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Coláiste na hOllscoile Corcaigh

Opportunities to measure and improve antimicrobial stewardship in the Irish hospital setting

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Pharmacy

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Table of abbreviations

ACF: Autocorrelation function

ADR: Adverse drug reactions

AIK: Akaike Information Criterion

AIRE: Appraisal of Indicators through Research and Evaluation

AMR: Antimicrobial Resistance

AMS: Antimicrobial Stewardship

ARIMA: Autoregressive Integrated Moving Average

ATC: Anatomical Therapeutic Chemical

CAP: Community Acquired Pneumonia

CFIR: Consolidated Framework for Implementation Research

CPE: Carbapenemase-producing Enterobacterales

DDD: Defined Daily Dose

DOT: Days Of Therapy

EARS-Net: European Antimicrobial Resistance Surveillance Network

EUCAST: European Committee on Antimicrobial Susceptibility Testing

HIQA: Health Information and Quality Authority

HPSC: Health Protection Surveillance Centre

HTA: Health Technology Assessment

ICU: Intensive Care Unit

IDSA: Infectious Diseases Society America

IPC: Infection Prevention and Control

MRSA: Methicillin-resistant *Staphylococcus aureus*

PACF: Partial Autocorrelation Function

PCT: Procalcitonin

PPS: Point Prevalence Study

PRAC: Pharmacovigilance Risk Assessment Committee of the European Medicines Agency

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QI: Quality indicators

RCT: Randomised controlled trial

RTI: Respiratory Tract Infection

SARI: Strategy for the Control of Antimicrobial Resistance in Ireland

SHEA: Society for Healthcare Epidemiology of America

SPC: Summaries of Product Characteristics

STROBE: Strengthening the reporting of observational studies in Epidemiology

UCC: University College Cork

UK: United Kingdom

USA: United States of America

UTI: Urinary Tract Infection

VAP: Ventilator-Associated Pneumonia

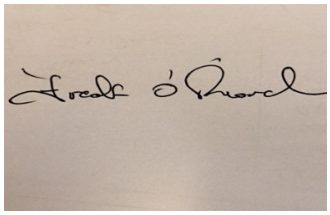
VRE: Vancomycin-resistance in *Enterococcus faecium*

WHO: World Health Organisation

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Signed: Date: 20th February 2022



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Publications and Presentations

Publications:

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O'Riordan F, Shiely F, Byrne S, Fleming A. A qualitative process evaluation of the introduction of procalcitonin testing as an antimicrobial stewardship intervention. International Journal of Clinical Pharmacy. 2021 June; 43(3):532-540.

O'Riordan F, Shiely F, Byrne S, Fleming A. Quality indicators for hospital antimicrobial stewardship programmes: a systematic review. Journal of Antimicrobial Chemotherapy. 2021 June; 76(6) 1406-1419.

O'Riordan F, Shiely F, Byrne S, O'Brien D, Ronayne A, Fleming A. Antimicrobial use and antimicrobial resistance in Enterobacterales species and *Enterococcus faecium*: a time series analysis. Journal of Hospital Infection. 2022 February; 120 :57-64

Conference Presentations:

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A feasibility study to investigate the effects of procalcitonin testing on antimicrobial prescribing in lower respiratory tract infections in an Irish hospital.

- British Society of Antimicrobial Chemotherapy Spring Conference, International Convention Centre, Birmingham, UK 21st-22nd March 2019.
- School of Pharmacy, University College Cork, Research Conference Day, 23rd May 2019.
- UCC New Horizons Research conference December 5th 2019.

A process evaluation of a feasibility study of the introduction of procalcitonin testing in an Irish University Hospital.

- Royal College of Physicians of Ireland, Faculty of Public Health Medicine, Winter Scientific Meeting, Dublin, December 4th 2019.
- Health Services Research & Pharmacy Practice 2020 Annual Conference, Cardiff University on April 16th and 17th 2020. International Journal of Pharmacy Practice 2020; 28(Supplement S1):64.

Quality indicators for hospital antimicrobial stewardship programmes: a systematic review.

- British Society of Antimicrobial Chemotherapy Spring Conference, Held online 29th -30th April 2021.

Oral presentations:

Irish Society of Clinical Microbiologist Spring Meeting, Radisson Hotel, Golden Lane, Dublin 29th March 2019.

A feasibility study to investigate the effects of procalcitonin testing on antimicrobial prescribing in lower respiratory tract infections in the Mercy University Hospital.

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AMS InSight Webinar October 2021

Antimicrobial use and antimicrobial resistance in Enterobacterales species and *Enterococcus faecium*: a time series analysis.

Thesis abstract

Background

Antimicrobial resistance (AMR) is one of the most significant threats to public health and increasing levels of resistance among gram negative organisms, and levels of vancomycin-resistant *Enterococcus faecium* (VRE) are of concern across Europe and in Ireland. Antimicrobial stewardship (AMS) programmes are well established in the Irish hospital setting but it is important that they continue to respond and evolve to the threat of AMR. This can be achieved by investigating new interventions and adopting new diagnostics methods to support hospital AMS programmes and other opportunities to measure and improve AMS programmes.

Aim

The overall aim of this research thesis was to investigate opportunities to measure and improve the delivery of AMS programmes in the Irish hospital setting.

Methods

A randomised feasibility study was conducted to investigate the implementation of Procalcitonin (PCT) testing in patients with a respiratory tract infection (RTI) as an intervention to support the AMS programme in an Irish hospital setting. An in-depth qualitative process evaluation (PE) of the PCT intervention was conducted to examine the implementation process and to determine the barriers and facilitators to the implementation of PCT as an AMS intervention. The Consolidated Framework for Implementation Research (CFIR) was used to guide data collection, analysis, and interpretation.

A systematic review of quality indicators (QIs) for hospital AMS programmes was undertaken, with a critical appraisal of their methodological qualities using the Appraisal of Indicators through Research and Evaluation (AIRE) instrument.

A time series analysis (TSA) of antimicrobial consumption (AC) data and AMR data was conducted to investigate trends, and possible relationships between AC and AMR.

Results

The feasibility study determined that the introduction of PCT testing in patients with a RTI had a positive impact on antimicrobial prescribing resulting in a significant decrease in duration of antimicrobial prescriptions and decreased length of hospital stay. The qualitative PE identified positive elements of the implementation process along with modifications to improve the delivery of the intervention. The contextual factors which can act as barriers and facilitators to the implementation of AMS interventions were identified and included the concepts of fear, risk and the influence of respiratory clinicians on AMS interventions.

The systematic review collated an extensive range of QIs for AMS programmes in the hospital setting which predominantly consisted of process (e.g. infection diagnosis) and structural indicators (e.g. AMS governance), with few outcome indicators developed, a major deficiency in this area. There was limited reporting of information about validation and piloting of QIs sets in practice which is an essential element of the QI development process.

The TSA analysis of AC and AMR rates found decreasing or relatively stable rates of AMR in Enterobacterales and VRE isolates but increasing incidence of carbapenem resistance which must be addressed as part of the local AMS programme.

Conclusion

This thesis presents a comprehensive and detailed body of research investigating AMS opportunities in the Irish hospital setting. The results of this research indicate that AMS programmes will need to continue to evolve, and dedicated resources will be required to support research in AMS practice. This will include optimising the use of new diagnostic tools such as PCT to support physicians in making antimicrobial prescribing decisions; the incorporation of QIs to assess and improve AMS programmes; and the implementation of in-depth surveillance analysis of AC and AMR using TSA. These measures have the potential to make substantial contributions to hospital AMS measures locally and internationally.

Chapter 1 Introduction

This chapter will describe the context of the research undertaken in this thesis, beginning with an overview of antimicrobial resistance (AMR) and its association with antimicrobial prescribing which has led to the establishment of antimicrobial stewardship (AMS) programmes to address the problem in Irish hospitals.

This research thesis will address how AMS programmes can evolve, including the design and implementation of new interventions to support the AMS programme, assess the ways in which to measure the quality of an AMS programme, and how to measure and adapt to the evolving AMR trend in the hospital setting.

1.1 Antimicrobial resistance

AMR is one of the most significant threats to public health (1) and we face the very real possibility of a 'post antibiotic era in which common infections could once again kill' (2). AMR is a natural evolutionary response where the microorganism develops the ability to grow and reproduce, or to survive exposure to an antimicrobial agent. It results in an antimicrobial that was previously effective, becoming no longer effective to treat an infection or disease caused by a microorganism. The spread of AMR is facilitated by interspecies resistance-gene transfer, poor sanitation, and hygiene, in communities and in hospitals, and the increasing frequency of global, travel trade and disease transmission (2).

The serious nature of the AMR problem is occurring at the same time that there is a limited pipeline of new antibiotics (3). AMR is a global problem (4) threatening the role that antimicrobials have played in safeguarding the overall health of human societies and potentially undermining some of the achievements of modern medicine including major surgeries, organ transplantation and cancer chemotherapy (5).

It has been estimated that up to 25,000 people in Europe (6) and 35,000 in the United States of America (USA) (7), die from antibiotic resistant bacteria annually. Furthermore, it has been projected that by 2050, up to 10 million people will die

annually from multi-drug resistant infections, along with significant economic costs unless action is taken to address AMR (8).

Infections caused by multi-drug resistant bacteria are associated with longer durations of illness and increased morbidity and mortality, increasing healthcare costs, treatment failure (1, 9, 10), and the inability to conduct procedures that rely on effective antimicrobials to prevent infections (4).

At a European Union (EU) level there are increasing concerns regarding the levels of resistance in gram negative organisms such as *Escherichia coli* and *Klebsiella pneumoniae* and levels of vancomycin-resistance in the gram positive organism *Enterococcus faecium* (VRE) (11) and these trends are also developing in Ireland (12). The Health Protection Surveillance Centre (HPSC) annual epidemiology report for 2018 (13) highlighted that the number of invasive infections reported have increased by almost 20% with large increases seen in *Pseudomonas aeruginosa* (54%), *Streptococcus pneumoniae* (39%), *K. pneumoniae* (36%) and *E. coli* (20%). Ireland was the EU country with the lowest proportion of fully susceptible *E. coli* blood stream infections (BSI) in 2018. The report also highlighted that Ireland also has one of the highest rates of Methicillin-resistant *Staphylococcus aureus* (MRSA) in Europe along with a high proportion of VRE.

Extended-spectrum β-lactamase (ESBL) resistance in *E. coli* and *K. pneumoniae* infections have become more common, along with increased prevalence of carbapenemase-producing Enterobacterales (CPE) in surveillance and diagnostic samples in Irish hospital laboratories (14). CPE has also been isolated at a local level in recent years (15). Hospitals can be considered '*hotspots*' for resistance because of the vulnerable patient population and the combination of significant volumes of various antibiotics and the prevalence of pathogenic bacteria, both of which create the ideal setting to foster resistance emergence, and allow for the exchange of resistance genes and their spread (16).

A recently published report by the Health Information and Quality Authority (HIQA) (2021) found that there is a significant economic burden associated with AMR and

significant additional cost to Irish hospitals for the treatment of infections that are resistant to antimicrobials compared with treating infections that respond well to antimicrobials (17). The study found that 4700 resistant infections occurred in the 50 public hospitals in Ireland which resulted in 215 deaths. The increased length of hospital stay and provision of additional bed days to these patients cost an additional €12 million in 2019 which is probably an underestimate of the overall cost (17).

1.2 Antimicrobial prescribing

Antimicrobials are one of the most prescribed drugs in human medicine and have dramatically improved the prognosis of patients with bacterial infections. Antimicrobials are prescribed predominantly in the community setting (18), however the concentration of antibiotic prescribing is higher in the inpatient hospital setting with 32% of inpatients prescribed antimicrobials across European hospitals, and Irish hospitals had a prevalence of almost 40% (19). Antimicrobial use is not without risk and at least 20% of hospitalised patients suffer adverse drug reactions (ADR) related to antimicrobial use including gastro-intestinal symptoms, renal impairment (20), and the effects of antimicrobial use on the gut microbiome (21) are of increasing interest. Of further concern was the finding that 20% of ADR were attributable to antibiotics inappropriately prescribed for conditions for which they were not indicated (20). It is estimated that up to 50% of all antimicrobials prescribed to people are considered inappropriate (22). This may be due to unnecessary antimicrobial use, but also where antimicrobials are required the selection, dose, route of administration and duration of treatment may be inappropriate (23, 24).

The use, misuse, or overuse of antimicrobial drugs is considered to be a major driving force of AMR (4). There is a well-established link between inappropriate and excessive use of antimicrobials and selection for AMR (25, 26) and antimicrobial use is generally recognised as the primary driver of AMR (27, 28). For these reasons antimicrobial prescribing is considered the single most modifiable means of decreasing AMR (29).

Antimicrobial prescribing is a complex and challenging process and the appropriate use of antibiotics in hospitals entails balancing their potent ability to treat infections reducing mortality and morbidity, and their potentially hazardous and unintended

effects. Clinical signs and laboratory findings may be subtle in the early stages of infection and most antibiotic prescribing remains largely empiric (i.e. 'best guess') for moderate to severe bacterial infections, without knowledge of the pathogen or its susceptibility. A study in the USA found that broad-spectrum empirical therapy is common, even in the absence of clinical signs of infection and de-escalation of therapy within 5 days of commencing treatment occurred in fewer than one in three inpatients (30). In another recent study almost one-fifth of hospitalized patients treated for pneumonia did not have any of the cardinal signs of pneumonia on the first day of treatment and antibiotics were continued for 3 days or longer after all signs were normal in more than a third of patients (31).

Most hospital inpatients are treated for infections by non-infection specialists, and while they may be specialists in their own field, they may lack the expertise required to make informed decisions about antibiotic choices (32). This can affect the quality of antibiotic prescribing where prescribers opt for broad-spectrum agents to ensure effective therapy and for longer durations than required (32).

1.3 The influence of social and contextual factors on antimicrobial prescribing

Despite mounting alarm regarding the future availability and effectiveness of antibiotics, changing how doctors prescribe has been challenging and, in many cases, ineffectual (33, 34). Interventions to improve prescribing are reliant on changes in the behaviour of individual prescribers but the behavioural determinants and social norms which influence prescribing are rarely considered in the design and evaluation of interventions (35). This has led to increasing recognition of the influence of cultural, contextual and behavioural factors on antibiotic prescribing and the need to consider these when developing or implementing interventions to improve antibiotic prescribing (36).

Prescribers feel a sense of safety and comfort with the use of broad spectrum empiric antimicrobial therapy, irrespective of the guideline recommendations (36), and are often reluctant to deescalate therapy based on microbiology results due to an attitude of *"never change a winning team"* (37).

An Australian study has shown prescribers prioritise individual patient care over the broader public health considerations of AMR, due to the perception that overprescribing of antibiotics carried minimal risk to themselves or the patient when compared to under-prescribing which was associated with legal and reputational risks (38). These findings suggest that prescribers have an inability to associate their own behaviours with the emergence of AMR, while simultaneously tending towards over-prescription of antimicrobials to treat the patient in their care (38). These factors are not confined to the hospital setting, with balancing safety and risk concerns also influencing prescribing decisions in the primary care setting (39).

A further contextual influence in the hospital setting relates to professional hierarchies and prescribing etiquette, which can lead to sub-optimal antibiotic prescribing as they limit a multi-disciplinary approach and the involvement of junior members of teams, pharmacists, and nurses in key decision-making (33, 40). The benefits of a multidisciplinary team (MDT) approach to healthcare are well established, as is the link between enhanced clinical expertise and provision of better care (41), however this does not always apply to antimicrobial prescribing advice:

> *"Clinicians do not accept the interference of clinical pharmacists and, to a lesser extent, medical microbiologists in clinical antibiotic management"* (37).

1.4 Antimicrobial stewardship

Antimicrobial stewardship (AMS) has been defined by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) as:

> *"co-ordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration"* (42).

The purpose of AMS is to promote the prudent use of antimicrobials, which optimise patient outcomes and minimise the unintended consequences of antimicrobial use,

which are the risk of ADR, toxicity and the emergence and spread of AMR (42). Hospital AMS programs consist of a comprehensive and multifaceted range of evidence-based interventions which have been shown to safely reduce excessive antibiotic prescribing and are an important element in tackling AMR (43). Examples of hospital AMS interventions which have demonstrated benefits in terms of clinical outcome, adverse events, treatment costs and AMR rates include empiric treatment according to local or national guidelines, de-escalation of treatment, parenteral to oral switch, therapeutic drug monitoring, and restricted antimicrobial lists (44). Other studies have demonstrated reduced length of hospital stay (45) and cost savings associated with AMS (46, 47). AMS programmes can be both labour and resource intensive which can limit implementation in low-to-middle income countries, and this prompted the publication of 'core elements' of AMS programmes (48).

1.5 Antimicrobial stewardship in the Irish hospital system

The Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) was launched in 2001 on behalf of the Irish Department of Health and Children. It established the scale of the AMR problem in Ireland and included recommendations for the improvement of surveillance of AMR and antibiotic consumption, improved infection control services and promotion of strategies to promote appropriate prescribing of antimicrobials (49). HIQA was established in 2007 under the Health Act 2007 with the aim of driving continuous improvement in Ireland's health and social care services. Formal hospital AMS programmes were established following the publication by HIQA of the '*The National Standards for the Prevention and Control of Healthcare Associated Infections*' in 2009 and their subsequent update in 2017 (50). This publication includes Standard 3.6 which states: *"An antimicrobial stewardship programme is in place to ensure safe antimicrobial prescribing for patients".* In 2009 SARI published '*Guidelines for antimicrobial stewardship in hospitals in Ireland'* (51). These guidelines outlined evidence-based principles which should be implemented by all publicly-funded acute hospitals in Ireland, recommendations for the national coordination of AMS, key governance and workforce requirements to enable effective implementation of AMS programmes and core high impact evidence-based AMS interventions to implement.

In 2016 HIQA published a review of AMS in public acute hospitals (52). The report found that in the majority of hospitals good progress had been made with the implementation of AMS best practice. This included:

- an appropriate complement of well-trained and well-led specialized staff, working as a team (medical microbiologists, infectious diseases physicians, clinical pharmacists)
- a support framework which includes good laboratory, information technology, surveillance and clinical pharmacy resources, and
- appropriate governance arrangements with effective senior management support.

Notable success has been identified in higher performing hospitals in the development of:

- regularly reviewed evidence-based empiric prescribing guidelines
- protected antimicrobial prescribing rights for key strategic antimicrobial agents
- point-of-care interventions involving direct feedback to prescribers in the clinical environment by specialised staff e.g. dose optimisation, therapeutic drug monitoring
- good collaboration between hospitals to make best use of resources, and
- the integration of antimicrobial stewardship with wider medication safety and risk management programmes.

More recently the *'Start smart, then focus'* (53) antibiotic care bundle has been implemented in Irish hospitals (54).

1.6 Antimicrobial surveillance in Ireland

Antimicrobial consumption (AC) in Ireland is measured using the standardised World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) Classification of defined daily dose (DDD). A DDD is the assumed average maintenance dose per day for a drug used for its main indication in an adult, and normalised per 100 hospital/bed days (antibiotic use density) (55). The rate of AC in Ireland is in the mid-to high range in comparison with other EU countries for both the

outpatient setting and the hospital setting according to the Health Protection Surveillance Centre (HPSC) (56). The overall Irish combined community and hospital use total has shown a statistically significant increase between 2010-2019, at a time where the overall EU AC rate has decreased and can be seen in Table 1.1 below (57).

Table 1.1 Total antimicrobial consumption (community and hospital sector) for Ireland and the EU, 2010–2019 (expressed as DDD per 1 000 inhabitants per day) (57)

	Year									
	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Ireland	19.0	20.8	21.0	21.6	21.0	23.0	22.0	20.9	21.4	21.7
EU	20.9	20.9	21.0	21.5	21.1	21.5	20.7	20.2	20.1	19.4

In the acute hospital setting the national median rate of AC has increased by 16% between 2009 and 2019 to 78.9 defined daily doses (DDD) per 100 bed days used and can be seen in Table 1.2 and Figure 1.1 (56). During this time the consumption of most antimicrobial classes has increased, including third generation cephalosporins use by a third, and the steady increase in broad-spectrum combination penicillin (co-amoxiclav and piperacillin/tazobactam) which now make up approximately 33% of AC in the Irish hospital setting (56).

Table 1.2-Annual rate of hospital consumption of systemic antibacterial drugs in DDD per 100 BDU (56)

	2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
National median	69.3	67.0	66.8	71.3	73.2	76.7	75.6	73.9	73.0	76.8	77.9	79.5	78.1
National minimum	14.8	15.5	17.6	21.3	20.3	25.4	27.9	23.6	25.9	23.5	27.9	27.9	29.7
National maximum	98.9	103.6	99.9	111.8	122.7	115.1	101.8	113.4	100.3	107.2	116.8	117.2	112.5
Overall national mean	68.6	68.9	67.6	70.1	73.3	74.2	74	75.5	73.8	76.7	78.3	79.1	77.8

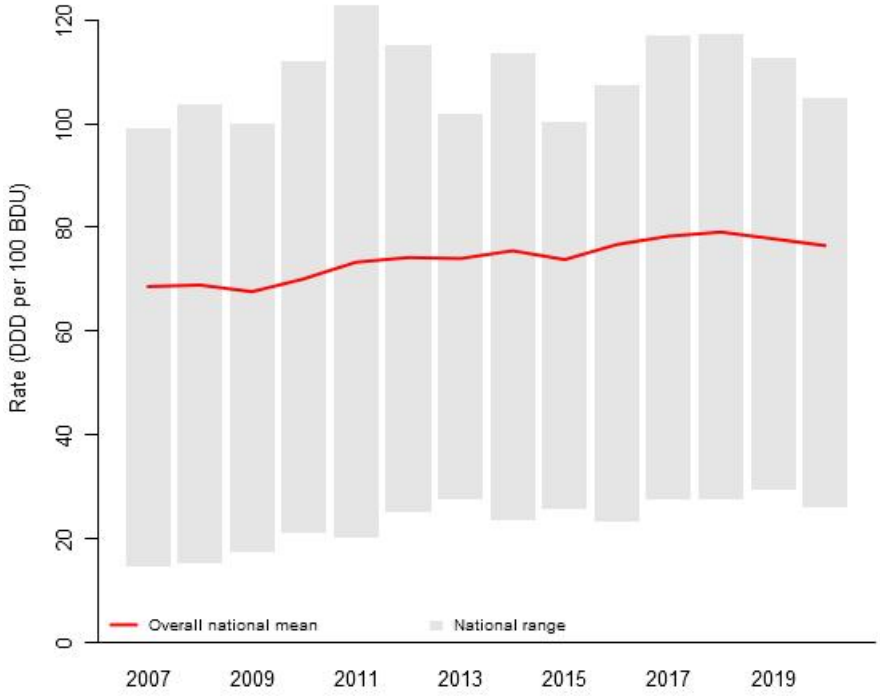

Figure 1.1 Annual rate of hospital consumption of systemic antibacterial drugs in DDD per 100 BDU. The grey bars show the range of use (lowest to highest) and the red line shows the national mean among acute hospitals (56)

The ATC/DDD method for measuring AC is widely used but it has limitations, for example in relation to dose adjustments in patients with renal impairment, paediatric patient antibiotic use and occasional doses administered to patients, the use in these instances may differ from the WHO-approved DDD (58). Hospital case-mix has a considerable impact on the AC of a hospital and antibiotic prescribing may be influenced more by this than specific infections or the presence of resistant organisms (59). The hospital case-mix also influences the length of hospital stay (LOS), with hospitals with long mean LOS (fewer admissions) showing relatively high antibiotic use when measured using the ATC/DDD method (59). LOS is largely influenced by the type of services offered by a given hospital and both short and long hospital stays have been independently correlated with antimicrobial use along with admission for an infectious disease or a surgical diagnosis (60). This has led to research to identify suitable case-mix adjustment models, including in the Irish hospital setting (61), but further research is needed in this area (61, 62).

Nationally, annual point prevalence surveys (PPS) are used to monitor trends in prescribing and identification of priorities for quality improvement in antimicrobial use in hospitals and are conducted by the antimicrobial pharmacists and AMS teams. The European Surveillance of Antimicrobial Consumption PPS methodology is used as it can be successfully applied at a national level (23). PPS provide information on prescribing practices at a particular point in time, which can help identify prescribing trends, areas for intervention, measure local guideline compliance and measure the success of AMS interventions. The most recently available complete PPS results were from 2019 (63). This showed that a median prevalence of 40% of patients were prescribed antimicrobials, broad-spectrum combination penicillin (co-amoxiclav and piperacillin/tazobactam) accounted for 37% of the prescribed antibiotic courses, 67% of antibiotic courses were prescribed by the IV route, with respiratory tract infections being the most common indication for antimicrobials. Areas of concern related to the finding that greater than 25% of courses were greater than 7 days in duration, and one of the main recommendations was to reduce the duration of pneumonia treatment (63). Figures 1.2 and 1.3 contain initial results from the 2020 PPS and the 2019 data for the most frequently prescribed antimicrobials and the most common diagnostic sites of infection.

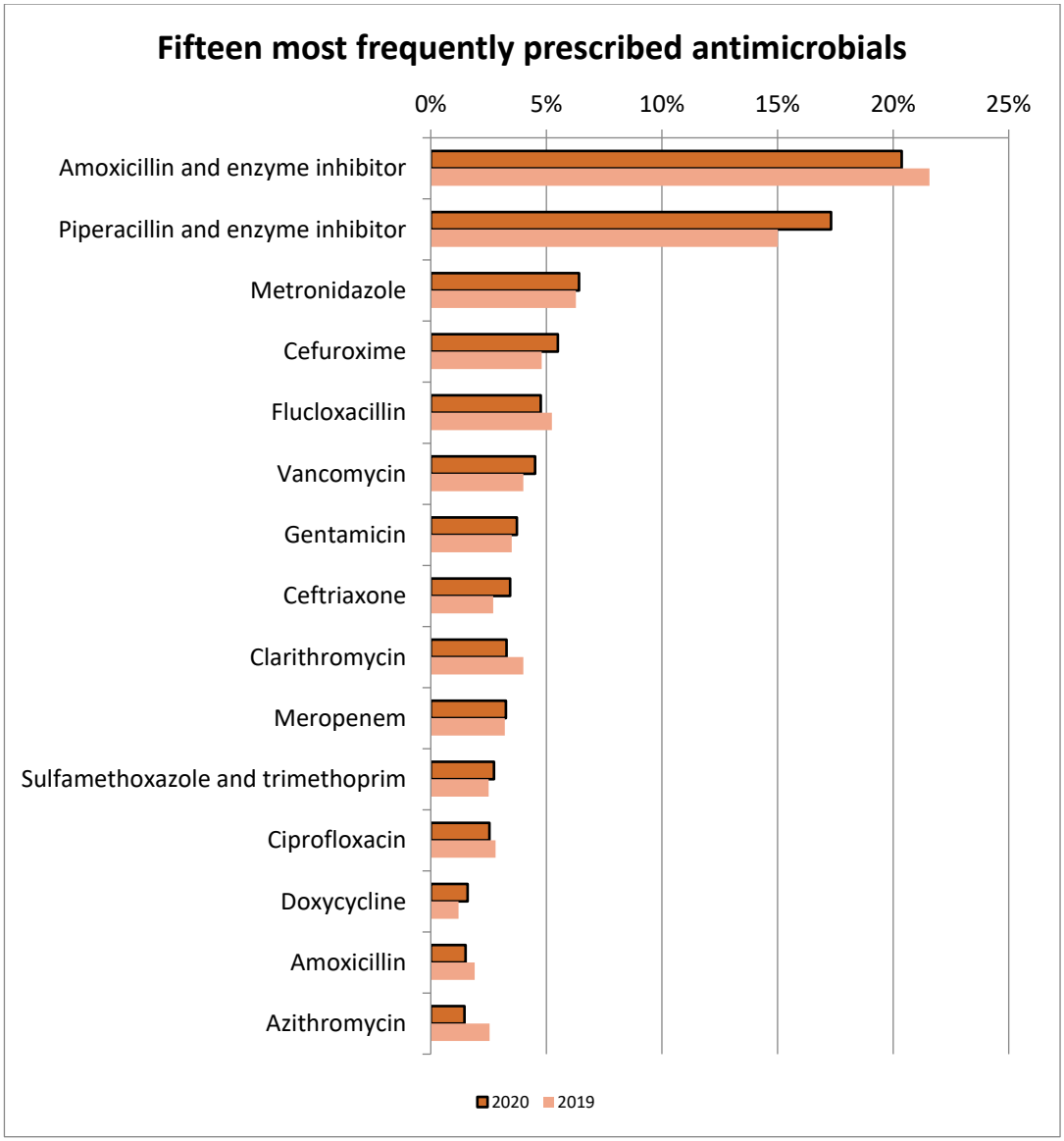

Figure 1.2 Top 15 most frequently prescribed antimicrobials in Irish hospitals in 2019 and 2020 (63)

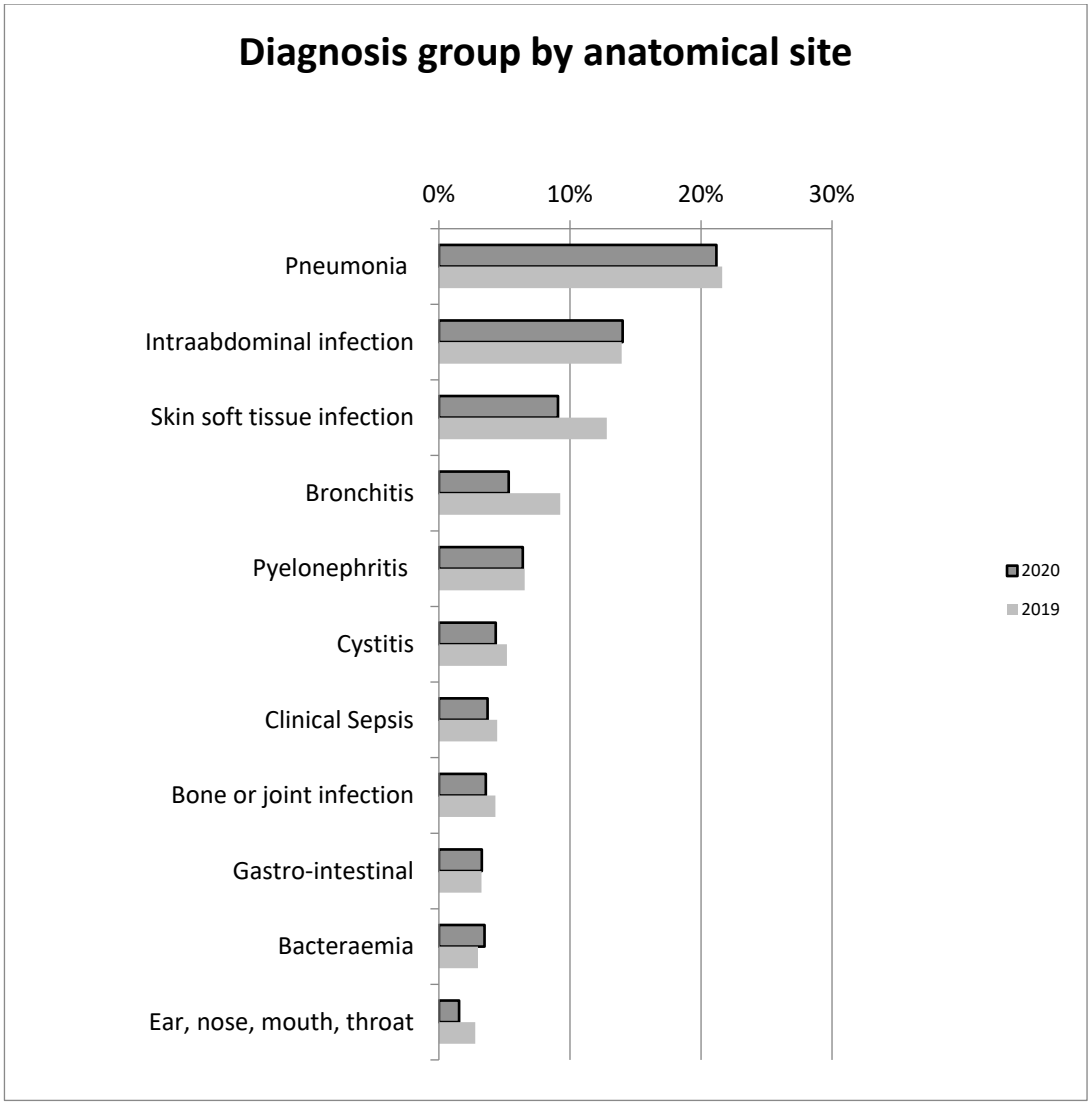

Figure 1.3 Diagnostic site of infections indicated for antibiotic prescriptions in Irish hospitals 2019 and 2020 (63)

At a European level the most recent hospital PPS in 2016/2017 found a prevalence of 30.5% of inpatients were prescribed an antimicrobial, 72% of antimicrobials were administered parenterally, and respiratory tract infections (RTI) were the most common indications for the prescription of antimicrobials (19).

It is important to note that PPS do have some limitations. The study design of a PPS only allows for the capture of antimicrobial prescribing data at a given point in time. While PPS can be used to evaluate any prescribing trends, the time period is short, and this may not provide enough information about trends or patterns of antimicrobial prescribing.

1.7 This research in the context of national policy

As already set out in this chapter, the problem of AMR continues to grow despite the development and implementation of AMS programmes in Ireland and worldwide. This suggests that AMS programmes need to evolve in response. This research thesis will address the gaps in the research. This will include the design and implementation of new interventions to support the AMS programme using diagnostics, to assess the ways in which to measure the quality of hospital AMS programmes, and the application of advanced statistical analysis to measure AC and evolving AMR trends in the hospital setting.

The Irish government published Ireland's National Action Plan on Antimicrobial Resistance 2017-2020 (64) and this thesis aligns with specific strategic objectives two and five of this plan: enhance surveillance of antibiotic resistance and antibiotic use; promote research and sustainable investment in new medicines, diagnostic tools, vaccines and other interventions.

1.8 Interventions to improve antimicrobial prescribing. Incorporating new diagnostics

The reduction in the length of antimicrobials courses has been suggested as the strategy most likely to be effective in reducing AMR (65). It is also important to maintain heterogeneity in the prescribing of antimicrobial agents and to avoid the concentration of selection pressure (66). Advances in diagnostic testing offer potential solutions to these problems (66) and greater utilisation of rapid diagnostic tests and biomarkers has been highlighted as an important factor in addressing AMR by improving infection diagnosis, supporting prescribing decisions and AMS programmes (67). Rapid diagnostics have the potential to reduce the time to accurate infection diagnosis, to provide earlier effective, targeted antimicrobial recommendations and to decrease the use of unnecessary empirical therapies, however, concerns exist that diagnostics are not being integrated into clinical care optimally (68). For this reason it is now recognised that close collaboration between the laboratory and the AMS stewardship team offers the best approach to utilise the developments in diagnostic stewardship while reducing unnecessary testing and improve patient care (69). It is also important to note that new infection diagnostic tests have been found to be most effective when implemented as part of AMS

programmes (70). The goal of diagnostic stewardship is to select the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve health care resources (71). Diagnostic stewardship can act as a way to guide appropriate clinical behaviour but care must be taken to reduce unnecessary testing and false-positive results which may result in inappropriate/unnecessary treatment. A successful example of the benefits of molecular diagnostic methods is the BioFire FilmArray® respiratory panel to improve patient care and AMS decisions (72, 73). These tests have demonstrated high degrees of sensitivity and specificity for respiratory pathogens (e.g. *S. pneumoniae)* (72). They provide timelier pathogen identification which allows for more prompt adjustment of antimicrobial therapy to targeted rather than empiric antimicrobial treatment and thus improving patient care, optimising infection treatment while reducing unnecessary antimicrobial exposure (73).

As well as the standard approach to identification of pathogens, diagnostics based on the host response to infection can also provide useful information. Procalcitonin (PCT) is a biomarker which correlates well with bacterial infections and has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with respiratory tract infections (74-77). The findings of a recent Cochrane review (76) supports its use in the context of AMS in safely reducing antimicrobial consumption by 2.4 days in patients with RTIs.

The first element of this research thesis involved local interest of the AMS team into using PCT to support the AMS programme (Chapter two). Gaps existed in the research to support PCT testing for the Irish hospital setting so there was a clinical need to generate robust evidence to support its introduction. Further gaps exist in the research examining the implementation of PCT interventions and the updated Cochrane review (43) of AMS interventions recommended the barriers and facilitators to implementation are explored during studies of new AMS interventions using process evaluations (PE). It is important to recognise that barriers do exist to the uptake of new diagnostic technologies and delivery into health systems. These include physicians' attitudes towards diagnostic testing, regulatory approval, recommendation by guidelines, social, ethical, economical, and political factors (4). The second element

of this research thesis involved a qualitative PE of the implementation of the PCT intervention to support the AMS programme (Chapter three).

1.9 Measuring the quality of AMS programmes

In the past cost savings were among the initial incentives for hospitals to implement AMS programmes (78). However cost savings alone are an unreliable indicator of performance (79) and measures to demonstrate the clinical and economic values of AMS programmes are required (80), and are an area of increasing interest (81).

Quality indicators (QIs) can measure the appropriateness of healthcare and can be defined as '*measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care provided*' (82).

In the AMS context:

> "*a QI reflects the degree to which antibiotic use is correct or appropriate while in contrast, a quantity metric reflects the volume or the costs of antibiotic use"* (83).

QIs can also measure the quality of care by examining the structures, processes, and outcomes of care (84, 85). A broad range of QIs have been developed for AMS and they include QIs to measure and compare AMS programmes in the EU and US (86), to assess responsible antibiotic use in the inpatient setting (83), to measure appropriate antibiotic use in hospitalised adults (87) and for specific infectious processes such as sepsis (88) and urinary tract infections (89).

It is important that QIs provide accurate measures of quality, requiring them to adhere to certain quality requirements. On review of the literature the evidence of AMS QIs assessing their methodological quality was lacking. The third element of this research thesis involved the systematic review and critical appraisal of the methodological quality of QIs to assess AMS programmes (Chapter four).

1.10 AMS surveillance

Surveillance has an important role in tackling AMR (1). There is considerable variability in the level of surveillance across the world but where data is available, it is very useful for orientating treatment choices, understanding AMR trends, and, identifying priority areas for interventions to contain resistance (90).

The '*One Health Report on Antimicrobial Use and Antimicrobial Resistance'* in Ireland highlighted a number of issues with antimicrobial and AMR surveillance in Ireland (91). Currently, national AC surveillance does not include information on the appropriateness of the antimicrobials that are prescribed in either the hospital or community setting, or to the level of the prescriber, both of which limit the capacity to develop educational programmes.

Human AMR surveillance focuses on trends in invasive infections such as blood stream infections in hospital patients, while other more common types of infection (e.g. Urinary Tract Infection's (UTIs), wound infections) and infections in settings outside of hospitals are not currently subject to national surveillance. Addressing such surveillance gaps will improve Irelands ability to respond to current and emerging AMR threats and support AMS efforts to provide better evidence for decision making (91).

The AMR trends of most concern in Ireland and the EU currently are the increasing prevalence and levels of resistance in gram negative organisms (including *E. coli, K. pneumoniae* and CPE) and levels of gram positive resistance in VRE (11, 12). Blood stream infections with third generation cephalosporin-resistant *E. coli* are associated with significant increase in mortality and an excess LOS of 5 days when compared to susceptible organisms (92). CPE also poses a serious clinical threat due to the limited treatment options available (93) and CPE prevalence is increasing in surveillance and diagnostic samples in Irish hospital laboratories (14).

While there are many factors which contribute to the spread and selection of AMR the link between antimicrobial use and AMR are well-established (25, 26) and has contributed to the rise in AMR among the Enterobacterales species (94). Ireland has seen increasing rates of AC (56) and increasing rates of AMR (11, 12) so it is important to examine the relationship between AC and AMR. The fourth element of this research thesis involved the time series analysis of how AC may be related to AMR rates in an Irish hospital setting (Chapter five).

1.11 Methodologies applied in the research

1.11.1 Feasibility study of the PCT intervention

As already established in this chapter antimicrobial prescribing is a complex process and influenced by multiple contextual factors, therefore AMS interventions can thus be considered complex interventions as defined by the UK Medical Research Council (MRC) and require in-depth evaluation (95). In considering the introduction of PCT testing to support the AMS programme a feasibility study was considered the optimal approach. The MRC guidance explicitly recommends conducting feasibility (or pilot) studies during the development of an intervention and prior to undertaking a main larger randomized controlled trial (RCT) to identify problems which might occur, such as; if modifications are required to the intervention, to determine if a study is achievable, and where there is outcome evaluation the feasibility phase increases the likelihood of researchers evaluating the optimum intervention using the most appropriate and efficient recruitment practices and trial design (96). If fundamental problems in the intervention or trial design can be identified during a feasibility study, this allows for a return to the development phase rather than the potential of conducting an ineffective expensive trial (97). The key stages recommended in the development of complex interventions are outlined in Figure 1.4 below. Feasibility studies should be complemented by a PE as qualitative data is particularly useful during any feasibility study (98) leading to improved development and implementation of interventions (99) as seen in a PE of the appropriateness of antipsychotic prescribing in nursing homes (100).

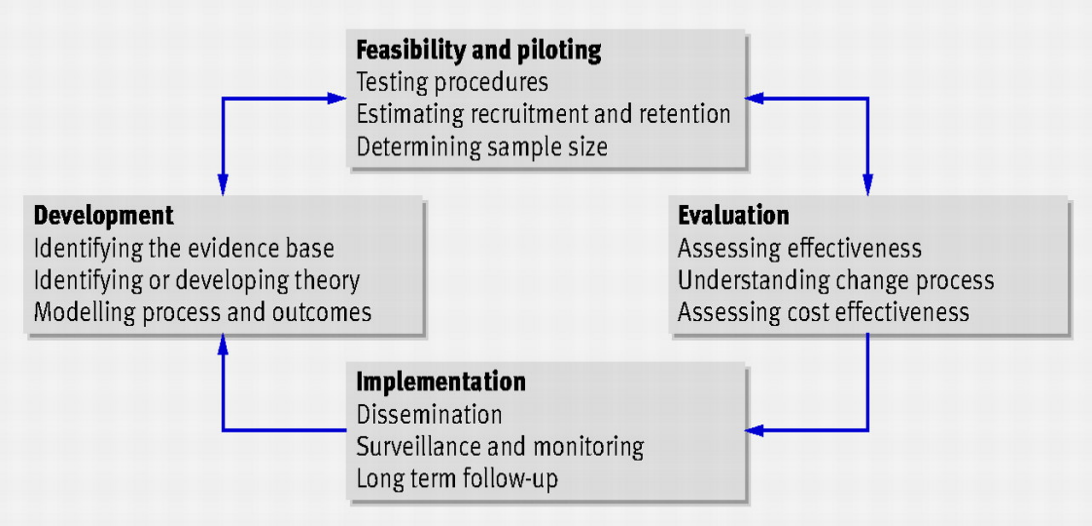

Figure 1.4 Key elements of the development and evaluation process of a complex intervention (Medical Research Council 2008)

1.11.2 Process evaluation of the PCT feasibility study

A PE can be used to assess the fidelity and quality of implementation, clarify causal mechanisms, and consider the context and the mechanisms that are producing the outcome without assuming that the intervention itself leads to the outcome. This provides information on how the intervention is operationalised in practice and is vital in building the evidence base to support the intervention that will inform policy makers and practice (95). PEs are particularly important in complex interventions in the healthcare setting as a means to identify the underlying cause of the success or failure of any intervention because occasionally even highly successful quality improvement interventions (101) have proven difficult to replicate in different contexts (102). The implementation of an intervention may result in a culture change in an institution but a similar effect may not occur in other institutions due to fundamental differences e.g. in how the intervention was delivered (102). There have been recommendations that studies of AMS interventions should use qualitative research such as a PE alongside the study, to determine the consequences of an intervention (43). Furthermore, recommendations for built-in PE and fidelity assessments of AMS interventions along with the identification of barriers and facilitators to implementation of AMS interventions have been identified as AMS research priorities (103).

A PE should incorporate a theoretical framework to guide data collection, analysis and interpretation as part of implementation research. Theoretical frameworks have a predictive capacity to identify or explain causal mechanisms of implementation. This allows for the identification of the determinants of implementation and the influence of contextual factors which influenced implementation where the research was conducted and so aiding in our ability to generalise study findings (104).

The Consolidated Framework for Implementation Research (CFIR) (105) can be used to guide data collection, analysis, and interpretation of qualitative research such as a PE. The CFIR is a meta-theoretical framework based on existing determinant frameworks and multiple implementation theories which provides a roadmap of constructs to monitor the implementation process (105). The CFIR can be applied at any stage of the evaluation process of an intervention, it provides a framework to investigate and assess the complex multi-level nature of implementation in the healthcare setting and provides a way in which to organise and communicate findings. It can be used to guide exploration to determine the factors which influenced outcomes such as implementation effectiveness and intervention effectiveness and is useful to investigate the barriers and facilitators to effective intervention implementation (104). Such findings are useful to inform the adaptation of the intervention, implementation process, scale up of the intervention and sustainability (104). The CFIR recognises that implementation is a multidimensional phenomenon with multiple interacting influences and relationships within and across levels and different types of determinants from the individual to the organisation to beyond (106). The domains of the CFIR can be seen in Figure 1.4.

The CFIR has been used successfully in several qualitative studies relating to prescribing. These include a study of the barriers and facilitators of the evidence-based management of patients with bacterial infections by dental practitioners (107), and an exploration of the factors influencing rheumatologists prescribing of biological treatments (108).

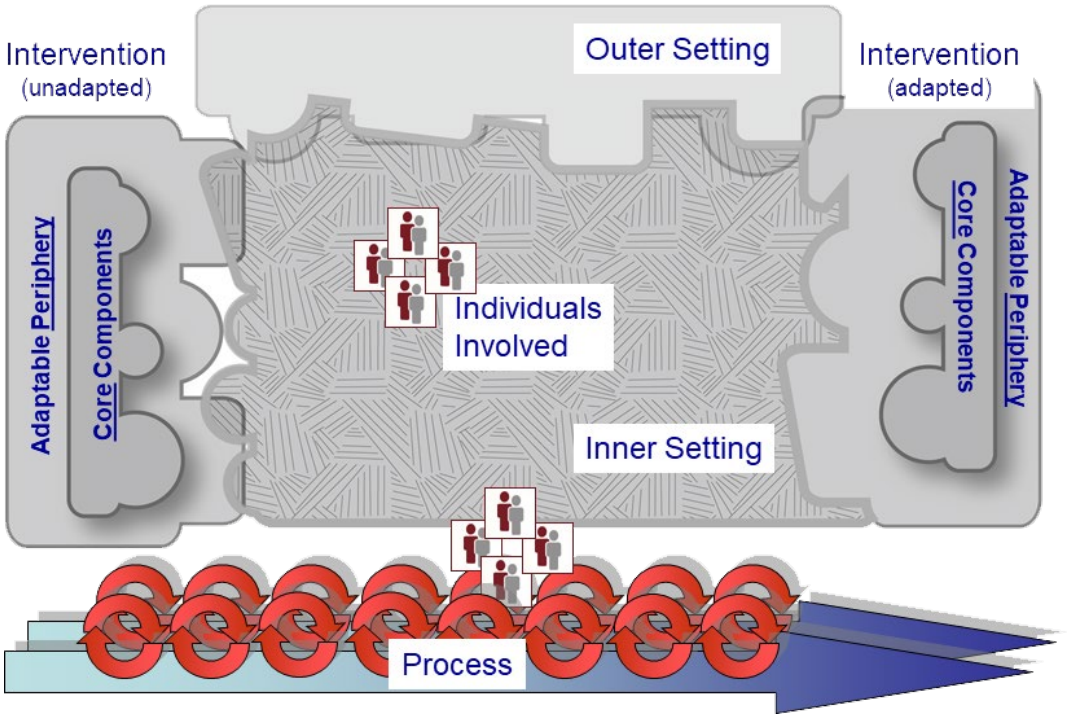

Figure 1.5 Domains of the Consolidated Framework for Implementation Research (CFIR) (from https://cfirguide.org/)

1.11.3 Assessing the quality indicators for AMS programmes

It is important to know what QIs are available, and to have an insight into their characteristics and methodological quality to support stakeholders in selecting the right indicators for their quality purpose and to prevent the development of new indicators for quality domains which are already covered sufficiently. It is likely that some variability exists in the development of QIs despite the criteria for the development of QIs and key quality requirements being well established. The overview will identify shortcomings in the existing QI sets along with giving guidance for further development or improvement.

The Appraisal of Indicators through Research and Evaluation (AIRE) Instrument (109) is a validated instrument designed to appraise the quality of QIs (110) and has been used in several similar studies (111-113). The AIRE instrument is divided into four quality domains of a QI and consists of 20 criteria which are applied to each complete set of QIs. Three domains address the methodological quality of QIs: 'Stakeholder involvement', 'Scientific evidence' and 'Additional evidence, formulation and usage'. The fourth domain: 'Purpose, relevance and organisational context' reflect the relevance of the QIs within a particular context rather than

methodological quality. Table 1.3 presents the domains and items of the AIRE instrument.

Table 1.3 Appraisal of Indicators through Research and Evaluation (AIRE) domains and items (109)

AIRE domain	AIRE items
Purpose, relevance and organisational context	1. The goal of the study has been clearly described
	2. The publications rationale for measures development has been clearly described
	3. The organizational context of the measures has been described in detail (about whom does the measure provide information
	4. The quality domains that the measures address have been described in detail
	5. The healthcare process covered by the measures has been described and defined in detail
Stakeholder involvement	6. The group developing the indicator includes individuals from relevant professional groups
	7. Considering the purpose of the indicator, all relevant stakeholders have been involved at some stage of the development process
	8. The indicator has been formally endorsed
Scientific evidence	9. Systematic methods were used to search for scientific evidence
	10. The indicator is based on recommendations from an evidence-based guideline or studies published in peer-reviewed scientific journals
	11. The supporting evidence has been critically appraised
Additional evidence, formulation, usage	12. The numerator and denominator are described in detail
	13. The target patient population of the indicator is defined clearly
	14. A strategy for risk adjustment has been considered and described (‘case-mix adjustment’)
	15. The indicator measures what it is intended to measure (validity)
	16. The indicator measures accurately and consistently (reliability)
	17. The indicator has sufficient discriminative power
	18. The indicator has been piloted in practice
	19. The efforts needed for data collection have been considered
	20. Specific instructions for presenting and interpreting the indicator results are provided

1.11.4 Time Series Analysis of AC and AMR

Temporally sequenced observations of AC and AMR data are not independent so the application of simple regression analysis would be inappropriate (114). Time series analysis (TSA) has been used to investigate possible correlations between AC and AMR where the data are measured repeatedly at equal intervals of time (114-116). In contrast to other statistical methods, TSA considers that a possible relationship exists between consecutive observations of a variable rather than assuming that the observed data are realisations of independent random variables (117). The Box–Jenkins method of TSA modelling provides a practical method to analyse the temporal behaviour of a given variable, expressed as a function of its previous values, trends and abrupt changes in the recent past (117). TSA methodology is also recommended by the Outbreak Reports and Intervention studies of Nosocomial infection (ORION) statement which aimed to improve the standards of research and publications in the area (118).

The analysis of the trends and possible relationships between AC and AMR data was conducted using TSA (Chapter 5).

1.12 Philosophical paradigm

The choice of research methods used in this thesis were determined by the research aims in Chapters two, three, four and five and this approach is underpinned by a pragmatic research philosophy. Pragmatic research *"answers important questions about how an intervention can be used in actual clinical care"* (119).

Pragmatic research is particularly applicable to the clinical practice setting because it contains a specific focus on the effective adoption, implementation and maintenance of evidence-based interventions into practice (120) while also considering contextual influences on an intervention (119). The research aims and methods applied in each chapter were:

Chapter two: To determine if PCT testing is an effective and worthwhile intervention to introduce in a University Teaching Hospital to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs. A randomised feasibility method (96) was used based on the MRC

recommendations (95) aligning with the effective adoption of evidence-based interventions into practice (120) of pragmatic research.

Chapter three: To explore how and why the introduction of a PCT intervention worked or did not work in an Irish hospital setting. A qualitative process evaluation was conducted based on MRC recommendations (95) using the CFIR to investigate the organisational context and influences on the intervention (105). This research method is further supported by the definition of a pragmatic, formative process evaluation as *"the application of formative PE criteria to interventions that have ostensibly been formulated, and are likely in routine practice, but have not been subjected to rigorous scientific development and evaluation"* (121).

Chapter four: To identify existing QIs of AMS programmes in the hospital setting, describe the methodological approaches used in their development, differentiate between the types of indicators (structure, process or outcome), and critically appraise the methodological quality of the identified QI sets. A systematic review was conducted and critical appraisal of the methodological quality of the identified QI sets was conducted using the validated AIRE Instrument (109, 110). This allowed for consideration of the appropriateness or practical application of the QI sets to inform AMS programmes; a pragmatic research approach.

Chapter five: To investigate the trends and possible relationships between AC and AMR in Enterobacterales species, and the proportion of *E. faecium* isolates resistant to vancomycin, between 2017-2020 in an Irish hospital setting. TSA was used in this study as it was a pragmatic approach to the application of the most appropriate form of statistical analysis of the available data (117) and was supported by the ORION statement (118).

1.13 Research team

The research studies contained in Chapters two and five were conducted in the Mercy University Hospital where I work as an Antimicrobial Pharmacist. In addition to my PhD supervisors from a Pharmacy and Public Health background, these research studies involved collaboration with a wider research team including statisticians, Consultant-led medical teams and laboratory scientists. I was the primary researcher for both studies, coordinating and conducting the research.

The co-authors and collaborators for Chapter two were:

Dr Deirdre O'Brien, Consultant Microbiologist in the MUH and head of the microbiology laboratory where the PCT testing was conducted. She collaborated in sourcing research funding from the Cork Kerry SARI committee to conduct the research and negotiated the placement of the BioMeriux miniVIDAS PCT testing instrument for the duration of the study and staff training. She was involved in conveying the PCT results and prescribing recommendations to the respiratory teams in my absence. She reviewed the study manuscript prior to submission for publication.

Statistical analysis for Chapter two was supported by Dr Brendan Palmer and Dr Darren Dahly from the UCC Clinical Research Facility Cork. They reviewed the study manuscript prior to submission for publication.

Dr Terry O'Connor and Dr David Curran are Consultant Respiratory Physicians in the MUH and participated in the PCT study. They reviewed the study manuscript prior to submission for publication.

The co-authors and collaborators for Chapter five were:

Dr Deirdre O'Brien and Dr Aoife Ronayne, both Consultant Microbiologists in the MUH, where the AMR data was sourced. Both reviewed the study manuscript prior to submission for publication.

1.14 Thesis aims and objectives

Aim

The overall aim of this research thesis was to investigate opportunities to measure and improve the delivery of AMS programmes in the Irish hospital setting.

Objectives

The objectives of research were:

1. To investigate Procalcitonin testing as an AMS programme intervention:
    - To conduct a feasibility study of the implementation of PCT as an intervention to support the AMS programme in an Irish hospital setting in patients admitted with a RTI.
    - To conduct an in-depth qualitative process evaluation of the PCT intervention examining the implementation process and to determine the barriers and facilitators to the implementation of PCT as an AMS intervention in an Irish hospital setting.

2. To review opportunities to measure the quality of AMS programmes and the possible influence of AC on gram negative resistance rates and rates of VRE:
    - To conduct a detailed systematic review of quality indicators for hospital AMS programmes and critically appraise their methodological qualities.
    - To investigate the trends in AC and AMR, and to explore possible associations between antimicrobial consumption data and antimicrobial resistance data.

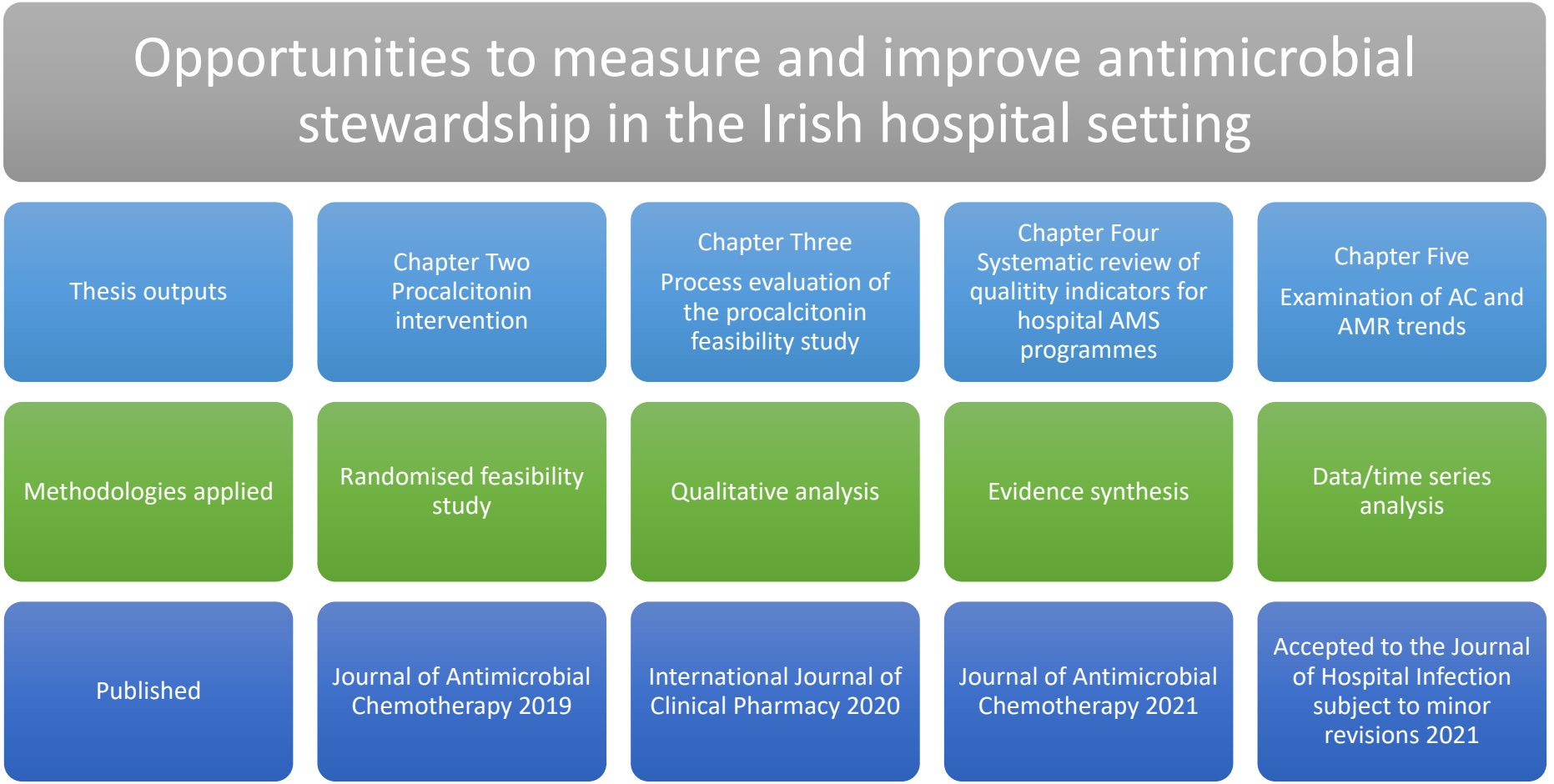

Figure 1.6 Overview of studies conducted as part of this thesis

Chapter 2 An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish University Hospital setting - a feasibility study

Authors

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2.1 Abstract

Synopsis

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for respiratory tract infections (RTIs). Procalcitonin (PCT) has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs but recent study results have been variable.

Methods

We conducted a feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI to determine if PCT testing is an effective and worthwhile intervention to introduce to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

Results

A total of 79 patients were randomised to the intervention PCT guided treatment group and 40 patients to the standard care respiratory control group.

The addition of PCT testing led to a significant decrease in duration of antimicrobial prescriptions (mean 6.8 versus 8.9 days p=0.012) and decreased length of hospital stay (median 7 versus 8 days, p=0.009) between the PCT and respiratory control group. PCT did not demonstrate a significant reduction in antimicrobial consumption when measured as DDDs and days of therapy.

Conclusions

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. The successful implementation of PCT testing in a randomised controlled trial requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomised controlled trial would be beneficial to further explore the positive aspects of these findings.

2.2 Introduction

Antimicrobial resistance (AMR) is a major risk to public health globally that leads to increasing healthcare costs, treatment failure, and increased morbidity and mortality (1, 9, 10). There is a strong association between sub-optimal antimicrobial prescribing and AMR (122). To optimise prescribing, hospital antimicrobial stewardship (AMS) programmes should target areas of high antimicrobial prescribing. One such area is respiratory tract infections (RTIs). Shorter antimicrobial courses offer one potential solution to the overuse of antimicrobials for RTIs (123) and there is evidence to support such strategies (124, 125) even in severe hospital infections (126).

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for RTIs (127-130). This contributes to over-use and/or sub-optimal use of antimicrobials (131, 132) for RTIs such as community acquired pneumonia (CAP), including prolonged treatment courses of up to 11 days (133), without a correlation between duration of treatment and infection severity (133, 134). Physicians are often reluctant to shorten antimicrobial course durations due to the fear of incomplete pathogen eradication which could potentially lead to relapse and associated morbidity and mortality (124). There is also a high rate of antimicrobial continuation where viral infections (135), including influenza (136), are identified due to overriding concerns about secondary bacterial infections. However, a recent study has shown a bacterial co-infection rate of only 40% (129).

To address these issues, there is a growing interest in the use of novel diagnostic techniques and biomarkers as an AMS tool (70). It is important that AMS programmes investigate the opportunity afforded by these new techniques and the potential they offer to optimise antimicrobial treatment more promptly (66) and change prescribing behaviour (67). Procalcitonin (PCT) testing is one such diagnostic technique. PCT is a peptide precursor to the hormone calcitonin. It is usually undetected but is upregulated in response to a bacterial infection following stimulation of bacterial-induced cytokines (137). Upregulation of PCT is blocked in viral infections due to the release of the cytokine interferon gamma, resulting in a higher specificity of PCT to distinguish between bacterial and viral infections when compared to other inflammatory markers such as CRP (138). PCT levels decrease rapidly when patients

are recovering from infection (139). Hence it offers the potential to support clinical decision making for the initiation and discontinuation of antimicrobials in patients with a clinical suspicion of a bacterial infection when considered along with the clinical assessment of the patients. PCT has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs (74-77) but findings from recent studies have been variable (140, 141), so it is unclear if it is an effective intervention as part of an AMS programme.

The purpose of this study was to conduct a feasibility study to determine if PCT testing is an effective and worthwhile intervention to introduce in a University Teaching Hospital to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

2.3 Methods

We conducted a single centre, randomised, open-label feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI under the care of the respiratory medicine team during on-call acute unselected general medical take to determine if PCT testing had an impact on antimicrobial consumption and patient's length of stay (LOS) in hospital. The study was conducted in a single 321 bed inner city, voluntary acute University Teaching Hospital, which is part of the South/South West Hospital Group (142) in the Republic of Ireland. It is a Model 3 (smaller general) (143) hospital with a 24-hour emergency department, ICU and admits undifferentiated acute medical and surgical patients. The hospital has an established AMS programme, and no significant changes were made to the AMS policies or programme during this study.

2.3.1 Ethics

The study was approved by the local ethics committee (approval code ECM 4 (w) and ECM 3 (III)) (Appendix 1). Written informed consent was obtained from all participants prior to study enrolment.

2.3.2 Education and training

The microbiology laboratory scientists received technical advice and training on the operation of the PCT assay from the manufacturer prior to study commencement. They also received a presentation on the introduction of PCT testing in the hospital.

The respiratory medicine team received presentations at the respiratory journal club meetings and provision of written materials electronically. Presentations consisted of evidence supporting PCT use in practice, limitations of PCT testing, PCT measurement, and interpretation using a PCT-based antimicrobial prescribing algorithm (Appendix 2). Presentations (Appendix 3) were given prior to the study commencement and following medical staff rotation changes. The study protocol, study flow chart and the PCT-based antimicrobial prescribing algorithm was provided to all participating physicians electronically.

2.3.3 Recruitment and consent

Inclusion criteria

Adult patients ≥18 years of age, admitted to hospital under the care of the respiratory teams with an initial diagnosis of an acute lower RTI [i.e. Community acquired pneumonia (144) with severity defined by CURB-65 score (145), Lower RTIs (146), exacerbation of asthma (147), COPD (148), bronchiectasis (149), interstitial lung disease (150) and influenza (146)] and commenced on antimicrobial therapy were identified from the daily admission census or by the respiratory medicine teams.

The randomisation process stratified patients according to presence or absence of severe COPD GOLD Stage D criteria 2017 (148) to ensure balanced treatment allocation. Patients were then randomly allocated in a 2:1 ratio to either the PCT guided treatment group or the standard care respiratory control group. Randomisation was carried out using sequentially numbered opaque sealed envelopes. A second general control group of patients admitted under general medicine teams with a diagnosed acute lower RTI and received standard care (no PCT measurement) was recruited to provide a comparison of antimicrobial prescribing in RTIs by non-respiratory specialist physicians in the hospital.

Exclusion Criteria

Exclusion criteria were: unable to give written informed consent due to language restrictions, cognitive impairment or severe dementia; re-admission to hospital within

30 days of previous admission; immunosuppression (neutropenic, chemotherapy, radiation therapy or immunosuppressive therapy) other than corticosteroid use; life-threatening medical co-morbidities leading to possible imminent death, Do Not Resuscitate (DNR) status; patients with concurrent chronic infections necessitating prolonged antimicrobial treatment (cystic fibrosis, tuberculosis, infective endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis); patients with >24 hours of appropriate antimicrobial therapy prior to initial PCT level; active intravenous drug users; pregnant women.

2.3.4 Intervention

PCT testing was commenced in the microbiology department following completion of staff training and instrument validation. It was available during routine working hours (Monday to Friday, 9am-5pm). PCT serum concentrations were measured using the VIDAS BRAHMS PCT (assay range 0.05-200 µg/L) (Biomerieux, France).

PCT serum concentrations were interpreted using an evidence-based algorithm (Appendix 2) (151) which has been validated in previous studies (77, 140) recommending antimicrobials strongly discouraged for PCT levels < 0.1 µg/L, discouraged for levels 0.1 to 0.25 µg/L, encouraged for levels > 0.25 to 0.5 µg/L and strongly encouraged for levels > 0.5 µg/L. The algorithm also included specific overruling criteria where antimicrobials could be considered in the case of respiratory or haemodynamic instability; life-threatening co-morbidity; need for ICU admission; PCT < 0.1 µg /mL: CAP with CURB 65 > 3, COPD stage IV; PCT < 0.25 µg/mL: CAP with CURB 65 > 2; localised infection (abscess, empyema); immunocompromised (other than corticosteroids); concomitant infection in need of antimicrobials.

The antimicrobial prescribing advice generated from the PCT algorithm was verbally communicated to the respiratory medicine team and this advice was non-binding. The respiratory medicine team retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm generated antimicrobial prescribing advice. The algorithm adherence for antimicrobial prescribing recommendations was recorded at 24 hours following the PCT test for all patients along with the rational for prescribing decisions. Algorithm adherence was defined as antimicrobial therapy that

was continued or discontinued in accordance with the PCT cut-off ranges. Non-adherence was defined as antimicrobial therapy that was not discontinued despite low PCT levels. Over-riding criteria were not considered when measuring adherence but were recorded as reasons for non-adherence.

Patients were followed until their discharge. A further follow up of medical records took place at 30 days post admission to identify re-admitted patients and re-admitted patients with infection re-lapse.

Patient recruitment ran from June 1st 2017 to May 31st 2018. Figure 2.1 represents the patient hospital journey with an RTI.

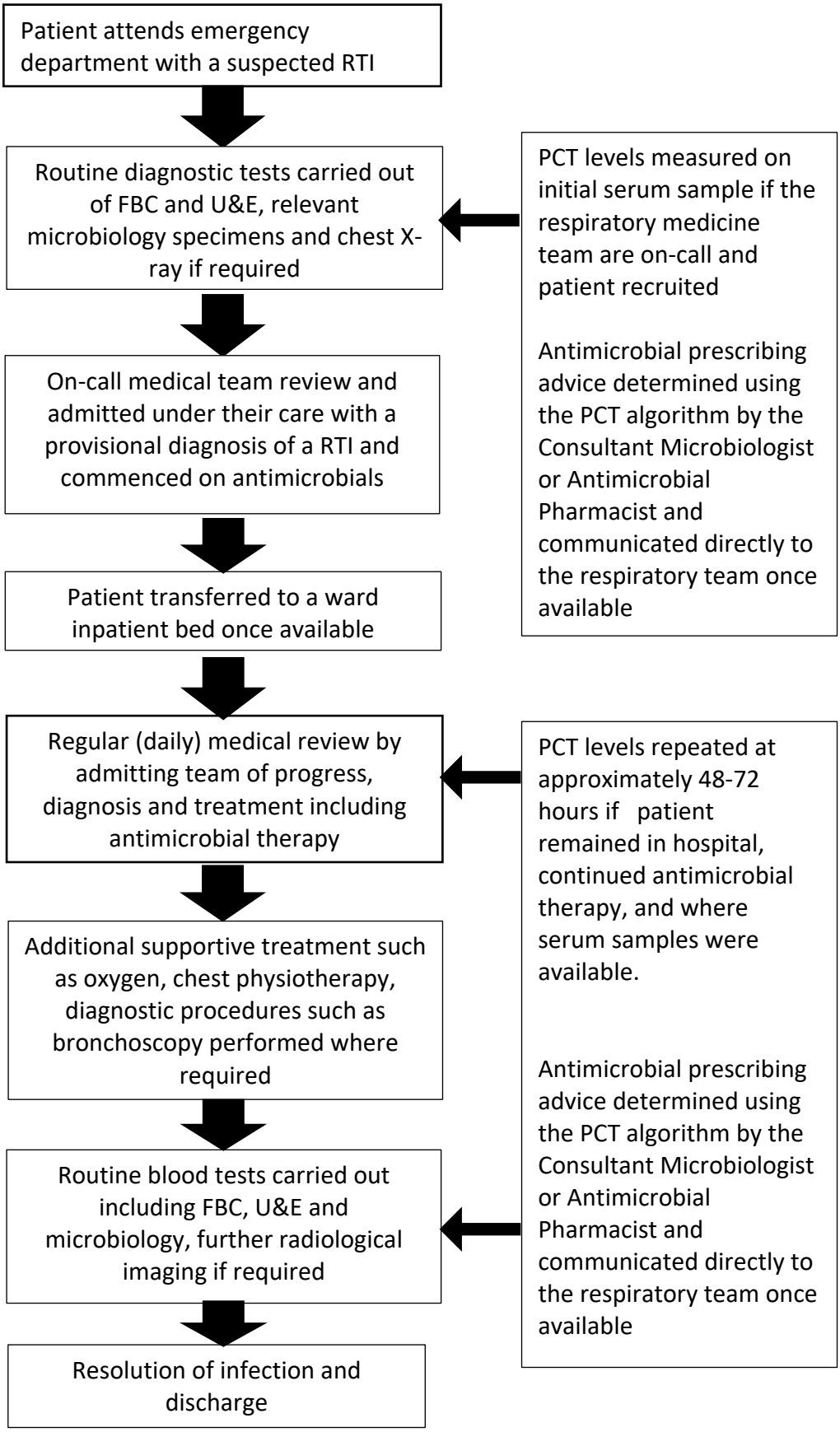

Figure 2.1 Patient hospital journey with a respiratory tract infection. RTI Respiratory tract infection, PCT: procalcitonin, FBC: full blood count, U&E: urea and electrolytes

2.3.5 Outcomes

The primary outcomes were to quantify the individual inpatient antimicrobial consumption, prescription duration and the inpatient LOS. Following a recent systematic review which recommended that antimicrobial use should be expressed in at least two metrics simultaneously (152), antimicrobial consumption was measured using DDDs, days of therapy (DOTs) and prescription duration. DDDs were calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index of the WHO Collaborating Centre for Drug Statistics Methodology (55) but were not adjusted for hospital activity. Days Of Therapy (DOT) (58) calculates individual patient-days of antimicrobial exposure and accounts for dosing and frequency of each drug. Antimicrobial prescription duration was measured in days (defined as the number of days between the commencement and discontinuation of antimicrobials). The LOS was defined as date of discharge less date of admission.

Secondary outcomes were number of infection and antimicrobial related adverse events during inpatient LOS including mortality, hospital re-admission, and infection re-lapse requiring re-admission both within 30 days. Algorithm adherence for antimicrobial prescribing recommendations was measured.

A qualitative process evaluation of the study was conducted in parallel with this feasibility study and will be reported in a subsequent paper.

2.3.6 Statistical methods

A Microsoft Access database (version 1903) was developed to record the study data. Statistical analysis was conducted using R (version 3.4.0) and was conducted on an intention to treat basis.

The primary outcome of antimicrobial consumption between the PCT and respiratory control arms was evaluated using the non-parametric Wilcoxon Rank Sum test. A Kaplan-Meier curve was used to analyse the median time to discharge between the PCT and respiratory control group.

Chi-square tests were used to evaluate differences between the PCT and respiratory control arms for all secondary outcomes - number of adverse events, re-admission and infection re-lapse requiring re-admission both within 30 days.

2.4 Results

The respiratory medical teams admitted 823 general medical patients of whom 313 patients were classified as a respiratory infection or respiratory disorder during the recruitment period of June 1st 2017 to May 31st 2018. A CONSORT flow diagram of recruitment can be seen in Figure 2.2.

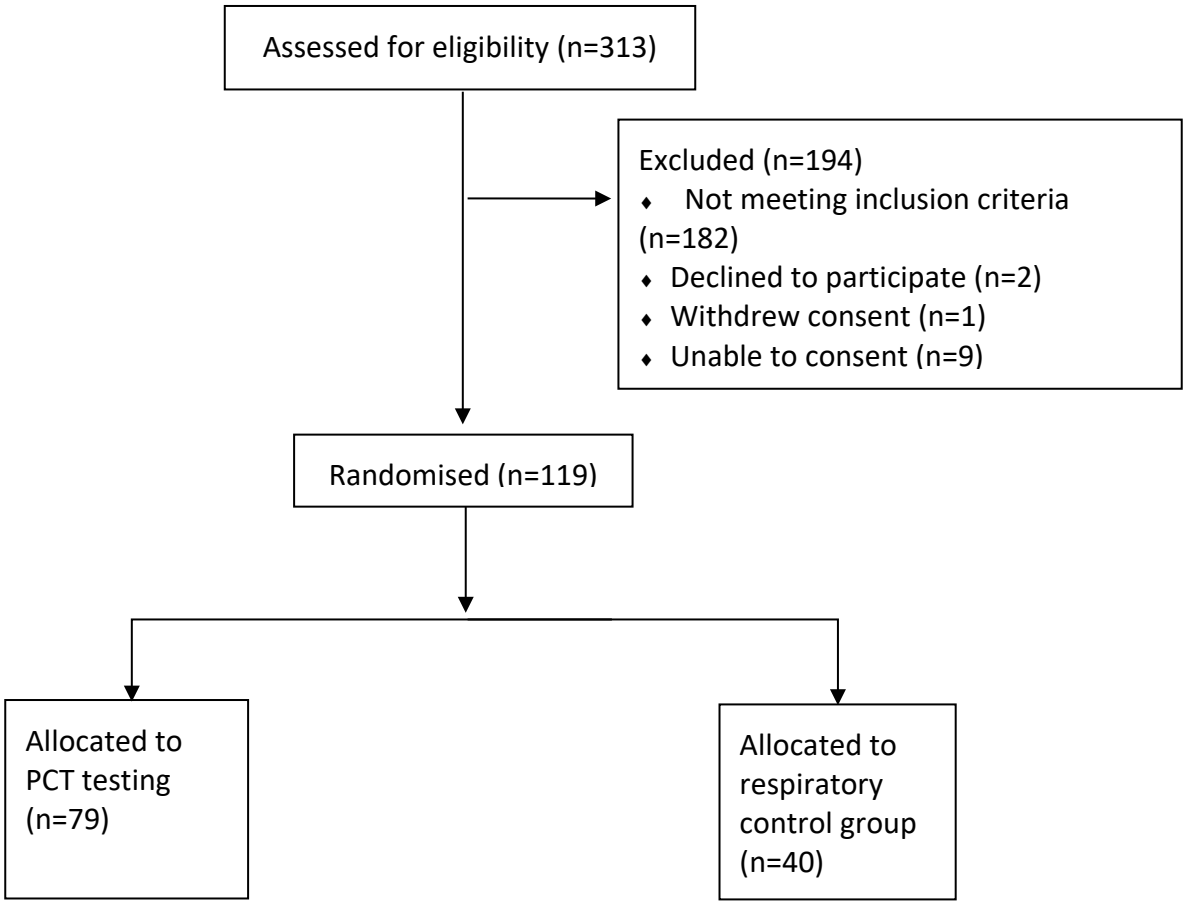

Figure 2.2 CONSORT 2010 Flow Diagram

A further 48 patients were recruited to the general control group. Three patients who were identified as suitable to enter the general control group were not recruited due to confusion, isolation due to infection and refused consent.
Demographic data and study overview are contained in Table 2.1. Clinical findings of patients on admission to hospital are contained in Table 2.2.

There were several differences between the baseline characteristics of the PCT group and respiratory control group. The PCT group contained more male patients (60% versus 42%), active smokers (25% versus 12.5%) and patients with pre-existing COPD A-C (29% versus 25%).

There were several differences in final diagnosis between the PCT group and the respiratory control group with asthma (3.4% versus 15%), CAP (16.6% versus 7.5%), LRTI (35% versus 17.5%. CAP severity in the PCT group had CURB-65 scores ranging from 0 to 3 with a mean of 1.87 while the CAP severity in the respiratory control group had CURB-65 scores ranging from 0 to 1 with a mean of 0.66.
The clinical findings on admission were similar between groups with two exceptions where the PCT group had a higher percentage of patients who were productive of sputum on admission (49% versus 37%) and patients prescribed antibiotics prior to admission (35% versus 25%).

Table 2.1 Demographic data and study overview

Variable		Study Group			
		Overall	PCT arm	Respiratory Control arm	General Control arm
Participants n (%)		167 (100%)	79 (47.3%)	40 (24.0%)	48 (28.7%)
Gender	**Female**	79 (47.3%)	31 (39.2%)	23 (57.5%)	25 (52.1%)
	Male	88 (52.7%)	48 (60.8%)	17 (42.5%)	23 (47.9%)
Age (years) Mean ± SD		68.7 ± 14	68.6 ± 13.6	68.4 ± 15.3	69.1 ± 13.9
Co-existing conditions and risk factors					
Smoking Status	**Non-smoker**	50 (30.3%)	26 (32.9%)	13 (32.5%)	11 (23.9%)
	Smoker	33 (20%)	20 (25.3%)	5 (12.5%)	8 (17.4%)
	Ex-smoker	82 (49.7%)	33 (41.8%)	22 (55%)	27 (58.7%)
Asthma		28 (16.8%)	13 (16.5%)	10 (25%)	5 (10.4%)
COPD A-C		58 (34.7%)	23 (29.1%)	10 (25%)	25 (52%)
COPD D		24 (14.4%)	10 (12.7%)	5 (12.5%)	9 (18.8%)
Bronchiectasis		16 (9.6%)	9 (11.4%)	3 (7.5%)	4 (8.3%)
Interstitial lung disease		7 (4.2%)	4 (5%)	2 (5%)	1 (2.1%)
Final diagnosis					
Asthma		11 (6.6%)	3 (3.4%)	6 (15%)	2 (4.2%)
Community acquired pneumonia		18 (10.8%)	8 (16.6%)	3 (7.5%)	7 (14.6%)
COPD		62 (37.1%)	24 (30.4%)	13 (32.5%)	25 (52%)
Lower respiratory tract infection		45 (27%)	28 (35%)	7 (17.5%)	10 (20.8%)
Other lower respiratory tract infections		20 (11.4%)	10 (12.6%)	7 (17.5%)	3 (6.2%)
Non-respiratory related		11 (6.6%)	6 (7.6%)	4 (10%)	1 (2.1%)

Table 2.2 Clinical findings on admission to hospital (values shown as means +/- SD unless otherwise stated)

	Total (n = 167)	PCT (n = 79)	Respiratory Control (n = 40)	General control (n = 48)
Respiratory rate- breaths/minute	22.1 ± 5	22.1 ± 5.4	21.1 ± 3.7	22.7 ± 5.2
Systolic blood pressure- mmHg	133 ± 23.1	130.9 ± 22.9	136 ± 20.9	134 ± 25
Diastolic blood pressure- mmHg	75 ± 14.1	74.8 ± 12	78.6 ± 14.8	72.3 ± 16.1
Heart rate- beats/minute	91.8 ± 20.1	93.4 ± 23.3	91.2 ± 16.7	89.8 ± 16.7
Temperature- °C	36.8 ± 0.8	36.8 ± 0.8	36.9 ± 0.8	36.8 ± 0.9
Rigors - no. (%)	24 (14.4%)	11 (13.9%)	6 (15%)	7 (14.6%)
Fever - no. (%)	18 (10.8%)	8 (10.1%)	5 (12.5%)	5 (10.4%)
Chills - no. (%)	15 (9%)	10 (12.7%)	1 (2.5%)	4 (8.3%)
Number of clinical signs of infection	1.8 ± 1.3	1.9 ± 1.3	1.7 ± 1.2	1.8 ± 1.3
Documented signs of respiratory illness				
Cough - no. (%)	132 (79%)	64 (81%)	31 (77.5%)	37 (77%)
Shortness of breath - no. (%)	101 (60.5%)	45 (57%)	23 (57.5%)	33 (68.7%)
Productive of sputum - no. (%)	81 (48.5%)	39 (49.4%)	15 (37.5%)	27 (56.2%)
Dyspnoea - no. (%)	49 (29.3%)	22 (27.8%)	10 (25%)	17 (35.4%)
Pleuritic pain - no. (%)	26 (15.6%)	10 (12.7%)	9 (22.5%)	7 (14.6%)
Respiratory failure - no. (%)	19 (11.4%)	8 (10.1%)	5 (12.5%)	6 (12.5%)
Abnormal chest exam - no. (%)	144 (86.2%)	70 (88.6%)	31 (77.5%)	43 (89.6%)
Abnormal radiological findings - no. (%)	94 (56.3%)	42 (53.2%)	21 (52.5%)	28 (58.3%)
CURB-65 score (CAP patients)	1.56 ± 1.05	1.87 ± 1.05	0.66 ± 0.47	1.57 ± 1.05
Number of signs of acute respiratory illness	3.9 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	4 ± 1.3
Antimicrobials prescribed pre-admission - no. (%)	59 (35.3%)	28 (35.4%)	10 (25%)	21 (43.7%)
Corticosteroids prescribed pre-admission - no. (%)	34 (20.4%)	14 (17.7%)	7 (17.5%)	13 (27%)
Infection source				
Community - no. (%)	149 (89.2%)	70 (88.6%)	32 (80%)	47 (98%)
Healthcare - no. (%)	13 (7.8%)	6 (7.6%)	6 (15%)	1 (2%)
Hospital - no. (%)	5 (3%)	3 (3.8%)	2 (5%)	0 (0%)

2.4.1 Procalcitonin testing and results

The 79 patients randomised to the PCT group had a total of 163 PCT levels taken (median of 2 tests per patient (range 1-6). Overall the PCT levels had a median of 0.075µg/L (IQR 0.05 – 0.26). The initial PCT level was ≤0.24 µg/L for 58 patients (including 38 patients with an initial PCT level of ≤0.05 µg/L). Our primary outcome was to determine the inpatient antimicrobial consumption, duration of antimicrobial treatment and hospital LOS. The main outcomes can be seen in Table 2.3 and Figure 2.3. Statistical analysis was conducted on the PCT and respiratory control groups and does not include comparison with the general control group.

Table 2.3 Primary and secondary outcome data

Primary outcomes Mean ± SD (Median)	**PCT (n = 79)**	**Respiratory Control (n = 40)**	**General control (n = 48)**	**p value**
Defined daily doses per patient	11.1 ± 7.5 (8.66)	13.1 ± 10.7 (9.57)	18.5 ± 11 (16.5)	0.218
Days of therapy per patient	8.9 ± 6.3 (7.5)	11 ± 7.6 (8.25)	13.7 ± 11.1 (11.63)	0.077
Total duration of inpatient antimicrobials (days)	6.8 ± 2.8 (7)	8.9 ± 4 (8)	8.4 ± 3.6 (8)	0.0125*
Length of hospital stay (days)	7.4 ± 4.3 (7)	10.5 ± 6.1 (8)	8.9 ± 3.8 (8)	0.009*
Secondary outcomes n (%)				
Hospital readmission within 30 days	7 (8.9%)	8 (20%)	7 (14.6%)	0.1507
Relapse of infection within 30 days	6 (7.6%)	8 (20%)	6 (12.5%)	0.0924
Adverse events	6 (7.6%)	3 (7.5%)	4 (8.3%)	0.9852

*= statistical significance was set as <0.05, p-values relate to the comparison between the PCT and respiratory control groups

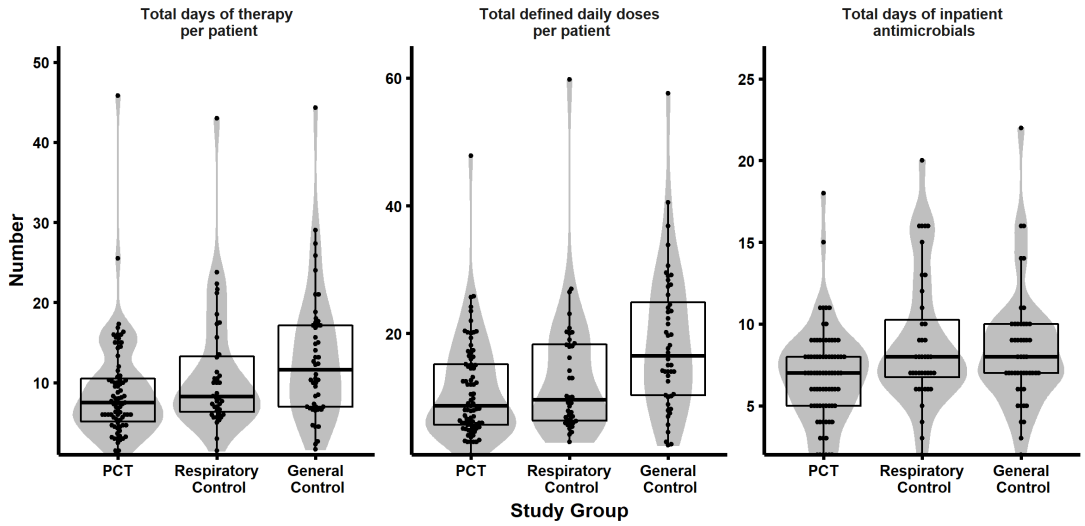

Figure 2.3 Main antimicrobial consumption outcomes.

There was no significant difference in antimicrobial exposure or usage per patient when measured as DDD (11.1 ± 7.5 versus 13.1 ± 10.7, p=0.218) (mean ± SD) or DOT (8.9 ± 6.3 versus 11 ± 7.6, p=0.077) of patients between the PCT and respiratory control group. Median values of both metrics DDD (8.66 versus 9.57) and DOT (7.5 versus 8.25) showed a decrease of 9% in antimicrobial consumption per patient.

There was a significant difference in the antimicrobial duration in days between the PCT and respiratory control groups (median 7 versus 8 days, p=0.0125). There was also a significant difference between the PCT and respiratory control groups in the median LOS (p=0.009) and this can also be seen in the Kaplan–Meier curves in Figure 2.4.

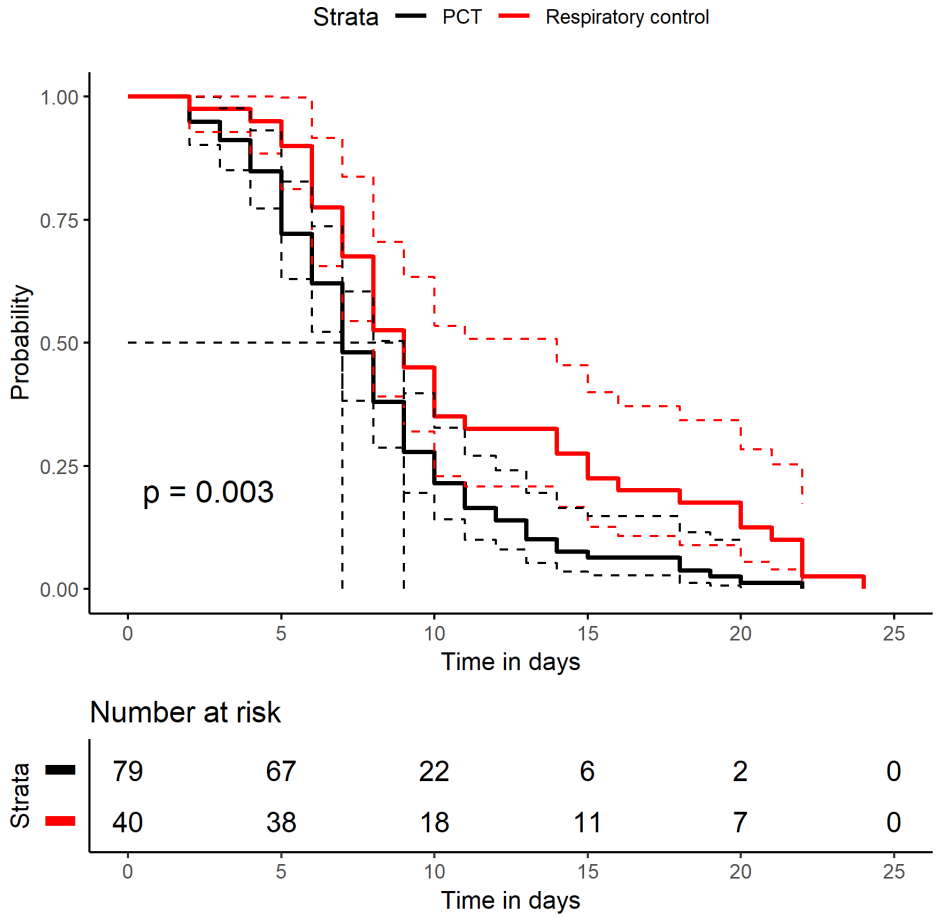

Figure 2.4 Comparison of time to discharge probability for PCT versus respiratory control arms-Kaplan–Meier curves. Median probability of discharge is given by the horizontal dashed line. The grey and black lines show the 95% CIs

In the analysis of secondary outcomes there was no significant differences between the PCT and respiratory control groups in the incidence of adverse events during inpatient hospital stay (p=0.9852), the rate of hospital re-admission (p=0.1507), and the rate of infection re-lapse requiring re-admission both within 30 days (p=0.0924). Algorithm compliance is displayed in Table 2.4.

Table 2.4 PCT algorithm compliance

PCT level (μg/L)	Algorithm recommendation	Number of patients	Number of PCT test results	Number of patients compliant with algorithm	Number of patients non-compliant with algorithm	Percentage of patients compliant with algorithm
≤0.05 to <0.25	Antimicrobial therapy discouraged	67	119	7	60	10%
≥0.25	Antimicrobial therapy encouraged	25	44	25	0	100%

Overall PCT algorithm compliance per patient was 35% within 24 hours of PCT level being taken. Twenty five patients had high PCT levels (≥ 0.25μg/L) where the algorithm recommendation was to continue antimicrobial treatment and algorithm compliance was 100%. Sixty seven patients had low PCT levels (< 0.25μg/L) where the algorithm recommendation was to discontinue antimicrobial treatment and algorithm compliance was low (10%). In these instances, the reasons for non-adherence were based on a clinical decision in 55/112 (49%) PCT levels with the remaining 57/112 (51%) PCT levels based on meeting various algorithm overriding criteria [respiratory or haemodynamic instability; life threatening co-morbidity; need for ICU admission; localised infection (abscess, empyema)].

Seven patients had their antimicrobial treatment discontinued in compliance with the algorithm when PCT levels were low (< 0.25μg/L). This resulted in shorter course lengths in five patients (< 7 days) one course length completion as planned at 7 days, and early antimicrobial discontinuation (day 2) in a patient with influenzae. There were no hospital readmissions among these patients.

In a further nine patients where there was initial non-compliance with the algorithm recommendations when measured at 24 hours, their antimicrobial treatment was

subsequently modified resulting in a shorter course length in seven patients (< 7 days) and two further patients discontinued antimicrobials prior to discharge (one patient re-admitted with infection).

Algorithm compliance by indication was as follows; CAP (80%), asthma (50%) LRTI (30%), COPD (12.5%) and influenza virus (42%). PCT levels and algorithm compliance were found to be low in patients with COPD stage D and structural lung conditions like bronchiectasis and interstitial lung disease. In these cases, the clinical judgement of physicians was to over-ride the algorithm recommendations and continue antimicrobials.

2.4.2 Microbiology positive specimens

38 patients (23%) had positive microbiology results: 13 influenzae virus, 10 bacterial isolates from respiratory specimens and 7 yeast isolates from respiratory specimens.

2.4.3 Adverse events

Infection and antimicrobial related adverse events included gastro-intestinal (antimicrobial related diarrhoea one patient) renal function (acute kidney injury secondary to antimicrobials one patient), liver function (increased liver function tests secondary to antimicrobials one patient), respiratory disorders (hospital acquired pneumonia, hospital acquired influenzae, respiratory deterioration, three patients) and other events two patients.

2.4.4 Mortality during the study

Five patients included in the study died during their hospital stay, four from the PCT group and one from the respiratory control group (age range 75-94 years). All had multiple co-morbidities including cardiac (congestive cardiac failure, atrial fibrillation), renal and new or existing cancer diagnosis. Antimicrobial treatment decisions for these patients were based on clinical decisions.

2.5 Discussion

This feasibility study of the introduction of PCT testing has shown a positive effect on antimicrobial prescribing resulting in a decrease in the duration of antimicrobial courses in patients with RTIs and a decrease in LOS without an increase in adverse events or re-admission to hospital. The median duration of antimicrobial treatment was reduced from 8 to 7 days and antimicrobial consumption fell by 9% when measured as DDD and DOT. This study confirms the findings of previous PCT trials (77, 153) that it is an effective and worthwhile intervention to safely reduce antimicrobial exposure in patients with RTIs and supporting the AMS programme. However, there were several findings which may have influenced the outcomes and these need to be considered when viewing the overall results and considering progression to and design of a full randomised controlled trial (RCT).

Overall PCT algorithm compliance was 35%, and compliance with stopping recommendations was 10% when PCT levels were low (<0.25 μg/L). The reasons for non-compliance were clinical judgement (49%) and meeting pre-determined over-riding criteria (51%). PCT was a new diagnostic test in the hospital and physicians can require time to become familiar with and develop confidence in the use of PCT testing (154). Other studies have found algorithm compliance can be variable ranging from 35% to 80% (153). An international, multicentre study found that centres with experience of using PCT and ongoing reinforcement of PCT guided AMS had higher algorithm compliance than PCT naive centres (153). Protocol driven studies (77, 155) have also shown higher algorithm compliance and greater impact on antimicrobial prescriptions than studies taking a quality improvement implementation approach (140).

Algorithm compliance must improve significantly in a future trial to maximise the potential impact of PCT testing on antimicrobial prescribing decisions but also acknowledging the limitations of PCT and that physicians cannot rely on PCT alone to guide antibiotic therapy (138). In a future trial this should be addressed by a more comprehensive educational programme and more effective incorporation into the AMS programme to re-enforce PCT recommendations. Such an approach has been shown to be effective (141, 155, 156) and required for interventions such as PCT to

realise their full benefit (70). The educational element of this study may not have been sufficient. A future trial should consider the inclusion of more frequent educational presentations prior to and during the intervention and include case reviews of PCT patients. Consideration should be given to the development of pocket cards, incorporation into local electronic antimicrobial prescribing guidelines and availability of results on the hospital electronic laboratory system (155).

Delays in availability of PCT results may have also decreased the impact of the intervention and contributed to poor algorithm compliance with 38% of PCT serum results not available until the next day (24 hours after the serum sample was taken). This included results which were delayed or unavailable for 12 patients until after they were discharged. In a future trial prompt availability of PCT levels is important. This would allow physicians to consider PCT along with routine biochemistry and blood analysis, and the patients' clinical parameters at the point of care when making antimicrobial prescribing decisions. Consideration should be given to measurement of algorithm adherence at 48 hours to account for unforeseen delays PCT result availability or delayed physician review of PCT results.

There were several factors involved in patient recruitment which may have influenced the primary outcomes of the study and should be addressed in a future trial design. These were the variation in infection severity between the PCT and respiratory control groups and the inclusion of patients who were already prescribed antimicrobials prior to hospital admission. These factors can be addressed in a suitably powered future RCT with the inclusion of illness severity scores, along with the use of multivariate and sub-group analysis.

A future RCT would include a broader range of physicians rather than respiratory specialists alone. Antimicrobial consumption in the general control group of patients in this study was higher than in either of the respiratory groups. The addition of a PCT testing to the existing AMS programme may have the potential to have a greater impact on this patient group.

2.5.1 Strengths and limitations

The study was conducted in a setting where PCT was a newly available test to physicians. A broad range of RTIs were recruited and the study took place over a calendar year and included seasonal variation in illness and prescribing. Patients were randomised to intervention or control, thus reducing selection bias. Serial PCT measurements were available to guide antimicrobial prescribing.

The study had some limitations. The study population had a clinical need for antimicrobial treatment so the study was designed to examine the duration of therapy and LOS, rather than investigating the potential to withhold antimicrobial therapy. The study results may have been influenced by a study effect. Both the PCT and respiratory control groups were treated by the same group of physicians who all received education and as they were aware that their behaviour was being monitored which may have resulted in a Hawthorne effect (157). The intervention was limited to one medical speciality which may limit its generalisability to other medical specialties and settings. The need for consent and PCT results which were not available at the point of clinical decision making in a small number of cases.

2.6 Conclusion

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. Several factors were identified which may have influenced the outcomes and the intervention implementation. The successful implementation of PCT testing requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomised controlled trial would be beneficial to further explore the positive aspects of these findings.

Chapter 3 A qualitative process evaluation of the introduction of procalcitonin testing as an antimicrobial stewardship intervention

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3.1 Abstract

Background

Successful antimicrobial stewardship interventions are imperative in today's environment of antimicrobial resistance. New antimicrobial stewardship interventions should include qualitative analysis such as a process evaluation to determine which elements within an intervention are effective and provide insight into the context in which the intervention is introduced.

Objective

To assess the implementation process and explore the contextual factors which influenced implementation.

Setting

An academic teaching hospital in Cork, Ireland.

Methods

A process evaluation was conducted on completion of a feasibility study of the introduction of a procalcitonin antimicrobial stewardship intervention. The process evaluation consisted of semi-structured face-to-face interviews of key stakeholders including participating (senior) doctors (5), medical laboratory scientists (3) and a hospital administrator. The Consolidated Framework for Implementation Research was used to guide data collection, analysis, and interpretation.

Main outcome measures

Qualitative assessment of the intervention implementation process, the contextual factors which influenced implementation and identification of improvements to the intervention and its implementation and determine if proceeding to a randomised controlled trial would be appropriate.

Results

Analysis of the interviews identified three main themes. (i) The procalcitonin intervention and implementation process was viewed positively to support prescribing decisions. Participants identified modifications to procalcitonin processing and availability to improve implementation and allow procalcitonin to be "*more of a clinical influence"*.

ii) In the antimicrobial stewardship context the concept of fear of missing an infection and risks of potentially serious outcomes for patients emerged.

(iii) The hospital context consisted of barriers such as available resources and facilitators including the hospital culture of quality improvement.

Conclusion

This process evaluation provides a detailed analysis of the implementation of procalcitonin testing as an antimicrobial stewardship intervention. The positive findings of this process evaluation and feasibility study should be built upon and a full randomised controlled trial and economic evaluation should be conducted in a variety of hospital settings to confirm the effectiveness of procalcitonin as an antimicrobial stewardship intervention.

3.2 Introduction

Antimicrobial resistance (AMR) is a significant risk to human health and we face the very real possibility of a 'post antibiotic era in which common infections could once again kill' (2). Antimicrobial stewardship (AMS) programmes are well established and include interventions to improve antimicrobial prescribing (42, 51, 53). Some AMS interventions can lack sustainability (158) which may be related to contextual factors of those interventions, but these have been poorly investigated particularly their role in the effectiveness of interventions and sustainability on a larger scale (159). This has prompted the suggestion that interventions should look to include components that enhance enablement for the implementation of evidence-based practice (159), defined as *'increasing means or reducing barriers to increase capability or opportunity'* (159, 160). Furthermore a recent Cochrane review of interventions to improve antimicrobial prescribing for hospital patients (43) has advocated for greater use of qualitative research such as a process evaluation (PE) of a trial to determine which elements within an intervention are effective.

A qualitative PE (98) assesses the fidelity and quality of implementation, providing insight into the context into which the intervention is introduced, clarifies causal mechanisms of the intervention without assuming that the intervention itself leads to the outcome and builds the evidence base to support the intervention that will inform policy makers and practice (161). A PE is important in complex interventions in the healthcare setting as a means to identify the underlying cause of the success or failure of interventions because occasionally even highly successful quality improvement interventions (101) have proven difficult to replicate in different contexts due to fundamental differences in how the intervention was delivered (102). A PE is an important element of implementation research and should incorporate a theoretical framework to guide data collection, analysis and interpretation. Theoretical frameworks have a predictive capacity to identify or explain causal mechanisms of implementation. This allows for identification of contextual factors that influenced implementation and so aids our ability to generalise study findings (104).

Greater utilisation of rapid diagnostic tests and biomarkers has been highlighted as an important factor in addressing AMR by improving infection diagnosis, supporting prescribing decisions and AMS programmes (67). Procalcitonin (PCT) is a biomarker

which has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with respiratory tract infections (74-77). The findings of a recent Cochrane review (76) supports its use in the context of AMS in safely reducing antimicrobial consumption by 2.4 days in patients with respiratory tract infections. We have previously reported the positive influence of PCT on antimicrobial prescribing following the introduction of PCT testing in a feasibility study (162). The study identified some variability in the use and interpretation of PCT levels suggesting a range of factors influenced implementation and should be explored to improve the effectiveness of intervention implementation in the future.

Feasibility studies should be complemented by a qualitative PE (98) to facilitate improved development and implementation of interventions (99). This is particularly relevant when introducing new diagnostic tests to support AMS to assess how best to use such new tests (163) and reporting of qualitative analysis of PCT implementation has been limited (164, 165).

3.2.1 Aim of the study

To explore how and why the introduction of a PCT intervention worked or did not work in an Irish hospital setting. The study objectives were to gain an understanding and assessment of the fidelity and quality of the implementation process, explore the contextual factors which influenced implementation, identify the barriers and facilitators to implementation and inform improvements to the intervention and its implementation if proceeding to a randomised controlled trial was deemed appropriate.

3.2.2 Ethics

The study was approved by the Clinical Research Ethics Committee of University College Cork and the Cork Teaching Hospitals [reference code ECM 4 (w) and ECM 3 (III) Appendix 1]. Written informed consent was obtained from all participants prior to the interviews and confidentiality of the participants was assured.

3.3 Methods

The Standards for Reporting Qualitative Research were used to guide the development of this manuscript (166).

A qualitative PE was conducted of a single centre, randomised, open-label feasibility study (162) of the introduction of PCT testing in patients admitted to hospital with a lower respiratory tract infection, under the care of the respiratory medicine team, during on-call acute unselected general medical take. The feasibility study ran from June 1st 2017 to May 31st 2018 and was conducted in a single, 321 bed model 3 (smaller general) (143) inner city, voluntary acute University Teaching Hospital, which is part of the South/South West Hospital Group (142) in the Republic of Ireland. The PE was conducted following completion of the feasibility study.

The Consolidated Framework for Implementation Research (CFIR) (105) was used to guide data collection, analysis, and interpretation. It is a meta-theoretical framework based on existing determinant frameworks and multiple implementation theories which provides a roadmap of constructs to monitor the implementation process (105) by recognising that implementation is a multidimensional phenomenon with multiple interacting influences from the individual to the organisation and beyond (106). The CFIR was chosen because it can be applied at any stage of the evaluation process of an intervention, it provides a framework to investigate and assess the complex multi-level nature of implementation in the healthcare setting including barriers and facilitators to effective intervention implementation (104) and provides a way in which to organise and communicate findings.

3.3.1 Participants

An invitation to participate in the study was issued in person or by email to key stakeholders involved in the feasibility study or would be involved in the decision to implement PCT testing in the hospital in the future. All agreed to participate but one medical doctor later withdrew due to scheduling constraints. Participants included five medical doctors (DR1-5) (three respiratory clinicians and two general clinicians), three medical laboratory scientists (MS1-3) and a hospital administrator (ADM). The interviews ranged in length from 6 to 29 minutes with a mean duration of 16 minutes.

3.3.2 Data collection

Semi-structured face-to-face interviews were conducted by the primary researcher. Interviews took places in the hospital where the study was conducted at a date and time that was convenient for participants. The interview topic guide was developed by

two researchers (FOR and AF), both pharmacists with experience of AMS. The interview topic guide was informed by the most relevant CFIR constructs (105) which were used as a 'check-list' of variables for consideration. The topic guide was refined following a pilot interview with a medical doctor who participated in the feasibility study. Pilot interview data were included in the study due to the limited number of medical doctors participating directly in the feasibility study.

Interviews with medical laboratory scientists focused on the provision of PCT testing in the laboratory, the interviews with doctors focused on the use of PCT in making antimicrobial prescribing decisions while the interviews of participants with managerial responsibilities and the hospital administrator focused on implementation of PCT testing on a larger, ongoing scale in the hospital. Issues and opinions on AMS and the hospital context for change and quality improvement were asked of all participants.

All interviews were digitally recorded and transcribed verbatim by a professional transcription service. The accuracy and quality of the transcripts was checked against the original recordings and any identifiable data was removed from the transcripts (by FOR).

3.3.3 Data analysis

Interview analysis used the framework method (167, 168) which provides a systematic step-wise approach to produce structured outputs of summarised data and is most commonly used for the thematic analysis of semi-structured interview transcripts (167). It consists of the following steps 1. Transcription of the interviews, 2. Familiarisation with the interview data 3. Coding of the data using the CFIR constructs as deductive codes (open coding was applied when themes emerged during the familiarisation process that did not fit within the definitions of the CFIR constructs) 4. Charting and indexing of the data using a thematic framework 5. Interpretation and analysis of the data.

The interview transcripts were coded independently by two researchers (FOR and AF) using the CFIR constructs and open coding by thematic analysis. All 39 constructs of the CFIR were used as the a priori codebook for this qualitative study. Important domains and constructs were identified based on the frequency of their appearance in the interviews, the degree of importance articulated by the participants or the

researchers, or both. Emergent themes were reviewed throughout the interview process and the team made an assessment as to when data saturation had occurred. All authors reviewed the final codes. Discrepancies were resolved through discussion.

3.4 Results

Nine interviews were conducted with hospital staff to explore the different aspects of the PCT intervention implementation in the hospital setting. Participant's roles in implementation are contained in Table 3.1.

Table 3.1 Health professionals` role during the PCT implementation

Health professional	**Role in implementation**
Hospital administrator	Hospital-wide managerial responsibilities and oversight of funding decisions
Respiratory clinicians	Involved in the PCT intervention implementation and assessment
Clinicians	Provided insight into the contextual elements of implementation
Medical laboratory scientists	Laboratory processing of the PCT tests

The results have been informed by the CFIR and are categorised into three themes. 1. The PCT intervention and the implementation process, 2. The AMS/AMR context and 3. The hospital/organisational context. Within these themes participants described a range of factors that interact with each other and the intervention to produce an effect as a facilitator or barrier to implementation. The CFIR constructs identified in the themes are listed in Table 3.2. They are supported by qualitative excerpts from the interviews (Tables S1, S2 and S3 available as supplementary data, Appendix 4). The constructs of the CFIR are highlighted in bold in the text.

Table 3.2 Consolidated framework for implementation research domains and constructs associated with qualitative themes

Theme	CFIR domains	CFIR constructs
PCT intervention and implementation process	Intervention characteristics	Evidence strength and quality, Relative advantage, Adaptability, Trialability, Complexity, Design quality and packaging, Costs (opportunity)
	Process	Champions, Reflecting and evaluation
	Characteristics of the individual	Self-efficacy
Antimicrobial stewardship/antimicrobial resistance context	Outer setting	Patient needs and resources, Cosmopolitanism, External policy and incentives
	Inner setting	Culture, Tension for change, Relative priority Leadership engagement, Available resources,
Hospital/organisational context	Inner setting	Structural characteristics, Networks and communications, Culture, Leadership engagement
	Process	Champions, Available resources

3.4.1 Theme 1: PCT intervention and implementation process

Participants described the PCT intervention as having a well-established evidence base to support its use and clinical situations where it could act as an "*extra marker"* to support antimicrobial prescribing decisions. These decisions require clinicians to balance the need to adequately treat patients while also safely minimising antibiotic exposure and is a situation where '*PCT would actually play a very useful role.'* The

feasibility study design and accompanying PE aligned with the **trialability** construct by providing participants the opportunity to test PCT on a smaller scale, develop experience, reflect on the intervention, suggest changes to improve the intervention and adaptation in the future. Participants provided specific examples of clinical situations where PCT supported antimicrobial prescribing decisions along with examples of where it was considered of less benefit. Overall participants felt more confident in the role of PCT in the acute infective setting and less confident in the reliability of PCT in patients with underlying chronic lung disease. (Indicative quotations are shown in Table S1, Appendix 4)

Several elements of the '**adaptable periphery**' (105) emerged which could be modified to improve the processing of samples in the laboratory and the subsequent availability of the PCT results to clinicians. They included processing of the test more efficiently as part of a patients biochemistry profile by the biochemistry laboratory rather than processing samples in the microbiology laboratory (which occurred in this study). This would facilitate more prompt availability of results as part of the standard admission point of care blood test results. The changes suggested to the laboratory processing of the results were due to the elements of the intervention which aligned to the **complexity** construct and were considered barriers to implementation. (Indicative quotations are shown in Table S1, Appendix 4)

Participants commented positively on the education and training provided and were engaged with the intervention and its intended purpose of improving antimicrobial prescribing. (Indicative quotations are shown in Table S1, Appendix 4)

Participants suggested several other general recommendations to facilitate implementation of PCT testing which aligned to the **reflecting and evaluation** construct. They included recommendations for a *"multi-modal"* educational plan, the need to identify the role of PCT, *"it's place in the hierarchy"* and to consider potential unintended consequences of its use. Participants also highlighted the need to gain support and endorsement from hospital management and senior clinicians and using public forums within the hospital such as *"grand rounds"* to facilitate this objective and engage **champions** (individuals) who actively associate themselves to support the intervention during implementation.

Several potential barriers to implementation were also identified by participants. One participant highlighted that PCT '*has been around for quite some time'* and questioned it's **relative advantage** over C—reactive protein as an indicator of viral infections.

The barrier of additional costs and availability of resources to support new interventions in the hospital means they would require '*a really strong business case to suggest why we should add a resource'.* The **opportunity cost** associated with implementing a PCT intervention was also raised with the suggestion that alternative AMS interventions may be a more beneficial use of resources but this would require an economic assessment to determine the most cost-effective intervention.

The respiratory specialist participants in the study expressed a strong sense of **self-efficacy** and confidence in their professional knowledge and clinical experience of treating respiratory tract infections and making antimicrobial prescribing decisions *"it's very much linked to what we do"*. They highlighted situations where they have come into conflict with the AMS team in relation to compliance with antimicrobial guidelines highlighting they "*don't inappropriately apply the guidelines as opposed to that we ignore them"*. These findings were considered a potential barrier to implementation of AMS interventions.

3.4.2 Theme 2: Antimicrobial stewardship and antimicrobial resistance context

The need to address the problems associated with AMR were seen as facilitators to AMS interventions. Patient safety was seen as a priority but participants highlighted the increasing complexity and difficulties in managing patients with resistant infections. The management of patients with carbapenemase producing *Enterobacteriaceae* emerged as an example of the organisational approach to the problem of AMR and elements of this approach were considered as facilitators of implementation. The hospital *"eventually"* realised the problems associated with carbapenemase producing *Enterobacteriaceae* following communication between national and local level management resulting in greater **leadership engagement** at local level to address the problem. These factors created a **tension for change** to respond to this problem within the organisation and the need to take a long term rather than a short term view to respond to the problem. (Indicative quotations are shown in Table S2, Appendix 4)

The **culture** within the hospital in relation to antimicrobial prescribing emerged as a barrier to implementation of AMS interventions. The concepts of fear and risk aversion were a significant influence on antimicrobial prescribing decisions. Fear arose in relation to the *'possibility of missing infection'* in patients and the associated

potential for negative clinical outcomes for those patients related to an inadequately treated infection and the associated feelings of clinical responsibility (indicative quotations are shown in Table S2, Appendix 4). This fear was accompanied by the *'fear of litigious issues'* and the need for *'self-protection'*. Clinicians described the risk-aversion and need for self-protection as motivating factors for the prescription of antimicrobial courses to patients "*even in times that maybe the front-line clinician themselves maybe isn't convinced fully that it's a bacterial infection"*. There was acknowledgement of antimicrobial over-prescribing but these risks were outweighed by the needs of the individual complex sick patient admitted to hospital. A possible explanation for this which emerged was that the longer term consequences of AMR "*aren't as apparent"* and may be perceived to be less important than the treatment of current patients. There was also an acknowledgement that the problem requires a significant amount of behavioural change as the *"habits of the prescribing hand are firm and hard to change"*.

3.4.3 Theme 3: Hospital/organisational context

All participants described a range of factors which act as barriers or facilitators of implementation. A growing culture of quality improvement in the hospital was described by all participants aligning with the **culture** construct. There were some differing individual perspectives on the degree of **leadership engagement** with quality improvement in the hospital with an acknowledgement that senior clinicians could be more engaged with it. The development of structural *"scaffolding"* to support a clinical lead with dedicated time to encourage and support quality improvement work was identified as a facilitator of future interventions. (Indicative quotations are shown in Table S3, Appendix 4)

Communication was seen as an important facilitator of interventions aligning with the **networks and communication** construct. The hospital size was seen as a positive factor to encourage greater engagement with colleagues. Communication between medical teams and the AMS team was seen as good and had a positive influence on antimicrobial prescribing. However inter-departmental communication, and communication between senior clinicians and hospital management emerged as a barrier to implementation. (Indicative quotations are shown in Table S3, Appendix 4)

Available resources emerged as a barrier to implementation in relation to the limitations of the funding model of Irish healthcare where despite the intensions of staff there is limited opportunities to *"invest to get future success"*. Participants also raised issues related to the perception of how resources are distributed within the hospital "*it does seem to be he who shouts loudest"*.

3.5 Discussion

This study provides a detailed PE of the introduction of PCT testing as an AMS intervention. The CFIR guided a systematic assessment of the intervention and implementation process, identification of barriers and facilitators of implementation, and provided an insight into the contextual factors which influence AMS in the Irish hospital setting. The findings provide actionable recommendations to successfully implement a PCT intervention.

The main findings of this study identified the positive elements of the intervention and implementation process while also exploring the barriers to implementation related to the intervention and the contextual barriers of the study setting to be overcome to successfully implement a PCT intervention. Participants engaged with the intervention, the education provided, assessed the supporting evidence for the intervention, gained experience of the intervention, reflected on its clinical value and proposed modifications to the intervention delivery which would improve implementation in a future randomised controlled trial. All these elements promote successful adaptation of interventions (105) and it has also been shown that previous experience of PCT testing leads to greater confidence in the application of PCT as an AMS intervention (169).

The adaptability and trialability constructs identified the most relevant factors to improve the delivery and selection of patients to maximise the benefits of the intervention. PCT levels were tested in the microbiology laboratory during this study and while the test itself was relatively quick to process there were several factors which led to delays in the availability of the results. These delays in availability resulted in clinicians feeling that *"hearing afterwards it was something that you know, you felt almost it was a feedback after the decision had been made"* rather than contributing to the clinical decision-making process. Processing of the PCT level in the biochemistry laboratory emerged as a solution to this problem and the PCT levels should be available as part of the admission list of blood results at the point of care to allow the results to be "*more of a clinical influence"* on prescribing.

The participating respiratory clinicians expressed a strong degree of self-efficacy in relation to their expert knowledge and clinical experience in treating respiratory tract

infections while also acknowledging the diagnostic difficulties associated with respiratory tract infections. These findings suggest that respiratory clinicians could be perceived as barriers to implementation of AMS interventions and are similar to those found in a recent study which highlighted the barriers to integrating AMS processes within respiratory medicine (170). The perception that unsolicited AMS input is considered an imposition on specialist territory and clinical autonomy among some medical specialists who consider themselves 'experts in their own fields' is a considerable barrier to AMS interventions (171).

One clinician highlighted that PCT '*has been around for quite some time'* and questioned its relative advantage over other infection markers. However most participants viewed the intervention positively which suggests that PCT is a potentially effective intervention as it combines clinician enablement, improved diagnostics to support AMS but requires engagement with clinicians to optimise effectiveness. An intervention of this nature would fulfil the recommendations of a recent study (172) to overcome barriers in AMS in respiratory medicine. These findings align with a qualitative study of clinicians experience with PCT where the intervention was viewed positively as an AMS adjunct but it could not replace other tests or clinical judgement (173).

The CFIR provided a framework to explore the two main contextual factors of AMS and the hospital/organisational context into which the intervention was introduced. Contextual factors influencing AMS interventions have been poorly explored in the past (159) and a lack of understanding of the contextual factors contributing to a given problem can lead to sub-optimal implementation (174).

The concepts of fear and risk-aversion were prominent themes in the AMS/AMR context. The care of their patients and patient safety is the primary concern for clinicians (175). Patients admitted to hospital with a suspected infection are perceived to be more *'complex'* and *'sick'* which heightens the fear of missing an infection and the potentially serious outcomes for patients including death which heavily influences antimicrobial prescribing decisions. Fear of adverse clinical outcomes especially in hospital patients has a powerful influence on antimicrobial prescribing which can escalate the risk perception of clinicians (171). Clinicians were risk-averse even in

situations where the risk of a bacterial infection is low *'I think a lot of people will still cover with antibiotics'.* Clinicians also cited concerns on a personnel level perceiving a need for self-protection and a fear of litigation which results in the prescription of antimicrobials "*just in case*". Justification of the fear of litigation may be due to the fact that medical negligence suits filed in the Irish High court have increased by 136% from 2007 and 2018 (176) and clinical negligence claims against the NHS in the UK have doubled over a similar period (177). In the ever-increasing litigious world we live in, this is a significant barrier going forward.

The findings demonstrate that clinicians consider the short terms risks to patients and themselves more heavily than the longer term consequences of AMR which "*aren't as apparent"* when making antimicrobial prescribing decisions similar to the findings of a recent systematic review (178). Risk, real or perceived, is challenging to mitigate against. AMS programmes must acknowledge the experiences of risk faced by clinicians when designing AMS interventions. An intervention such as PCT acting as an "*extra marker"* of the infection process offers clinicians further information when making antimicrobial prescribing decisions potentially reducing the perceived risks for both patient and clinician.

The hospital context consisted of both barriers and facilitators to implementation. The hospital administrator highlighted the recognition of the problems associated with AMR having gained greater insight during the hospitals response to a carbapenemase producing *Enterobacteriaceae* outbreak and the significant costs associated with it. Unfortunately the realities of managing limited resources in a hospital environment where the short term demands of trying to *"push people through the system"* is difficult and limits the ability of hospitals to invest in new interventions or diagnostics to mitigate the long-term consequences of AMR. These findings are similar to the findings of another study investigating the perspective of hospital managers on optimising antimicrobial use (179). A medical laboratory scientist expressed frustration with the economic constraints of the healthcare system where it appears that resources are allocated to *'he who shouts loudest'.* In the current setting of a resource limited health service new interventions such as PCT must be supported by '*a really strong business case'* and an economic evaluation of the intervention should be incorporated into a future trial particularly in the Irish hospital setting. PCT testing

has been shown to be a cost-effective AMS intervention in the U.S. setting (180) but the overuse of PCT testing has also been highlighted (181). Long term investment in the health system is necessary to alter the realities of AMR. This is particularly important given our current population demographic in Ireland where the proportion of the population over 65 years is expected to increase to 1.6 million in the next 35 years (182).

Positive findings from the hospital context included the recognition of developing a culture of quality improvement in the hospital. Additional resources and support are required to develop the *"scaffolding"* within the hospital but this is an important facilitator for the development of new interventions. We know from previous work that organisations which have a patient centred culture are more likely to implement change effectively (183). Communications within an organisation has been recognised as being important in intervention implementation. There was some variation in the assessment of it in the hospital context and both positive and negative aspects were identified. The small size of the hospital was noted as having a beneficial effect on communication in this study. Implementation has been described as a 'social process' which is intertwined with the context in which it takes place (184). The importance of factors such as gaining 'consultant buy-in' and using educational forums such as grand rounds to encourage engagement and discussion of interventions by senior clinicians are noted.

3.5.1 Strengths and limitations

The findings of this study and our earlier quantitative work (162) support the finding that PCT is an effective intervention and thus support the recommendations to link the CFIR constructs to intervention outcomes (104). We have outlined the justification for our choice of the CFIR (104). The study included a broad range of participants not just those directly involved in the study implementation.

The study had several limitations. The study took place in a single hospital setting and contextual influences may differ in other hospitals and this may limit its transferability. However, as this is a feasibility study, this could not be mitigated for in this instance. Only one hospital administrator was interviewed which limits the insight from the administrative perspective on the hospital context. However due to

the single study site it was only possible to interview one administrator who would have the knowledge to provide these details. The feasibility study and PE were conducted by the same researchers increasing the risk of positive reporting. There was also a risk of the Hawthorne effect during the data collection process as it is possible the interviewer could have influenced the way people behave or respond. Efforts to avoid or minimise bias and the Hawthorne effect included purposive sampling and inclusion of a diverse sample of individuals.

3.6 Conclusion

This PE provides a detailed qualitative analysis of the implementation of PCT testing as an AMS intervention. Positive elements of intervention implementation were highlighted along with modifications to improve the delivery of the intervention such as the prompt availability of PCT levels at the point of care to allow the test to be "*more of a clinical influence"* on prescribing. Contextual factors which influence implementation were identified and explored including the concepts of fear, risk and the influence of respiratory clinicians on AMS interventions. We would recommend that the positive findings of this PE and feasibility study should be built upon and that a full randomised controlled trial and economic evaluation should be conducted in a variety of hospital settings to confirm the effectiveness of PCT as an AMS intervention.

Chapter 4 Quality indicators for hospital antimicrobial stewardship programmes: a systematic review

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4.1 Abstract

Background

Measuring the quality and effectiveness of antimicrobial stewardship (AMS) programmes with quality indicators (QIs) is an area of increasing interest. We conducted a systematic review to identify QIs of AMS programmes in the hospital setting and critically appraise their methodological quality.

Methods

We searched the Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL, Scopus/web of science databases and the grey literature for studies which defined and/or described the development process and characteristics of the QIs developed. The Appraisal of Indicators through Research and Evaluation (AIRE) instrument was used to critically appraise the methodological quality of the QI sets.

Results

We identified 16 studies of QI sets consisting of 229 QIs. The QI sets addressed a broad range of areas of AMS in the hospital setting and consisted of 75% process indicators, 24% structural indicators and 1% outcome indicators. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified.

Conclusion

The QIs identified in this study focused on process and structural indicators with few outcome indicators developed, a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS. Testing of the QIs in practice is an essential methodological element of the QI development process and should be included in the QI development study or as planned validation work.

4.2 Introduction

Antimicrobial resistance (AMR) is a major threat to public health contributing to increasing rates of illness, death and significant economic costs (2, 8). Antimicrobial stewardship (AMS) programmes have been implemented to address the escalating threat to human health posed by AMR. AMS aims to optimise antimicrobial use in order to maximise the probabilities of clinical cure or prevention of infection while minimising unintended consequences such as toxicity and the selection of pathogenic organisms (e.g. *Clostridioides difficile*) (43). AMS is an important element of patient safety and a widely applied quality improvement initiative (29). Implementation guidelines for AMS programmes place a strong emphasis on improving the quality of antimicrobial use (51) and evaluation of AMS programmes, but do not identify specific indicators of performance (42).

Measuring the quality of healthcare can be achieved by using quality indicators (QIs). QIs are defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care provided' (82). QIs can measure the quality of care by examining the structures, processes, and outcomes of care (84, 85). This acknowledges that good structures increase the likelihood of good processes, and good processes increase the likelihood of good outcomes (84).

To ensure QIs provide accurate measures of quality, they must adhere to certain quality requirements. QIs should be evidence-based (185), but in situations where scientific evidence is lacking, QIs can be defined by an expert panel of professionals using consensus techniques such as the Delphi technique or RAND/UCLA (Research and Development Corporation) (University of California, Los Angeles) appropriateness method (186). The systematic method of combining scientific evidence and expert opinion is the most rigorous method to develop quality indicators as it provides face and content validity (187). Furthermore QIs should be tested during their development (187) to demonstrate they are acceptable to users (those being assessed and their assessors), feasible to measure, reliable and reproducible, sensitive to change and validated so as to ensure that they will produce consistent and credible measures of the quality of care (85, 188).

Cost savings were among the initial incentives for hospitals to implement AMS programmes (78). However, this is injudicious because factors such as antimicrobial

patent expiry, drug shortages and the increasing prevalence of multi-drug resistant organisms requiring the use of more expensive agents, all of which are beyond the control of an AMS programme. Thus cost savings alone is an unreliable indicator of performance (79) and makes a further case for measures to demonstrate the clinical and economic values of AMS programmes (80). Measuring the effectiveness of AMS programmes is thus important and is an area of increasing interest (81).

The purpose of this systematic review is to identify existing QIs of AMS programmes in the hospital setting, describe the methodological approaches used in their development, differentiate between the types of indicators (structure, process or outcome), and critically appraise the methodological quality of the identified QI sets using the Appraisal of Indicators through Research and Evaluation (AIRE) instrument (109).

4.3 Methods

This study was conducted and reported according to the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) (189).

4.3.1 Search strategy

An initial search for other systematic reviews of QIs for AMS programmes in hospitals identified two existing reviews (190, 191). However, neither study undertook a quality assessment of the methodological development of the QIs sets identified.

The search strategy aimed to identify publications concerning the development, testing or implementation of indicators of the quality of AMS programmes and antimicrobial prescribing. The Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL and Scopus/web of science databases were searched. A manual search of the grey literature, including conference proceedings, reports and thesis, was also conducted to find information regarding QI development initiatives which were not published in peer-reviewed journals. The reference lists of full text articles identified were screened to find other relevant studies. No language restrictions were imposed on the search algorithms. Searches were limited to studies of humans. The search period ran from the inception of the databases to the 1/12/2019 and the search was repeated on the 26/9/2020. The search terms were:

Anti-infective agents [MeSH] OR Antibiotic prophylaxis [MeSH] OR Antibiotic* [tiab] OR Antimicrobial*[tiab] OR Anti microbial*[tiab] OR Anti infective*[tiab] OR Antiinfective*[tiab] OR Antibacterial*[tiab] OR Anti bacterial*[tiab]	AND	Quality indicators, health care [MeSH] OR Quality indicator*[tiab] OR Quality measure*[tiab] OR Quality metric*[tiab] OR Quality criteria[tiab] OR Qualitative measure*[tiab] OR Quality improvement [ti]

Inclusion criteria and study selection

Studies were eligible for inclusion if they met the following criteria:

1. The study defines and/or describes the development process and characteristics of the QIs developed.
2. The identified QIs are applicable to adult patients in the hospital setting and related to the overall assessment of AMS programmes or the assessment of AMS related to specific clinical indications [e.g. Sepsis, Community Acquired Pneumonia (CAP), Urinary Tract Infections (UTIs)) or settings (e.g. Intensive Care Unit (ICU)].
3. Where the set of QIs were updated the publication describing the updated QIs was selected for inclusion.

Exclusion Criteria

1. Editorials, letters to the editor, comments, and narrative case reports.
2. Publications describing the application of existing QIs in clinical practice or reviews of sets of QIs.

Following completion of the database searches, the identified references were entered into a bibliographical database and duplicates removed. The title and abstracts of these references were screened for relevance (keywords in the title, abstract or study subject headings) by one reviewer (FOR). The resulting abstracts were included for full text review by two reviewers (FOR and AF) independently, according to inclusion criteria, and any disagreements resolved by consensus. If no consensus could be reached a third reviewer (FS) was consulted. The reference lists of the selected publications were then screened for other relevant studies that had not been identified in the electronic database searches.

4.3.2 Data extraction

A data extraction form was designed and used to extract relevant information about the QIs from the included articles (Supplementary data SD1, Appendix 5).

Categorising and grouping of the extracted QIs

The QIs extracted were categorised as structural, process or outcome QIs, classified by theme within each category and where there was conceptual, or content overlap in the description of the QI they were grouped together as agreed on by all authors.

4.3.3 Critical appraisal

The AIRE instrument (109) was used to appraise the methodological quality of the QI sets included in this study. It is a validated instrument which has been designed to assess the quality of QIs (110). It addresses four quality domains of a QI and consists of 20 items which are applied to each completed set of QIs. Three domains address the methodological quality of QIs and were used in this review: 'Stakeholder involvement', 'Scientific evidence' and 'Additional evidence, formulation and usage'. The fourth domain: 'purpose, relevance and organisational context' reflect the relevance of the QIs within a particular context rather than methodological quality so was not used in this review. Table 4.1 contains the AIRE domains and items applied in this study. Each item consists of a statement which is scored according to a 4-point Likert scale [1 'strongly disagree or no information provided' to 4 'strongly agree'(confident that the criterion has been fulfilled)]. Scores for each domain were calculated by summing up the scores for each individual item in a category and standardising the total as a percentage of the maximum possible score for the domain. The AIRE instrument was completed by two reviewers independently (FOR and AF or FS) for each complete QI set rather than for each QI individually as most studies gave general information for the QI sets concerning development and supporting evidence. (Further details about the AIRE instrument and its scoring system are contained in Supplementary data SD2, Appendix 5). The scores for each domain are independent and should not be aggregated into a single total quality score. The standardised scores for each domain range from 0% to 100%, with a score of 50% or higher indicating a higher methodological quality for each domain of the instrument (109).

Table 4.1 AIRE domains and items (109)

AIRE domain	AIRE items
Stakeholder involvement	1. The group developing the indicator includes individuals from relevant professional groups
	2. Considering the purpose of the indicator, all relevant stakeholders have been involved at some stage of the development process
	3. The indicator has been formally endorsed
Scientific evidence	4. Systematic methods were used to search for scientific evidence
	5. The indicator is based on recommendations from an evidence-based guideline or studies published in peer-reviewed scientific journals
	6. The supporting evidence has been critically appraised
Additional evidence, formulation, usage	7. The numerator and denominator are described in detail
	8. The target patient population of the indicator is defined clearly
	9. A strategy for risk adjustment has been considered and described ('case-mix adjustment')
	10. The indicator measures what it is intended to measure (validity)
	11. The indicator measures accurately and consistently (reliability)
	12. The indicator has sufficient discriminative power
	13. The indicator has been piloted in practice
	14. The efforts needed for data collection have been considered
	15. Specific instructions for presenting and interpreting the indicator results are provided

4.3.4 Inter-rater reliability between reviewers

The inter-rater reliability between the three reviewers was assessed by comparing the individual scores per AIRE item for two separate publications included in this study by calculating the weighted Cohen's Kappa (192). The inter-rater reliability between (FOR and AF) and (FOR and FS) amounted to 0.69 and 0.73 respectively. (Supplementary data SD3, Appendix 5). A Cohen's Kappa of between 0.61 and 0.80 is considered substantial agreement (192).

4.4 Results

4.4.1 Search results

The PRISMA flow diagram of the selection process and reasons for exclusion is seen in Figure 1. The systematic literature search identified 4833 potentially relevant studies. Following screening of titles and abstracts, 85 potentially relevant studies were selected for full-text screening. Six additional studies were included in the full text screening after reference screening of the selected publications. 75 studies were excluded and 16 publications of QI sets were included in this review.

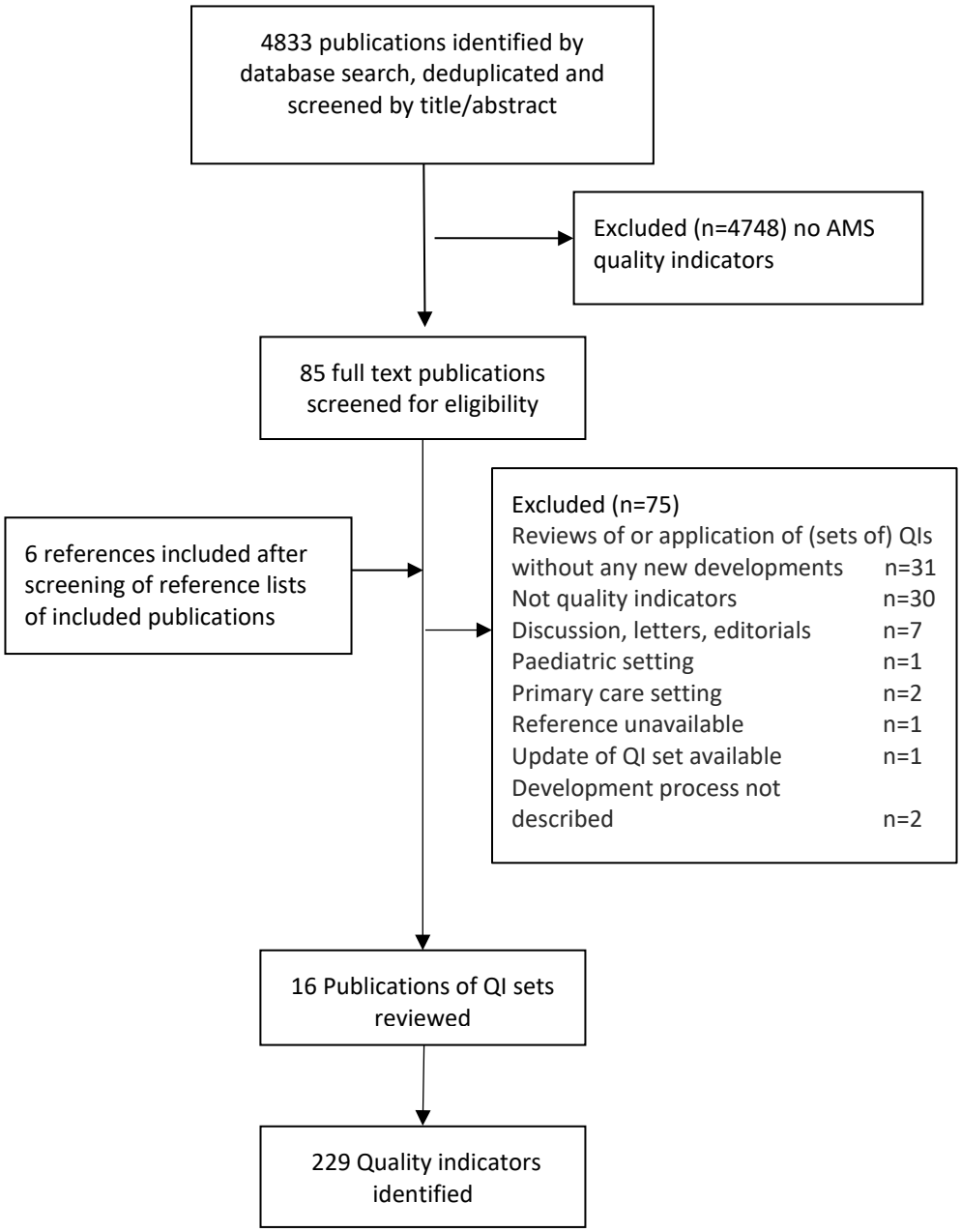

Figure 4.1 PRISMA flow diagram of literature search

4.4.2 Study characteristics

Table 4.2 presents an overview of the studies included in this review. Most included studies originated from Europe (11) followed by the UK (2), the USA (1) and Indonesia (1), one further study involved an assessment of USA and European hospitals.

The most common study design used in QI development involved a combination of a literature review (8) or review of clinical evidence and/or clinical guidelines (4), and, a consensus process [RAND modified Delphi (7), modified Delphi (2), RAND/UCLA appropriateness (2) or Delphi (1)] involving national or international multi-disciplinary expert panels. Other techniques included: a literature review and consensus, a multi-disciplinary team consensus, a national target for *C. difficile* and a national working group evidence base review.

The 16 QI sets addressed a broad range of areas of AMS in the hospital setting. These included 7 sets of QIs to address specific infections [community acquired pneumonia (CAP), COPD, urinary tract infection (UTI), Sepsis, *C. difficile* infection (CDI)], 1 set of generic QIs to assess antibiotic use in the treatment of all bacterial infections in hospital, 4 sets for specific hospital settings (e.g. ICU, High Dependency Unit (HDU)) and 4 sets of broader QIs to evaluate AMS programmes or hospital antimicrobial prescribing or to compare hospital AMS programmes.

Table 4.2 Characteristics of the AMS quality indicator sets

Author, year, location	Aim/focus	Study description	Stakeholder involvement	Number of AMS indicators per type
Berenholtz (193) 2007, USA	Sepsis care	Interdisciplinary panel literature review and a modified Delphi procedure with a multi-disciplinary expert panel from multiple hospitals	Physicians, nurses and pharmacist with expertise in sepsis, critical care and infectious diseases (ID), and experts in developing quality measures	Process:6 Structural:0
Buyle(194) 2013, Europe	Structural indicators to evaluate AMS programmes	Literature review and consensus process with a 13-member multi-disciplinary panel from multiple (4) countries	5 ID specialists, 2 clinical microbiologists, 3 hospital pharmacists, 3 quality of health-care experts	Process:0 Structural:10
Coll(195) 2012, UK	AMS in a high dependency unit	Multi-disciplinary team agreement, reference to the evidence base, national strategy and local policy	Multi-disciplinary team	Process: 30 Structural:0
Farida(196) 2015, Indonesia	Development of QIs for the antimicrobial management of CAP	QI development based on a previous study and guideline review followed by a 2 step Delphi procedure with an 18-member national multi-disciplinary expert panel	10 internists, 3 internist-pulmonologists, 2 pharmacists, 3 clinical microbiologists	Process:6 Structural:0
Thern(197) 2014, Europe	Hospital antimicrobial prescribing quality indicators	Literature review and RAND/UCLA appropriateness consensus with a multi-disciplinary expert panel from multiple hospitals	Clinicians, hospital pharmacists, microbiologists, infection control doctors	Process:21 Structural:21
Hermanides(89) 2008, Europe	QIs for the antibiotic treatment of complicated UTIs	Evidence-based guidelines used in a 3-step modified Delphi approach with a 13-member multi-disciplinary expert panel from multiple hospitals	2 Medical microbiologists, 4 ID specialists, 2 hospital pharmacists, 2 urologists, 2 nephrologists, 1 gynaecologist	Process:13 Structural:0
Kallen(198) 2018, Europe	QIs for appropriate antibiotic use in the ICU	Literature review and four round modified RAND Delphi procedure with a 15-member multi-disciplinary expert panel of Dutch experts	3 anaesthesiologists-intensivists, 3 internist-intensivists, 1 intensivist-infectious diseases physician, 3 internists-ID physicians, 2 clinical	Process:3 Structural:1 (1 quality metric)

			microbiologists, 3 clinical pharmacists	
Monnier (83) 2018, Europe	QIs for responsible inpatient antibiotic use	Systematic literature review and a four step RAND modified Delphi method with a 25-member international multi-disciplinary expert panel	Medical community (15) public health and patients (12); antibiotic R&D (14); and payers, policymakers, governments and regulators (11).	Process:35 Structural:14 Outcome:2
Pollack(86) 2016, USA & Europe	QIs to assess and compare AMS programmes among US and EU hospitals	Literature review followed by modified Delphi process using RAND/UCLA appropriateness method with a 20-member multi-disciplinary multinational expert panel	Clinical medicine, pharmacy, public health	Process:10 Structural:7
Schouten(199) 2005, Europe	Measurement of the quality of antibiotic use in CAP & COPD	Literature and guideline review and a four step modified Delphi procedure with an 11-member medical opinion leader expert panel from multiple hospitals	Medical microbiology, ID, respiratory medicine, quality of care medicine	Process:15 Structural:0
Schouten(200) 2012, Europe	QI bundle for ICU antimicrobial use	Literature search followed by a 2 round RAND modified Delphi method with an 11 member multi-disciplinary expert panel from 6 EU countries	11 member multi-disciplinary expert panel	Process: 6 Structural:0
Sneddon(201) 2012, UK	QIs to support a 50% reduction in CDI and improve prescribing practice	Development and implementation of QIs based on national CDI target reduction	Scottish Antimicrobial Prescribing Group	Process:2 Structural:0
Ten Oever(202) 2019, Europe	QIs for the management of *Staphylococcus aureus* bacteraemia	Systematic literature review followed by a RAND modified Delphi procedure with an international expert panel of medical professionals	Medical professionals (MD)	Process:11 Structural:0
van den Bosch(88) 2014, Europe	QIs for antimicrobial treatment in	QIs from national sepsis guidelines followed by a RAND modified	4 ID physicians, 2 medical microbiologists, 2	Process:5 Structural:0

	adults with sepsis	Delphi consensus with a 14-member multi-disciplinary expert panel from multiple hospitals	hospital pharmacists, 3 intensive care specialists, two haematologists, 1 general surgeon	
van den Bosch(87) 2015, Europe	QIs to measure appropriate antimicrobial use in hospitalised adults	Literature review followed by a RAND modified Delphi consensus with a 17-member international multi-disciplinary expert panel	5 medical microbiologists, 4 ID specialists, 2 clinical hospital pharmacists, 2 general surgeons, 2 pulmonologists, and 2 gynaecologists	Process: 9 Structural:2
Vera(203) 2014, Europe	QIs for antimicrobial use in critically ill (ICU) patients	Selection of QIs proposed by Spanish working group of Infectious Diseases followed by validity and reliability confirmation and review of supporting evidence	Spanish working group of Infectious Diseases	Process:10 Structural:0

4.4.3 Stakeholder involvement

The most common stakeholders involved in the QI development process were infectious diseases specialists, medical microbiologists, hospital pharmacists and physicians/clinicians. Their expertise was supplemented by various specialists depending on the QIs to be developed (i.e. ICU care involved intensivists, CAP and COPD QIs involved respiratory physicians, UTI QIs involved urologists, nephrologists and a gynaecologist). One study reported the participation of patients, payers and policy makers. Five studies reported general details of the stakeholder participants (i.e. multi-disciplinary team or expert group, medical professionals) rather than specific details.

4.4.4 Quality indicators

A total of 229 QIs were extracted from the 16 included studies and the full list is available as supplementary data SD4. QIs were grouped together and duplicates removed where there was conceptual or content overlap and several QIs were extracted from multiple publications. Table 4.3 contains a description of each unique QI, categorisation of the QI as structural, process or outcome indicators, classification of QIs by theme within each category, and identification of the studies in which they appeared.

Structural Indicators

55 structural QIs (55/229, 24%) were derived from six studies which aimed to provide a quality assessment of the organisational framework, multi-disciplinary expertise, resources, and supportive activities required to implement an AMS programme. QIs with conceptual or content overlap were grouped together and were classified by themes which were developed and agreed on by all authors. The themes identified were: (1) AMS governance, leadership and accountability [3 indicators, 4 studies], (2) AMS expertise and resources [4 indicators, 3 studies], (3) AMS policies and programmes to improve prescribing [6 indicators, 4 studies], (4) antimicrobial guidelines [4 indicators, 6 studies], (5) AMS education [1 indicator, 3 studies] and (6) microbiology laboratory standards, antimicrobial resistance surveillance and feedback [3 indicators, 3 studies].

Process Indicators

172 process indicators (172/229, 75%) were derived from fifteen studies which aimed to assess the general clinical management of all infections, or specific infections, or patient populations. QIs with conceptual or content overlap were grouped together and were classified into four themes: (1) Infection diagnostics [4 indicators, 9 studies], (2) Pharmacy-supported interventions [7 indicators, 8 studies], (3) Elements of good antimicrobial prescribing practice [12 indicators, 12 studies] and (4) Indicators for specific infectious conditions/settings [54 indicators, 10 studies].

Outcome Indicators

Two outcome indicators (2/229, 1%) were identified, recommending the monitoring of clinical outcomes of patients receiving antibiotics and the monitoring of the rate of nosocomial CDI.

Table 4.3 Quality indicators

Indicator	Source (s), Reference(s)	Description of the indicator
Structural Indicators by theme		
AMS governance, leadership and accountability	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014 Thern 2014, Monnier 2018, Pollack 2016	Establish a multi-disciplinary AMS committee that meets regularly. AMS representation and membership of the hospitals drugs and therapeutic committee. Strategic report submitted to D&T and hospital management including quantitative objectives and selected performance indicators.
AMS multi-disciplinary expertise and resources	Buyle 2013, Pollack 2016 Monnier 2018 Pollack 2016 Pollack 2016	Dedicated physician and pharmacist resources to provide AMS advice (and AMS leadership). Antibiotics from the antibiotic formulary should not be out of stock at the health care facility. Salary support for dedicated time for antimicrobial stewardship activities. Information technology capability to support the needs of the AMS activities.
AMS policies and programmes to improve antimicrobial prescribing	Buyle 2013, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016 Thern 2014, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014, Pollack 2016	AMS programme should be in place (including reports, objectives, performance indicators). Audit and feedback to prescribers of antimicrobial consumption and prescribing practices (including indications, surgical prophylaxis choice and duration). Restricted antimicrobials requiring approval. Regular AMS ward rounds and availability of expert consultation advice.

	Thern 2014 Monnier 2018 Pollack 2016	Written recommendation for parenteral-to-oral switch antimicrobial therapy. Prophylactic antibiotics should be added to a pre-operative checklist. Policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions.
Antimicrobial guidelines	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016, van den Bosch 2014, van den Bosch 2015 Buyle 2013, Thern 2014 Buyle 2013, Thern 2014, Monnier 2018 Thern 2014	Antimicrobial guidelines (correspond to national guideline but should be adapted based on local resistance patterns and updated biannually). Surgical antimicrobial policy. Antimicrobial formulary. Electronically available guideline/ decision making aids.
AMS education	Buyle 2013, Thern 2014, Monnier 2018	AMS prescriber education provided.
Microbiology laboratory standards, antimicrobial resistance surveillance and feedback	Thern 2014 Thern 2014, Monnier 2018 Thern 2014, Monnier 2018, Pollack 2016	Written in-house preanalytical requirements for microbiological samples (including rejection criteria). Use of selected antibiograms (adapted according to local guidelines). Reporting of AMR resistance rates, C.*difficile* incidence, nosocomial sepsis/bactaremia rates for clinical isolates available annually (and for specific services).
Process indicators by theme		
Infection diagnostics	Coll 2012, Thern 2014, Hermanides 2008, Kallen 2018, Monnier 2018, Schouten 2005, Schouten 2012, van den Bosch 2014, van den Bosch 2015, Farida 2014	Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken (sputum, urine,etc).

	Coll 2012, Monnier 2018 Monnier 2018 Monnier 2018	The results of bacteriological sensitivity(s) is documented. Microbiological investigations should be performed according to guidelines. Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.
Pharmacy-supported interventions	Coll 2012, Monnier 2018 Coll 2012, Monnier 2018 Monnier 2018 Coll 2012, Kallen 2018, Monnier 2018, Ten Oever 2019, Van der Bosch 2015 Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Ten Oever 2019, van den Bosch 2015 Thern 2014 Monnier 2018	Allergy status and documentation. Interaction management with concurrent medication. Contraindications should be taken into account when prescribing antibiotics. Therapeutic drug monitoring of vancomycin and gentamicin is conducted correctly and documented. Monitoring and adjustment of antimicrobial treatment for renal impairment. Oral administration of drugs with high bioavailability. The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.
Important elements of good antimicrobial prescribing practice	Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Schouten 2012, Ten Oever 2019, van den Bosch 2014, Van der Bosch 2015 Coll 2012, Hermanides 2008, Schouten 2012, Sneddon 2012, Farida 2014	Empiric systemic antimicrobial therapy should be compliant/prescribed according to local policy guidelines (choice, route, dosage). Documentation of an antimicrobial plan including indication for prescribing, intended duration of treatment. Prompt administration of antimicrobial within 4 hours of presentation.

	Monnier 2018, Schouten 2005, van den Bosch 2015	Antimicrobial treatment is reviewed according to clinical response and/or sensitivities.
	Coll 2012, Monnier 2018, Schouten 2012	Empiric systemic antimicrobial therapy should be changed to pathogen-directed therapy if culture results become available.
	Coll 2012, Hermanides 2008, Monnier 2018, Farida 2014	Prompt switching from IV route of administration to oral when clinically appropriate.
	Schouten 2005, Schouten 2012, Van der Bosch 2014, Van der Bosch 2015	Duration of antibiotic therapy should be compliant with guidelines.
	Monnier 2018, Schouten 2005	Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection.
	Monnier 2018, van den Bosch 2015	Antimicrobial treatment is discontinued on completion of the documented course.
	Coll 2012, Hermanides 2008, Monnier 2018, Schouten 2012	Antibiotic prescriptions that deviate from guidelines should be justified.
	Monnier 2018, van den Bosch 2015	Prescribed antibiotics should actually be administered to the patients.
	Monnier 2018 van den Bosch 2015	The maximum duration of empirical systemic antibiotic treatment should be 7 days.
Specific infectious conditions/settings		
Surgical antimicrobial prophylaxis (SAP)	Thern 2014, Monnier 2018, Sneddon 2012	SAP (drug and dosage): administered according to local guidelines. SAP administered within 1 hour before incision. SAP discontinued within 1 day (24 hours).
Community acquired pneumonia (CAP)	Schouten 2005, Farida 2014	Prescribe antibiotic therapy for exacerbations only when indicated. Optimal duration of antibiotic therapy from 5-7 days.

COPD	Schouten 2005	Prescribe antibiotic therapy for exacerbations only when indicated. Optimal duration of antibiotic therapy from 5-7 days.
Hospital acquired pneumonia	Thern 2014	Duration of therapy no longer than 10 days.
Urinary tract infections	Thern 2014	Documentation of positive urine culture. Duration of pyelonephritis therapy not longer than 10 days (patients on general ward). Oral antimicrobial drugs initiated not later than day 5 (pyelonephritis, patients on normal wards only). No antimicrobials for asymptomatic, catheter-associated bacteriuria.
	Hermanides 2008	Selective use of fluoroquinolones (only as oral or in beta-lactam allergy/anaphylaxis). Duration of treatment for at least 10 days (in accordance with national guideline). Prescription of treatment for men in accordance with national guidelines. Start iv antibiotics in pregnant women with pyelonephritis. Do not prescribe antibiotic prophylaxis to patients with a urinary catheter in place. Change urinary catheter within 24 hours of initiation of antibiotic treatment. Consider all diabetic patients with cystitis as having a complicated UTI and treat with empiric treatment according to national guidelines.
Blood stream infections (BSI)	Thern 2014	Additional monitoring-Heart ultrasound (TEE) within 10 days.

Staphylococcus aureus BSI	Ten Oever 2019	Collection of follow-up blood cultures 4-7 days after collection of first positive blood culture. Follow-up blood cultures after initiation of antimicrobial therapy should be done regardless of clinical evolution. Collection of repeat blood cultures should be performed until first negative blood culture. Initial antibiotic therapy should be administered intravenously in patients with SAB. Initial therapy should be intravenous (flu)cloxacillin (or nafcillin or oxacillin) or cefazolin in the case of methicillin-susceptible strains in patients with SAB. Antibiotic therapy should be initiated within 24 h after first positive blood culture. Appropriate treatment should be adapted within the first 24 h after a methicillin susceptibility result is available, if so required. Appropriate duration of IV antibiotic treatment should be at least 14 days for uncomplicated SAB. Appropriate duration of IV antibiotic treatment should be at least 28 days for SAB complicated by metastatic abscesses or deep foci of infection. IV-to-oral switch should not be performed in uncomplicated SAB after 48–72 h. IV-to-oral switch should not be performed in complicated SAB after 48–72 h. Other management aspects: Infectious disease specialist consultation should be performed in patients with SAB.

		SAB should be documented in the medical discharge summary.
Multi drug resistant infection management	Thern 2014	Infection and/or colonization by MDR organisms explicitly listed on discharge summary.
Sepsis	Monnier 2018, van den Bosch 2014 Berenholtz 2007	Antimicrobial therapy in adult patients with sepsis should be started intravenously. Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock. Vancomycin prescribing-% of sepsis patients with unidentified organism received vancomycin within 24 hours of identification. Median time to vancomycin following sepsis diagnosis. % of patients with sepsis and an unidentified organism who received a recommended broad spectrum antibiotic within 24 hours of sepsis diagnosis. Median time to broad spectrum antibiotic initiation following sepsis diagnosis. % of patients with sepsis who had 2 sets of blood cultures collected within 24 hours following sepsis identification. % of patients with sepsis and an organism other than MRSA or MRSE (metacillin-resistant *Staphylococcus epidermis)* who had vancomycin discontinued within 96 hours of diagnosis.

ICU	Kallen 2018	Perform surveillance cultures if selective digestive or oropharyngeal decontamination is applied at the ICU . Biannual face-to-face meetings between ICU and microbiology staff in which local resistance rates are discussed.
	Vera 2014	**Antimicrobial use in the intensive care unit Formula**: Total number of days of use of antimicrobial agent /Total number of days of ICU patients ×100. **Non-empirical antimicrobial use Formula**: Total antimicrobials used to treat infections in a directed manner /Total of antimicrobials used to treat infections ×100. **Changes in antimicrobials used as treatment Formula:** Total number of antimicrobials changed to another antimicrobial / Total of antimicrobials used to treat infections × 100. **Days without antimicrobial use in ICU Formula:** Total number of ICU days without antimicrobials / Total number of days of ICU patients × 100. **Days free of antimicrobials in patients on antimicrobial treatment Formula**: Number of days free of antimicrobials in patients on antimicrobial treatment / Total days in ICU of patients on antimicrobial treatment × 100 . **Number of days of antimicrobials for surgical prophylaxis Formula**: Number of days of use of

		antimicrobials for surgical prophylaxis / Total number of patients with surgical prophylaxis treatment × 100. **Inappropriate empirical antimicrobial treatment Formula:** Total number of inappropriate empirical antimicrobials / Total number of empirical antimicrobials used to treat infections × 100. **Empirical antimicrobials changed because they are inadequate Formula:** Number of empirical antimicrobials changed because they are inadequate Total number of empirical antimicrobials used to treat infections × 100. **Empirical antimicrobial changed for de-escalation Formula:** Number of empirical antimicrobials changed by adjustment or de-escalation Total number of empirical antimicrobials used to treat infections × 100. **Patients with severe sepsis/septic shock treated with antimicrobials in the first three hours Formula:** Number of patients with severe sepsis/septic shock, treated with antimicrobials in the first 3 hours / Total number of patients with severe sepsis/septic shock × 100.
Outcome indicators by theme		
Clinical outcome	Monnier 2018	Clinical outcomes of patients receiving antibiotics should be monitored at the health care facility. Rates of nosocomial *C. difficile* should be monitored at the health care facility.

4.4.5 Methodological quality

Table 4.4 presents the results of the critical appraisal of the methodological quality of the 16 QI sets assessed with the AIRE instrument. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified and this was reflected in the AIRE instrument domain scores. Most of the indicator sets achieved a score of 50% or higher indicating a high methodological quality in the first AIRE domain of 'stakeholder involvement'. The 10 studies with a high 'stakeholder involvement' domain score detailed the constituent stakeholders involved in the QI development process which ranged from medical opinion leaders (199) to broad multidisciplinary groups (87). Studies considered to be of lower methodological quality for this domain did not include sufficient information within the publications regarding the relevant stakeholders' involvement in the QI development process. Most studies had a low score for the AIRE item within this domain of 'the indicator has been formally endorsed' with only one study providing this information (QI set endorsed and used by the European Centre for Disease Prevention and Control) (83).

The 'scientific evidence' domain of the QI development process was well reported and most studies (12) were considered to be of high methodological quality. Four studies were considered to be of low quality as they received low or no score due to the absence of information regarding the search methods, evidence base, or the evidence-based appraisal techniques applied to develop the QI sets.

The lowest overall methodological quality was seen in the 'additional evidence, formulation, usage' domain where only 7 studies scored greater than 50%. The AIRE items within this domain which were allocated the lowest scores were 'a strategy for risk adjustment has been considered and described', 'the indicator has sufficient discriminative power' and 'specific instructions for presenting and interpreting the indicator results are provided'. Only 8 studies included information regarding the piloting of indicators in practice.

Five QI sets were considered to have a high methodological quality in all three AIRE domains (89, 194, 196, 197, 198) and only one QI set had scores of less than 50% across all three AIRE domains (203).

Table 4.4 Critical appraisal of the publications using the AIRE instrument

Publication	Aire Items																	
	Stakeholder involvement			Domain score	Scientific methods			Domain score	Additional evidence, formulation, usage									Domain score
	1	2	3		4	5	6		7	8	9	10	11	12	13	14	15	
Berenholtz(193) 2007	4,4	4,4	1,1	**67%**	3,2	4,4	3,3	**72%**	4,4	4,4	3,3	1,1	1,1	3,3	1,1	3,3	1,1	**44%**
Buyle(194) 2013	4,4	4,4	1,1	**67%**	2,3	4,4	2,1	**56%**	1,1	4,3	1,3	2,1	2,1	3,3	4,4	4,3	3,3	**52%**
Coll(195) 2012	3,3	3,3	1,1	**44%**	1,2	4,4	2,1	**44%**	1,1	4,4	1,1	2,1	2,1	3,2	4,4	1,1	4,4	**43%**
Farida(196) 2015	4,4	4,4	1,1	**67%**	3,3	4,4	4,4	**89%**	1,1	4,4	1,2	4,4	4,4	3,3	4,4	4,4	1,1	**65%**
Thern(197) 2014	4,3	4,3	1,1	**56%**	3,3	4,3	1,1	**50%**	1,1	4,3	1,2	3,3	3,3	1,2	4,4	4,4	1,1	**50%**
Hermanides(89) 2008	4,4	4,4	1,1	**67%**	3,2	4,4	4,4	**83%**	1,1	4,4	4,4	4,4	4,4	4,3	4,4	4,4	1,1	**76%**
Kallen(198) 2018	4,4	4,4	1,1	**67%**	4,4	4,4	1,1	**83%**	4,4	4,4	3,4	4,4	3,3	3,3	1,1	4,4	4,4	**80%**
Monnier (83) 2018	4,4	4,4	3,3	**89%**	4,4	4,4	1,1	**67%**	1,1	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**11%**
Pollack(86) 2016	4,4	4,4	1,1	**67%**	4,4	4,4	2,2	**78%**	3,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	1,1	**28%**
Schouten(199) 2005	2,2	3,3	1,1	**39%**	4,4	4,4	4,3	**94%**	2,2	4,4	4,4	4,4	4,4	4,4	4,4	4,4	1,1	**83%**
Schouten(200) 2012	2,2	1,1	1,1	**11%**	1,1	2,2	1,1	**11%**	2,2	4,4	1,1	3,3	1,1	1,1	4,4	4,3	1,1	**43%**

Sneddon(201) 2012	2,2	1,1	1,1	**11%**	1,1	1,1	1,1	**0%**	4,3	4,4	1,1	4,1	4,4	1,1	4,4	2,2	4,4	**61%**
Ten Oever(202) 2019	3,3	3,3	1,1	**44%**	4,4	4,4	4,4	**100%**	2,2	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**15%**
van den Bosch(88) 2014	4,3	4,4	1,1	**61%**	1,1	4,3	3,3	**50%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**22%**
van den Bosch(87) 2015	4,3	4,4	1,1	**61%**	3,4	4,4	4,4	**94%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**22%**
Vera(203) 2014	1,1	1,1	1,1	**0%**	1,1	1,1	1,1	**0%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	3,3	**37%**

4.5 Discussion

To our knowledge, this is the first systematic review to provide an overview and critical appraisal of the methodological quality of QIs for AMS in the hospital setting. A total of 229 QIs were identified from sixteen studies. Process indicators accounted for 75% of the extracted QIs and focused on the clinical management of infections. Structural indicators accounted for 24% of the extracted QIs focussing on the organisational requirements of AMS programmes, and 1% of the extracted QIs assessed outcomes of care. The findings of the critical appraisal of QIs using the AIRE instrument indicate considerable variation in the methodological quality and applicability of the QI sets developed.

Most studies involved a comprehensive QI development process consisting of an appraisal of the evidence base followed by an expert panel consensus process. There was some variability in the constituents of stakeholders involved in the development of QI sets and several studies did not provide details of the participants of the expert group. The involvement of a diverse range of stakeholders strengthens the results of the consensus process, and enhances the credibility and acceptability of the QIs (204). Patient participation as members of the expert panel of key stakeholders in the QI development is often overlooked (205) but is of increasing importance (206). Future studies should ensure the inclusion of a broad range of relevant stakeholders including patients, who all have an interest in the QIs to be developed.

Process indicators for AMS programmes accounted for 75% of the indicators identified. They focused on the general clinical management of infection and antibiotic treatment along with more specific indicators for infectious processes such as sepsis, CAP, COPD and UTIs. Process indicators offer hospitals the ability to assess the core competencies of antimicrobial prescribing (207) and the opportunity to adapt education and training of prescribers based on the findings. The high proportion of AMS process indicators may be related to the findings that process interventions are considered the most effective AMS strategies to improve antimicrobial prescribing in hospital (43).

Structural indicators for AMS programmes accounted for 24% of the indicators identified. They focused on the organisational requirements and necessity for a core multi-disciplinary AMS team of infectious diseases specialists, microbiologists and pharmacists providing leadership and expertise to implement and support a multi-

faceted AMS programme. AMS programmes are resource intensive which influences the variability in the implementation of hospital AMS programmes worldwide (208). Core elements for AMS programme (48) have been developed which can be adapted depending on the resources available in different countries and hospitals. Structural indicators offer the opportunity to measure the implementation of the proposed core elements and for benchmarking of performance between hospitals, within countries and across jurisdictions and to identify outliers.

The low number of outcome indicators identified is reflective of the ongoing challenges of AMS programmes to accurately measure and demonstrate their impact on patient outcomes (81, 209). Expert panels developing quality measures consider outcome measures important (81, 210) but are often reluctant to include such measures in QI sets due to the need for risk adjustment for confounding factors (211). These include changes in the hospital setting such as the patterns of bacterial prevalence, patient demographics, patient case-mix, and infection control interventions and their intensity, all of which can influence AMR and antimicrobial prescribing. Other barriers include concerns that overall clinical outcomes (such as mortality) may be insensitive to changes as a result of interventions such as IV to oral switching, and perceived feasibility issues with other outcome measures (210). In such situations where there is a difficulty in developing an accurate case-mix adjustment system for outcome indicators then alternative strategies may be more effective at measuring the quality of care.

Process and structural indicators can act as direct measures of the quality of healthcare, where a link has been demonstrated between a given process and outcome (212). They are relatively easy to measure as the information is accessible from medical records or other hospital sources. They usually assess a clearly defined patient population and thus there is less need for risk adjustment. The availability of such measures and their practicality means they can be used as alternative outcome measures as they are easier to interpret and more sensitive to changes in the quality of care (212). The AMS process indicators (use of empiric antimicrobial therapy according to guidelines, de-escalation of therapy, IV to oral switching, therapeutic drug monitoring) and structural indicators [(use of a list of restricted antibiotics and bedside consultation (especially in *S. aureus* bacteraemia)] have demonstrated significant benefit to clinical outcomes, adverse events and costs (44). The process measure of documented indications for antimicrobial prescriptions has also shown a positive influence on patient outcomes

(213). Furthermore a recent study of UK hospitals has evaluated the impact of AMS process and structural indicators (similar to those extracted in this study) on antimicrobial prescribing as an outcome measure and has shown promising results (209).

A further possible approach for the development of outcome measures may be to consider using indirect evidence for the success of a process indicator as an outcome. This may be in the form of 'not showing harm' as an outcome for a process indicators such as de-escalation of therapy, or, IV to oral switching, where such interventions could decrease the likelihood of catheter-related infections/events without demonstrating an impact on more traditional outcomes such as mortality or AMR rates (44).

The development of future QIs must address the lack of outcome indicators currently available while acknowledging the difficulties in their development such as risk adjustment and case-mix, along with the multitude of other factors which can influence AMR. The potential use of AMS process and structural indicators with a direct link to outcomes should also be explored further as surrogate AMS outcome measure (209).

The methodological requirements for the development of QIs are well established (85, 187). Most studies concentrated on the development of the QIs and were considered to be of high methodological quality in the 'stakeholder involvement' and 'scientific evidence' domains. However, studies scored poorly in the 'additional evidence, formulation, usage' domain due to limited reporting of information about validation and piloting of the QIs in practice or testing of the clinimetric characteristics. Such practice testing prior to wider usage of QIs is essential (214) as the validation and clinimetric testing of QIs is important to demonstrate the applicability and implementability of QI sets in practice, in different settings and to demonstrate the robustness of the indicators. The studies which were considered to be of the highest methodological quality scored well in all three AIRE domains and recognised the need to test indicators in the setting where they are intended for use (89, 194, 196-198).

Several studies, which were considered to be of high methodological quality in the first two AIRE domains had low scores in the third domain (83, 86-88, 193). Some studies acknowledged the need for piloting and clinimetric testing of their QIs prior to use on a wider scale (83, 86, 87, 197, 202). The QIs from two studies (87, 197) have undergone subsequent clinimetric testing (215, 216). This resulted in one QI set

reducing the 11 initial QIs to 7, based on applicability (215) and of 33 QIs assessed reduced to 18 process indicators considered suitable to identify processes with a greater need for improvement within an AMS programme (216). This supports the findings seen in other studies which have shown that 10-20% of developed QIs are not measurable in practice (217). The implementability, applicability and feasibility testing of indicator measurement are important considerations and should be conducted as part of the development process but also in new settings where the QIs are to be potentially applied. Potential users need to know if they will be able to retrieve the data to assess the QI from sources such as the medical records and this may vary between countries and sometimes within clinical settings (89, 215).

Point prevalence surveys are one of the most frequently used methods to assess the quality of antimicrobial prescribing in the hospital setting (19) and have been used to test QIs sets (215, 216). They are a particularly useful method of assessing the impact of process indicators on patient care and outcomes (23) in practice so future QI development studies should consider if new process QI sets can be incorporated and applied in point prevalence surveys.

4.5.1 Strengths and limitations of this study

To our knowledge, this is the first systematic review of the QIs for AMS programmes which has included a critical appraisal of the methodological quality of the QI sets, and is considered to be a strength of this study.

The selection of articles, data extraction and quality assessment with the AIRE assessment tool was conducted by two reviewers independently and showed good inter-rater reliability which increases the overall reliability of the results. This review included QIs assessing specific infectious conditions as well as broader QIs of AMS programmes so provides a comprehensive overview of AMS programme QIs.

We may have missed some QI sets which have not been published in an article or report. However, it is unlikely that validated and reliable QI sets for AMS have not been published in peer-reviewed literature.

The AIRE instrument used in this study to assess the methodological quality of studies mainly focusses on the QI development process and scores are allocated based on the information contained within the published article. Unfortunately, the process of developing QIs was not always reported in detail in studies and this resulted in some

studies being assigned lower scores for these criteria. As a result of this limitation the methodological quality of the QIs identified in this article may have been underestimated by using the AIRE instrument. There were, however, some studies which acknowledged the need to conduct piloting and clinimetric testing of their indicators so the low scores in these situations were accurate. A further limitation of this study was that we relied solely on the information contained within the published article.

4.6 Conclusions

This review provides an overview and critical appraisal of the methodological quality of QIs of AMS programmes. The study highlights the continuing need for transparent, valid and feasible QIs. Studies to date have focused on process and structural indicators with few outcome indicators developed, a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS. Testing of the QIs in practice should be an essential element of the QI development process and should be included in the QI development study or as planned validation work.

Chapter 5 Antimicrobial use and antimicrobial resistance in Enterobacterales species and *Enterococcus faecium*: a time series analysis.

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5.1 Abstract

Introduction

Irish and European antimicrobial resistance (AMR) surveillance data has highlighted increasing levels of resistance in Enterobacterales species and vancomycin resistance in *Enterococcus faecium* (VRE). Antimicrobial consumption (AC) in the Irish hospital setting is increasing.

Methods

A retrospective time series analysis (TSA) was conducted to evaluate the trends and possible relationship between AC of selected antimicrobials and the incidence of AMR in clinical isolates of Enterobacterales species and *E. faecium* isolates resistant to vancomycin, from January 2017 to December 2020.

Results

Increased AC was seen in ceftriaxone ($p = 0.0006$), piperacillin/tazobactam ($p = 0.03$) and meropenem ($p = 0.054$) while ciprofloxacin and gentamicin use decreased.

The rates of AMR of *E. coli* were trending downwards, AMR rates of *K. pneumoniae* was stable or decreasing, while AMR rates for the other Enterobacterales increased modestly with the greatest concern related to the increase in ertapenem resistance from 0.581% in 2017 to 5.19% in 2020 ($p = 0.003$). The rate of VRE decreased from 64% in 2017 to 53% in 2020 ($p = 0.1$).

TSA identified a correlation between piperacillin/tazobactam use and the decreasing rate of ceftriaxone resistance in *E. coli* isolates.

Conclusion

The decreasing or relatively stable rates of AMR found in Enterobacterales and VRE isolates in this study reflect the positive effect of the hospital AMS programme. The increasing incidence of CPE seen in this study should be addressed as part of the local AMS programme. The COVID-19 pandemic resulted in increased broad-spectrum antimicrobial use, however, it is too early to determine the impact of these changes on AMR rates.

5.2 Introduction

Antimicrobial resistance (AMR) is a significant threat to public health (1). The increasing levels of resistance among gram negative Enterobacterales organisms, and levels of vancomycin-resistance among the gram positive *Enterococcus faecium* (VRE) organism are causing concern across Europe (11) and in Ireland (12).

The well-established link between inappropriate and excessive use of antimicrobials and selection for AMR (25) has contributed to the rise in AMR among the Enterobacterales species (94). Antimicrobial stewardship (AMS) interventions are an important element in tackling AMR and are well established in the Irish hospital setting (51). However, the median overall rate of antimicrobial consumption (AC) in the Irish hospital setting has increased by 16% between 2009 and 2019 (56).
The COVID-19 pandemic associated with the novel coronavirus, SARS-CoV-2 (218), has had a significant impact on healthcare systems and delivery worldwide (219). Many routine AMS activities have been reduced and the impact of this on the incidence of AMR are yet to be determined (220). Furthermore, evidence suggests that there has been widespread and excessive prescription of antimicrobials due to the similarities between the clinical presentation, and difficulties in differentiating between COVID-19 and bacterial pneumonia, along with the absence of antiviral treatments with proven efficacy (221).

There is a lack of studies linking AC and AMR in the Irish hospital setting. Given the prevailing trends in AC and AMR in Ireland and the knowledge that AC is generally recognised as the primary driver of AMR, it is important to investigate how changes in AC influence bacterial susceptibility and at what time scale. This will assist in the development of policies to manage AMR particularly following the COVID-19 pandemic.
In this study we aim to investigate the trends and possible relationships between AC and AMR in Enterobacterales species, and the proportion of *Enterococcus faecium* isolates resistant to vancomycin, between 2017-2020 in an Irish hospital setting. The AMR data will also be compared with EU and other Irish hospital data.

5.3 Methods

5.3.1 Hospital setting

The study hospital is a 271 bed, inner city, acute University Teaching Hospital, in the Republic of Ireland. The hospital is comprised of various medical and surgical specialities, a paediatric unit, and a general intensive care unit. The hospital established a formal AMS programme in 2007. Key AMS events and policies implemented prior to and during the study period are summarised in Table 5.1.

Table 5.1 Chronology of important events in the hospital AMS programme

Year	Event/intervention	Effect and/or rational
2007	Appointment of an antimicrobial pharmacist	Establishment of a formal hospital AMS programme including annual point prevalence surveys and quarterly AC monitoring with feedback to hospital staff and at grand rounds
2009	Publication of the SARI Guidelines for antimicrobial stewardship in hospitals in Ireland (51)	Rationale for AMS in Irish hospitals and recommended AMS structures and interventions
2016	SPC changes to piperacillin/tazobactam dosing recommendations for nosocomial infections & severe pneumonia from 8-hourly intervals to 6-hourly.	Increased consumption which has not been accounted for in revised versions of the WHO DDD values.
2017	World-wide supply shortage of piperacillin/tazobactam	Reduced availability and adjustment of antimicrobial prescribing guidelines
2017-2018	Procalcitonin feasibility study in the hospital (162, 222) Investigation of its effect on antimicrobial prescribing in respiratory tract infections	Routine Procalcitonin testing has not yet been implemented
2018	The first hospital-acquired CPE case was identified in the study hospital in December 2017 with a further four cases identified in January 2018 (15)	Universal screening commencement for CPE for all hospital inpatients and grand round presentation in 2018
2018	JAMA (223) clinical trial comparing Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for patients with *E. coli* or *K. pneumoniae* Bloodstream Infection and Ceftriaxone Resistance	Increased use of meropenem to treat blood stream infections caused by *E. coli* or *K. pneumoniae* resistant to ceftriaxone
2018	Update of hospital antimicrobial prescribing guidelines	Empiric guidelines included recommendations for the use of carbapenems for multi-drug resistant infections
2019	EUCAST clinical breakpoint (v 9.0, valid from 1 January 2019 (224)	Recommended changes included higher antimicrobial doses for the treatment of Enterobacterales (gentamicin) and *Pseudomonas* (piperacillin/tazobactam, ceftazidime, ciprofloxacin, amikacin and gentamicin)
2019	The European Medicines Agency (safety committee PRAC) review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics (225)	A final legally binding decision by the European Commission in March 2019 recommended increased caution with usage
2019	Grand rounds presentation including presentation of a review of the restricted antimicrobial prescribing process	Update of the restricted antimicrobial prescribing policy
2020	March 9th 2020 1st in-patient diagnosed with Covid-19	Reduced core AMS activity (in person ward rounds, audits, AMS meetings, education and training activities) HSE interim guidelines on COVID-19 treatment guidelines

5.3.2 Antimicrobial consumption

Inclusion criteria

Quarterly aggregated hospital AC data (dispensed to inpatients on all hospital wards) for antimicrobial agents indicated in the treatment of infections caused by the Enterobacterales species were collated. This consisted of the following antimicrobial agents: Ceftriaxone, Ciprofloxacin, Levofloxacin, Ertapenem, Meropenem, Piperacillin/tazobactam, Gentamicin, Co-trimoxazole and Aztreonam. Data was also collated for Vancomycin.

Exclusion criteria

Antimicrobials dispensed to the out-patient setting.

Antimicrobials not indicated for the treatment of infections caused by the Enterobacterales species.

The AC data was obtained from the hospital pharmacy electronic dispensing records for the study period (1/1/2017 to the 31/12/2020). The data was converted to the standardised WHO's Anatomical Therapeutic Chemical (ATC) Classification of defined daily dose (DDD and antibiotic usage was expressed as quarterly aggregated DDDs according to the 2018 ATC classification and normalised per 100 hospital/bed days used (BDU) (55).

5.3.3 Antimicrobial resistance data

Inclusion criteria

Clinical microbiology specimens (blood, sterile fluid, sputum, urine, wound and anaerobic specimens) which identified the following organisms: *E. faecium*, *E. coli, K .pneumoniae* and other Enterobacterales species processed from patients during an inpatient hospital stay during the study period.

Exclusion criteria

Duplicate isolates from the same patient (226).

Microbiological isolates from community samples or outpatient clinics.

AMR data was collected from the hospital Microbiology laboratory database for the study period (1/1/2017 to the 31/12/2020). Bacterial identification and antibacterial

susceptibility testing were performed in the clinical microbiology laboratory of the hospital using the Vitek®2 (bioMérieux) system according to the manufacturer's guidelines. Antimicrobial susceptibility was assessed according to the recommendations of the European Committee for Antimicrobial Susceptibility Testing (EUCAST) antimicrobial susceptibility testing references and definitions (227). Percentage resistance to a specified antimicrobial were calculated for the selected bacteria. The resistance rate was defined as the percentage of total isolates that were resistant to the selected agent. All non-susceptible isolates (i.e. resistant and intermediate) were considered resistant.

5.3.4 Additional AMR data

The European Antimicrobial Resistance Surveillance Network (EARS-Net) reports population-weighted EU/EEA wide AMR rates (12) using data submitted by medical microbiology laboratories including the study hospital. While there is some variability in reporting across Europe, data from Ireland is estimated to cover 96% of the population with a high geographical, hospital, patient and isolate representativeness. This AMR data is based on antimicrobial susceptibility testing generated using EUCAST methodology for invasive (blood or cerebrospinal fluid) isolates. Where groups of antimicrobials are reported, the reported figure is based on the result for the antimicrobial showing the highest level of resistance (12). EU and National data is only available for VRE, *E. coli* and *K. pneumoniae*.

5.3.5 Statistical analysis

Initial analysis of the evolving trends in AC and AMR rates was conducted by linear regression analysis. Further analysis was conducted using time series analysis (TSA), which has been used previously to investigate possible correlations between AC and AMR where the data are measured repeatedly at equal intervals of time (114-116). The Box–Jenkins method of TSA modelling was used to develop univariate autoregressive integrated moving average (ARIMA) models of the AC and AMR data (117). Each time series was checked for stationary requirements (constant mean, variance and autocorrelation through time), with the unit root test (augmented Dickey–Fuller test); Some series did not need any transformation while some series required suitable differencing or other types of transformations, e.g., logarithmic

transformation, to obtain a stationary series; Once the series was stationary the sample autocorrelation function (ACF) and partial autocorrelation function (PACF) were used to identify the auto-regressive (AR), moving-average (MA) or mixed behaviour (ARMA). The ARIMA (p,d,q) model notation consists of *p,* the order of AR terms, *d,* the order of non-seasonal differencing operations, and *q,* the order of MA terms. Having constructed separate models for each antibiotic and resistance time series, we then diagnosed them for acceptability using the Akaike Information Criterion (AIK) and the Ljung- Box statistic for white noise for residuals.

Following the development of univariate ARIMA models, a linear transfer function modelling method (114, 116) was used to investigate the dynamic relationship between antimicrobial use and the incidence of resistant isolates, considering possible time delays (lag times). In this study the output or response was the percentage of AMR and the explanatory variable was AC. The cross-correlation function (CCF) between the residuals of the two ARIMA models was used to determine the correlations between the antibiotic use series and the incidence of resistant isolates. The transfer function model was then estimated with significance tests for parameter estimates at a p value of <0.05 used to eliminate unnecessary terms. The most parsimonious model was chosen, i.e. the model with the fewest parameters and highest biological plausibility. All final model residuals passed a 'white noise' test (based on the Ljung–Box statistics). For each model, the R^2 coefficient was calculated as goodness-of-fit measure, expressing the fraction of the variance of the dependent variable explained by the dynamic regression model. For the purposes of this manuscript only the significant findings are reported.

All statistical analyses were performed with R version 4.0.3 (228).

The study is reported according to the Strengthening the reporting of observational studies in Epidemiology (STROBE) statement: guidance for reporting observational studies(229) and the STROBE-AMS recommendations for reporting epidemiology studies of AMR and informing improvement in AMS (230).

5.3.6 Ethics

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals [Reference numbers ECM4(p) and ECM3(xx) Appendix 6].

5.4 Results

5.4.1 Hospital trends in AC

The trends in AC of the individual antimicrobials can be seen in Figure 5.1. Increasing trends were seen in ceftriaxone consumption (p= 0.0006), Piperacillin/tazobactam consumption (p = 0.03) and meropenem consumption (p = 0.054). Decreasing trends were seen in ciprofloxacin consumption (p = 0.0012) and gentamicin consumption (p= 0.057). Further trend analysis of AC is contained in Table 5.2.

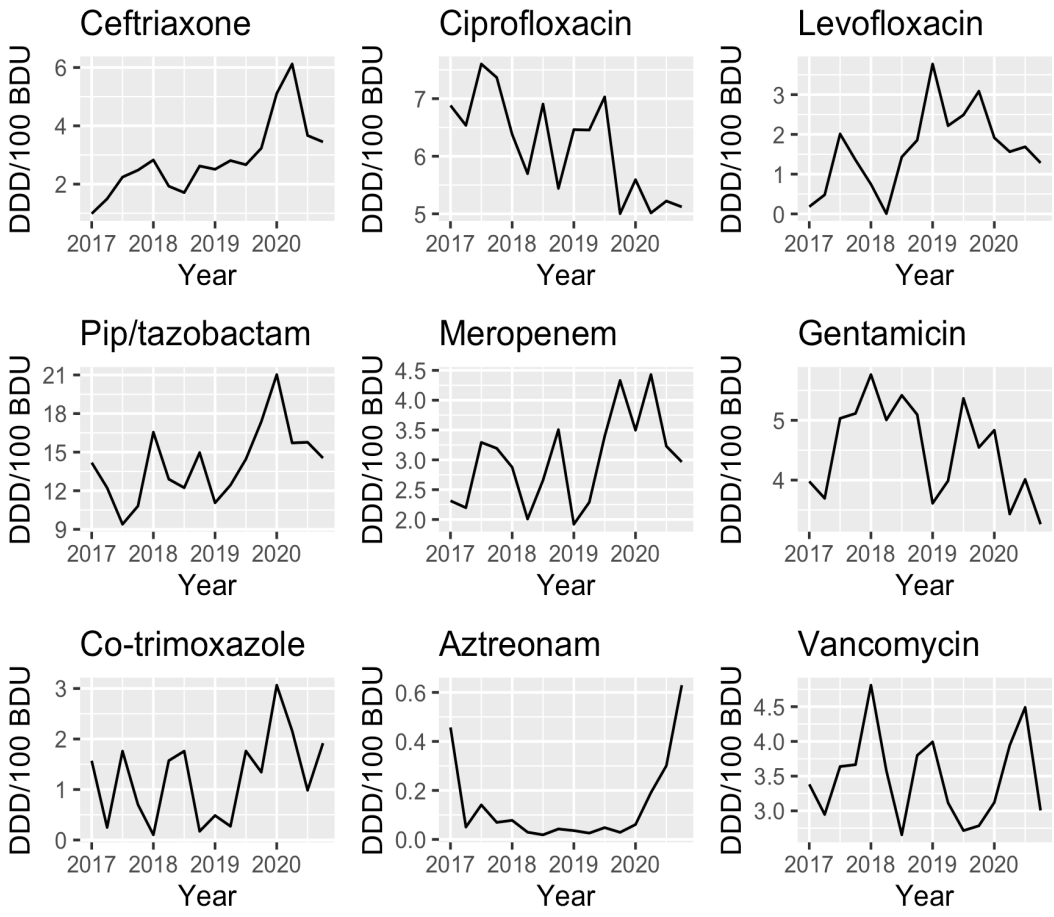

Figure 5.1 Quarterly antimicrobial consumption rates of selected antimicrobials from Q1 2017 to Q4 2020

Table 5.2 Annual antimicrobial consumption trends for in-patient antibiotic use in the study hospital 2017-2020 (Mean annual DDD/100 bed days)

Antimicrobial	2017	2018	2019	2020	Trend	p-value of trend
Third Generation cephalosporin						
Ceftriaxone	1.8	2.27	2.8	4.59	Increasing	0.0006
Carbapenems						
Ertapenem	0	0	0.0497	0.212	Increasing	0.011
Meropenem	2.75	2.76	2.98	3.53	Increasing	0.054
Fluroquinolones						
Ciprofloxacin	7.1	6.11	6.24	5.24	Decreasing	0.0012
Levofloxacin	1.01	1.01	2.89	1.61	Increasing	0.076
Aminoglycosides						
Gentamicin	4.45	5.32	4.38	3.88	Decreasing	0.057
Broad spectrum penicillin combination						
Piperacillin-tazobactam	11.7	14.2	13.8	16.8	Increasing	0.03
Other antimicrobials						
Aztreonam	0.18	0.0422	0.0347	0.296	Increasing	0.371
Co-trimoxazole	1.07	0.902	0.966	2.03	Increasing	0.15
Vancomycin	3.41	3.71	3.15	3.64	Stable	0.86

5.4.2 Hospital trends in AMR

The rates of AMR for *E. coli, K. pneumoniae* and VRE have been collated and are compared with Irish and European resistance figures in Table 5.3.

Table 5.3 Percentage of non-duplicate clinical isolates of E. coli, K. pneumoniae and E. faecium resistant to selected antimicrobials from the study hospital (Hosp), Ireland and the EU 2017-2019

Bacteria	Antimicrobial agent/Group	2017			2018			2019			2020
		Hosp	Ire	EU	Hosp	Ire	EU	Hosp	Ire	EU	Hosp
E. coli	Third generation cephalosporin*	21	12	14.9	15.8	12.9	15.1	13.2	12	15.1	14.2
	Carbapenems**	1.4	0	0.1	1.6	0	0.1	1.1	0	0.3	0
	Fluoroquinolones#	32.5	23.6	25.7	31.5	23.9	25.3	27.7	20.4	23.8	25.7
	Aminoglycosides	12.7	11.9	11.4	10.4	11.7	11.1	11.4	11.8	10.8	9.1
K. pneumoniae	Third generation cephalosporin*	19.6	14.9	31.2	17.8	14.5	31.7	11.9	17.6	31.3	10.8
	Carbapenems**	0	0.2	7.1	1.4	0.6	7.5	0	0.9	7.9	1.92
	Fluoroquinolones#	22.4	5.9	30.5	23.3	8.1	19.5	8	5.3	19.3	12.5
	Aminoglycosides	17.8	11.9	24.1	14.6	13	22.7	10	11	22.3	3.85
E. faecium	Vancomycin resistance	64.1	38.2	14.9	56.3	40.2	17.3	48.6	38.4	18.3	53

*EU and Ire data relates to cefotaxime/ceftriaxone/ceftazidime, study hospital data relates to ceftriaxone resistance

** EU and Ire data relates to imipenem/meropenem, study hospital data relates to ertapenem resistance

EU and Ire data relates to ciprofloxacin/levofloxacin/ofloxacin, study hospital data relates to ciprofloxacin resistance

5.4.3 E. coli

The number of clinical isolates of *E. coli* per year ranged from 233 in 2017 to 211 in 2020. The evolving trends in *E. coli* resistance to selected antimicrobials can be seen in Figure 5.2. The rates of resistance to the listed antimicrobials in the clinical isolates of *E. coli* were all trending downwards [e.g. Ceftriaxone p = 0.136, Ciprofloxacin p = 0.138, Piperacillin/tazobactam p = 0.143], except for co-trimoxazole (p = 0.69). Fluoroquinolone resistance rates in the hospital have fallen since 2017 (p = 0.138) but are consistently higher than national and EU rates. The presence of the ESBL resistance mechanism in the study hospital *E. coli* isolates ranged from 19.8% in 2017 to 14.1% in 2020 (p = 0.323). Further details on the annual rates of resistance are contained in table 5.4.

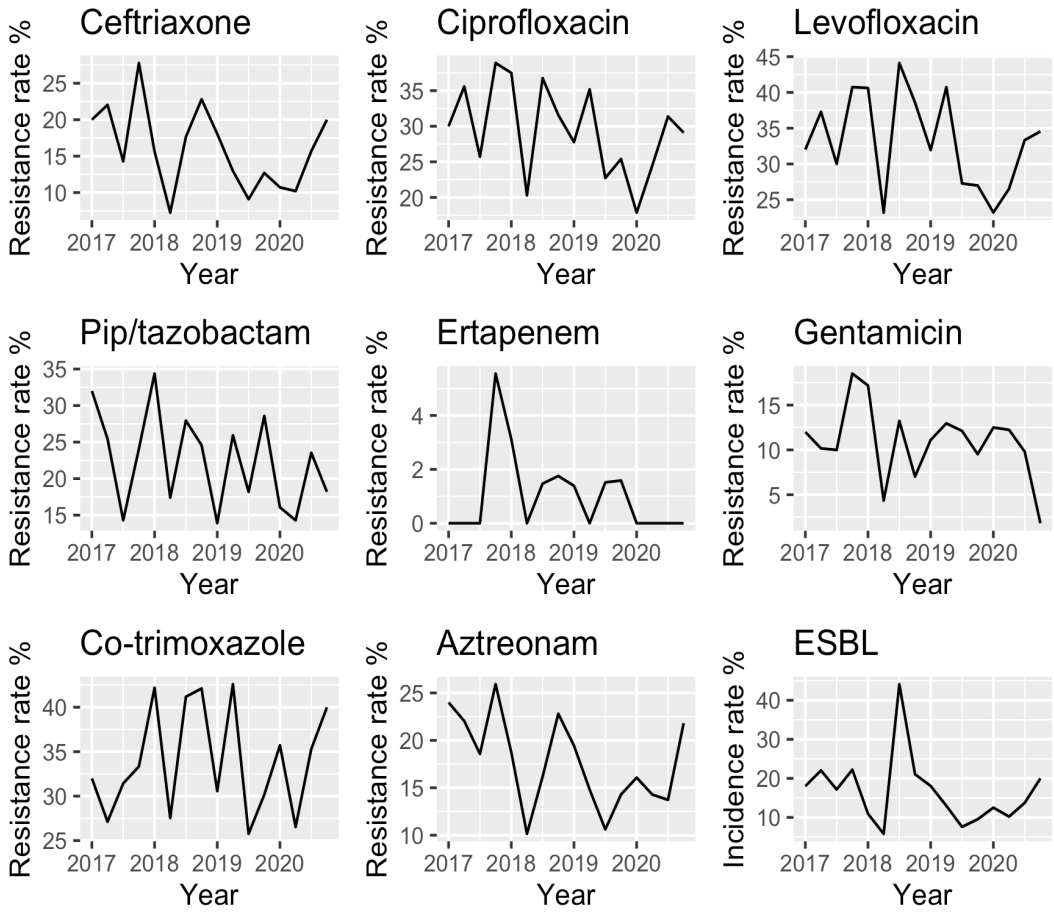

Figure 5.2 Quarterly E. coli resistance rates to selected antimicrobials from Q1 2017 to Q4 2020

Table 5.4 Percentage of non-duplicate clinical isolates of E. coli antibiotic resistance trends in the MUH (Annual mean quarterly resistance %)

Antibiotics	2017	2018	2019	2020	Trend	p-value of trend
Number of Isolates	233	258	255	211		
Ceftriaxone	21	15.8	13.2	14.2	Decreasing	0.136
Ciprofloxacin	32.5	31.5	27.8	25.7	Decreasing	0.138
Levofloxacin	35	36.6	31.7	29.4	Decreasing	0.233
Co-trimoxazole	31	38.3	32.3	34.4	Stable	0.69
Ertapenem	1.39	1.59	1.12	0	Stable	0.32
Meropenem	0	0.39	0	0	Stable	0.467
Piperacillin-tazobactam	23.9	26.1	21.6	18	Stable	0.143
Gentamicin	12.7	10.4	11.4	9.09	Stable	0.206
Aztreonam	22.6	17	14.8	16.5	Decreasing	0.07

5.4.4 K. pneumoniae

The number of clinical isolates of *K. pneumoniae* per year ranged from 72 in 2017 to 59 in 2020. The evolving trends in *K. pneumoniae resistance* to selected antimicrobials can be seen in Figure 5.3. The rates of resistance to the listed antimicrobials in the clinical isolates of *K. pneumoniae* were stable or trending downwards. Third generation cephalosporin resistance was considerably higher in the EU than in Ireland, and in the study hospital. Carbapenem resistance rates were higher in the EU, but were trending slowly upwards in Ireland, and fluctuating in the study hospital based on ertapenem resistance rates. Fluoroquinolone resistance was lower in 2017 in the study hospital (22%) than the EU (30%); the hospital rate has fallen below the EU rate but remains above the national rate in the following years as can be seen in the ciprofloxacin and levofloxacin rates in Table 5.3 and Figure 5.3. The presence of the ESBL resistance mechanism in *K. pneumoniae* isolates ranged from 19.8% in 2017 to 8.88% in 2020 (p = 0.0254) in the study hospital. Further details on the annual rates of resistance are contained in Table 5.5.

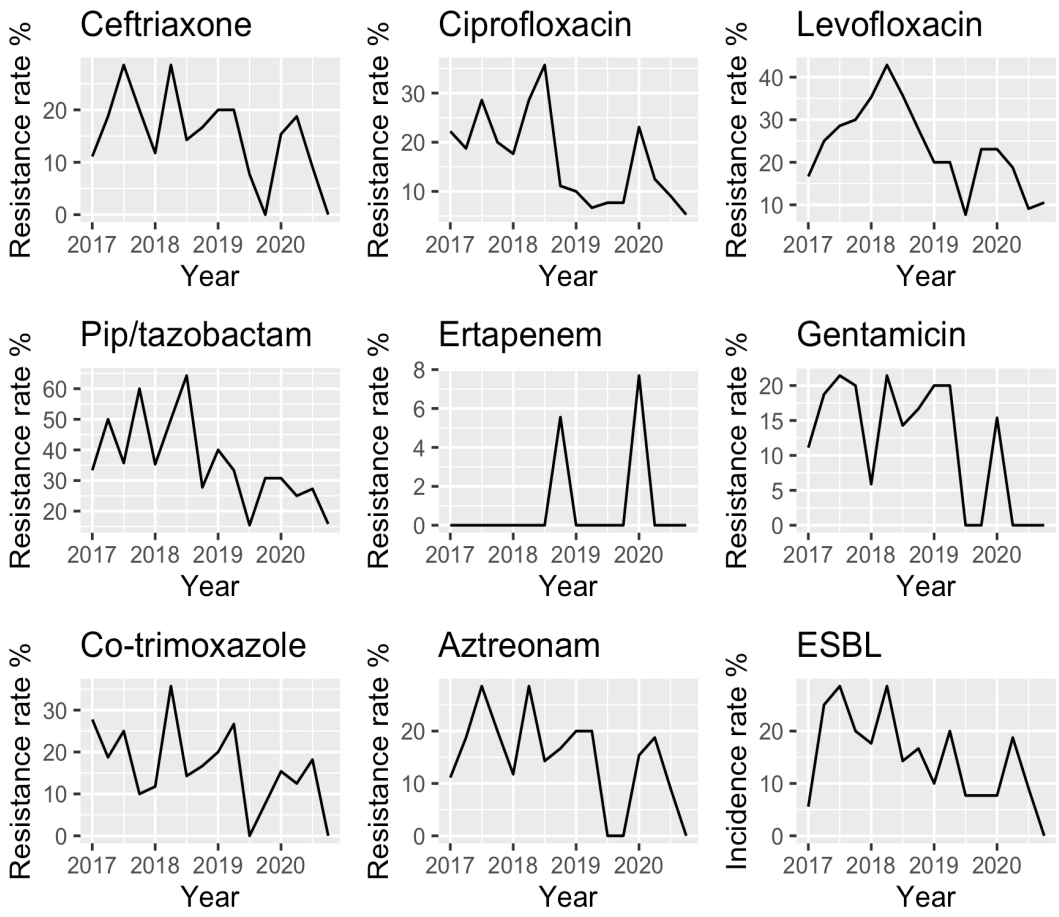

Figure 5.3 Quarterly Klebsiella pneumoniae resistance rates to selected antimicrobials from Q1 2017 to Q4 2020

Table 5.5 Percentage of non-duplicate clinical isolates of Klebsiella pneumoniae antibiotic resistance trends (Annual mean quarterly resistance %)

Antibiotics	**2017**	**2018**	**2019**	**2020**	**Trend**	**p-value of trend**
Number of Isolates	72	63	51	59		
Ceftriaxone	19.6	17.8	11.9	10.8	Decreasing	0.043
Ciprofloxacin	22.4	23.3	8.01	12.5	Decreasing	0.014
Levofloxacin	25.1	35.4	17.7	15.4	Decreasing	0.0255
Co-trimoxazole	20.4	19.6	13.6	11.5	Decreasing	0.053
Ertapenem	0	1.39	0	1.92	Increasing	0.471
Meropenem	0	1.39	0	1.92	Increasing	0.471
Piperacillin-tazobactam	44.8	44.3	29.9	24.7	Decreasing	0.012
Gentamicin	17.8	14.6	10	3.85	Decreasing	<0.01
Aztreonam	19.6	17.8	10	10.8	Decreasing	0.0462

5.4.5 Other Enterobacterales species (excluding *K. pneumoniae* and *E. coli*)

The number of clinical isolates of other Enterobacterales species per year ranged from 165 in 2017 to 133 in 2020. The most frequently isolated other Enterobacterales species were: *Citrobacter, Enterobacter, Proteus* and *Serratia.* The evolving resistance trends in the other Enterobacterales species to selected antimicrobials can be seen in Figure 5.4. While there were some increases in the rates of resistance to most antimicrobials during the study period the trend of greatest concern was in ertapenem resistance which increased from 0.581% in 2017 to 5.19% in 2020 (p = 0.003).

The presence of ESBL positive Enterobacterales isolates was insignificant (1.43% in 2017 to 0% in 2020, [p = 0.013]). Further details on the annual rates of resistance are contained in Table 5.6.

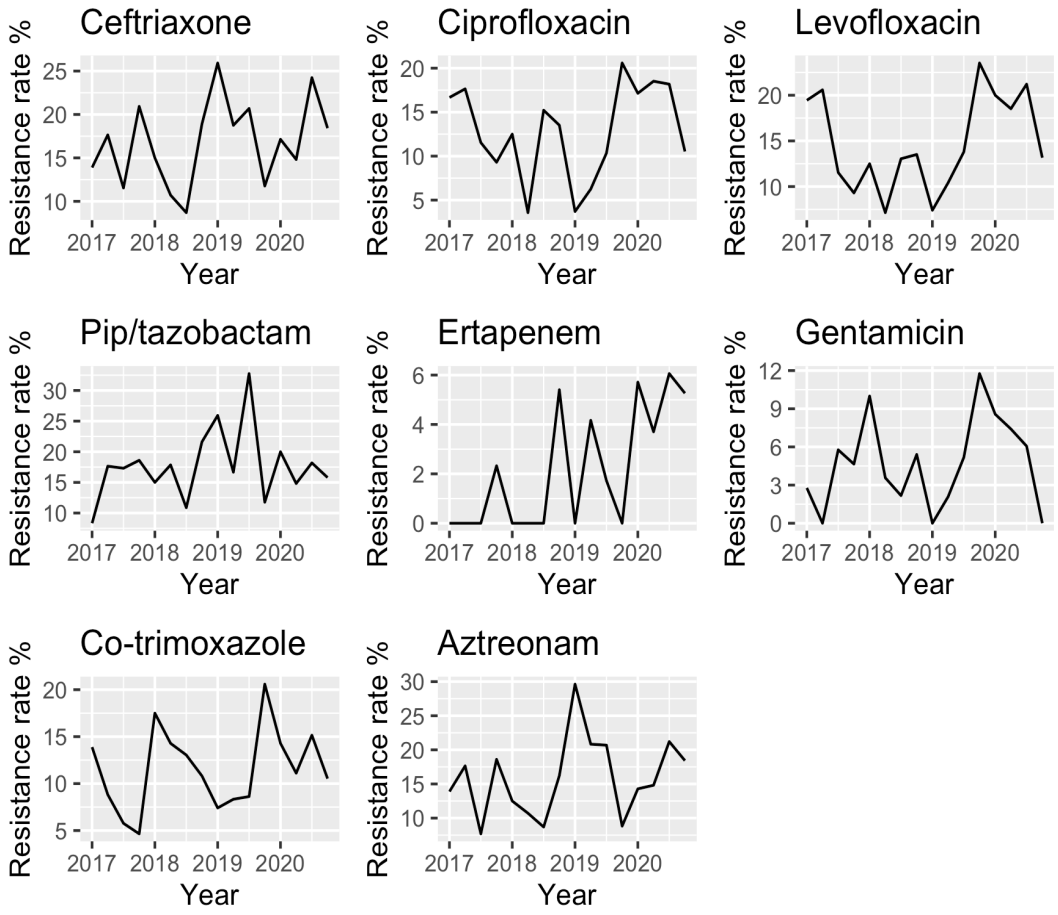

Figure 5.4 Quarterly resistance rates for other Enterobacterales species to selected antimicrobials from Q1 2017 to Q4 2020

Table 5.6 Percentage of non-duplicate clinical isolates of other Enterobacterales species antibiotic resistance trends (Annual mean quarterly resistance %)

Antibiotics	2017	2018	2019	2020	Trend	p-value of trend
Number of Isolates	165	151	167	133		
Ceftriaxone	16	13.3	19.3	18.7	Stable	0.231
Ciprofloxacin	13.8	11.2	10.2	16.1	Fluctuating	0.571
Levofloxacin	15.2	11.5	13.8	18.2	Fluctuating	0.353
Co-trimoxazole	8.28	13.9	11.2	12.8	Increasing	0.353
Ertapenem	0.581	1.35	1.47	5.19	Increasing	0.003
Meropenem	0	0.676	0	0	Stable	0.918
Piperacillin-tazobactam	15.5	16.3	21.8	17.2	Increasing	0.426
Gentamicin	3.3	5.29	4.76	5.51	Increasing	0.44
Aztreonam	14.5	12	20	17.2	Fluctuating	0.3

The most frequently isolated other Enterobacterales species were:

2017 –165 isolates *(Citrobacter (21), Enterobacter(55), Proteus(28), Serratia(21))*

2018-151 isolates *(Citrobacter (20), Enterobacter(39), Proteus(35), Serratia(20))*

2019-167 isolates *(Citrobacter (16), Enterobacter(59), Proteus(30), Serratia(22))*

2020-133 isolates *(Citrobacter (12), Enterobacter(34), Proteus(36), Serratia(21))*

5.4.6 E. faecium

The number of clinical isolates of *E. faecium* per year ranged from 116 in 2017 to 124 in 2020. In the study hospital the rate of VRE has decreased from 64% in 2017 to 53% in 2020 ($p = 0.1$) but is considerably higher than seen both nationally and in the remainder of the EU.

5.4.7 Incidence and dynamic regression of *E. coli* resistance to ceftriaxone and the influence of piperacillin/tazobactam

For ceftriaxone resistance in *E. coli* we identified an ARIMA model (117) with one significant moving average term of order 2. The transfer function model was developed which explained 86% (R^2=86) of the variation in incidence with piperacillin/tazobactam consumption as a statistically significant explanatory variable for ceftriaxone resistance in *E. coli*. A 1% increase in piperacillin/tazobactam use would result in a 1.33% decrease in ceftriaxone resistance immediately and a further 0.488 % decrease in 3 months. The transfer function model also included the moving average term of the resistance rate itself with a lag of 6 months. Further details are contained in Table 5.7.

Table 5.7 Multivariate transfer function model of piperacillin/tazobactam use and temporal relationship with the incidence of non-duplicate clinical isolates of E. coli resistant to ceftriaxone

(Intercept)	53.930 *** [9.003]
Piperacillin/tazobactam lag 0	-1.333 ** [-4.564]
Piperacillin/tazobactam lag 1	-0.488 [-2.246]
Moving average term 2	-0.839 *** [-6.509]
N	12
R squared	0.864
logLik	-23.135
AIC	56.270

*** p < 0.001; ** p < 0.01; * p < 0.05. T statistics in brackets.

5.5 Discussion

This study contains an analysis of the rates of AC and AMR in an Irish teaching hospital using TSA. The findings show that while overall AC rates and broad-spectrum antimicrobial (ceftriaxone, piperacillin/tazobactam and meropenem) use increased over the study period there was not a corresponding increase in rates of AMR, in fact the rates of resistance decreased or remained stable with a few exceptions. These findings suggest that hospital AC is just one of several factors that influence the rates of AMR seen in the hospital setting.

Analysis of AMR trends in this study showed hospital rates of resistance in *E. coli* and *K. pneumoniae* were decreasing or stable. The rates of AMR in the other Enterobacterales isolates were relatively stable or slowly increasing. The rate of ertapenem resistance (CPE) in *K. pneumoniae* and other Enterobacterales isolates is increasing, following a national trend of increasing incidence of CPE and the diagnosis of invasive CPE infections (14). The rate of VRE in the study hospital has fallen from 64% in 2017 to 53% in 2020 but is higher than national and EU figures.

The decreasing or stabilising rates of AMR among Enterobacterales isolates seen in this study is encouraging and suggests the hospital AMS programme is having a positive impact on gram negative AMR rates (231). A recent analysis of AC and AMR data from the EU has identified similar findings in terms of stabilisation of AMR rates in *E. coli* and *K. pneumoniae*, which was associated with the positive effects of AMS initiatives (232). The decrease in the rate of VRE in this study is also encouraging as historically, AMS programmes have been less effective in reducing the incidence rates of VRE (231). It is important that the increasing incidence of CPE seen in this study is addressed as part of the local AMS programme. The most effective AMS interventions to target CPE are those which address carbapenem use and incorporate education and restrictive measures (233, 234). The reduction in AMS activities (220) seen during the COVID-19 pandemic is likely to have contributed to the increased carbapenem use seen during this study.

When each of the AC-AMR combinations (e.g. AC and ertapenem resistance, AC and VRE rates) were cross-correlated using linear regression of the ARIMA model residuals, only one significant correlation between antimicrobial use and AMR was identified. This may have been because it is difficult to demonstrate a statistically

significant correlation due to the complex and evolving nature of AMR despite the link between AMR and AC being well established (235). A recent study from the Netherlands in the outpatient setting found that the association between antimicrobial use and resistance was weak (236). Suggested factors for the lack of correlation included patient related factors (e.g. age, sex), individual patient antimicrobial exposure, resistance mechanisms to antimicrobials between different bacteria (236) and the interaction with the use of other antimicrobials (114).

In this study a correlation between piperacillin/tazobactam use and the rate of resistance to ceftriaxone in *E. coli* was observed using TSA. Over the study period the rate of resistance to ceftriaxone in *E. coli* decreased while the use of ceftriaxone increased particularly in 2020. The increased consumption of ceftriaxone during 2020 did not appear to have an immediate impact on the rate of ceftriaxone resistance but this should be monitored due to a potential lag in the influence of the increased use on rates of resistance. The use of piperacillin/tazobactam also increased during the study period but using TSA a correlation was identified with the decrease in ceftriaxone resistance in *E. coli.* This effect has also been seen in a study involving the substitution of piperacillin/tazobactam for a broad-spectrum cephalosporin (ceftazidime) which resulted in decreasing levels of ceftazidime resistance in other Enterobacterales species *(K. pneumoniae* and *Proteus mirabilis)* (237). Resistance strain dynamics can play an important role in changes in AMR rates in *E. coli* species and are influenced by antimicrobial consumption changes (116). In situations where there are high levels of resistance to third generation cephalosporins such as ceftriaxone as seen in the study hospital, efforts to substitute ceftriaxone with piperacillin/tazobactam should be considered.

The consumption of broad spectrum antimicrobials ceftriaxone, piperacillin/tazobactam and meropenem, increased over the course of the study with a particularly large increase in 2020, during the COVID-19 pandemic. As expected, the increased consumption of these antimicrobials was associated with the treatment of suspected pneumonia in patients with suspected or proven COVID-19 following national recommendations for AMS strategies during the pandemic (238). Studies have estimated that up to 72% of hospitalised COVID-19 patients received antimicrobials while the rate of bacterial co-infection ranged from 6% (239) to 11% (240). Such instances of poor AMS highlight the challenges faced in the delivery of AMS programmes during the pandemic (240) and the negative impact it has had on

AMS activities (220). The increases in the prescribing of broad-spectrum antimicrobials and decreased AMS activities has led to concerns that AMR may proliferate in hospitals because of COVID 19. However, the COVID-19 pandemic does not appear to have resulted in significant changes to AMR rates seen in the study hospital in 2020, or elsewhere to date (241).

One potential benefit of the COVID-19 pandemic was the enhancement of Infection Prevention and Control (IPC) (242) practices. AMS programmes are more effective when implemented alongside IPC measures (231) as antimicrobial use selects for AMR, it's dissemination is facilitated by suboptimal IPC practices and AC. While some AMS activities decreased during the COVID-19 pandemic, IPC was brought to the fore, and an increased recognition of the importance of IPC in reducing the transmission of infection resulted.

The focus of this study was on AC and AMR in the hospital setting but it is important to acknowledge the impact of community antimicrobial use has on AMR, as antimicrobial use in one setting can impact AMR in the other. This 'spill-over' effect has previously been suggested as a reason for not detecting AC and AMR correlations particularly in smaller patient populations (243). The response to the COVID-19 pandemic are also likely to impact AC and AMR in the community, decreased international travel, social distancing and mask wearing all reducing the transmission of infection (241). The implications of changes to community AC and other changes in response to the COVID 19 pandemic will be important to explore.

5.5.1 Limitations of the study

The study was ecological in nature and did not analyse AMR and AC data at the patient level and nor did not control for patient-related factors. The study was unable to determine if individual patients identified with a resistant organism were exposed to the most relevant antimicrobial, other antimicrobials or risk-factors conventionally associated with resistance which means we cannot exclude confounding factors that may be responsible for the observed relationships.

Patient demographic data were only available for AMR and not AC, limiting the value of trying to include variables such as age, sex and location in our analysis. However,

given the large sample size, effects of sampling variation in patient-level characteristics should theoretically be negligible.

This study only included clinical isolates and not routine surveillance cultures leading to a risk of selection bias due to an underestimate of the incidence of resistance. It is possible that not all patients with infections in the hospital may have been identified, some diagnosed infections may not have had specimens sent to the microbiology laboratory for investigations, and some specimens from infected patients may not have grown a microorganism to identify and submit for antimicrobial susceptibility tests.

This was a single centre retrospective study which makes it difficult to explore the complex relationship further. Future studies involving multi-centres and community practice would allow the examination of the relationships more fully.

Other studies have suggested more frequent observations should be used when conducting TSA (115) however this was not practical for this study. The use of a longer reporting period should be considered in future studies with the use of monthly data to increase sensitivity to identify possible correlations.

5.6 Conclusion

The decreasing or relatively stable rates of AMR found in the Enterobacterales and VRE isolates in this study are a positive response to the hospital AMS programme. Broad spectrum AC increased over the course of the study with a particularly large increase in response to the COVID-19 pandemic. Much of the increase during the COVID-19 pandemic may have been unnecessary and occurred at a time of decreased AMS programme activities but has not resulted in changes to AMR rates to date. IPC practices have improved in response to the COVID-19 pandemic and continue to contribute to the effectiveness of AMS programmes.

Future research should explore the possible link between AC and AMR in the local community as well as the hospital setting, and patient level AC and AMR data would be a significant advantage for this. The use of TSA to analyse routine AC and AMR data as part of AMS programmes should also be considered, as it would allow for the identification and analysis of correlations such as that between piperacillin/tazobactam and ceftriaxone resistance in *E. coli* identified in this study to be investigated further.

Chapter 6 Discussion

6.1 Chapter overview

This doctoral thesis investigated opportunities to measure and improve the delivery of antimicrobial stewardship (AMS) programmes in the Irish hospital setting. This included the introduction of procalcitonin testing to support the AMS programme, evaluating quality indicators for hospital AMS programmes and analysis of the trends and possible relationships between antimicrobial consumption and antimicrobial resistance. This discussion will provide an overview of the main findings arising from this body of work and interpretation within the context of previous research. The theoretical and clinical implications and recommendations for policy and AMS programmes, along with areas of future research will be discussed.

6.2 Summary and interpretation of the main findings

The main findings arising from the studies in this thesis are as follows:

Procalcitonin is a useful AMS intervention reducing antimicrobial duration and length of hospital stay in patients with a respiratory tract infection when accompanied by a successful implementation process (Studies 1 and 2).

Quality indicators for hospital AMS programmes are an important means of measuring and identifying areas for improvement (Study 3).

Time Series Analysis is a suitable method to analyse antimicrobial consumption and antimicrobial resistance trends and to identify changes and guide interventions (Study 4).

6.3 Procalcitonin intervention

The main aim of this research thesis was to investigate opportunities to measure and improve the delivery of AMS programmes in the Irish hospital setting (Chapter one, Figure 1.6). The first objective was to investigate if the implementation of procalcitonin (PCT) testing for patients with respiratory tract infections (RTI) supported the AMS programme by conducting a randomised feasibility study (Study 1) and a process evaluation (PE) (Study 2). PCT testing was conducted in the microbiology laboratory and the PCT serum concentrations were interpreted using a validated evidence-based algorithm (151) to generate antimicrobial prescribing recommendations which were communicated to the participating respiratory physicians. The physicians retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm generated antimicrobial prescribing advice. The findings from Study 1 were that PCT testing had a positive effect on antimicrobial prescribing contributing to a significant reduction in the duration of antimicrobial prescriptions and in the length of hospital stay in patients with RTI (162), which are important goals for AMS programmes. These findings support the conclusion of a Cochrane systematic review and meta-analysis which supported the role of PCT in supporting AMS in patients with RTI (76). This was evident despite a relatively low compliance rate of 35% with the antimicrobial prescribing recommendations generated using a PCT-based algorithm. Other published studies have shown that PCT algorithm compliance can be variable (153), thus our study is not unusual in this regard. Variable PCT algorithm compliance does not appear to reduce the overall

impact of the PCT intervention. Studies such as the ICU based PRORATA trial which had a 53% algorithm adherence resulted in a significant decrease in antimicrobial duration of 2-3 days in patients receiving PCT guided care (244). It is important to acknowledge that physicians can require time to become familiar with, and develop confidence in the use of new diagnostic tests such as PCT (154) and centres with experience of using PCT along with ongoing reinforcement of PCT guided antimicrobial stewardship had higher algorithm compliance than PCT naive centres (153). Studies where PCT was introduced as part of an AMS programme have been found to successfully decrease antimicrobial use (155, 245). The integration of new rapid diagnostic tests continues to have an important role in AMS programmes to improve patient outcomes (246).

It is important to acknowledge that the use of PCT testing remains controversial. NICE (UK) failed to recommend its use in the UK NHS based on a Health Technology Assessment (HTA) (247). The HTA questioned whether the observed costs and effects are directly attributable to PCT testing, and the generalisability of findings of existing studies into the UK health service setting (247). NICE have since commissioned 3 studies into the use of PCT; ADAPT Sepsis (adult sepsis in the ICU), PRONTO (adult ED sepsis) and BATCH (paediatric sepsis) (248).

Despite the failure of NICE to endorse the use of PCT, its use has grown substantially in the NHS since the onset of the COVID-19 pandemic with up to 50% of NHS hospitals using PCT in emergency/acute admissions (248). There are, however, concerns regarding variability in implementation (248) but this will be addressed in the recently commissioned PEACH study (Procalcitonin: Evaluation of Antibiotic use in COVID-19 Hospitalised patients) (249). The PEACH study will determine whether, and how, PCT testing should be deployed to protect patients from antimicrobial overuse during the COVID 19 pandemic.

At a local level, barriers including the PCT test costs and the availability of adequate AMS resources, particularly during the COVID-19 pandemic, to support implementation based on the recommendations of Studies 1 and 2 in the study hospital setting have meant that an opportunity to implement PCT locally has not been possible to date.

AMS programmes are resource intensive and costs (i.e. personnel, new diagnostics) are a well-known barrier to implementation of AMS initiatives (250), however the cost savings associated with a relatively small decrease in length of hospital can result in significant cost savings which far outweigh additional costs of new tests such as PCT (251).

6.4 Process evaluation of the procalcitonin intervention

On completion of the PCT feasibility study a qualitative PE (Study 2) was conducted with the aim of exploring if and why the PCT intervention worked or did not work in an Irish hospital setting (222). Study 2 identified the positive elements of the successful implementation process employed during Study 1. These included the PCT evidence-base, participant engagement with the intervention, good communication between the AMS team and medical teams, education and training received and the developing culture of quality improvement in the hospital (105). The engagement of participants was also evidenced by their recommendations to facilitate improved implementation of the intervention in the future.

A recent qualitative study of Norwegian hospital physicians' experience with PCT supported the findings of Studies 1 and 2, including a positive opinion of PCT as an additional infection marker, implementation as part of the AMS programme and the need for ongoing education to support implementation (173).

The implementation process of an intervention such as PCT is of critical importance. The sub-optimal implementation of a PCT-based algorithm in a study in the USA of 20,750 critically ill patients with sepsis in 107 hospitals where PCT was available, found PCT use was not associated with improved antimicrobial use or other clinical outcomes (252). PCT testing was not implemented as per protocol which was found to be efficacious in other clinical studies (77, 155). The study found only 18% of patients had PCT levels checked, the checking of PCT levels was characterised by the taking of single and infrequent PCT levels, contributing to the disappointing study findings (252).

As well as assessing the fidelity and quality of a complex health-care intervention such as PCT to facilitate improved development and implementation of the intervention

(99), Study 2 also provides an important exploration of the contextual influences on the implementation process. Two main barriers to the implementation of AMS interventions such as PCT to modify prescribing behaviour, emerged during Study 2. Professional hierarchies are an established barrier to AMS interventions due to the perceived professional knowledge and clinical experience of 'experts in their own fields' (171). In Study 2 the participating respiratory medicine physicians cited their experience of diagnosis and treatment of respiratory tract infections, making antimicrobial prescribing decisions, and also noted examples of conflict with the AMS team in relation to guidelines (222). These findings are similar to the findings of other qualitative studies investigating the relationship between respiratory medicine and AMS teams (170, 172). Knowledge of these barriers, better engagement and communication between the AMS team and respiratory medicine are essential to help overcome such barriers as intervention implementation is a '*social process'* (184).

A further barrier which emerged in Study 2 was the culture of risk aversion in infection treatment and the difficulties in changing the '*just in case*' antimicrobial prescribing practices (222). A systematic review of qualitative studies of physicians antimicrobial prescribing behaviour found fear was considered the most influential factor on physicians antimicrobial prescribing behaviour (253). In another systematic review of qualitative studies of antimicrobial prescribing behaviour physicians appear to have an inability to associate their own behaviours with the emergence of AMR, while simultaneously tending towards over-prescription of antimicrobials (178). Diagnostic uncertainty has been suggested as a contributory factors in the over-prescription of antimicrobials (253). Therefore, interventions such as PCT, which provide further clinical information in relation to infections can be considered as a useful additional diagnostic tool to support physicians and change risk perceptions facilitating changes in prescribing practices. PCT has a role as an infection 'adjunct' marker. It should be evaluated as a part of the overall clinical picture and assessment of patients (138) and it should reduce some physician anxiety regarding missing infections.

6.5 Measuring the quality of hospital AMS programmes

The second objective of this thesis (Chapter one, Figure 1.6) was to review opportunities to measure the quality of hospital AMS programmes and to investigate

the possible influence of antimicrobial consumption on antimicrobial resistance with a focus on Enterobacterales species resistance rates and vancomycin-resistant *Enterococcus* (VRE).

The first aspect of this objective was addressed by conducting a systematic review of quality indicators (QIs) for AMS programmes in the hospital setting (Study 3). The findings of Study 3 were a collation of an extensive range of 229 QIs which addressed the processes, structural elements and to a lesser degree outcome measures for AMS programmes. A critical appraisal and evaluation of the methodological qualities of the QIs was also conducted, an important and novel element of this review (254). The importance of this aspect of the review is underlined when it has been estimated that 10-20% of developed QIs are not measurable in practice (217), failing the essential requirement that QIs are able to demonstrate to potential users that the QIs '*can be used to assess the quality of care provided*' (82).

One of the most significant findings of this review was the considerable lack of outcome indicators developed to accurately measure and demonstrate the impact of AMS programmes on patient outcomes. This deficiency has also been noted by other recent studies and reflects an ongoing challenge for AMS programmes (81, 209). The lack of outcome indicators has been attributed to the difficulty in developing risk adjustment for confounding factors (211). However, it is encouraging that other studies have begun to address this problem by using process and structural indicators which can act as direct measures of the quality of healthcare, where a link has been demonstrated between a given process and outcome (212).

The broad range of process indicators identified in this review will allow institutions the ability to develop quality improvement programmes by targeting specific therapeutic areas (e.g. sepsis, CAP, COPD and UTIs) or locations within the hospital (e.g. ICU, HDU). The structural indicators can be applied by institutions to measure the implementation of the important structural elements of an AMS programme and identify deficiencies to be addressed in the future. They can also be used to benchmark performance between hospitals, within countries and across jurisdictions and to identify outliers. The generic QIs developed by van den Bosch (87) can be applied across hospital settings. Including the relevant process QIs as part of a hospital point prevalence survey is a useful means of assessing the impact of process indicators on patient care and outcomes (23). When considering the assessment of an AMS

programme an individual hospital should consider the most relevant and feasible QIs for their particular setting. This will include an assessment of the resource requirements to measure QIs can vary depending on the setting and infrastructure particularly IT.

6.6 Antimicrobial consumption and antimicrobial resistance

The second aspect of this objective involved the investigation of the possible influence of AC on AMR with a focus on Enterobacterales species resistance rates and vancomycin-resistant *Enterococcus* (VRE). The main finding from this study (Study 4) was that while overall AC rates had increased during the study period there was not a corresponding increase in the rates of AMR. The study found that trends in AMR rates for *E. coli, K. pneumoniae* and VRE had stabilised but an increasing resistance trend was seen in carbapenemase-producing Enterobacterales (CPE). Given the limited choice of therapeutic treatment options for CPE it is important that these rates of resistance, are monitored on an ongoing basis in order to determine if new AMS interventions are necessary.

A recent analysis of AC and AMR in Europe found a stabilising rate of AC in contrast to the increasing AC rate in Study 4, however the AMR rates of *E. coli, K. pneumoniae* and VRE have decreased or stabilised in both studies (232). This is an important finding which demonstrates that AMS programmes are impacting AMR rates. The linking of AC and microbiology outcome data is an important requirement to building a robust evidence base to guide clinical practice, a finding which a systematic review of the quality of studies evaluating AMS interventions has found is often lacking in AMR studies (255). The study identified a correlation between piperacillin/tazobactam use and the rate of resistance to ceftriaxone in *E. coli* using TSA. This is an interesting finding as it can be difficult to demonstrate a statistically significant correlation due to the complex and evolving nature of AMR (235). This correlation warrants further investigation in the future to determine if the substitution of ceftriaxone with piperacillin/tazobactam should be considered by AMS programmes.

6.7 Implications for public health

The findings of this thesis have important implications for public health, as well as in the local hospital setting. From a public health perspective the 'spill-over' effect (243) of AMR between the hospital and the wider community must be considered. The increasing rate of CPE may warrant greater surveillance in the community along with the need for increased screening of patients on admission to hospital for CPE colonisation.

The finding of Study 4 will play a role in the update of the Cork/Kerry hospital antimicrobial prescribing guidelines where local AMR rates are considered along with the latest evidence when drafting the recommendations and the researcher (FOR) participates on this review group. The high VRE rate and increasing incidence of CPE will be important considerations for the guideline review. With the increasing CPE incidence, consideration to include empiric treatment guidelines for CPE may be required.

6.8 Implications for practice

The *European One Health* initiative highlighted deficiencies in AC and AMR surveillance in Ireland which must be addressed to respond to current and emerging AMR threats and support AMS efforts to provide better evidence for decision making (91). The application of TSA methodology in Study 4 provides an effective method to analyse AC and AMR rates. Improved surveillance resources for AC and AMR would allow enhanced analysis of this data and the opportunity to promptly respond to any changes. TSA can also be applied to forecast future AMR rates (256). However, it is important to acknowledge that such forecasts cannot account for future changes in infection control measures, antimicrobial consumption changes and other factors within a hospital setting. TSA would also allow for the investigation of seasonal variation in antimicrobial use. A recent systematic review has identified a consistent winter peak and seasonal variation in AMR rates in *Streptococcus pneumoniae* to penicillin and all antimicrobials independently of geographic region (257). The inclusion of all clinically relevant specimens from the hospital in Study 4 provided a broader reflection of the AMR rates than the standard EUCAST methodology (227) which only includes invasive (blood or cerebrospinal fluid) isolates. Consideration

should be given to the use of all clinically relevant specimens, where available, when conducting AMR analysis in an institution or broader area.

6.9 Specific recommendations for AMS research:

- Future research in this area should consider a full randomised controlled trial and economic evaluation in a variety of hospital settings to confirm the effectiveness of PCT as an AMS intervention in patients with respiratory tract infections.
- Further research to investigate the potential role of PCT as an AMS intervention for other bacterial infection indications.
- Future qualitative research of the barriers and facilitators to AMS programmes and interventions.
- Future research into the development of AMS interventions should consider the contextual influences which will determine the success or failure of the intervention.
- Future research should address the deficit in outcome QIs for AMS programmes and continue to evaluate the use of existing process or structural indicators which have demonstrated significant benefit to clinical outcomes, adverse events, and costs.
- Further research into specific AMS intervention to target the increasing rates of CPE.
- Further research into the application of TSA to analyse the relationships between AC and AMR in the hospital and community setting.
- Further research into the AMR 'spill-over' effect between the hospital setting and community setting with an initial focus on CPE.

6.10 Specific recommendations for AMS policy:

- PCT should be considered as a AMS intervention to improve antimicrobial use in hospitals.
- Consideration should be given to incorporate additional process indicators as part of the National point prevalence surveys targeting specific areas of practice.

- Consideration should be given to the use of TSA to enhance the surveillance of AC and AMR rates.
- Consideration should be given to conducting CPE surveillance in the community to determine its prevalence in the population and develop plans to address the findings.
- The HPSC should consider the inclusion of all clinical isolates when determining national AMR rates.

6.11 Specific recommendations for AMS practice:

- Introduce PCT testing as an AMS intervention.
- Apply QIs to identify deficiencies and drive improvement in AMS programmes.
- Introduce TSA to enhance the surveillance of AC and AMR to identify changes and risks, which would allow for prompt changes to AMS policy and practice in response.

6.12 Conclusion

This thesis presents a comprehensive and detailed body of research investigating AMS opportunities in the Irish hospital setting. It has achieved its aim of investigating opportunities to measure and improve the delivery of AMS programmes in the Irish hospital setting by successfully demonstrating that a PCT testing intervention supports the AMS programme when supported by a detailed and robust implementation process. An extensive range of QIs for AMS programmes in hospital have been collated and critically appraised. TSA has been applied to explore the relationship between AC and AMR.

The results of this research indicate that AMS programmes will need to continue to evolve, and dedicated resources will be required to support research in AMS practice. This will include optimising the use of new diagnostic tools such as PCT to support physicians in making antimicrobial prescribing decisions; the incorporation of QIs to assess and improve AMS programmes; and the implementation of in-depth surveillance analysis of AC and AMR using TSA. These measures have the potential to make substantial contributions to hospital AMS measures locally and internationally.

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Appendix 1.

Ethical approval for Studies 1 and 2 (Chapters 2 and 3).

UCC
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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

ECM 4 (w) 07/02/17 & ECM 3 (III) 04/04/17

27th March 2017

Dr Aoife Fleming
Lecturer in Clinical Pharmacy
University College Cork
Room UG04
Cavanagh Pharmacy Building
College Road
Cork

Re: Randomised feasibility study of the use of procalcitonin serum level testing to support the antimicrobial stewardship programme for the treatment of patients admitted to hospital with respiratory tract infections.

Dear Dr Fleming

The Chairman approved the following:

- Cover Letter dated 16th March 2017
- Revised Application Form
- Medical Chart Data Collection Sheets
- Consent Form for Doctor Interviews
- Interview Questions for Doctors
- Participant information leaflet and consent form for control arm 1
- Participant information leaflet and consent form for control arm 2
- Participant information leaflet and consent form for active arm
- Interview questions for doctors.

Full approval is now granted to begin this study.

Yours sincerely

Professor Michael G Molloy
Chairman
Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Ollscoil na hÉireann, Corcaigh - National University of Ireland, Cork

Appendix 2.

Supplementary material for Study 1 (Chapter 2).

SUPPLEMENTARY DATA S1

RespPCT-Procalcitonin-based algorithm to support antibiotic prescribing decisions in patients with lower respiratory tract infections

RespPCT Inclusion Criteria:

1. Adult patients (≥18years old) admitted to hospital from the community or a nursing home under the care of a medical team with an acute RTI and commenced on antimicrobials.
2. Provision of informed consent in accordance with local ethics approval (See Appendix 1 for Clinical Research Ethics Committee approval letter, Appendix 2 for Participant information leaflet and consent forms (intervention and control groups).

RespPCT Exclusion Criteria:

1. Patients unable to give written informed consent due to language restrictions, cognitive impairment or severe dementia
2. Re-admission to hospital within 30 days of previous admission
3. Immunosuppression (neutropenic, chemotherapy, radiation therapy or immunosuppressive therapy) other than corticosteroid use
4. Life-threatening medical co-morbidities leading to possible imminent death, DNR status
5. Patients with chronic infections necessitating prolonged antimicrobial treatment (Cystic Fibrosis, Tuberculosis, infective endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis)
6. Patients with >24 hours of appropriate antimicrobial therapy prior to initial PCT level
7. Active intravenous drug users
8. Pregnant women

Warning PCT results do not replace clinical assessment and judgement.

Low (mortality) risk LRTI: low acuity non-pneumonia infections- acute bronchitis, acute exacerbations of COPD or asthma
Moderate risk LRTI: CAP patients in the ED or hospital wards (CURB-65 SCORE 2-3)
High risk LRTI: Severe (CAP) pneumonia patients in the ED or hospital wards (CURB-65 SCORE 4-5)

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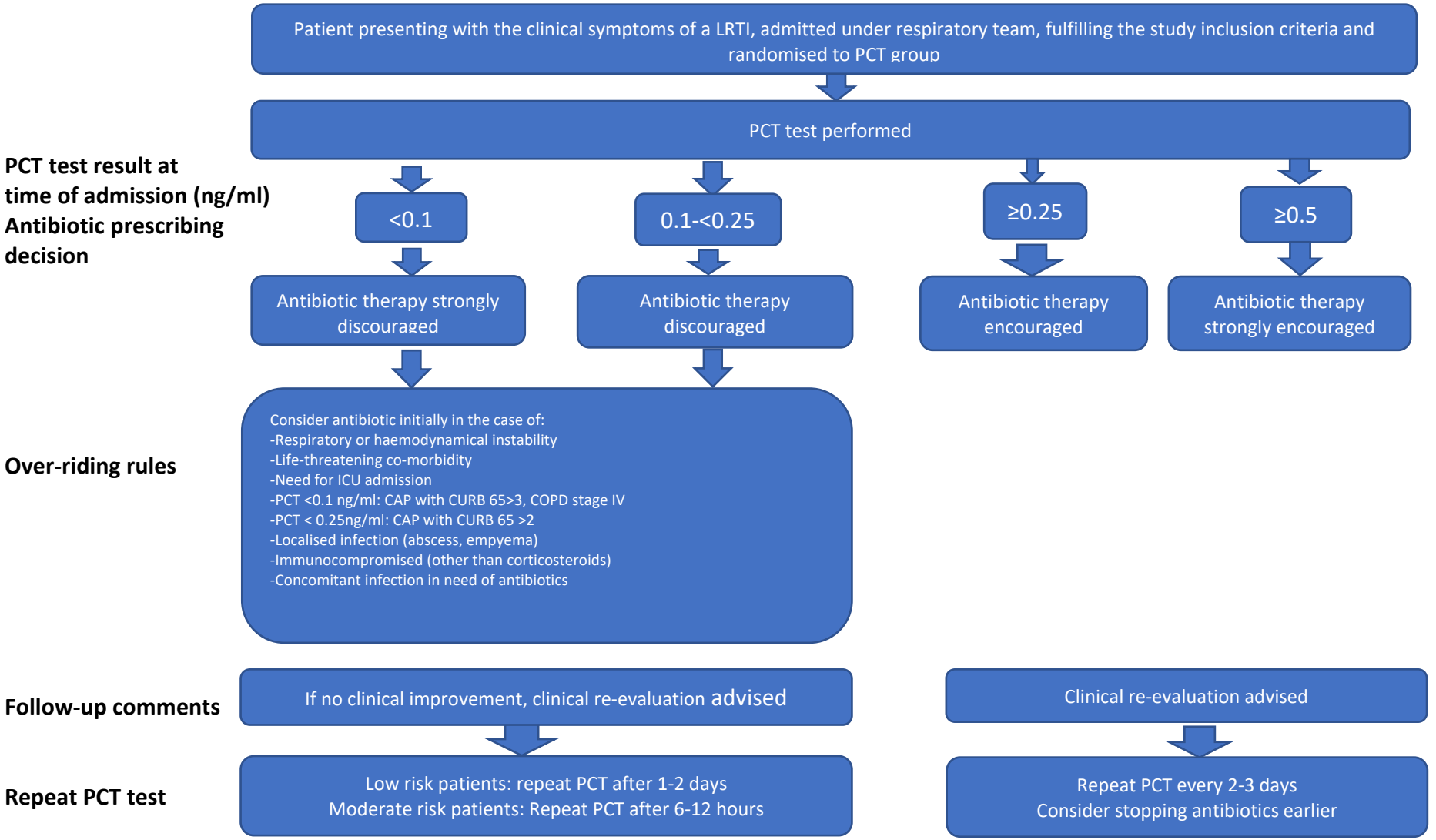
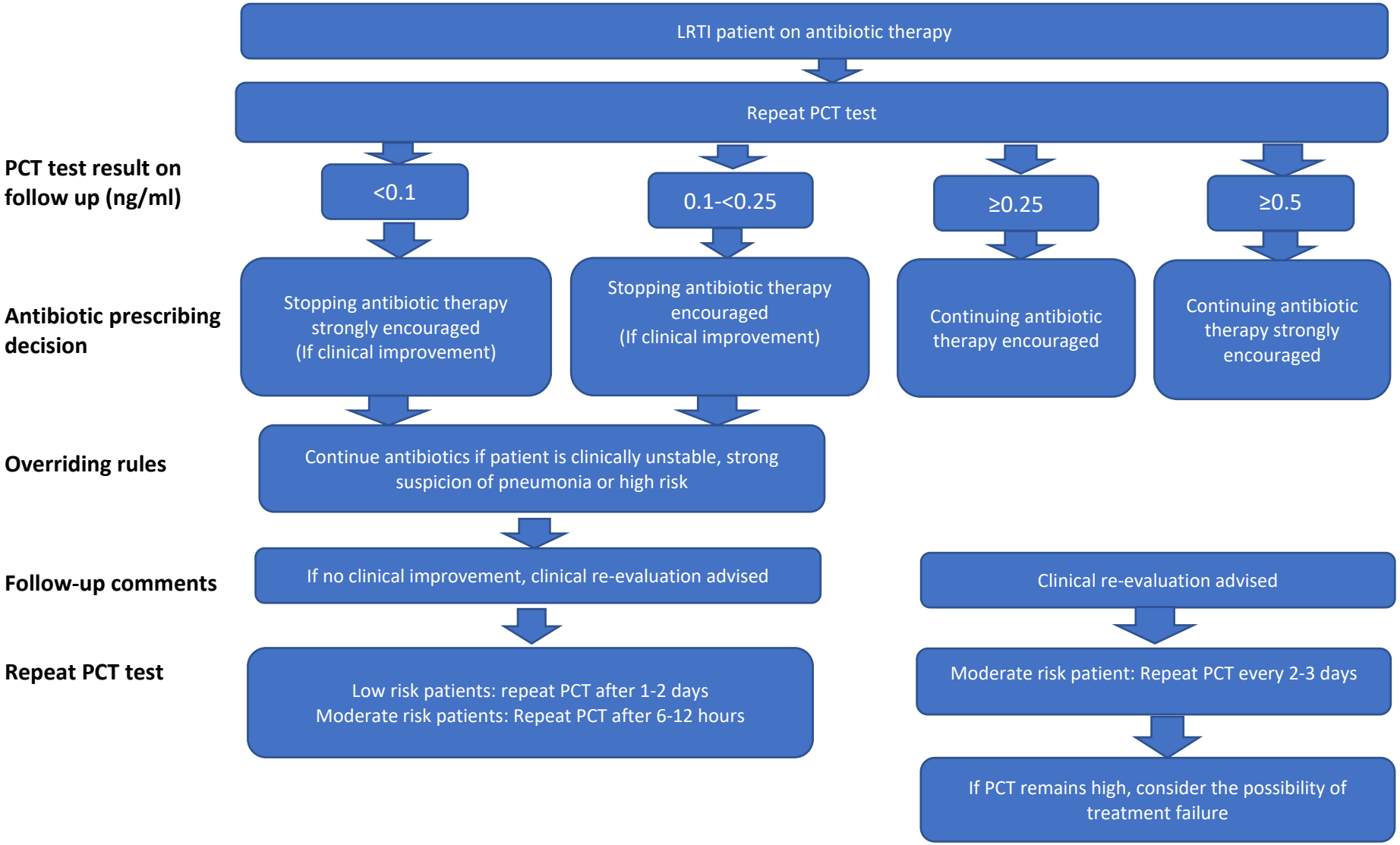
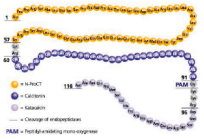

Patient presenting with the clinical symptoms of a LRTI, admitted under respiratory team, fulfilling the study inclusion criteria and randomised to PCT group
PCT test performed
PCT test result at time of admission (ng/ml)
Antibiotic prescribing decision
<0.1
0.1-<0.25
≥0.25
≥0.5
Antibiotic therapy strongly discouraged
Antibiotic therapy discouraged
Antibiotic therapy encouraged
Antibiotic therapy strongly encouraged
Over-riding rules
Consider antibiotic initially in the case of:
-Respiratory or haemodynamical instability
-Life-threatening co-morbidity
-Need for ICU admission
-PCT <0.1 ng/ml: CAP with CURB 65>3, COPD stage IV
-PCT < 0.25ng/ml: CAP with CURB 65 >2
-Localised infection (abscess, empyema)
-Immunocompromised (other than corticosteroids)
-Concomitant infection in need of antibiotics
Follow-up comments
If no clinical improvement, clinical re-evaluation advised
Clinical re-evaluation advised
Repeat PCT test
Low risk patients: repeat PCT after 1-2 days
Moderate risk patients: Repeat PCT after 6-12 hours
Repeat PCT every 2-3 days
Consider stopping antibiotics earlier


LRTI patient on antibiotic therapy
Repeat PCT test
PCT test result on follow up (ng/ml)
<0.1
0.1-<0.25
≥0.25
≥0.5
Antibiotic prescribing decision
Stopping antibiotic therapy strongly encouraged (If clinical improvement)
Stopping antibiotic therapy encouraged (If clinical improvement)
Continuing antibiotic therapy encouraged
Continuing antibiotic therapy strongly encouraged
Overriding rules
Continue antibiotics if patient is clinically unstable, strong suspicion of pneumonia or high risk
Follow-up comments
If no clinical improvement, clinical re-evaluation advised
Clinical re-evaluation advised
Repeat PCT test
Low risk patients: repeat PCT after 1-2 days
Moderate risk patients: Repeat PCT after 6-12 hours
Moderate risk patient: Repeat PCT every 2-3 days
If PCT remains high, consider the possibility of treatment failure

Appendix 3

Procalcitonin feasibility study education and training presentation

Procalcitonin-what can we do with this biomarker?



1

Objectives for this presentation

- Understand what procalcitonin (PCT) is and its clinical role
- Recognise the clinical situations where PCT may be useful
- Recognise the limitations and drawbacks of PCT
- Review the evidence to support PCT use in decreasing antimicrobial use in respiratory tract infections
- Proposed RespPCT study and how it will allow for individual tailoring of antibiotic therapy to the presence and resolution of a systemic bacterial infection

2

- Feasibility study to assess can the PCT test be implemented in the MUH, does it support antibiotic prescribing decision-making and reduce antibiotic consumption in the MUH, is it effective and could it be rolled out to the rest of the hospital and if so how?
- Being undertaken as part of a PhD study with UCC and CRF. The equipment has been supplied by Biomerieux for the duration of the trial and the test kits have been purchased using an educational grant from the Cork/Kerry regional SARI fund

Background

- Antimicrobial over and inappropriate use
- Side effects and adverse effects
- Directly related to the emergence and dissemination of antimicrobial resistance according to epidemiological studies
- In the MUH-increasing levels of ESBL's, VRE and risk of CRE
- Significant threat to public health

Respiratory tract infections

- Respiratory tract infections are the most frequent indication for antibiotics
- Significant prevalence of viral aetiology
- Antibiotic resistance
- Diagnosis of infection is difficult
- Is there a way to tailor antibiotic therapy to the presence and resolution of a systemic bacterial infection in an individual patient?

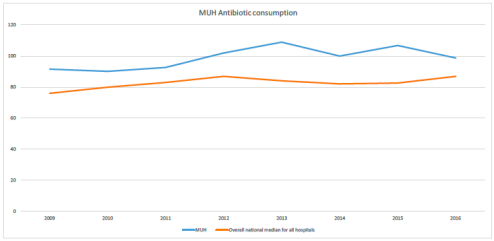
5

Antimicrobial stewardship

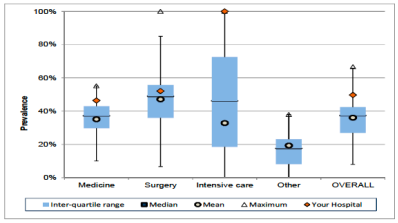
- IDSA-'stewardship of antimicrobials is an apt descriptor of related activities that help optimise antimicrobial therapy ensuring the best clinical outcome for the patient while lowering the risk of subsequent development of antimicrobial resistance'
- Well established AMS programme in the MUH

6

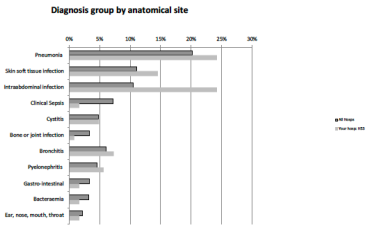
MUH antibiotic consumption



Prevalence of antimicrobial prescribing in the MUH and nationally by speciality



Anatomical site of infection in MUH patients



9

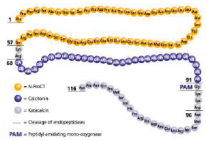
Better diagnostics

- Distinguish between viral and bacterial infections
- Provide further information regarding a patients progress on treatment
- Is there a role for biomarkers?
- Procalcitonin

10

Procalcitonin

- Procalcitonin is a peptide precursor of the hormone calcitonin consisting of 116 amino acids

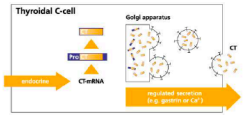


11

Role of PCT under normal conditions

Release of Calcitonin in the context of endocrine regulation:

- Synthesis in healthy people in the C-Cells of the thyroid
- PCT is enzymatically converted to calcitonin and then stored in endocrine granules
- Released only under certain stress (e.g. magnesium, gastrin) and acts to reduce blood calcium levels

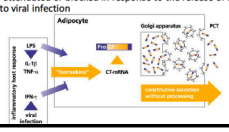


P. Linscheid, Endocrinology 2003

12

Role of PCT in bacterial infection

- Alternative (cytokine-like) pathway during sepsis: 'hormokine'
- Bacterial lipopolysaccaride (endotoxins), TNF and interleukin 1 stimulate the production of procalcitonin in all parenchymal tissues as part of the early phases of the innate immune response
- Non endocrine tissue i.e. Liver, Lung, Brain etc. do not have endocrine granules where calcitonin can be stored.
- PCT is immediately released into the bloodstream
- This process can be attenuated or blocked in response to the release of interferon-γ which occurs in response to viral infection



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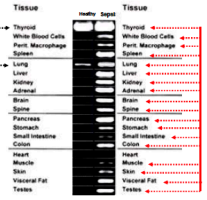
Calcitonin and Procalcitonin sources

Calcitonin: Sources of production in healthy people

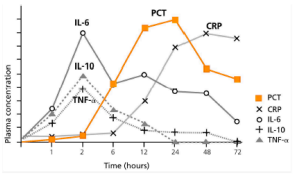


PCT: Sources of production in patients with an infection

Muller B et al. J Clin Endocrin Metab 2002;86:396-404

14

Kinetic profiles of different biomarkers for bacterial infections



- PCT levels, can be observed within 3-6 hours after an infectious challenge with a peak - up to 1000 ng/ml - after 6-12 hrs. Half-life: ~24hrs
- Specific to bacterial origin of infection and reflects the severity of the infection

Brunkhorst FM et al., Intens. Care Med 1998;24:888-892

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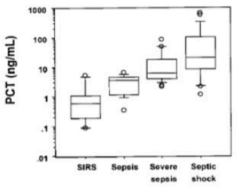
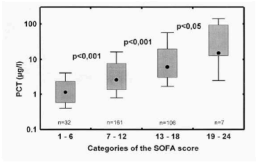
Procalcitonin correlation with disease severity- Sepsis and organ dysfunction





Harbarth S et al. Am J Respir Crit Care Med 2001;164:396-402
Meisner M et al. Critical Care 1999;3:45-50.

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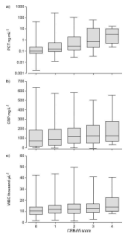
Admission levels of a) procalcitonin (PCT), b) C-reactive protein (CRP) and c) leukocyte (WBC) count in community-acquired pneumonia patients classified into CURB-65



S. Krüger et al. Eur Respir J 2008;31:349-355

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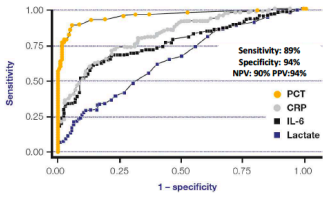
Adding PCT results to clinical assessment improves the accuracy of the early clinical diagnosis of sepsis



- PCT levels accurately differentiate sepsis from noninfectious inflammation
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

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Procalcitonin: advantages over other markers

- Specific for bacterial infections (vs inflammation in general)
- Rapidly rises and declines with immune control of infection
- -50% daily decrease associated with control of infection by host immune system / antimicrobials
- Excellent correlation with severity of illness (higher levels in more severely ill)
- PCT is not impaired by neutropenia or other immunocompromised states

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Does PCT increase in any other situations?

- **MAJOR STRESS** (severe trauma, surgery, acute respiratory distress syndrome, multi-organ failure, post-transplantation rejection, cardiogenic shock, severe burns, stroke)
- In the absence of infection the levels trend down
- Aortocoronary bypass surgery
- **NON BACTERIAL CYTOKINE ACTIVATION**
- Some forms of vasculitis and acute graft vs host disease
- Malaria and some fungal infections
- Chronic renal disease
- **DYSREGULATED PCT PRODUCTION**-treatment with immunotherapy agents- anti-lymphocyte globulins, IL-2, Granulocyte transfusions, OKT3, alemtuzamab
- **PARANEOPLASTIC SYNDROMES** due to medullary thyroid and small cell lung cancer.

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Low serum PCT levels

- Levels can also remain low in some microbiologically proven bacterial infections, either because the infection remains contained in a tissue compartment that can synthesize PCT locally without systemic release, thereby explaining low serum levels despite true infection, or because of a 24-48 hour lag time in infection onset to peak PCT release- important to consider all clinical factors when making decisions in severe infections.

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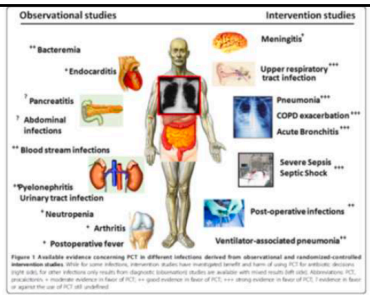

Schuetz et al. BMC Medicine 2011;9:107

22

Is there evidence to show PCT is safe and effective for respiratory patients?

- **Cochrane systematic review** RCT of PCT in acute RTI concluded that "procalcitonin may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy in patients with a clinical suspicion of infection. Randomized controlled trials have demonstrated that such a strategy works, particularly in patients with an infection of the respiratory tract."
- Not associated with higher mortality or treatment failures
- Significant reduction in antimicrobial consumption across different clinical settings and respiratory diagnosis

Schuetz et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2012 Sep 12;9:CD007498.

23

PCT in antibiotic management of LRTI

- Meta-analysis of 8 studies with 3431 patients included found the use of PCT in LRTI resulted in a 31% decrease in antibiotic prescriptions and a decrease in antibiotic duration of 1.3 days.(including pneumonia, exacerbations of chronic bronchitis, and other assorted lower respiratory tract infections-bronchitis, asthma exacerbation, etc)
- PCT use is safe and unlikely to result in patient harm

Li H, et al. Antimicrob Agents Chemother. 2011;55:5900-6.

24

ProHOSP trial

- Multicentre non-inferiority in 6 Swiss hospitals of 1359 patients
  -Adults with LRTI presenting to ED
  -Excluded immunosuppressed, HAP, those with the need for prolonged antibiotics
- PCT levels at admission and if antibiotics started on day 3, 5,7
- With recommendations to stop based on algorithm. Over-ruling allowed due to haemodynamic instability, severe disease, legionella antigen positive

Schuetz P et al. *J Am Med Assoc.* 2009;302(10):1059-66

25

ProHOSP results

- 90.8% compliance with algorithm
- Non-compliance was with discontinuation of antibiotics based on the clinical judgement of the treating physician
- Reduction in mean antibiotic exposure of 32-65%
- Reduction in the rate of antibiotic prescriptions 8-27%
- Most change seen in the COPD and acute bronchitis patients
- Shorter durations, fewer antibiotics and fewer antibiotic side effects

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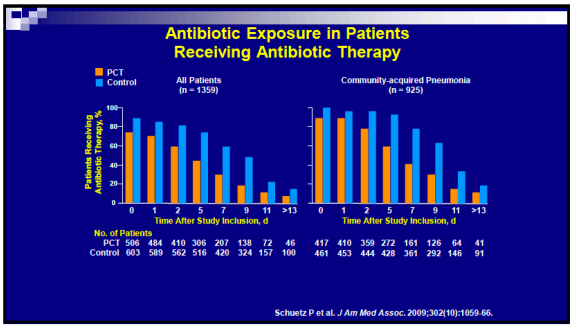

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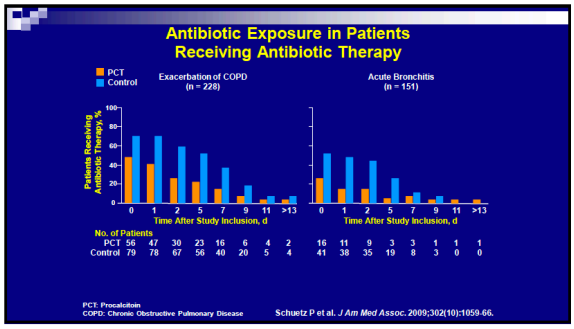

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SAPS study

- Multicentre non-inferiority RCT in the Netherlands
- ICU adult patients receiving antibiotics for a presumed or proven infection
- Intervention-discontinue antibiotic treatment in case PCT has decreased by more than 80% of its peak level (relative stopping threshold) or decrease to a value of 0.5ng/ml (absolute stopping threshold)

De Jong et al. Lancet Infect Dis 2016; 16: 819–27

29

SAPS study

- Resulted in a 2 day shorter medium antibiotic duration in the PCT group (25%)
- Achieved with a 44% adherence to the stopping rule within 24 hours of reaching stopping threshold and up to 97% adherence within 48 hours.
- Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection.
- This reduction was associated with a significant decrease in mortality.
- Procalcitonin concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship

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So why is it not widely used?

- Cost
- In the critical care settings safety has been questioned mainly based on the findings of two studies
- PRORATA study
- PASS-trial

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PRORATA TRIAL

- Prospective multicentre open label trial of PCT to guide duration for infection in ICU
- 307 PCT with algorithm
- 314 control group
- Used a stopping criterion of procalcitonin at 20% or lower of its peak value or procalcitonin at 0·5 µg/L or lower. This trial showed a 25% reduction in antibiotic exposure (treatment duration) albeit in a context of relatively long duration of antibiotic treatment (14.3 VS 11.6 days) and was non-inferior for mortality at 28 days
- **However, a non-significant, but higher, 60-day mortality in its procalcitonin arm raised safety concerns regarding the reliability of procalcitonin (30% VS 26.1%) and adverse effects after hospital discharge were possible.**

Bouadma et al. Lancet 2010;375:463-74

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PASS trial

- Diagnostic and therapeutic measures were escalated based on increasing PCT concentrations greater than 1µg/l (excluding antibiotics)
- Similar survival but in the PCT group more investigational procedures, increased side effects and organ- related harm due to the intensified antibiotic efforts, resulting in longer ICU stays than those not in the PCT group.
- Criticism of this trial related to the escalation algorithm which was counter-intuitive in the setting.
- Additionally surgical patients were included that may have shown unspecific PCT increases which may not point to a post operative infection.
- PCT samples were also shipped to a central study lab which often delayed the communication of the results

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PCT in treatment guidelines

- Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2016 (Crit Care med 2017;3:1-67)
- PCT 'can be used to support shortening duration of antimicrobials in sepsis patients' and 'can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis but subsequently have limited clinical evidence of infection'
- Management of adults with hospital-acquired and ventilator-associated pneumonia 2016 IDSA and ATS (CID 2016;63(3):e61-111)
- For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone
- Both BTS and IDSA CAP guidelines are under review currently

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Proposed role in treatment and antimicrobial decision making

- Procalcitonin can be used to assist in the diagnosis of infection and to support antimicrobial therapy decisions.
- **Decisions regarding antimicrobial therapy should NOT be based solely on procalcitonin serum concentrations and** procalcitonin should be placed into the clinical context of each patient scenario considering the site of possible infection, the likelihood of bacterial infection, the severity of illness, and any other pertinent clinical data
- Differentiation of viral vs bacterial respiratory tract infections
- Assist in monitoring response to antimicrobial therapy (source control) in bacterial pneumonias and RTIs
- Determining duration of antimicrobial therapy
- Support the AMS programme to optimise antimicrobial prescribing

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RespPCT proposal

- 3 arms to the study with an allocation ratio of 1:2:2
- Control group-general medical admissions (non-resp)
- Control 2- resp admissions non PCT
- Intervention arm-PCT group
- Stratification based on COPD stage IV and stages I-III
- Randomisation using SNOSE (sequentially numbered opaque sealed envelopes)

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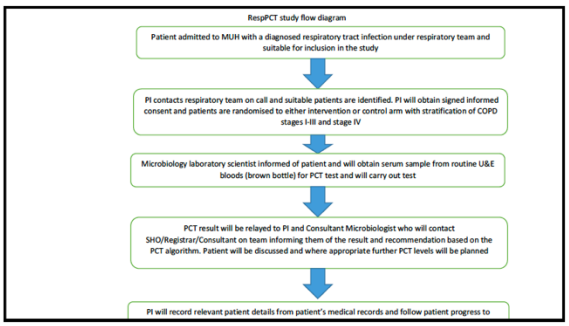

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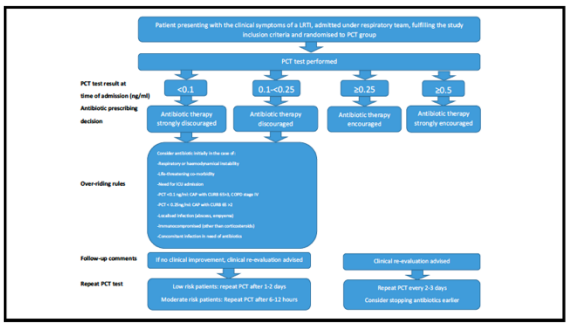

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Conclusion

- Optimisation of antibiotic prescribing
- Role for biomarkers-Procalcitonin
- Procalcitonin in respiratory tract infections
- RespPCT study

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- Thank you for your time

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Appendix 4

Supplementary material for Study 2 (Chapter 3)

Supplementary data
Table S1. PCT intervention and implementation

CFIR domains and constructs	Barrier and/or Facilitator to intervention implementation	Illustrative quote
Intervention characteristics domain		
Evidence strength and quality	PCT as a useful biomarker (**Facilitator**)	*'it's a very useful biomarker in terms of deciding when to initiate antibiotics and indeed when to discontinue antibiotics and studies haven't shown a detrimental effect on patient outcomes' (DR5)*
	Perceived role for PCT **(Facilitator)**	*'it's a difficult balance to achieve. I mean ideally you want to minimise the exposure to antibiotics but at the same time you want to ensure that a patient is adequately treated and I suppose that's where procalcitonin would actually play a very useful role.' (DR4)*
Relative advantage	PCT to provide re-assurance for prescribing decisions **(Facilitator)**	*'I suppose the question is whether you use it to replace something or whether you use it to compliment … on somebody that, you know, is a little bit vague, you think they're probably settling down but you're not quite sure in the CRP's, you know, maybe stuck at 100. It might be nice to do it then and say oh look, his procalcitonin is going down …you've just got that extra marker. Or you know the way periodically you see a patient and their white cells has normalised but their CRP is still 128 and you're kind of saying do you still have residual infection or is it just the CRP lagging behind your white cell count so it might be nice in that setting as well. ' (DR1)*
	Questioning the advantage of PCT over CRP **(Barrier)**	*'it has been around for quite some time now. But you wonder would it ultimately supplant to CRP because I know CRP can go up in viral infection too. ' (DR5)*
	Participant yet to be convinced of the advantage of PCT (**Barrier)**	*'it all depends on how much it's going to cost. I personally would think that an additional stewardship round a week, might actually lead to more benefit to the hospital than additional procalcitonin….you'd need to do kind of health benefit economics assessment and all of that sort of stuff ' (DR2)*
Adaptability	Processing the PCT test in the biochemistry laboratory would be more efficient **(Facilitator)**	*'I think it would definitely make more sense to have it run as part of the biochemistry panel because it's put on – it would be quicker, the results would be available more easily, and it would take less time and less labour involved for the scientists. Yeah. And definitely better for the doctors because they could access the results quicker.' (MS1)* *'I think it lends itself much more for greater efficiency if it was in the biochemistry laboratory' (MS3)*
	Availability of results with other biochemistry results and documented in the medical notes from admission **(Facilitator)**	*'Yes to both, I think if it was there as part of the …standard admission list FBC, biochemistry profile, CRP, procalcitonin, I think you know, it probably would have made more of a clinical influence rather than us hearing afterwards, you know, hearing afterwards it was something that you know, you felt almost it was a feedback after the decision had been made. ' (DR5)*
Trialability	Reflecting on the positive elements of the test **(Facilitator)**	*'I do remember a few and they tended to be more people with, you know, bog standard pneumonia where it was reducing and we kind of, it probably mirrored their CRP etc. and we kind of said yeah, you know,*

		they're ready for orals. And I suppose it kind of reinforces the decision that fine, this is all part of the trend of improvement.' (DR1) *'it feels to me like there were a few individual cases where we had high procalcitonin levels that influenced us to continue antibiotics. To be fair they were patients that had already been initiated and I certainly remember one that had a low procalcitonin that wasn't on antibiotics and so that seemed to back up our clinical sense.' (DR5)*
	Situations where PCT was less effective **(Barrier)**	*'There was one or two of the more chronic infected patients, like you say, the bronchiectasis where I was kind of like nah.' (DR1)* *'my feeling is that it's probably more value in the acute infective setting in that it may be less reliable in the patient with chronic lung disease' (DR5)*
	Consideration for the roll out of the test **(Facilitator)**	*'I think perhaps in a selective group of patients. I don't think, you know, especially if it's going to be extra cost and you certainly don't need it in everyone. And you so you probably have to restrict it to consultant decision to order it isn't it as opposed to, you know, the intern going well I'm filling the blood forms alright, procalcitonin, on the form.' (DR1)* *'But equally you're going to have to be very defined in who is allowed order the test because otherwise you'll find that you've got about, you know, 20 million procalcitonin ordered and people didn't necessarily need them or they didn't necessarily add anything to the information you already had. ' (DR1)*
	Questioning the benefits of including LOS as an outcome to convince management to fund the intervention **(Barrier)**	*'I know a lot of things focus on reducing length of stay but like, to be honest, in our life, in our reducing length of stay, we are not really saving any money, in the way we are managing. So that is the unfortunate thing.' (ADM)*
Complexity	Processing time for the samples was short **(Facilitator)**	*'it took 20 minutes to run and at the end of the 20 minutes, the result printed out. (MS1)* *'turnaround time would be probably like two hours.' (MS2)*
	Extra workload to process the samples, priority of existing work and sample exclusion criteria **(Barrier)**	*'you know, it's busy inside in micro too. It's kind of hard to find the time.' (MS2)* *'Sometimes they were too old and sometimes they were the right sample type, like lithium heparin' (MS1)* *'we're not that familiar with biochemistry. Like, I'm not on call in bio. I'm on call in haematology so it's hard enough to find samples and whatever.' (MS2)*
Design quality and packaging	Training provided **(Facilitator)** Doctors frequent change-overs **(Barrier)**	*'I think we did receive adequate training to be fair. I suppose the only thing is that with the interns and SHO's changing over and moving through then they're not as aware of it isn't it.' (DR1)*
Costs and opportunity cost	New interventions when being assessed would require strong evidence of economic and clinical gain due to scarce resources **(Barrier)**	*'I think, adding resource is probably not an option. I think that is the reality of life in our situation. There would want to be a really strong business case to suggest why we should add a resource. ' (ADM)*
Process domain		
Champions	Persuading key decision makers **(Facilitator)**	*'I think getting the consultant cohort on board is paramount to that actually.' (DR4)* *'firstly persuading your audience of the value of what you're trying to change, you know, interacting with the*

		kind of senior management, the clinical director and then disseminating information ' (DR5)
Reflecting and evaluation	Important information to include when rolling out the test **(Facilitator)**	*'telling people about it's place in the hierarchy and it's role and it's positive predictive values, it's pre-test probability of these things coming into play. And it's negative predictive value and the like. So the, I think that explaining to people that where it fits in among their clinical judgement, is what's important that it tells us - that it's not a binary test, yes/no anti-biotic, yes/no but how it influences how much you should allow it influence your judgement.' (DR2)*
	Plan for unintended consequence **(Facilitator)**	*'you would want some criteria, I suppose what you don't want is everyone fearing they have to get a procalcitonin before they stop an antibiotic or something, you know? So, you just want to be careful of any unintended consequences' (DR3)*
	Educational plan **(Facilitator)**	*'I'd say having it discussed at ground rounds, having it endorsed by the clinical director, having it endorsed and agreed upon by the consultant body and therefore if there's endorsements by senior people in public settings. ' (DR2)* *a multi-modal way of education.' (DR2)*
Characteristics of the individual domain		
Self-efficacy	Confidence in participants of their ability and personal experience to treat infections **(Barrier)**	'*we have a sense be it right or wrong that we've a reasonably good sense of antibiotic choices, it's very much linked to what we do' (DR5)* *'guidelines are always just guidelines you know. Every patient is different, so sometimes choices are made that are away from the guidelines and hopefully that's based on experience and you know, factors that are pertinent to the particular patient' (DR5)* *'I suppose it's more, like it's probably more a case of we don't inappropriately apply the guidelines as opposed to that we ignore them.' (DR1)* *'I think general medics don't get the concept of chronic infection or chronic lung disease.' (DR1)*

Table S2. Antimicrobial stewardship and antimicrobial resistance context

CFIR construct	Barrier and/or facilitator	Illustrative quote
Outer setting domain		
Patient needs and resources	Patient safety is a priority (**Facilitator)** Patient complexity impact **(Barrier)** Increased patient needs in treating AMR **(Barrier)**	*'Patient safety is an important element' (DR3)* *'I do think like the patient cohort that we're dealing with are complex'*(DR3) *'people stay in beds longer and they don't get out of hospital and we are prescribing drugs to people which is wasteful' (ADM).*
External policies and incentives	Acknowledgement of the problem of CPE and assessment of the hospitals response **(Facilitator)**	*CPE is a 'very serious issue'* (ADM) '*I think the hospital has responded to it strongly, to be honest. I would admire the way we have responded. We are probably a little bit ahead of the curve'* (ADM)
Cosmopolitanism	Engagement with the HCAI national lead as an external change agent or 'champion' to drive the response to CPE **(Facilitator)**	*'The National HCAI lead coming here and explaining it and then eventually, you begin to think, this risk is real, and we need to do something.'* (ADM)
Inner setting domain		
Tension for change	Impact of AMR on treatment occurring as a result of antibiotic overuse **(Barrier)** Consequences of AMR on resources **(Facilitator)**	AMR '*is making treatment more difficult and I suppose I probably would be leaning on the side that we probably overly use antibiotics in a clinical nature*' (DR3) *'the result is that people stay in beds longer and they don't get out of hospital and we are prescribing drugs to people which is wasteful*' (ADM)
Relative priority	Example of how the hospital prioritises AMR issues when necessary **(Facilitator)**	CPE- '*We don't have the money to be spending on it, but you know, we have no choice. I think this is a situation where you have no choice. You have to do it, you know. So, I am kind of comfortable where the hospital is in relation to it and how it has responded*' (ADM)
Leadership engagement	The hospitals commitment to other interventions/equipment to respond to AMR and an example of taking a long term rather than a short-term view **(Facilitator)**	'*We need to be state-of-the-art, so that is the goal. I think that anything about getting there is only a barrier that has to be overcome.' 'I think our focus would be to get there, not to look at the stumbling blocks.*' (ADM)
Available resources	Aspirational with the acknowledgement that to deal with AMS/AMR requires investment in diagnostics and other resources **(Facilitator)**	*CPE- 'We don't have the money to be spending on it, but you know, we have no choice.' (ADM)* *'it requires extra resources to actually do the work up' (MS3)* *'if you want to do things better, there is going to be a cost. It is not as if I think that it is going to save us money, you know. I don't even think that way. (ADM)*
Culture	Fear (of missing an infection, of litigation and self-protection influence prescribing behaviour) **(Barrier)**	*'by definition patients admitted to hospital are sick and like I say, I guess clinicians worry about the possibility of missing infection' (DR5)* *'fear of litigious issues or maybe you know, a bit of self-protection of covering all bases. So, I think there probably are antibiotics prescribed even in times that maybe the front-line clinician themselves maybe isn't convinced fully that it's a bacterial infection. Either in terms of getting that patient home and less fear of them bouncing back or*

		you know, just sort of covering everything safely there, giving antibiotics.' (DR3)
	Risk-aversion (driving over-prescribing even where doctors believe there is a low risk of infection) **(Barrier)**	*'There probably is, you know, it's a local, regional and a global problem in terms of over prescribing. But as I say it's difficult when you're face to face with somebody who might have an infection you know, some people 100% have an infection, some people maybe it's 10% but if you've a very sick patient who - by definition patients who come through the emergency department tend to be very sick. And there's a 10% chance I think a lot of people will still cover with antibiotics. (DR5)*
	Consequences of inappropriate antibiotic use are not immediately apparent **(Barrier)**	*'the longer consequences aren't as apparent'(DR3)*
	Significant difficulty to change prescribing behaviour **(Barrier)**	*'a significant element of behavioural and cultural change for people which is challenging.' (DR3)* *'People can be resistant to change, people are stuck in their ways. And the habits of the prescribing hand are firm and hard to change we do know that. So yeah, people can be stubborn but I think when you gain a critical mass of people buying into something, it takes care of the rest. It takes care of the resistant people, if it becomes part of the routine then it's like a tidal wave it just becomes standard practise.' (DR5)*

Table S3. Hospital/organisational context

CFIR construct	Barrier and/or facilitator	Illustrative quote
Inner setting domain		
Structural characteristics	Medical team hierarchy and prescribing decisions **(Barrier)**	*'those decisions would be consultant or registrar'*
	Medical team change-over frequency **(Barrier)**	*I suppose the only thing is that with the interns and SHO's changing over and moving through then they're not as aware of it isn't it.' (DR1)*
		'Yeah but there's nothing you can do about that because, you know, it's just part of the system'(DR1)
	But with consultant engagement this could be overcome **(Facilitator)**	*'I think if the consultants became engaged with it I think that the high turnover of staff wouldn't be a major issue' (DR2)*
Networks and communications	Importance of communication **(Facilitator)**	*'communication is such a huge deal in every aspect of medicine. ' (DR2)*
	Small hospital size encourages better engagement with colleagues **(Facilitator)**	*'I think it's the old cliché, you know, the smaller hospital colleagues tend to be more interactive and interpersonal' (DR5)*
	Impact of AMS team communication **(Facilitator)**	*'There's probably more interaction (here) than' in other hospitals where the AMS team came and said 'we've audited your antibiotic usage and you do this, this, this and this wrong. And then obviously you get people's back up and then when you talk through it, people are kind of able to justify why they've done a, b, c, d, e with their antibiotics. And like, you know, it's just a case of you didn't come and engage and ask why did you do that?' (DR1)*
	Organisational communication could be improved between departments **(Barrier)**	*'I suppose communication is always a problem. It's in an organisation like this where we're all in our little silos around the place and we're all doing our own little – we've our own little patch and we're doing our own bit of it. But whether there's joint up thinking in the whole thing then' (MS3)*
	And management and senior clinicians **(Barrier)**	*'there is not enough interaction with consultants really'* *'They are a separate body of people out there. They are not part of the hospital. They might be trying things and we mightn't even know it. I don't know but I think there is a distance there. There is a barrier there which isn't great. It is not healthy. I could never imagine that it would be that way, that there would be such a barrier between consultants and a hospital trying to operate.' (ADM)*
Culture	Culture in relation to sourcing resource allocation **(Barrier)**	*'it does seem to be he who shouts loudest. And sometimes you do feel like you're nagging, but I guess that's what you have to do. Just keep beating the drum and telling them this is what's available out there. This is what we can do if you give us the resources.' (MS3)*
	Positive implementation climate/quality improvement culture in the hospital **(Facilitator)**	*'the vast majority of people come into healthcare every day and they're trying to do their best, they're trying to work. I do think most people in healthcare all at the same time are seeing what they can do to improve the system.' (DR3)*

		'we've good examples of some quality improvement work' (DR3) *'I think there has been a culture of quality improvement that is more noticeable over the last number of years. ' (DR4)*
	Contrast of examples of less enthusiasm toward QI in the hospital **(Barrier)**	*'yes, but not a wholeheartedly resounding, yes. I think there's definite leadership among certain of the management people. It's just hard to be leading on everything' (DR2)* *Implementation climate in relation to QI: 'If there is, I haven't really witnessed it would be the honest answer' (DR1)* *'I suppose there could be more engagement from consultants with regards to quality improvement projects that are being put out' (DR4)* *'My impression would be… What? There's certainly I think – there's a willingness to improve on quality. But whether it's backed up by resources, I'm not so sure. There might be more talk than there is action' (MS3)*
Leadership engagement	Management commitment to encourage improvement **(Facilitator)**	*'it takes a bit of time. But then, you just have to go above making it happen, in this impossible world.' (ADM)*
	With the acknowledgement that there should be more engagement with senior clinicians **(Barrier)**	*'they are on their own. It is a pity it is that way. It is not right. It is not healthy. There should be much more engagement.' (ADM)*
	Acknowledgement of the need for involvement in QI but limited time to do so **(Facilitator)**	*'there's always scope for improvement on that front, you know, that work is never done. And one of the problems is …that people are consumed by clinical activity and maybe less involved in kind of quality improvement than they should be.' (DR5)*
Process domain		
Champions	Need to engage consultants and senior clinicians to nurture implementation **(Facilitator)**	*'I think getting the consultant cohort on board is paramount to that actually.' (DR4)* *'you're not necessarily going to reach all consultants through that forum (grand rounds), you know. So, maybe a clinical director would have a role there in terms of engaging consultants, to a large extent' (DR4)*
Available resources	Funding constraints within the Irish health care system **(Barrier)**	*'We have got X to spend, we can spend that and don't spend more. I mean that is clear. There is that priority and that probably from a financial stand point is the primary one. It doesn't mean you want to change things. You always want to change things and improve things and all of that you know.' (ADM)* *Resources required 'we have to constantly justify just where we are rather than the idea we might invest to get future success, it does not seem to me to be very easy on the system.' (DR3)*
	Ongoing need for further resources **(Barrier)**	*'We have gotten extra resources. But they're not enough. And we need more' (MS3)*

Process evaluation interview topic guide post procalcitonin testing introduction:

Theme 4-characteristics of individual

Background information- current/recent position in the resp team/gen med

What is your attitude and perception of antimicrobial resistance?

Does it impact on your practice and antibiotic prescribing decisions (course lengths)? Have any factors influenced your attitude?

Overall in the MUH and specifically in the treatment of patients admitted with respiratory tract infections, do you think there is an overuse of antibiotics and are course lengths a contributory factor? If yes- is enough being done to address it?

Do you think it is important for a hospital to have an AMS programme to address AMR?

Are you familiar with the elements of the AMS programme in this hospital such as the antimicrobial guidelines, protected antimicrobial policy, weekly ams rounds, education and advice etc? Are they accessible and do you use them?

(T3) Can you comment on the nature and quality of communication & interactions between teams and the AMS team (micro/ID/pharmacy) within this hospital both formal and informal?

Theme 3 Inner settings

One of the main aims of the AMS programme is to reduce inappropriate or unnecessary prescribing of antibiotics. When considering your own practice do you think it is possible to balance the aims of the ams programme to reduce antibiotic use and that of the clinical need of treating your patients with infections adequately and the perceived risks and possible consequences of inadequate treatment?

Are there any extra resources that could be put in place to provide support or further clarity to support your prescribing decisions?

Do you think there is a role for biomarkers to support the ams programme? And PCT in particular?

T3 Implementation climate within the hospital

Do you think there is a culture/incentive/policy/values to improve the care of patients in the hospital and the treatment of infections and abx prescribing? Promotion of quality improvement?

Theme 2 Outer settings

Do you feel there is any peer pressure/ competitive pressure to implement this or other interventions before other hospitals?

Do you feel there are any external (regional or national) policy or incentives to encourage the implementation of this or similar interventions?

Theme 1 intervention characteristics

When considering ownership and implementation of this intervention does the fact that this trial of PCT testing to support prescribing decisions was introduced to the hospital by the AMS team influence its acceptability to you?

Which elements of the PCT intervention training did you receive-email with study literature-did you read? outline of the study from PI, feedback of results and interpretation of PCT levels, did you receive or request any further studies or information from the PI? Was this sufficient?

What is your perception of the quality and validity of evidence supporting the theory that the intervention of using PCT testing to support the AMS programme will have the desired outcome of reducing antibiotic usage and shorten length of stay in patients with RTI's?

Has participation in this research increased your awareness of PCT testing and based on this and other evidence, and are you sufficiently familiar with its use now to consider it along with other markers when reviewing patients with RTI's?

Do you think implementing PCT testing is a worthwhile intervention or is there an alternative intervention to reducing antimicrobial use in patients admitted to hospital with a respiratory tract infection?

Do you think PCT testing can be adapted and refined to meet the requirements of this hospital? Could you suggest the key elements of the education and training programme to result in the greatest impact?

Theme 3 Inner settings

Readiness for implementation –is there a culture of quality improvement and willingness to adapt new interventions within this hospital?

Sub constructs

Do you think there is leadership engagement-commitment, involvement and accountability of leaders with the implementation of this intervention?

What elements of leadership engagement would be required (most influential) to implement this intervention successfully in the rest of the hospital?

To successfully implement this intervention what resources would be required in terms of education and training and what forms would be required/most effective.

Access to knowledge and information-what information and forms of information about the intervention and how to incorporate it best

PCT use and training

Did you find it a useful test and do you think it contributed to an improvement in patient care?

Do you have a patient example where you used pct to support your prescribing decisions?

Could you discuss a recent patient example where PCT results were available and your clinical judgement made you consider an alternative course rather than that suggested by the PCT algorithm?

Do you feel you received adequate education and training on the background and rational for the use of procalcitonin.

Do you feel you received adequate education and training and support on the use of PCT and interpretation of the results?

Do you feel you received adequate education and training and support on the use of the PCT algorithm?

Is there any changes you could suggest to improve the delivery of the education, training and support you received during the introduction of the pct test?

Do you think this would be a useful test to make available to other services in the hospital and if so who and why?

How confident are you to include pct measurements as part of the other patient factors when making prescribing decisions for a patient with a LRTI?

Any other comments regarding the PCT test?

Appendix 5

Supplemental material for Study 3 (Chapter 4).

Supplementary data SD1. Data extraction form

Reference:	
Author:	
Year published:	
Study location:	
Area of AMS applicable to:	
Study design/ methodology to develop the QIs:	
Number of QI's developed	
Types of QI's developed (i.e. Process, structure or outcome)	
The QIs developed	
Methodological assessment with AIRE criteria completed	

Supplementary data SD2. AIRE instrument description and scoring

The AIRE instrument is divided into four quality domains of a QI and consists of 20 criteria which are applied to each completed set of QIs. Three domains address the methodological quality of QIs and were used in this review: 'Stakeholder involvement', 'Scientific evidence' and 'Additional evidence, formulation and usage'. The fourth domain: 'purpose, relevance and organisational context' reflect the relevance of the QIs within a particular context rather than methodological quality so was not used.

Scoring of the AIRE instrument items

Each of the included domains consisted of several item statements and were assigned a score by each reviewer according to a 4-point Likert scale

1-'strongly disagree' (confident that the criterion has not been fulfilled or no information is available);

2- 'disagree' (disagree or unsure whether the criterion has been fulfilled)

3-'agree' (fairly confident the criterion has been fulfilled)

4-'strongly agree' (confident that the criterion has been fulfilled).

The scores from each reviewer were summed to provide a 'total score' per quality domains.

A standardised domain score was then calculated according to the instrument's guidelines with the following formula: (total score—minimum possible score) / (maximum score—minimum possible score) x 100%.

A higher standardized score indicates a higher methodological level of quality (range 0–100%). QI sets were considered to have a high methodological quality for a domain if they scored 50% or higher, which correlates with an overall "agree" or "strongly agree". Domain scores are independent and should not be combined into a single quality score

AIRE domain	AIRE items
Stakeholder involvement	1. The group developing the indicator includes individuals from relevant professional groups
	2. Considering the purpose of the indicator, all relevant stakeholders have been involved at some stage of the development process
	3. The indicator has been formally endorsed
Scientific evidence	4. Systematic methods were used to search for scientific evidence
	5. The indicator is based on recommendations from an evidence-based guideline or studies published in peer-reviewed scientific journals
	6. The supporting evidence has been critically appraised
Additional evidence, formulation, usage	7. The numerator and denominator are described in detail
	8. The target patient population of the indicator is defined clearly
	9. A strategy for risk adjustment has been considered and described (‘case-mix adjustment’)
	10. The indicator measures what it is intended to measure (validity)
	11. The indicator measures accurately and consistently (reliability)
	12. The indicator has sufficient discriminative power
	13. The indicator has been piloted in practice
	14. The efforts needed for data collection have been considered
	15. Specific instructions for presenting and interpreting the indicator results are provided

Supplementary data SD3. Inter rater reliability AIRE instrument

Weighted Cohens Kappa (FOR &AF)= 0.69

Article Berenholtz	AIRE domains and items														
	Stakeholder involvement			Scientific evidence			Additional evidence, formulation, usage								
Reviewer:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
FOR	4	4	1	3	4	3	4	4	3	1	1	3	1	3	1
AF	4	4	1	2	4	3	4	4	3	1	1	3	1	3	1

Article Thern	AIRE domains and items														
	Stakeholder involvement			Scientific evidence			Additional evidence, formulation, usage								
Reviewer:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
FOR	4	4	1	3	4	1	1	4	1	3	3	1	4	4	1
AF	3	3	1	3	3	1	1	3	2	3	3	2	4	4	1

Weighted Cohens Kappa (FOR & FS)= 0.73

Schouten 2005 Reviewer:	AIRE domains and items														
	Stakeholder involvement			Scientific evidence			Additional evidence, formulation, usage								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
FOR	2	3	1	4	4	4	2	4	4	4	4	4	4	4	1
FS	2	3	1	4	4	3	2	4	4	4	4	4	4	4	1

Van den Bosch 2015	AIRE domains and items														
	Stakeholder involvement			Scientific evidence			Additional evidence, formulation, usage								
Reviewer:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
FOR	4	4	1	3	4	4	4	4	1	1	1	1	1	1	1
FS	3	4	1	4	4	4	4	4	1	1	1	1	1	1	1

Supplementary data SD4. Quality indicators extracted

Berenholtz 2007 (Sepsis-refers to severe sepsis or septic shock)

1. The percentage of patients with sepsis and an unidentified organism received vancomycin within 24 hours of identification
2. Median time to vancomycin initiation following sepsis diagnosis
3. The percentage of patients with sepsis and an unidentified organism who received a recommended broad spectrum antibiotic within 24 hours of sepsis identification
4. Median time to broad spectrum antibiotic initiation following sepsis diagnosis
5. The percentage of patients with sepsis who had 2 sets of blood cultures collected within 24 hours following sepsis identification
6. The percentage of patients with sepsis and an organism other than MRSA or MRSE (metacillin-resistant *Staphylococcus epidermis*) who had vancomycin discontinued within 96 hours of diagnosis.

Buyle 2013

1. (Services) Bedside expert consultant advice regarding antibiotics by microbiologist/infectious disease specialist/antibiotic officer on request available on the same day
2. (Services) Regular ward rounds by members of the AMT (multi-disciplinary antibiotic management team) performed (at least weekly)
3. (Services) Clinical audit of prescribers' compliance with local clinical guidelines/guide performed by AMT/AB officer
4. (Tools) Antimicrobial formulary list biannually updated
5. (Tools) Local clinical practice guidelines for microbiologically documented therapy updated biannually
6. (Tools) Local clinical practice guidelines for empirical therapy available
7. (Tools) Local clinical practice guidelines for surgical antimicrobial prophylaxis available
8. (Human resources and mandate) Formal mandate for hospital multi-disciplinary antibiotic management team (AMT) existing
9. (Human resources and mandate) AB officer or AMT member is member of the drugs and therapeutics committee
10. (Personnel development) Prescriber education by personalised interactive methods (like daily ward rounds) performed

Coll 2012

Bacterial specimens

1. Bacterial specimens are taken before initiation of antimicrobial treatment and there is evidence of analysis at the laboratory

Allergy status

2. Patients allergy status is documented at the time antimicrobial(s) to be prescribed
3. The nature and severity of the past allergic reaction is documented
4. Patients with a history of anaphylaxis (wheezing, collapse or an itchy rapid onset, urticarial rash) immediately after penicillin therapy should not receive antimicrobial treatment with a beta lactam antimicrobial is prescribed alternative drug class
5. Patients with a history of minor rash (non-confluent, non-pruritic, restricted to a small area of the body, or occurring more than 72 h after penicillin administration) is prescribed a cephalosporin or carbapenem if indicated

Guideline compliance

6. Choice of antimicrobial treatment is compliant with local policy
7. The route of administration of antimicrobial is compliant with local policy
8. The dosage regimen of prescribed antimicrobial is compliant with local policy

Renal impairment

9. Review and adjustment of dosage regimen as recommended in the guidelines is documented in mild renal impairment (CrCl = 20–50 ml/min)
10. Review and adjustment of dosage regimen as recommended in the guidelines is documented in moderate renal impairment (CrCl = 10–20 ml/min)
11. Review and adjustment of dosage regimen as recommended in the guidelines is documented in severe renal impairment (CrCl <10 ml/min)

Interaction management plan

12. Identified interactions between antimicrobial regimen and concurrent medications are documented with a recommended management plan of the interaction

Documentation

13. The indication for prescribing of antimicrobial treatment is documented
14. The intended duration of antimicrobial treatment is documented

Therapeutic drug monitoring

15. The gentamicin level is taken at the correct time recommended by the antimicrobial guidelines
16. The measured gentamicin level is documented
17. The gentamicin dosage regimen is managed according to the guideline and a management plan is documented
18. The vancomycin level is taken at the correct time
19. The measured vancomycin level is documented

20. The vancomycin dosage regimen is managed according to the guideline and a management plan is documented

Improvement in renal impairment

21. Due to an improvement in mild renal impairment review and adjustment of dosage regimen is documented
22. Due to an improvement in moderate renal impairment) review and adjustment of dosage regimen is documented
23. Due to an improvement in severe renal impairment review and adjustment of dosage regimen is documented

Interactions

24. Documented interaction management plan (criteria 12) is followed

De-escalation

25. The results of bacteriological sensitivity(s) is documented
26. The choice of antimicrobial treatment is reviewed according to clinical response and/or sensitivities
27. The intravenous route of administration is switched to the oral route at an appropriate time (48 h after initiation and if not clinically indicated, requirement for intravenous route is reviewed every 24 h)
28. The indication for prescribing an oral antimicrobial as a result of an intravenous to oral switch is documented in the case notes or the inpatient medication administration chart
29. The intended duration of oral antimicrobial treatment as a result of an intravenous to oral switch is documented
30. Antimicrobial treatment is discontinued on completion of the documented course

Farida 2014

1. Take two sets of blood samples for culture
2. Obtain sputum samples for Gram stain and culture
3. Obtain sputum sample and start antibiotic therapy in the emergency department
4. Timely initiation of antibiotic therapy within four hours after presentation
5. Switching from iv to oral therapy when clinically stable
6. Length of therapy is five days for uncomplicated CAP (CURB score ≤ 2)

Thern 2014

Structural indicators

1. (Prerequisites) MDT AMS team authorised by hospital management , headed by ID physician (or trained abx expert) plus a pharmacist
2. AMS team represented in the drugs and therapeutic committee

3. Minimum of 2 AMS team meetings annually (minuted)
4. ABS strategic report to D&T and hospital management includes quantitative objectives with selected performance indicators
5. Written in-house preanalytical requirements for microbiologic samples (including rejection criteria)
6. Antimicrobial drug use data (as DDD/RDD or PDD per 100 occupied bed [patient] days and/or admission) available for several clinical divisions or departments (division-specific or aggregated for surgical and nonsurgical services and/or for general wards vs intensive care units) at least annually (in total and detailing the most important antibiotic classes)
7. Rate of oral vs. parenteral dispensed or prescribed daily doses of the most important and relevant drugs or drug classes available at least once per year for several clinical services
8. Other resistance rates and corresponding incidence figures (for clinical isolates) available at least once per year for several clinical services (divisions/departments)
9. Incidence figures for *C. difficile* associated diarrhoea available for several clinical services (division-specific and/or general wards vs. intensive care units) at least once per year
10. Hospital-wide incidence figures for nosocomial sepsis/bacteraemia available at least once per year
11. In-house list of anti-infectives (formulary, see above) which is up to date (not older than 2 years) available
12. Prescriptions concerning restricted / alert anti-infectives from a defined list are approved for specific patients, not generically
13. Written, locally consented practice guidelines (see above) available and updated (not older than 2 years)
14. Written, locally consented practice guidelines for surgical prophylaxis available and updated (not older than 2 years) available
15. Written recommendation for parenteral-to-oral switch antimicrobial therapy (prerequisites / criteria and drugs) available and updated (not older than 2 years)
16. Regular ward rounds of members of ABS team together with the attending physicians (at least 3 clinical services/departments, at least 3 times each in the previous 12 months)
17. Educational sessions by the ABS team and/or ABS representatives about locally consented guidelines (tailored to division or at least differentiating conservative vs. surgical specialities) at least every other year
18. In-house and/or extramural ABS-relevant continuing medical education about antimicrobial therapy and prophylaxis for at least 10% of medical staff who are not ABS representatives (at least 4 documented CME credits relevant for ABS per year)
19. ABS-relevant continuing medical education for ABS team members and ABS representatives from clinical services (at least 8 documented CME credits relevant for ABS per year)
20. Use of selected antibiograms (adapted according to local guidelines)

21. Locally consented guidelines / decision-making aids electronically available (e.g. via physician's computer, PDA or smartphone)

Process indicators CAP

1. Initial therapy (drugs and dosing) according to local / national guideline
2. Obtain blood cultures (2 sets) on the day of initialization of antibiotic therapy
3. Combination therapy, if any, no longer than three days (patients on general ward)
4. Duration of therapy no longer than 7 days (patients on general ward)

Process indicators HAP

1. Initial therapy (drugs) according to local / national guideline
2. Obtain blood cultures (2 sets) on the day of start of therapy
3. Duration of therapy no longer than 10 days

Process indicators BSI

1. Heart ultrasound (TEE) within 10 days of collection of first blood culture that became positive (etiologies of bacteremia/sepsis: *Staphylococcus aureus*, streptococci, enterococci (non-nosocomial), HACEK)
2. Collection of follow-up blood cultures 4-7 days after collection of first blood culture that became positive (etiology of bacteremia/sepsis: *Staphylococcus aureus* or patients with fungemia)

Process indicators UTI

1. Documented positive urine culture (significant bacteriuria, no mixed flora)
2. Initial therapy (drugs and dosing) according to local / national guideline
3. Duration of pyelonephritis therapy not longer than 10 days (patients on general ward)
4. Oral antimicrobial drugs initiated not later than day 5 (pyelonephritis, patients on normal wards only)
5. No antimicrobials for asymptomatic, catheter- associated bacteruria

Process indicators (Other empiric therapy, iv/po switching, renal adjustment)

1. Initial empiric therapy (drugs, before/without knowledge of etiology) according to local guideline
2. Oral administration of drugs with high bioavailability (fluoroquinolones [except norfloxacin], clindamycin, doxycycline, linezolid, metronidazole, rifampin, fluconazole, voriconazole) (not for patients with resorption disorders, short bowel syndrome, emesis, severe sepsis / septic shock)
3. Dosing adjustments for patients with reduced renal function within 2 days

Process indicators (Surgical antimicrobial prophylaxis)

1. Antibiotic prophylaxis (drugs, dosage) administered according to local guideline
2. Antibiotic prophylaxis administered within 1h before incision
3. Antibiotic prophylaxis stopped within 1 day (<24 h)

Process indicators (MDR management)

1. Infection and/or colonization by multidrug- resistant (MDR) organisms explicitly listed in discharge summary

Hermanides 2008

1. Performance of urine culture
2. Prescription of treatment in accordance with empiric guidelines
3. Tailoring of treatment on the basis of culture results
4. Switch to oral treatment when possible (after 48-72 hours based on clinical condition)
5. Selective use of fluoroquinolones (only as oral or in beta-lactam allergy/anaphylaxis)
6. Duration of treatment for at least 10 days (in accordance with national guideline)
7. Initiation of treatment within 4 hours after clinical presentation
8. Prescription of treatment for men in accordance with national guidelines
9. Start iv antibiotics in pregnant women with pyelonephritis
10. Do not prescribe antibiotic prophylaxis to patients with a urinary catheter in place
11. Change urinary catheter within 24 hours of initiation of antibiotic treatment
12. Consider all diabetic patients with cystitis as having a complicated UTI and treat with empiric treatment according to national guidelines
13. Adaptation of the dosage on the basis of renal function

Kallen 2018

1. Perform at least two sets of blood cultures before start of empirical systemic therapy
2. Perform therapeutic drug monitoring in patients treated with vancomycin or aminoglycosides
3. Perform surveillance cultures if selective digestive or oropharyngeal decontamination is applied at the ICU
4. Biannual face-to-face meetings between ICU and microbiology staff in which local resistance rates are discussed

Quantity metric

5. Quantitative antibiotic use at the ICU expressed in days of therapy (DOT).

Monnier 2018

Antibiotic Prescribing

1. Antibiotics should be prescribed according to local practice guidelines.
2. Antibiotics should be prescribed according to national guidelines when no local guidelines are available.
3. Antibiotic prescriptions that deviate from guidelines should be justified.

Antibiotic Stewardship

4. Surveillance of antibiotic use and resistance should be performed at least once per year at the health care facility.
5. An antibiotic formulary should be available and updated continuously at the health care facility.
6. An approval system should be in place for prescriptions of restricted antibiotics at the health care facility.
7. An antibiotic stewardship programme (antibiotic prescribing control programme and/or antibiotic prescribing policy) should be in place at the health care facility.
8. Antibiotic prescribing should be compliant with recommendations from infectious disease and/or microbiology specialist(s).
9. Audits of antibiotic use by the antibiotic stewardship team should be performed regularly at the health care facility.
10. A multidisciplinary antibiotic stewardship team appointed by the health care facility management should have meetings at least twice a year and make a report with objectives and selected performance indicators.

Availability

11. Antibiotics from the antibiotic formulary should not be out of stock at the health care facility.

Diagnostics

12. Two sets of blood culture should be taken before antibiotic administration when bacteraemia is suspected.
13. Specimens for culture from suspected sites of infection should be collected before antibiotic administration.
14. Microbiological investigations should be performed according to guidelines.

Documentation

15. An antibiotic plan should be documented in the medical record at the start of the antibiotic treatment. Antibiotic plan includes: indication, name, doses, duration, route, and interval of administration.
16. Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.
17. The results of bacteriological sensitivities should be documented in the medical records.

Dosing

18. Dosing and dosing interval of antibiotics should be prescribed according to guidelines.
19. Dosing and dosing interval of renally eliminated antibiotics should be adapted to the patient’s renal function.

20. The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.

Duration-Discontinuation

21. Duration of antibiotic therapy should be compliant with guidelines.
22. Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection.
23. Antibiotic therapy should be discontinued on completion of the documented antibiotic course.

Education

24. Educational sessions about practical guidelines should be organized for medical staff and should have a predetermined attendance target.

Guidelines

25. A local antibiotic guideline should be present at the health care facility.
26. An evaluation whether an update should be considered for the local antibiotic guideline should be done once a year.
27. The local guidelines should correspond to the national guideline but should be adapted based on local resistance patterns.

Outcome

28. Clinical outcomes of patients receiving antibiotics should be monitored at the health care facility.
29. Rates of nosocomial Clostridium difficile should be monitored at the health care facility.

Prescribing-Administration

30. Prescribed antibiotics should actually be administered to the patients.

Route

31. The route of administration of antibiotics should be compliant with guidelines.
32. Antibiotic therapy in adult patients with sepsis should be started intravenously.
33. Switching from intravenous to oral antibiotic(s) should be performed according to guidelines.
34. Switching from intravenous to oral antibiotic(s) should be done within 48–72 hours based on the clinical condition and when oral treatment is adequate.

Safety/General

35. Contraindications should be taken into account when prescribing antibiotics.

Safety/Allergy

36. Allergy status should be taken into account when antibiotics are prescribed.
37. Allergy status (including nature and severity) of the patient should be documented in the medical records when antibiotics are prescribed.
38. Patients with a history of anaphylaxis after penicillin therapy should be prescribed an alternative drug class
39. Medical staff should be educated regarding cross-allergy with cephalosporins in patients with penicillin allergy.

Safety/Interaction

40. Identified interactions between antibiotic regimen and concurrent medications should be documented in the medical record with a recommended management plan to deal with the interaction.

Safety/Toxicity

41. Duration of administration of intravenous antibiotics should be compliant with guidelines.

Selective Reporting

42. The microbiological laboratory should report individual selective susceptibly reports (or antibiograms) adapted to local guidelines.
    A selective susceptibly report (or antibiogram) is a report of a selection of antibiotic sensitivities, based on bacteriological activity, broadness of spectrum or toxicity.

Spectrum

43. The prescribed antibiotic should be active against all the likely causative pathogens.

Streamlining/De-escalation

44. Broad-spectrum empirical antibiotic therapy should be changed to pathogen-directed therapy as soon as culture results become available.
45. The choice of antibiotic treatment should be reviewed and modified based on clinical response.
46. Antibiotics for empirical therapy should be reviewed within the third day of treatment or when microbiological results become available.

Surgical prophylaxis

47. Prophylactic antibiotics should be added to a pre-operative checklist.

Therapeutic Drug Monitoring

48. Therapeutic Drug Monitoring should be performed for antibiotics with a narrow therapeutic spectrum and an increased risk of toxicity according to guidelines.
49. If antibiotic Therapeutic Drug Monitoring levels are not in the reference range, doses should be adjusted appropriately after the results become available.
50. Therapeutic Drug Monitoring levels of antibiotics should be documented in the medical records.

Timing

51. Timeliness of administration of antibiotic therapy and prophylaxis should be compliant with guidelines.

Pollack 2016

Infrastructure

1. Does your facility have a formal antimicrobial stewardship program accountable for ensuring appropriate antimicrobial use?

2. Does your facility have a formal organizational structure responsible for antimicrobial stewardship (eg, a multidisciplinary committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee, or other relevant structure)?

3. Is an antimicrobial stewardship team available at your facility (eg, greater than one staff member supporting clinical decisions to ensure appropriate antimicrobial use)?

4. Is there a physician identified as a leader for antimicrobial stewardship activities at your facility?

5. Is there a pharmacist responsible for ensuring appropriate antimicrobial use at your facility?
6. Does your facility provide any salary support for dedicated time for antimicrobial stewardship activities (eg, percentage of full-time equivalent [FTE] staff for ensuring appropriate antimicrobial use)?
7. Does your facility have the information technology (IT) capability to support the needs of the antimicrobial stewardship activities?

Policy and practice

8. Does your facility have facility-specific treatment recommendations based on local antimicrobial susceptibility to assist with antimicrobial selection for common clinical conditions?
9. Does your facility have a written policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions?
10. Is it routine practice for specified antimicrobial agents to be approved by a physician or pharmacist in your facility (eg, preauthorization)?
11. Is there a formal procedure for a physician, pharmacist, or other staff member to review the appropriateness of an antimicrobial at or after 48 hours from the initial order (post-prescription review)?

Monitoring and feedback

12. Has your facility produced a cumulative antimicrobial susceptibility report in the past year?
13. Does your facility monitor if the indication is captured in the medical record for all antimicrobial prescriptions?
14. Does your facility audit or review surgical antimicrobial prophylaxis choice and duration?
15. Are results of antimicrobial audits or reviews communicated directly with prescribers?
16. Does your facility monitor antimicrobial use by grams (Defined Daily Dose [DDD]) or counts (Days of Therapy [DOT]) of antimicrobial(s) by patients per days?
17. Has an annual report focused on antimicrobial stewardship (summary antimicrobial use and/or practices improvement initiatives) been produced for your facility in the past year?

Schouten 2005

CAP

1. Timely initiation of antibiotic therapy (within 4 h after presentation)
2. Empirical antibiotic regimen at correct indication and according to guidelines
3. Stop antibiotic therapy if no fever for 3 consecutive days

4. Obtaining two sets of blood samples for culture
5. Urine antigen testing for *Legionella* species on clinical suspicion

COPD alone

6. Prescribe antibiotic therapy for exacerbations only when indicated
7. Optimal duration of antibiotic therapy from 5-7 days

Both CAP & COPD

8. Adapting dose and dose interval of antibiotics according to renal function
9. Switch from intravenous to oral therapy according to existing criteria and clinical stability
10. Changing broad-spectrum, empirical therapy to pathogen-directed therapy (streamlining therapy)
11. Obtaining sputum samples for Gram staining and culture

Schouten 2012

1. Clinical rationale of starting AB documented in the chart (day 1)
2. Appropriate microbiological cultures according to local and/or international guidelines (day 1);
3. Choice of empiric therapy according to local and/or international guidelines (day 1)
4. Review of diagnosis according to microbiological results (day 2, 3, 4, 5)
5. De-escalation therapy to be considered in patients with microbiological diagnosis according to the susceptibility pattern of the isolate (day 2, 3, 4, 5)
6. Withdrawal of therapy to be considered in patients with a definitive non-infectious diagnosis (day 3, 4, 5)

Sneddon 2012

1. Indication recorded and empirical antibiotic choice compliant with local policy. Target ≥95% compliance.
2. Duration of surgical prophylaxis <24 hours and choice compliant with local policy. Target ≥95% compliance.

Ten Oever 2019 (Antimicrobial therapeutic interventions only)

Blood cultures

1. Follow-up blood cultures after initiation of antimicrobial therapy should be done regardless of clinical evolution.
2. Collection of repeat blood cultures should be performed until first negative blood culture.

Antibiotic treatment

3. Initial antibiotic therapy should be administered intravenously in patients with SAB.
4. Initial therapy should be intravenous (flu)cloxacillin (or nafcillin or oxacillin) or cefazolin in the case of methicillin-susceptible strains in patients with SAB.

5. Antibiotic therapy should be initiated within 24 h after first positive blood culture.
6. Appropriate treatment should be adapted within the first 24 h after a methicillin susceptibility result is available, if so required.
7. The dosage of antibiotic treatment should be according to (national) guidelines in patients with SAB.
8. Appropriate duration of intravenous antibiotic treatment should be at least 14 days for uncomplicated SAB.
9. Appropriate duration of intravenous antibiotic treatment should be at least 28 days for SAB complicated by metastatic abscesses or deep foci of infection
10. Therapeutic drug monitoring should be performed when SAB is treated with vancomycin.
11. Antibiotic treatment therapy for patients with SAB should be adjusted according renal function.
12. Intravenous-to-oral switch should not be performed in uncomplicated SAB after 48–72 h.
13. Intravenous-to-oral switch should not be performed in complicated SAB after 48–72 h.

Other management aspects

14. Infectious disease specialist consultation should be performed in patients with SAB.
15. SAB should be documented in the medical discharge summary.

Van der Bosch 2014

1. Antimicrobial therapy in adult patients with sepsis should be started intravenously.
2. Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock.
3. Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken.
4. Empiric systemic antimicrobial therapy should be changed to pathogen-directed therapy if culture results become available.
5. Empiric systemic antimicrobial therapy (only choice of antimicrobial agent) should be prescribed according to the national guideline. The local guidelines should correspond to the national guideline but should deviate based on local resistance patterns.

Van der Bosch 2015

1. Before starting systemic antibiotic therapy, at least two sets of blood cultures should be taken.
2. When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started (cultures should be taken until a maximum of 24 h after antibiotics are started).
3. Empirical systemic antibiotic therapy should be prescribed according to the local guidelines.
4. A current local antibiotic guideline should be present in the hospital and an evaluation whether an update should be considered should be done every three years.
5. Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.
6. Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available.
7. Dose and dosing intervals of systemic antibiotics should be adapted to renal function.
8. Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate.
9. An antibiotic plan should be documented on the case notes at the start of systemic antibiotic treatment.
10. Therapeutic drug monitoring should be performed when the treatment duration is more than three days for aminoglycosides and more than five days for vancomycin.
11. Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be seven days.

Vera 2014

1. **Antimicrobial use in the intensive care unit Formula**: Total number of days of use of antimicrobial agent /Total number of days of ICU patients ×100
2. **Non-empirical antimicrobial use Formula**: Total antimicrobials used to treat infections in a directed manner /Total of antimicrobials used to treat infections ×100
3. **Changes in antimicrobials used as treatment Formula:** Total number of antimicrobials changed to another antimicrobial / Total of antimicrobials used to treat infections × 100
4. **Days without antimicrobial use in ICU Formula:** Total number of ICU days without antimicrobials / Total number of days of ICU patients × 100
5. **Days free of antimicrobials in patients on antimicrobial treatment Formula**: Number of days free of antimicrobials in patients on antimicrobial treatment / Total days in ICU of patients on antimicrobial treatment × 100

6. **Number of days of antimicrobials for surgical prophylaxis Formula**: Number of days of use of antimicrobials for surgical prophylaxis / Total number of patients with surgical prophylaxis treatment × 100
7. **Inappropriate empirical antimicrobial treatment Formula:** Total number of inappropriate empirical antimicrobials / Total number of empirical antimicrobials used to treat infections × 100
8. **Empirical antimicrobials changed because they are inadequate Formula:** Number of empirical antimicrobials changed because they are inadequate / Total number of empirical antimicrobials used to treat infections × 100
9. **Empirical antimicrobial changed for de-escalation Formula:** Number of empirical antimicrobials changed by adjustment or de-escalation / Total number of empirical antimicrobials used to treat infections × 100
10. **Patients with severe sepsis/septic shock treated with antimicrobials in the first three hours Formula:** Number of patients with severe sepsis/septic shock, treated with antimicrobials in the first 3 hours / Total number of patients with severe sepsis/septic shock

Appendix 6

Ethical approval for Study 4 (Chapter 5)

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

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University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (p) 09/02/2021
& ECM 3 (xx) 09/03/2021

Date: 1st March 2021

Dr Deirdre O'Brien
Consultant Microbiologist
Mercy University Hospital
Grenville Place
Cork

Study Title: AMRACMUH: A retrospective interrupted time series analysis to determine the impact of the Covid 19 pandemic on antimicrobial consumption and rates of resistance of multi-drug resistant organisms in a hospital with an established antimicrobial stewardship programme.

Dear Dr O'Brien

The following documents have been approved:

- Revised Application Form
- Revised Data Collection Sheet Version 2 dated 16th February 2021.

Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 7

Published PhD papers

J Antimicrob Chemother 2019; **74**: 3352–3361
doi:10.1093/jac/dkz313 Advance Access publication 19 July 2019

Journal of Antimicrobial Chemotherapy

An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish university hospital setting: a feasibility study

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Background: Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for respiratory tract infections (RTIs). Procalcitonin (PCT) has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs, but recent study results have been variable.

Methods: We conducted a feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI to determine if PCT testing is an effective and worthwhile intervention to introduce to support the existing antimicrobial stewardship (AMS) programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

Results: A total of 79 patients were randomized to the intervention PCT-guided treatment group and 40 patients to the standard care respiratory control group. The addition of PCT testing led to a significant decrease in duration of antimicrobial prescriptions (mean 6.8 versus 8.9 days, $P=0.012$) and decreased length of hospital stay (median 7 versus 8 days, $P=0.009$) between the PCT and respiratory control group. PCT did not demonstrate a significant reduction in antimicrobial consumption when measured as DDDs and days of therapy.

Conclusions: PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. The successful implementation of PCT testing in a randomized controlled trial requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomized controlled trial would be beneficial to further explore the positive aspects of these findings.

Introduction

Antimicrobial resistance (AMR) is a major risk to public health globally that leads to increasing healthcare costs, treatment failure and increased morbidity and mortality.[1–3] There is a strong association between suboptimal antimicrobial prescribing and AMR.[4] To optimize prescribing, hospital antimicrobial stewardship (AMS) programmes should target areas of high antimicrobial prescribing. One such area is respiratory tract infections (RTIs). Shorter antimicrobial courses offer one potential solution to the overuse of antimicrobials for RTIs[5] and there is evidence to support such strategies,[6,7] even in severe hospital infections.[8]

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for RTIs.[9–12] This contributes to overuse and/or suboptimal use of antimicrobials[13,14] for RTIs such as community-acquired pneumonia (CAP), including prolonged treatment courses of up to 11 days,[15] without a correlation between duration of treatment and infection severity.[15,16] Physicians are often reluctant to shorten antimicrobial course durations due to the fear of incomplete pathogen eradication, which could potentially lead to relapse and associated morbidity and mortality.[6] There is also a high rate of antimicrobial continuation where viral infections,[17] including influenza,[18] are identified due to overriding concerns about secondary bacterial

infections. However, a recent study has shown a bacterial co-infection rate of only 40%.[11]

To address these issues, there is a growing interest in the use of novel diagnostic techniques and biomarkers as an AMS tool.[19] It is important that AMS programmes investigate the opportunity afforded by these new techniques and the potential they offer to optimize antimicrobial treatment more promptly[20] and change prescribing behaviour.[21] Procalcitonin (PCT) testing is one such diagnostic technique. PCT is a peptide precursor to the hormone calcitonin. It is usually undetected but is upregulated in response to a bacterial infection following stimulation of bacteria-induced cytokines.[22] Upregulation of PCT is blocked in viral infections due to the release of the cytokine IFNγ, resulting in a higher specificity of PCT to distinguish between bacterial and viral infections when compared with other inflammatory markers such as C-reactive protein (CRP).[23] PCT levels decrease rapidly when patients are recovering from infection.[24] Hence it offers the potential to support clinical decision-making for the initiation and discontinuation of antimicrobials in patients with a clinical suspicion of a bacterial infection when considered along with the clinical assessment of the patients. PCT has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs,[25–28] but findings from recent studies have been variable,[29,30] so it is unclear if it is an effective intervention as part of an AMS programme.

The purpose of this study was to conduct a feasibility study to determine if PCT testing is an effective and worthwhile intervention to introduce in a university teaching hospital to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

Methods

We conducted a single-centre, randomized, open-label feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI (LRTI) under the care of the respiratory medicine team during on-call acute unselected general medical take to determine if PCT testing had an impact on antimicrobial consumption and patient's length of stay (LOS) in hospital. The study was conducted in a single 321 bed inner city, voluntary acute university teaching hospital, which is part of the South/South West Hospital Group[31] in the Republic of Ireland. It is a Model 3 (smaller general)[32] hospital with a 24 h emergency department and ICU, and admits undifferentiated acute medical and surgical patients. The hospital has an established AMS programme, and no significant changes were made to the AMS policies or programme during this study.

Ethics

The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals [approval code ECM 4 (w) and ECM 3 (III)]. Written informed consent was obtained from all participants prior to study enrolment.

Education and training

The microbiology laboratory scientists received technical advice and training on the operation of the PCT assay from the manufacturer prior to study commencement. They also received a presentation on the introduction of PCT testing in the hospital.

The respiratory medicine team received three presentations at the respiratory journal club meetings and provision of written materials electronically. Presentations consisted of evidence supporting PCT use in practice, limitations of PCT testing, PCT measurement, and interpretation using a PCT-based antimicrobial prescribing algorithm (Appendix S1, available as Supplementary data at *JAC* Online). Presentations were given prior to the study commencement and following medical staff rotation changes. The study protocol (Appendix S2), study flow chart and the PCT-based antimicrobial prescribing algorithm were provided to all physicians electronically.

Recruitment and consent

Inclusion criteria

Adult patients ≥18 years of age, admitted to hospital under the care of the respiratory teams with an initial diagnosis of an acute LRTI (i.e. CAP[33] with severity defined by CURB-65 score[34], LRTIs[35], exacerbation of asthma[36], COPD[37], bronchiectasis[38], interstitial lung disease[39] and influenza[35]) and commenced on antimicrobial therapy were identified from the daily admission census or by the respiratory medicine teams.

The randomization process stratified patients according to presence or absence of severe COPD GOLD Stage D criteria 2017[37] to ensure balanced treatment allocation. Patients were then randomly allocated in a 2:1 ratio to either the PCT-guided treatment group or the standard care respiratory control group. Randomization was carried out using sequentially numbered opaque sealed envelopes. A second general control group of patients admitted under general medicine teams with a diagnosed acute LRTI and who received standard care (no PCT measurement) was recruited to provide a comparison of antimicrobial prescribing in RTIs by non-respiratory specialist physicians in the hospital.

Exclusion criteria

Exclusion criteria were: unable to give written informed consent due to language restrictions; cognitive impairment or severe dementia; readmission to hospital within 30 days of previous admission; immunosuppression (neutropenic, chemotherapy, radiation therapy or immunosuppressive therapy) other than corticosteroid use; life-threatening medical comorbidities leading to possible imminent death; do not resuscitate (DNR) status; concurrent chronic infections necessitating prolonged antimicrobial treatment (cystic fibrosis, TB, infective endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis); >24 h of appropriate antimicrobial therapy prior to initial PCT level; active IVDUs; and pregnant women.

Intervention

PCT testing was commenced in the microbiology department following completion of staff training and instrument validation. It was available during routine working hours (Monday to Friday, 9 am–5 pm). PCT serum concentrations were measured using the VIDAS BRAHMS PCT (assay range 0.05–200 μg/L) (bioMérieux, France).

PCT serum concentrations were interpreted using an evidence-based algorithm (Appendix S1),[40] which has been validated in previous studies[28,29] recommending antimicrobials strongly discouraged for PCT levels <0.1 μg/L, discouraged for levels 0.1–0.25 μg/L, encouraged for levels >0.25–0.5 μg/L and strongly encouraged for levels >0.5 μg/L. The algorithm also included specific overruling criteria where antimicrobials could be considered in the case of respiratory or haemodynamic instability; life-threatening comorbidity; need for ICU admission; PCT <0.1 μg/mL: and CAP with CURB-65 >3 or COPD stage IV; PCT <0.25 μg/mL: CAP with CURB-65 >2; localized infection (abscess, empyema); immunocompromised (other than corticosteroids); or concomitant infection in need of antimicrobials.

The antimicrobial prescribing advice generated from the PCT algorithm was verbally communicated to the respiratory medicine team, and this advice was non-binding. The respiratory medicine team retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm-generated antimicrobial prescribing advice. The algorithm adherence for antimicrobial prescribing recommendations was recorded

at 24 h following the PCT test for all patients along with the rationale for prescribing decisions. Algorithm adherence was defined as antimicrobial therapy that was continued or discontinued in accordance with the PCT cut-off ranges. Non-adherence was defined as antimicrobial therapy that was not discontinued despite low PCT levels. Overriding criteria were not considered when measuring adherence but were recorded as reasons for non-adherence.

Patients were followed until their discharge. A further follow-up of medical records took place at 30 days after admission to identify readmitted patients and readmitted patients with infection relapse.

Patient recruitment ran from 1 June 2017 to 31 May 2018. Figure 1 represents the patient hospital journey with an RTI.

Outcomes

The primary outcomes were to quantify the individual inpatient antimicrobial consumption, prescription duration and the inpatient LOS. Following a recent systematic review which recommended that antimicrobial use should be expressed in at least two metrics simultaneously,[41] antimicrobial consumption was measured using DDDs, days of therapy (DOT) and prescription duration. DDDs were calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index of the WHO Collaborating Centre for Drug Statistics Methodology,[42] but were not adjusted for hospital activity. DOT[43] calculates individual patient-days of antimicrobial exposure and accounts for dosing and frequency of each drug. Antimicrobial prescription duration was measured in days (defined as the number of days between the commencement and discontinuation of antimicrobials). The LOS was defined as the date of discharge minus the date of admission.

Secondary outcomes were number of infection- and antimicrobial-related adverse events during inpatient LOS including mortality, hospital readmission within 30 days and infection relapse requiring readmission within 30 days. Algorithm adherence for antimicrobial prescribing recommendations was measured.

A qualitative process evaluation of the study was conducted in parallel with this feasibility study and will be reported in a subsequent paper.

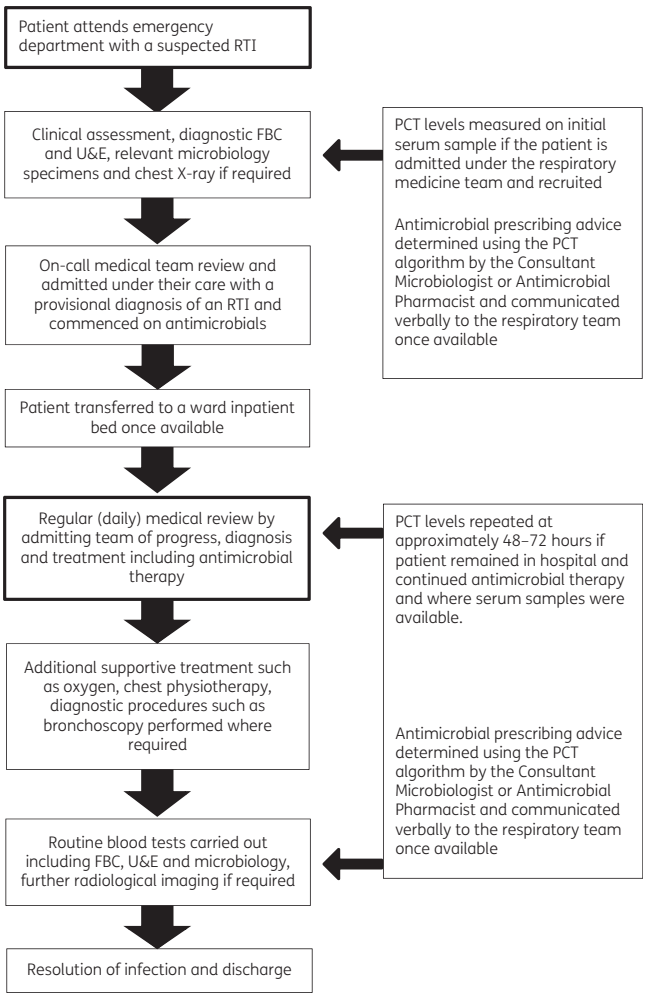

Figure 1. Patient hospital journey with an RTI. FBC, full blood count; U&E, urea and electrolytes.

Statistical methods

A Microsoft Access database (version 1903) was developed to record the study data. Statistical analysis was conducted using R (version 3.4.0) and was carried out on an ITT basis.

The primary outcome of antimicrobial consumption between the PCT and respiratory control arms was evaluated using the non-parametric Wilcoxon Rank Sum test. A Kaplan–Meier curve was used to analyse the median time to discharge between the PCT and respiratory control groups.

χ^2 Tests were used to evaluate differences between the PCT and respiratory control arms for all secondary outcomes, i.e. the number of adverse events and readmissions and infection relapses requiring readmission both within 30 days.

Results

The respiratory medical teams admitted 823 general medical patients of whom 313 patients were classified as having a respiratory infection or respiratory disorder during the recruitment period of 1 June 2017 to 31 May 2018. A CONSORT flow diagram of recruitment can be seen in Figure 2.

A further 48 patients were recruited to the general control group.

Demographic data and study overview are presented in Table 1. Clinical findings of patients on admission to hospital are given in Table 2.

There were several differences between the baseline characteristics of the PCT group and the respiratory control group. The PCT group contained more male patients (60% versus 42%) and active smokers (25% versus 12.5%).

There were several differences in final diagnosis between the PCT group and the respiratory control group with asthma (3.8% versus 15%), CAP (10% versus 7.5%) and LRTI (30.4% versus 17.5%). CAP severity in the PCT group had CURB-65 scores ranging from 0 to 3 with a mean of 1.87, while the CAP severity in the respiratory control group had CURB-65 scores ranging from 0 to 1 with a mean of 0.66.

The clinical findings on admission were similar between the PCT and respiratory control groups, with two exceptions where the PCT group had a higher percentage of patients who were productive of sputum on admission (49% versus 37%) and patients prescribed antibiotics prior to admission (35% versus 25%).

PCT testing and results

The 79 patients randomized to the PCT group had a total of 163 PCT levels taken [median of 2 tests per patient (range 1–6)]. Overall the PCT levels had a median value of 0.075 μg/L (IQR

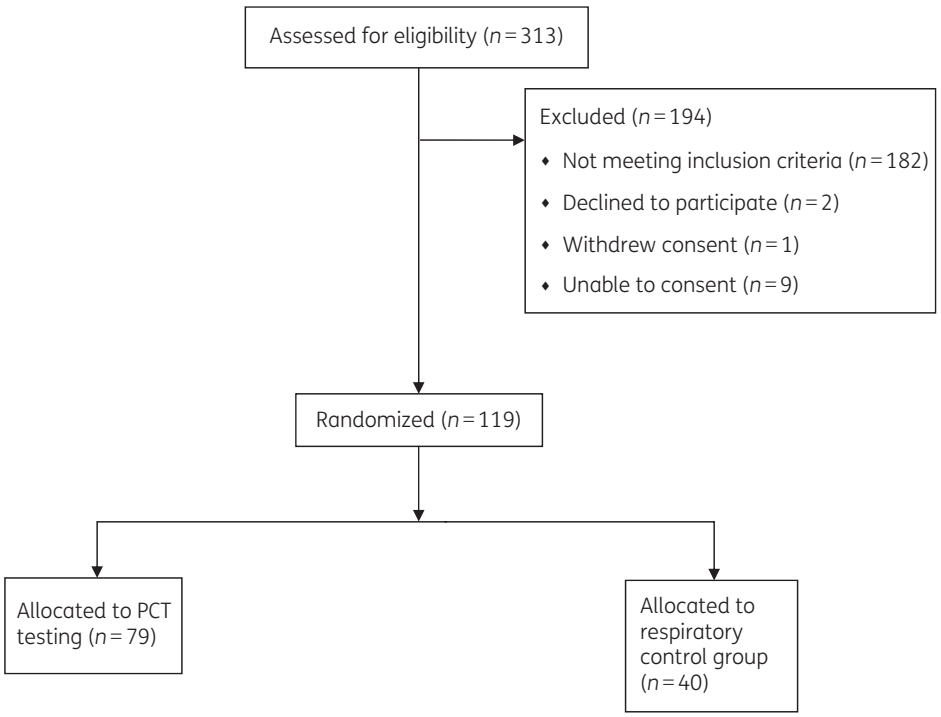

Figure 2. CONSORT 2010 flow diagram.

Table 1. Demographic data and study overview

	Study group			
Variable	overall	PCT	respiratory control	general control
Participants, *n* (%)	167 (100)	79 (47.3)	40 (24.0)	48 (28.7)
Gender, *n* (%)				
female	79 (47.3)	31 (39.2)	23 (57.5)	25 (52.1)
male	88 (52.7)	48 (60.8)	17 (42.5)	23 (47.9)
Age, years (mean ± SD)	68.7 ± 14	68.6 ± 13.6	68.4 ± 15.3	69.1 ± 13.9
Co-existing conditions and risk factors, *n* (%)				
smoking status				
non-smoker	50 (30)	26 (32.9)	13 (32.5)	11 (23)
smoker	33 (20)	20 (25.3)	5 (12.5)	8 (16.6)
ex-smoker	84 (50)	33 (41.8)	22 (55)	29 (60.4)
asthma	28 (16.8)	13 (16.5)	10 (25)	5 (10.4)
COPD A–C	58 (34.7)	23 (29.1)	10 (25)	25 (52)
COPD D	24 (14.4)	10 (12.7)	5 (12.5)	9 (18.8)
bronchiectasis	16 (9.6)	9 (11.4)	3 (7.5)	4 (8.3)
interstitial lung disease	7 (4.2)	4 (5)	2 (5)	1 (2.1)
Final diagnosis, *n* (%)				
asthma	11 (6.6)	3 (3.8)	6 (15)	2 (4.2)
CAP	18 (10.8)	8 (10)	3 (7.5)	7 (14.6)
COPD	62 (37.1)	24 (30.4)	13 (32.5)	25 (52)
LRTI	45 (27)	28 (35.4)	7 (17.5)	10 (20.8)
other LRTIs	20 (12)	10 (12.6)	7 (17.5)	3 (6.2)
non-respiratory related	11 (6.6)	6 (7.6)	4 (10)	1 (2.1)

Table 2. Clinical findings on admission to hospital

	Total (*n*=167)	PCT (*n*=79)	Respiratory control (*n*=40)	General control (*n*=48)
Respiratory rate, breaths/min	22.1 ± 5	22.1 ± 5.4	21.1 ± 3.7	22.7 ± 5.2
Systolic blood pressure, mmHg	133 ± 23.1	130.9 ± 22.9	136 ± 20.9	134 ± 25
Diastolic blood pressure, mmHg	75 ± 14.1	74.8 ± 12	78.6 ± 14.8	72.3 ± 16.1
Heart rate, beats/min	91.8 ± 20.1	93.4 ± 23.3	91.2 ± 16.7	89.8 ± 16.7
Temperature, °C	36.8 ± 0.8	36.8 ± 0.8	36.9 ± 0.8	36.8 ± 0.9
Rigors, *n* (%)	24 (14.4)	11 (13.9)	6 (15)	7 (14.6)
Fever, *n* (%)	18 (10.8)	8 (10.1)	5 (12.5)	5 (10.4)
Chills, *n* (%)	15 (9)	10 (12.7)	1 (2.5)	4 (8.3)
Number of clinical signs of infection	1.8 ± 1.3	1.9 ± 1.3	1.7 ± 1.2	1.8 ± 1.3
Documented signs of respiratory illness				
cough, *n* (%)	132 (79)	64 (81)	31 (77.5)	37 (77)
shortness of breath, *n* (%)	101 (60.5)	45 (57)	23 (57.5)	33 (68.7)
productive of sputum, *n* (%)	81 (48.5)	39 (49.4)	15 (37.5)	27 (56.2)
dyspnoea, *n* (%)	49 (29.3)	22 (27.8)	10 (25)	17 (35.4)
pleuritic pain, *n* (%)	26 (15.6)	10 (12.7)	9 (22.5)	7 (14.6)
respiratory failure, *n* (%)	19 (11.4)	8 (10.1)	5 (12.5)	6 (12.5)
abnormal chest exam, *n* (%)	144 (86.2)	70 (88.6)	31 (77.5)	43 (89.6)
abnormal radiological findings, *n* (%)	94 (56.3)	42 (53.2)	21 (52.5)	28 (58.3)
CURB-65 score (CAP patients)	1.56 ± 1.05	1.87 ± 1.05	0.66 ± 0.47	1.57 ± 1.05
number of signs of acute respiratory illness	3.9 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	4 ± 1.3
Antimicrobials prescribed pre-admission, *n* (%)	59 (35.3)	28 (35.4)	10 (25)	21 (43.7)
Corticosteroids prescribed pre-admission, *n* (%)	34 (20.4)	14 (17.7)	7 (17.5)	13 (27)
Infection source				
community, *n* (%)	149 (89.2)	70 (88.6)	32 (80)	47 (98)
healthcare, *n* (%)	13 (7.8)	6 (7.6)	6 (15)	1 (2)
hospital, *n* (%)	5 (3)	3 (3.8)	2 (5)	0 (0)

Values are shown as mean ± SD unless otherwise stated.

0.05–0.26). The initial PCT level was ≤0.24 μg/L for 58 patients (including 38 patients with an initial PCT level of ≤0.05 μg/L). The study outcomes can be seen in Table 3 and Figure 3. Statistical analysis was conducted on the PCT and respiratory control group only, and does not include comparison with the general control group.

There was no significant difference in antimicrobial consumption when measured as DDDs (11.1±7.5 versus 13.1±10.7, *P*=0.218) (mean ± SD) or DOT (8.9±6.3 versus 11±7.6, *P*=0.077) of patients between the PCT and respiratory control group. Median values of both metrics, DDD (8.66 versus 9.57) and DOT (7.5 versus 8.25), showed a decrease of 9% in antimicrobial consumption per patient.

There was a significant difference in the antimicrobial duration in days between the PCT and respiratory control groups (median 7 versus 8 days, *P*=0.0125). There was also a significant difference between the PCT and respiratory control groups in the median LOS (*P*=0.009), and this can also be seen in the Kaplan–Meier curves in Figure 4.

In the analysis of secondary outcomes, there was no significant difference between the PCT and respiratory control group in the incidence of adverse events during inpatient hospital stay (*P*=0.9852), the rate of hospital readmission (*P*=0.1507) and the rate of infection relapse requiring readmission both within 30 days (*P*=0.0924).

Algorithm compliance is displayed in Table 4. Overall PCT algorithm compliance per patient was 35% within 24 h of the PCT level being taken. Twenty-five patients had high PCT levels (≥0.25 μg/L) where the algorithm recommendation was to continue antimicrobial treatment and algorithm compliance was 100%. Sixty-seven patients had low PCT levels (<0.25 μg/L) where the algorithm recommendation was to discontinue antimicrobial treatment and algorithm compliance was low (10%). In these instances, the reasons for non-adherence were based on a clinical decision in 55/112 (49%) PCT levels, with the remaining 57/112 (51%) PCT levels based on meeting various algorithm overriding criteria [respiratory or haemodynamic instability; life-threatening comorbidity; need for ICU admission; or localized infection (abscess, empyema)].

Seven patients had their antimicrobial treatment discontinued in compliance with the algorithm when PCT levels were low (<0.25 μg/L). This resulted in shorter course lengths in five patients (<7 days), one course length completion as planned at 7 days and early antimicrobial discontinuation (day 2) in a patient with influenza. There were no hospital readmissions among these patients.

In a further nine patients where there was initial non-compliance with the algorithm recommendations when measured at 24 h, their antimicrobial treatment was subsequently modified, resulting in a shorter course length in seven patients (<7 days), and two further patients discontinued antimicrobials

Table 3. Primary and secondary outcome data

	PCT (n=79)	Respiratory control (n=40)	General control (n=48)	P value
Primary outcomes, mean ± SD (median)				
DDDs per patient	11.1 ± 7.5 (8.66)	13.1 ± 10.7 (9.57)	18.5 ± 11 (16.5)	0.218
DOT per patient	8.9 ± 6.3 (7.5)	11 ± 7.6 (8.25)	13.7 ± 11.1 (11.63)	0.077
total duration of inpatient antimicrobials (days)	6.8 ± 2.8 (7)	8.9 ± 4 (8)	8.4 ± 3.6 (8)	0.0125*
LOS (days)	7.4 ± 4.3 (7)	10.5 ± 6.1 (8)	8.9 ± 3.8 (8)	0.009*
Secondary outcomes, n (%)				
hospital readmission within 30 days	7 (8.9)	8 (20)	7 (14.6)	0.1507
relapse of infection within 30 days	6 (7.6)	8 (20)	6 (12.5)	0.0924
adverse events	6 (7.6)	3 (7.5)	4 (8.3)	0.9852

*Statistical significance was set as $P<0.05$, and P values relate to the comparison between the PCT and respiratory control groups.

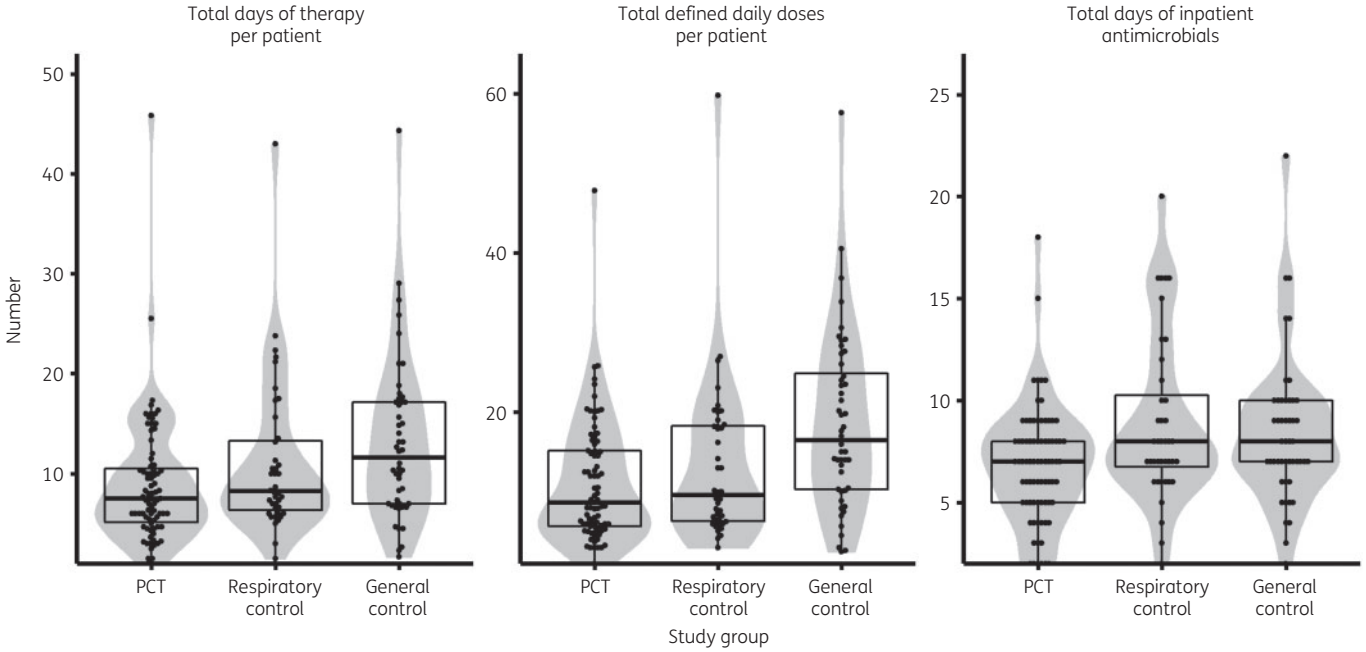

Figure 3. Main antimicrobial consumption outcomes.

prior to discharge. There was one patient readmitted to hospital with infection among these patients.

Algorithm compliance by indication was as follows; CAP (80%), asthma (50%), LRTI (30%), COPD (12.5%) and influenza virus (42%). PCT levels and algorithm compliance were found to be low in patients with COPD stage D and structural lung conditions such as bronchiectasis and interstitial lung disease. In these cases, the clinical judgement of physicians was to override the algorithm recommendations and continue antimicrobials.

Microbiology-positive specimens

Thirty-eight patients (23%) had positive microbiology results. Relevant respiratory results included: 13 influenza virus, 10 bacterial isolates from respiratory specimens and 7 yeast isolates from respiratory specimens.

Adverse events

Infection- and antimicrobial-related adverse events included gastrointestinal (antimicrobial-related diarrhoea, one patient) renal function (acute kidney injury secondary to antimicrobials, one patient), liver function (increased liver function tests secondary to antimicrobials, one patient), respiratory disorders (hospital-acquired pneumonia, hospital-acquired influenza and respiratory deterioration, three patients) and other events (two patients).

Mortality during the study

Five patients included in the study died during their hospital stay: four from the PCT group and one from the respiratory control group (age range 75–94 years). All had multiple comorbidities including cardiac (congestive cardiac failure, atrial fibrillation), renal and

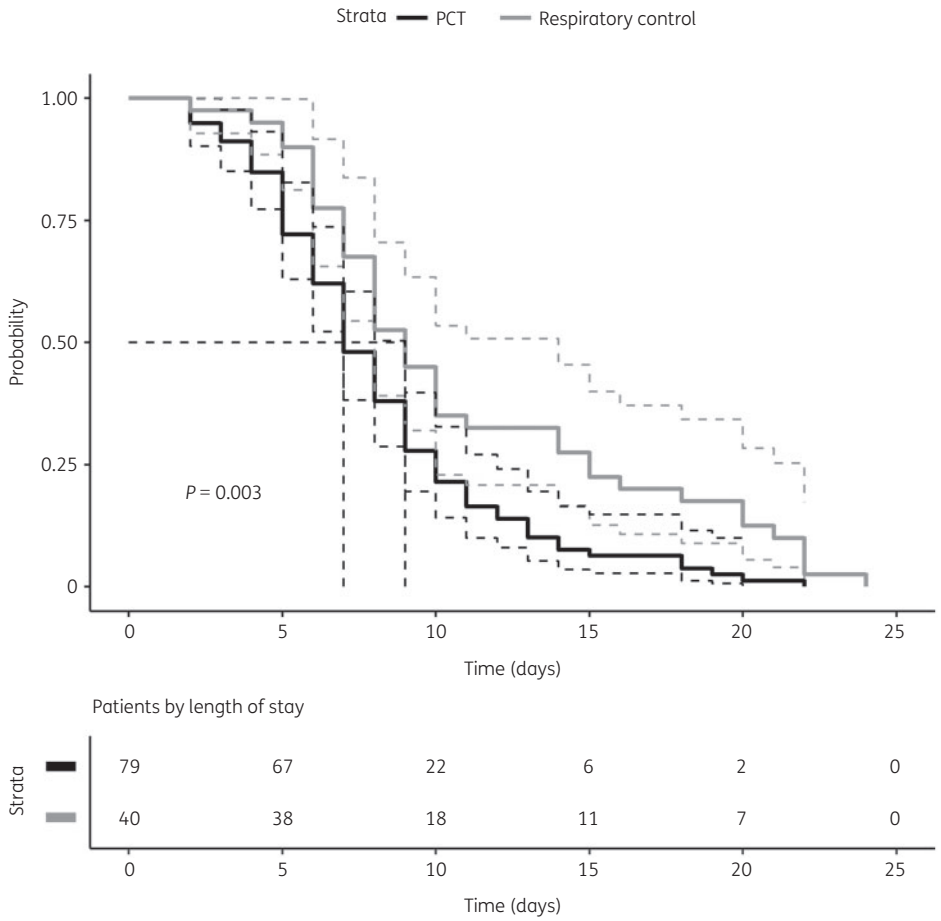

Figure 4. Comparison of time to discharge probability for PCT versus respiratory control arms: Kaplan–Meier curves. Median probability of discharge is given by the horizontal dashed line. The grey and black dashed lines show the 95% CIs.

Table 4. PCT algorithm compliance

PCT level (μg/L)	Algorithm recommendation	No. of patients	No. of PCT test results	No. of patients compliant with algorithm	No. of patients non-compliant with algorithm	% of patients compliant with algorithm
≤0.05 to <0.25	antimicrobial therapy discouraged	67	119	7	60	10%
≥0.25	antimicrobial therapy encouraged	25	44	25	0	100%

new or existing cancer diagnosis. Antimicrobial treatment decisions for these patients were based on clinical decisions.

Discussion

This feasibility study of the introduction of PCT testing has shown a positive effect on antimicrobial prescribing resulting in a decrease in the duration of antimicrobial courses in patients with RTIs and a decrease in LOS without an increase in adverse events or readmission to hospital. The median duration of antimicrobial treatment was reduced from 8 to 7 days, and antimicrobial consumption fell by 9% when measured as DDD and DOT. This study confirms the findings of previous PCT trials[28,44] that it is an effective and worthwhile intervention to safely reduce antimicrobial exposure in patients with RTIs and supports the AMS programme. However, there were several findings that may have influenced the outcomes and these need to be considered when viewing the overall results and considering progression to, and design of, a full randomized controlled trial (RCT).

Overall PCT algorithm compliance was 35%, and compliance with stopping recommendations was 10% when PCT levels were low (<0.25 μg/L). The reasons for non-compliance were clinical judgement (49%) and meeting pre-determined overriding criteria (51%). PCT was a new diagnostic test in the hospital, and physicians can require time to become familiar with and develop confidence in the use of PCT testing.[45] Other studies have found

that algorithm compliance can be variable, ranging from 35% to 80%.[44] An international, multicentre study found that centres with experience of using PCT and ongoing reinforcement of PCT-guided AMS had higher algorithm compliance than PCT-naive centres.[44] Protocol-driven studies[28,46] have also shown higher algorithm compliance and greater impact on antimicrobial prescriptions than studies taking a quality improvement implementation approach.[29]

Algorithm compliance must improve significantly in a future trial to maximize the potential impact of PCT testing on antimicrobial prescribing decisions but also acknowledging the limitations of PCT and that physicians cannot rely on PCT alone to guide antibiotic therapy.[23] In a future trial, this should be addressed by a more comprehensive educational programme and more effective incorporation into the AMS programme to reinforce PCT recommendations. Such an approach has been shown to be effective[30,46,47] and is required for interventions such as PCT to realize their full benefit.[19] The educational element of this study may not have been sufficient. A future trial should consider the inclusion of more frequent educational presentations prior to and during the intervention, and include case reviews of PCT patients. Consideration should be given to the development of pocket cards, incorporation into local electronic antimicrobial prescribing guidelines and availability of results on the hospital electronic laboratory reporting system.[46]

Delays in availability of PCT results may have also decreased the impact of the intervention and contributed to poor algorithm compliance, with 38% of PCT serum results not available until the next day (24 h after the serum sample was taken). This included results which were delayed or unavailable for 12 patients until after they were discharged. In a future trial, prompt availability of PCT levels is important. This would allow physicians to consider PCT along with routine biochemistry and blood analysis and the patients' clinical parameters at the point of care when making antimicrobial prescribing decisions. Consideration should be given to measurement of algorithm adherence at 48 h to account for unforeseen delays in PCT result availability or delayed physician review of PCT results.

There were several factors involved in patient recruitment which may have influenced the primary outcomes of the study and should be addressed in a future trial design. These were the variation in infection severity between the PCT and respiratory control groups and the inclusion of patients who were already prescribed antimicrobials prior to hospital admission. These factors can be addressed in a suitably powered future RCT with the inclusion of illness severity scores and the use of multivariate and subgroup analysis.

A future RCT would include a broader range of physicians rather than respiratory specialists alone. Antimicrobial consumption in the general control group of patients in this study was higher than in either of the respiratory groups. The addition of PCT testing to the existing AMS programme may have the potential to have a greater impact on this patient group.

Strengths and limitations

The study was conducted in a setting where PCT was a newly available test to physicians. A broad range of RTIs were recruited. The study took place over a calendar year and included seasonal variation in illness and prescribing. Patients were randomized to intervention or control, thus reducing selection bias. Serial PCT measurements were available to guide antimicrobial prescribing.

The study had some limitations. The study population had a clinical need for antimicrobial treatment, so the study was designed to examine the duration of therapy and LOS, rather than investigating the potential to withhold antimicrobial therapy. The study results may have been influenced by a study effect. Both the PCT and respiratory control groups were treated by the same group of physicians who all received education and, as they were aware that their behaviour was being monitored, this may have resulted in a Hawthorne effect.[48] The intervention was confined to one medical speciality which may limit its generalizability to other medical specialties and settings. Further limitations included the need for patient consent, and PCT results which were not available at the point of clinical decision-making in a small number of cases.

Conclusions

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. Several factors were identified which may have influenced the outcomes and the intervention implementation. The successful implementation of PCT testing requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger RCT would be beneficial to further explore the positive aspects of these findings.

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Transparency declarations

None to declare.

Supplementary data

Supplementary Appendices S1 and S2 are available as Supplementary data at *JAC* Online.

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A qualitative process evaluation of the introduction of procalcitonin testing as an antimicrobial stewardship intervention

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RESEARCH ARTICLE

A qualitative process evaluation of the introduction of procalcitonin testing as an antimicrobial stewardship intervention

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Abstract

Background Successful antimicrobial stewardship interventions are imperative in today's environment of antimicrobial resistance. New antimicrobial stewardship interventions should include qualitative analysis such as a process evaluation to determine which elements within an intervention are effective and provide insight into the context in which the intervention is introduced. *Objective* To assess the implementation process and explore the contextual factors which influenced implementation. *Setting* An academic teaching hospital in Cork, Ireland. *Methods* A process evaluation was conducted on completion of a feasibility study of the introduction of a procalcitonin antimicrobial stewardship intervention. The process evaluation consisted of semi-structured face-to-face interviews of key stakeholders including participating (senior) doctors (5), medical laboratory scientists (3) and a hospital administrator. The Consolidated Framework for Implementation Research was used to guide data collection, analysis, and interpretation. *Main outcome measures* Qualitative assessment of the intervention implementation process, the contextual factors which influenced implementation and identification of improvements to the intervention and its implementation and determine if proceeding to a randomised controlled trial would be appropriate. *Results* Analysis of the interviews identified three main themes. (1) The procalcitonin intervention and implementation process was viewed positively to support prescribing decisions. Participants identified modifications to procalcitonin processing and availability to improve implementation and allow procalcitonin to be "more of a clinical influence". (2) In the antimicrobial stewardship context the concept of fear of missing an infection and risks of potentially serious outcomes for patients emerged. (3) The hospital context consisted of barriers such as available resources and facilitators including the hospital culture of quality improvement. *Conclusion* This process evaluation provides a detailed analysis of the implementation of procalcitonin testing as an antimicrobial stewardship intervention. The positive findings of this process evaluation and feasibility study should be built upon and a full randomised controlled trial and economic evaluation should be conducted in a variety of hospital settings to confirm the effectiveness of procalcitonin as an antimicrobial stewardship intervention.

Keywords Antimicrobial stewardship · Consolidated framework for implementation research · Procalcitonin · Process evaluation · Respiratory tract infections

Impacts on practice

- Procalcitonin is a useful additional antimicrobial stewardship intervention.
- The fear of missing infections and the risk of negative clinical outcomes for patients significantly influences antimicrobial prescribing decisions and must be considered when designing antimicrobial stewardship interventions.
- A culture of quality improvement within a hospital is an important facilitator of antimicrobial stewardship programmes.

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Introduction

Antimicrobial resistance (AMR) is a significant risk to human health and we face the very real possibility of a "post antibiotic era in which common infections could once again kill" [1]. Antimicrobial stewardship(AMS) programmes are well established and include interventions to improve antimicrobial prescribing [2–4]. Some AMS interventions can lack sustainability [5] which may be related to contextual factors of those interventions, but these have been poorly investigated particularly their role in the effectiveness of interventions and sustainability on a larger scale [6]. This has prompted the suggestion that interventions should look to include components that enhance enablement for the implementation of evidence-based practice, [6] defined as "increasing means or reducing barriers to increase capability or opportunity" [6, 7]. Furthermore a recent Cochrane review of interventions to improve antimicrobial prescribing for hospital patients [8] has advocated for greater use of qualitative research such as a process evaluation (PE) of a trial to determine which elements within an intervention are effective.

A qualitative PE [9] assesses the fidelity and quality of implementation, providing insight into the context into which the intervention is introduced, clarifies causal mechanisms of the intervention without assuming that the intervention itself leads to the outcome and builds the evidence base to support the intervention that will inform policy makers and practice [10]. A PE is important in complex interventions in the healthcare setting as a means to identify the underlying cause of the success or failure of interventions because occasionally even highly successful quality improvement interventions [11] have proven difficult to replicate in different contexts due to fundamental differences in how the intervention was delivered [12]. A PE is an important element of implementation research and should incorporate a theoretical framework to guide data collection, analysis and interpretation. Theoretical frameworks have a predictive capacity to identify or explain causal mechanisms of implementation. This allows for identification of contextual factors that influenced implementation and so aids our ability to generalise study findings. [13].

Greater utilisation of rapid diagnostic tests and biomarkers has been highlighted as an important factor in addressing AMR by improving infection diagnosis, supporting prescribing decisions and AMS programmes [14]. Procalcitonin is a biomarker which has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with respiratory tract infections [15–18]. The findings of a recent Cochrane review [17] supports its use in the context of AMS in safely reducing antimicrobial consumption by 2.4 days in patients with respiratory tract infections. We have previously reported the positive influence of procalcitonin on antimicrobial prescribing following the introduction of procalcitonin testing in a feasibility study [19]. The study identified some variability in the use and interpretation of procalcitonin levels suggesting a range of factors influenced implementation and should be explored to improve the effectiveness of intervention implementation in the future.

Feasibility studies should be complemented by a qualitative PE [9] to facilitate improved development and implementation of interventions [20]. This is particularly relevant when introducing new diagnostic tests to support AMS to assess how best to use such new tests [21] and reporting of qualitative analysis of procalcitonin implementation has been limited [22, 23].

Aim of the study

To explore how and why the introduction of a procalcitonin intervention worked or did not work in an Irish hospital setting. The study objectives were to gain an understanding and assessment of the fidelity and quality of the implementation process, explore the contextual factors which influenced implementation, identify the barriers and facilitators to implementation and inform improvements to the intervention and its implementation if proceeding to a randomised controlled trial was deemed appropriate.

Ethics approval

The study was approved by the Clinical Research Ethics Committee of University College Cork and the Cork Teaching Hospitals [reference code ECM 4 (w) and ECM 3 (III)]. Written informed consent was obtained from all participants prior to the interviews and confidentiality of the participants was assured.

Methods

The Standards for Reporting Qualitative Research were used to guide the development of this manuscript [24].

A qualitative PE was conducted of a single centre, randomised, open-label feasibility study [19] of the introduction of procalcitonin testing in patients admitted to hospital with a lower respiratory tract infection, under the care of the respiratory medicine team, during on-call acute unselected general medical take. The feasibility study ran from June 1st 2017 to May 31st 2018 and was conducted in a single, 321 bed model 3 (smaller general) [25] inner city, voluntary acute University Teaching Hospital, which is part of the South/South West Hospital Group [26] in the Republic

of Ireland. The PE was conducted following completion of the feasibility study.

The Consolidated Framework for Implementation Research (CFIR) [27] was used to guide data collection, analysis, and interpretation. It is a meta-theoretical framework based on existing determinant frameworks and multiple implementation theories which provides a roadmap of constructs to monitor the implementation process [27] by recognising that implementation is a multidimensional phenomenon with multiple interacting influences from the individual to the organisation and beyond [28]. The CFIR was chosen because it can be applied at any stage of the evaluation process of an intervention, it provides a framework to investigate and assess the complex multi-level nature of implementation in the healthcare setting including barriers and facilitators to effective intervention implementation [13] and provides a way in which to organise and communicate findings.

Participants

An invitation to participate in the study was issued in person or by email to key stakeholders involved in the feasibility study or would be involved in the decision to implement procalcitonin testing in the hospital in the future. All agreed to participate but one medical doctor later withdrew due to scheduling constraints. Participants included five medical doctors (DR1-5) (3 respiratory clinicians and 2 general clinicians), three medical laboratory scientists (MS1-3) and a hospital administrator (ADM). The interviews ranged in length from 6 to 29 min with a mean duration of 16 min.

Data collection

Semi-structured face-to-face interviews were conducted by the primary researcher. Interviews took places in the hospital where the study was conducted at a date and time that was convenient for participants. The interview topic guide was developed by two researchers (FOR and AF), both pharmacists with experience of AMS. The interview topic guide was informed by the most relevant CFIR constructs [27] which were used as a 'check-list' of variables for consideration. The topic guide was refined following a pilot interview with a medical doctor who participated in the feasibility study. Pilot interview data were included in the study due to the limited number of medical doctors participating directly in the feasibility study.

Interviews with medical laboratory scientists focused on the provision of procalcitonin testing in the laboratory, the interviews with doctors focused on the use of procalcitonin in making antimicrobial prescribing decisions while the interviews of participants with managerial responsibilities and the hospital administrator focused on implementation of procalcitonin testing on a larger, ongoing scale in the hospital. Issues and opinions on AMS and the hospital context for change and quality improvement were asked of all participants.

All interviews were digitally recorded and transcribed verbatim by a professional transcription service. The accuracy and quality of the transcripts was checked against the original recordings and any identifiable data was removed from the transcripts (by FOR).

Data analysis

Interview analysis used the framework method [29, 30] which provides a systematic step-wise approach to produce structured outputs of summarised data and is most commonly used for the thematic analysis of semi-structured interview transcripts [29]. It consists of the following steps (1) Transcription of the interviews, (2) Familiarisation with the interview data (3) Coding of the data using the CFIR constructs as deductive codes (open coding was applied when themes emerged during the familiarisation process that did not fit within the definitions of the CFIR constructs) (4) Charting and indexing of the data using a thematic framework 5. Interpretation and analysis of the data.

The interview transcripts were coded independently by two researchers (FOR and AF) using the CFIR constructs and open coding by thematic analysis. All 39 constructs of the CFIR were used as the a priori codebook for this qualitative study. Important domains and constructs were identified based on the frequency of their appearance in the interviews, the degree of importance articulated by the participants or the researchers, or both. Emergent themes were reviewed throughout the interview process and the team made an assessment as to when data saturation had occurred. All authors reviewed the final codes. Discrepancies were resolved through discussion.

Results

Nine interviews were conducted with hospital staff to explore the different aspects of the procalcitonin intervention implementation in the hospital setting. Participants roles in implementation are contained in Table 1. The results have been informed by the CFIR and are categorised into three themes. (1) The procalcitonin intervention and the implementation process, (2) The AMS/AMR context and (3) The hospital/organisational context. Within these themes participants described a range of factors that interact with each other and the intervention to produce an effect as a facilitator or barrier to implementation. The CFIR constructs identified in the themes are listed in Table 2 below. They are supported by qualitative excerpts from the interviews (Tables S1, S2

Table 1 Health professionals' role during the procalcitonin implementation

Health professional	Role in implementation
Hospital administrator	Hospital-wide managerial responsibilities and oversight of funding decisions
Respiratory clinicians	Involved in the procalcitonin intervention implementation and assessment
Clinicians	Provided insight into the contextual elements of implementation
Medical laboratory scientists	Laboratory processing of the procalcitonin tests

Table 2 Consolidated framework for implementation research domains and constructs associated with qualitative themes

Theme	CFIR domains	CFIR constructs
Procalcitonin intervention and implementation process	Intervention characteristics	Evidence strength and quality, relative advantage, adaptability, trialability, complexity, design quality and packaging, costs (opportunity)
	Process	Champions, reflecting and evaluation
	Characteristics of the individual	Self-efficacy
Antimicrobial stewardship/ antimicrobial resistance context	Outer setting	Patient needs and resources, cosmopolitanism, external policy and incentives
	Inner setting	Culture, tension for change, relative priority leadership engagement, available resources,
Hospital/organisational context	Inner setting	Structural characteristics, networks and communications, culture, leadership engagement
	Process	Champions, available resources

and S3 available as supplementary data). The constructs of the CFIR are highlighted in bold in the text.

Theme 1: Procalcitonin intervention and implementation process

Participants described the procalcitonin intervention as having a well-established evidence base to support its use and clinical situations where it could act as an "extra marker" to support antimicrobial prescribing decisions. These decisions require clinicians to balance the need to adequately treat patients while also safely minimising antibiotic exposure and is a situation where "procalcitonin would actually play a very useful role." The feasibility study design and accompanying PE aligned with the trialability construct by providing participants the opportunity to test procalcitonin on a smaller scale, develop experience, reflect on the intervention, suggest changes to improve the intervention and adaptation in the future. Participants provided specific examples of clinical situations where procalcitonin supported antimicrobial prescribing decisions along with examples of where it was considered of less benefit. Overall participants felt more confident in the role of procalcitonin in the acute infective setting and less confident in the reliability of procalcitonin in patients with underlying chronic lung disease. (Indicative quotations are shown in Table S1)

Several elements of the 'adaptable periphery' [27] emerged which could be modified to improve the processing of samples in the laboratory and the subsequent availability of the procalcitonin results to clinicians. They included processing of the test more efficiently as part of a patients biochemistry profile by the biochemistry laboratory rather than processing samples in the microbiology laboratory (which occurred in this study). This would facilitate more prompt availability of results as part of the standard admission point of care blood test results. The changes suggested to the laboratory processing of the results were due to the elements of the intervention which aligned to the complexity construct and were considered barriers to implementation. (Indicative quotations are shown in Table S1)

Participants commented positively on the education and training provided and were engaged with the intervention and its intended purpose of improving antimicrobial prescribing. (Indicative quotations are shown in Table S1)

Participants suggested several other general recommendations to facilitate implementation of procalcitonin testing which aligned to the reflecting and evaluation construct. They included recommendations for a "multi-modal" educational plan, the need to identify the role of procalcitonin, "it's place in the hierarchy" and to consider potential unintended consequences of its use. Participants also highlighted the need to gain support and endorsement from hospital management and senior clinicians and using public forums within the hospital such as "grand rounds" to facilitate this objective and engage champions (individuals) who actively associate themselves to support the intervention during implementation.

Several potential barriers to implementation were also identified by participants. One participant highlighted that procalcitonin "has been around for quite some time" and

questioned it's relative advantage over C—reactive protein as an indicator of viral infections. The barrier of additional costs and availability of resources to support new interventions in the hospital means they would require "a really strong business case to suggest why we should add a resource". The opportunity cost associated with implementing a procalcitonin intervention was also raised with the suggestion that alternative AMS interventions may be a more beneficial use of resources but this would require an economic assessment to determine the most cost-effective intervention.

The respiratory specialist participants in the study expressed a strong sense of self-efficacy and confidence in their professional knowledge and clinical experience of treating respiratory tract infections and making antimicrobial prescribing decisions "it's very much linked to what we do". They highlighted situations where they have come into conflict with the AMS team in relation to compliance with antimicrobial guidelines highlighting they "don't inappropriately apply the guidelines as opposed to that we ignore them". These findings were considered a potential barrier to implementation of AMS interventions.

Theme 2: Antimicrobial stewardship and antimicrobial resistance context

The need to address the problems associated with AMR were seen as facilitators to AMS interventions. Patient safety was seen as a priority but participants highlighted the increasing complexity and difficulties in managing patients with resistant infections. The management of patients with carbapenemase producing *Enterobacteriaceae* emerged as an example of the organisational approach to the problem of AMR and elements of this approach were considered as facilitators of implementation. The hospital "eventually" realised the problems associated with carbapenemase producing *Enterobacteriaceae* following communication between national and local level management resulting in greater leadership engagement at local level to address the problem. These factors created a tension for change to respond to this problem within the organisation and the need to take a long term rather than a short term view to respond to the problem. (Indicative quotations are shown in Table S2)

The culture within the hospital in relation to antimicrobial prescribing emerged as a barrier to implementation of AMS interventions. The concepts of fear and risk aversion were a significant influence on antimicrobial prescribing decisions. Fear arose in relation to the "possibility of missing infection" in patients and the associated potential for negative clinical outcomes for those patients related to an inadequately treated infection and the associated feelings of clinical responsibility (indicative quotations are shown in Table S2). This fear was accompanied by the "fear of litigious issues" and the need for "self-protection". Clinicians described the risk-aversion and need for self-protection as motivating factors for the prescription of antimicrobial courses to patients "even in times that maybe the front-line clinician themselves maybe isn't convinced fully that it's a bacterial infection". There was acknowledgement of antimicrobial over-prescribing but these risks were outweighed by the needs of the individual complex sick patient admitted to hospital. A possible explanation for this which emerged was that the longer term consequences of AMR "aren't as apparent" and may be perceived to be less important than the treatment of current patients. There was also an acknowledgement that the problem requires a significant amount of behavioural change as the "habits of the prescribing hand are firm and hard to change".

Theme 3: Hospital/organisational context

All participants described a range of factors which act as barriers or facilitators of implementation. A growing culture of quality improvement in the hospital was described by all participants aligning with the culture construct. There were some differing individual perspectives on the degree of leadership engagement with quality improvement in the hospital with an acknowledgement that senior clinicians could be more engaged with it. The development of structural "scaffolding" to support a clinical lead with dedicated time to encourage and support quality improvement work was identified as a facilitator of future interventions. (Indicative quotations are shown in Table S3)

Communication was seen as an important facilitator of interventions aligning with the networks and communication construct. The hospital size was seen as a positive factor to encourage greater engagement with colleagues. Communication between medical teams and the AMS team was seen as good and had a positive influence on antimicrobial prescribing. However inter-departmental communication, and communication between senior clinicians and hospital management emerged as a barrier to implementation. (Indicative quotations are shown in Table S3)

Available resources emerged as a barrier to implementation in relation to the limitations of the funding model of Irish healthcare where despite the intensions of staff there is limited opportunities to "invest to get future success". Participants also raised issues related to the perception of how resources are distributed within the hospital "it does seem to be he who shouts loudest".

Discussion

This study provides a detailed PE of the introduction of procalcitonin testing as an AMS intervention. The CFIR guided a systematic assessment of the intervention and

implementation process, identification of barriers and facilitators of implementation, and provided an insight into the contextual factors which influence AMS in the Irish hospital setting. The findings provide actionable recommendations to successfully implement a procalcitonin intervention.

The main findings of this study identified the positive elements of the intervention and implementation process while also exploring the barriers to implementation related to the intervention and the contextual barriers of the study setting to be overcome to successfully implement a procalcitonin intervention. Participants engaged with the intervention, the education provided, assessed the supporting evidence for the intervention, gained experience of the intervention, reflected on its clinical value and proposed modifications to the intervention delivery which would improve implementation in a future randomised controlled trial. All these elements promote successful adaptation of interventions [27] and it has also been shown that previous experience of procalcitonin testing leads to greater confidence in the application of procalcitonin as an AMS intervention [31].

The adaptability and trialability constructs identified the most relevant factors to improve the delivery and selection of patients to maximise the benefits of the intervention. Procalcitonin levels were tested in the microbiology laboratory during this study and while the test itself was relatively quick to process there were several factors which led to delays in the availability of the results. These delays in availability resulted in clinicians feeling that "hearing afterwards it was something that you know, you felt almost it was a feedback after the decision had been made" rather than contributing to the clinical decision-making process. Processing of the procalcitonin level in the biochemistry laboratory emerged as a solution to this problem and the procalcitonin levels should be available as part of the admission list of blood results at the point of care to allow the results to be "more of a clinical influence" on prescribing.

The participating respiratory clinicians expressed a strong degree of self-efficacy in relation to their expert knowledge and clinical experience in treating respiratory tract infections while also acknowledging the diagnostic difficulties associated with respiratory tract infections. These findings suggest that respiratory clinicians could be perceived as barriers to implementation of AMS interventions and are similar to those found in a recent study which highlighted the barriers to integrating AMS processes within respiratory medicine [32]. The perception that unsolicited AMS input is considered an imposition on specialist territory and clinical autonomy among some medical specialists who consider themselves 'experts in their own fields' is a considerable barrier to AMS interventions [33].

One clinician highlighted that procalcitonin "has been around for quite some time' and questioned it's relative advantage over other infection markers. However most participants viewed the intervention positively which suggests that procalcitonin is a potentially effective intervention as it combines clinician enablement, improved diagnostics to support AMS but requires engagement with clinicians to optimise effectiveness. An intervention of this nature would fulfil the recommendations of a recent study [34] to overcome barriers in AMS in respiratory medicine. These findings align with a qualitative study of clinicians experience with procalcitonin where the intervention was viewed positively as an AMS adjunct but it could not replace other tests or clinical judgement [35].

The CFIR provided a framework to explore the two main contextual factors of AMS and the hospital/organisational context into which the intervention was introduced. Contextual factors influencing AMS interventions have been poorly explored in the past [6] and a lack of understanding of the contextual factors contributing to a given problem can lead to sub-optimal implementation [36].

The concepts of fear and risk-aversion were prominent themes in the AMS/AMR context. The care of their patients and patient safety is the primary concern for clinicians [37]. Patients admitted to hospital with a suspected infection are perceived to be more "complex" and "sick" which heightens the fear of missing an infection and the potentially serious outcomes for patients including death which heavily influences antimicrobial prescribing decisions. Fear of adverse clinical outcomes especially in hospital patients has a powerful influence on antimicrobial prescribing which can escalate the risk perception of clinicians [33]. Clinicians were risk-averse even in situations where the risk of a bacterial infection is low "I think a lot of people will still cover with antibiotics". Clinicians also cited concerns on a personnel level perceiving a need for self-protection and a fear of litigation which results in the prescription of antimicrobials "just in case". Justification of the fear of litigation may be due to the fact that medical negligence suits filed in the Irish High court have increased by 136% from 2007 and 2018 [38] and clinical negligence claims against the NHS in the UK have doubled over a similar period [39]. In the ever-increasing litigious world we live in, this is a significant barrier going forward.

The findings demonstrate that clinicians consider the short terms risks to patients and themselves more heavily than the longer term consequences of AMR which "aren't as apparent" when making antimicrobial prescribing decisions similar to the findings of a recent systematic review [40]. Risk, real or perceived, is challenging to mitigate against. AMS programmes must acknowledge the experiences of risk faced by clinicians when designing AMS interventions. An intervention such as procalcitonin acting as an "extra marker" of the infection process offers clinicians further information when making antimicrobial

prescribing decisions potentially reducing the perceived risks for both patient and clinician.

The hospital context consisted of both barriers and facilitators to implementation. The hospital administrator highlighted the recognition of the problems associated with AMR having gained greater insight during the hospitals response to a carbapenemase producing *Enterobacteriaceae* outbreak and the significant costs associated with it. Unfortunately the realities of managing limited resources in a hospital environment where the short term demands of trying to "push people through the system" is difficult and limits the ability of hospitals to invest in new interventions or diagnostics to mitigate the long-term consequences of AMR. These findings are similar to the findings of another study investigating the perspective of hospital managers on optimising antimicrobial use [41]. A medical laboratory scientist expressed frustration with the economic constraints of the healthcare system where it appears that resources are allocated to "he who shouts loudest". In the current setting of a resource limited health service new interventi*ons such as procalcitonin must be supported by* "a really strong business case" and an economic evaluation of the intervention should be incorporated into a future trial particularly in the Irish hospital setting. Procalcitonin testing has been shown to be a cost-effective AMS intervention in the U.S. setting [42] but the overuse of procalcitonin testing has also been highlighted [43]. Long term investment in the health system is necessary to alter the realities of AMR. This is particularly important given our current population demographic in Ireland where the proportion of the population over 65 years is expected to increase to 1.6 million in the next 35 years [44].

Positive findings from the hospital context included the recognition of developing a culture of quality improvement in the hospital. Additional resources and support are required to develop the *"*scaffolding*"* within the hospital but this is an important facilitator for the development of new interventions. We know from previous work that organisations which have a patient centred culture are more likely to implement change effectively [45]. Communications within an organisation has been recognised as being important in intervention implementation. There was some variation in the assessment of it in the hospital context and both positive and negative aspects were identified. The small size of the hospital was noted as having a beneficial effect on communication in this study. Implementation has been described as a 'social process' which is intertwined with the context in which it takes place [46]. The importance of factors such as gaining "consultant buy-in" and using educational forums such as grand rounds to encourage engagement and discussion of interventions by senior clinicians are noted.

Strengths and limitations

The findings of this study and our earlier quantitative work [19] support the finding that procalcitonin is an effective intervention and thus support the recommendations to link the CFIR constructs to intervention outcomes [13]. We have outlined the justification for our choice of the CFIR [13]. The study included a broad range of participants not just those directly involved in the study implementation.

The study had several limitations. The study took place in a single hospital setting and contextual influences may differ in other hospitals and this may limit its transferability. However, as this is a feasibility study, this could not be mitigated for in this instance. Only one hospital administrator was interviewed which limits the insight from the administrative perspective on the hospital context. However due to the single study site it was only possible to interview one administrator who would have the knowledge to provide these details. The feasibility study and PE were conducted by the same researchers increasing the risk of positive reporting. There was also a risk of the hawthorn effect during the data collection process as it is possible the interviewer could have influenced the way people behave or respond. Efforts to avoid or minimise bias and the hawthorn effect included purposive sampling and inclusion of a diverse sample of individuals.

Conclusion

This PE provides a detailed qualitative analysis of the implementation of procalcitonin testing as an AMS intervention. Positive elements of intervention implementation were highlighted along with modifications to improve the delivery of the intervention such as the prompt availability of procalcitonin levels at the point of care to allow the test to be "more of a clinical influence" on prescribing. Contextual factors which influence implementation were identified and explored including the concepts of fear, risk and the influence of respiratory clinicians on AMS interventions. We would recommend that the positive findings of this PE and feasibility study should be built upon and that a full randomised controlled trial and economic evaluation should be conducted in a variety of hospital settings to confirm the effectiveness of procalcitonin as an AMS intervention.

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Quality indicators for hospital antimicrobial stewardship programmes: a systematic review

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Background: Measuring the quality and effectiveness of antimicrobial stewardship (AMS) programmes with quality indicators (QIs) is an area of increasing interest. We conducted a systematic review to identify QIs of AMS programmes in the hospital setting and critically appraise their methodological quality.

Methods: We searched the Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL, Scopus/web of science databases and the grey literature for studies that defined and/or described the development process and characteristics of the QIs developed. The Appraisal of Indicators through Research and Evaluation (AIRE) instrument was used to critically appraise the methodological quality of the QI sets.

Results: We identified 16 studies of QI sets consisting of 229 QIs. The QI sets addressed a broad range of areas of AMS in the hospital setting and consisted of 75% process indicators, 24% structural indicators and 1% outcome indicators. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified.

Conclusions: The QIs identified in this study focused on process and structural indicators with few outcome indicators developed—a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS. Testing of the QIs in practice is an essential methodological element of the QI development process and should be included in the QI development study or as planned validation work.

Introduction

Antimicrobial resistance (AMR) is a major threat to public health, contributing to increasing rates of illness, death and significant economic costs.[1,2] Antimicrobial stewardship (AMS) programmes have been implemented to address the escalating threat to human health posed by AMR. AMS aims to optimize antimicrobial use in order to maximize the probabilities of clinical cure or prevention of infection while minimizing unintended consequences such as toxicity and the selection of pathogenic organisms (e.g. *Clostridioides difficile*).[3] AMS is an important element of patient safety and a widely applied quality improvement initiative.[4] Implementation guidelines for AMS programmes place a strong emphasis on improving the quality of antimicrobial use[5] and evaluation of AMS programmes, but do not identify specific indicators of performance.[6]

Measuring the quality of healthcare can be achieved by using quality indicators (QIs). QIs are defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care provided'.[7] QIs can measure the quality of care by examining the structures, processes and outcomes of care.[8,9] This acknowledges that good structures increase the likelihood of good processes, and good processes increase the likelihood of good outcomes.[8]

To ensure QIs provide accurate measures of quality, they must adhere to certain quality requirements. QIs should be evidence based,[10] but in situations where scientific evidence is lacking, QIs can be defined by an expert panel of professionals using consensus techniques such as the Delphi technique or RAND/UCLA (Research and Development Corporation) (University of California, Los Angeles) appropriateness method.[11] The systematic method of combining scientific evidence and expert opinion is the most rigorous method to develop QIs as it provides face and content validity.[12] Furthermore, QIs should be tested during their development[12] to demonstrate they are acceptable to users (those being assessed and their assessors), feasible to measure, reliable and reproducible, sensitive to change and validated so

as to ensure that they will produce consistent and credible measures of the quality of care.[9,13]

Cost savings were among the initial incentives for hospitals to implement AMS programmes.[14] However, this is injudicious because factors such as antimicrobial patent expiry, drug shortages and the increasing prevalence of MDR organisms requiring the use of more expensive agents, all of which are beyond the control of an AMS programme. Thus, cost savings alone is an unreliable indicator of performance[15] and makes a further case for measures to demonstrate the clinical and economic values of AMS programmes.[16] Measuring the effectiveness of AMS programmes is thus important and is an area of increasing interest.[17]

The purpose of this systematic review was to identify existing QIs of AMS programmes in the hospital setting, describe the methodological approaches used in their development, differentiate between the types of indicators (structure, process, or outcome) and critically appraise the methodological quality of the identified QI sets using the Appraisal of Indicators through Research and Evaluation (AIRE) instrument.

Methods

This study was conducted and reported according to the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA).[18]

Search strategy

An initial search for other systematic reviews of QIs for AMS programmes in hospitals identified two existing reviews.[19,20] However, neither study undertook a quality assessment of the methodological development of the QIs sets identified.

The search strategy aimed to identify publications concerning the development, testing, or implementation of indicators of the quality of AMS programmes and antimicrobial prescribing. The Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL and Scopus/web of science databases were searched. A manual search of the grey literature, including conference proceedings, reports and theses, was also conducted to find information regarding QI development initiatives that were not published in peer-reviewed journals. The reference lists of full-text articles identified were screened to find other relevant studies. No language restrictions were imposed on the search algorithms. Searches were limited to studies of humans. The search period ran from the inception of the databases to the 1 December 2019 and the search was repeated on the 26 September 2020. The search terms were: Anti-infective agents [MeSH] OR Antibiotic prophylaxis [MeSH] OR Antibiotic* [tiab] OR Antimicrobial*[tiab] OR Anti microbial*[tiab] OR Anti infective*[tiab] OR Antiinfective*[tiab] OR Antibacterial*[tiab] OR Anti bacterial*[tiab] AND Quality indicators, health care [MeSH] OR Quality indicator*[tiab] OR Quality measure*[tiab] OR Quality metric*[tiab] OR Quality criteria[tiab] OR Qualitative measure*[tiab] OR Quality improvement [ti].

Inclusion criteria and study selection

Studies were eligible for inclusion if they met the following criteria:

1. The study defines and/or describes the development process and characteristics of the QIs developed.
2. The identified QIs are applicable to adult patients in the hospital setting and related to the overall assessment of AMS programmes or the assessment of AMS related to specific clinical indications [e.g. sepsis, Community Acquired Pneumonia (CAP), Urinary Tract Infections (UTIs)] or settings (e.g. ICU).
3. Where the set of QIs were updated the publication describing the updated QIs was selected for inclusion.

Exclusion criteria

The exclusion criteria were:

1. Editorials, letters to the editor, comments, and narrative case reports.
2. Publications describing the application of existing QIs in clinical practice or reviews of sets of QIs.

Following completion of the database searches, the identified references were entered into a bibliographical database and duplicates removed. The title and abstracts of these references were screened for relevance (keywords in the title, abstract or study subject headings) by one reviewer (F.O.R.). The resulting abstracts were included for full-text review by two reviewers (F.O.R. and A.F.) independently, according to inclusion criteria, and any disagreements resolved by consensus. If no consensus could be reached, a third reviewer (F.S.) was consulted. The reference lists of the selected publications were then screened for other relevant studies that had not been identified in the electronic database searches.

Data extraction

A data extraction form was designed and used to extract relevant information about the QIs from the included articles (File S1, available as Supplementary data at *JAC* Online).

Categorizing and grouping of the extracted QIs

The QIs extracted were categorized as structural, process, or outcome QIs, classified by theme within each category, and where there was conceptual, or content overlap in the description of the QI they were grouped together as agreed on by all authors.

Critical appraisal

The AIRE instrument[21] was used to appraise the methodological quality of the QI sets included in this study. It is a validated instrument that has been designed to assess the quality of QIs.[22] It addresses four quality domains of a QI and consists of 20 items, which are applied to each completed set of QIs. Three domains address the methodological quality of QIs and were used in this review: 'Stakeholder involvement', 'Scientific evidence' and 'Additional evidence, formulation and usage'. The fourth domain ('purpose, relevance and organisational context') reflects the relevance of the QIs within a particular context rather than methodological quality so was not used in this review. Table 1 contains the AIRE domains and items applied in this study. Each item consists of a statement that is scored according to a 4-point Likert scale [from 1 'strongly disagree or no information provided' to 4 'strongly agree' (confident that the criterion has been fulfilled)]. Scores for each domain were calculated by summing up the scores for each individual item in a category and standardizing the total as a percentage of the maximum possible score for the domain. The AIRE instrument was completed by two reviewers independently (F.O.R. and A.F. or F.S.) for each complete QI set rather than for each QI individually as most studies gave general information for the QI sets concerning development and supporting evidence. (Further details about the AIRE instrument and its scoring system are contained in File S2.) The scores for each domain are independent and should not be aggregated into a single total quality score. The standardized scores for each domain range from 0% to 100%, with a score of 50% or higher indicating a higher methodological quality for each domain of the instrument.[21]

Table 1. AIRE domains and items[21]

AIRE domain	AIRE items
Stakeholder involvement	1. The group developing the indicator includes individuals from relevant professional groups
	2. Considering the purpose of the indicator, all relevant stakeholders have been involved at some stage of the development process
	3. The indicator has been formally endorsed
Scientific evidence	4. Systematic methods were used to search for scientific evidence
	5. The indicator is based on recommendations from an evidence-based guideline or studies published in peer-reviewed scientific journals
	6. The supporting evidence has been critically appraised
Additional evidence, formulation, usage	7. The numerator and denominator are described in detail
	8. The target patient population of the indicator is defined clearly
	9. A strategy for risk adjustment has been considered and described ('case-mix adjustment')
	10. The indicator measures what it is intended to measure (validity)
	11. The indicator measures accurately and consistently (reliability)
	12. The indicator has sufficient discriminative power
	13. The indicator has been piloted in practice
	14. The efforts needed for data collection have been considered
	15. Specific instructions for presenting and interpreting the indicator results are provided

Inter-rater reliability between reviewers

The inter-rater reliability between the three reviewers was assessed by comparing the individual scores per AIRE item for two separate publications included in this study by calculating the weighted Cohen's Kappa. The inter-rater reliability between (F.O.R. and A.F.) and (F.O.R. and F.S.) amounted to 0.69 and 0.73, respectively (File S3). A Cohen's Kappa of between 0.61 and 0.80 is considered substantial agreement.

Results

Search results

The PRISMA flow diagram of the study selection process and reasons for exclusion is seen in Figure 1. The systematic literature search identified 4833 potentially relevant studies. Following screening of titles and abstracts, 85 potentially relevant studies were selected for full-text screening. Six additional studies were included in the full-text screening after reference screening of the selected publications. Seventy-five studies were excluded, and 16 publications of QI sets were included in this review.

Study characteristics

Table 2 presents an overview of the studies included in this review. Most included studies originated from Europe ($n = 11$) followed by the UK ($n = 2$), the USA ($n = 1$) and Indonesia ($n = 1$); one further study involved an assessment of USA and European hospitals.

The most common study design used in QI development involved a combination of a literature review ($n = 8$) or review of clinical evidence and/or clinical guidelines ($n = 4$), and a consensus process [RAND-modified Delphi ($n = 7$), modified Delphi ($n = 2$), RAND/UCLA appropriateness ($n = 2$) or Delphi ($n = 1$)], involving national or international multidisciplinary expert panels. Other techniques included: a literature review and consensus; a multidisciplinary team consensus; a national target for *C. difficile*; and a national working group evidence base review.

The 16 QI sets addressed a broad range of areas of AMS in the hospital setting. These included seven sets of QIs to address specific infections [CAP, COPD, UTI, sepsis, *C. difficile* infection (CDI)], one set of generic QIs to assess antibiotic use in the treatment of all bacterial infections in hospital, four sets for specific hospital settings [e.g. ICU, High Dependency Unit (HDU)] and four sets of broader QIs to evaluate AMS programmes or hospital antimicrobial prescribing or to compare hospital AMS programmes.

Stakeholder involvement

The most common stakeholders involved in the QI development process were infectious diseases specialists, medical microbiologists, hospital pharmacists and physicians/clinicians. Their expertise was supplemented by various specialists depending on the QIs to be developed (i.e. ICU care involved intensivists, CAP and COPD QIs involved respiratory physicians, UTI QIs involved urologists, nephrologists and a gynaecologist). One study reported the participation of patients, payers and policy makers. Five studies reported general details of the stakeholder participants (i.e. multidisciplinary team or expert group, medical professionals) rather than specific details.

Quality indicators

A total of 229 QIs were extracted from the 16 included studies and the full list is available as File S4. QIs were grouped together and duplicates removed where there was conceptual or content overlap and several QIs were extracted from multiple publications. Table 3 contains a description of each unique QI, categorization of the QI as structural, process or outcome indicators, classification of QIs by theme within each category, and identification of the studies in which they appeared.

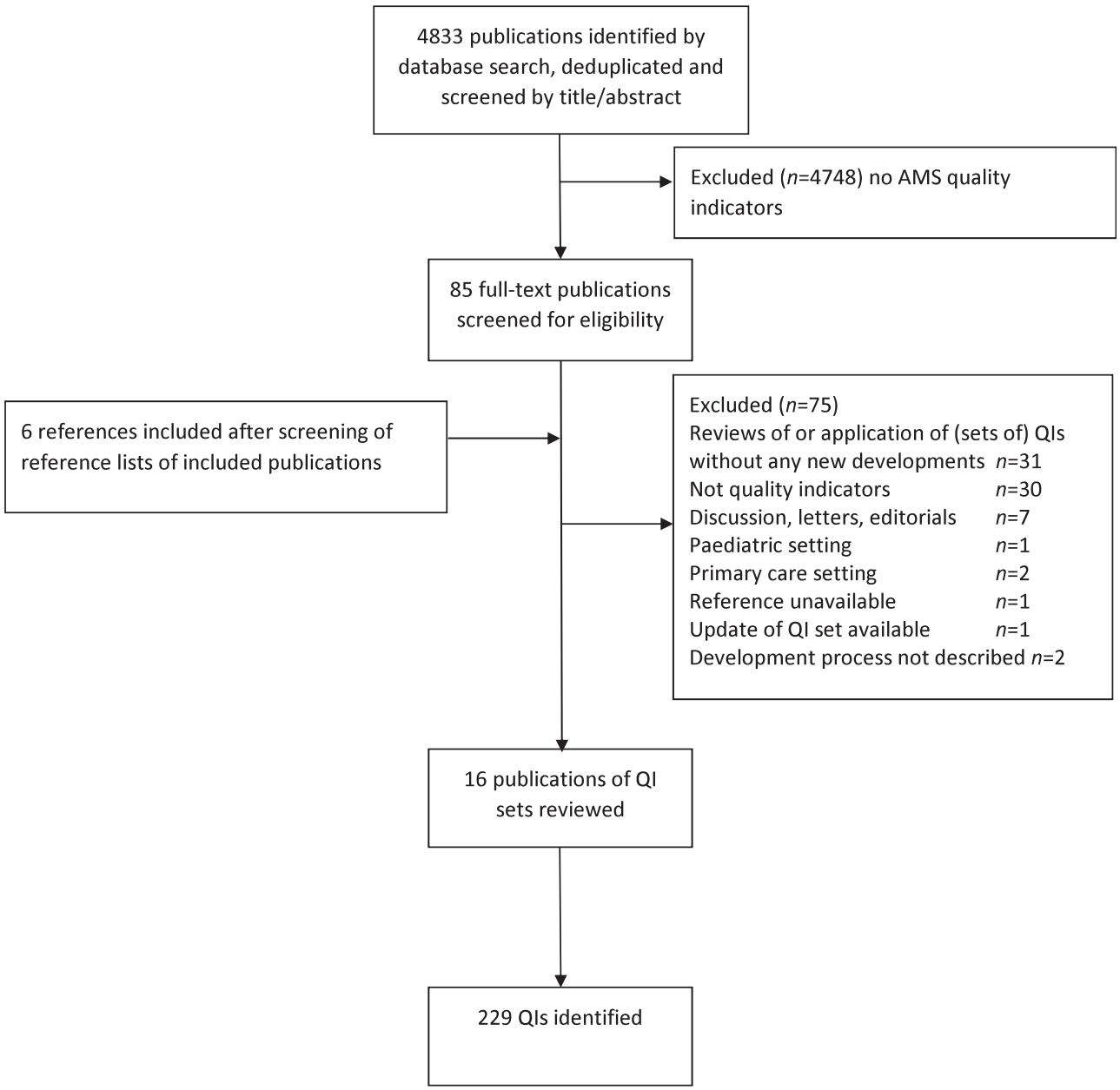

Figure 1. PRISMA flow diagram of literature search.

Structural indicators

Fifty-five structural QIs (55/229, 24%) were derived from six studies, which aimed to provide a quality assessment of the organizational framework, multidisciplinary expertise, resources and supportive activities required to implement an AMS programme. QIs with conceptual or content overlap were grouped together and were classified by themes, which were developed and agreed on by all authors. The themes identified were: (i) AMS governance, leadership and accountability (3 indicators, 4 studies); (ii) AMS expertise and resources (4 indicators, 3 studies); (iii) AMS policies and programmes to improve prescribing (6 indicators, 4 studies); (iv) antimicrobial guidelines (4 indicators, 6 studies); (v) AMS education (1 indicator, 3 studies); and (vi) microbiology laboratory standards, antimicrobial resistance surveillance and feedback (3 indicators, 3 studies).

Process indicators

One hundred and seventy-two process indicators (172/229, 75%) were derived from 15 studies, which aimed to assess the general clinical management of all infections, or specific infections, or patient populations. QIs with conceptual or content overlap were grouped together and were classified into four themes: (i) infection diagnostics (4 indicators, 9 studies); (ii) pharmacy-supported interventions (7 indicators, 8 studies); (iii) elements of good antimicrobial prescribing practice (12 indicators, 12 studies); and (iv)

Table 2. Characteristics of the AMS QI sets

Author, year, location	Aim/focus	Study description	Stakeholder involvement	Number of AMS indicators per type
Berenholtz[23] 2007, USA	Sepsis care	Interdisciplinary panel literature review and a modified Delphi procedure with a multidisciplinary expert panel from multiple hospitals	Physicians, nurses and pharmacist with expertise in sepsis, critical care and infectious diseases (ID), and experts in developing quality measures	Process: 6; Structural: 0
Buyle[24] 2013, Europe	Structural indicators to evaluate AMS programmes	Literature review and consensus process with a 13-member multidisciplinary panel from multiple (4) countries	5 ID specialists, 2 clinical microbiologists, 3 hospital pharmacists, 3 quality of healthcare experts	Process: 0; Structural: 10
Coll[25] 2012, UK	AMS in a high-dependency unit	Multidisciplinary team agreement, reference to the evidence base, national strategy and local policy	Multidisciplinary team	Process: 30; Structural: 0
Farida[26] 2015, Indonesia	Development of QIs for the antimicrobial management of CAP	QI development based on a previous study and guideline review followed by a 2-step Delphi procedure with an 18-member national multidisciplinary expert panel	10 internists, 3 internist-pulmonologists, 2 pharmacists, 3 clinical microbiologists	Process: 6; Structural: 0
Thern[27] 2014, Europe	Hospital antimicrobial prescribing QIs	Literature review and RAND/UCLA appropriateness consensus with a multidisciplinary expert panel from multiple hospitals	Clinicians, hospital pharmacists, microbiologists, infection control doctors	Process: 21; Structural: 21
Hermanides[28] 2008, Europe	QIs for the antibiotic treatment of complicated UTIs	Evidence-based guidelines used in a 3-step modified Delphi approach with a 13-member multidisciplinary expert panel from multiple hospitals	2 medical microbiologists, 4 ID specialists, 2 hospital pharmacists, 2 urologists, 2 nephrologists, 1 gynaecologist	Process: 13; Structural: 0
Kallen[29] 2018, Europe	QIs for appropriate antibiotic use in the ICU	Literature review and four-round modified RAND Delphi procedure with a 15-member multidisciplinary expert panel of Dutch experts	3 anaesthesiologists-intensivists, 3 internist-intensivists, 1 intensivist-infectious diseases physician, 3 internists-ID physicians, 2 clinical microbiologists, 3 clinical pharmacists	Process: 3; Structural: 1 (1 quality metric)
Monnier[30] 2018, Europe	QIs for responsible inpatient antibiotic use	Systematic literature review and a four-step RAND-modified Delphi method with a 25-member international multidisciplinary expert panel	Medical community (15) public health and patients (12); antibiotic R&D (14); and payers, policy makers, governments and regulators (11).	Process: 35; Structural: 14; Outcome: 2
Pollack[31] 2016, USA and Europe	QIs to assess and compare AMS programmes among US and EU hospitals	Literature review followed by modified Delphi process using RAND/UCLA appropriateness method with a 20-member multidisciplinary multinational expert panel	Clinical medicine, pharmacy, public health	Process: 10; Structural: 7
Schouten[32] 2005, Europe	Measurement of the quality of antibiotic use in CAP and COPD	Literature and guideline review and a four-step modified Delphi procedure with an 11-member medical opinion leader expert panel from multiple hospitals	Medical microbiology, ID, respiratory medicine, quality of care medicine	Process: 15; Structural: 0

Continued

Table 2. *Continued*

Author, year, location	Aim/focus	Study description	Stakeholder involvement	Number of AMS indicators per type
Schouten[33] 2012, Europe	QI bundle for ICU antimicrobial use	Literature search followed by a 2-round RAND-modified Delphi method with an 11-member multidisciplinary expert panel from six EU countries	11-member multidisciplinary expert panel	Process: 6; Structural: 0
Sneddon[34] 2012, UK	QIs to support a 50% reduction in CDI and improve prescribing practice	Development and implementation of QIs based on national CDI target reduction	Scottish Antimicrobial Prescribing Group	Process: 2; Structural: 0
Ten Oever[35] 2019, Europe	QIs for the management of *Staphylococcus aureus* bacteraemia	Systematic literature review followed by a RAND-modified Delphi procedure with an international expert panel of medical professionals	Medical professionals (MD)	Process: 11; Structural: 0
van den Bosch[36] 2014, Europe	QIs for antimicrobial treatment in adults with sepsis	QIs from national sepsis guidelines followed by a RAND-modified Delphi consensus with a 14-member multidisciplinary expert panel from multiple hospitals	4 ID physicians, 2 medical microbiologists, 2 hospital pharmacists, 3 intensive care specialists, 2 haematologists, 1 general surgeon	Process: 5; Structural: 0
van den Bosch[37] 2015, Europe	QIs to measure appropriate antimicrobial use in hospitalized adults	Literature review followed by a RAND modified Delphi consensus with a 17-member international multidisciplinary expert panel	5 medical microbiologists, 4 ID specialists, 2 clinical hospital pharmacists, 2 general surgeons, 2 pulmonologists and 2 gynaecologists	Process: 9; Structural: 2
Vera[38] 2014, Europe	QIs for antimicrobial use in critically ill (ICU) patients	Selection of QIs proposed by Spanish working group of Infectious Diseases followed by validity and reliability confirmation and review of supporting evidence	Spanish working group of Infectious Diseases	Process: 10; Structural: 0

indicators for specific infectious conditions/settings (54 indicators, 10 studies).

Outcome indicators

Two outcome indicators (2/229, 1%) were identified, recommending the monitoring of clinical outcomes of patients receiving antibiotics and the monitoring of the rate of nosocomial CDI.

Methodological quality

Table 4 presents the results of the critical appraisal of the methodological quality of the 16 QI sets assessed with the AIRE instrument. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified and this was reflected in the AIRE instrument domain scores. Most of the indicator sets achieved a score of 50% or higher, indicating a high methodological quality in the first AIRE domain of 'stakeholder involvement'. The 10 studies with a high 'stakeholder involvement' domain score detailed the constituent stakeholders involved in the QI development process, which ranged from medical opinion leaders[32] to broad multidisciplinary groups.[37] Studies considered to be of lower methodological quality for this domain did not include sufficient information within the publications regarding the relevant stakeholders' involvement in the QI development process. Most studies had a low score for the AIRE item within this domain of 'the indicator has been formally endorsed' with only one study providing this information (QI set endorsed and used by the ECDC).[30]

The 'scientific evidence' domain of the QI development process was well reported and most studies ($n = 12$) were considered to be of high methodological quality. Four studies were considered to be of low quality as they received low or no score due to the absence of information regarding the search methods, evidence base, or the evidence-based appraisal techniques applied to develop the QI sets.

The lowest overall methodological quality was seen in the 'additional evidence, formulation, usage' domain where only seven

Table 3. Quality indicators

Indicator	Source (s), Reference(s)	Description of the indicator
Structural indicators by theme		
AMS governance, leadership and accountability	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016	Establish a multidisciplinary AMS committee that meets regularly.
	Buyle 2013, Thern 2014	AMS representation and membership of the hospitals drugs and therapeutic committee.
	Thern 2014, Monnier 2018, Pollack 2016	Strategic report submitted to D&T and hospital management including quantitative objectives and selected performance indicators.
AMS multidisciplinary expertise and resources	Buyle 2013, Pollack 2016	Dedicated physician and pharmacist resources to provide AMS advice (and AMS leadership).
	Monnier 2018	Antibiotics from the antibiotic formulary should not be out of stock at the healthcare facility.
	Pollack 2016	Salary support for dedicated time for antimicrobial stewardship activities.
	Pollack 2016	Information technology capability to support the needs of the AMS activities.
AMS policies and programmes to improve antimicrobial prescribing	Buyle 2013, Monnier 2018, Pollack 2016	AMS programme should be in place (including reports, objectives, performance indicators).
	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016	Audit and feedback to prescribers of antimicrobial consumption and prescribing practices (including indications, surgical prophylaxis choice and duration).
	Thern 2014, Monnier 2018, Pollack 2016	Restricted antimicrobials requiring approval.
	Buyle 2013, Thern 2014, Pollack 2016	Regular AMS ward rounds and availability of expert consultation advice.
	Thern 2014	Written recommendation for parenteral-to-oral switch antimicrobial therapy.
	Monnier 2018	Prophylactic antibiotics should be added to a pre-operative checklist.
	Pollack 2016	Policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions.
Antimicrobial guidelines	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016, van den Bosch 2014, van den Bosch 2015	Antimicrobial guidelines (correspond to national guideline but should be adapted based on local resistance patterns and updated biannually).
	Buyle 2013, Thern 2014	Surgical antimicrobial policy.
	Buyle 2013, Thern 2014, Monnier 2018	Antimicrobial formulary.
	Thern 2014	Electronically available guideline/decision-making aids.
AMS education	Buyle 2013, Thern 2014, Monnier 2018	AMS prescriber education provided.
Microbiology laboratory standards, antimicrobial resistance surveillance and feedback	Thern 2014	Written in-house preanalytical requirements for microbiological samples (including rejection criteria).
	Thern 2014, Monnier 2018	Use of selected antibiograms (adapted according to local guidelines).
	Thern 2014, Monnier 2018, Pollack 2016	Reporting of AMR resistance rates, *C. difficile* incidence, nosocomial sepsis/bacteraemia rates for clinical isolates available annually (and for specific services).
Process indicators by theme		
Infection diagnostics	Coll 2012, Thern 2014, Hermanides 2008, Kallen 2018, Monnier 2018, Schouten 2005, Schouten 2012, van den Bosch 2014, van den Bosch 2015, Farida 2015.	Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken (sputum, urine, etc.).
	Coll 2012, Monnier 2018	The results of bacteriological sensitivity(s) is documented.
	Monnier 2018	Microbiological investigations should be performed according to guidelines.
	Monnier 2018	Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.
Pharmacy-supported interventions	Coll 2012, Monnier 2018	Allergy status and documentation.
	Coll 2012, Monnier 2018	Interaction management with concurrent medication.
	Monnier 2018	Contra-indications should be taken into account when prescribing antibiotics.

	Coll 2012, Kallen 2018, Monnier 2018, Ten Oever 2019, van den Bosch 2015	Therapeutic drug monitoring of vancomycin and gentamicin is conducted correctly and documented.
	Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Ten Oever 2019, van den Bosch 2015	Monitoring and adjustment of antimicrobial treatment for renal impairment.
	Thern 2014	Oral administration of drugs with high bioavailability.
	Monnier 2018	The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.
Important elements of good antimicrobial prescribing practice	Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Schouten 2012, Ten Oever 2019, van den Bosch 2014, van den Bosch 2015	Empirical systemic antimicrobial therapy should be compliant/prescribed according to local policy guidelines (choice, route, dosage).
	Coll 2012, Hermanides 2008, Schouten 2012, Sneddon 2012	Documentation of an antimicrobial plan including indication for prescribing, intended duration of treatment.
	Farida 2015, Monnier 2018, Schouten 2005, van den Bosch 2015	Prompt administration of antimicrobial within 4 hours of presentation.
	Coll 2012, Monnier 2018, Schouten 2012	Antimicrobial treatment is reviewed according to clinical response and/or sensitivities.
	Coll 2012, Hermanides 2008, Monnier 2018, Schouten 2005, Schouten 2012, van den Bosch 2014, van den Bosch 2015	Empirical systemic antimicrobial therapy should be changed to pathogen-directed therapy if culture results become available.
	Monnier 2018, Schouten 2005, Farida 2015	Prompt switching from IV route of administration to oral when clinically appropriate.
	Monnier 2018, van den Bosch 2015	Duration of antibiotic therapy should be compliant with guidelines.
	Coll 2012, Hermanides 2008, Monnier 2018, Schouten 2012	Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection.
	Monnier 2018, van den Bosch 2015	Antimicrobial treatment is discontinued on completion of the documented course.
	Monnier 2018	Antibiotic prescriptions that deviate from guidelines should be justified.
	van den Bosch 2015	Prescribed antibiotics should actually be administered to the patients.
		The maximum duration of empirical systemic antibiotic treatment should be 7 days.
Specific infectious conditions/settings		
Surgical antimicrobial prophylaxis (SAP)	Thern 2014, Monnier 2018, Sneddon 2012	SAP (drug and dosage): administered according to local guidelines.
		SAP administered within 1 hour before incision.
		SAP discontinued with 1 day (24 hours).
Community-acquired pneumonia	Schouten 2005, Farida 2015	Prescribe antibiotic therapy for exacerbations only when indicated.
		Optimal duration of antibiotic therapy from 5 - 7 days.
COPD	Schouten 2005	Prescribe antibiotic therapy for exacerbations only when indicated.
		Optimal duration of antibiotic therapy from 5 - 7 days.
Hospital-acquired pneumonia	Thern 2014	Duration of therapy no longer than 10 days.
Urinary tract infections	Thern 2014	Documentation of positive urine culture.
		Duration of pyelonephritis therapy not longer than 10 days (patients on general ward).
		Oral antimicrobial drugs initiated not later than day 5 (pyelonephritis, patients on normal wards only).
		No antimicrobials for asymptomatic, catheter-associated bacteriuria.
	Hermanides 2008	Selective use of fluoroquinolones (only as oral or in β-lactam allergy/anaphylaxis).
		Duration of treatment for at least 10 days (in accordance with national guideline).
		Prescription of treatment for men in accordance with national guidelines.

Continued

Table 3. *Continued*

Indicator	Source (s), Reference(s)	Description of the indicator
		Start IV antibiotics in pregnant women with pyelonephritis.
		Do not prescribe antibiotic prophylaxis to patients with a urinary catheter in place.
		Change urinary catheter within 24 hours of initiation of antibiotic treatment.
		Consider all diabetic patients with cystitis as having a complicated UTI and treat with empirical treatment according to national guidelines.
Bloodstream infections (BSI)	Thern 2014	Additional monitoring-Heart ultrasound (TEE) within 10 days.
		Collection of follow-up blood cultures 4 - 7 days after collection of first positive blood culture.
*Staphylococcus aureus*BSI	Ten Oever 2019	Follow-up blood cultures after initiation of antimicrobial therapy should be done regardless of clinical evolution.
		Collection of repeat blood cultures should be performed until first negative blood culture.
		Initial antibiotic therapy should be administered intravenously in patients with SAB.
		Initial therapy should be IV (flu)cloxacillin (or nafcillin or oxacillin) or cefazolin in the case of methicillin-susceptible strains in patients with SAB.
		Antibiotic therapy should be initiated within 24 h after first positive blood culture.
		Appropriate treatment should be adapted within the first 24 h after a methicillin susceptibility result is available, if so required.
		Appropriate duration of IV antibiotic treatment should be at least 14 days for uncomplicated SAB.
		Appropriate duration of IV antibiotic treatment should be at least 28 days for SAB complicated by metastatic abscesses or deep foci of infection.
		IV-to-oral switch should not be performed in uncomplicated SAB after 48–72 h.
		IV-to-oral switch should not be performed in complicated SAB after 48–72 h.
		Other management aspects:
		Infectious disease specialist consultation should be performed in patients with SAB.
		SAB should be documented in the medical discharge summary.
MDR infection management	Thern 2014	Infection and/or colonization by MDR organisms explicitly listed on discharge summary.
Sepsis	Monnier 2018, van den Bosch 2014	Antimicrobial therapy in adult patients with sepsis should be started intravenously.
		Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock.
	Berenholtz 2007	Vancomycin prescribing–% of sepsis patients with unidentified organism received vancomycin within 24 hours of identification.
		Median time to vancomycin following sepsis diagnosis.
		% of patients with sepsis and an unidentified organism who received a recommended broad-spectrum antibiotic within 24 hours of sepsis diagnosis.
		Median time to broad-spectrum antibiotic initiation following sepsis diagnosis.
		% of patients with sepsis who had two sets of blood cultures collected within 24 hours following sepsis identification.
		% of patients with sepsis and an organism other than MRSA or MRSE (metacillin-resistant *Staphylococcus epidermis*) who had vancomycin discontinued within 96 hours of diagnosis.
ICU	Kallen 2018	Perform surveillance cultures if selective digestive or oropharyngeal decontamination is applied at the ICU.
		Biannual face-to-face meetings between ICU and microbiology staff in which local resistance rates are discussed.

	Vera 2014	Antimicrobial use in the intensive care unit Formula: Total number of days of use of antimicrobial agent/Total number of days of ICU patients ×100. Non-empirical antimicrobial use Formula: Total antimicrobials used to treat infections in a directed manner/Total of antimicrobials used to treat infections ×100. Changes in antimicrobials used as treatment Formula: Total number of antimicrobials changed to another antimicrobial/Total of antimicrobials used to treat infections × 100. Days without antimicrobial use in ICU Formula: Total number of ICU days without antimicrobials/Total number of days of ICU patients × 100. Days free of antimicrobials in patients on antimicrobial treatment Formula: Number of days free of antimicrobials in patients on antimicrobial treatment/Total days in ICU of patients on antimicrobial treatment × 100. Number of days of antimicrobials for surgical prophylaxis Formula: Number of days of use of antimicrobials for surgical prophylaxis/Total number of patients with surgical prophylaxis treatment × 100. Inappropriate empirical antimicrobial treatment Formula: Total number of inappropriate empirical antimicrobials/Total number of empirical antimicrobials used to treat infections × 100. Empirical antimicrobials changed because they are inadequate Formula: Number of empirical antimicrobials changed because they are inadequate/Total number of empirical antimicrobials used to treat infections × 100. Empirical antimicrobial changed for de-escalation Formula: Number of empirical antimicrobials changed by adjustment or de-escalation/Total number of empirical antimicrobials used to treat infections × 100. Patients with severe sepsis/septic shock treated with antimicrobials in the first three hours Formula: Number of patients with severe sepsis/septic shock, treated with antimicrobials in the first 3 hours/Total number of patients with severe sepsis/septic shock × 100.
Outcome indicators by theme		
Clinical outcome	Monnier 2018	Clinical outcomes of patients receiving antibiotics should be monitored at the healthcare facility. Rates of nosocomial *C. difficile* should be monitored at the healthcare facility.

Table 4. Critical appraisal of the publications using the AIRE instrument

	Aire Items																
	Stakeholder involvement			Domain	Scientific methods			Domain	Additional evidence, formulation, usage								Domain
Publication	1	2	3	score	4	5	6	score	7	8	9	10	11	12	13	14	15	score
Berenholtz[23] 2007	4,4	4,4	1,1	67%	3,2	4,4	3,3	72%	4,4	4,4	3,3	1,1	1,1	3,3	1,1	3,3	1,1	44%
Buyle[24] 2013	4,4	4,4	1,1	67%	2,3	4,4	2,1	56%	1,1	4,3	1,3	2,1	2,1	3,3	4,4	4,3	3,3	52%
Coll[25] 2012	3,3	3,3	1,1	44%	1,2	4,4	2,1	44%	1,1	4,4	1,1	2,1	2,1	3,2	4,4	1,1	4,4	43%
Farida[26] 2015	4,4	4,4	1,1	67%	3,3	4,4	4,4	89%	1,1	4,4	1,2	4,4	4,4	3,3	4,4	4,4	1,1	65%
Thern[27] 2014	4,3	4,3	1,1	56%	3,3	4,3	1,1	50%	1,1	4,3	1,2	3,3	3,3	1,2	4,4	4,4	1,1	50%
Hermanides[28] 2008	4,4	4,4	1,1	67%	3,2	4,4	4,4	83%	1,1	4,4	4,4	4,4	4,4	4,3	4,4	4,4	1,1	76%
Kallen[29] 2018	4,4	4,4	1,1	67%	4,4	4,4	1,1	83%	4,4	4,4	3,4	4,4	3,3	3,3	1,1	4,4	4,4	80%
Monnier[30] 2018	4,4	4,4	3,3	89%	4,4	4,4	1,1	67%	1,1	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	11%
Pollack[31] 2016	4,4	4,4	1,1	67%	4,4	4,4	2,2	78%	3,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	1,1	28%
Schouten[32] 2005	2,2	3,3	1,1	39%	4,4	4,4	4,3	94%	2,2	4,4	4,4	4,4	4,4	4,4	4,4	4,4	1,1	83%
Schouten[33] 2012	2,2	1,1	1,1	11%	1,1	2,2	1,1	11%	2,2	4,4	1,1	3,3	1,1	1,1	4,4	4,3	1,1	43%
Sneddon[34] 2012	2,2	1,1	1,1	11%	1,1	1,1	1,1	0%	4,3	4,4	1,1	4,1	4,4	1,1	4,4	2,2	4,4	61%
Ten Oever[35] 2019	3,3	3,3	1,1	44%	4,4	4,4	4,4	100%	2,2	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	15%
van den Bosch[36] 2014	4,3	4,4	1,1	61%	1,1	4,3	3,3	50%	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	22%
van den Bosch[37] 2015	4,3	4,4	1,1	61%	3,4	4,4	4,4	94%	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	22%
Vera[38] 2014	1,1	1,1	1,1	0%	1,1	1,1	1,1	0%	4,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	3,3	37%

studies scored greater than 50%. The AIRE items within this domain that were allocated the lowest scores were 'a strategy for risk adjustment has been considered and described', 'the indicator has sufficient discriminative power' and 'specific instructions for presenting and interpreting the indicator results are provided'. Only eight studies included information regarding the piloting of indicators in practice.

Five QI sets were considered to have a high methodological quality in all three AIRE domains[24,26–29] and only one QI set had scores of less than 50% across all three AIRE domains.[38]

Discussion

To our knowledge, this is the first systematic review to provide an overview and critical appraisal of the methodological quality of QIs for AMS in the hospital setting. A total of 229 QIs were identified from 16 studies. Process indicators accounted for 75% of the extracted QIs and focused on the clinical management of infections. Structural indicators accounted for 24% of the extracted QIs focusing on the organizational requirements of AMS programmes and 1% of the extracted QIs assessed outcomes of care. The findings of the critical appraisal of QIs using the AIRE instrument indicate considerable variation in the methodological quality and applicability of the QI sets developed.

Most studies involved a comprehensive QI development process consisting of an appraisal of the evidence base followed by an expert panel consensus process. There was some variability in the constituents of stakeholders involved in the development of QI sets and several studies did not provide details of the participants of the expert group. The involvement of a diverse range of stakeholders strengthens the results of the consensus process and enhances the credibility and acceptability of the QIs.[39] Patient participation as members of the expert panel of key stakeholders in the QI development is often overlooked[40] but is of increasing importance.[41] Future studies should ensure the inclusion of a broad range of relevant stakeholders, including patients, who all have an interest in the QIs to be developed.

Process indicators for AMS programmes accounted for 75% of the indicators identified. They focused on the general clinical management of infection and antibiotic treatment along with more specific indicators for infectious processes such as sepsis, CAP, COPD and UTIs. Process indicators offer hospitals the ability to assess the core competencies of antimicrobial prescribing[42] and the opportunity to adapt education and training of prescribers based on the findings. The high proportion of AMS process indicators may be related to the findings that process interventions are considered the most effective AMS strategies to improve antimicrobial prescribing in hospital.[3]

Structural indicators for AMS programmes accounted for 24% of the indicators identified. They focused on the organizational requirements and necessity for a core multidisciplinary AMS team of infectious diseases specialists, microbiologists and pharmacists providing leadership and expertise to implement and support a multifaceted AMS programme. AMS programmes are resource intensive, which influences the variability in the implementation of hospital AMS programmes worldwide.[43] Core elements for AMS programme[44] have been developed, which can be adapted depending on the resources available in different countries and hospitals. Structural indicators offer the opportunity to measure the implementation of the proposed core elements and for

benchmarking of performance between hospitals, within countries and across jurisdictions and to identify outliers.

The low number of outcome indicators identified is reflective of the ongoing challenges of AMS programmes to accurately measure and demonstrate their impact on patient outcomes.[17,45] Expert panels developing quality measures consider outcome measures important[17,46] but are often reluctant to include such measures in QI sets due to the need for risk adjustment for confounding factors.[47] These include changes in the hospital setting such as the patterns of bacterial prevalence, patient demographics, patient case-mix, and infection control interventions and their intensity, all of which can influence AMR and antimicrobial prescribing. Other barriers include concerns that overall clinical outcomes (such as mortality) may be insensitive to changes as a result of interventions such as IV to oral switching, and perceived feasibility issues with other outcome measures.[46] In such situations where there is a difficulty in developing an accurate case-mix adjustment system for outcome indicators, then alternative strategies may be more effective at measuring the quality of care.

Process and structural indicators can act as direct measures of the quality of healthcare, where a link has been demonstrated between a given process and outcome.[48] They are relatively easy to measure as the information is accessible from medical records or other hospital sources. They usually assess a clearly defined patient population and thus there is less need for risk adjustment. The availability of such measures and their practicality means they can be used as alternative outcome measures as they are easier to interpret and more sensitive to changes in the quality of care.[48] The AMS process indicators (use of empirical antimicrobial therapy according to guidelines, de-escalation of therapy, IV to oral switching, therapeutic drug monitoring) and structural indicators [use of a list of restricted antibiotics and bedside consultation (especially in *Staphylococcus aureus* bacteraemia)] have demonstrated significant benefit to clinical outcomes, adverse events and costs.[49] The process measure of documented indications for antimicrobial prescriptions has also shown a positive influence on patient outcomes.[50] Furthermore, a recent study of UK hospitals has evaluated the impact of AMS process and structural indicators (similar to those extracted in this study) on antimicrobial prescribing as an outcome measure and has shown promising results.[45]

A further possible approach for the development of outcome measures may be to consider using indirect evidence for the success of a process indicator as an outcome. Process indicators such as de-escalation of therapy, or IV to oral switching could be used to assess an outcome such as 'not showing harm' where such indicators could decrease the likelihood of catheter-related infections/events without demonstrating an impact on more traditional outcomes such as mortality or AMR rates.[49]

The development of future QIs must address the lack of outcome indicators currently available while acknowledging the difficulties in their development such as risk adjustment and case-mix, along with the multitude of other factors which can influence AMR. The potential use of AMS process and structural indicators with a direct link to outcomes should also be explored further as surrogate AMS outcome measure.[45]

The methodological requirements for the development of QIs are well established.[9,12] Most studies concentrated on the development of the QIs and were considered to be of high methodological quality in the 'stakeholder involvement' and 'scientific evidence' domains. However, studies scored poorly in the 'additional evidence, formulation, usage' domain due to limited reporting of information about validation and piloting of the QIs in practice or testing of the clinimetric characteristics. Such practice testing prior to wider usage of QIs is essential[40] as the validation and clinimetric testing of QIs is important to demonstrate the applicability and implementability of QI sets in practice, in different settings and to demonstrate the robustness of the indicators. The studies that were considered to be of the highest methodological quality scored well in all three AIRE domains and recognized the need to test indicators in the setting where they are intended for use.[24,26–29]

Several studies, which were considered to be of high methodological quality in the first two AIRE domains, had low scores in the third domain.[23,30,31,36,37] Some studies acknowledged the need for piloting and clinimetric testing of their QIs prior to use on a wider scale.[27,30,31,35,37] The QIs from two studies[27,37] have undergone subsequent clinimetric testing.[51,52] This resulted in one QI set reducing the 11 initial QIs to 7, based on applicability,[51] and of 33 QIs assessed reduced to 18 process indicators considered suitable to identify processes with a greater need for improvement within an AMS programme.[52] This supports the findings seen in other studies, which have shown that 10%–20% of developed QIs are not measurable in practice.[53] The implementability, applicability and feasibility testing of indicator measurements are important considerations and should be conducted as part of the development process but also in new settings where the QIs are to be potentially applied. Potential users need to know if they will be able to retrieve the data to assess the QI from sources such as medical records and this may vary between countries and sometimes within clinical settings.[28,30,51]

Point-prevalence surveys are one of the most frequently used methods to assess the quality of antimicrobial prescribing in the hospital setting[54] and have been used to test QIs sets.[51,52] They are a particularly useful method of assessing the impact of process indicators on patient care and outcomes[55] in practice so future QI development studies should consider if new process QI sets can be incorporated and applied in point-prevalence surveys.

Strengths and limitations of this study

To our knowledge, this is the first systematic review of the QIs for AMS programmes that has included a critical appraisal of the methodological quality of the QI sets, and is considered to be a strength of this study.

The selection of articles, data extraction and quality assessment with the AIRE assessment tool was conducted by two reviewers independently and showed good inter-rater reliability, which increases the overall reliability of the results. This review included QIs assessing specific infectious conditions as well as broader QIs of AMS programmes so provides a comprehensive overview of AMS programme QIs.

We may have missed some QI sets, which have not been published in an article or report. However, it is unlikely that validated and reliable QI sets for AMS have not been published in peer-reviewed literature.

The AIRE instrument used in this study to assess the methodological quality of studies mainly focuses on the QI development process and scores are allocated based on the information

contained within the published article. Unfortunately, the process of developing QIs was not always reported in detail in studies and this resulted in some studies being assigned lower scores for these criteria. As a result of this limitation the methodological quality of the QIs identified in this article may have been underestimated by using the AIRE instrument. There were, however, some studies that acknowledged the need to conduct piloting and clinimetric testing of their indicators so the low scores in these situations were accurate. A further limitation of this study was that we relied solely on the information contained within the published article.

Conclusions

This review provides an overview and critical appraisal of the methodological quality of QIs of AMS programmes. The study highlights the continuing need for transparent, valid and feasible QIs. Studies to date have focused on process and structural indicators with few outcome indicators developed—a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS. Testing of the QIs in practice should be an essential element of the QI development process and should be included in the QI development study or as planned validation work.

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Transparency declarations

None to declare.

Author contributions

F.O.R. conceptualized the study, performed the literature search, performed the selection of articles and the data extraction, performed the critical appraisal using the AIRE instrument, interpretation and analysis, drafted and revised the manuscript and tables. A.F. conceptualized the study, performed the selection of articles, performed the critical appraisal using the AIRE instrument and critically reviewed and revised the manuscript. S.B. critically reviewed and revised the manuscript. F.S. consulted in the selection of articles, performed the critical appraisal using the AIRE instrument and critically reviewed and revised the manuscript.

Supplementary data

Files S1 to S4 are available as Supplementary data at *JAC* Online.

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Antimicrobial use and antimicrobial resistance in Enterobacterales and *Enterococcus faecium*: a time series analysis

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SUMMARY

Background: Irish and European antimicrobial resistance (AMR) surveillance data have highlighted increasing AMR in Enterobacterales and vancomycin resistance in *Enterococcus faecium* (VRE). Antimicrobial consumption (AC) in Irish hospital settings is also increasing.
Methods: A retrospective time series analysis (TSA) was conducted to evaluate the trends and possible relationship between AC of selected antimicrobials and AMR in Enterobacterales and vancomycin resistance in *E. faecium*, from January 2017 to December 2020.
Results: Increased AC was seen with ceftriaxone ($P = 0.0006$), piperacillin/tazobactam ($P = 0.03$) and meropenem ($P = 0.054$), while ciprofloxacin and gentamicin use trended downwards. AMR rates in *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacterales were largely stable or decreasing, an increase in ertapenem resistance in the latter from 0.58% in 2017 to 5.19% in 2020 ($P = 0.003$) being the main concern. The proportion of *E. faecium* that was VRE did not changed significantly (64% in 2017; 53% in 2020, $P = 0.1$). TSA identified a correlation between piperacillin/tazobactam use and the decreasing rate of ceftriaxone resistance in *E. coli*.
Conclusion: Our data suggest that the hospital antimicrobial stewardship programme is largely containing, but not reducing AMR in key nosocomial pathogens. An increase in AC following the COVID-19 pandemic appears as yet to have had no impact on AMR rates.

Introduction

Antimicrobial resistance (AMR) is a significant threat to public health [1]. Increasing rates of AMR among Enterobacterales and of vancomycin-resistance in *Enterococcus faecium* (VRE) are causing concern across Europe [2] and in Ireland [3].

There is a well-established link between inappropriate and excessive antimicrobial use and selection of AMR [4]; AMR in Enterobacterales is of particular concern [5]. Antimicrobial stewardship (AMS) interventions are an important element in tackling AMR and are well established in Irish hospitals [6]. However, the median overall rate of antimicrobial consumption

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(AC) in Irish hospitals increased by 16% between 2009 and 2019 [7]. The COVID-19 pandemic has had a significant impact on healthcare systems and delivery worldwide [8]. Many routine AMS activities have been reduced and the impact of this on AMR is yet to be determined [9]. Furthermore, evidence suggests that there has been widespread and excessive prescription of antimicrobials in COVID-19 patients due to the difficulty in identifying which patients have bacterial pneumonia [10].

There is a lack of studies linking AC and AMR in the Irish hospital setting. Given the prevailing trends in AC and AMR in Ireland and the knowledge that AC is generally recognized as the primary driver of AMR, it is important to investigate how changes in AC influence bacterial susceptibilities. Such information could inform development of policies to manage AMR, particularly following the COVID-19 pandemic.

In this study we aim to investigate the trends and possible relationships between AC and AMR in Enterobacterales species, and the proportion of *E. faecium* that are VRE, between 2017 and 2020 in an Irish hospital. These AMR data were also compared with EU and other Irish hospital data.

Methods

Hospital setting

The study hospital is a 271-bed, inner-city, acute University Teaching Hospital, in the Republic of Ireland. The hospital is comprised of various medical and surgical specialities, a paediatric unit, and a general intensive care unit. The hospital established a formal AMS programme in 2007. Key AMS events and policies implemented prior to and during the study period are summarized in Supplementary Table S1.

Antimicrobial consumption

Quarterly aggregated hospital AC data (dispensed to inpatients on all hospital wards) for antimicrobial agents indicated for treatment of infections caused by Enterobacterales were collated. These antibiotics were ceftriaxone, ciprofloxacin, levofloxacin, ertapenem, meropenem, piperacillin/tazobactam, gentamicin, co-trimoxazole and aztreonam; vancomycin usage data were also collected. Antimicrobials dispensed to the outpatient setting were excluded.

AC data were obtained from the hospital pharmacy electronic dispensing records for the study period (1st January 2017 to 31st December 2020). These data were converted to the standardized WHO's Anatomical Therapeutic Chemical (ATC) Classification of defined daily dose (DDD) and antibiotic usage was expressed as quarterly aggregated DDDs according to the 2018 ATC classification and normalized per 100 hospital/bed days used (BDU) [11].

Microbiology and AMR data

Isolates of Enterobacterales from clinical microbiology specimens (blood, sterile fluid, sputum, urine and wound samples) from inpatients were included. Duplicate isolates from the same patient [12] were excluded. Bacterial identification and antibacterial susceptibility testing was performed in the hospital clinical microbiology laboratory using the Vitek®2 (bioMérieux) system according to the manufacturer's guidelines. Antimicrobial susceptibilities were assessed according to European Committee for Antimicrobial Susceptibility Testing (EUCAST) [13]. All non-susceptible isolates (i.e. resistant and intermediate) were considered resistant. AMR data were extracted from the hospital microbiology laboratory database. We also compared our data to European Antimicrobial Resistance Surveillance Network (EARS-Net) reports of population-weighted EU-/EEA-wide AMR rates [3]. These are based on data on *E. faecium*, *Escherichia coli*, and *Klebsiella pneumoniae* in invasive samples (blood or cerebrospinal fluid) and submitted by medical microbiology laboratories across Europe, including the study hospital. While there is some variability in reporting, data from Ireland is estimated to cover 96% of the population.

Statistical analysis

Initial analysis of the evolving trends in AC and AMR rates was conducted by linear regression analysis. Further analysis was conducted using time series analysis (TSA), which has been used previously to investigate possible correlations between AC and AMR where the data are measured repeatedly at equal intervals of time [14–16]. The Box–Jenkins method of TSA modelling was used to develop univariate autoregressive integrated moving average (ARIMA) models of the AC and AMR data [17]. Following the development of univariate ARIMA models, a linear transfer function modelling method [15,16] was used to investigate the dynamic relationship between antimicrobial use and the incidence of resistant isolates, considering possible time delays (lag times). These methods are described in detail in the Supplementary data. All statistical analyses were performed with R version 4.0.3.

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidance for reporting observational studies [18] and the STROBE-AMS recommendations for reporting epidemiology studies of AMR and informing improvement in AMS [19].

Ethics

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (reference numbers ECM4(p) and ECM3(xx)).

Results

Hospital trends in AC

The trends in AC of the individual antimicrobials can be seen in Figure 1. Increasing trends were seen in ceftriaxone consumption ($P = 0.0006$), piperacillin/tazobactam consumption ($P = 0.03$) and meropenem consumption ($P = 0.054$). Decreasing trends were seen in ciprofloxacin consumption ($P = 0.0012$) and gentamicin consumption ($P = 0.057$). Further trend analysis of AC is contained in Supplementary Table S2.

Hospital trends in AMR

The annual rates of AMR for *E. coli and K. pneumoniae*, and of vancomycin resistance in enterococci and VRE incidence in our hospital, and compared with Irish and European resistance

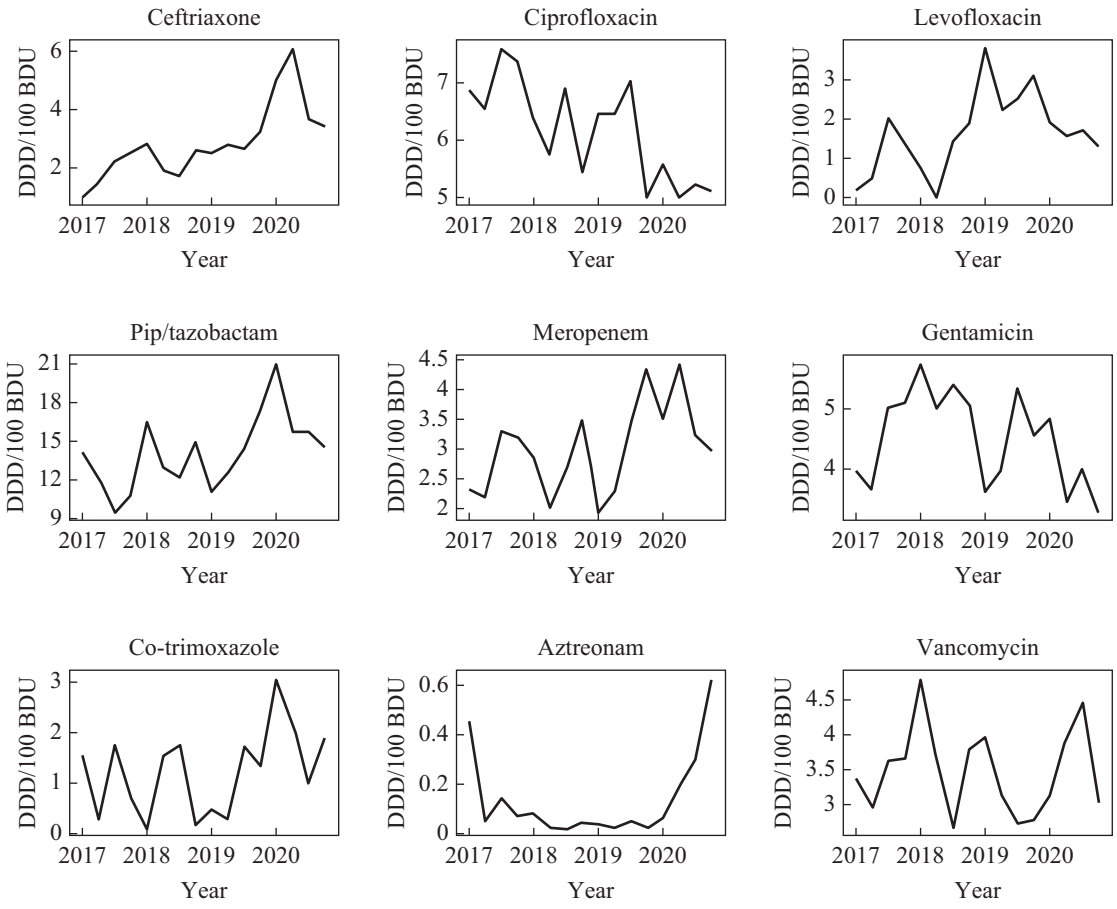

Figure 1. Quarterly antimicrobial consumption rates of selected antimicrobials from Q1 2017 to Q4 2020. BDU, bed days used; DDD, defined daily dose.

data are shown in Table I. Figures 2–4 show quarterly trends in AMR for *E. coli*, *K. pneumoniae* and other Enterobacterales, respectively.

For *E. coli*, although the graphs suggest that resistance rates were trending downwards for most antibiotics except co-trimoxazole, the differences did not reach statistical significance (e.g., ceftriaxone $P = 0.136$, ciprofloxacin $P = 0.138$, piperacillin/tazobactam $P = 0.143$). Notably, fluoroquinolone resistance rates were consistently higher than national and EU rates. The proportion of *E. coli* that were ESBL producers was

Table I
Percentage of clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus faecium* resistant to selected antimicrobials from the study hospital (Hosp), Ireland (Ire) and the European Union (EU) 2017–2019

Bacteria	Antimicrobial agent/group	2017			2018			2019			2020
		Hosp	Ire	EU	Hosp	Ire	EU	Hosp	Ire	EU	Hosp
E. coli	Third-generation cephalosporin*	21	12	14.9	15.8	12.9	15.1	13.2	12	15.1	14.2
	Carbapenems**	1.4	0	0.1	1.6	0	0.1	1.1	0	0.3	0
	Fluoroquinolones#	32.5	23.6	25.7	31.5	23.9	25.3	27.7	20.4	23.8	25.7
	Aminoglycosides	12.7	11.9	11.4	10.4	11.7	11.1	11.4	11.8	10.8	9.1
K. pneumoniae	Third-generation cephalosporin*	19.6	14.9	31.2	17.8	14.5	31.7	11.9	17.6	31.3	10.8
	Carbapenems**	0	0.2	7.1	1.4	0.6	7.5	0	0.9	7.9	1.92
	Fluoroquinolones#	22.4	5.9	30.5	23.3	8.1	19.5	8	5.3	19.3	12.5
	Aminoglycosides	17.8	11.9	24.1	14.6	13	22.7	10	11	22.3	3.85
E. faecium	Vancomycin resistance	64.1	38.2	14.9	56.3	40.2	17.3	48.6	38.4	18.3	53

Only study hospital data was available for 2020 at the time of writing.
* EU and Ire data relates to cefotaxime/ceftriaxone/ceftazidime, study hospital data relates to ceftriaxone resistance.
** EU and Ire data relates to imipenem/meropenem, study hospital data relates to ertapenem resistance.
\# EU and Ire data relates to ciprofloxacin/levofloxacin/ofloxacin, study hospital data relates to ciprofloxacin resistance.

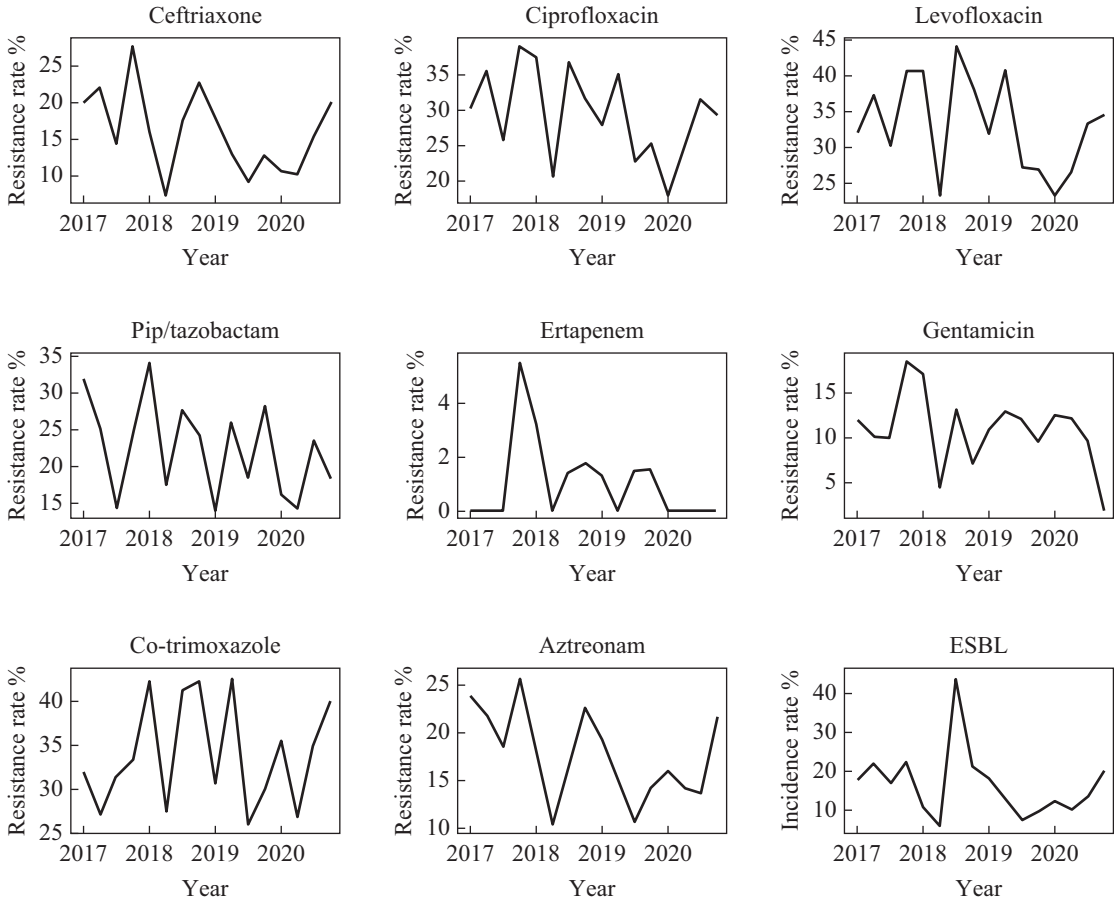

Figure 2. Quarterly *Escherichia coli* resistance rates to selected antimicrobials from Q1 2017 to Q4 2020. ESBL, extended-spectrum beta-lactamase.

19.8% in 2017, compared with 14.1% in 2020 ($P = 0.323$). Further details on the annual rates of resistance in *E. coli* are given in Supplementary Table S3.

Likewise, there were no statistically significant trends in resistance to antibiotics amongst *K. pneumoniae* (Figure 3). Third-generation cephalosporin resistance was considerably higher in the EU than in Ireland or the study hospital. Fluoroquinolone resistance rates fell faster, but later, than in either the EU or Ireland. Further details on the annual rates of resistance in *K. pneumoniae* are given in Supplementary Table S3. The proportion of *K. pneumoniae* isolates that were ESBL-producing fell from 19.8% in 2017 to 8.88% in 2020 ($P = 0.0254$). Further details on the annual rates of resistance in *K. pneumoniae* are contained in Supplementary Table S4.

Trends in antibiotic resistance amongst other Enterobacterales are shown in Figure 4. The most common genera in this category were *Citrobacter, Enterobacter, Proteus* and *Serratia*. The most important trend was the rise in ertapenem resistance from 0.58% in 2017 to 5.19% in 2020 ($P = 0.003$). Further details on the annual rates of resistance are contained in Supplementary Table S5.

There was no significant change in the rates of vancomycin resistance in *E. faecium* over the study period ($P = 0.1$). However, the rate in our hospital was considerably higher than the rates nationally, or in the EU.

Incidence and dynamic regression of E. coli resistance to ceftriaxone and the influence of piperacillin/tazobactam

For ceftriaxone resistance in *E. coli* we identified an ARIMA model [17] with one significant moving average term of order 2. The transfer function model was developed which explained 86% ($R^2 = 86$) of the variation in incidence with piperacillin/tazobactam consumption as a statistically significant explanatory variable for ceftriaxone resistance in *E. coli*. A 1% increase in piperacillin/tazobactam use would result in a 1.33% decrease in ceftriaxone resistance immediately and a further 0.488 % decrease in 3 months. The transfer function model also included the moving average term of the resistance rate itself with a lag of 6 months. Further details are given in Supplementary Table S5.

Discussion

This study contains an analysis of the rates of AC and AMR in an Irish teaching hospital using TSA. The findings show that while overall AC rates and broad-spectrum antimicrobial (ceftriaxone, piperacillin/tazobactam and meropenem) use increased over the study period there was not a corresponding

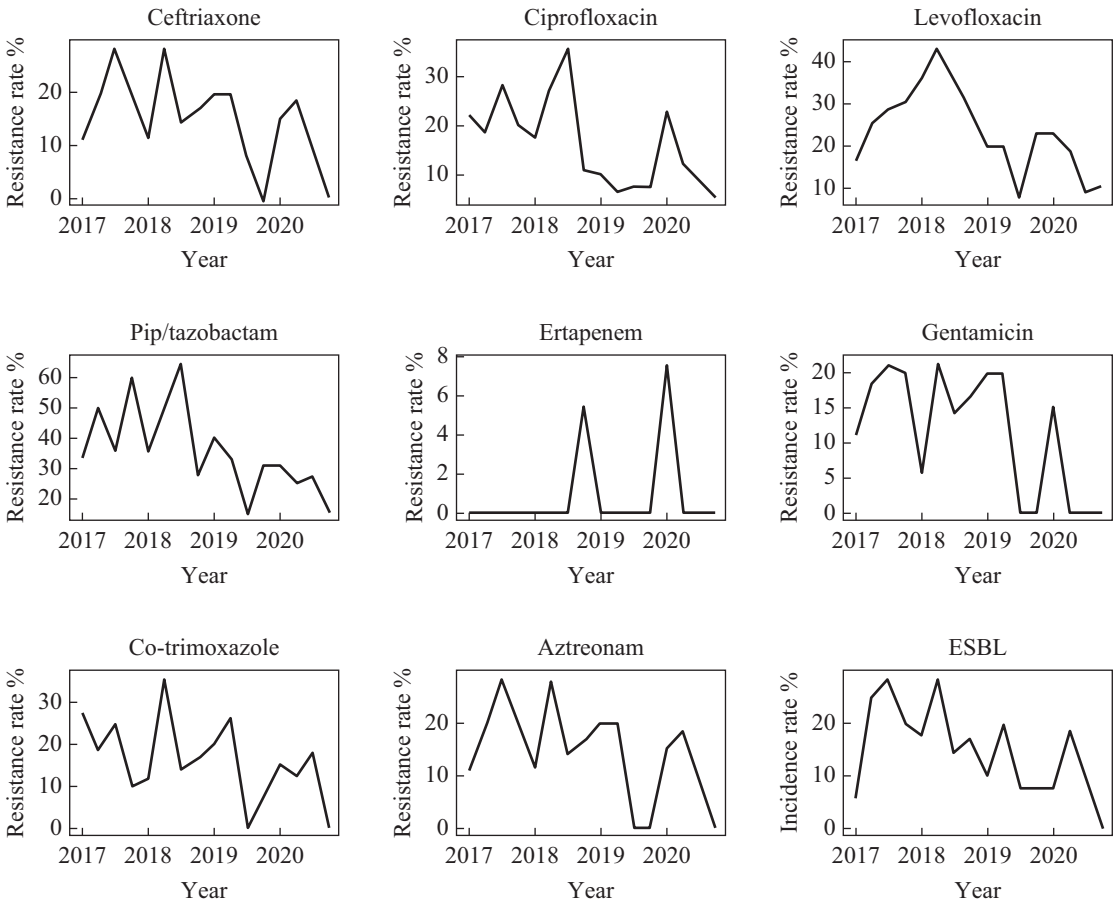

Figure 3. Quarterly *Klebsiella pneumoniae* resistance rates to selected antimicrobials from Q1 2017 to Q4 2020. ESBL, extended-spectrum beta-lactamase.

increase generally in rates of AMR. These findings suggest that hospital AC is just one of several factors that influence the rates of AMR seen in the hospital setting. The main trend of concern is rising rates of ertapenem resistance, especially in the group of 'other Enterobacterales', which follows a national trend [20].

Nevertheless, we feel that overall, our data do indicate that the hospital AMS programme is having a positive impact on Gram-negative AMR rates [21]. A recent analysis of AC and AMR data from the EU similarly identified stabilization of AMR rates in *E. coli* and *K. pneumoniae* attributed to the impact of AMS initiatives [22]. We note that others have reported that AMS programmes have been reported to be less effective in reducing VRE rates [21]. Further work is required to address the increasing frequency of carbapenemase-producing Enterobacterales (CPE). The most effective AMS interventions targeting CPE are those that address carbapenem use and incorporate education and restrictive measures [23,24]. The reduction in AMS activities [9] seen during the COVID-19 pandemic is likely to have contributed to the increased carbapenem use seen during this study.

When each of the AC-AMR combinations (e.g., AC and ertapenem resistance, AC and VRE rates) were cross-correlated using linear regression of the ARIMA model residuals, only one significant correlation between antimicrobial use and AMR was identified. This may have been because it is difficult to demonstrate a statistically significant correlation due to the complex and evolving nature of AMR despite the link between AMR and AC being well established [25]. A recent study from the Netherlands in the outpatient setting found that the association between antimicrobial use and resistance was weak [26]. Suggested factors for the lack of correlation included patient-related factors (e.g., age, sex), individual patient antimicrobial exposure, resistance mechanisms to antimicrobials between different bacteria [26] and the interaction with the use of other antimicrobials [15].

In this study a correlation between piperacillin/tazobactam use and the rate of resistance to ceftriaxone in *E. coli* was observed using TSA. Over the study period the rate of resistance to ceftriaxone in *E. coli* decreased while the use of ceftriaxone increased particularly in 2020. The increased consumption of ceftriaxone during 2020 did not appear to have an immediate impact on the rate of ceftriaxone resistance but this should be monitored due to a potential lag in the influence of the increased use on rates of resistance. The use of piperacillin/tazobactam also tended to increase during the study period but using TSA a correlation was identified with the decrease in ceftriaxone resistance in *E. coli*. This effect has also been seen in a study involving the substitution of piperacillin/tazobactam for a broad-spectrum cephalosporin (ceftazidime) which resulted in decreasing levels of ceftazidime resistance in other Enterobacterales [27]. Resistance strain

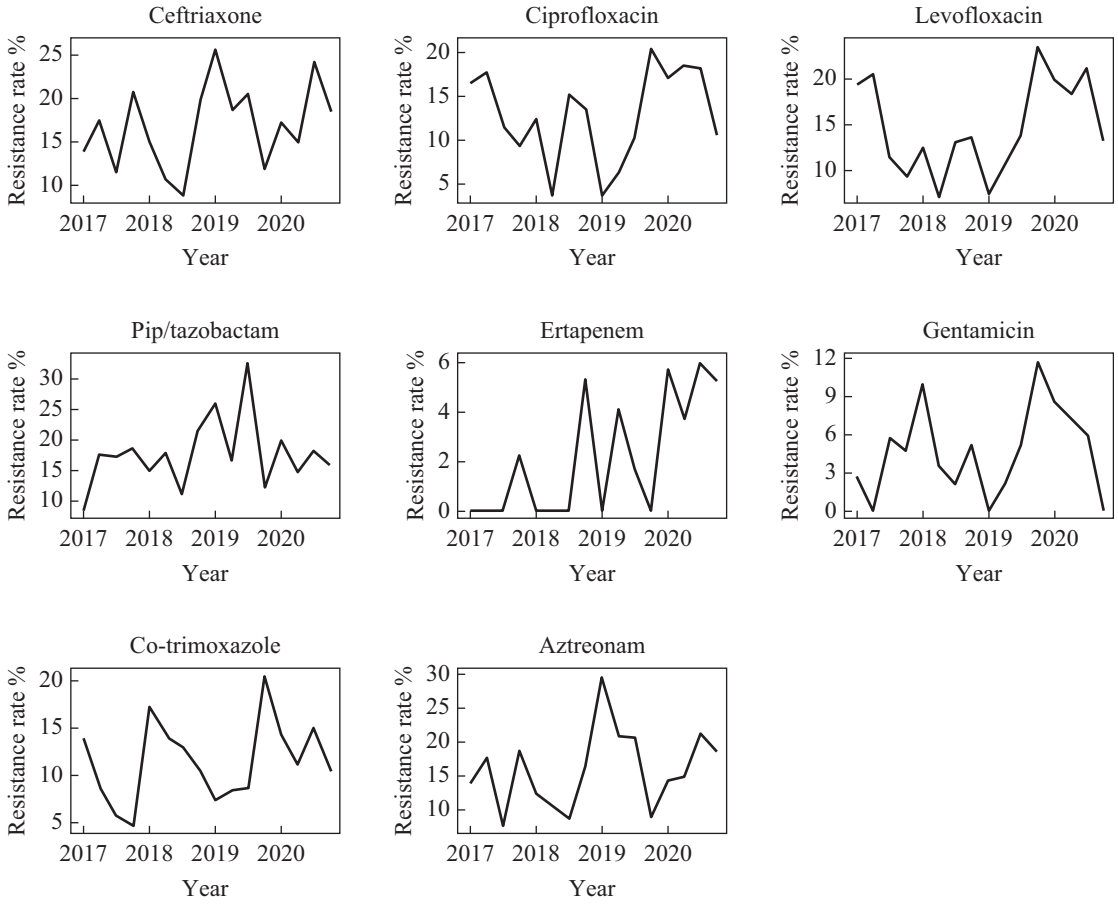

Figure 4. Quarterly resistance rates for other Enterobacterales species to selected antimicrobials from Q1 2017 to Q4 2020.

dynamics can play an important role in changes in AMR rates in *E. coli* species and are influenced by antimicrobial consumption changes [16]. In situations where there are high levels of resistance to third-generation cephalosporins such as ceftriaxone, as seen in the study hospital, efforts to substitute ceftriaxone with piperacillin/tazobactam should be considered.

Consumption of broad-spectrum antimicrobials, ceftriaxone, piperacillin/tazobactam and meropenem, increased over the course of the study, especially in 2020, during the COVID-19 pandemic. Much of this increase was associated with treatment of suspected pneumonia in patients with suspected or proven COVID-19 [28]. Studies have estimated that up to 72% of hospitalized COVID-19 patients received antimicrobials, while the rate of bacterial co-infection ranged from 6% to 11% [29,30]. Increased prescribing of broad-spectrum antimicrobials and decreased AMS activities has led to concerns that AMR may proliferate in hospitals because of COVID 19. However, thus far the COVID-19 pandemic appears to have had limited impact on AMR rates, either in our hospital or elsewhere [31]. One potential explanation for this is that the COVID-19 pandemic has improved infection prevention and control practices [32]; AMS programmes are more effective when implemented alongside infection prevention and control measures [21].

The focus of this study was on AC and AMR in the hospital setting but it is important to acknowledge the impact of community antimicrobial use has on AMR, as antimicrobial use in one setting can impact AMR in the other [33]. The COVID-19 pandemic is likely to have impacted on AC and AMR in the community, through factors such as decreased travel and socialising, as well as factors such as social distancing and hand hygiene. Other limitations of this study are that it was a single-centre retrospective study, meaning that the findings may not be generalizable. Also, the study only encompassed samples collected for routine clinical reasons. By not undertaking systematic screening of all hospitalized patients, there is a risk that the AMR data are not representative of the whole hospital population. Other studies have suggested more frequent observations should be used when conducting TSA [14] however this was not practical for our study. The use of a longer reporting period should be considered in future studies with the use of monthly data to increase sensitivity to identify possible correlations.

In conclusion, the decreasing or generally stable rates of AMR found in this study provide some assurance that the hospital AMS programme is assisting in controlling AMR, although a rise in ertapenem resistance in Enterobacterales is concerning. We also noted that broad-spectrum AC increased in association with the COVID-19 pandemic, and suggest that improved infection prevention and control practice may have been important in containing AMR during this period. Wider use of TSA to analyse routine AC and AMR data as part of AMS

programmes should be considered, as it allows investigation of correlations between antibiotic use and resistance to other antibiotics.

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Conflict of interest statement
None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.11.003.

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