees discussed that because the patient was stable enough not to be admitted to the hospital but shows positive culture for Gram-negative, CSA's were considered for oral dosage form availability.

"I prescribe them because we are always trying to discharge patients as early as possible and they are two antimicrobials that mean that we can either keep patients at home or discharge patients from hospital earlier when otherwise they would've required intravenous antimicrobials" (B8, Acute Care Consultant)

"We have used that [pivmecillinam] as an oral agent rather than treating in as somebody who's not septic and not unwell" (B9, Care of elderly Consultant)

"Well, the only option here is meropenem because they have got multi-drug resistance. But actually, you can give them pivmecillinam, fosfomycin orally and get them home" (C2, Medicine Consultant)

4.4.7.2. Knowledge:

Interviewees discuss knowledge about CSA's as a supportive lever in daily practice. The source of knowledge developed by education improves confidence in prescribing. Thus, two subthemes developed under knowledge; confidence in using and educational need.

Confidence

Confidence in prescribing CSA's from the interviewee's point of view came from two sources, familiarity with and individual CSA's drug profile and from clinical experience

of their use. The availability of oral dosage forms of pivmecillinam and fosfomycin was a major advantage in using these CSA. By knowing this information, prescribers felt more confidence in selecting them. In addition, having them in future local guidelines with specified doses will further support confidence in prescribing.

> *"Having standard doses is a lot easier for us"* (C3, Senior Registrar Medicine)

> *"We are always trying to discharge patients as early as possible, and they are two antimicrobials that mean that we can either keep patients at home or discharge patients from hospital earlier when otherwise they would've required intravenous antimicrobials"* (B8, Acute care Consultant)

> *"…in medical school I was more aware of aztreonam"* (C6, FY-2 Medicine)

> *"Knowing that there are alternatives around and learning more about them with microbiology support"* (A2, Medical Registrar)

"I think actually having them on the guidelines, having the dosages there and the regimes there is very helpful." (C8, Senior registrar ID)

Experience of CSA use was a positive lever supporting prescribing, with greater frequency of usage promoting confidence in prescribing.

"I think seeing it work in those circumstances kind of gives you confidence in its use" (C7, Microbiology Consultant)

"Having experience using them and feeling comfortable using them helps" (B5, ID consultant)

"It took us a bit of time to gain experience with it" (A9, Senior Registrar ID)

"We are quite comfortable just adding in either temocillin or aztreonam… If two years ago you asked me the same question, I would say, "No, we are not comfortable using aztreonam and

temocillin." Because it was not widespread" (C3, Senior Registrar Medicine)

Education

Education related to CSA's improves knowledge among prescribers. Interviewees provided different examples and opinions about educational improvements that happened locally or feeds positively into their practice of CSA use. Generally, there were three educational areas, from interviewee's point of view, that improved knowledge about CSA's; educational activities, resources, and meropenem overuse awareness. Different types of educational activities were the most common one; in presentation format or on the one-to-one discussion.

"…they give presentations here within the hospital about use of antimicrobials and aztreonam, and temocillin has come in the last, I would say much more in the last few years, talking about using it." (C3, Senior registrar Medicine)

"I was trained if someone had been on gentamicin for like three days they would switch them to aztreonam if they still required cover." (C6, FY-2 Medicine)

"Spread of knowledge…having someone who has clinical expertise and respect" (B4, ID Consultant)

"I find helpful and helpful when speaking to clinicians is to be able to quote our local resistant rates. In comparison to our antimicrobials that they are really familiar with…It is just trying to give them that reinforcement for them" (C7, Microbiology Consultant)

Some interviewees, from two health boards, discussed that available resources supported them in prescribing CSA's. There were reports about having posters, treatment charts, and therapeutic handbooks that promote the use of CSA's which improved their knowledge about CSAs.

"So we have a guidance in terms of a poster that's on every ward. That kind of flowchart for infections. We also have therapeutics handbook, which gives quite clear guidance on many infections" (C4, ST Medicine)

"I think having the algorithm for primary and secondary care available in [health board name] has been really helpful" (C7, Microbiology Consultant)

"…very useful…like the antimicrobial charts that are produced on the handbook, that just means when people are looking it up it prompts them to consider these as an alternative" (D1, Respiratory Consultant)

From the results, only three interviewees, from specialised teams, reported that awareness of meropenem overuse encouraged them to use CSA's aiming to preserve broad-spectrum antimicrobials.

"I think that is probably the greatest lever…the apocalypse, of antimicrobials. And the future is perhaps too esoteric and woolly to really make it a lever individually even in the infection group" (B4, ID Consultant)

"The pressure to try and stop co-amoxiclav and tazocin use… resistant rates" (C7, Microbiology Consultant)

"…trained and worked in an environment where I am to promote stewardship and preserving these broad-spectrum agents is just what we do." (B5, ID Consultant)

4.4.7.3. Stories of success:

In this minor theme, the researcher analysed shared success stories told by interviewees. These stories were thought to be helpful and supportive of prescribing CSA's; cost, resistance to change, and high demanding wards. Upon drafting this element of PhD research, the project steering group discussed the possibility that cost might influence CSA consumption (discussed in detail in section 4.2.6.1). In the following exemplification we can see how clinical microbiologists may overcome this issue;

"I think that was all agreed between AMT and the board. They were fully aware of the cost when they moved forward with this" (C7, Microbiology Consultant)

Another case discussed was by an ID consultant, they faced reluctance in prescribing from a specific department in their local hospital;

"if anyone is repeatedly not prescribing to the guidance or making things difficult for the department or difficult for the juniors, then someone senior from Antimicrobial Management team would have a meeting with them and just be really open about" (C7, ID Consultant)

High demanding speciality wards can be a challenging area to support. However, two interviewees discussed how they successfully overcame this challenge and improved prescribing quality.

"We have a permanent pharmacist on this ward. So I just say to my pharmacist, "I need temocillin." She tells me what to do and prescribe. They are here all the time... We meet our microbiologist every week. We have a multi-disciplinary team meeting… We have a lot of support compared to many." (C9, Haematology Consultant)

"the ID ward rounds… we have got such a good relationship with them I think is because of a lot of discussions that took place over a long period of time on these ward rounds. To the point where

actually we do not need them so much anymore, but when we ask them for help, it is given almost straight away." (D1, Respiratory Consultant)

4.4.8. Barriers to prescribing CSA's

From interviewees that have prescribed CSA's, two follow-up questions were discussed to explore levers and barriers that they encounter when prescribing CSAs. Thematic analysis of barriers topic resulted in two major themes, local system and knowledge, and one minor theme, special cases. All interviewees that had prescribed CSAs before answered and discussed this topic. Table 17 lists a summary of themes and codes yielded from thematic analysis of prescribing levers. Appendix #15 shows additional supporting quotes.

Table 17 Summary of CSA's prescribing barriers themes and codes

Code	Subtheme	Theme
Micro/ID advice *Microbiology reports*	Recommendation of prescribing	Local system
Guidelines *Stock and availability* *Formulary approval status* *Authorisation mechanism* *Cost*	Organisational influenced prescribing	
Patient factors		
Drugs profile *Experience of use* *Last resort choice* *Temocillin dosing*	Confidence	Knowledge
Habits and behaviours *Pricing* *Published evidence* *Place in guidelines*	Education	

4.4.8.1. Local system:

In this theme, the local system was considered as a barrier to prescribing CSAs from different perspectives. Two subthemes were developed under local system influence; recommendation of prescribing and organisational influence prescribing. Further, a minor subtheme includes patients' related factors that influenced the prescribing of CSAs.

Recommendation of prescribing

From the results, interviewees reported that specialised teams and microbiological evidence might not recommend or mention CSAs. Two interviewees discussed that

microbiologists did not often recommend CSAs and one hinted that contacting a microbiologist can be time-consuming in some cases.

> *"They are rarely if ever, suggested by the microbiologist as an alternative when you are phoning up and asking."* (B8, Acute care Consultant)

> *"It is not recommended that often by microbiology"* (B2, Anaesthesia/ITU Consultant)

> *"…discussing with microbiologists, it is also a nuisance at times too"* (A7, Respiratory Consultant)

Furthermore, one microbiologist admit that they hindered use of fosfomycin by GP's;

> *"We only give the GPs routinely three antimicrobials; trimethoprim, nitrofurantoin, and gentamicin speaking about UTI cause that where we tend to use fosfomycin. So if they want to use fosfomycin, they have to come through us; we do not routinely*

give it up. That is a good barrier I think!" (A5, Microbiology Consultant)

Microbiology reports not releasing or including CSAs in them was the most common barrier in prescribing. This issue was discussed mainly by non-specialised teams and ID teams too.

"I think the only thing that sometimes can cause problems are if there are sensitivities to these agents not reported… there are limited options available listed in terms of sensitivities because the lab have a say in terms of reporting sensitivity patterns" (A9, Senior Registrar ID)

"…you still have to ask for extended testing on the sensitives to get fosfomycin and pivmecillinam sensitivity… people do not know they exist because they are not on their routine sensitivity reports" (B8, Acute care Consultant)

"They avoid putting some drugs on the sensitivities as well that they do not want us to use" (B9, Care of elderly Consultant)

"…for standard UTI's and things, you do not see pivmecillinam and fosfomycin featured in highly" (C8, Senior Registrar ID)

Only one interviewee hinted that he might not be confident in culture and sensitivity report.

"Sometimes the in vitro sensitivities do not marry up with response in vivo, particularly for the chronic patients" (D1, Respiratory Consultant)

<u>Organisational influenced prescribing of CSAs</u>

The organisation can become a barrier for prescribers when initiating CSAs. From the results analyses, a group of factors related to local organisational influence prescribing CSAs. Some local health boards exclude CSA's from local guidelines which are seen as a barrier in prescribing.

"…they do not have a place in the guideline" (B8, Acute care Consultant)

"…they are not really described in the antimicrobial guidance" (A2, Medical Registrar)

The stock of CSAs in local health boards and their availability on-site were the most discussed barrier when prescribing CSAs, identified by 14 interviewees from both specialised and non-specialised teams.

"Stock…ability to get the drug" (A4, ID Consultant)

"I know availability has been an issue at various times…wards would not stock them…they were not available in the ward, and if you need to give it within the next hour or two, sometimes you would end up using an alternative cause you cannot get it...we were unable to source aztreonam for a time" (C4, ST Medicine)

"…there was recently an aztreonam shortage" (B2, Anaesthesia/ITU Consultant)

"…they cannot get the drug when we make the decision" (A7, Respiratory Consultant)

"…there have been a bit of delay in getting it." (B9, Care of elderly Consultant)

"…getting consistent availability of the drug… it is not kept as a stock item. And having delays in the prescribing" (B4, ID Consultant)

There were four interviewees, three specialist and one non-specialist that think CSAs are costly and might not be justified.

"They are expensive, though. Aztreonam is expensive, and temocillin is very expensive" (B1, Microbiology Consultant)

"…that was our major problem with aztreonam the supply issues and cost" (B3, ID Consultant)

"Temocillin, given the cost, has been used less than aztreonam"

(B4, ID Consultant)

"…people perceive them to be expensive" (B8, Acute care Consultant)

One ID consultant discussed that by not including aztreonam to local formulary is a barrier of prescribing.

"…aztreonam here because it is not on formulary" (A4, ID Consultant)

Only one interviewee mentioned that authorisation mechanism for CSAs could be time-consuming and limit their prescribing.

"The authorisation process…discussing with microbiologists" (A7, Respiratory Consultant)

Patient-related factors

Only a few interviewees discussed the individual patient clinical condition as a barrier to prescribing CSAs. Most highlighted it was an unstable patient who created clinical dilemmas on whether a CSA should be given.

> *"I guess in somebody who is critically unwell, and you do not have sensitivities, and if you do not know what you are treating 100%, then you maybe have a kind of second thought."* (C8, Senior Registrar ID)

> *"…perception amongst some of our intensive care colleagues ... that aztreonam is no good an antimicrobial as tazocin… worried about covering Pseudomonas infection"* (B1, Microbiology Consultant)

4.4.8.2. Knowledge:

Interviewees discuss knowledge about CSAs as a limitation barrier in daily practice. The lack of knowledge toward CSAs affects confidence in prescribing and identified educational needs. Thus, two subthemes developed under knowledge; confidence in use and education needs.

Confidence

From the results, a lack of confidence in CSAs among interviewees was a major barrier in prescribing. Lack of confidence could be explained by a gap in knowledge about and individual CSAs drug profile, limited experience of use of a given agent, or unawareness of the antimicrobial spectrum of activity of the individual CSA.

> *"Lack of awareness of their spectrum, of what they cover."* (B7, FY-2 Medicine)

> *"…less commonly used, so you are not used to knowing the dosing and the indications"* (C6, FY-2 Medicine)

> *"…side effect profile…Drug interactions"* (A6, Haematology Consultant)

> *"The main limitations are inexperience and unfamiliarity with the actual agent's …personal experience with the antimicrobials is also a barrier, in that we do not know is it a useful antimicrobial or not."* (C3, Senior Registrar Medicine)

The lack of confidence in CSAs was also seen by specialised team interviewees as a barrier in prescribing for them and a barrier in convincing non-specialised teams.

> *"Other clinicians; they are not confident in those antimicrobials…Knowledge yes, so these are antimicrobials that clinicians are not used to using"* (A5, Microbiology Consultant)

> *"We do not have the clinically experience or reassurance of, you know, people doing well on these. It is only with using it and seeing it work well that gives you the confidence to prescribe it more"… "The big barrier is lack of familiarity. Lack of experience"… "I would not treat somebody who was actually unwell with pivmecillinam"* (C7, Microbiology Consultant)

> *"…the dosages that you need, and the appropriations that you need, I had a bit of an issue using it on a couple of occasions, where you did, the pharmacist needs to get involved quite a few times to kinds of smooth out the process. I think again that is because we are not used to prescribing it, so I think if it was*

something that you did more, then it would become a smoother process" (C8, Senior Registrar ID)

"Perception amongst some of our intensive care colleagues ... that aztreonam is no good an antimicrobial as tazocin" (B1, Microbiology Consultant)

"The lack of published studies makes me a little bit concerned" (C7, Microbiology Consultant)

Temocillin and fosfomycin dosing issue came into the discussion as causative of less sureness in using it.

"The oral and IV dosing of fosfomycin, I cap, we do not have confidence that we know the correct dosing… the pharmco-dynamics, pharmco-kinetic concerns I have around pivmecillinam and fosfomycin really understanding whether they can be effectively used*"* (B4, ID Consultant)

"Temocillin. I think we are not sure what the optimal dose is" (C7, Microbiology Consultant)

Education

Education needs related to CSAs knowledge among prescribers were identified by a few interviewees. They had different examples and opinions about educational gaps that need to be fulfilled. Generally, there were four educational areas, from individual interviewee's points of view that needed to be focused on; changing habits and behaviour, place of CSAs in guidelines, availability of published evidence, and pricing of CSAs. There were a few habit and behaviour related actions that needed to be improved by educational activities. The perception that CSAs are not as clinically effective as other agents and CSAs should only be initiated by specialised teams.

"Perception amongst some of our intensive care colleagues ... that aztreonam is no good an antimicrobial as tazocin"… "There is always a bit of nervousness about using new and different antimicrobials." (B1, Microbiology Consultant)

"The perception that perhaps we are trying to stop them using the really good stuff. I think that is the psychology. I think that is what they are thinking." (C7, Microbiology Consultant)

"Expect microbiologists to be the leaders in these antimicrobials"

(A5, Microbiology Consultant)

Unfamiliarity with CSAs place in clinical guidelines was reported by some interviewees as a barrier and an educational need.

"I am not even familiar of situations you would use as antimicrobials." (B7, FY-2 Medicine)

"…another barrier is awareness. Particularly in junior staff" (B9, Care of elderly Consultant)

"…further education" (A6, Haematology Consultant)

Lack of published evidence supporting the use of CSAs was discussed by one microbiologists as a barrier that needs to be improved.

"I would not treat somebody who was actually unwell with pivmecillinam"… "The lack of published studies makes me a little bit concerned" (C7, Microbiology Consultant)

One interviewee mentioned that CSA's pricing issue needs to be addressed;

"…people perceive them to be expensive" (B8, Acute care Consultant)

4.4.9. Reasons for never prescribing CSAs

From 28 interviewees included in this research, only three (10%) had not prescribed any CSAs. All three were from the same health board, two juniors and one general surgery consultant. However, the general surgeon consultant was fully aware of CSAs and justified never using it by not seeing a patient indicated for their application.

"I will prescribe it personally always on microbiology advice. As far as I know, we did not really need to. There was no...For the patients that sort of, I managed." (C1, General Surgery Consultant)

From the other two interviewees, CT Medicine mentioned that they had not seen it and agreed that there is a lack of knowledge.

> "*I do not know that. I just haven't come across it…knowledge issue… I do not know even know if it appears in the guidelines anywhere. I would think it would be on micro advice*… doesn't include it in the guidelines.*"* (B6, CT Medicine)

The other interviewee was an FY-2 Medicine, who recalled seeing patients on fosfomycin but not under their direct care. There was a clear gap of knowledge toward CSA's and hinted that only microbiology could advise using.

> *"I do not know, and again under microbiology advice so I do not know if that was there. Their rational as a meropenem sparing drug or if it was per sensitivities… I guess, lack of awareness of their spectrum, of what they cover. I would say that is probably why, because I certainly wouldn't be confident knowing which situations that those would apply"* (B7, FY-2 Medicine)

4.4.10. Overall use improvement for meropenem and CSAs

All interviewees were asked an open-end question aiming to encourage discussion and sharing of their thoughts of meropenem and CSAs in daily clinical practice. All participants were excited to share what they thought and what might support them to improve their prescribing. The discussion was open and sometimes repetitive to what they mentioned during the interview.

Thematic analysis of this transcribed data revealed four major themes or supporting meropenem and CSA prescribing; limitations, responsibilities, organisational level, and education. Under each theme, subthemes were developed during thematic analyses. Limitation theme includes interviewees' thoughts about what hinders them in better prescribing meropenem and CSAs. Four subthemes were seen: targeted wards and patients, technical factors, inappropriate use justification, and limitation of resources. The second theme was responsibilities that are distributed between practitioners from health board leaders, Micro/ID teams, and AMT's.

Thirdly, organisational level influence to prescribing meropenem and CSAs developed three major subthemes, local policies and restrictions, guidelines, and communication. Finally, the importance of education was the fourth theme identified from this analyses. The education theme included three major subthemes;

references and resources, training activities, and increase the level of awareness. Each theme, sub-theme, and code is summarised in table 18. Appendix #15 shows additional supporting quotes.

4.4.10.1. Limitations

In this theme, any type of difficulties that interviewees encountered or thought limited the rational use of meropenem, or better use of CSAs was included. Further to the thematic analyses, all discussed information falls in four subthemes, target wards and patients, technical factors, inappropriate use of other antimicrobials, and resources.

Table 18 Summary of overall use improvement of meropenem and CSA's themes and codes

Code	Subtheme	Theme
Patient condition *High-risk wards*	Target wards and patients	Limitations
Review techniques/daily practice *Feedback between teams* *Lack of evidence/source of infection*	Technical factors	
Piperacillin/tazobactam overuse *Others*	Inappropriate use reasons	
Time *Cost* *Workforce*	Resources	
Health boards leaders *Seniors/consultants*	Health boards leaders and leadership	Responsibilities
Active involvement *Communication* *Improve service provided*	Micro/ID	
Stewardship teams *Multidisciplinary teams, pharmacists, nurses*	AMT	
CSA'S approval *Prescribing restrictions policies*	Local policies and restrictions	Organisational level
Sampling time and techniques *Testing and suppressing alternatives*	Microbiology reports and sampling	
Restrict meropenem featuring in guidelines *Feature CSA's more* *De-escalation guideline*	Guidelines	
Between teams *Between health board leaders and teams* *Seniors vs juniors*	Communication	
Auditing *Electronic systems*		
Handbook/posters *Electronic resources*	References and resources	Education
Meropenem use and review importance *CSA's*	Training and education activities	
Meropenem overuse issue *Alternatives availability and place in guidelines*	Awareness	
Culture and prescribers behaviour		

Target wards and patients:

Interviewees discussed difficulties in special need patients, those in high-risk wards and with life threating conditions. They are common users of meropenem and good candidates for CSAs.

> *"Patients that I have seen on meropenem, it is mostly immuno-suppressed patients, so patients having chemotherapy, patients with haematological problems"* (C4, ST Medicine)

To overcome that, several successful attempts were implemented in high demanding wards targeting difficult patients which supported attending teams in better prescribing. Interviewees reported these experiences as useful support and should be circulated to others.

> *"I think we are very lucky. We have a lot of support compared to many"* (C9, Haematology Consultant)

> *"I think focusing on the areas where it is used most, which would be respiratory and I would imagine general surgery, strokes,*

hospital HDU, ITU, and haematology." (A7, Respiratory Consultant)

"The infectious disease consultants have been keen to try and do infection ward rounds which they do with microbiologists." (D1, Respiratory Consultant)

"High dependency unit, both medical and surgical unite, and intensive care unit although they initiate it quicker and can initiated it independently they are regularly reviewed by the microbiologist team anyway" (A8, General Surgery Consultant)

"Availability of our consultant microbiologists on call and our sort of healthy relationship with them fostering what I would say is good antimicrobial prescribing" (A3, ITU Consultant)

"Microbiologists were very proactive. They used to do daily ward runs in intensive care, high dependency, with the pharmacists. It was good team" (C1, General Surgery Consultant)

Technical factors:

Reviewing techniques in daily practice, feedback between different teams and lack of infection source or evidence are three coded elements under the subtheme of technical factors. The review process improvement was extensively discussed previously (section 4.2.3.), and the following are added-on thoughts from interviewees.

> *"Having a daily review checkbox or sticker thing might help with some of these antimicrobials that we use as last lines…"Is it still appropriate to continue or when was the last discussion with ID or microbiology?" Might be useful"* (C3, Senior Registrar Medicine)

> *"…stickers of red, amber, green, where you have an antimicrobial"* (A7, Respiratory Consultant)

> *"Having a separate prescribing documents"* (A2, Medical Registrar)

Improved feedback technique between teams was mentioned by two interviewees;

> *"…there should be an advice about for how long or when this would need to be reviewed…reviewing it right from the beginning"* (B2, Anaesthesia/ITU Consultant)

> *"…balance between antimicrobial stewardship and rapid access to essential therapy…feedback loop in specialist practice"* (A4, ID Consultant)

Two interviewees discussed that they face difficulties with identifying the source of infection or patients with missed samples as reasons for unjustifiable use of meropenem.

> *"…you do not often identify a source of infection, so they are given very broad spectrum"* (C4, ST Medicine)

> *"A lot of people are treated on antimicrobials and don't have the samples sent, and then you are a bit stuck because you are basically empirically treating them forever and then it is very*

difficult to know how to rationalise antimicrobials" (C6, FY-2 Medicine)

Reasons for inappropriate use:

Overall, most of the interviewees agreed that meropenem is overused and should be controlled. In this subtheme, we grouped opinions from interviewees that might influence meropenem inappropriate prescribing. Although piperacillin-tazobactam use was not covered by the interview schedule, few interviewees discussed overuse of it and relate to meropenem consumption by both specialised and non-specialised teams. Note that, Tazocin® and Piptaz® are trade names of piperacillin-tazobactam.

"Tazocin is a very good question because I think it gets used a lot more freely. Not always with microbiology advice. I have seen it prescribed a lot and have myself used it a lot even without consultant advice" (B7, FY-2 Medicine)

"…tazocin before we even get any blood tests off, so we are not going to reduce tazocin usage while we have it as first-line agents" (B8, Acute care Consultant)

"…our tazocin use; which we use a lot of but I think we can step back from that now and start to use alternatives" (A5, Microbiology Consultant)

"…they worry about effective microbial in where that perception is that if you use tazocin or meropenem you could quickly get the correct antimicrobials into an individual…tazocin is a bigger problem for us than meropenem" (B4, ID Consultant)

"I think we have gotten too comfortable with tazocin" (C2, Medicine Consultant)

"We have definitely tried to use less by using more tazocin." (A6, Haematology Consultant)

Only one interviewee hinted that meropenem is overused due to easy accessibility;

"The fact that it is easy to get it" (B3, ID Consultant)

Resources:

Limitations in different types of resources; time, cost, and workforce, were mentioned briefly as an area of improvement.

> *"If you do not have adequate consultants for that knowledge you are not going to get your guidelines reviewed and changed"* (A5, Microbiology Consultant)

> *"I think one issue probably is Antimicrobial Management teams not having enough time and resource to actually go and have these dialogues with the different departments"* (B5, ID Consultant)

> *"They are expensive… aztreonam and temocillin are more expensive than tazocin"* (B1, Microbiology Consultant)

However, the expense of CSAs issue was resolved and mentioned in the following.

"I think that was all agreed between AMT and the board. They were fully aware of the cost when they moved forward with this."

(C7, Microbiology Consultant)

4.4.10.2. Responsibilities

To improve meropenem and CSAs use, interviewees discussed shared responsibility between different teams and level of authority. Thematic analysis for responsibilities theme developed three subthemes that represent a group of health care providers responsible for improving the use of meropenem and CSAs. Health boards leaders and the role of leadership is the first subtheme, specialised Micro/ID teams secondly, and the third subtheme is AMT's.

Health boards leaders and leadership:

Interviewees discussed having an active leader, responsible specialised team member, or a senior professional mentor positively influence meropenem and CSAs quality of prescribing.

"I think the agenda that has now been set by the chief medical officer for Scotland about realistic medicine is probably a good

idea…You do not have to exhaust every possible antimicrobial before you let the patient die" (B1, Microbiology Consultant)

"I chat with the trainees a lot about why do we think this is. I think the trainees definitely have a culture of we are avoiding tazocin and meropenem unless we really have to use them. If we are going to use them, we need to document on a patient notepad why you have chosen that over and above temocillin or aztreonam… a real encouragement to the junior staff. If they are seeing a consultant use these antimicrobials in ITU patients" (C7, Microbiology Consultant)

"Senior, education and mentor…If your consultant is happy to teach you, then you are on the ward rounds, and you ask, why are we using IV meropenem? Then he or she will explain therefore, that is really helpful" (C5, FY-1 Medicine)

Microbiology/ID:

The results from the interviews show that almost all of the participants highlight the importance of Micro/ID teams in supporting meropenem and CSA prescribing. Active

involvement from Micro/ID teams positively influenced non-specialised teams practised where it is applied and requested to be available if not employed.

> *"…availability of our consultant microbiologists on call and our sort of healthy relationship with them fostering what I would say is good antimicrobial prescribing"* (A3, ITU Consultant)

> *"…much safer to have a microbiologist or you have a microbiologist advice before you initiate, instead of using it on a widespread base… having the input of a microbiologist practically for these sort of drugs is a good idea"* (A8, General Surgery Consultant)

> *"…good access to a microbiologist who can advise you with the appropriate antimicrobial"* (B2, Anaesthesia/ITU Consultant)

> *"Microbiology advice really or ID advice is probably the core to keeping in control of that"* (C2, Medicine Consultant)

In addition, Micro/ID teams agree and acknowledge their importance to support non-specialised teams.

> *"…working more closely routinely with clinical surgical colleagues we hope that we can foster confidence in decisions such that they are comfortable with us moving away and deescalating and preventing use of meropenem… greater involvement in routinely in more areas is probably the only way that we are going to reduce antimicrobial usage"* (B4, ID Consultant)

> *"The consult service and the microbiologist as well, kind of advocating the use of the alternative agents, is really neat to work together"* (C8, Senior Registrar ID)

> *"…having adequate involvement of specialist to really review your antimicrobials guideline, and having them go to the wards and get changes. You know, enforce that change, and enforce the recommendation"* (A5, Microbiology Consultant)

Open channels of communications between Micro/ID and other teams were also discussed as a supportive measure mostly by non-specialised teams.

> *"…microbiologists and the infectious diseases team here are very open, easily accessible, and easy to talk to. It is easy here to not use meropenem"* (C3, Senior Registrar Medicine)

> *"We always ask the microbiologist and give them the information… microbiologists were very proactive… I think the key person after the clinician would be the microbiologist… If you have any doubt, pick up the phone, speak to the microbiologist"* (C1, General Surgery Consultant)

> *"Microbiologists here run a fairly hands-on on-call service, and someone is available 24 hours a day seven days a week"* (A4, ID Consultant)

> *"If the clinician does not pick up the phone to speak to the microbiologist, then the microbiologist will not know about them."* (C1, General Surgery Consultant)

Further, few examples of improved delivered service by Micro/ID were mentioned by some interviewees that upscale the quality of meropenem or CSA prescribing.

> *"I think one of the really good things had been one of our consultants here like I said, is using them a lot in ITU. I think that has been a real encouragement to the junior staff. If they are seeing a consultant use these antimicrobials in ITU patients, well wow. You know, these must be good. They feel I think, empowered to suggest them."* (C7, Microbiology Consultant)

> *"They used to come twice a week and actually out of that we gained a lot of knowledge and experience, and what some of the alternatives were and I think we do use them more… Because of that exposure, they have not felt the need to come and nag us quite so much. We do have a good relationship with them…. because of a lot of discussions that took place over a long period of time on these ward rounds. To the point where actually we do not need them so much anymore, but when we ask them for help it is given almost straight away… Having another team who knows more about this coming in and holding your hand through the*

process of saying well actually it is okay to do this" (D1, Respiratory Consultant)

AMTs:

The role of a multidisciplinary, antimicrobial management team was discussed and valued by respondents. Both specialist and non-specialist team members mentioned the importance of AMT. There were positive feedbacks from having a ward-based antimicrobial pharmacist, and the service of antimicrobial nurses.

"…dedicated pharmacist on the ward would make a difference…an antimicrobial outreach group" (A7, Respiratory Consultant)

"There is possibly a need for additional input from people who are confident in using other antimicrobials, whether that is a microbiologist, an infectious diseases doctor or a pharmacist or nurse, particularly trained in antimicrobial prescribing…more routine in stewardship, clinical stewardship on the ground" (B4, ID Consultant)

"We have an Antimicrobial advanced nurse practitioner, and microbial stewardship" (B5, ID Consultant)

"Because you have got a combination of microbiology, microbiology pharmacists and infectious disease consultant who does the ward round that's a very potent mix of expertise to argue with." (D1, Respiratory Consultant)

4.4.10.3. Organisational level

Organisational level heavily influences the use of meropenem and CSAs according to interviewees. This main theme developed four subthemes and two minor codes after thematic analysis that includes all interviewees' thoughts and opinions related to organisational influence. Local policies and restrictions, microbiology reports and sampling, guidelines, and communication are the four main subthemes followed by auditing and electronic systems minor codes.

Local policies and restrictions:

High alert antimicrobial prescribing policies and restriction regulations are a common practice in health boards. As discussed previously in chapter 2, meropenem is restricted in most health boards and commentary was provided about the support of

this practice. However, restrictions applied to CSA's were not mentioned by any interviewee.

> *"I think it probably is good that that's [restriction] is in place. Otherwise, people ... everyone would be prescribing it. It would become like tazocin"* (B6, CT Medicine)

> *"…an authorisation code is a good thing"* (A8, Surgery Consultant)

> *"…having it restricted to consultant level, that is a way for better use of meropenem"* (B8, Acute Care Medicine)

> *"I would never take the decision to prescribe meropenem independently…prescribing restriction on meropenem to consultants"* (C6, FY-2 Medicine)

The decision of including and excluding an antimicrobial from local formerly decided by various mechanism, never the less, some CSA's are not approved in two of the included health boards, but only two interviewees share their thoughts about this.

"I am not sure all these drugs are available in my trust" (A3, ITU Consultant)

"I think having the alternative agents available" (C8, Senior Registrar ID)

Microbiology reports and sampling:

There were two issues coded and discussed under this subtheme, sampling errors and selective suppression of sensitivity data. One interviewee mentioned that he had seen patients with no samples sent or samples sent after antimicrobials initiation, and how that impacted upon clinical practice.

"A lot of people are treated on antimicrobials and don't have the samples sent, and then you are a bit stuck because you are basically empirically treating them forever and then it is very difficult to know how to rationalise antimicrobials" (C6, FY-2 Medicine)

Selective suppression of sensitivity and reporting CSAs had an impact on prescribing, there is an agreement that featuring CSAs in microbiology reports is essential;

> *"Appearing on the sensitivities that would improve our knowledge base of our awareness"* (A3, ITU Consultant)

> *"I would like to see pivmecillinam and fosfomycin on the standardised microbiology reports"* (B8, Acute care Consultant)

> *"…culture result that had pivmecillinam there, they would prescribe it"* (B5, ID Consultant)

In addition, a microbiologist shared their positive experience with selective suppression of meropenem and piperacillin-tazobactam.

> *"I think we are definitely very conscious about not de-suppressing tazocin and meropenem in reports. We would never do it automatically. It would never ever go out. Anything has a tazocin or meropenem sensitivity now, would queue for a medic to authorise. I think very much so that it is the real rarity that we*

would ever release these. Particularly meropenem…I definitely feel our de-suppression of tazocin and meropenem must be really quite low" (C7, Microbiology Consultant)

Guidelines:

Local guidelines are a major influencer in prescribing meropenem and CSAs, as seen previously. In this subtheme, we included further information that was shared by interviewees in response to this part. Three codes were developed, the benefit of detailing meropenem recommendation in local guidelines, promotion of CSAs in clinical guidelines, and the need of de-escalation guidance. Both specialist and non-specialist teams highlighted the importance of guidelines in controlling meropenem and supporting CSA use.

"…being aware that there are alternatives to meropenem, and why it would be better to use alternatives, in that handbook would be helpful" (C5, FY-1 Medicine)

"If they are featured more within guidelines, then we might!" (A6, Haematology Consultant)

"…being aware of these options and having them as part of guidelines" (C2, Medicine Consultant)

"If guidance change to use more of these antimicrobials, I would say five years ago, most of us have never heard of before. Once all of us are more comfortable using it, then we will use it more, because you build up the experience." (C3, Senior Registrar Medicine)

"I think it had been on guidelines. Quite clearly visible on guidelines." (C7, Microbiology Consultant)

Two feedbacks discussed the need for a de-escalation policy for cases that use meropenem or broad-spectrum antimicrobials.

"It does say that these are the kind of escalation policies, and then it will not give any dosage. It will just say, who will speak under micro advice, but actually, if there was a couple of lines that say, actually, when prescribing IV Meropenem, consider alternatives such as X Y Z for these reasons" (C5, FY-1 Medicine)

"I guess it is kind of about breaking it down at the kind of post empirical stage I think." (C6, FY-2 Medicine)

Communication:

The importance of open communication between leaders and teams, specialised and non-specialised team, and within the team have been highlighted in several parts of this study. Furthermore, in this part, open communication benefit and need are discussed as an important action to improve meropenem and CSA prescribing quality by both specialist and non-specialist interviewees.

"Availability of our consultant microbiologists on call and our sort of healthy relationship with them fostering what I would say is good antimicrobial prescribing" (A3, ITU Consultant)

"The microbiologists and the infectious diseases team here are very open, easily accessible, and easy to talk to." (C3, Senior Registrar Medicine)

"If the clinician does not pick up the phone to speak to the microbiologist, then the microbiologist will not know about them."… "We always ask the microbiologist and give them the information…"If you have any doubt, pick up the phone, speak to the microbiologist."" (C1, General surgery Consultant)

"Working more closely routinely with clinical surgical colleagues we hope that we can foster confidence in decisions such that they are comfortable with us moving away and deescalating and preventing use of meropenem…greater involvement in routinely in more areas is probably the only way that we are going to reduce antimicrobial usage" (B4, ID Consultant)

"We do have kind of weekly meetings, and ground rounds, and things like that. I guess to kind of refresh a bit would not necessarily go unnoticed" (C8, Senior Registrar ID)

"Consultant-consultant conversation about your patient and involvement of other speciality is normally in the patient best interest" (A8, General Surgery Consultant)

"…always be encouraged to just ask, why are we using this particular antimicrobial, and kind of feel supported in actually asking the consultant, have we considered any alternatives?" (C5, FY-1 Medicine)

Auditing:

An interesting discussion raised by three specialist team members, two ID and one microbiologist since they are the main prescribers and authorisers of meropenem. They were discussing the need for an auditing mechanism to feedback on prescribing habits among them and colleagues from other specialist teams.

"Antimicrobial prescribing practice is never audited by anyone…the feedback loop in specialist practice…audit case notes" (A4, ID Consultant)

"…track individual prescribing…have post prescribing review…we might find that micro prescribing is very different from what my colleague would prescribe or not prescribe, so we set the bar as an ID doctor, or a microbiologist has said it is okay, and that is okay"…"I might be the big meropenem user and the drive of the

meropenem use and not my other colleagues, and we are not… I could be the driver for the surgeons using" (B3, ID Consultant)

"Look to see where the problems are, and which of the antimicrobials you are using a lot of…surveillance can changes behaviour" (A5, Microbiology Consultant)

Electronic system:

The use of advanced electronic systems was discussed, such as the availability of e-learning module, electronic prescribing, and smartphone applications. One consultant shared a positive experience with electronic training handout;

"…trainees have information on their induction manual that could be improved to some e-learning module that I could point toward faculty tutors" (A3, ITU Consultant)

Two specialist consultants suggested the benefit of having an electronic prescribing system;

"…having something like electronic prescribing would improve things" (B3, ID Consultant)

"…electronic prescribing, not just for safety issues, but so we can get out data! We just don't know what's happening in the hospital settings. We know what's happening in GPs settings, but not hospital we do not have a clue" (A5, Microbiology Consultant)

Finally, a consultant share a positive experience with smartphone application available at his health board that includes the local therapeutic handbook;

"I use the app…Put it in the app, and that is how it disseminates better than I would say anything else." (D1, Respiratory Consultant)

4.4.10.4. Education

The response of interviewees document a high demand for educational benefit and need toward prescribing meropenem and CSAs. The importance of education was discussed by all participants in different areas. From the thematic analysis, three

major subthemes were developed related to education; references and resources, training and education activities, and level of awareness. Furthermore, one code was added to include any issues related to cultural and behavioural effects on prescribing.

References and resources:

Different examples were mentioned as a useful source of information for prescribing, electronic, hard copies, and posters. The quality of prescribing was said to be improved with such available recourses.

> *"Trainees have information on their induction manual that could be improved to some e-learning module that I could point toward faculty tutors…Cost on the alongside, ecologically, antimicrobials, I think would be useful within an e-learning module, so people would be aware of the cost of these drugs"* (A3, ITU Consultant)

> *"…probably we do not prescribe it, because it is not in the book"* (C5, FY-1 Medicine)

"My Bible as an FY1 is the [health board name] Therapeutic Handbook. It is my go-to whenever I am prescribing" (C5, FY-1 Medicine)

"The handbook for guidance of treatment of infections…Put it in the app, and that is how it disseminates better than I would say anything else" (D1, Respiratory Consultant)

Training and educational activities:

Training and educational activities were seen in previous parts of this section, improving meropenem prescribing and levers or barriers with CSA's. However, in this part, we focused on any added information by interviewees that they have not discussed or highlighted again. There are two needs for training and education on both sides, meropenem prescribing and review and CSA's. Three interviewees mentioned that education about what added-on benefits of using meropenem over other agents should be highlighted;

"…mandatory training the microbiologist contribute information in a talk on antimicrobials, but specifically carbapenem, that is useful as a consultant" (A3, ITU Consultant)

"To know what additional cover we are getting with meropenem that we are not getting with tazocin" (A6, Haematology Consultant)

"…educating people, I do not think most people if you ask them could not tell you what they are covering with meropenem. In terms of what the antimicrobial spectrum is." (D1, Respiratory Consultant)

The gap in the clinical knowledge of CSAs was discussed by four interviewees, mostly non-specialists.

"I guess I do not know much about the alternatives. Fosfomycin and the other ones you mentioned. I guess more education about those would be good" (B6, CT Medicine)

"I think an education session on the alternatives would be beneficial. I would like to know more about their use and how to use them" (B7, FY-2 Medicine)

"…lack of knowledge about them and it will probably take a few years for people to get more familiar with them" (C4, ST Medicine)

"There is a gap of knowledge that we can fulfil." (C6, FY-2 Medicine)

"Not having the familiarity with other agents because we do not use them as much, have less of a confidence that this will be effective." (B9, Care of elderly Consultant)

Also, a microbiologist added to this by saying;

"I think just education. I feel like if ever I am talking to clinicians about antimicrobials, I try to bring in aztreonam and temocillin because I am aware that they are not comfortable with them" (C7, Microbiology Consultant)

Two interviewees discussed CSA dosing as a challenge needed to be addressed;

> *"The most important thing is letting people know about appropriate dosing."* (A9, Senior Registrar ID)

> *"If we have good alternatives, easy to dose alternatives, it might reduce the use of meropenem."* (C3, Senior Registrar Medicine)

Two interviewees gave an interesting opinion for delivering training and educational activates. One suggested that there should be some focus on the undergraduate level, the other said focusing on the registrar level;

> *"…coming out of medical school I think I probably wouldn't even heard of most of those antimicrobials, and so maybe bringing them into early undergraduate education would be useful"* (A2, Medical Registrar)

> *"…focusing on at least registrar level education is first of all easier because they do not move as much and secondly more long lasting because they make these decisions more often in more acute*

situations and as they go through will continue to make those decisions" (D1, Respiratory Consultant)

Awareness:

Interviewees have suggested elevating the level of awareness toward meropenem overuse risk and availability of alternatives. There is a lack of awareness about resistance related to meropenem overuse, and meropenem is the only available choice.

"I think meropenem still, in the culture, felt to be a very good antimicrobial. It is an antimicrobial where we go to when we find everything is going wrong with the patient." (C3, Senior Registrar Medicine)

"What are the potential dangers of using meropenem too widely?" (A6, Haematology Consultant)

"I think they have got a vague awareness of antimicrobials resistance" (B9, Care of elderly Consultant)

There is a need to increase the awareness level of CSAs role and ability to efficiently use them rather than meropenem. This was raised mostly by consultants' respondents.

> *"Awareness of these agents within the general physician population would be useful because I think it is probably not something we think about."* (C2, Medicine Consultant)

> *"The awareness of alternatives like aztreonam and temocillin and their familiarity with using them is probably not that great…I do not think they could tell you the alternatives even less, and I do not even think they are really aware of what they should be covering given the clinical situation."* (D1, Respiratory Consultant)

> *"We often think of alternatives…we are hyper-aware of the issues around carbapenem overuse"* (B4, ID Consultant)

Culture and prescribers behaviour:

Under this code, shared opinions about cultural and prescribing behaviour mentioned at the end are listed. Three interviewees report the worry about effective therapy;

> *"They worry about effective microbial in where that perception is that if you use tazocin or meropenem, you could quickly get the correct antimicrobials into an individual"* (B4, ID Consultant)

> *"It is important to review the patient and review the antimicrobials daily, and I think some people maybe escalate antimicrobials too quickly"* (C8, Senior Registrar ID)

> *"Some people would maybe think....use carbapenem instead of source control or other things like that"* (A8, Surgery Consultant)

4.5. Discussion

Twenty-eight doctors from four health boards participated in this qualitative interview-based study to describe the perceptions of front-line practitioners regarding the meropenem and CSA's prescribing influential factors in clinical practice. The doctors interviewed in the study were experienced in prescribing meropenem and CSAs and were selected to represent all specialities at all seniority levels. Although previous studies have been conducted on the causes of antimicrobial overuse, most of these studies did not specifically investigate the cause of meropenem overuse as the main aim, or investigated the causes of undocumented/followed-up or de-escalated meropenem or underuse of CSAs thereby providing limited details about the topic. The interviews identified some recurrent factors reported as contributing to the overuse of meropenem. After multiple meetings and discussions with the project steering group, the collected data were sub-divided into three major topics to include all resulted themes, initiation phase, continuation phase, and overall areas of quality improvement, all of which were identified as contributing factors to meropenem overuse, under documentation and follow-up, and use of CSAs. In addition, some factors associated with local practice were also identified. These factors were shown as areas to be addressed. Figure 4.3 summarises the major themes arising from the data under each of these headings.

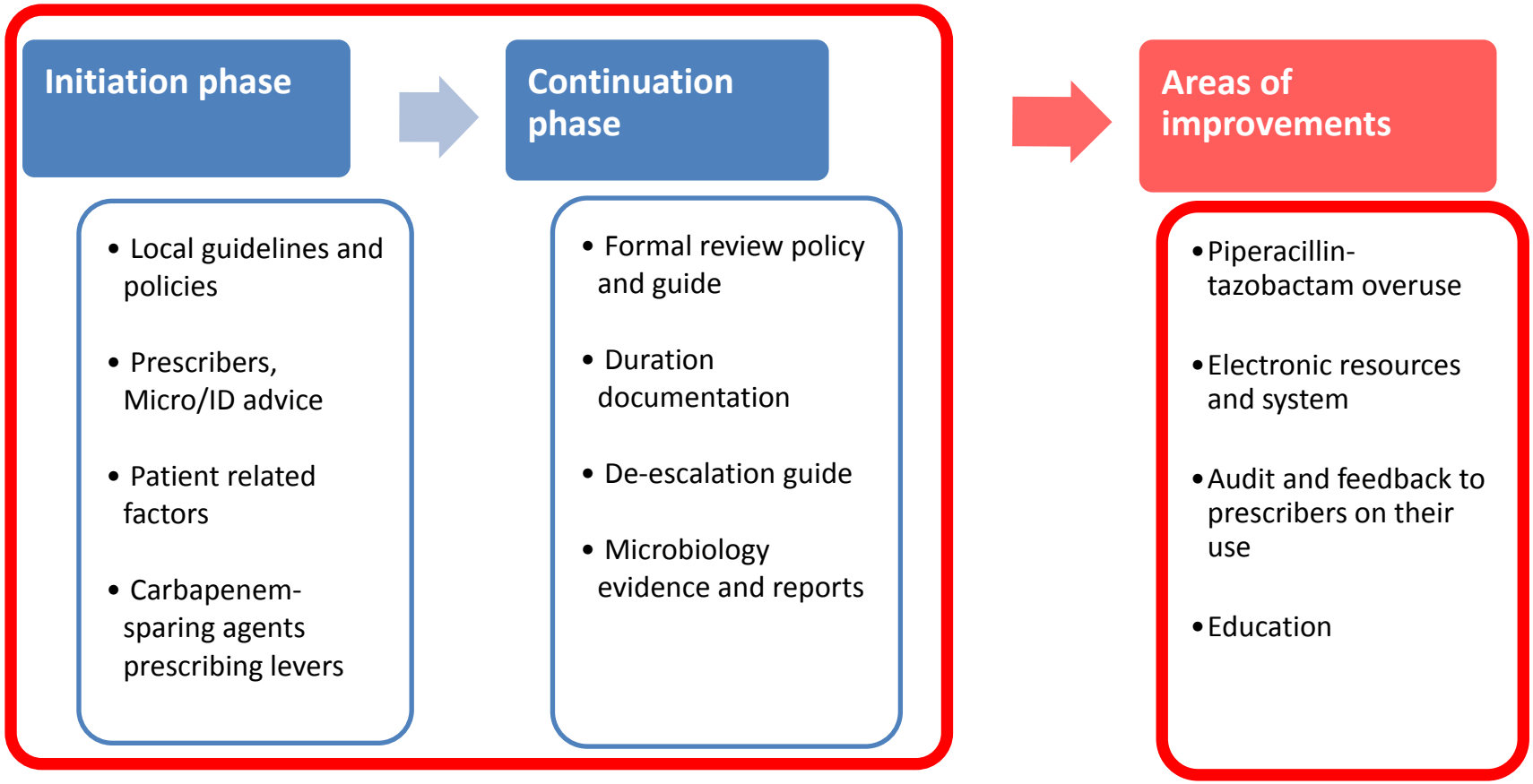


Figure 4.3 Major themes derived from interviews conducted June to November 2016 (n=28)

4.5.1. Initiation phase:

The main influences in meropenem and CSA prescribing decisions mentioned by the interviewees were local systems, the prescriber, patient-ward related, and CSA's prescribing levers and barriers. Each one of these themes has been previously identified by other researchers and has been highlighted in published national recommendations on prescribing antimicrobials [55, 65, 84, 96, 188, 263-265].

4.5.1.1. Local system:

Implementation of prescribing guidelines based on each health board needs, resistance rates, and available resources have been proven to be valuable in improving antimicrobials prescribing [84, 263-265]. Furthermore, implementing local guidelines is heavily promoted by national plans for improving antimicrobials prescribed being and controlling AMR [55, 188]. NICE guidance under Antimicrobial stewardship also recommends the use of guidelines: antimicrobials prescribing [96] and the CDC "Hospitals antimicrobials stewardship programs" core elements publication [65].

There were positive opinions about available guidelines from interviewees. The role of guidelines was highlighted mostly by interviewees from two health boards, Tayside

and GGC. Both health boards have detailed guidelines on antimicrobials used limiting the use of meropenem and extensively promoting the use of CSA's. By selecting to omit meropenem from guidelines and featuring CSA's, interviewees from both health boards discussed that such action influenced the prescribing decision of meropenem and increased use and confidence in CSAs. NHS Tayside in 2015 published an article to share their experience with CSA's, especially aztreonam which was embedded within local prescribing guidelines in December 2013. They report that, with continuous education and training, using aztreonam, and to a lesser extent temocillin, as an 'additional Gram-negative agent' may offer greater flexibility of treatment options and reduce the selective pressure from the use of carbapenems and piperacillin-tazobactam [266]. On the other hand, interviewees from the other two health boards mentioned that advanced or detailed guidelines would improve the use of meropenem and increase the knowledge and confidence in CSA's.

Having a detailed guideline focusing on a group of antimicrobial was successfully implemented in NHS Scotland. The Gentamicin and Vancomycin Quality Improvement Programme (GaV) work targeted vancomycin and gentamicin use across NHS Scotland with guidelines on use and dosing [210]. Although the examined guideline was standardised to a national level, the benefits reported, in term of having guidelines, were similar to our findings.

Restrictions of prescribing by code were used in Fife health board. The feedback from that health board interviewees was overall positive. The use of code limits overuse of meropenem and shift prescribers into the habit of contacting an authoriser (specialist) for approval and discussion. Applying restrictions to a targeted antimicrobial would also positively influence local resistance rates [267]. In an Irish study [268], aiming to explore the impact of antimicrobial use on the incident and resistance pattern of ESBL bacteria, supports the value of restricting the use of certain antimicrobial classes to control ESBL, and demonstrates the feasibility of reversing resistance patterns post successful antimicrobial restriction.

Nevertheless, the use of a code system was reported to be time-consuming for the specialist team, and one interviewee found difficulty in seeking approval. There were a few published articles that agree on the increased risk of delay in therapy when restrictions are applied [269-271]. Nevertheless, this was not reported by any interviewee.

4.5.1.2. The prescriber:

From the results, the decision of prescribing meropenem and CSAs were influenced by the prescriber themselves and what information they possess. There were differences when a decision comes from a specialist team compared to the non-specialist team, a decision supported by recommendations from Micro/ID teams, and

ones that made with positive evidence of microbiological culture and sensitivity reports.

Specialist vs non-specialist

In all four health boards, meropenem is a restricted item and only authorised by a microbiology consultant (all four health boards) or an ID Consultant (two health boards). From the results, all non-specialist interviewees mentioned that they would seek a specialist team approval before initiating meropenem. In the two average sized health boards, Fife and Forth Valley, only microbiology consultants can approve meropenem. All interviewees from these health boards commented that they have to seek approval and ask for advice from microbiology. This was regulated in Fife by a code authorisation system linked to the pharmacy, which might explain high adherence and utilisation of the process. Furthermore, the microbiology team was highly regarded and very cooperative with non-specialist teams. Nevertheless, negative feedbacks from non-specialist teams on Fife's coding system were limited. On the other hand, GGC and Tayside have an outreach specialist team that provide consultation services on-site and antimicrobial ward rounds on regular bases. Non-specialist teams in both health boards discussed that such action facilitates authorisation and prescribing decision for both meropenem and CSA agents.

Junior interviewees reported that the decision of prescribing meropenem and CSAs were mostly a guideline or a senior's decision. The availability of local guidelines promoting CSAs and microbiological reports encouraged them to learn more about them. Also, they reported that their prescribing behaviour is strongly influenced by supervising physicians prescribing attitude. This was reported in a study investigating factors influencing prescribing behaviour and showed similar results [272].

Micro/ID decision

Although The Code of Practice on the prevention and control of infections and related guidance applies to all healthcare providers [273]; there are great responsibilities on specialised teams in meropenem and CSAs prescribing decision. Not only because these agents restricted to them, but results show that non-specialist teams tend to pass the liability of prescribing these agents on, i.e. they only prescribe it if Micro/ID advice it. From specialist team interviewees, having an active team, and active members of the team improve the service and overcome any limitations due to staffing or increased workflow.

In Fife and Forth Valley health boards, specialist teams were covering a relatively small sized population, and they have open relationships with other teams with easy access and a 24/7 service. The feedback from non-specialist team interviewees in these health boards was positive and supportive. However, in GGC and Tayside,

where they provide service for a much larger population, a multidisciplinary AMT and antimicrobial ward rounds were used to overcome any possible limitations due to increased workload. Thus, having such close relation helps not only in improving the decision of prescribing but elevates the knowledge level within different teams to meropenem quality prescribing and CSA usability [266, 274-276].

Microbiology reports

Another major prescribing decision influencer was positive evidence in culture and sensitivity reports. Prescribers, specialist and non-specialist, feels more confident when prescribing meropenem with available positive evidence. This is logically sound, as national recommendations on improving antimicrobial prescribing stress the need of positive culture to support prescribing decision [277]. From one microbiologist interview, reports excluding meropenem sensitivity were used to control consumption of such agents; controlling the consumption of meropenem use by not suppressing it in reports. The microbiologist supports this method and clarifies that this would be done if suitable alternatives are positive. Such activities have been reported in the literature, with selective reporting of ciprofloxacin by a microbiologist in a hospital setting [278]. The author reports that they successfully reduced the mean monthly consumption of ciprofloxacin over 24 months follow-up from 87 to 39 DDD per 1,000 patient days. The conclusion was that selective reporting of ciprofloxacin susceptibility might be a valuable intervention to reduce targeted

antimicrobial utilisation and should be considered as part of a broader multimodal antimicrobial stewardship program [278].

Selective reporting of microbiology results is an intervention that has been used to improve the quality of antimicrobials prescribing and controlling resistance. In a recently published work aiming to identify where and how selective reporting was implemented across Europe, 11 out of 36 countries (31%) had fully implemented selective reporting, with partial implementation in 4 (11%), and a further 21 (58%) not adopting such an approach. The most frequent application of selective reporting was in uncomplicated community-acquired infections, particularly in UTI and skin and soft tissues infections. The list of reported antimicrobials ranged from a few first-line options to longer reports where only last-resort antimicrobials were concealed. The study shows that selective reporting was poorly implemented in Europe because of a lack of guidelines, poor system support, insufficient resources, and lack of professionals' capability [279].

On the other hand, the decision of prescribing CSAs was highly affected by culture and sensitivity report. Interviewees with previous CSAs prescribing experience agree that featuring CSAs in microbiological reports was a major lever in prescribing; not only in decision making but increase awareness and knowledge about CSAs. In contrast, interviewees with limited previous experience around CSAs prescribing criticised microbiological reports for omitting such alternatives in reports and

suggests more highlights on CSAs in culture and sensitivity reports as a measure of improvement. Although there was some technical difficulty in testing the sensitivity of some of the CSAs, microbiology laboratories should stay well-informed of newly-added or reintroduced drugs and assess the laboratory's capacity to perform cultures and sensitivities against appropriate pathogens [280]. Some studies suggest an association between the antimicrobials suppressed in antimicrobial susceptibility reporting and the use of these antimicrobials by prescribers [281]. Another study found that antimicrobials were half as likely to be prescribed when susceptibility results from noncritical cultures not suggestive of infection were suppressed [277]. Furthermore, a study showed that reporting of cephalexin instead of amoxicillin-clavulanic in culture reports caused a high modification of the use of these two agents in the intervention period even when healthcare providers were not aware of the alteration [282].

4.5.1.3. Patient-ward factors:

Meropenem is a very broad-spectrum antimicrobial used mostly with critical patients and in specific wards. As discussed previously, meropenem common indications are mostly seen in patients in high-risk units such as ITU, haematology, and oncology. It is also commonly used with cystic fibrosis cases under respiratory services. In recent years, national and international recommendations for improving quality of overall antimicrobials use supports more attention to higher usage areas. Most interviewees

in our research programme from high-risk wards and acknowledge additional attention from specialised teams' point of view.

Within two health boards, GGC and Tayside, interviewees have highly evaluated the focused attention and close advice from Micro/ID teams and integrated it into daily practice. In GGC, febrile neutropenia detailed guidelines and a ward-based antimicrobial team that attend on a daily bases were implemented to improve prescribing decision and were found to have a positive impact. Furthermore, the respiratory team at GGC discussed that regular visits, open communication, and one-to-one discussion helped, not only improve prescribing but added knowledge to the extent that daily visits are not essential as before. In a Canadian study, the benefit of knowledge exchange, peer-to-peer communication, and decision support from the specialised team were factors that built a positive culture of practice within an ITU. In addition, such interventions lead to significant cost reduction of anti-pseudomonal antimicrobial agents use [283].

4.5.1.4. CSA prescribing levers and barriers:

In addition to previously discussed influencing factors, our results showed factors specifically related to CSAs prescribing. These factors are affecting prescribing decision as levers when available or implemented and as barriers when not in place.

Factors such as confidence in use, stock and availability, and cost were noted from the results.

CSAs are recently re-introduced antimicrobials, mostly to have alternatives for MDR cases. Evidence supporting these agents are a mixture of out of date and very recent publications. Thus, some practitioners, specialist and non-specialist, might feel under confident and inexperienced using them. Familiarity with an individual CSAs drug profile was seen as a lever. By knowing that there are oral alternatives to treat Gram-negative resistance infections. This familiarity was developed over a period and with the help of local guidelines detailing the use of CSAs and specialist team exposing non-specialist teams for the availability of alternatives [188].

Stock status of CSAs and availability to access limits the decision of prescribing. There was a shortage in stock of some agents, and few reported that this influenced the discussion of prescribing. Furthermore, the availability of CSAs at an easy access location facilitate initiating therapy as soon as possible for emergency cases [125]. Having consistency of supply and availability would improve the prescribing of CSAs. In a recently published study, 701 ID physicians were surveyed to determine the impact of antimicrobials shortage on practice. From the result, the majority (73%) of ID physicians reported the shortages affected patient care or outcomes by the use of broader-spectrum (75%), they were more costly (58%), less effective second-line choices (45%), or more toxic agents (37%). To help them overcome shortage issues,

the prominent role of specialised teams and AMT and effective communication channels were assisting in dealing with the availability of antimicrobials [284].

There was a discussion, within the project steering group, when designing this project that cost of CSAs may influence the prescribing decision. Cost of these agents was discussed by a few interviewees, and all agreed that once justified to local authorities, the cost was not an issue.

4.5.2. Continuation phase:

Results about continuation phase were mostly meropenem oriented. However, the response from interviewees was mixed and can be generalised to improving the quality of reviewing any antimicrobial. There were four major areas related to review meropenem prescriptions; process, documentation, and de-escalation.

Review and follow-up:

From the NAS-PPS results (Chapter 3), follow-up of initiated prescriptions was a major area of improvement. In this part of the research, most interviewees said that they clinically review patients on a daily base in routine clinical rounds, but nothing specific for antimicrobials. However, the major issue was that the initial prescriber or

authoriser; usually a specialist team member, would not necessarily review the patient again unless contacted by attending team. Thus, there is a loss of continuation of follow-up and reliance on attending teams to seek follow-up. Some interviewees reported that to overcome this issue, daily rounds from specialist teams and AMTs aids in reviewing on a daily bases. Such activity was reported in the literature to be expected from specialist teams [285, 286], and others showed improvement in continuation of therapy and success rates [287-290].

From the results, there was a general agreement that a standardised protocol of review should be impeded, and health boards should set a quality indicator target of 24hr or 48hr review policy. In the Netherlands, a study was performed to assess the benefits of having an automated day-2 review of antimicrobials prescribed at a university medical centre over one year period. The resultant data were positive with a significant reduction in mean antimicrobial consumption (from 8.17 to 5.93 DDD/patient), and length of stay (7.57 to 6.2 days) [291]. Establishing a quality indicator of reviewing prescriptions within 24-48hrs was supported by the success of the quality indicator impeded previously for writing an indication of any prescribed antimicrobials promoted by SAPG (chapter 3) [292, 293].

Documentation:

Proper documentation of every step taken during an individual patient's antimicrobial therapy is a core element for successful prescribing and antimicrobial stewardship programs [42, 65, 96, 188, 294]. Interviewees reported that meropenem treatment plans are mostly documented in medical notes, especially by consultants, and to a less extent on a KARDEX, mostly by juniors. There were limited reported attempts by interviewees aiming to improve antimicrobial documentation by having a separate sheet dedicated for antimicrobials in each medical note and an antimicrobial list for each patient in the ward to be used in a daily ward round checklist. The use of an antimicrobial checklist to ensure appropriateness and follow-up might improve practice [295]. However, multiple barriers influence the acceptance of an antimicrobials checklist. In a survey performed at nine Dutch hospitals where an antimicrobials checklist had been adopted, 219 completed questioners identified six potential barriers. Barriers identified were the lack of expectation of improvement in antimicrobial prescribing, lack of expected patients' agreement by the use of checklist use, lack of feasibility of the checklist, previous negative experiences with different checklists, the complexity of the antimicrobial checklist and the lack of nurses' expectation of checklist use [296]. Thus, adopting the use of an antimicrobials checklist might have benefits but are faced with multiple barriers that need to be addressed.

The main concern in the use of documentation is the appropriate selection of duration. Interviewees admitted that duration of treatment documentation or plan was limited and in some cases difficult. Based on the feedback from interviewees, multiple factors can contribute to this issue; lack of positive microbiological sample or sample errors, the severity of cases, and unidentified responsibility of who is responsible for setting the duration; i.e. the authoriser or attending team [188]. To overcome this issue, respondents suggested the use of electronic prescribing systems and increased awareness to the importance of such action. In Fife Health board, where a code system is implemented, authorising code is valid for a pre-sited duration, three days if unplanned duration and a follow-up with the authoriser is required for a new code. Such action was appreciated by respondents from Fife and encourage reviewing not only by themselves but also from nursing staff.

Furthermore, respondents suggested having a review date, and a duration plan upon initiation of meropenem would improve reviewing and duration documentation. An antimicrobial "time out" prompts a reassessment of the continuing need and choice when the clinical picture is clearer and more evidence is available [65, 286, 294, 297]

De-escalation:

Practice promoting antimicrobial de-escalation are expected to, by reducing antimicrobial load, impact beneficial on the emergence of resistance, the prevention

of secondary infections, cost levels and adverse drug reactions [267]. The decision of stepping down from meropenem to a narrower spectrum antimicrobial or even an oral alternative was faced with a lack of confidence; especially in the absence of positive microbiological cultures, and the gap in knowledge of alternatives [195, 298-300]. This was much more common with junior prescribers as they felt unsure where to go next from meropenem and passed the responsibility of de-escalation to senior level [272, 301]. From respondents, there is a need for a more detailed de-escalation policy to be used for complicated cases, were meropenem is used, and IVOS policy should include an IV (broad-spectrum) to IV (narrow-spectrum) switch recommendations. Safety and clinical outcomes of carbapenem de-escalation, as part of an ASP program, was evaluated in one study. The study included 300 cases, single-centre with 1500 bed capacity, and the policy implemented for de-escalation was performed by AMT and the choice of antimicrobials for de-escalation in empirical therapy was governed by the hospital antimicrobial guidelines. Out of the 300 cases, 204 cases were included, and the clinical success rate was similar between de-escalated vs not de-escalated (89.7% vs 88.5%), survivals rate was similar. However, the duration of carbapenem therapy was shorter (six vs eight days), the rate of reported adverse drug reactions was lower (5.4% vs 12.5%), and there was less diarrhoea (4.4% vs 12.5%). The study concluded that such an action is safe, practical, and highly valuable [302].

4.5.3. Overall areas of quality improvement:

The interviewees repeatedly identified a number of areas in which activity could be challenged; guidelines role in improving the quality of meropenem prescribing and the promotion of CSA's, active involvement from specialised teams to daily practice and attending teams, and open communication channels within the team and across specialities. The importance of each area was related to prescribing decision (initiation) and continuation phase and discussed previously.

In addition, results showed general areas of improvement that were related specifically to neither initiation nor continuation phase and considered as a general area of improvements. Overuse of piperacillin-tazobactam, audit and feedback, electronic resources, and educational needs were the most repetitive areas.

Overuse of piperacillin-tazobactam

Increase in piperacillin-tazobactam consumption was noted by several respondents who considered this may be a result of an unrestricted prescribing policy, free availability, and high familiarity resulting in the common practice of using piperacillin-tazobactam instead of meropenem or CSAs. The consequences can be an increase in the risk of developing more antimicrobial resistance and overuse of a valuable antimicrobial, piperacillin-tazobactam, principally used prior to a carbapenem [303].

Audits and feedbacks

Specialist clinicians raised the issue of audit and feedback to prescribers on their carbapenem use, or any other antimicrobials, as a means to promote discussion amongst peers and support development of best practice. Overall antimicrobial audit and feedback to prescriber is highlighted in national guidelines and recommendations for better prescribing of antimicrobials [55, 65, 96, 188, 263]. In carbapenem use, as a result of high restriction, specialist consultants are the most common non-audited prescribers, and they are considered to be the role-model and expert; where audit might be limited and sensitive. Practitioners might find questioning their colleagues' antimicrobial prescribing decisions difficult due to obstacles of hierarchy, infrequent face-to-face encounters, and the awkwardness of these conversations [272]. Nevertheless, the importance of auditing and feeding back to prescribers, from different specialities, is considered a major key to improving the quality of antimicrobial prescribing [263].

Electronic resources

From the results, there were two different experiences of using advanced electronics to improve the quality of prescribing. At Forth Valley health board, electronic prescribing was recently implemented, four months prior interviews time, and feedback was generally positive. A respondent from Forth Valley discussed the

possibility of integrating prescribing guidelines, authorisation, mandatory duration, and follow-up reminders into the system. The use of health information systems to improve prescribing of antimicrobials is recommended, where resources permit [304, 305].

The other electronic experience was within GGC health board; local therapeutic guideline is published and updated electronically, available online and within the intranet, and downloadable on smartphones as an application format. Positive feedback from GGC respondent was noted especially with junior practitioners. A study was conducted to answer if the use of smartphone application improves trainees' knowledge about antimicrobials or not. The results showed that including antibiogram and treatment algorithm increased knowledge of prescribing antimicrobials in the context of local antimicrobial resistance patterns. The author highlighted that smartphone apps could be a useful and innovative means of delivering medical education [306]. However, the study was conducted on trainees which expected to be at a young age with more acceptance to new technology. Another study agrees that a smartphone app is an effective and acceptable format to deliver guidance on antimicrobial prescribing. However, they noted that reduced use of the app was associated with the influence of senior physicians' preferences for antimicrobial prescribing and their greater likelihood of ignoring guideline recommendations [307].

Education

Overall, the need for education and increased awareness about the targeted issues identified in this project was discussed by all interviewees. Educational activity should include regular updates on antimicrobial prescribing trends and rate, antimicrobial resistance rate (locally and nationally), and address local and national issues [65, 188, 308]. Awareness of meropenem overuse and importance of quality prescribing and review should be considered [195, 309, 310].

There is a noticeable educational need on the availability and use of CSA's to improve prescribing them and increase confidence about them. There are discussions about the amount and quality of undergraduate and postgraduate learning material. In our research, only one interviewee comments that he had not seen CSA's in his undergraduate time and introduced to it recently. Junior doctors reported in a study investigating reasons for guidelines failure that medical school teaching is very influential [301]. In a recently published cross-sectional survey, 179 participants including respondents in the final year of medical school, from 29 countries across Europe, were asked if they felt prepared to prescribe antimicrobials responsibly. Results showed that Students felt at least sufficiently prepared on a mean of 71.2% of topics assessed. However, the rate of students asking for more education on prudent antimicrobial use or general antimicrobial use was 66.1%. Furthermore, higher prevalence rates of antimicrobial-nonsusceptible bacteria were associated

with lower preparedness scores and higher self-reported needs for further education [311].

4.6. Summary

This part of the research was rich in data and revealed an insightful opinion from front-line clinicians. Interviewees suggested that many prescribers are not confident in reviewing antimicrobial therapy in critical patients with a severe infection where oral switch options may be uncertain. There is a perceived need for additional input from infection specialists by non-specialised teams.

Although carbapenems, and to some extent piperacillin-tazobactam, are often prescribed following advice from microbiology/ID, there is a perception that there is a relative lack of follow-up discussion between the attending team and authoriser or initiator. In addition, the discrepancy in the testing or suppression of full microbiology culture and sensitivity reports can lead the prescriber to keep patients on the original treatment despite clinical improvement and lack of positive microbiology. This can be addressed through antimicrobial ward rounds and more direct involvement from the specialist team. Furthermore, there appears to be a learning need to upskill prescriber's knowledge and confidence, as well as to develop systems to more easily identify prescription of these antimicrobials to facilitate review using new

technology. Evidence from the interviews clearly identified that there is a need for a whole-system approach that contains the three arms of practice, organisational systems and local policies (the work environment), enhanced communication within the multidisciplinary team (the practicing clinicians), and better stock availability and utilisation of CSAs (the targeted medicines).

Chapter Five:

General Discussion and Conclusion

5.1. Overview:

In this final chapter, a summary of key research findings, overall discussion and conclusions drawn from this research are offered, followed by a section addressing the impact of this research on local policies and practice. In addition, this chapter concludes by strength and weaknesses of current research, suggestions for further research, and an overall conclusion.

5.2. Evaluating NHS Scotland adaptation and implementation of SAPG MDRGNB guidance:

The self-assessment survey (Chapter 2) showed that the SAPG MDRGNB guidance was implemented in most NHS Scotland health boards. The survey provided essential baseline information and feedback to SAPG about their guidance against MDRGNB and what were the current policies and regulations surrounding targeted antimicrobials. Meropenem was the most commonly approved carbapenem (100% of health boards), followed by ertapenem (80% of health boards) predominately for OPAT use, and imipenem only in three health boards (20%). Meropenem was highly controlled, regulated, and more often subject to prescribing restrictions (100% all health boards) than piperacillin-tazobactam (7 out of 15 health boards, 47%) and

authorisation for use was typically through specialised teams; a microbiologist or an infection specialist, for both agents. Furthermore, the survey showed variation in adopting and implementing the SAPG guidance which lead to inconsistence practice between health boards. Also, variation in adaptation can impact the aim of the guidance, thus, the researcher was motivated to explore front-line practice in chapter three and point of view in chapter four.

The researcher found variation between health boards in the approach of microbiology laboratories practice towards antimicrobial stewardship, nationally and locally, and the suppression and release of antimicrobial susceptibility testing results occurs via a variety of mechanisms. The results from this research raised the appetite and scope amongst laboratory clinicians and scientists for standardisation, which is currently being progressed via collaboration and communication between SAPG and the Scottish Microbiology and Virology Network.

CSAs approval status within NHS Scotland health boards local policies was varied and generally low (Section 2.3.4). Once a health board chose not to approve an agent at their area; limitation of use, availability and stock shortage, and unawareness of CSAs should be expected. These were later aroused and discussed at front-line interviews (chapter 4). CSAs were only used for specific indications at most health boards, on specialist advice and only two health boards (out of 15 health boards) have embraced their use through inclusion and featuring in local antimicrobial guidance. This

therefore considerably limits the acceptance and utilisation of these agents within health boards.

Feedback from survey respondents highlighted that CSAs higher costs compared with generic meropenem or piperacillin-tazobactam and issues with stock shortages are major barriers to their adoption. However, on chapter 4, some interviewees mentioned that cost barrier was solved by justifying and supporting the price tag on CSAs to local authorities.

The older CSAs have a limited evidence base to support their adaptation and further studies are required to demonstrate their clinical efficacy in the current resistance landscape [312]. However, new agents are coming to market (e.g. ceftolozane-tazobactam) and these may also offer a clinical alternative to carbapenems, although their clinical utilisation will also have to be carefully controlled to prolong their clinical life.

SAPG utilises periodic online surveys of AMTs to obtain feedback on implementation and adaptation of national stewardship initiatives, barriers to implementation and suggestions for future enhancements. The current survey (Chapter 2) on the use of carbapenems and piperacillin-tazobactam focused on the implementation of national guidance and SAPG MDRGNB guidance, which were reviewed and updated in 2016

[313], after the release of research results, to reflect the findings of this work and additional evidence from the literature. The updated version of SAPG MDRGNB guidance adopted and utilised this current research results to support recommendations and facilitate adaptation of such guidance.

A multilevel approach to hospital stewardship was highlighted in a recent Cochrane review [263], and it is therefore encouraging that our survey confirmed that implementation of local guidance was supported by education for key clinical staff. However, implementation may benefit from an expanded audience, such as wider inclusion of nurses and pharmacists [215].

Although 80% of health boards integrate antimicrobial prescribing into routine training, expanding education and training on carbapenems and piperacillin-tazobactam beyond junior and middle-grade doctors to include consultants may be helpful to ensure enhanced leadership for better prescribing of targeted antimicrobials and to drive behaviour change. Also, the targeted antimicrobials are mostly restricted and prescribed by high-graded doctors. Antimicrobial pharmacists are also a key source of specialist advice for clinical teams in Scotland, and training for nursing staff is also valuable owing to their evolving role in antimicrobial stewardship, both locally and globally [192].

In addition to the reported results, the survey confirmed that most health boards (85%) monitor consumption of carbapenems and piperacillin-tazobactam quarterly as recommended in national surveillance guidance [240]. Consumption reports are shared at AMT meetings and, in many health boards, with Infection Prevention and Control Committees (77%), supporting a combined approach to improve prescribing quality. Increased awareness of local and national consumption trends is crucial to improving prescribing practice and to assessing the impact of implemented interventions [267].

The survey results described the local application processes to support appropriate utilisation of carbapenems and piperacillin-tazobactam, and how each health board adopted SAPG MDRGNB guidance recommendations. Fourteen out of fifteen health boards (93%) either updated local clinical guidelines based on the SAPG MDRGNB guidance recommendations or reviewed their local guidelines and found them to be in-line with the SAPG MDRGNB guidance. However, from a stewardship perspective it was important to understand how this translated into prescribing practice, which was the key aim of the PPS conducted in the second study (Chapter 3).

5.3. Evaluating the use of meropenem and piperacillin-tazobactam within NHS Scotland:

National PPSs are used worldwide [246] and throughout Europe [314] to evaluate the prevalence of HAIs and overall antimicrobial prescribing, and have provided SAPG with quantitative and qualitative data to focus on areas for quality improvement [82].

Conducting a national PPS can be challenging to organise and perform in a professional matter. Our research was successful in collecting national data from 13 out of 15 health boards which represented 99.2% of the Scottish population. A total of 12,478 inpatients in 38 hospitals were included in the survey and 466 patients were eligible (3.7%) for study inclusion. Meropenem was observed in 129 patients (27.7% of eligible patients) and piperacillin-tazobactam in 337 patients (72.3% of eligible patients).

From the 2009 ESAC-PPS, 81% of all prescribed antimicrobials in NHS Scotland were compliant with local policy, compared to 82.5% in Europe [70]. After the implementation of prescribing indicators in 2009, results improved to 82.8% in 2011 [35] and up to 87.2% in 2016 [82]. In the present PPS study, national data shows that compliance with local policy was 88% for meropenem and 70% for piperacillin-tazobactam meaning that both agents fell behind the overall 87% (in 2016)

compliance rate for antimicrobial prescribing, in Scotland [82]. Nevertheless, comparison showed that practitioners were accepting and supporting change which increased local policy compliance and adherence.

From the bespoke PPS results, the lack of good documentation for piperacillin-tazobactam use may reflect its place as the 'go to' antimicrobial for severe infection or therapy uncertainty. Further analysis of the current PPS data (Chapter 3) showed that carbapenem utilisation was < 2% of all antimicrobials included in all health boards and < 1% in many. However, piperacillin-tazobactam utilisation varied from 1% to > 6%, possibly reflecting different controls over use, rather than clinical justified consumption. Another key finding from the PPS was that over half of patients had received antimicrobials for > 72 hours and about one-third of these patients had no documented review/stop date written in their medical notes. Nevertheless, NHS Scotland documentation of a review/stop date was better than reported in other countries [246]. However, these findings informed SAPG's work on antimicrobial review to support clinical teams through education and quality improvement tools to improve prescribing practice quality. Currently, SAPG included review/stop date documentation as an important part in updated version of SAPG MDRGNB guidance to using our results as an evidence of gap in practice.

5.4. Evaluating the impact of SAPG MDRGNB guidance on front-line practitioners:

From the interviewee's feedback (Chapter 4), targeted antimicrobials prescribing initiation were influenced by local systems, the prescriber, and patient-ward factors. The role of guidelines was highlighted mostly by interviewees from two health boards, Tayside and GGC. Both health boards have detailed guidelines on antimicrobials used limiting the use of meropenem and extensively promoting the use of CSA's, such action influenced the prescribing decision of meropenem and increased use and confidence in CSAs. There were differences when a decision comes from a specialist team compared to the non-specialist team, a decision supported by recommendations from Micro/ID teams, and ones that made with positive evidence of microbiological culture and sensitivity reports. Since targeted agents are broad-spectrum or uncommon, non-specialist teams appreciate initiation decision coming from specialised teams or with a microbiological evidence. Although, such actions require a framework suitable for available resources and manpower available at local health board. Nevertheless, a clear framework and utilisation of available resources will improve prescribing decision, which was the case at Tayside and GGC health boards. Furthermore, additional attention should be applied on high-risk wards and critical patients will not only guaranty safer practice but could elevate knowledge level on attending teams since they have to face targeted antimicrobials more than others.

The interviews with front-line clinicians (Chapter 4) suggest that many prescribers are not confident in reviewing IV antimicrobial therapy in patients with high risks or severe infection where oral switch options may be unclear, and there is a perceived need for additional input from infection specialists and clearer de-escalation policies. Interviewees discussed that current IVOS policies fail to support broad-spectrum antimicrobials, especially meropenem, and only focus on stepping down to an oral agent, which may not always be suitable in cases initiated with meropenem. In fact, interviewees suggested that IVOS should possibly include stepping down to an IV narrow-spectrum antimicrobial to support such decisions.

Although meropenem, and to some extent piperacillin-tazobactam, are often prescribed following advice from microbiology or an infectious specialist, there was a general perception that there was a relative lack of follow-up discussion between the clinical team and authoriser, i.e. microbiologist or infectious disease specialists. In addition, variance in the suppression or release of full microbiology culture and sensitivity reports can lead to continuing patients on the initially started treatment despite clinical improvement and lack of positive microbiology results.

This can be challenged through antimicrobial ward rounds [96], but these are unlikely to capture all patients prescribed these agents in a timely efficient manner.

Therefore, there appears to be a learning need to elevate individual prescriber's knowledge, as well as developing systems to more easily identify prescribing of these antimicrobials to facilitate review and follow-ups.

Evidence from the in-depth interviews (Chapter 4) clearly identified that there was a need for a whole-systematic approach that includes the organisational systems and local policies (the environment), improved open communication within the multidisciplinary team (the clinicians), and better availability and utilisation of CSAs (the medicines). The researcher acknowledges that selection bias was a limitation of this phase of the programme because we involved clinicians in only 4 out of 15 health boards selected based on previously discussed methods (section 4.3.1). However, they represented health boards of varying size, a mix of teaching hospitals and district generals, and urban and rural populations.

5.5. Overall implications and summary of findings:

The current research successfully have a full circle of knowledge on the prescribing of carbapenems, piperacillin-tazobactam, and CSAs. The study explored the current regulatory status of targeted antimicrobials, current prescribing practice, and clinicians' views and opinions on the use of such agents and guidance. For example, from the results, approving CSAs at local health boards was different between health

boards (chapter 2) and that had reflected on the decision of prescribing (Chapter 4). Another example was the results of review/stop date documentations (Chapter 3), which was then justified in the interviews section (Chapter 4) by reluctance in duration documentation due to uncertainty or unclear responsibilities among attending teams and specialised teams.

During the course of the three years of quality assurance evaluation research, national use data of carbapenems and piperacillin-tazobactam has decreased. Although there was some variation between health boards in terms of reduced consumption. Some of this change can be attributed to the various elements of the programme. The impact on consumption may be a Hawthorne effect [315], as research results were shared frequently with SAPG members, but measurement and in-depth study of organisational systems coupled with continuous feedback of findings through multiple forums appears to be supportive in reducing use. During the last three years, consumption of CSAs has shown some increased in few health boards, particularly aztreonam and temocillin has been more accepted and featured in local guidelines. However, SAPG annual consumption reports [240] does not study the correlation between increases in use of CSAs and changes in resistance rates at health boards that uses CSAs.

SAPG had previously successfully completed a similar quality improvement programme for gentamicin and vancomycin [210], and this current research on

carbapenems and piperacillin-tazobactam applied a similar approach. Such programmes utilise several methods to gain intelligence about clinical practice habits and identify target areas for potential quality improvement.

The study findings are continuing to shape the direction of NHS Scotland and SAPG quality improvement initiatives, including:

- Highlighting the need to promote and feature CSAs in local and national guidelines and ensure availability and continuity of stock.
- Working with microbiology and infectious specialist to develop a standardised approach to antimicrobial susceptibility testing and reporting.
- Encouraging health boards to develop local systems to identify initiation of a carbapenem, or piperacillin-tazobactam, to enable a formal review process by the attending clinical team and/or microbiology or infection specialists, and continuation of follow-up process.
- Highlight the significance of antimicrobial stewardship programs and teams. Also, expand involvements of other healthcare providers such as nurses and pharmacists.
- Developing a national standard and supporting toolkit for review of IV antimicrobial therapy, IVOS, escalating and de-escalating guidelines.

5.6. Overall strength and weaknesses of current research:

Conducting a multilevel, multiple parts researches are always challenging and can be difficult in some scenarios. Our current research was no exception, as the current research have its own strengths and weaknesses.

One of the major strengths that the current research had, is the project steering group supervising and discussing every step of the project on regular bases. The project steering group was consisted of members from different backgrounds; Infectious disease consultant, microbiology consultant, senior clinical pharmacist, data analytics specialist, psychologist, academia, and members of SAPG. This strengthen the research to successfully reach its proposed aim and objectives. In addition, the data collection of all parts were rationalised and designed to targeted audience as much as possible to grant successful collection of data. On top of that, the research was supported by SAPG chairman and members, as they were regularly updated with the progress and results of the research, and given the chance to feedback and challenge the researcher on any uncertainty.

On the other hand, one of the weakness that the current research faced was supporting quality improvements results. The research suggested several quality improvements areas that would improve prescribing quality. However, if these areas

were tested on a representative number of health boards for a period of time and then results compared (pre- vs post-intervention) to support our suggestions, recommendations will be more supported with evidence. However, SAPG is currently conducting a research on this matter.

The conducted survey (Chapter 2) was strong in representing results from the words of each health board leader (AMT leader). The results showed what each AMT health boards apply, which provided a baseline information to build on in the future. However, respondents might gave information that were not locally followed or misinterpreted by practitioners.

The PPS (Chapter 3) was a good representation of what was the current practice at patients' level. The results had identified gaps in prescribing practices that would not be easily identified otherwise. However, local guidelines might be different between health boards; a local guideline might be broad to include every single patient on targeted antimicrobial or vice versa. The research was not able to capture this in detail, however, provided an idea and a starting point for local authorities to work on. In addition, the result would be more powerful if the CSAs were included, however, this was not possible at current usage rate and variable approval status of CSAs.

The front-line practitioners' interviewees (Chapter 4) was rich in data and extensively analysed. The interviewees' opinions were from different specialities, experience, and role in health board. This strengthen the result in capturing a wide versatile thoughts and experience. However, the result would've been stronger if more health boards where included. Nevertheless, the results were sound and reached an acceptable level of knowledge based on the given time and available resources.

5.7. Limitations:

Several limitations were identified in the methods used in this thesis. In the self-assessment study (Chapter 2), potential uninformative answers were considered a main limitation of feedback, although it was considered an accepted method to collect baseline information [185]. The AMT leaders were encouraged by the SAPG chairperson to participate in the research, open communication channels between them and the researcher were available, and importance of informative answers was highlighted in the supportive documents; i.e. study brief and protocol.

The PPS study (chapter 3) was limited by the usability of NAS-PPS database. The data entry stage was slow and frustrating in some cases. However, this was solved by the availability of technical support provided by both NAS-PPS developers and super-users assigned during the data collection stage. In addition, the resultant data were

provided in two stages, early results and follow-up results. However, sufficient data to fulfil research objectives were eventually available for analysis.

In the interview studies (Chapter 4), generalisability of the results might be limited by the relatively small sample size. However, feedback saturation was reached as no new themes emerged in the final interviews, and the sample size was likely to be sufficient for the purpose of this study. Another issue that may limit the generalisability of the results is that the study was only conducted in four health boards and therefore the interviewees views explored may be limited to the study site. However, any effect of this limitation may be reduced as many participants had previous experience in other hospitals and thus provided diverse views. Some interviewees may have been subject to desirability bias [316] and might have presented a favourable and positive image of themselves, their wards or the studied health board. However, the research team believes that this influence was minimal as interviewees were informed about the benefits of such research in improving prescribing quality, and this helped interviewees to feel more comfortable when discussing current topic. In addition, participants were informed that participation was entirely voluntary and confidential.

Another limitation faced during the interview study (Chapter 4) was the omission of piperacillin-tazobactam questions from the interview schedule. Piperacillin-tazobactam was initially planned to be included in early drafts of the interview

schedule, however, the length of the interview would have exceeded an acceptable time to accommodate interviewees' busy schedules. Nevertheless, piperacillin-tazobactam arose during discussions with interviewees at the third section of the interview when asked about general area of improvements.

5.8. Future work:

- An updated self-assessment survey using the same methodology used in current research to evaluate the impact of SAPG MDRGNB guidance updated version, 2016, and continuous SAPG efforts to improve prescribing quality. Comparing current results with the new survey will feedback to stakeholders on their progress in the fight against MDRGNB and improve utilisation of targeted antimicrobials.
- Conducting a PPS focusing on the utilisation of CSAs across NHS Scotland, which will provide detailed information regarding their use in real situation clinical practice.
- Testing key quality improvement area resulted from this research in a representative number of health boards to investigate applicability and potential benefits.
- Studying the correlation between increase use of CSAs in some health boards and the local resistance rates to promote CSAs use.

5.9. Overall conclusion:

This work demonstrates how a multifaceted quality improvement research can be used to collect intelligence, promote behaviour change and implement targeted interventions to optimise use of last resorts, very broad-spectrum antimicrobials. Recent trends in Scotland in the use of these antimicrobials continue to show a downward trend, and rates are significantly lower than in other UK nations [317]. Comparison with other European countries [318] suggests that Scotland is 'bucking the trend' of stable or increasing rates of carbapenem and piperacillin-tazobactam use. We consider this three-part improvement project will be of interest to stewardship colleagues as it can be applied to other antimicrobials to investigate and inform safe and effective clinical practice.

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Appendix

See attached CD for electronic appendix