Bridging the evidence gap for implementing antibiotic stewardship in Norway: Interventions, process measures and patient outcomes related to antibiotic prescribing in hospitals

Jannicke Slettli Wathne

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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SCIENTIFIC ENVIRONMENT

This PhD and doctoral training was performed at the Department of Clinical Science, Faculty of Medicine, University of Bergen. I have also taken part in the Norwegian PhD School of Pharmacy throughout this work and attended courses at the University of Oslo.

The research project emanated from the Norwegian Advisory Unit for Antibiotic Use in Hospitals (KAS), hosted by the Patient Safety Unit, Department of Research and Development, Haukeland University Hospital.

Main supervisor was PhD Ingrid Smith (WHO), and co-supervisors were Professor Stig Harthug (UiB/KAS) and Professor Hege Salvesen Blix (UiO/FHI).

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Norwegian Advisory Unit for
Antibiotic Use in Hospitals

ABBREVIATIONS

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship/Antibiotic stewardship
AMS-programme	Antimicrobial stewardship programme/Antibiotic stewardship programme
AWaRe	Access, Watch, Reserve (Classification of antibiotics in the WHO Model List of Essential Medicines)
CAP	Community acquired pneumonia
CCI	Charlson Comorbidity Index
CDC	The American Centers for Disease Control and Prevention
C. Diff.	*Clostridium difficile*
CI	Confidence Interval
CRB-65	Confusion, Respiration, Blood pressure and age equal to or over 65 years (clinical score)
c-RCT	Cluster Randomised Controlled Trial
CRF	Case Report Form
DDD	Defined Daily Dose
eGFR	Estimated Glomerular Filtration Rate
EML	Essential Medicines List (World Health Organization Model List of Essential Medicines)
EPOC	Effective Practice and Organisation of Care Group (Cochrane Review Group)
ESAC-net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended spectrum beta-lactamases
ESGAP	The European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship
ESCMID	The European Society of Clinical Microbiology and Infectious Diseases

ICD-10	International Classification of Diseases (version 10)
ID	Infectious Diseases
IDSA	The Infectious Diseases Society of America
IPC	Infection prevention and control
ITS	Interrupted Time Series
KAS	Norwegian Advisory Unit for Antibiotic Use in Hospitals
LOS	Length of stay (in hospital)
LRTI	Lower respiratory tract infection
LTCF	Long-term care fascilities
MDR	Multidrug resistant
MRSA	Methicillin Resistant Staphylococcus Aureus
NORM	Norwegian Surveillance Programme for Antimicrobial Resistance in Human Pathogens
OR	Odds Ratio
PIDS	The Pediatric Infectious Diseases Society
PBP	Penicillin-binding-protein
QI	Quality Indicator
RCT	Randomized Controlled Trial
RR	Relative risk
SHEA	The Society for Healthcare Epidemiology of America
SHR	Subdistribution Hazard Ratio
SIRS	Systemic Inflammatory Response Syndrome
SSTI	Skin- and soft tissue infection
UiB	University of Bergen
UiO	University of Oslo
UTI	Urinary Tract Infection
WHO	World Health Organization

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ABSTRACT

Background: Antimicrobial resistance is a major challenge for patient safety worldwide, as a growing number of infections become difficult to treat and the advances made in modern medicine are threatened. Overuse and misuse of antibiotics accelerates the development of resistance. Optimizing treatment for the patients of today, while conserving effective antibiotics for future patients is therefore of great importance. Antimicrobial stewardship is a strategy and coherent set of actions which promote responsible use of antibiotics.

Objectives: The main aim of this project was to contribute to the knowledge needed to implement antibiotic stewardship in Norwegian hospitals through a) determining the impact of audit with feedback and academic detailing with local target setting on antibiotic prescribing practice b) understanding how patient outcomes are associated with adherence to clinical guidelins on initiation of antibiotic treatment and c) determining whether targets for antimicrobial stewardship interventions can be identified through analysing the antibiotic prescribing process in Norwegian hospitals with patient-level data.

Materials and methods: All three substudies were part of a combined multicentre study, performed within the specialties of pulmonary medicine, infectious diseases and gastroenterology at three hospitals in Western Norway. Study 1 included 1802 patients and was a randomised, controlled intervention study, assessing the impact of academic detailing, audit with feedback and local target setting on adherence to antibiotic guidelines and changes in locally defined targets. Study 2 and 3 were observational cohort studies, including 1756 patients and 1235 patients, respectively.

Results: In study 1 there was an absolute increase in adherence to guidelines of 6% across all intervention wards (p=0.04). When analysed per specialty, pulmonary intervention wards had a 14% absolute increase in adherence (p=0.003), while other

intervention wards had no observed impact of interventions on adherence. Intervention wards receiving audit with feedback decreased the use of broad-spectrum antibiotics (level and trend). Local target setting at one of the pulmonary wards led to a 30% increase in targeted prescribing behaviour ($p<0.001$). In study 2, guideline-adherent prescribing was associated with lower in-hospital (OR=0.46, p=0.003) and 30-day mortality (OR=0.48, p=0.001). There was also a trend towards shorter length of stay (-0.47 days) when guidelines were followed. Analysing the process of antibiotic prescribing in hospitals (study 3) identified 5 main targets for antimicrobial stewardship interventions: a) adherence to guidelines, b) prescribing in the emergency room, c) prescribing for patients admitted from other institution, d) understanding cultural and contextual drivers of antibiotic prescribing and e) duration of treatment.

Conclusions: The impact of antimicrobial stewardship interventions on prescribing practice was dependent both on the context (e.g. specialty) in which interventions were implemented and how they were implemented. Pulmonary intervention wards increased adherence to guidelines with both audit with feedback and academic detailing, and additional impact was seen when locally defined targets were identified. We have shown that adherence to Norwegian antibiotic guidelines was associated with favourable patient outcomes across a range of common infectious diseases, both in terms of in-hospital- and 30-day mortality. Targets for antimicrobial stewardship interventions in hospitals were identified through analysis of patient-level, antibiotic prescribing data from admission to discharge and WHO AWaRe categories provided a useful system for analysing antibiotic regimens throughout the hospital stay. Although the studies were performed in Norwegian hospitals, we believe that the methods and findings will be applicable in other clinical settings where antibiotic prescribing and related patient outcomes is to be analysed and improved.

LIST OF PUBLICATIONS

PAPER I

Wathne JS, Kleppe LKS, Harthug S, Blix HS, Nilsen RM, Charani E, The Bergen Intervention Teams*, Smith, I. *The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study.* Antimicrobial Resistance & Infection Control. 2018;7(1):109.

* The Bergen Intervention Teams: Markussen DL, Thelle A, Neteland M, Hope O.

PAPER II

Wathne JS, Harthug S, Kleppe LKS, Blix HS, Nilsen RM, Charani E, Smith I. *The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study.* Antimicrobial Resistance & Infection Control. 2019;8(1):63

PAPER III

Wathne JS, Skodvin B, Harthug S, Blix HS, Charani E, Kleppe LKS, Nilsen RM, Vukovic M, Smith I. *Identifying targets for antibiotic stewardship interventions through analysis of the antibiotic prescribing process in hospitals - a multicentre observational cohort study.*

[Submitted]

CONTENTS

1. INTRODUCTION

Antimicrobial resistance (AMR) has become a global crisis, as microbes, in particular bacteria, have become increasingly resistant to antibiotics [1]. Today, an estimated 700 000 deaths are caused by infections with antibiotic-resistant microbes globally, of which 33 000 deaths are in the European Union and the European Economic Area [1-3]. The most alarming predictions of the implications of AMR are heavily debated, but suggests that by 2050, the number of deaths could increase to 10 million per year globally, unless prompt action is taken [3, 4]. Development of AMR is fueled by decades of overuse and misuse of antibiotics in multiple sectors and environmental pollution [5-8].

AMR is not a new phenomenon. Although recognized by the communities of microbiologists and infectious disease physicians at an early stage, raising awareness of this important challenge has taken time. WHO published its first global strategy on AMR in 2001 [9]. However, it was more recent, among others with the publication of the O'Neill report in 2014 and the Global Action Plan on AMR in 2015, that AMR was globally recognized as a public health threat, which, if not reversed, could put an end to modern medicine and cause millions of deaths worldwide [3, 10]. It was also recognized that joint efforts across all sectors involved in antibiotic production, policymaking, prescribing, handling and use were necessary to curb AMR [6, 11]. This prompted more coordinated actions on AMR from governments, professional bodies, scientists and healthcare workers, such as national action plans on AMR, surveillance of AMR and antibiotic use, research and development on new antibiotics and policies to optimize antibiotic use both at community- and hospital levels [3, 8, 10, 12-21].

Norway has had strict policies for antibiotic use and low rates of AMR, which has made it possible to continue the use of narrow-spectrum antibiotics for a wide range of diagnoses [22-24]. Outbreaks caused by resistant bacteria in hospitals and long-term care fascilities (LTCF) and patients dying from multidrug resistant (MDR) bacterial infections are however increasing across the world, and Norway is no longer an

exception [2, 3, 25-27]. The studies undertaken as part of this PhD-project aimed to increase the understanding of how antibiotics are used in Norwegian hospital settings, how patient outcomes are associated with antibiotic prescribing and how prescribing practices can be improved.

1.1 ANTIMICROBIALS

Antimicrobials are substances that inhibit the growth of – or kill microorganisms, such as bacteria, viruses, funghi and parasites and are therefore divided into antibacterials, antivirals, antifungals and antiparasitic drugs [28]. This thesis will focus solely on the use of antibacterials and the term antibiotics will be used.

Antibiotics are one of the greatest achievements in the field of medicine, saving countless lives since their introduction into clinical practice [29]. Between 1937 and 1943, maternal mortality in the United States declined by 24-36%, mortality due to pneumonia declined by 17-32% and scarlet fever mortality declined by 52-65%, due to sulphonamides [29, 30]. With the introduction of penicillin, mortality associated with pneumococcal pneumonia and bacteraemia declined from 20-40% to 5% and 50-80% to 18-20%, respectively [31].

The term *antibiotics* are now used both for synthetically produced chemotherapeutic agents with antimicrobial effects (e.g. sulphonamides and fluoroquinolones) and the antibiotics which originates from microorganisms (e.g. penicillin). The arsenic-based chemical known as Salvarsan, was the first antibacterial agent used in the modern antibiotic era, synthesized by Erlich in 1907 and used to treat syphilis [29, 32]. Next in line was the Sulphonamides, which were the first antibiotics produced in large scale and put into practice in 1935, followed by penicillin in 1941 [29].

Even though antibiotics are perceived as miracle drugs, the benefit of prescribing antibiotics should always outweigh the risks. Misuse and overuse of antibiotics increases antimicrobial resistance in the society, and antibiotics also have potential

adverse effects for the individual patient. Allergies and diarrhea are common when a patient is treated with antibiotics and some antibiotics, especially clindamycin, cephalosporins and quinolones, are especially prone to cause a serious, secondary bowl infection with toxin-producing *Clostridium difficile* (C.diff) [33]. In addition to eradicating pathogenic bacteria, taking antibiotics changes the commensal flora, including the useful bacteria in our microbiome. The impact on the commensal flora are increased with the use of broad spectrum antibiotics, killing more bacterial species than the narrow-spectrum antibiotics. Bacteria help us digest food, produce vitamins and protects us from overgrowth of pathogenic bacteria and funghi, including multidrug resistant bacteria. The way the microbiota is changed and the impact this has on human health is not fully understood, but changes in the microbiotia have been linked to overveight, diabetes, cancer and inflammatory bowl disease [34]. How the routes of administration of antibiotics affect the gut microbiome is also an area that needs future research [34].

1.2 ANTIMICROBIAL RESISTANCE

AMR is defined as "the ability of a microorganism (e.g., a bacterium, a virus, or a parasite, such as the malaria parasite) to resist the action of an antimicrobial agent" [28]. AMR is seen in both bacteria, funghi, viruses and parasites, but will in this thesis be discussed in relation to bacterial resistance only.

AMR was described already in the 1945 Nobel Lecture from the famous discoverer of penicillin, Alexander Fleming, and resistant strains of *Staphylococcus aureus* were reported in patients receiving penicillin therapy as early as 1942 [35, 36]. Bacteria can be naturally resistant to some antibiotics, a trait known as intrinsic or inherited resistance [28]. Examples are gram-negative bacteria being resistant to glycopeptideantibiotics (e.g. vancomycin) because the outer membrane of gram-negative bacteria renders the targeted peptidoglycan cell wall inaccessible to the drug [37]. Resistance can also be developed through mutation in the bacterial genes and be passed on to the next

generation of bacteria (vertical transmission) or bacterial resistance genes can be passed on from one bacterial species to another (horizontial transmission) [28].

Important mechanisms of antibiotic resistance are 1) antibiotic inactivation, 2) target alterations and 3) decreased access to the target site [38]. Some bacteria can produce beta-lactamases, enzymes that inactivates beta-lactam antibiotics by openening the beta-lactam ring in their chemical structure [37]. Beta-lactamases inactivates penicillins and first generation cephalosporins, while extended spectrum beta-lactamases (ESBL) inactivates both penicillins, higher generation cephalosporins and monobactams [37]. Carbapenemases are beta-lactamases that also inactivates carbapenems, an important class of last resort antibiotics [37]. ESBLs and carbapenemases are found in gram-negative bacteria, such as Enterobacteriacae, *Klebsiella pneumoniae* and *Escherichia coli* [37]. To protect beta-lactam antibiotics from being inactivated by beta-lactamases, enzyme-inhibitors have been developed and added to some antibiotic formulations, such as piperacillin-tazobactam, amoxicillin-clavulanic acid and ceftazidim-avibaktam. The most predominant mechanism of resistance to beta-lactam antibiotics in gram-positive bacteria is alteration of the target molecule, penicillin-binding-protein (PBP), as seen in methicillin resistant *Staphylococcus aureus* (MRSA) [37]. Resistance can also be manifested by a change in antibiotic permeability of the outer membrane, a mechanism escpecially seen in gram-negative bacteria, which renders the antibiotic ineffective because it does not reach the target site. Decreased permeability can for example be seen in some of the beta-lactam antibiotics (e.g. aztreonam, ceftazidim and imipenem) [39]. Another mechanism of resistance is upregulation of efflux pumps, where antibiotics are pumped out of the cell where they should exert their effect. Both upregulation of efflux pumps and alteration of target molecules are seen with tetracyclins and fluoroquinolones [37].

When bacteria are exposed to antibiotics, sensitive bacteria will die, while resistant bacteria will survive and prosper, a process which may result in the selection of

bacteria resistant to antibiotics. This can happen during treatment of infectious diseases with antibiotics, both in hospital and community settings. Resistant bacteria can further spread among humans, animals and in the environment, and resistance genes can be transferred to other bacteria. Even though bacteria may have developed or acquired resistance elsewhere, resistant bacteria are often detected in hospital settings through the processes of diagnosing infectious diseases or screening the patient during admission. Resistant strains spreading in the hospital environment is a fear for healthcare workers, patients and managers.

A few decades have passed since Flemings Nobel Lecture and AMR rates have steadily increased to become a serious threat to the effective treatment of infectious diseases [8].

1.3 HOW TO COMBAT AMR

AMR can only be contained and fought if action is taken across all relevant areas and sectors [1] (Figure 1).

1.3.1 Governance

The WHO Action Plan on AMR in 2015, called for action in the individual member states. National action plans agains AMR have since been developed by more than 100 countries across the world [1]. Resistant bacteria know no boundaries and AMR can not be solved within an individual country alone. Both global and national governance are needed and the work must be prioritized across human- and animal health, agriculture and the environment, so that the necessary human, structural and financial resources are made available in all sectors with joint efforts to maximise the effect of actions taken [40-43].

1.3.2 Vaccination

Vaccination is important in combating AMR in multiple ways. Available vaccines reduce the prevalence of both bacterial and viral infections. As viral infections are often inappropriately treated with antibiotics and also give rise to secondary bacterial

infections, reducing both bacterial and viral infections will contribute to a reduction in the need for antibiotics [10, 44]. Effective, worldwide vaccination programmes are therefore an important contribution to combating AMR.

1.3.3 Infection prevention and control (IPC)

Infection prevention and control (IPC) are complementary to antimicrobial stewardship and both are needed to help curb resistance [45]. Effective infection prevention and control measures lower the need for antibiotic treatment through reducing the spread of infectious agents, which in turn prevents bacterial infections. As a consequence, less antibiotic treatment is needed [46]. IPC is escpecially challenging in low- and middle-income countries where even basic measures like access to clean water in healthcare institutions can be lacking [46]. Securing access to efficient hand hygiene, environmental cleaning, disinfection, sterilisation and education of staff in IPC are some of the core elements needed for IPC in healthcare facilities [46].

1.3.4 Access to antibiotics

Globally, there is also a lack of access to antibiotics, and it is estimated that more people die from not having access to antibiotics than from infections with multidrug (MDR) resistant microorganisms [31]. In countries where over-the-counter use of antibiotics is commonplace, substandard and falsified medicines are more prevalent and adds to other challenges of inappropriate use, such as unsuitable choice of drug, dose and duration of treatment [47].

Availability of antibiotics is an increasing challenge also in high-income countries, and Norway has experienced shortages of both broad-spectrum- and old, narrow-spectrum antibiotics the last few years, leaving us with fewer treatment options [48]. Old antibiotics may give limited return of investment for pharmaceutical companies and are therefore not marketed. Physicians may then be forced to prescribe unnecessary broad-spectrum antibiotics when the preferred narrow-spectrum antibiotics are unavailable [49].

There needs to be a balance between policies, laws and regulations that maintain control of the use of these valuable medicines and yet securing that antibiotics are available to those who need them. This requires a sustainable system where healthcare workers are able to make good and qualified decisions on prescribing and dispensing and have both old and new antibiotics at hand [47, 50].

1.3.5 Development of new antibiotics

Although some new antibiotics substances have been introduced in clinical practice in recent years, new classes of antibiotics have not been discovered since the 1980s [51]. The discovery void and the dry pipelines related to antibiotics from the pharmaceutical industry, represents a tremendous challenge as we currently cannot count on new antibiotics to save us from the threat of AMR [52-54]. The business models for the industry rely on large sales volumes to justify development costs. As antibiotics have become a resource which we must spare in order to contain AMR, we need new business models (i.e. public-private partnerships) and incentives to ensure continued discovery and development of antibiotics [50, 55-57].

1.3.6 Alternative treatment options

With increasing rates of AMR, alternative treatment options for infections with multidrug resistant bacteria are investigated. An old technique, which was mostly abandoned with the introduction of antibiotics, uses bacteriophage therapy to kill resistant bacteria. This technique has been in continous use in Eastern Europe, but is now re-discovered also in the western world and recently saved the life of a 15-year old girl in England [58, 59]. Use of immune-based therapies or treatments attacking host targets rather than microbial targets, such as blocking the effect of bacterial toxins or modifying host inflammation response are being studied [60]. Another option includes new individualized cocktails of antibiotics, drawing on collateral antibiotic susceptibility, where resistance to one antibiotic agent increases susceptibility to other antibiotics [61]. Innovative, alternative treatment options should be investigated as part of the fight against AMR.

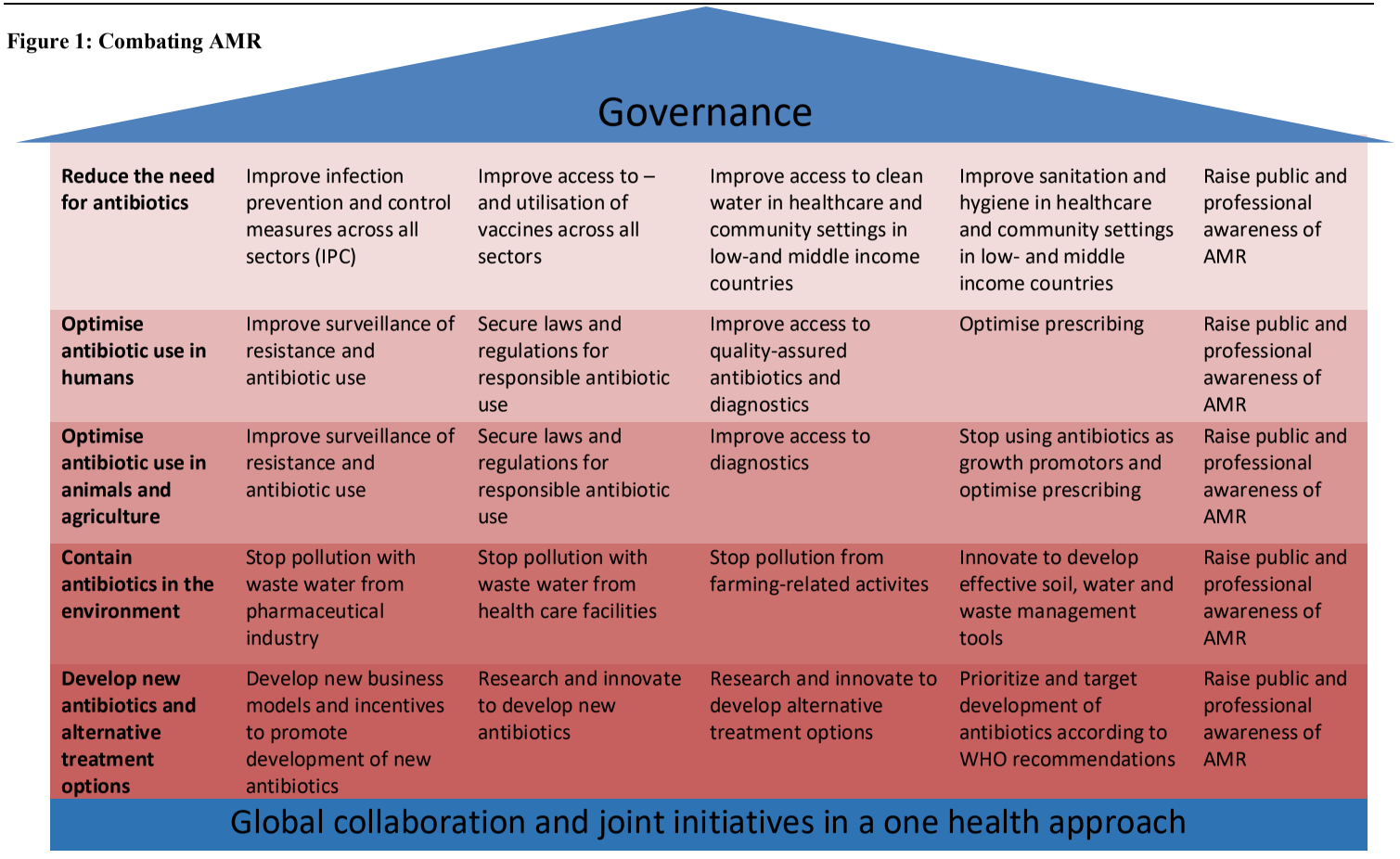
1.3.7 The "One health" perspective

Substantial amounts of antibiotics are used outside human medicine, to promote animal growth and prevent infections in livestock, for treatment of companion animals and in agriculture. In the United States, 80% of all antibiotics sold are used in animals, while in Norway, 89% of antibiotics sold are for human use [62, 63]. AMR arise from all antibiotic use, regardless of sector and a "One health" perspective, combining efforts and resources from human, animal, food and environmental health is therefore needed to tackle and contain resistance [10, 11, 31].

1.3.8 Reducing environmental pollution

Antibiotic waste in sewer systems and as wastewater of antibiotic production must be addressed, as this can affect development of resistance in environmental bacteria [6, 64, 65]. Vast amounts of antibiotics, with concentrations exceeding "safe" levels by up to 300 times, are found in rivers across the world, and in effluents from a wastewater treatment plant in India, high levels of broad-spectrum antibiotics was detected [66, 67]. Measures need to be taken to reduce environmental pollution with antibiotics.

Figure 1: Combating AMR



1.3.9 Public awareness

Raising public awareness regarding the use of antibiotics and the challenges of resistance, may relieve the perceived pressure on physicians to prescribe antibiotics or decrease self medication with antibiotics [68-70]. An increased understanding of which infections are self-limiting, when antibiotics may be useful and when they do more harm then good is necessary and a state of mind in all levels of society as described in the catchphrase "Antibiotics – only when needed." Travelling to countries with high prevalence of antibiotic resistance poses a risk for being colonized or even infected with multidrug-resistant bacteria [71, 72]. Both the public and healthcare personell need to be aware to be sure that this information is conveyed or asked for if a patient is seeking help for an infection upon return from travel. Taking part in ordinary vaccination programmes in their home country and securing additional vaccines before travel to other countries with different panorama of infectious diseases are important contributions from the public in the fight against AMR.

1.3.10 Surveillance, microbiology and rapid diagnostics

Guidelines for antibiotic use are built on an understanding of the aetiology of infections and levels of resistance in causative bacteria. Resistance data are supplied through surveillance systems at microbiology labs or prevalence studies performed in a local context to inform policy makers and guideline developers [23, 73]. Identifying the cause of an infection or eliminating infection as a potential diagnosis are important contributions to optimising antibiotic use in healthcare. However, communication barriers between microbiology labs and clinical units and challenges related to long turn-around-times and lack of availability of microbiological test results, have limited their use [74-77]. Fortunately, rapid diagnostics are evolving, reducing turn-around-times and improving access to valuable test results, supporting the prescriber in making wise choices regarding prescribing (or no prescribing) of antibiotics and improving patient outcome [77-80]. Although the term is heavily debated, the involvement of

laboratories in the fight against AMR is currently being referred to as diagnostic stewardship [79, 81]. Access to microbiological diagnostics and surveillance data are important in all countries to inform day-to-day clinical practice and the development of guidelines for prudent antibiotic use.

1.3.11 Optimising the use of existing antibiotics

One of the keys to preserving antibiotics and curbing the selection of resistant bacteria is to optimise the use of existing antibiotics. The catch phrase "The more we use them, the more we lose them" is an easily conveyed message, describing the relationship between antibiotic use and AMR. Antibiotics should be prescribed only when needed, with an optimal selection of antibiotics in the correct doses and administration forms, administered at the right time and interval and for the shortest possible duration. Clinical guidelines, informing prescribers about prudent and appropriate antibiotic use in the local context are one of the keys to optimising the use of antibiotics.

1.4 CHALLENGES OF ANTIBIOTIC PRESCRIBING AND USE

Antibiotics are used for the treatment of bacterial infections and surgical prophylaxis, a practice which has drastically reduced mortality from infectious diseases [29]. Furthermore, the great advances in modern medicine the last 70 years, including prostetic surgery, cancer therapy and transplant medicine would not have been possible without effective antibiotics to prevent and handle complications resulting from these procedures [10]. Increasing AMR rates are making it more and more difficult to find effective antibiotic options to treat these complications, which ultimately may jeopardize these achievements because the procedures become too risky to perform.

In 2012, 20 to 55% of patients in acute care hospitals across Europe were prescribed antibiotics [82]. It is estimated that in up to 50% of cases where antibiotics are prescribed in hospitals and up to 75% of prescriptions in long-term care facilities,

antibiotics are inappropriate (not needed or suboptimal) [14, 15, 83]. One main challenge that needs to be addressed is therefore overuse and misuse of antibiotics.

Both AMR and antibiotic consumption differs from country to country and also within countries and institutions [8, 73, 84-87]. Countries with extensive antibiotic use also have high levels of AMR [5, 88]. The global consumption of antibiotics in human medicine increased by 65% between 2000 and 2015 [89]. Together, Brazil, Russia, India, China and South Africa make up 40% of the worlds population but accounted for three-quarters of the 36% increase in the period between 2000 and 2010 [31]. Still, there are great challenges related to limited access to antibiotics in low- and middle-income countries, with more people dying from lack of antibiotics than antibiotic resistance [31]. In children younger than 5 years, access to antibiotics could potentially reduce deaths from community-aquired pneumonia by 75.4%, saving close to 450 000 lives across 101 countries [31].

For the individual physician making treatment decisions on behalf of a patient, antibiotic prescribing could potentially include an ethical dilemma, weighing individual patient risk against societal risk [90]. Maximum coverage in all empirical antibiotic treatment regimens with broad-spectrum antibiotics today are expected to cause a rapid increase in rates of resistance, leaving antibiotics without effect for future patients [91]. Balancing this risk can be challenging and guidelines may help by incorporating available evidence and risk assessment into recommendations, allowing individual physicians to lean on guidelines when making clinical decisions.

Securing access to antibiotics for those who will benefit from them, but at the same time ensuring that antibiotics are used responsibly to minimize AMR are key challenges today. AMR can not be resolved in high-income countries alone but needs a worldwide engagement and inverventions across all sectors and levels of care [41-43].

1.5 AMR AND ANTIBIOTIC USE IN NORWAY

Norway is at the lower end of both antibiotic use and levels of resistance, with exceptionally low levels of antibiotics used in agriculture and fish farming [23]. An important contribution to the low levels of antibiotic use in humans was a unique regulatory paragraph implemented in Norway between 1938 and 1994, called the "need clause." This paragraph allowed Norway to only register drugs and drug formulations which were considered needed in the Norwegian setting, until the adaptation to European legislation in the 1990s [22]. This postponed the introduction of many antibiotics in Norway and was also crucial in securing that antibiotics are not sold over-the-counter, but are for prescription use only [22]. In Norway, 82% of antibiotics for use in humans are prescribed in primary care, and only 8% of antibiotics are used in hospitals [23]. This could suggest that antibiotic use in hospitals are of limited importance and that all efforts should be placed in securing prudent prescribing in primary care. Norway does however have a limited number of broad-spectrum antibiotics available for oral treatment, leaving many broad-spectrum antibiotics to be used mainly within the hospital setting. Hospitals are a setting where frail, sick and immunocompromised patients are gathered in a confined area with high antibiotic pressure and extensive use of broad-spectrum antibiotics, and is therefore an ideal environment for the selection and spread of antibiotic resistant bacteria. Responsible use of antibiotics in the hospital setting is therefore of great importance. More advanced antibiotic therapy is increasingly given in long term care facilities (LTCF), adding to the rationale of a call for action also in these institutions [92, 93].

The link between antibiotic use and AMR is widely acknowledged, but how the distribution of antibiotic use in the society is associated with AMR has only just been investigated. Studies suggests that to reduce AMR, we gain more by reducing the broadly distributed, low-intensity use in a broad population, compared to intense, repeated use in single patients [5, 85].

Norway has had several policy documents, outlining the threat of AMR, and in December 2015, the *National action plan against antibiotic resistance in health services* followed the *National strategy against antibiotic resistance* (2015-2020) [13, 94-96]. The national action plan covers measures directed at the public, hospitals and primary care, including general practitioners, dentists, emergency wards physicians and other primary care healthcare institutions [95]. Some of the goals outlined are a 30% reduction in total antibiotic use, measured from 2012 to 2020 (DDD/1000 inhabitants/day) and a 30% reduction in the use of a selection of broad-spectrum antibiotics in hospitals (DDD/100 bed days) during the same period. In 2018, a 24% reduction in the total use of antibiotics had been achieved, while the hospitals had reduced broad spectrum antibiotics by 12 % [63].

1.6 MEASURING ANTIBIOTIC USE

1.6.1 Defined daily doses

Consumption of antibiotics is most often measured and monitored by the use of antibiotic sales statistics, coupled with activity data. European Contries, including Norway, have been collecting data on antibiotic use for many years, but low- and middle income countries in particular, struggle with collecting reliable data [23, 84]. WHO Defined Daily Doses (DDD) is primarily used as the nominator in drug statistics. The DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [97]. In hospitals, the unit of measurement is usually DDD/100 hospital bed days or DDD/100 admissions, while primary care usually measures DDD/1000 inhabitants per day [23, 84]. Sales data can for example be made available from pharmacies or wholesalers and be combined with data from hospital administrative systems and national registries where such systems are in place. DDDs for parental antibiotics used in hospitals are sometimes artificially low compared to normal hospital dosing as DDD is a theoretical unit that do not often change, while there in hospitals has been a steady increase in dosing over the years. To make up for this difference, hospital adjusted DDDs have been proposed [98]. It

should however be noted that the DDDs for many important antibiotics (e.g. ampicillin, meropenem) were increased in the latest WHO ATC/DDD Index update in 2019 [99].

1.6.2 WHO AWaRe categories

In the 20th edition of the Model List of Essential Medicines in 2017, the World Health Organization (WHO) grouped antibiotics into access, watch and reserve-categories (AWaRe) and the list was recently updated [100, 101]. Access group antibiotics should be widely available, affordable and quality assured. First or second choice antibiotics for reviewed clinical syndromes were assigned to this group. Antibiotics in the watch group have a higher potential for resistance, are first or second choice treatment for only a limited number of indications and should be prioritized as key targets of stewardship programmes and monitoring. Reserve group antibiotics are the "last resort" options which should be protected and preserved and included as a focal point of stewardship programmes to secure available treatment options in life-threatening infections with multidrug resistant bacteria [100, 102]. Although not all antibiotics are included in AWaRe, this new categorization of antibiotics is a new option for measuring and comparing antibiotic prescribing and use. Antibiotic consumption according to AWaRe differs substantially between countries and continents. Classified by the WHO Model List of Essential Medicines from 2017, the Nordic countries use less than 20% Watch group antibiotics, whereas in Georgia, Jordan and Japan, corresponding figures were 52%, 59% and 76%, respectively [84].

1.6.3 Quality indicators

While sales statistics are easily collected, these types of aggregated data do not reveal antibiotic prescribing patterns at patient level and do not connect indication for treatment with the antibiotics used. It is therefore difficult to use only this kind of data to identify challenges in prescribing practices and plan targeted interventions to improve prescribing practice. For the purpose of analyzing and enhancing prescribing quality, audits are frequently used for data collection. It allows more in-depth

knowledge of prescribing practice in relation to indications for antibiotic treatment and development of tailored interventions in the local context.

Quality indicators (QI) for measuring the appropriateness of antibiotic prescribing can be helpful in identifying areas with room for improvement [103, 104]. The degree of adherence to clinical antibiotic guidelines is an often reported QI in studies evaluating implementation of antibiotic stewardship interventions in hospitals and ranges from 43 to 90% adherence with guideline recommendations [105].

1.7 ANTIMICROBIAL STEWARDSHIP

1.7.1 What is antimicrobial stewardship?

The term stewardship was first introduced in relation to antibiotics by McGowan and Gerding in 1996 with regards to ensuring optimal antimicrobial use and consideration of the long-term effects of antimicrobial selection, dosage and duration of treatment on development of resistance when deciding on antimicrobial treatment [106].

There is no single, global definition of antimicrobial stewardship (AMS), but it has most recently been defined by the European Society for Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship (ESGAP) as a strategy, a coherent set of actions which promote using antimicrobials responsibly [107]. In comparison, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) and the Pediatric Infectious Diseases Society (PIDS) have made a consensus statement, defining antibiotic stewardship as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” [108]. For the purpose of this thesis, only stewardship related to antibiotics will be discussed and the term AMS will refer to antibiotic stewardship.

1.7.2 Antimicrobial stewardship programmes in hospitals

Core elements of antimicrobial stewardship programmes (AMS-programmes) and handbooks of AMS have been published by multiple professional bodies like The Infectious Disease Society of America (IDSA), The American Centers for Disease Control and Prevention (CDC) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [14, 21, 108-111]. To ensure that AMS-programmes have an impact in the hospitals in which they are implemented, these core elements should be in place. Structure, process and outcome indicators which can help assess and compare the AMS-programmes have also been proposed, both at hospital- and national levels [103, 112-115].

Commitment from senior hospital management leaders towards AMS-programmes is a core element to secure credibility and legitimacy to the programme and the necessary focus and resources for the stewardship programme, both in terms of human recources, but also financing and resources related to information technology [109, 110].

Expertise on infection management and *laboratory and imaging services* with timely results should be available. *Clinical antibiotic guidelines* based on published evidence and data on local susceptibility should be available to prescribers, along with *policies regarding documentation of antibiotic treatment plans* and *available advice from an AMS-team*. The *AMS-team* should include *healthcare professionals trained in infection management and stewardship*, such as physicians, pharmacists and nurses [110]. Other valuable members are a clinical microbiologist, information system specialist, an infection control professional and a hospital epidemiologist [14].

Another core element is to secure *accountability* and assign *responsibilities* in a stewardship programme to the hospital management, AMS-committee, AMS team and the clinical staff. A healthcare professional should be identified as leader of the stewardship team and a physician leader is often beneficial for the implementation of the programme [110]. Stewardship programmes should take action and implement

interventions aimed at optimising antibiotic use, such as review of antibiotic therapy or audit with feedback. Providing clinicans with valuable *education* on antibiotic prescribing and resistance, and providing the AMS-team also with *practical training* in stewardship is recommended [110]. The stewardship team should have clearly defined roles and responsibilities, incuding *monitoring, surveillance and reporting* of process and outcome measures and *quality indicators.* This can include monitoring total antibiotic use and use of broad-spectrum antibiotics, rates of resistance, degree of adherence to guidelines, rate of review of therapy, adherence to interventions or agreed goals [108-110]. *Feeding back this information to clinicians and leaders* aids in the implementation and sustainability of AMS-programmes. *Procedures of collaboration* with other relevant hospital commitees should also be in place [14, 110].

ESCMID has developed generic competencies (knowledge, attitudes and skills) in antimicrobial prescribing and stewardship which can be used in training for independent prescribers, like hospital physicians [116]. Specialist antimicrobial stewardship knowledge are outlined in a comprehensive overview of knowledge and skills required for leaders of antimicrobial stewardship programmes by SHEA and partnering societies, and includes the following ten categories 1) general principles of antimicrobial stewardship, 2) stewardship interventions, 3) antimicrobials, 4) microbiology and diagnostics, 5) common infectious syndromes, 6) measurement and analysis, 7) informatics, 8) programme building and leadership, 9) special populations and non-acute hospital settings and 10) infection control [117].

1.7.3 Antibiotic prescribing in hospitals

Antibiotic prescribing in hospitals is dependent on both culture, context and individual behaviour [76, 118-121]. A recent study from England shows that medical and surgical teams have different perceptions and norms of antibiotic prescribing. Medical teams have a higher extent of team perspective with input from other professionals, while surgical teams perceive antibiotic decision making as a nonsurgical intervention, leaving to a greater extent junior staff or other specialties to prescribe antibiotics [118]. In Norwegian hospitals, junior physicians rely on clinical

guidelines for antibiotic prescribing and the input from infectious disease-physicians (ID-physicians) are perceived as highly valuable [76]. In England, hierarchy is more pronounced, and the head of the department will influence prescribing policy to a great extent [119]. The perceived value of - and confidence in clinical guidelines will also affect prescribing practice [122]. Ownership to guidelines is important in all areas of practice, but in infectious diseases, bacterial aetiology of infections and local resistance patterns will differ between countries and regions, meaning guidelines must be informed by local context [122].

As antibiotic use and development of AMR is closely linkend, the decision of antibiotic prescribing does not only influence the patient of today, but also our future patients. Diagnostic uncertainty and a perception of AMR not being an imminent threat, are however factors that may cause antibiotics to be prescribed also against advice in clinical guidelines [122-125]. Another important factor affecting prescribing practice is the fear for a patients wellbeing, leading to prescription of antibiotics "just in case" or prescription of more broad spectrum than recommended [125]. When attempting to change antibiotic prescribing it is therefore important to take into account the balance between the perceived individual patient risk and the societal risk if antibiotics are rendered ineffective [90].

1.7.4 AMS interventions

To curb and contain resistance, interventions must be applied across all sectors and include the public. A new term, drawing on the success of the "carbon footprint" has been proposed as a communication tool to make the public aware of the magnitude of antibiotic use and how reduction in overuse and misuse of antibiotics worldwide can be achieved in all sectors (human, animal and agriculture/industry) [126]. The term is called "the antibiotic footprint" and the goal is to reduce antibiotic consumption to a minimum [126]. For the purpose of this thesis, only health system interventions applied in the hospital setting will be described in more detail.

Health system interventions are divided into four categories and defined by the Effective Practice and Organisation of Care (EPOC) as [127]:

1. Delivery arrangements: changes in how, when and where healthcare is organized and delivered and who delivers care. This category includes for example the subcategory of *environment* - changes to physical healthcare environment, like altering equipment, the subcategory of *outreach services* and the subcategory of *health information systems*.

2. Financial arrangements: changes in how funds are collected, insurance schemes, how services are purchased and the use of targeted financial incentives or disincentives.

3. Governance arrangements: rules or processes that affect the way in which powers are exercised, particularly with regard to authority, accountability, openness, participation and coherence. The category includes for example the subcategories of *prescribing* and *authority and accountability for quality and practice* – exemplified by implementation of clinical guidelines.

4. Implementation strategies: interventions designed to bring about changes in healthcare organizations, the behaviour of healthcare professionals or the use of health services by healthcare recipients. The subcategories of *organisational culture*, *audit and feedback*, *educational outreach and tailored interventions* are included here.

AMS- interventions in hospitals are found mainly in the categories of delivery arrangements and implementation strategies and can again be divided into environmental restructuring, restrictive and enabling/persuasive interventions [105].

Environmental restructuring interventions apply changes to the physical prerequisites, for example by changing from paper to electronic medical charts, introducing new rapid diagnostics, reminders (e.g. posters/pocket cards summarising

antibiotic polices) and changing the physical environment where prescribing is performed [105].

Restrictive interventions are defined as "using rules to reduce the opportunity to engage in target behaviour (or increase the target behaviour by reducing the opportunity to engage in competing behaviours) [105]." Examples of restrictive interventions are applying formulary restrictions or pre-approval, automatic stop orders or selective reporting of laboratory susceptibilities [105]. Restrictive interventions are effective in reducing broad-spectrum antibiotic use, but sustained effects are more likely if restriction is combined with enabling interventions [105].

Making it easier for clinicans to access information which is needed for appropriate prescribing are known as *enablement strategies* [21]. This could be easy access to guidelines, decision support or microbiological test results.

Interventions aimed at improving knowledge and changing attitudes and beliefs about antibiotic prescribing are also called *enabling interventions* or *persuasive interventions*, and examples are education, audit with feedback and academic detailing [21, 105]. Educational meetings or distribution of educational material are frequently used in AMS-programmes, but this type of intervention is of limited efficiency when used alone [14, 105]. Audit with feedback, where a summary of clinical performance over a specified period of time is fed back to clinicans, is however a more effective intervention [105]. Educational outreach are interventions where a trained person meets with providers in their practice setting to give information, intending to change the providers practice [128]. Academic detailing is such an intervention where information is given and current practice is discussed [128]. Persuasive interventions are effective and may be easier to implement in a variety of settings as they are more readily accepted by clinicians [21, 129].

Information technology can also be applied to change behavior, through development of applications supporting prudent prescribing, "serious" gaming - educating

clinicians and the public - and clinical decision support systems, helping clinicans to prescribe, review and discontinue antibiotic treatment appropriately [130-132].

1.7.5 Outcome of AMS

AMS-studies often report *process indicators* of appropriate antibiotic use, like the rate of review of antibiotic therapy or change in antibiotic use. Process indicators are important in order to evaluate whether interventions are implemented or not. The ultimate goals of AMS are however to improve *patient outcome,* (e.g. morbidity and mortality) and lower or contain *antibiotic resistance rates.* It is often difficult to show an effect on resistance rates following individual intervention studies, as the studies are normally confined in length of follow-up, resistance rates are influenced by many other variables and individual studies lack power to detect these differences [133]. To be able to assess cost-effectiveness of stewardship activities, *economic outcomes* (e.g. costs/savings) should also be reported more often [134].

Qualitative methodology is needed to understand the way stewardship changes prescribing behaviour and beliefs and perceptions of antibiotics in institutions and the society.

1.8 BEHAVIOUR CHANGE FRAMEWORKS

Behaviour change interventions can help close the gap between recommended, evidence based clinical practice and actual practice in hospitals. As hospitals differ from each other and wards within hospitals differ, taking the specific context into consideration can help increase effect of such interventions. Social- and behavioural sciences provide different frameworks for behaviour change which can be utilized in AMS, such as the COM-B-model and the Theoretical Domains Framework [135]. The COM-B-model postulates that in order for behaviour to occur or change, a person needs to be *capable* (have knowledge and skills), have the *opportunity* (physically and socially) and have *motivation* in order for a certain *behaviour* to occur [135]. The Theoretical Domains Framework incorporates barriers and enablers which can

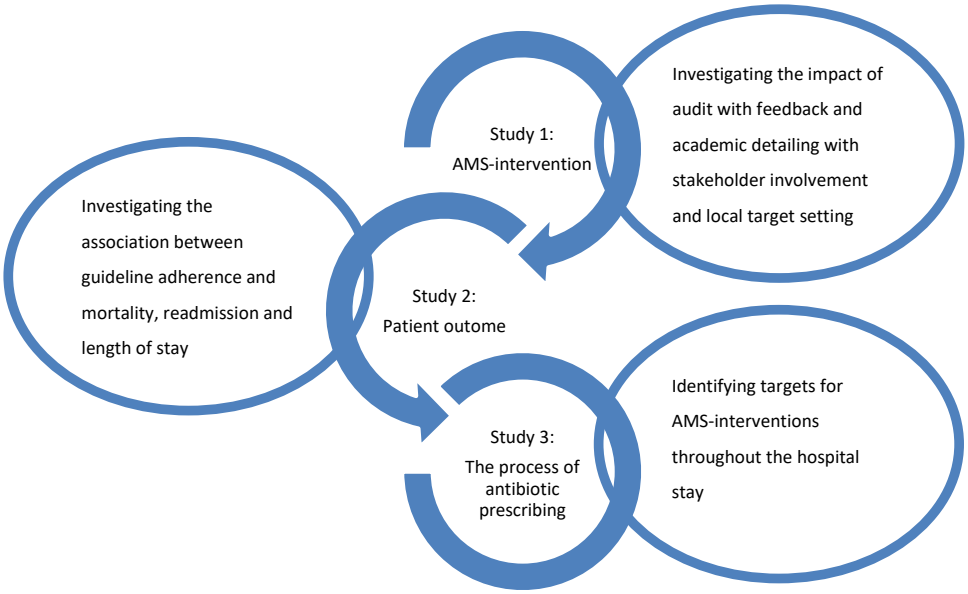
influence behaviour and can be linked to the COM-B. The domains (e.g. knowledge, skill, environmental context, resources, beliefs, goals etc) can be subcategories of the three pre-conditions of the COM-B, (Capability, Opportunity and Motivation) [135, 136]. Flottorp et al have provided a comprehensive checklist which includes 57 potential determinants of practice, grouped in seven domains: [1)] guideline factors (e.g compatibility with current practice and source of recommendations), [2)] individual health professional factors (e.g. knowledge and skills, agreement with recommendations), [3)] patient factors (e.g. patient needs and preferences , [4)] professional interactions (e.g. communication and influence), [5)] incentives and resources (e.g. information system, assistance for clinicians), [6)] capacity for organisational change (e.g. capable leadership, relative strength of supporters and opponents) and [7)] social, political and legal factors (economic constraints on the healthcare budget, payer or funder policies) [137]. Frameworks and checklists like these can be used both as tools for planning behaviour change interventions and to improve the reporting of such studies.

2. AIMS AND OBJECTIVES

The overall aim for this PhD-project was to gain knowledge needed to implement antibiotic stewardship in Norwegian hospitals through determining

- the impact of antibiotic stewardship interventions in a Norwegian hospital setting
- how patient outcome is associated with antibiotic prescribing practice and
- if analysis of patient-level antibiotic prescribing data throughout hospital admission can identify targets for antibiotic stewardship interventions.

Figure 2: Overview of studies and aims:



2.1 STUDY I

Aim

The aim of this study was to investigate the impact of behaviour change interventions, with stakeholder involvement and local target setting, on change in

antibiotic prescribing practices in hospitals. The findings of this study are reported in paper I.

Objectives

To investigate to what degree implementing audit with feedback and academic detailing with stakeholder involvement and local target setting affects a) adherence to national clinical practice guidelines for antibiotic use in hospitals and b) use of broad spectrum antibiotics and c) locally set targets, across hospitals in Western Norway.

2.2 STUDY II

Aim

This study aimed to investigate how appropriate, guideline-adherent antibiotic prescribing was associated with patient outcomes. The results from this study are reported in paper II.

Objectives

To analyse the association between adherence to national guidelines for antibiotic use in hospitals at inititation of treatment, and in-hospital- and 30-day mortality, readmission and length of stay (LOS) for inpatients.

2.3 STUDY III

Aim

The aim of the study was to describe and analyse the process of antibiotic prescribing from admission to discharge to identify targets for antibiotic stewardship interventions. The results from this study are reported in paper III.

Objectives

a) To describe and analyse the process of initiating, modifying and stopping antibiotics throughout the hospital stay.

b) To identify factors associated with non-adherence to national guidelines for antibiotic use in hospitals.

c) To explore if WHO AWaRe-categories are useful for analysis of patient-level prescription data in hospitals.

d) To explore if we can identify targets for antibiotic stewardship interventions through the knowledge gained from a-c.

3. MATERIALS AND METHODS

3.1 OVERVIEW

Table 1 gives an overview of included papers, materials and statistical analyses applied.

Table 1: Overview of papers

Paper	Title	Material	Statistical analysis
I	The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study.	Data from patient medical records during hospital admission (N=1802) Activity adjusted antibiotic sales statistics.	Chi-square test Logistic and linear regression Interrupted time series analysis
II	The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: Results from a Norwegian multicentre, observational cohort study.	Data from patient medical records during hospital admission (N=1756)	Descriptive statistics Univariate and multivariate linear and logistic regression Fine and Gray-model with competing risk analysis
III	Identifying targets for antibiotic stewardship interventions through analysis of the antibiotic prescribing process in hospitals - a multicentre observational cohort study	Data from patient medical records during hospital admission (N=1235)	Descriptive statistics Univariate and multivariate logistic regression

3.2 STUDY DESIGN

Study 1 was a randomised, controlled intervention study, where hospitalised patients were included prospectively on initiation of antibiotic treatment. Data were gathered retrospectively after hospital discharge. Primary outcome measures were adherence to the national guideline for antibiotic use in hospitals, change in agreed target areas of follow-up from intervention sessions and change in the total activity-adjusted use of broad-spectrum antibiotics.

Study 2 and 3 were both observational cohort studies and used data collected in the intervention study. In study 2, primary outcome measures were mortality, readmission and length of stay, and outcomes were analysed according to status for adherence to guideline on treatment initiation, with adjustment for probable confounders.

In study 3, we focused on the process of antibiotic prescribing. Primary outcome measure was the type of antibiotic regimens used throughout the admission, grouped by WHO AWaRe categories and adherence to guidelines on initiation of treatment. Secondary outcome measures were 1) the patterns of antibiotic prescribing from admission to discharge, grouped by diagnoses and 2) non-adherence to guideline. In the latter analysis, factors associated with non-adherence were investigated.

3.3 SETTING

All three studies were conducted at Haukeland University Hospital, Stavanger University Hospital and Haraldsplass Deaconess Hospital within the specialties of infectious diseases, pulmonary medicine and gastroenterology. Haukeland University Hospital and Stavanger University Hospital are tertiary care hospitals with 1100 and 600 beds, respectively. Haraldsplass Deaconess Hospital is a not-for-profit, privately owned hospital with 160 beds, in close collaboration with Haukeland University Hospital.

3.4 PARTICIPANTS

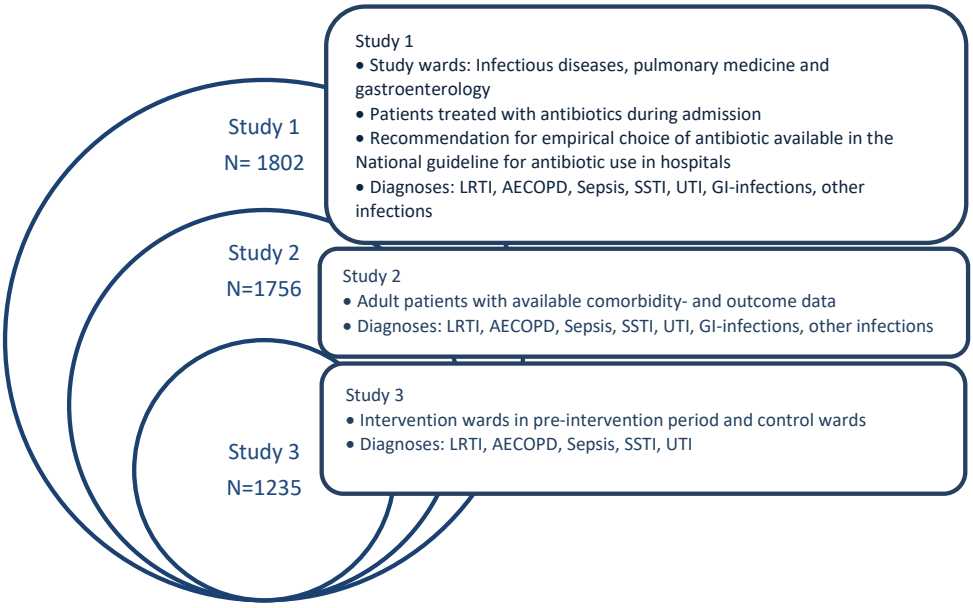
The participants included in all three studies, were patients receiving antibiotics during admission to one of the study wards between February and July of 2014. For overview of participants, see Figure 3. Study 1 included 1802 patients, of which 1279 were included pre-intervention and 523 post-intervention. Pre-intervention, 478 patients were included in audit with feedback, 451 in academic detailing and 350 in the control group. Post-intervention 182 patients were included in audit with feedback, 172 in academic detailing and 169 in the control group. Only the first stay of readmitted patients was included.

Five physicians and two pharmacists working at the included hospitals were part of the intervention teams in study 1. All physicians working at the intervention study wards were invited to attend the interventions sessions and attendance ranged from an estimated 70 to 100% at the study wards.

Study 2 included adult patients from the cohort of study 1 (N=1756). Patients for whom outcome data was unavailable (tourists etc) and/or comorbidity data was not possible to retrieve from the hospital administrative system, were excluded.

In study 3, the cohort consisted of patients from study 2 (N=1235), with diagnoses belonging in the groups of lower respiratory tract infections (LRTI), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), Sepsis, skin- and soft-tissue infections (SSTI) and urinary tract infections (UTI). The groups of post-intervention patients from intervention wards and patients with diagnoses categorized in the groups of gastrointestinal infections (“GI-infections”) and “Other diagnoses” were excluded.

Figure 3: Patients from the intervention study cohort included in the three studies:



3.5 DATA COLLECTION AND HANDLING

The main data collection for all three studies was manually performed, extracting data from electronic medical records by the use of paper case report forms (CRFs). Included data were patient demographics, indications for antibiotic treatment, antibiotics prescribed, and doses given during admission, antibiotics prescribed upon discharge, microbiological test results, patient outcome (mortality, readmission and length of stay), estimated glomerular filtration rate on admission and admittance from- or discharge to other hospitals or nursing homes.

For study 1, additional data regarding the use of broad spectrum antibiotics at ward level were extracted from the hospital pharmacies sales statistics and adjusted per 100 bed days, using data from the hospital administrative system.

For study 2 and 3, additional data on coded diagnoses present at discharge (ICD-10-codes) were extracted from the hospital administrative system and used to calculate Charlson Comorbidity Index (CCI) [138, 139].

Data were manually plotted into the statistical software SPSS for Windows, version 24, with coded variables and later transferred to STATA SE version 15 (Stata Statistical Software, College Station, TX, USA). Data validation was performed by manually checking plotted data against CRFs upon database completion. Missing data were sought in the electronic medical record and CRF and database completed when possible.

3.6 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 24 and Stata SE version 15 for study 1 and Stata SE version 15 for study 2 and 3.

3.6.1 Paper I

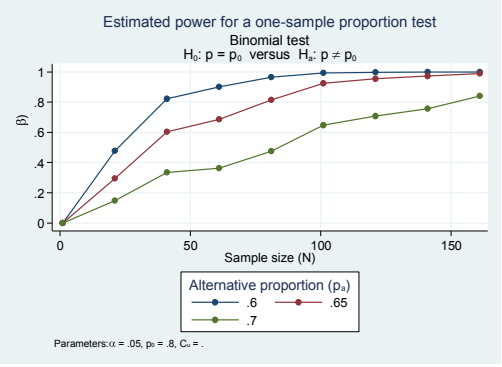
To assess the effect of the antibiotic stewardship interventions audit with feedback and academic detaling, analysis was performed both per intervention group and per specialty. Analysis per cluster was originally planned, but due to fewer patients than expected in the post-intervention period, this was not performed. Pearsons' chi-square was used to test categorical data and two-sample t-test was used for continuous data. By using simple logistic and linear regresson models, we evaluated the group-by-period interaction term to test whether adherence to guidelines and patient outcome in intervention groups and specialties changed differently over time, when compared to the control group.

Interrupted time series (ITS) analysis was used to assess the level- and trend of activity-adjusted broad spectrum antibiotic use, through the method described by the Effective Practice and Organisation of Care Group (EPOC group) [140]. A significance level of 5% was used for all analyses.

Sample size

Sample size calculations performed before initiation of study 1 was based on adherence to guidelines. Baseline adherence was unknown, and we therefore used two approaches for sample size calculations in the study protocol. For the intervention study, a baseline adherence to guidelines of 50% and an improvement in adherence to guidelines of 20% following interventions was assumed for each cluster. With a power of 80% and significance level of 5%, we needed 93 patients included before and after interventions in each cluster. It was proposed in the original study protocol that adherence to guidelines in antibiotic prescribing should be 80% or more and we therefore did an additional calculation, using a one-sample binomial test for proportions. With 80% power and type 1 error of 0.025 (one sided), the smallest sample needed to detect a statistically significant difference between adherence of 70% vs a reference rate of 80%, was 155 patients. As baseline adherence was unknown, we therefore aimed to include at least 155 patients in each cluster before and after interventions (Figure 4).

Figure 4: Power calculations



3.6.2 Paper II

Chi-square test and two-sample t-test were used to analyse differences in patient characteristics between the two groups of adherence and non-adherence to guidelines. In assessment of the association between adherence to guidelines and patient outcomes (mortality, readmission and length of stay), we used univariate and multivariate logistic and linear regression. In multivariate regression analysis we adjusted for indication for treatment, comorbidity (CCI), age group, admittance from institution, sex and seasonality. A Fine and Gray-model was also fitted as a sensitivity analysis to analyse length of stay with in-hospital death as competing risk. A p-value below 0.05 was considered statistically significant for all analysis.

3.6.3 Paper III

In paper III we studied the process of antibiotic prescribing by a) looking at the degree of antibiotics prescribed belonging to the different groups in the WHO AWaRe categories, b) process measures of antibiotic prescribing and c) factors associated with non-adherence to guidelines. Descriptive statistics were used to analyse a) and b), while factors associated with non-adherence to guidelines were analysed using multiple logistic regression analysis.

3.7 ETHICS

This research was conducted in accordance with national and institutional standards and the Declaration of Helsinki and approved by the data protection officer (2013/9352) and local managers. The regional ethical committee approved the waiver of informed consent (2013/1305).

4. RESULTS

4.1 PAPER I: AMS-INTERVENTIONS

The overall impact of audit with feedback and academic detaling across intervention wards was an absolute increase in adherence to antibiotic guidelines from 60% to 66% (p=0.04). This impact was however not significant when compared with control wards (time-by-period interaction). When comparing pulmonary medicine wards with control wards, the total impact of interventions was significant, with an increased adherence to guidelines of 14% (p=0.034). For the specialties of gastroenterology and infectious diseases there was no total impact of interventions. Main results from study 1 and 2 are given in Figure 5.

Activity adjusted use of broad-spectrum antibiotics was analysed using interrupted time series. For the audit with feedback wards, the trend showed significant decrease in the use of broad-spectrum antibiotics and the level of broad-spectrum antibiotic use was reduced at both 12 and 18 months post intervention. For the groups of academic detailing and control and for intervention wards per speciality, there was no significant change in broad-spectrum antibiotic use.

During the interventions, the physicians at the intervention wards were encouraged to set local targets for follow-up. The pulmonary ward at hospital A targeted an increase in the use of penicillin 2 mill x 4 for patients with pneumonia and AECOPD and managed to increase the use by 30% ($p<0.001$), following the intervention. The ward of gastroenterology at hospital A targeted a reduction in the use of ciprofloxacin and this was reduced at all timepoints following the intervention, although not statistically significant. The other intervention wards did not identify any targets or did not achieve consensus on 1-2 measurable targets.

Compared with control wards, mortality, readmission and length of stay for intervention groups and specialties was not significantly changed during this study.

4.2 PAPER II: PATIENT OUTCOME WHEN ADHERING TO GUIDELINES

When investigating the association between adherence to the national antibiotic guideline and patient outcomes, we found that both in-hospital and 30-day all cause mortality was lower in the adherent group. For 30-day mortality, the adherent group had an odds-ratio (OR) of 0.48, p=0.003, while for in-hospital mortality OR=0.46 with p=0.001. 30-day readmission was not associated with adherence to guidelines, but there was a trend towards shorter length of stay for patients (-0.47 days, 95% CI (-1.02, 0.07, p= 0.081) for patients treated according to antibiotic guidelines and discharged alive. This was supported by competing risk analysis of LOS, where the subdistribution hazard ratio for discharge in the adherent group was higher, compared to the non-adherent group (SHR=1.17, 95% CI (1.02, 1.34)).

Figure 5: Main results from study 1 (orange) and study 2 (blue)

4.3 PAPER III: THE PROCESS OF ANTIBIOTIC PRESCRIBING IN HOSPITALS

A description of the main results from study 3 are given in Table 2, with more details given in the following paragraphs.

4.3.1 WHO AWaRe

When empirical antibiotic prescribing was according to the national antibiotic guideline for antibiotic prescribing in hospitals, 89% of antibiotic regimes were classified in the access category of the WHO AWaRe categories, containing antibiotics with the least potential of increasing AMR. When empirical prescribing was non-adherent, only 49% of antibiotic regimens were in the access category, but the proportion av access-group antibiotics increased for the second regimen (61%) and for antibiotics prescribed upon discharge (74%).

4.3.2 Antibiotic prescribing - process measures

Initiation of treatment

Antibiotics were most often initiated in the emergency department (83.6%), but this varied from 64.8% for patients with UTI to 96.8% for patients with sepsis. 63% of patients received empirical treatment according to guidelines on initiation of therapy. Initiating therapy at the ward was associated with non-adherence to guidelines with an OR= 1.7 and 95% CI (1.24, 2.36).

When patients were admitted from an institution, they were more likely to receive non-adherent empirical treatment (OR=1.44, 95% CI (1.04, 2.0)). Compared to hospital A, being admitted to hospital B was beneficial in terms of avoiding non-adherence to guidelines on initiation of treatment with an OR of 0.63 and 95% CI of (0.46, 0.86).

During admission

The majority of patients (61.4%) had their first antibiotic regimen changed during admission. For 20.6% of patients, the initial antibiotic regimen was kept throughout the admission, but changed at discharge.

Oral antibiotic therapy was prescribed for 84.5% of patients during the course of treatment. For UTI patients, mean day of first oral treatment was 2.7 days 95% CI (2.3, 3.1), while patients diagnosed with sepsis had a mean first day of oral treatment at 5.1 days 95% CI (4.6, 5.5).

At discharge

A minority of patients were considered cured at discharge, with 77.4% of patients continuing antibiotics when leaving the hospital. The mean total days of antibiotic treatment was 10.6 days across diagnosis and the mean days of in-house and post-dishcarge therapy did not vary much between the groups of diagnoses. Patients with sepsis had the longest duration of in-house therapy, with a mean of 6.6 days. The highest number of post-discharge days of therapy (7.1 days) was prescribed to patients with SSTI, while 5.8 days were the mean days of post-discharge therapy for all groups in total.

Table 2: The process of antibiotic prescribing in hospitals and targets for antibiotic stewardship interventions:

Initiating therapy	Modifying therapy	Stopping therapy

• Empirical AB therapy was started in the ER for 83.6 % of patients
• Empirical AB therapy was adherent to guideline for 63 % of patients
• Non-adherence was associated with:
  • Initiation of therapy at the ward: OR=1.7
  • Admittance from institution: OR=1.44
  • Admittance to hospital B: OR=0.63
  • Indication for treatment ≠ LRTI
• When treatment was adherent: 89% of AB-regimens were in the WHO Access group only
• When treatment was non-adherent: 49% of AB-regimens were in the WHO-Access group only
	• Empirical AB therapy was stopped for 9.72% of patients without new AB prescribed
	• Empirical AB therapy was de-escalated for 56.4% of patients
	• Empirical AB therapy was escalated for 18.2% of patients
	• Empirical AB therapy were modified at day 3.6 (mean)
	• Oral antibiotics was prescribed for 84.5% of patients, mean first day 4.1
	• When empirical AB treatment were non-adherent, modification of therapy led to more patients receiving antibiotics from the WHO-Access group only
		• At discharge, 77.4 % of patients were prescribed antibiotics
		• If empirical AB treatment were adherent, 85% of discharge antibiotics were in the WHO-Access group only, compared to 74% for patients receiving non-adherent empirical treatment
		• More than 3 different antibiotic regimens were prescribed for 9.4% of patients, but most patients had 2 regimens prescribed (54.3%)
		• Days of antibiotic treatment (mean):
		  • In-house: 6.2
		  • After discharge: 5.8
		  • Total: 10.6
		• Mean days of antibiotic therapy was similar across very different groups of diagnosis

Targets identified:

1. Promoting adherence to guidelines when prescribing empirical antibiotic therapy
2. Targeting antibiotic prescribing in the ER, focusing on first line clinical staff
3. Understanding drivers of non-adherence for patients admitted from institutions
4. Understanding the cultural and contextual drivers for antibiotic prescribing across institutions and specialties
5. Focusing on reducing duration of therapy safely , in accordance with emerging evidence on duration of antibiotic treatment

AB: Antibiotic

5. DISCUSSION

Through this PhD-project, we aimed to contribute to the knowledge and understanding needed for implementing antibiotic stewardship in Norwegian hospital settings. The national guideline for antibiotic use in hospitals is a cornerstone in this work, constituting evidence based and desired practice. The research has taken us from exploring the effect of tailored AMS-interventions, through investigating how adherence to guidelines affect patient outcomes and lastly investigating the antibiotic prescribing process from admission to discharge to find factors that are associated with non-adherence to guidelines and targets for antibiotic stewardship interventions. In the following, methodology and results of the included studies will be discussed, highlighting strengths and weaknesses which could impact reliability, internal- and external validity and discuss our work in relation to others'.

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 Internal validity

Internal validity reflects the confidence that we can place in the findings of a study, meaning that the study measured what it intended to measure and the research questions could be answered correctly, in a manner free from bias [141, 142]. Some factors affecting validity are only applicable to study 1 and are hence only discussed in relation to this study. Additional details of strengths and limitations are included in the published papers. Internationally recommended checklists have been applied when reporting on all three studies, with the use of the extended CONSORT checklist for study 1 and the STROBE checklist for study 2 and 3 [143-145].

Selection bias

Study design and randomization

Proper study design is vital to secure internal validity of the study. Many studies investigating AMS-interventions have been uncontrolled before-after studies, and

interventions were often a response to an outbreak [105, 146]. These studies are prone to bias, often with outcome measures normalising and "regressing to the mean" when the outbreak is over [146].

Study I was a multicentre, cluster randomised, controlled intervention study, performed in a "normal" clinical setting with control wards in all hospitals to be able to control for random time effects. The clusters were wards within three specialties at three different hospitals with limited flow of staff between them. The gold standard of intervention research, the randomised controlled trial (RCT), would mean randomising individual patients within the wards to control or intervention. Although this would make the intervention and control groups more homogenous, it is not applicable in this type of study, because it would cause contamination between the groups as the same physicians would treat both control- and intervention group patients and hence it would be impossible to assess the effect of the interventions. A cluster randomised, controlled study is therefore considered a strong and recommended design for studies investigating stewardship interventions, reducing risk for bias [146]. Randomization for study 1 was performed by drawing lots of hospitals and intervention groups per specialty. As there were only two hospitals with gastroenterology wards, only one intervention and one control group were drawn for this specialty. Randomization decreases the likelihood of selection bias when allocating interventions to the participating wards.

Study 2 and 3 were both multicentre, observational cohort studies, mainly utilizing data collected during Study 1. Observational cohort studies are considered a weaker design than experimental studies, as they are susceptible to selection bias and loss to follow-up and used for assessing associations, but not causation. The cohorts of study 2 and 3 were derived from the intervention study cohort, with prospectively included patients and retrospectively collected data to allow for sufficient time to have past after discharge to record 30-day mortality and 30-day readmission.

Confounding by indication

Guidelines for antibiotic use should incorporate existing evidence on aethiology of infections, treatment options and local resistance patterns in recommendations, securing safe treatment for the individual patient with minimal impact on both the individual patient's microbiota and the environment. The main outcome measures in Study 1 were adherence to guidelines, use of broad-spectrum antibiotics and change in locally targeted prescribing behaviour. Adhering to guidelines could be affected by the prescribers' perception of the balance between the present risk of the individual patient and the future risk for the society with increasing AMR if broad-spectrum antibiotics are prescribed [122]. The prescriber's trust in guidelines could therefore also influence treatment decisions, along with a fear for the patient's wellbeing [122]. At the time the intervention study was initiated, the newly released Norwegian antibiotic guidelines had been developed with broad involvement from more than 80 physicans throughout the country and the trust in the guidelines was perceived to be high. Increased severity of infection could still likely fuel a fear for underprescribing, such as the use of narrow-spectrum antibiotics or lower doses [122]. Severity of infections were however not recorded, and it is therefore a possibility that severity of infections could have varied pre- and post interventions and also between the specialties, introducing selection bias or confounding by indication. Recorded patient characteristics were however similar in the pre- and post intervention periods.

This potential bias could also have an effect on the results in study 2, the cohort study investigating the effect of adherence to guideline on patient outcome. If the more severely ill patients are more likely to receive non-adherent treatment, this could affect the association between guideline adherence and mortality, readmission and length of stay. The association we found between adherence to guideline and low mortality could be overestimated if this assumption is true for our study population. We also know that there were more patients admitted from institutions in the non-adherent group, which is suggestive of more comorbidities, but also that physicians consider the risk of resistant pathogens to be higher. The non-adherent group also had

more patients with GI-infections, UTIs and "other" infections, and since the case-mix was different, this could potentially influence the results. To increase internal validity, we adjusted analysis for major confounding factors, such as morbidity (through Charlson Comorbidity Index) and admission from other institution, indication for treatment, age, sex and seasonality. Although previous studies have reported favourable outcomes of adherent prescribing, to the best of our knowledge, no such study have been performed in the Norwegian context [134].

Assessment of adherence was for all patients based on the indication for treatment given in the patients' medical notes. The indication was usually a preliminary diagnosis given in admission notes and could change as more diagnostic information (microbiological test results, x-rays etc.) became available during the hospital stay. Even though the diagnosis may have changed during admission, the first indication for treatment is still what the physician based the choice of initial empirical antibiotic regimen on and it reflects real-life hospital practice, where decisions are based on available knowledge at the time. In study 3 we looked at the consistency between indication for treatment and infection discharge diagnosis (if present). There was low consistency for the group of patients with sepsis compared to other groups. This could mean that patients were diagnosed with suspected sepsis, but the diagnosis were later modified, but it could also be due to lack in documentation, as the focus of infections is often documented at discharge. In study 2, we did a sensitivity analysis for 30-day mortality, where we substituted indication for treatment with discharge diagnosis in regression analysis. This only changed the estimate to a minor degree for the association between adherent treatment and 30-day mortality.

The main data collection was performed by manual data extraction from the patients' electronic medical record. Collection of individual patient data was extremely labour intensive, and it was necessary to restrict the data collection period. Performing a feasibility study could have been beneficial, especially with regards to assessing time for data collection and completeness of data. Originally, we also wanted to include

information from radiology and other examinations performed, but this was not feasible given the extra time for data extraction and was dropped from the case report form at an early stage. Inclusion of more data could however made validation of indication for treatment possible.

Detection bias

When assessing adherence to guideline, a syntax was made in SPSS, connecting indication for treatment with antibiotics and combination of antibiotics and assigning a status of regarded [1)] adherent, first line treatment, [2)] alternative treatments and [3)] other, non-adherent treatments, effectively blinding the assessment of adherence to avoid detection bias (systematic differences in outcome assessment). Patients with antibiotic allergies or kidney failure were assessed manually to check if alternative treatments were to be regarded adherent. This assessment was performed blinded to study period, also to avoid introducing detection bias. This schematic way of assessing adherence could however potentially have made us miss some cases were comorbidity or other individual factors would explain a different choice of therapy.

Data on mortality, readmission and length of stay, were collected from electronic medical records. Readmissions were only identified if the patients were readmitted to the same hospital they were discharged from, which is a limitation to the study.

Performance bias

Except from intervention-team physicians, intervention-ward physicians were not informed of the study taking place in the pre-intervention phase of study 1. Control-ward physicians were not aware that the study took place, throughout the study period, minimizing bias of change in behaviour due to the fact that ones' behaviour is studied (Hawthorne-effect).

During data collection of individual patient data, we only recorded antibiotic treatment given and not other types of active treatment and care given during admission. This could potentially introduce performance bias when looking at outcome measures of mortality, readmission and length of stay if there were systematic differences in the care provided, other than antibiotics.

There was no regularly collected data which could be used as a substitute to assess adherence to guidelines. Assessing long-term sustainability of interventions was therefore difficult and we needed to find a proxy indicator for sustainability of intervention. The use of broad-spectrum antibiotics was therefore analysed. This has its limitations, because it is difficult to relate this directly to the interventions, but as the Norwegian guidelines mostly recommend narrow-spectrum antibiotics in the empirical regimen it was considered a relevant indicator. We used interrupted time-series analysis based on the methodology from Cochrane Effective Practice and Organisation of Care (EPOC) resources when examining these data [140]. This methodology is also recommended for AMS-studies as it is a strong design with high validity if time-varying confounding is considered [146]. This was possible because control wards were included in the study. In December 2015, when the Norwegian Action Plan against antibiotic resistance was released, we chose to end data collection of the time-series data because the release of the action plan could potentially have made an impact on the time-series data, but also because it is unlikely that the interventions would have a prolonged effect beyond this date.

Attrition bias

Only 1 patient withdrew from the study, minimizing the risk of a biased study population due to attrition.

Sample size

Power calculations were performed to assure that we included enough patients to see an effect of the interventions in study 1. Calculations were based on an expected increase in adherence to guidelines of 20% in each intervention ward, an assumption which did not hold in the intervention study. There was however very limited information informing the assumptions of the calculations, like the baseline degree of adherence in our hospital setting and the effect that could be expected in our setting. To overcome these barriers, a pilot study could have been performed, providing baseline data for calculations and secure sufficient power to analyse effect of interventions at each intervention ward.

When performing sample size calculations, we did not incorporate an intra-cluster correlation coefficient (ICC) or comparison with a control group in the calculations, which is a study limitation. Data informing calculations of the ICC-coefficient was not available at this time, but an estimation could possibly have been included, based on previous literature. We did however calculate the ICC-coefficient when data was available, based on adherence to guideline, showing that the ICC-coefficient for this outcome was 0.012 with a 95% CI of (0.003, 0.053).

5.1.2 External validity

Study population

External validity reflects how generalizable the findings are to other settings. Our studies were performed in medical wards at three hospitals in Western Norway, within specialties of pulmonary medicine, infectious diseases and gastroenterology. We included almost all patients with infectious diseases which received antibiotics during admission, which increases generalizability. Inclusion and exclusion criteria and patient characteristics are described for all studies, making assessment of study population transparent. Patients who did not receive antibiotics during admission

were not included in this study and it is therefore a possibility that we missed patients in whom antibiotics should have been initiated.

Clinical context

Norway has low levels of antibiotic resistance in bacterial isolates from clinical specimens, which could affect the way clinicians look at the level of urgency with regards to antimicrobial resistance. The findings from study 1 may be generalizable in settings with similar levels of resistance and similar egaliatarian hospital systems and culture. The experiences from study 1, with regards to designing and implementing interventions and involving clinicians in target setting can be useful for all those who have a healthcare system which are less hierarchical.

Antibiotic guidelines in Norway recommend mostly narrow-spectrum antibiotics, belonging to the WHO AWaRe access group as first line treatment, which may be impossible in other settings with different resistance patterns. Results from study 2 may therefore be more easily applicable in settings with similar resistance and prescribing guidelines, like the Nordic countries or the Netherlands. Guidelines should however always represent best practice and as similar studies from other countries also have found favourable patient outcome when guidelines are used, the study contributes to the total evidence base, highlighting guideline adherent prescribing as safe and effective.

A thorough assessment of barriers and fascilitators that could affect the implementation of interventions in each of the study wards might have revealed cultural and contextual differences that could be addressed before and during the implementation of interventions and helped in interpretation of the variability of effects seen across the study wards [105, 135, 146].

Study 3 describes the prescribing patterns from admission to discharge and analyses factors associated with non-adherence to guideline. The use of AWaRe categories to analyse individual patient data throughout the admission is new. This method could be useful in all other hospitals to understand local prescribing challenges and identify

targets for change. The factors associated with non-adherence to guidelines are likely to be generalizable to hospitals which have the same organisational model as Norwegian hospital.

Temporal (time-dependent) factors

Over the last 5 years, the awareness of AMR has increased in all areas where antibiotics are utilized, and since 2016, all public hospitals in Norway have been obliged to implement AMS programmes. As awareness is an important first step in behaviour change, this could possibly influence the generalizability of results, leaving the hospitals more prepared and ready for change related to optimizing antibiotic use now, than during the intervention study in 2014. The guidelines for antibiotic use in hospitals have not changed notably since they were released in 2013 and neither has resistance rates in Norway [23, 24]. The results from study 2, showing that guideline adherent prescribing is associated with improved clinical outcomes are still relevant and similar results are expected in other settings where guidelines are based on available evidence on disease aethiology, effective bug-drug combinations and local resistance patterns. It is however vital to secure that the guidelines are updated regularly to secure that clinicans can continue to trust in the recommendations given.

In study 3, we looked at the prescribing process from different angles. As AWaRe categories, guidelines and clinical practice change, the results may become less relevant, but as we have reported all adjustments made to fit the Norwegian context, it is easy to compare with future changes and categories. The findings may also serve as a relevant and important baseline measurement for future comparisons when efforts have been made to improve prescribing. One important area which is currently highly debated, is the duration of treatment [147]. It is likely that we will see a substantial change in the duration of treatment in the following years and studies documenting length of treatment in different settings are important to track the changes over time.

5.1.3 Reliability

Data from electronic medical records were readily available, although the data extraction process was cumbersome. Electronic medical records are however primarily made for documenting treatment of patients, secondly for economically related information, and not for research. Data may be missing or not standardised, leaving room for interpretation. Through applying a standardized case report form, we tried to avoid interpretation, but a limitation to these studies is that six researchers took part in manual data collection and that individual researchers could have interpreted data differently. Manual plotting of data, limited to 3 people, could also have introduced errors in the database. All plotted data was validated in a separate process against the paper CRFs and if data was missing, completion of data was sought by revisiting the patient's electronic medical record to record missing data. Additionaly, data on 30 day-mortality were extracted from hospital administrative systems and compared with manually collected data from hospital A, showing that only 0.47% of patients had the wrong outcome registered in our database. Assuming that the error rate was similar for other variables, the reliability of the data collected is good.

5.2 DISCUSSION OF RESULTS AND LESSONS LEARNED

5.2.1 Effect of AMS-interventions

Clinical antibiotic guidelines are part of the foundation for AMS-programmes and adherence to guidelines is an important goal [134]. Norway is still at an early stage in implementing AMS-programmes, and reliable antibiotic guidelines, constituting best practice, are important in this work. We have shown that adherence to these guidelines is associated with favourable clinical outcomes across a wide range of common infectious diseases in Norwegian hospital settings. Norwegian studies focusing on appropriate, guideline-adherent antibiotic prescribing in hospitals are scarce. In a Norwegian paper from 2002, Berild et al found that compliance to local guidelines in a paediatric ward were more than 90% [148]. In comparison, we found that

adherence to guidelines increased from 60% at baseline to 66% post interventions across all interventions wards. Davey et al found in their review a 15% increase in appropriate prescribing, from 43 to 58 %, following various interventions to improve antibiotic prescribing to hospital inpatients [105].

Lower respiratory tract infections (LRTIs) are a frequent cause of hospital admissions. Although we saw in study 3 that other groups of infections were more likely to receive antibiotics non-adherent to guideline, the high volume of patients with LRTIs makes this group of diagnoses an important target for AMS-interventions because of the large potential impact on total antibiotic use in hospitals. LRTIs accounted for more than 80% of patients included in our pulmonary intervention wards, where we found a 14% increase in guideline-adherence post-interventions. Our findings are in line with Schouten et al, who found in their cRCT, targeting LRTIs, that guideline-adherent prescribing increased from 50.3% to 64.3% [149]. A single site study in Northern Norway, targeting community acquired pneumonia (CAP) and AECOPD through audit with feedback with local target setting in a ward of pulmonary medicine, found an increase in adherence from 61.7% to 83.8% [150]. Baseline adherence was similar to our intervention wards and the increase in adherence was comparable to the effects aimed for in our study. Although we were far from reaching our aim of a 20% total increase in guideline adherence across intervention wards, the 13% and 14% increases that we saw at the pulmonary intervention wards were encouraging and are likely to reflect that the focus of the interventions fitted the profile of the pulmonary wards to a greater extent than the wards of infectious diseases and gastroenterology.

Studies investigating AMS-interventions usually report process outomes or quality indicators, like obtaining blood cultures, adherence to guidelines, use of broad-spectrum antibiotics, timeliness of antibiotics, i.v. to oral switch and review of antibiotics [105, 151]. There has been a demand for studies including both intended and unintended consequences reporting both process outcomes, clinical patient outcome,

financial- and microbiological measures and adverse events, like *C.diff*-infections [33, 146]. Schweitzer et al found that most studies did not report clinical and microbiological outcome data and that studies in the community setting were of higher quality [133]. In addition to adherence to guidelines and use of broad-spectrum antibiotics, we included mortality, readmission and length of stay in our intervention study, but found that the interventions did not affect patient outcome. In their 2017-review, Hulscher et al reported that following guideline recommendations were associated with improved clinical outcomes, reduced costs, mortality and frequency of adverse events [134]. In study 2, we also found that adherence to guidelines improved mortality and length of stay, but we did unfortunately not include financial measures or adverse events.

We found a decreasing trend in- (-6.8 DDD/100 bed days, p=0.0.12) and drop in level of broad-spectrum antibiotic use pre- and post intervention (12 months: -29.3 DDD/100 bed days, p= 0.027, 18 months: -42.9 DDD/100 bed days, p= 0.016) for the audit with feedback group, but the groups receiving academic detailing or the control group did not show the same results. Both audit with feedback and academic detailing are shown to be effective, although audit with feedback may be perceived as more stringent [105]. The effect of audit with feedback on broad-spectrum antibiotic use was seen across both the specialty of pulmonary medicine and infectious diseases and the ward of infectious diseases contributed to this result to a great extent. The contribution to the effect from the two specialties could potentially be somewhat different, with pulmonary wards showing a more promt response to interventions, as seen when adherence to guidelines was measured. The ward of infectious diseases may have needed more time to digest the results from the audit and be convinced to adjust practice, as antibiotic prescribing is right in the heart of their specialty. A possible explanation is that the intervention increased awareness and organizational readiness for change and that this was not evident during the short post-intervention period with patient-level data, but could be seen in the long-term follow up of the use of broad-spectrum antibiotics [152]. Stenehjem et al saw in their cluster randomized

intervention study, including 15 small hospitals without routine ID-consultation available or an AMS-programme present prior to study initiation, that only the hospitals with the most intense intervention program (program 3), had a reduction in broad-spectrum antibiotic use [153]. Program 3 hospitals received advanced antibiotic stewardship education and tools, access to an infectious disease hotline, antibiotic utilization data, audit with feedback for the majority of antibiotics, locally controlled antibiotic restriction and an ID-trained clinician who approved restricted antibiotics and reviewed microbiology results. Broad spectrum antibiotic use had a rate ratio of 0.76 with 95% CI (0.63, 0.91) in the program 3 hospitals in the intervention period compared to the baseline period [153]. In comparison, none of the hospitals included in our study had AMS-programmes, all intervention wards were provided antibiotic utilization data, and all had access to ID-physicians for guidance.

Sustainability of effects following AMS-interventions is challenging and should be assessed, as evidence suggests that removal of interventions are associated with a reversal of effects [105]. To have a sustained effect of the interventions performed within the interventions study, repeated audits with feedback as part of normal clinical practice would then have to be implemented. Within the electronic medical record that was in use at the time, automatic data extraction on the use of antibiotics was not possible. The most challenging part of this study was data collection. Automated data extraction would make repeated audits feasible to implement and collection of data on antibiotic use easier. During the time that has passed since this study was performed, a new computerized physician order entry (CPOE)-system has been put in place, and progress have been made with regards to data extraction. To assess sustainability of interventions, we used antibiotic sales data from the hospital pharmacies, a commonly used source of outcome data, which has both its limitations and advantages [146]. Data are readily available and gives valuable information about the amount of broad-spectrum antibiotic use, but the lack of connection between indication for treatment and antibiotic use makes data interpretation challenging. When antibiotic sales data are used as an outcome measure, care should be taken to

avoid that shifts in prescribing practice goes undetected, possibly leading to unintended consequences, such as increased rate of adverse events (e.g. C.Diff-infections) or poorer patient outcome [146].

5.2.2 Local target setting

The intervention sessions were short – normally one hour – and was to include both a presentation from the intervention team and a discussion between clinicians and the team, aiming to also find one or two local targets in addition to the general target of increased adherence to guidelines. The process of finding local targets was not defined good enough from the research team during planning, leaving only one ward and intervention team with a consensus on a local target which was also possible to measure through the planned data collection. Two wards could not achieve consensus on 1-2 targets, one ward did not identify any targets and the fourth ward wanted to focus on reducing prescription of ciprofloxacin for inflammatory bowl disease (IBD) in exchange for co-trimoxazole. Treatment of IBD was not included in the antibiotic guidelines, had limited evidence and a limited number of patients admitted during study period. This was an important subject for the clincians, but it was not possible to see an effect on the outcome measure of adherence to guidelines in general or the local target. For the intervention ward that managed to identify a local, measurable target, the effect was very good, with a 30% increase in targeted prescribing behaviour, suggesting that this is indeed a very useful intervention when properly implemented. It may have been more difficult for the intervention wards receving academic detailing to set a target, with only individual patient cases and clinical experience as the foundation. Audit results were more tangible and clincians could see for themselves objective descriptions of the wards' prescribing at an aggregated level. Introducing SMART goals (specific, measurable, attractive/acceptable, realistic and time-bound) or the three questions asked within the Model for Improvement[1]

[1] 1. What are we trying to accomplish? 2. How will we know that a change is an improvement? 3. What changes can we make that will result in improvement?

could have helped clinicians and intervention teams in the process of finding local targets and ensured that all targets proposed were measurable [128, 154, 155].

5.2.3 Clinical context and AMS

The remarkable difference in the impact of interventions between the specialties was an interesting finding. Both audit with feedback and academic detailing are considered effective approaches for improving prescribing practices [105]. Adherence to guidelines increased at pulmonary intervention wards, regardless of the intervention applied, but the same effect could not be seen in other specialties. The fact that we did not find similar effects for the specialties of infectious diseases and gastroenterology, contributes to the evidence saying that effect of AMS-interventions is dependent both on the context in which interventions are implemented and how they are implemented [105, 146]. As previous studies have primarily looked at the difference in prescribing practices between medical and surgical specialties, our study suggests that medical specialties can not be treated equally when interventions are applied [118, 156]. The context and culture of each ward or department, baseline performance and the people involved in performing the interventions are likely to influence the results and should be taken into account [157]. To succeed with behaviour change, we therefore need to understand the context and culture in which we are implementing our interventions. When designing and implementing the interventions, we included clinicians well known in the intervention wards. Interventions were performed by teams of physicians and pharmacists and in all but one ward (gastroenterology), local champions were involved. They tailored feedback presentations to fit the need of the intervention wards and one added information about a previous local outbreak with resistant bacteria (VRE) to strengthen the message conveyed about the necessity of prudent prescribing. The outcome of an intervention study will be strongly affected by the barriers and fascilitators for implementation of the proposed interventions, including readiness for change in the organisation. The study was performed prior to the release of the Norwegian Action

Plan Against Antibiotic Resistance - when the focus on AMR in the hospitals were more limited - and a formal assessment of readiness for change was not made. Warrenman et al investigated determinants of antimicrobial prescribing in studies published from 2007 to 2017 and noted the increase in awareness of AMR during this period [158]. Clinicians must constantly weigh the threat of AMR against the fear for underprescribing for a sick patient. The awareness of AMR, combined with a sense of urgency related to AMR both in the local and global context and belief in guidelines as best practice are likely prerequisites for successful implementation of clinical guidelines on antibiotic prescribing. A more in-depth understanding of the challenges of each ward, why they prescribe the way the do and an assessment of barriers and fascilitators for implementing interventions in the separate wards could have improved the intervention outcome or at least helped explain the variability in impact that was seen across specialties and wards. The use of a framework for behavioural change during planning and reporting of the intervention study could also have helped with tailoring interventions and learning from the study findings [135, 136].

5.2.4 Empirical antibiotic prescribing

In study 3 we found that non-adherence was more likely at hospitals A and C, compared to hospital B and also when antibiotics were prescribed at the ward, compared to the emergency room. As almost 80% of antibiotics were initiated in the emergency room (ER), the finding suggests that physicians working primarily in the emergency wards are vital in securing guideline-adherent prescribing when initiating treatment. The ER-environment is hectic, and clinicians have identified the pace of the emergency departments as a structural barrier to AMS-programmes [129]. When the intervention study was performed, prescribing in the emergency rooms were mainly performed by junior physicians, a category of doctors which have reported to rely more on prescribing guidelines that their seniors [76]. The choice of treatment made in the ER is vital in the treatment of serious infections and also influence the choice of therapy at the wards for a long time, as seen in our third study, where mean day of

modification of empirical treatment was 3.6 days [159]. In study 2 we found that empirical antibiotic prescribing adherent to guidelines is associated with favourable patient outcome, both in terms of mortality and length of stay. This prescribing was mainly performed in the ER. We did however not see any association with guideline adherence and readmission. Schuts et al also showed in their 2016 systematic review the benefits of adherent prescribing, with a relative risk reduction for mortality of 35% when guidelines were followed. Including ER-physicians in AMS-interventions would likely have increased the impact of interventions on adherence to guidelines and should be considered for future AMS activities. The national antibiotic prescribing guideline is a cornerstone in the work performed both nationally and locally to implement AMS in all hospitals. With this study, we have added a piece of evidence suggesting that guideline adherence is safe and should be regarded best practice in Norwegian hospitals. Securing access to updated, clinical prescribing guidelines should therefore be of prime importance in the work against antimicrobial resistance as they benefit both the patient and the environment.

5.2.5 Are we AWaRe?

In study 3 we applied the AWaRe categories found in the 2017 WHO Essential Medicines List (EML) to describe and analyse the pattern of antibiotics prescribed throughout the hospital stay [102]. Not all antibiotics used in the Norwegian setting were included in AWaRe and we therefore made a modified list were mecillinam, pivmecillinam, methenamine and tobramycin were included in the Access category, and cefuroxime was added to the Watch category. The updated version of the WHO EML from June 2019 would not impact the results in our study [101]. The use of metenamine was very limited in our hospital population. Both in our study and in the studies by Hsia et al and Budd et al, the Access group was comprised of the core Access antibiotics only [160, 161]. In the English adaptation of the AWaRe-list, the England AWaRe index, they chose to add methenamin to a “other” category and tobramycine was added to the Watch-category [160]. If our categorisation was to be

used in the Norwegian primary care setting, the use of an "other"-category would be appropriate also for us. The use of methenamine is extensive in this setting and methenamine is excluded from the measurement of total antibiotic consumption in primary care when the progress towards the goals in the Norwegian Action Plan against AMR is assessed [12, 23]. Norwegian antibiotic guidelines are prudent and recommends access antibiotics for most infections as first line empirical regimen. We found that when guidelines were followed, 89% of antibiotic regimens were comprised of antibiotics within the access group only. We have not been able to identify other studies looking at patient level prescribing and adherence to guidelines in relation to AWaRe-categories, but Hsia et al found that based on antibiotic sales data, approximately 85% of oral antibiotics prescribed for children in Norway were Access antibiotics [161]. In the adjusted, England-adapted AWaRe-index, the status of 37 antibiotics were determined or changed compared to the original WHO AWaRe categories, including moving clindamycin and 1st generation cephalosporins from Access to Watch due to the association with increased risk of C. Difficile infections and moving carbapenems from Watch to Reserve [160]. In the study by Hsia et al, approximately 75% of oral antibiotics prescribed for children in the UK were within the Access category. In comparison, with the adjusted index, 49.7% of prescribed antibiotics were in the Access-category in the acute hospital sector in England [160]. The variations in classifications of antibiotics in the limited number of studies which have made use of the AWaRe categories, makes it challenging to compare results between studies. Local resistance patterns may warrant adjustments in AWaRe categories in different countries but including a more comprehensive list of antibiotics by the WHO could also help future studies wanting to utilize AWaRe as a tool for AMS-initiatives.

5.2.6 Duration of therapy

Duration of antibiotic therapy has been heavily debated the last few years, sparked by the BMJ-paper called "The antibiotic course has had its day" by Llewelyn et al in 2017 [147]. There has been limited evidence for the duration of therapy which have been

recommended in current clinical practice guidelines and there is an increasing evidence base proposing that "shorter is better" [162-166]. We found in study 3 that the duration of treatment was surprisingly similar across a wide range of diagnoses. There seems to be a need for adjustment of both guidelines and clinical practice to incorporate new evidence, but also for more quality research providing a good foundation for future recommendations.

6. CONCLUSION

Through this research project we have added to the knowledge needed to implement antibiotic stewardship in Norwegian hospitals:

The impact of implementing different AMS-interventions on adherence to national antibiotic guidelines differed between specialties, while the use of broad-spectrum antibiotics declined (level and trend) across intervention wards receiving audit with feedback, regardless of specialty. Although local target setting was challenging, an impressive change in prescribing behaviour was observed when clinicians were able to set local targets, with the backdrop of audit data. Consequently, audit with feedback is an essential AMS-intervention that hospitals should perform, and engaging clinicans in local target setting should be encouraged. The impact of interventions will differ between departments, wards and/or patient population, depending on culture, context and tailoring of interventions.

Patients who received empirical treatment adherent to the national antibiotic guidelines had a significantly lower in-hospital and 30-day mortality compared to patients who received non-adherent treatment, and there was a trend towards shorter length of stay. This adds to the evidence suggesting that prescribing according to guidelines provides the best treatment for patients and should be aimed for. Since the majority of patients were prescribed empirical antibiotic treatment in the emergency room, antibiotic stewardship efforts should include the first line clinical staff that inhabits the emergency rooms. The vast majority of patients continued antibiotic therapy after discharge, contributing significantly to the total days of antibiotic therapy, and duration of antibiotic therapy was similar across very different groups of diagnoses. This suggests that therapy can be shortened safely for many patients, but it also highlights that guideline recommendations for duration of treatment should be reviewed.

Place of initiation of empirical therapy (hospital and ward vs ER), admittance from an institution and group of diagnosis were associated with non-adherence to clinical practice guidelines in our study. A deeper understanding of the reasons for non-adherence and an assessment of cultural and contextual factors affecting prescribing will be important when developing future interventions and implementation strategies in hospital settings. Analysis of patient-level, antibiotic prescribing data from admission to discharge gave valuable insight in the local prescribing processes and identified new targets for AMS-interventions. Similar analyses should be performed to inform stewardship work both inside and outside of study contexts.

WHO AWaRe-categories provided a useful system for grouping and analysing antibiotic regimens throughout the hospital stay, although modifications had to be made to include all antibiotics prescribed in this study setting. If more studies used this framework, it would be easier to compare antibiotic prescribing between countries and also see how guidelines and AWaRe-categories are connected in different parts of the world.

Even though the studies were performed in three Norwegian hospitals, we believe that methods and findings will be applicable in other clinical settings where antibiotic prescribing and related patient outcomes is to be analysed and improved.

7. FUTURE PERSPECTIVES

1. In all three studies included in this thesis, we excluded patients with a diagnosis for which there was no recommendations to guide empirical therapy, such as "infection – unknown focus." The treatment of- and patient outcomes related to the group of patients with very uncertain diagnoses on admission should be further investigated.

2. Future studies should include both severity of infections and an evaluation of non-adherence as under- or overtreatment, to further understand why non-adherence is associated with increased mortality. Adding information about severity of infections in a structured and easily detectable way in electronic medical records and medication charts is warranted.

3. To achieve increased and sustained impact of antibiotic stewardship interventions, they should be based on a thorough understanding of current practice, barriers and fascilitators to interventions and the context and culture in which they are implemented. Future studies should incorporate qualitative studies to analyse these dimensions before large scale interventions studies are initiated. This includes finding out how to best enable the clinicians – in every way-, so that correct prescribing is made easy.

4. Electronic medical records (EMR), including computerized physician order entry (CPOE) and clinical decision support systems (CDSS) should be incorporated in both hospital and primary care to ease the prescribing process and to allow automated data extraction. EMR and CPOE systems should be designed in a way that allows indication for treatment and corresponding medicines to be easily identified. Automated audit and feedback systems can then be implemented to inform practice on all levels, from the individual physician receiving feedback on his or her own

prescribing behaviour, to aggregated data on ward, department, hospital, regional, national and even global levels.

5. More studies investigating patient-level antibiotic prescription data and factors associated with non-adherence to guidelines would be valuable to compare our findings with hospitals across the world. The use of WHO AWaRe to group antibiotic regimens on a patient level has – to the best of our knowledge – not been performed previously and should be repeated in other settings. An extended list of AWaRe categories, including all available antibiotics, should be put in place as a reference for future studies to avoid that all countries or regions make their own version, which makes comparison difficult. Future studies should also present data for individual groups of diagnoses in addition to total use.

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9. APPENDICES

9.1 PAPER I

9.2 PAPER II

9.3 PAPER III (MANUSCRIPT)

9.4 CASE REPORT FORM (NORWEGIAN)

I

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The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study

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Abstract

Background: There is limited evidence from multicenter, randomized controlled studies to inform planning and implementation of antibiotic stewardship interventions in hospitals.

Methods: A cluster randomized, controlled, intervention study was performed in selected specialities (infectious diseases, pulmonary medicine and gastroenterology) at three emergency care hospitals in Western Norway. Interventions applied were audit with feedback and academic detailing. Implementation strategies included co-design of interventions with stakeholders in local intervention teams and prescribers setting local targets for change in antibiotic prescribing behaviour. Primary outcome measures were adherence to national guidelines, use of broad-spectrum antibiotics and change in locally defined targets of change in prescribing behaviour. Secondary outcome measures were length of stay, 30-day readmission, in-hospital- and 30-day mortality.

Results: One thousand eight hundred two patients receiving antibiotic treatment were included. Adherence to guidelines had an absolute increase from 60 to 66% for all intervention wards ($p = 0.04$). Effects differed across specialties and pulmonary intervention wards achieved a 14% absolute increase in adherence ($p = 0.003$), while no change was observed for other specialties. A pulmonary ward targeting increased use of penicillin G 2 mill IU ×4 for pneumonia and COPD exacerbations had an intended increase of 30% for this prescribing behaviour ($p < 0.001$).

Conclusions: Pulmonary wards had a higher increase in adherence, independent of applied intervention. The effect of antibiotic stewardship interventions is dependent on how and in which context they are implemented. Additional effects of interventions are seen when stakeholders discuss ward prescribing behaviour and agree on specific targets for changes in prescribing practice.

Keywords: Antibiotic stewardship, Intervention, cRCT, Audit with feedback, Academic detailing, Hospital, Goal setting

Background

Globally, the overuse and misuse of antibiotics, especially broad-spectrum agents, has accelerated the development and selection of resistant bacteria [1–3]. The increase in broad-spectrum antibiotic prescribing cannot be explained by increased antibiotic resistance alone [4]. Antibiotic stewardship programs have been introduced to hospitals worldwide to promote more prudent antibiotic use [5, 6]. The basis of stewardship programs are evidence based clinical guidelines for antibiotic prescribing to ensure effective treatment for individual patients, while minimizing development of antimicrobial resistance (AMR). Adherence to antibiotic guidelines varies among countries and institutions [6]. Interventions like audit with feedback, providing a summary of clinical performance over time and educational outreach through academic detailing have been shown to be effective in increasing

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adherence. However, the need for studies addressing cultural, contextual and behavioural determinants when developing, implementing and reporting stewardship interventions has been highlighted [6–9]. There is also a need for more studies that apply behaviour change theory to investigate effect on antibiotic use across hospitals, specialties and diagnoses to help identify the most effective means of implementing interventions that are transferable and generalizable [6, 10, 11]. We report here the findings of a multicentre, cluster randomized controlled intervention study, investigating the effect of behaviour change interventions with stakeholder involvement and local target setting for change in antibiotic prescribing [12].

Methods

Definitions

Substances of ATC-group J01 (Antibacterials for systemic use), metronidazole tablets (P01AB01) and vancomycin tablets (A07AA09) were included in the definition of antibiotics for this study [13]. Broad-spectrum antibiotics were defined as penicillins with enzyme inhibitor (J01CR), 2. and 3. generation cephalosporins (J01D C-D), carbapenems (J01DH) and quinolones (J01MA), the five groups targeted in the National Action Plan Against Antibiotic Resistance in Health Services [14, 15].

Study design

This prospective, cluster randomized, controlled intervention study was performed within three specialties at three emergency care and teaching hospitals as a parallel group study with three arms (Table 1).

Participants and data collection

Eligible clusters were wards within one of the medical specialties; infectious diseases, pulmonary medicine and gastroenterology at hospital A, B and C in Western Norway. Specialties were selected based on infectious diseases and pulmonary medicine having the highest consumption of antibiotics in the included hospitals. Gastroenterology was included since hospital B had a joint medication storage area for the ward of pulmonary medicine and the ward of gastroenterology. Hospital A and B were tertiary care hospitals with 1100 and 600 beds, respectively. Hospital C was a secondary care hospital with 160 beds. For description of case mix, see Table 2.

Patients who received antibiotics during hospitalization and were discharged from the study wards in the time period from 10th of February to 11th of July 2014 were eligible for inclusion in the study. Patients who received antibioticprophylaxis, had orthopaedic prosthesis infections, or had a hospital stay < 24 h or > 21 days were excluded. Patients whose indication for treatment was not in the antibiotic guideline or whose antibiotics were discontinued at day 1, was excluded. Only the first stay of readmitted patients was included. Patients were included consecutively. Patient data were collected manually from electronic medical records. Data collected included patient demographics, indication for antibiotic treatment, antibiotic prescribing, microbiological test results, estimated glomerular filtration rate (eGFR) on admission, length of stay, 30-day readmission, in-hospital and 30-day mortality and admittance from- or discharge to other hospitals or nursing homes. Indications for antibiotic treatment were registered as documented in the medical record and not assessed for validity.

Broad-spectrum antibiotic use for study wards in the period 2013–2015 was collected from the hospital pharmacies sales statistics and adjusted per 100 patient bed days.

Interventions

The primary intervention aim was to increase adherence to The National Guidelines for Antibiotic Use in Hospitals (hereafter guidelines), across diagnoses [16]. Each hospital assigned local intervention teams of 1–2 physicians and 1 pharmacist to co-design and implement the interventions. Authors I.S and J.S.W developed initial intervention concepts, which were discussed in a regional meeting with all project participants. Each intervention team then refined the interventions to fit their local context. A common presentation template was prepared for all intervention sessions with information about antibiotic resistance, the national antibiotic guideline, local antibiotic sales statistics and principals of antibiotic dosing. All intervention teams modified this material to fit the individual wards. Academic detailing sessions focused on recently admitted infectious diseases patients, including cases with treatment both adherent and non-adherent to guidelines. The teams' selection of patient cases decided the focus in wards receiving academic detailing.

Audit with feedback wards had predefined target areas of pneumonia and COPD exacerbations, as these patients were frequently admitted to both intervention wards. Fifty patients with these diagnosis were included consecutively from February to April 2014 to get a reasonable overview of prescribing practice over the given time period, without excessive workload for the intervention teams. For the audit data, intervention teams assessed adherence. The level of detail and focus in the feedback was at the discretion of the teams and varied between the two feedback wards.

Intervention ward physicians were invited to academic detailing- or audit with feedback- group sessions in May 2014, led by local intervention teams. No specific threshold for acceptable attendance was defined, but more than one meeting was held if the intervention team considered the attendance at the first meeting to be too low. Physicians present at the main session at each ward were invited to identify one or two specific challenges to be addressed as local targets for improvement of antibiotic prescribing based on discussions during the session. Specific actions to

Table 1 Overview of implemented interventions

Intervention	Hospital	Specialty	Intervention sessions	Attendance consultants/ residents (estimated)	Performed by	Special features of each intervention	Common features of intervention sessions for both audit with feedback and academic detailing
Audit with feedback	A	Pulmonary medicine	16.05.14	70%	Local pharmacist + study ward consultant	Focus areas: Pneumonia (CAP) COPD exacerbations - > Adherence to guideline (50 patients) Use of broad-spectrum antibiotics - > Indication for treatment (50 patients)	1. Verbal presentation including: - Antibiotic resistance - Antibiotic guideline - Dosing of antibiotics - Ward antibiotic sales statistics 2. Discussion among ward physicians: - Ward prescribing practice - Challenges - Target setting (1–2 targets)
	B	Infectious diseases	20.05.14 27.05.14	100%			
Academic detailing	A	Gastro-enterology	14.05.14	90%	Local ID-physician	Case discussions on recently discharged patients with infectious diseases. Variety of diagnoses, chosen by ID-physician	
	B	Pulmonary medicine	13.05.14 23.05.14	100%			
	C	Infectious diseases	20.05.14 21.05.14	70%			
Control	A	Infectious diseases					
	B	Gastro-enterology					
	C	Pulmonary medicine					

Table 2 Patient characteristics and patient outcome pre- and post-implementation of interventions, per intervention group and specialty

	Pulmonary medicine Period			Infectious diseases Period			Gastroenterology Period			Audit with feedback Period			Academic detailing Period			Control (all three specialities) Period		
	Pre $N = 427$ n (%)	Post $N = 162$ n (%)	*p*-value	Pre $N = 424$ n (%)	Post $N = 153$ n (%)	*p*-value	Pre $N = 78$ n (%)	Post $N = 39$ n (%)	*p*-value	Pre $N = 478$ n (%)	Post $N = 182$ n (%)	*p*-value	Pre $N = 451$ n (%)	Post $N = 172$ n (%)	*p*-value	Pre $N = 350$ n (%)	Post $N = 169$ n (%)	*p*-value
Age (mean - years)	69.6	68.99	0.66	67.5	64.4	0.10	68.9	64.8	0.35	67.1	66.1	0.51	70.2	67.1	0.05	63.2	65.7	0.22
Sex																		
Female	213 (49.9)	88 (54.3)	0.34	180 (42.5)	80 (52.3)	**0.04**	37 (47.4)	16 (41.0)	0.51	221 (46.2)	101 (55.5)	**0.03**	209 (46.3)	83 (48.3)	0.67	167 (47.7)	80 (47.3)	0.94
Male	214 (50.1)	74 (45.7)		244 (57.5)	73 (47.7)		41 (52.6)	23 (59)		257 (53.8)	81 (44.5)		242 (53.7)	89 (51.7)		183 (52.3)	89 (52.7)	
Admitted from hospital/nursing home	55 (12.9)	15 (9.3)	0.23	68 (16.0)	30 (19.7)	0.30	14 (18.0)	3 (7.7)	0.14	67 (14.0)	20 (11.0)	0.30	70 (15.5)	28 (16.4)	0.79	51 (14.6)	23 (13.6)	0.75
Indication for antibiotic treatment																		
Pneumonia	136 (31.9)	63 (38.9)	0.20	115 (27.1)	45 (29.6)	0.06	11 (14.1)	3 (7.7)	0.16	162 (33.9)	67 (36.8)	**0.01**	100 (22.2)	44 (25.7)	0.15	65 (18.7)	23 (13.6)	0.31
COPD exacerbation, infectious	183 (42.9)	63 (38.9)		59 (13.9)	7 (4.6)		1 (1.3)	2 (5.1)		132 (27.6)	34 (18.7)		111 (24.6)	38 (22.2)		25 (7.2)	15 (8.9)	
LRTI - Other	23 (5.4)	9 (5.6)		16 (3.7)	6 (3.95)		6 (7.7)	2 (5.1)		19 (4.0)	4 (2.2)		26 (5.8)	13 (7.6)		22 (6.3)	7 (4.1)	
Sepsis	40 (9.4)	17 (10.5)		61 (14.4)	24 (15.8)		16 (20.5)	5 (12.8)		57 (11.9)	26 (14.3)		60 (13.3)	20 (11.7)		73 (21.0)	50 (29.6)	
Skin and soft tissue	3 (0.7)	2 (1.2)		62 (14.6)	33 (21.7)		9 (11.5)	6 (15.4)		31 (6.5)	25 (13.7)		43 (9.5)	16 (9.4)		58 (16.7)	22 (13.0)	
Gastrointestinal tract	1 (0.2)	0 (0)		9 (2.12)	4 (2.6)		9 (11.5)	11 (28.2)		6 (1.3)	2 (1.1)		13 (2.8)	13 (7.6)		35 (10.1)	14 (8.3)	
Urinary tract	9 (2.1)	5 (3.1)		75 (17.7)	21 (13.8)		17 (21.8)	9 (23.1)		31 (6.5)	16 (8.8)		70 (15.5)	19 (11.1)		36 (10.3)	19 (11.2)	
Other	32 (7.5)	3 (1.9)		27 (6.4)	12 (7.9)		9 (11.5)	1 (2.6)		40 (8.4)	8 (4.4)		28 (6.2)	8 (4.7)		34 (9.8)	19 (11.2)	
Antibiotic allergies	62 (14.5)	28 (17.3)	0.41	35 (8.3)	19 (12.4)	0.13	8 (10.3)	4 (10.3)	0.99	59 (12.3)	26 (14.3)	0.51	46 (10.2)	25 (14.5)	0.13	25 (7.2)	17 (10.1)	0.18
Patient outcomes Δ																		
Length of stay (days)	7.2	6.9	0.40	6.5	6.5	0.99	7.0	6.1	0.30	7.2	6.5	**0.04**$^{\Delta}$	6.5	6.8	0.41	7.5	6.8	0.11
In-hospital mortality	30 (7.0)	7 (4.3)	0.23	12 (2.8)	4 (2.61)	0.89	3 (3.9)	2 (5.13)	0.76	28 (5.9)	9 (5.0)	0.65	17 (3.8)	4 (2.3)	0.37	13 (3.7)	3 (1.8)	0.23
30-day mortality	53 (12.4)	11 (6.8)	0.05	30 (7.1)	8 (5.3)	0.44	3 (3.9)	4 (10.3)	0.17	50 (10.5)	12 (6.6)	0.13	36 (8.0)	11 (6.4)	0.51	24 (6.9)	6 (3.6)	0.13
30-day readmission	117 (29.3)	38 (24.5)	0.26	78 (19.1)	18 (12.2)	0.06	16 (21.3)	6 (17.1)	0.61	111 (24.6)	36 (20.9)	0.33	100 (23.1)	26 (15.7)	**0.04**$^{\Delta}$	58 (17.5)	30 (18.6)	0.75

p-values are obtained by chi-square test (categorical variables) and t-test (continuous variables) per group

Δ Patient outcomes were also tested for interaction between intervention groups/specialty and period using linear and logistic regression. *p*-value interaction length of stay = 0.080. *p*-value interaction 30-day readmission = 0.105

achieve targets were not included in the target discussions. For details of interventions, see Table 1.

Outcomes

Primary outcome measures

1) Adherence to guidelines was assessed on the second day of treatment to allow sufficient time for patients to be reviewed by study ward physicians and measured as percentage of correctly prescribed empiric treatment (choice of active substance) before and after interventions [16]. CRB-65 was not routinely documented, so pneumonia and severe pneumonia was assessed together (both empiric treatments assessed as adherent). All hospitals were committed to use the national guideline, as recommendations were appropriate with regards to local antibiotic resistance patterns.
2) Use of broad-spectrum antibiotics was assessed as DDD/100 bed days in time series before and after intervention. Broad-spectrum antibiotic use was selected as an outcome measure because the guidelines mainly recommend narrow-spectrum antibiotics as empiric treatment and a shift towards guideline adherent prescribing was expected to cause a reduction in broad-spectrum antibiotic use.
3) Change in locally targeted prescribing behaviour was assessed according to the defined targets and compared before and after interventions.

Secondary outcome measures were length of stay, 30-day readmission and mortality (all cause in-house and 30-day mortality). Patient outcomes were measured to ensure that the interventions did not have any negative consequences for patient treatment.

Sample size

As baseline adherence to guidelines was unknown in Norway, calculation of the sample size prior to the study was challenging. According to the original research protocol, we assumed an absolute 20% improvement in adherence from 50% pre-intervention to 70% post-intervention for each cluster. Given a power of 80% and a type 1 error of 5%, the smallest number of subjects needed to detect this difference was 93 both before and after the intervention. Although this was sufficient for the current study, we calculated at least 155 patients before and after intervention to answer additional research questions listed in the original protocol. However, the sample size calculations did not include intra-cluster correlation coefficient (ICC) or comparison with a control group. Based on pre-intervention data of adherence to guideline, ICC coefficient for this outcome was 0.012 with 95% CI (0.003, 0.053).

Randomization

Authors I.S and J.S.W. performed randomization and assigned clusters to interventions by drawing lots of hospital and intervention groups per specialty. Across the hospitals, infectious diseases and pulmonary medicine received both academic detailing and audit with feedback and had a control group. Only two of the hospitals had specific gastroenterology wards, so this specialty received only one intervention and had a control group (Table 1).

Blinding

Prescribing physicians at the wards were not informed about the study being performed during the baseline period and were at that point blinded to intervention group, with the exception of the physicians assigned to the project teams. Control ward physicians were blinded throughout the study period.

Assessment of adherence to guidelines was performed blinded to the intervention- or treatment group, by using syntax in SPSS. An adherence variable was generated, combining the variable indication for treatment with the variable for prescribed treatment. First choice of empiric therapy was coded as adherent. Manual adjustment of adherence of antibiotic prescriptions was made in patients with antibiotic allergies or kidney failure.

Statistical analysis

Analyses were performed both per intervention group and per specialty, but due to fewer patients than expected in the post-intervention period, analysis per cluster was not performed. Differences in study group characteristics pre- and post-interventions were tested using Pearson's chi-square test for categorical data and independent two-sample t-test for continuous data. Pearsons chi-square test was also applied to test adherence to guidelines pre- and post-interventions for individual intervention groups and specialties. To test whether percentage of adherence to guidelines or patient outcomes in intervention and specialty groups changed differently over time compared with the control group, we evaluated the group-by-period interaction term in simple logistic or linear regression models, as appropriate. Adherence to guideline or patient outcome were dependent variables, with group of intervention (audit vs control/academic detailing vs control) or specialty (e.g. pulmonary medicine vs control/infectious diseases vs control) and period (before-after) were independent variables together with the interaction term. The level – and trend effect of broad-spectrum antibiotic use (sales statistics) pre- and post-intervention was estimated with the Interrupted Times Series (ITS) analysis method described by the Cochrane Effective Practice and Organisation of Care (EPOC) group [17]. All tests were two-sided and p-values < 0.05 was considered statistical significant for all analyses.

Statistical analysis was conducted using SPSS for Windows, version 24 and Stata SE for Windows, version 15.

Results

Patients

Two thousand four hundred five admissions were eligible for inclusion. After applying exclusion criteria, 1802 unique patients were included in analysis, 1279 and 523 patients in the pre- and post-intervention periods respectively (Table 2). The study period was fixed due to time-limited allocation of project resources and mandatory information of included patients. Interventions were conducted later than originally planned due to practical considerations at the study wards. This caused skewness in data with two thirds of the patients included pre-interventions (Table 2). Patient characteristics were similar pre- and post-interventions, except for some differences in distribution of diagnoses in the audit with feedback group (Table 2).

Primary outcomes

Adherence to guidelines

Across all intervention wards, adherence to guideline increased from 60% to 66% ($p = 0.04$), but when compared with the control group, this was not significant (Table 3). The effect of interventions differed largely between the specialties. Infectious diseases and gastroenterology wards displayed no effect of interventions on adherence, while pulmonary medicine wards displayed significant effect of interventions compared to the control group (Table 3). Academic detailing and audit with feedback increased total adherence to guideline by 14% and 13% respectively (absolute increase), in the pulmonary wards (not shown in tables).

The audit with feedback intervention specifically targeted pneumonia and COPD exacerbations. For these diagnoses, the pulmonary medicine ward increased adherence by 12% and infectious diseases ward by 2% (not shown in tables).

Use of broad-spectrum antibiotics

Interrupted time series analysis showed that the overall trend of activity-adjusted broad-spectrum antibiotic use pre- and post-interventions was significantly improved, as was the level at 12 and 18 months post intervention for the audit with feedback group (Appendix: Table 5 and Fig. 1). The gastroenterology intervention ward had a significant decrease in the use of broad-spectrum antibiotics at 3 and 6 months, but it increased thereafter (Appendix: Table 5 and Fig. 1). No significant change in broad-spectrum antibiotic use was seen at the intervention wards receiving academic detailing, the control group and for other intervention wards per specialty (Appendix: Table 5 and Fig. 1).

Local targets

Intervention wards were invited to set local targets for follow up after the intervention sessions (Table 4). The pulmonary ward at Hospital A had a significant and intended 30% increase in the targeted use of Penicillin G 2 mill IU × 4 for patients with pneumonia and COPD exacerbations post intervention ($p < 0.001$). The use of Ciprofloxacin at the ward of gastroenterology was reduced at all time points following the intervention, though not statistically significant (Appendix: Table 6). The other study wards either [a)] did not reach consensus on targets [b)] did not identify any targets or [c)] the identified target was not evaluable.

Secondary outcome measures

When analysed per intervention, there was a decrease of 0.7 days in the mean length of stay for patients in the audit with feedback group ($p = 0.037$) (Table 2). In the academic detailing group, 30-days readmission had an absolute decrease of 7.4% ($p = 0.044$). Compared with

Table 3 Percentage of adherence to antibiotic guidelines in periods before and after interventions were implemented

Group	Group description	N Before/ after	Period		Absolute Change %	P for change[a]	P for Interaction[b]
			Before n (%)	After n (%)			
Intervention							
Control	All specialties	350/169	174 (50)	84 (50)	0	0.998	
Interventions	All specialties	929/354	556 (60)	234 (66)	6	**0.04**	0.252
Academic detailing	All specialties	451/172	265 (59)	111 (65)	6	0.188	0.353
Audit with feedback	Infectious diseases + Pulmonary medicine	478/182	291 (61)	123 (68)	7	0.111	0.265
Specialty							
Pulmonary medicine	Both interventions	427/162	249 (58)	116 (72)	14	**0.003**	**0.034**
Infectious diseases	Both interventions	424/153	268 (63)	99 (65)	2	0.741	0.857
Gastroenterology	Academic detailing	78/39	39 (50)	19 (49)	-1	0.896	0.556

[a]By chi-square test per group
[b]By logistic regression of given group vs control wards (all specialties), giving the *p*-value for the interaction between group and period
P-values < 0.05 are given in boldface

Table 4 Local targets set by study intervention wards and outcome for targeted change in prescribing practice

Hospital	Ward	Intervention	Targets	Outcome
A	Pulmonary medicine	Audit with feedback	Increase the use of Penicillin G 2 mill IU × 4 to treat pneumonia (CAP) and infectious COPD exacerbations	30% increase ($p < 0.001$)[a]
A	Gastro enterology	Academic detailing	Reduce ciprofloxacin use for inflammatory bowel disease, and shift to Co-trimoxazol *(indication outside national antibiotic guideline)*	Too few patients with targeted indication to assess outcome by indication. Assessed by use of sales statistics. Reduction in use of Ciprofloxacin at 3, 6, 12 and 18 months following the intervention (not significant)[b] (Appendix Table 6).
B	Pulmonary medicine	Academic detailing	Target areas discussed: - Reevaluation of initiated treatment on arrival to ward and - after 48–72 h - Increase use of CRB-65 and antibiotic guideline	*Consensus on 1–2 targets not achieved*
B	Infectious diseases	Audit with feedback	Target areas discussed: - Increase use of Penicillin G 2 mill × 4 to treat infectious COPD exacerbations - Reassess length of iv-antibiotics for patients with osteomyelitis - Increase consultants presence in the emergency room to increase guidelines adherence on admission - Reevaluation of treatment during the patient stay	*Consensus on 1–2 targets not achieved*
C	Infectious diseases	Academic detailing	*No target area identified.*	*No target area identified*

[a]By chi-square test [b]By Interrupted time series analysis (Appendix Table 6)

the control group, these findings were not statistically significant. In-hospital death, 30-day mortality, 30-day readmission and length of stay for the other groups were not significantly changed (Table 2).

Discussion

This study highlights the effect of engaging local stakeholders (physicians) in setting specific targets for change in antibiotic prescribing behaviours. A specific target area, which is easy to remember and act upon, makes it possible to achieve change within a short timeframe, as observed in the pulmonary ward at Hospital A where adherence to targeted behaviour increased by 30%. Another finding was how the effect of interventions differed across specialties. Both interventions were more effective at the pulmonary wards, than wards of infectious diseases and gastroenterology.

Interventions to improve antibiotic prescribing practices have shown a 15% average increase in adherent prescribing in intervention wards, however the effect depends on how they are designed and implemented [6, 18]. When Schouten et al. tailored interventions to each intervention hospital; they achieved an average 14% increase in adherence to guidelines for empiric treatment of lower respiratory tract infections (LRTI). The level of change was very similar for all the intervention hospitals, although it was not stated how the patients were distributed across the wards of internal- and pulmonary medicine [19]. Their results are comparable to our findings at the pulmonary wards, with a 14% absolute change in adherence to guidelines, while it differs substantially from effects seen across infectious diseases and gastroenterology wards. A single site Norwegian study focusing on pneumonia and COPD exacerbations within pulmonary medicine, added a pocket guideline to their audit with feedback intervention [20]. From a baseline adherence of 62%, similar to our study, adherence was increased by 22%.

Involving clinicians in identifying challenges, finding solutions and setting local targets is both reasonable and recommended and has previously proven effective in increasing compliance to target behaviour [6, 21–23]. Jobson et al. increased the timeliness of antibiotics for febrile patients with central lines presenting in the ED from 63 to 99% [23]. They exceeded their goal of 90% timeliness through active engagement of the caregiving staff and the use of multiple plan-study-do-act-cycles (PDSA-cycles) [24]. At the pulmonary ward at hospital A, the audit data made it easy for clinicians to identify local challenges and set a specific, measureable, attractive and realistic target for change in prescribing behaviour and we found a similar change of 30% increase in target behaviour.

The wards receiving audit with feedback had different case-mix. In infectious diseases, 41% of patients were treated for pneumonia and COPD exacerbations, compared to 71% in the pulmonary ward. This could partly explain the lack of effect seen in the infectious disease ward, as pneumonia and COPD exacerbations were the selected focus for the feedback sessions. Empirical therapy according to guidelines across diagnoses was the main outcome measure for all intervention wards. Pre-audits at every intervention ward would have made it easier to identify each ward's prescribing challenges, and tailor the interventions to context specific improvement areas for each ward. As this study is

intervening in the very heart of ID-specialists' area of expertise, it may also be a bigger challenge to advocate a shift in prescribing practice towards general antibiotic guidelines, limiting the autonomy of the prescriber [25].

The national guideline was published approximately 6 months prior to study initiation and some wards had already started promoting its use [16]. A previous study by Skodvin et al. showed that interns and residents heavily relied on guidelines when initiating antibiotic treatment [26]. This could have caused a positive shift in prescribing practice already, decreasing the potential for absolute effect of interventions. Including physicians mainly working in the emergency room in interventions could have given increased effects, but intervention and control wards at the same hospital would then be challenging because of spill over effects between the wards.

Champions can play a powerful role in behaviour change [25, 26]. Special emphasis was made on using local champions for developing and implementing interventions as they are familiar to the ward physicians, know possible barriers and facilitators and could tailor the presentations to the ward's needs. Local involvement could also increase the chance of continuous work within the area after study completion. An example of tailoring is adding information about a previous local outbreak of Vancomycin-resistant enterococci (VRE) to the audit with feedback session at the pulmonary ward at Hospital A, to increase local ownership. At the gastroenterology ward, academic detailing was performed by an ID-physician. During evaluation, he suggested that including a physician from the gastroenterology ward could have increased the ownership of the intervention and the identified target. Interventions were only applied at one time-point during the study period. Adding more intervention sessions could probably have increased the effects seen [6].

We aimed to achieve responsible antibiotic prescribing practice in a complex hospital setting. This study is a "real-life" study, including the most common infections treated at hospitals in the western world and three specialties in three separate hospitals where patterns of prescribing may differ, as will patient mix. All three hospitals and specialties contributed both to the intervention and control groups, reducing the potential for confounding and increasing external validity of the findings. The study was initiated in a "normal" clinical situation and not as a response to an outbreak. Random time effects should therefore be reduced. Seasonality is likely, but the inclusion of control groups within the same time period allow us to control for the effects. Findings should be generalizable to other hospital wards within the same specialties and in settings with a similar, relatively flat organizational structure.

The short post-intervention period and skewness of data between pre- and post-intervention periods is the major limitation to this study, caused by the fixed date for study period when applying for study approval and the substantial workload for manual data collection of individual prescription data. This also led to insufficient power to look at intervention effect on adherence at each cluster. Activity-adjusted antibiotic sales statistics for broad-spectrum antibiotics provides however the opportunity to assess change in levels and trends of broad-spectrum antibiotic use, indicating prescribing behaviour over longer periods of time.

In our study we found that the context we implemented interventions in were even more important than the type of intervention selected. Tailoring the interventions to the local context and challenges of each study ward and more focus on using SMART[1] goals during the planning and implementation of interventions, could increase the possibility to get the desired outcomes. LRTIs are common in stewardship intervention studies [6, 18]. It is a wise place to start optimization of antibiotic prescribing, because the volume of patients secures great impact on total antibiotic use. More severe diagnoses, like infections in immunocompromised patients may be a bigger challenge to target in behaviour change. Especially inexperienced physicians may feel the need to secure adequate coverage with broad-spectrum antibiotics at treatment initiation and the thought of "never change a winning team" may lead to lack of re-evaluation and focusing treatment [26].

When designing behavioural change interventions in antibiotic stewardship programs, we need careful planning. Attention should be paid to local barriers and facilitators for change and we should have in-depth knowledge of local antibiotic prescribing practices and case mix to guide the focus of interventions.

Conclusions

Pulmonary intervention wards had an increase in adherence, independent of applied intervention, while no effect was seen at wards of infectious diseases and gastroenterology. This shows that the context in which interventions are implemented is important and may also indicate that pulmonary wards may be a good place to start when changing antibiotic prescribing behavior in similar hospital settings. We also showed that when ward physicians were actively involved in the process of discussing their own prescribing behavior and could identify and agree on specific targets for change in prescribing practice, great change was achieved within a short timeframe.

Endnotes

[1]SMART: Specific, Measurable, Attractive, Realistic and Time-bound

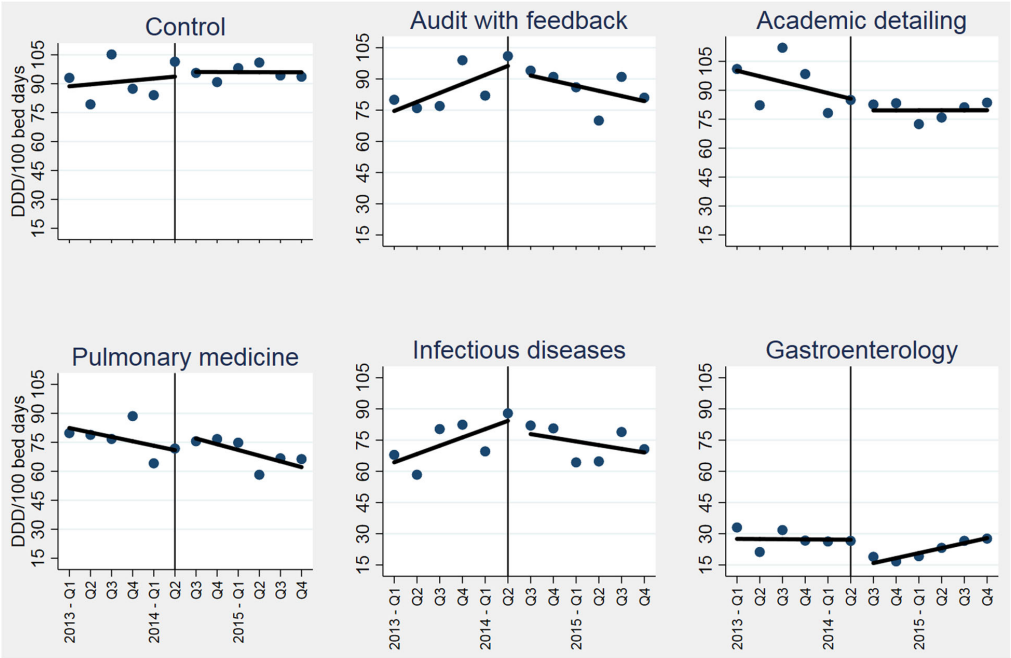
Appendix

Appendix show results for interrupted time series analysis of the use of broad- spectrum antibiotics for intervention groups and specialties:

Table 5 Interrupted time series analysis of the use of broad-spectrum antibiotics in defined daily doses per 100 bed days for intervention and control groups from 2013 to 2015

		Audit with feedback (Intervention wards)			Academic detailing (Intervention wards			Pulmonary medicine (Intervention wards)			Infectious diseases (Intervention wards)			Gastroenterology (Intervention ward)			Control (all specialties)		
		Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value
DDD per 100 bed days	Const	70.288	5.854	0.000	103.078	8.415	0.000	84.736	5.056	0.000	60.371	7.407	0.000	27.605	1.592	0.000	87.691	5.387	0.000
	AR	−0.495	0.326	0.172	−0.247	0.370	0.525	−0.429	0.348	0.257	−0.239	0.372	0.542	−0.796	0.203	0.006	−0.512	0.323	0.157
Pre-slope		4.332	1.523	**0.025**	−2.903	2.181	0.225	−2.292	1.312	0.124	3.985	1.926	0.077	−0.075	0.411	0.861	1.002	1.404	0.498
Difference between pre- and post-slope		−6.789	2.028	**0.012**	2.920	2.985	0.360	−0.669	1.770	0.717	−5.753	2.615	0.064	2.472	0.545	**0.003**	−1.033	1.863	0.597
Level effect																			
3 months		−8.971	7.809	0.288	−3.162	11.053	0.783	8.314	6.686	0.254	−10.360	9.839	0.327	−11.157	2.082	**0.001**	1.407	7.191	0.850
6 months		−15.761	8.313	0.100	−0.242	11.823	0.984	7.646	7.131	0.319	−16.112	10.503	0.169	−8.685	2.220	**0.006**	0.374	7.672	0.962
12 months		−29.338	10.490	**0.027**	5.599	15.115	0.722	6.308	9.052	0.508	−27.617	13.357	0.077	−3.740	2.811	0.225	−1.691	9.694	0.866
18 months		−42.916	13.561	**0.016**	11.439	19.708	0.580	4.971	11.751	0.685	−39.122	17.355	0.059	1.205	3.640	0.750	−3.757	12.525	0.773

Broad-spectrum antibiotics were defined as penicillins with enzyme inhibitor, 2. and 3. generation cephalosporins, carbapenems and quionolones



Broad-spectrum antibiotics were defined as penicillins with enzyme inhibitor, 2. and 3. generation cephalosporins, carbapenems and quionolones

Fig. 1 Use of broad-spectrum antibiotics at intervention wards and per specialty intervention wards compared to control wards

Table 6 Interrupted Time Series analysis of the use of Ciprofloxacin at the ward of Gastroenterology, Hospital A, from 2013 to 2015

		Estimate	SE	*p*-value
Ciprofloxacin DDD per 100 bed days	Constant	10.291	1.283	0.000
	AR	−0.090	0.520	0.868
Pre-slope		−0.169	0.341	0.636
Difference between pre- and post-slope		−0.106	0.461	0.825
Level effect				
3 months		−4.254	1.905	0.061
6 months		−4.360	1.956	0.061
12 months		−4.571	2.343	0.092
18 months		−4.783	2.975	0.152

Use of Ciprofloxacin is measured as quarterly sales of Ciprofloxacin, adjusted for bed days

Abbreviations

COPD: Chronic obstructive pulmonary disease; CRB-65: Score of community acquired pneumonia assessing: Confusion – Respiratory rate – Blood pressure – Age (65-years of age or older); eGFR: estimated Glomerular Filtration Rate; EPOC: Cochrane Effective Practice and Organization of Care; ITS: Interrupted time series; LRTI: Lower respiratory tract infection; SMART goals: Specific – Measurable – Achievable/Attractive – Realistic – Time-bound

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Availability of data and materials

The datasets generated and/or analysed during the current study regarding individual patient data are not publicly available in concordance with the approval from the Data Protection Officer (2013/9352), but are available from the corresponding author on reasonable request. Data regarding use of broad-spectrum antibiotics for interrupted time series analysis are available from the corresponding author upon request.

Authors' contributions

Study design and initial concept of interventions: JSW, IS. Development and implementation of interventions: JSW, IS, LKSK, AT, MIN, DLM, OH. Data collection and validation: JSW, IS, LKSK, MIN. Data analysis: JSW, RMN, IS, SH. Interpretation of data: JSW, IS, SH, HSB, LKSK, AT, DLM, EC. Writing of manuscript: JSW, IS. Critical assessment and approval of manuscript: IS, LKSK, SH, HSB, EC, RMN, AT, DLM, OH, MIN. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, national and institutional standards [27]. The study was approved by the Data Protection Officer (2013/9352) and the Western Regional Committee for Medical and Health Research Ethics approved the waiver of informed consent (2013/1305). All patients received written information about the study, with opportunity to withdraw from the study. The study was not registered in a clinical trial database as randomization was conducted at cluster level only, with primary aim of investigating the effect of interventions on ward prescribing behaviour. Individual patient treatment was at the discretion of the treating physician.

Consent for publication

Not applicable

Competing interests

J.S.W received a 3-month grant in patient safety research for preparation of the manuscript, but the funder has not played any role in the design, execution, analysis or reporting of the research. Competing interests for other authors: None to declare.

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RESEARCH Open Access

The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study

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Abstract

Background: Clinical antibiotic prescribing guidelines are essential in defining responsible use in the local context. Our objective was to investigate the association between adherence to national antibiotic prescribing guidelines and patient outcomes across a wide range of infectious diseases in hospital inpatients.

Methods: Over five months in 2014, inpatients receiving antibiotics under the care of pulmonary medicine, infectious diseases and gastroenterology specialties across three university hospitals in Western Norway were included in this observational cohort study. Patient and antibiotic prescribing data gathered from electronic medical records included indication for antibiotics, microbiology test results, discharge diagnoses, length of stay (LOS), comorbidity, estimated glomerular filtration rate (eGFR) on admission and patient outcomes (primary: 30-day mortality; secondary: in-hospital mortality, 30-day readmission and LOS). Antibiotic prescriptions were classified as adherent or non-adherent to national guidelines according to documented indication for treatment. Patient outcomes were analysed according to status for adherence to guidelines using multivariate logistic, linear and competing risk regression analysis with adjustments made for comorbidity, age, sex, indication for treatment, seasonality and whether the patient was admitted from an institution or not.

Results: In total, 1756 patients were included in the study. 30-day-mortality and in-hospital mortality were lower (OR = 0.48, $p = 0.003$ and OR = 0.46, $p = 0.001$) in the guideline adherent group, compared to the non-adherent group. Adherence to guideline did not affect 30-day readmission. In linear regression analysis there was a trend towards shorter LOS when LOS was analysed for patients discharged alive (predicted mean difference – 0.47, 95% CI (– 1.02, 0.07), $p = 0.081$). In competing risk analysis of LOS, the adherent group had a subdistribution hazard ratio (SHR) of 1.17 95% CI (1.02, 1.34), $p = 0.025$ for discharge compared to the non-adherent group.

Conclusions: Adhering to antibiotic guidelines when treating infections in hospital inpatients was associated with favourable patient outcomes in terms of mortality and LOS.

Keywords: Antimicrobial stewardship, Antibiotic stewardship, Antibiotic guidelines, Adherence, Patient outcome, Mortality, Readmission, Length of stay

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Background

Antibiotics constitute an important class of medicines, where the use of a substance has implications beyond the patient being treated. Antimicrobial stewardship is a systematic way to improve antibiotic use in hospitals and has most recently been defined as "a coherent set of actions which promote using antimicrobials responsibly" [1]. Clinical guidelines for antibiotic use are essential in defining responsible use in the local context and are one of the core elements of stewardship programmes [2]. Studying the association between antibiotic use and patient outcomes is of great importance and can imply whether guideline-adherent prescribing practice is safe and secures equal – or better patient outcome. Most studies in this field are performed within lower respiratory tract infections and many are prone to confounding by indication, because patients with less severe illness are more likely to have received the more narrow-spectrum, guideline adherent therapy [3].

Norway has low, but steadily increasing antibiotic resistance rates [4]. Seven months prior to this study, new national guidelines for antibiotic use in hospitals were published [5]. We aimed to investigate if appropriate prescribing practices for hospitalised patients with a broad spectrum of infectious diseases were associated with patient outcomes when adjusted for major confounding factors.

Methods

Study design and setting

We performed an observational study in the cohort of patients from a previously published cluster randomized controlled intervention study, which was performed at three emergency care and teaching hospitals in Western Norway [6]. Hospital A and B are tertiary care hospitals with 1100 and 600 beds, respectively. Hospital C is a secondary care hospital with 160 beds. Hospital A is in addition referral hospital for hospitals B and C. Three medical wards from hospital A and B (infectious diseases, pulmonary medicine and gastroenterology) and two medical wards from hospital C (infectious diseases/general medicine and pulmonary/cardiac medicine) were included in the study. All hospitals were committed to be using the national guideline for antibiotic use for hospital inpatients [5].

Data collection

Adult patients (over 18 years old) were included in the study if they received antibiotics for a suspected or confirmed infection during admission, were discharged from a study ward between the 10th of February and the 11th of July 2014 and had a hospital stay of > 24 h and ≤ 21 days. Minimum length of hospital stay was defined to assure that included patients were seen by study ward physicians and maximum length to make manual data collection throughout the hospital stay feasible. Patients who either only received antibiotic prophylaxis, had orthopaedic prosthesis infections or had an indication for treatment not covered by the national guidelines, were not included. For patients readmitted during the study period, only the first stay was included in analysis. Where data regarding outcome was not possible to retrieve (e.g. tourists), or comorbidity data was unavailable, the patient was excluded. Data were collected manually from electronic medical records, including admission notes, medical charts, physician's notes, discharge letters and laboratory results. Data included patient demographics, indication for antibiotic treatment, antibiotic use, microbiology test results, estimated glomerular filtration rate (eGFR) on admission, length of stay (LOS), 30-day readmission, in-hospital and 30-day mortality, comorbidity and admittance from- or discharge to institution. Mortality data was continuously updated within the electronic medical record, using data from the Norwegian National Registry [7] Supplementary data on main diagnosis at discharge and comorbidity was retrieved by extraction from electronic medical records. Readmissions were only captured if patients were readmitted to the same hospital as the patient was discharged from.

Definitions

All substances comprising the ATC-group "Antibacterials for systemic use" (J01), metronidazole tablets (P01AB01) and vancomycin tablets (A07AA09) were included in the definition of antibiotics for this study [8].

Outcome measures

Primary outcome measure was 30-day mortality, defined as all-cause mortality during hospital stay or within 30 days of discharge from hospital.

Secondary outcome measures were

a) In-hospital mortality, defined as all-cause in-hospital mortality during study admission.
b) 30-day readmission, defined as all-cause acute readmission to the same study hospital as the patient was discharged from, within 30 days of discharge, for patients discharged alive and not transferred to another hospital.
c) Length of stay, defined as number of days from admission to discharge for the entire hospital stay for patients discharged alive, except for time spent at a hospital rehabilitation centre after discharge from a study ward. LOS was also analysed for all patients, with in-hospital mortality as competing risk.

Study variable

Adherence to national antibiotic guidelines refers to the choice of active substance(s) for the initial indication for treatment. Dosing of the substance(s) was not considered. Adherence was assessed by using syntax in SPSS, combining the variable for indication for treatment with the variable for prescribed treatment. Only the first-choice empirical regimens were regarded adherent. For patients with antibiotic allergies or kidney failure where chosen treatment was an alternative guideline regimen (not first choice), manual adjustment of the adherence variable was performed consistently throughout the study population. CRB-65-score[1] and the severity of pneumonia were usually not explicitly stated in the patient notes. Less severe and severe community acquired pneumonia were therefore assessed together, meaning that first line treatments for both conditions were considered adherent. Some patients had more than one working diagnosis on initiation of therapy. An ID-physician (BS) reviewed the diagnoses and decided indication for treatment for these patients, expecting initial therapy to be based on the most severe working diagnosis. Infections described as "suspected pneumonia" or "unspecified lower respiratory tract infection" on admission were assessed for adherence as community- or hospital acquired pneumonia. A working diagnosis as "suspected urinary tract infection" (UTI) was assessed as adherent if treatment was according to guideline treatment for either pyelonephritis or cystitis. For the indication "suspected pneumonia/UTI", treatment according to guideline recommendation for either diagnosis were considered adherent.

Adjustment variables

Indication for treatment was the indication for first treatment with antibiotics and was always an infection. Physicians' notes were used to identify indication for treatment and indication was not further assessed for validity. Indications were grouped into six main categories (Table 1). Indications which did not fit into the main categories were included in a seventh category of "Other infections". Empirical antibiotic treatment was specific for each indication and varied within each group.

Comorbidity was defined using the Charlson Comorbidity Index (CCI) [9, 10]. For each patient, up to eight diagnoses were extracted from the hospital electronic medical record at discharge. All extracted diagnoses were included in the calculation of CCI, using Stata syntax [11]. Estimated glomerular filtration rate on admission was originally planned as an adjustment variable, but as renal disease is included in CCI, this was discarded from analysis. Age was coded in age groups, starting with patients up to and including the age of 45 and thereafter given in groups of 20 years to the last group of above 85 years. Admission from an institution was defined as patients admitted at an institution with 24/7 care, e.g. another hospital or nursing home, within 48 h of admission. Adjustment for seasonality was performed by using the week of admission as adjustment variable.

Statistics/analysis

To analyse differences in patient characteristics between the groups with adherent and non-adherent treatment, we used chi-square test and two-sample t-test for categorical and continuous data, respectively. Univariate and multivariate logistic and linear regression were used to study the association between guideline adherent prescribing practice and patient outcome. Indication for treatment, comorbidity (CCI), age group, admittance from institution, sex and seasonality (week of admission) were evaluated as adjustment variables. Variables that in univariate regression analysis of 30-day mortality had a p-value of less than 0.2 (all evaluated variables) were included in multivariate analyses for all studied outcomes. In addition, we used robust variance estimation of regression coefficients to account for clustered observations on the same hospital ward.

Two sensitivity analyses were performed for 30-day mortality. In the first, grouping of indication for treatment was replaced by grouped discharge diagnoses as adjustment variable to evaluate whether estimates of association would change if diagnoses had changed from admission to discharge. In the second sensitivity analysis, grouping of indication for treatment was replaced by individual indications as an adjustment variable to evaluate whether the grouping of indications could influence the results.

As the linear regression models of LOS did not account for in-hospital mortality, we also performed a sensitivity analyses for this outcome by fitting a Fine-Gray model with in-hospital mortality as competing risk. In this analysis, we report associations as the subdistribution hazard ratio (SHR) with 95% confidence intervals, which denotes the magnitude of the relative difference in the subdistribution hazard function between adherent and non-adherent groups [12].

A p-value of < 0.05 was considered statistically significant for all analyses. Statistical analysis was performed using Stata SE version 15 (Stata Statistical Software, College Station, TX, USA).

Results

During the study period, 1783 patients were eligible for inclusion. We were not able to retrieve comorbidity data for 22 patients. For 5 patients who were tourists, outcome data was unavailable. In final analyses, 1756 patients were therefore included.

Table 1 Grouping of indications for treatment

	Indication for treatment
Lower respiratory tract infections (LRTI)	Community acquired pneumonia (normal and severe), healthcare associated pneumonia (normal and severe), unspecified lower respiratory tract infections, unknown – suspected pneumonia, aspiration pneumonia, atypical pneumonia, lung abscess, empyema.
Acute exacerbations of chronic obstructive pulmonary disease (COPD with LRTI)	Patients with COPD, presenting with LRTI (community and healthcare associated)
Sepsis	Focus area; lower respiratory tract, urinary tract, unknown focus, soft tissue, abdomen and catheter.
Skin and soft tissue infections (SSTI)	Erysipelas, cellulitis, abscess, other skin and soft tissue infections, mastitis, necrotising soft tissue infections, postoperative wound infection.
Gastrointestinal tract infections (GI-infections)	Helicobacter pylori-infection, gastroenteritis, peritonitis, cholecystitis/cholangitis, *Clostridium difficile* (C.Diff).
Urinary tract infections (UTI)	UTI – unspecified, pyelonephritis, lower UTI/cystitis, unknown-suspected UTI, catheter associated UTI.
Other infections	Suspected both pneumonia and UTI, meningitis, neutropenic fever, osteomyelitis, tonsillitis, arthritis, endocarditis, sinusitis/otitis, and infected intravascular catheters

Indications within each group are given in decreasing order of frequency

There was a significant difference between the adherent and non-adherent group with regards to the groups of indication for treatment, with a higher percentage of LRTI's in the adherent group and more patients with GI-infections, UTIs and "other" infections in the non-adherent group (Table 2). The non-adherent group also had a higher proportion of patients admitted from an institution.

Thirty-day mortality and in-hospital mortality was significantly lower in patients receiving guideline adherent treatment, with an odds ratio (OR) of 0.48, with p = 0.003 for 30-day mortality and OR = 0.46, with p = 0.001 for in-hospital mortality (Table 3).

During admission, 70 patients died and 16 patients were discharged to another hospital, so in analysis of 30-day readmission and LOS, 1670 patients were included (Table 4). There was no evidence of any differences in 30-day readmission between patients receiving guideline adherent treatment or not. Comorbidity (CCI) and seasonality (the week of admission) were the only variables significantly associated with 30-day readmission. In the linear regression analysis of LOS, there was a trend towards shorter LOS when guideline adherent treatment was prescribed at treatment onset (− 0.47 days, p = 0.087) (Table 4). This result was supported by the competing risk analyses of LOS in which the adherent group was associated with a 17% increase in the rate of discharge, compared with the non-adherent group (Additional file 1: Table S1; SHR 1.17, 95% CI (1.02, 1.34), p = 0.025).

Other analysis

We performed two sensitivity analyses for 30-day mortality. In the first analysis, grouped indications for treatment were substituted with grouped discharge diagnoses, which could be infections or non-infections. The association between adherent treatment and mortality now had an OR = 0.51, 95% CI (0.33, 0.80) with p = 0.003 (not shown in tables). In the second analysis, grouped indications were substituted with the individual indications in the regression model. This changed the estimated OR from 0.48 to 0.54, 95% CI (0.30, 0.99), p = 0.045 (not shown in tables). For the last analysis, model fit was poor for indications with few patients and no observed mortality. Only 1591 patients were kept in the model for this analysis.

Discussion

The main findings of this study are that adherence to antibiotic guidelines at initiation of antibiotic therapy is associated with lower in-hospital- and 30-day mortality and shorter LOS. Adherence to guidelines was not significantly associated with 30-day readmission.

Structure and process indicators can help us evaluate whether our antibiotic stewardship efforts are moving us in the right direction [13–16]. A frequently asked question is whether behavioural change interventions lead to more appropriate antibiotic use, often measured as adherence to guidelines or profile of antibiotic consumption [3, 6, 17]. An equally important question is whether appropriate antibiotic use leads to the desired outcomes, like reduction in bacterial resistance rates, adverse events and mortality [3, 18]. Overprescribing outside guidelines often result from fear for the patients' well-being, and are linked to patients who are severely ill or have an unclear diagnosis [19]. The expectation of clinicians' to change their antibiotic prescribing behaviours needs to be supported by evidence-based guidelines and expert advice to reassure clinicians that guideline adherent antibiotic prescribing is safe and effective.

Table 2 Patient characteristics and outcome by adherence or non-adherence to guidelines

	Non-adherence (*N* = 667)	Adherence (*N* = 1089)	*P*-value
Patient characteristics			
Indication for treatment			
LRTI	161 (24.1)	372 (34.2)	**< 0.001**
COPD with LRTI	124 (18.6)	230 (21.1)	
Sepsis	111 (16.6)	180 (16.5)	
SSTI	72 (10.8)	115 (10.6)	
GI-infection	44 (6.6)	34 (3.1)	
UTI	80 (12.0)	99 (9.1)	
Other infections	75 (11.2)	59 (5.4)	
Charlson Comorbidity Index			
CCI = 0	240 (36.0)	432 (39.7)	0.083
CCI = 1	212 (31.8)	373 (34.3)	
CCI = 2	119 (17.8)	141 (13.0)	
CCI = 3	45 (6.8)	65 (6.0)	
CCI = 4	24 (3.6)	33 (3.0)	
CCI > 4	27 (4.1)	45 (4.1)	
Age, mean (std.dev.)	67.3 (18.2)	67.4 (19.1)	0.885
Age			
<=45	92 (13.8)	161 (14.8)	0.680
46–65	156 (23.4)	240 (22.0)	
66–85	320 (48.0)	508 (46.7)	
>85	99 (14.8)	180 (16.5)	
Admitted from institution	120 (18.0)	135 (12.4)	**0.001**
Discharged to institution	182 (29.0)	258 (24.4)	0.090
Sex			
Male	352 (52.8)	565 (51.9)	0.717
Female	315 (47.2)	524 (48.1)	
Outcome			
In-hospital mortality	38 (5.7)	32 (2.9)	**0.004**
30-day mortality	75 (11.2)	67 (6.2)	**< 0.001**
30-day readmission (*n* = 623/1047)	140 (22.5)	206 (19.7)	0.173
LOS[a], mean (std.dev.) (*n* = 623/1047)	7.3 (4.4)	6.7 (4.1)	**0.004**

[a]*LOS* = Length of stay. All analysis was performed using chi-square tests, except mean age and LOS which were analysed using two-sample t-test. *P*-values in boldface are statistically significant (<0.05)

Readmission as an outcome measure in relation to antibiotic prescribing is not frequently reported [18]. Three studies within community acquired pneumonia show no association between guideline adherence and 30-day readmission, which is in agreement with the findings in this present study [20–22].

Evidence on the association between guideline adherence and mortality is diverse. Arnold et al. found that in-hospital mortality in patients receiving guideline-adherent treatment for community acquired pneumonia was 8% (95% CI, 7–10%), compared to 17% (95% CI, 14–20%) in the group of nonadherence [23]. Asadi et al. did not find any effect on mortality alone when looking at this variable in hospitalised patients with community acquired pneumonia, although the composite endpoint of death or ICU-admissions favoured guideline adherence [24]. In a Danish study of CAP, with similar resistance rates and treatment guidelines as Norway, Egelund et al. found that patients treated with guideline adherent penicillin monotherapy had lower CURB-65 score, less comorbidity and less in-hospital mortality in unadjusted analysis, while no association between mortality and guideline adherence was found in

Table 3 Adjusted analysis of the association between guideline adherence, in-hospital and 30-day mortality

	All patients	In-hospital mortality			30-day mortality		
	(*N* = 1756)	(n_1 = 70)	(*N* = 1756)	P	(n_2 = 142)	(*N* = 1756)	P
	n (%)	n (%)	OR (95% CI)		n (%)	OR (95% CI)	
Adherence to guideline							
No	667 (38.0)	38 (5.7)	1.00		75 (11.2)	1.00	
Yes	1089 (62.0)	32 (2.9)	0.46 (0.29, 0.74)	0.001	67 (6.2)	0.48 (0.29, 0.78)	0.003
Indication for antibiotic treatment							
LRTI	533 (30.4)	35 (6.6)	1.00		69 (13.0)	1.00	
COPD with LRTI	354 (20.2)	11 (3.1)	0.44 (0.22, 0.86)	0.017	22 (6.2)	0.45 (0.35, 0.59)	< 0.001
Sepsis	291 (16.6)	14 (4.8)	0.69 (0.41, 1.15)	0.153	24 (8.3)	0.59 (0.36, 0.97)	0.038
SSTI	187 (10.7)	1 (0.5)	0.12 (0.02, 0.66)	0.015	3 (1.6)	0.17 (0.03, 1.09)	0.061
GI-infection	78 (4.4)	3 (3.9)	0.75 (0.10, 5.72)	0.782	6 (7.7)	0.78 (0.22, 2.80)	0.708
UTI	179 (10.2)	2 (1.1)	0.12 (0.27, 0.55)	0.006	11 (6.2)	0.35 (0.19, 0.63)	0.001
Other infections	134 (7.6)	4 (3.0)	0.35 (0.17, 0.72)	0.004	7 (5.2)	0.29 (0.19, 0.46)	< 0.001
Charlson Comorbidity Index							
CCI = 0	672 (38.3)	9 (1.3)	1.00		20 (3.0)	1.00	
CCI = 1	585 (33.3)	19 (3.3)	1.60 (0.52, 4.86)	0.411	36 (6.2)	1.40 (0.95, 2.04)	0.088
CCI = 2	260 (14.8)	16 (6.2)	2.66 (0.72, 9.83)	0.143	31 (11.9)	2.67 (1.45, 4.90)	**0.002**
CCI = 3	110 (6.3)	6 (5.5)	2.27 (0.60, 8.60)	0.228	16 (14.6)	3.18 (1.75, 5.78)	**< 0.001**
CCI = 4	57 (3.3)	8 (14.0)	6.39 (1.64, 24.93)	**0.008**	14 (24.6)	6.79 (3.31, 13.95)	**< 0.001**
CCI > 4	72 (4.1)	12 (16.7)	8.50 (3.80, 19.04)	**< 0.001**	25 (34.7)	12.04 (8.02, 18.08)	**< 0.001**
Age							
< =45	253 (14.4)	1 (0.4)	1.00		2 (0.8)	1.00	
46–65	396 (22.6)	7 (1.8)	2.35 (0.35, 15.70)	0.376	14 (3.5)	2.40 (0.53, 10.87)	0.257
66–85	828 (47.2)	39 (4.7)	5.42 (0.82, 35.67)	0.079	80 (9.7)	5.61 (1.51, 20.85)	**0.010**
> 85	279 (15.9)	23 (8.2)	10.13 (0.99, 103.78)	0.051	46 (16.5)	9.81 (1.91, 50.36)	**0.006**
Admitted from institution							
No	1501 (85.5)	46 (3.1)	1.00		88 (5.9)	1.00	
Yes	255 (14.5)	24 (9.4)	2.53 (1.45, 4.43)	**0.001**	54 (21.2)	3.74 (2.69, 5.20)	**< 0.001**
Sex							
Male	917 (52.2)	49 (5.3)	1.00		88 (9.6)	1.00	
Female	839 (47.8)	21 (2.5)	0.42 (0.28, 0.61)	**< 0.001**	54 (6.4)	0.59 (0.39, 0.90)	**0.015**
Week of admission[a]			0.96 (0.93, 0.99)	**0.005**		0.96 (0.93, 0.997)	**0.031**

[a]Adjustment for seasonality was performed by using the week of admission as adjustment variable
In-hospital – and 30-day mortality was analysed using multivariate, logistic regression analysis with adjustment for clustering at individual sites. All variables are included in adjusted analysis. *P*-values in boldface are statistically significant (<0.05)

adjusted analysis [25]. However, a systematic review by Schuts et al., including 37 studies, showed that when empirical therapy was prescribed according to guidelines, the relative risk reduction of mortality was 35% [18]. The majority of patients included in these studies had pulmonary infections. These patients constituted almost half of our patient material. Our findings are coherent with this recent review, as we found that the odds ratio of in-hospital and 30-day mortality for the entire patient material was 0.46 and 0.48, respectively when guidelines were followed.

LOS was also favourably associated with adherent treatment in this study. The SHR was 1.17 for patients with guideline-adherent treatment, meaning that the rate of discharge was 17% higher for this group compared to the rate for the non-adherent group. Although not significant, there was a trend towards shorter LOS when analysed with linear regression analysis. 0.47 days constitutes 6.8% of the mean

Table 4 Adjusted analysis of the association between guideline adherence, 30-day readmission and length of stay

	All patients	30 day readmission			Length of stay		
	(*N* = 1670)	(*N* = 346)	(*N* = 1670)	P	(*N* = 1670)	(*N* = 1670)	P
	n (%)	n (%)	OR (95%CI)		Mean (S.D)	Coeff. (95% C.I.)	
Adherence to guideline							
No	623 (37.3)	140 (22.5)	1.00		7.3 (4.4)		
Yes	1047 (62.7)	206 (19.7)	0.87 (0.67, 1.14)	0.321	6.7 (4.1)	−0.47 (−1.02, 0.07)	0.081
Indication for antibiotic treatment							
LRTI	492 (29.5)	100 (20.3)	1.00		7.0 (4.3)		
COPD with LRTI	341 (20.4)	88 (25.8)	1.17 (0.80, 1.73)	0.421	6.6 (3.8)	−0.79 (−1.65, 0.08)	0.069
Sepsis	275 (16.5)	46 (16.7)	0.81 (0.54, 1.21)	0.303	7.0 (3.9)	0.22 (−0.73, 1.18)	0.605
SSTI	184 (11.0)	29 (15.8)	0.89 (0.62, 1.28)	0.522	6.2 (4.1)	−0.17 (−1.44, 1.10)	0.761
GI-infection	75 (4.5)	18 (24.0)	1.26 (0.64, 2.51)	0.503	7.3 (4.2)	0.53 (− 0.75, 1.81)	0.363
UTI	176 (10.5)	43 (24.4)	1.30 (0.85, 2.01)	0.229	7.1 (4.4)	0.10 (−0.74, 0.95)	0.781
Other infections	127 (7.6)	22 (17.3)	0.78 (0.51, 1.18)	0.240	7.5 (5.1)	0.53 (−0.83, 1.89)	0.386
Charlson Comorbidity Index							
CCI = 0	656 (39.3)	97 (14.8)	1.00		6.3 (3.9)		
CCI = 1	562 (33.7)	117 (20.8)	1.35 (1.03, 1.76)	**0.029**	6.9 (4.0)	0.60 (−0.32, 1.53)	0.168
CCI = 2	241 (14.4)	73 (30.3)	2.26 (1.46, 3.52)	**< 0.001**	7.3 (4.2)	0.87 (0.06, 1.68)	**0.039**
CCI = 3	103 (6.2)	27 (26.2)	1.77 (1.12, 2.82)	**0.015**	7.7 (5.0)	1.30 (−0.79, 3.38)	0.185
CCI = 4	49 (2.9)	16 (32.7)	2.55 (1.73, 3.76)	**< 0.001**	9.1 (5.4)	2.64 (− 0.42, 5.70)	0.081
CCI > 4	59 (3.5)	16 (27.1)	1.88 (0.89, 3.95)	0.098	9.1 (5.2)	2.42 (1.15, 3.69)	**0.003**
Age							
< =45	250 (15.0)	37 (14.8)	1.00		5.7 (4.1)		
46–65	387 (23.2)	75 (19.4)	1.07 (0.71, 1.62)	0.743	6.6 (4.0)	0.74 (0.45, 1.03)	**0.001**
66–85	779 (46.7)	175 (22.5)	1.15 (0.70, 1.90)	0.576	7.3 (4.3)	1.20 (0.58, 1.83)	**0.002**
> 85	254 (15.2)	59 (23.2)	1.24 (0.62, 2.49)	0.549	7.2 (4.3)	1.00 (−0.19, 2.18)	0.087
Sex							
Male	856 (51.3)	182 (21.3)	1.00		6.9 (4.3)		
Female	814 (48.7)	164 (20.2)	0.94 (0.81, 1.09)	0.411	6.9 (4.1)	0.02 (−0.64, 0.69)	0.942
Admitted from institution							
No	1441 (86.3)	301 (20.9)	1.00		6.8 (4.2)		
Yes	229 (13.7)	45 (19.7)	0.85 (0.62, 1.16)	0.307	7.2 (4.5)	0.02 (−0.53, 0.57)	0.938
Week of admission[a]			0.98 (0.96, 1.00)	**0.040**		−0.05 (− 0.09, − 0.002)	**0.044**

[a]Adjustment for seasonality was performed by using the week of admission as adjustment variable
All variables are included in adjusted analysis. 30-day readmission and length of stay was analysed using multivariate logistic- and linear regression, respectively with adjustment for clustering at individual sites. *P*-values in boldface are statistically significant (<0.05)

LOS for the study population (6.9 days) and 10.9% of a mean hospital stay in Norway, which is currently 4.3 days for patients outside the psychiatric wards [26]. The finding is in line with Schuts et al. which found that LOS was lower in 17 of the 24 included studies assessing association between adherence to guideline and LOS, favouring adherence [18]. The studies included in this review did however mainly include patients with lower respiratory tract infections, while our cohort had a large diversity of infectious diseases, and a maximum LOS of 21 days.

In observational cohort studies, the major limitation will be the potential for selection bias, in this case meaning that the patients with less severe illness may be more likely to receive guideline-adherent treatment [3]. By adjusting for indication for treatment, comorbidity, age, sex and seasonality, we have aimed to reduce the chance of confounding, but there could be differences in severity within each of the groups of indications, which could explain some of the difference seen in mortality between the adherent and non-adherent group. We did not have data on

severity score, which could have helped us limit this factor. The grouping of indications is both a strength and a limitation. Looking at patient outcome and adherence across some of the most common infections seen in hospitals, makes the results more generalizable, but may also be more difficult to interpret. When working diagnosis on initiation of treatment was uncertain (eg "suspected UTI") or there were more than one working diagnoses, we assessed adherence based on the most likely indication for treatment. Using working diagnoses for this purpose is limiting the generalizability of the results to individual groups of patients with more strict definitions of diagnoses. It does however reflect the daily challenge in the clinical setting where decisions about treatment have to be made before all diagnostic tools have been applied and results received and indicates that adhering to the most relevant guideline is a strength in this situation.

There were more patients admitted from an institution in the non-adherent group. This may be because patients admitted from institutions have more co-morbid disease and therefore present with more challenging diagnoses. Physicians may also consider the risk of resistant pathogens as higher and therefore prescribe more broad-spectrum agents. Furthermore, patients admitted from other institutions may already have received first line agents. Patient characteristics such as age, sex and comorbidity were very similar between the groups of patients receiving adherent or non-adherent treatment according to guidelines. The groups of UTI's, "other" infections and GI-infections were however larger in the non-adherent group and LRTIs were larger in the adherent group. Prescribing for pneumonia and COPD exacerbations was the focus of the audit with feedback performed in the study wards in the underlying intervention study [6]. The mix of patients within the groups of indications varied to some extent, such as a higher number of pyelonephritis in the non-adherent group (38.8%) compared to the adherent group (23.2%) and higher number of sepsis with abdominal focus in non-adherent group (4.5%) compared to adherent group (0.6%). In a sensitivity analysis for 30-day mortality, the grouped indications were substituted with the individual indications. This only changed the estimated OR slightly, to 0.53. The difference seen between the groups can therefore not be explained by these factors alone. Another mechanism is of course that treatment recommended in guidelines is best practice - securing evidence based effective treatment of the infection, while minimizing ecologic effects, side effects and impact on the microbiotia and therefore is associated with better patient outcomes than non-adherent treatment.

We analysed according to the first indication for treatment, which was usually a working diagnosis on admission to the hospital. The diagnosis may have changed during the hospital stay. We therefore did a sensitivity analysis for 30-day mortality, where indication for treatment was substituted with discharge diagnosis. The OR for the association between adherent treatment and mortality only changed slightly, from 0.48 to 0.51.

Thirty-day readmission was defined as readmissions to the same hospital that the patient was discharged from. This could have caused an underestimation of readmissions if the patients were readmitted to other hospitals. As inclusion of patients were limited to a LOS of a maximum of 21 days, the mean LOS may be underestimated. Adherence to guideline within the group of excluded patients was not collected and is therefore unknown.

This was a multicentre study with patients included from three hospitals and three specialties, which increases generalizability. The number of included patients is also substantial and we adjusted for known risk factors for morbidity and mortality, such as age, comorbidity and admittance from an institution. Given that patients with a LOS longer than 21 days were excluded, this limits generalizability of the estimate for this outcome.

Norwegian guidelines were developed with broad involvement of more than 80 clinicians from all over the country [5, 27]. They are prudent, with mainly narrow-spectrum antibiotics as first-line empirical treatment [5]. It is of great importance that guidelines constitute best practice, to provide security for both the patient and the treating clinician, and secures standardized, safe and effective antibiotic treatment, also in the absence of an infectious diseases specialist.

This study builds on findings in previous studies, indicating that up-to-date, hospital antibiotic guidelines are safe and are associated with favourable clinical outcomes for inpatients. Antibiotic guidelines should be developed and regularly updated to ensure that they always promote best practice in the treatment of infectious diseases in the local context. Accurate, structured and easy-to-access documentation on severity of infections should be included in the electronic medical record to secure availability of this data in quality improvement processes, evaluation of treatment and research.

To be able to control for more factors in analyses, future studies should aim to collect information about severity of infections and whether empirical treatment provided adequate coverage for the individual patients.

Conclusion

Empirical treatment according to guidelines on initiation of antibiotic therapy is associated with favourable clinical outcomes, such as in-hospital and 30-day mortality in our population of hospital inpatients.

Endnotes

[1]CRB-65 (Severity assessment for pneumonia: Confusion, raised Respiratory rate, low Blood pressure and age 65 years or more).

Additional file

Additional file 1: Table S1. Length of stay analysed with competing risk analysis (Fine and Gray). (DOCX 19 kb)

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Availability of data and materials
The datasets generated and/or analysed during the current study regarding individual patient data are not publicly available in concordance with the approval from the Data Protection Officer (2013/9352), but are available from the corresponding author on reasonable request.

Authors' contributions
JSW, SH and IS designed the study and data was collected by JSW, IS, LKSK, MIN, BS and TV. Data validation was performed by JSW, IS, LKSK and BS, while JSW, RMN, IS and SH did the data analyses. All authors performed data interpretation. JSW and IS wrote the manuscript, while all authors performed critical assessment during the writing process, read and approved the final manuscript.

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, national and institutional standards [28]. The study was approved by the local data protection officer (2013/9352) and the regional ethical committee approved the waiver of informed consent (2013/1305). All patients were informed in writing about the study taking place and given the opportunity to withdraw.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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III

Identifying targets for antibiotic stewardship interventions through analysis of the antibiotic prescribing process in hospitals - a multicentre observational cohort study

Abstract

Background: In order to change antibiotic prescribing behaviour, we need to understand the prescribing process. The aim of this study was to identify targets for antibiotic stewardship interventions in hospitals through analysis of the antibiotic prescribing process from admission to discharge across five groups of infectious diseases.

Methods: We conducted a multi-centre, observational cohort study, including patients with lower respiratory tract infections, exacerbation of chronic obstructive pulmonary disease, skin- and soft tissue infections, urinary tract infections or sepsis, admitted to wards of infectious diseases, pulmonary medicine and gastroenterology at three teaching hospitals in Western Norway. Data was collected over a 5-month period and included antibiotics prescribed and administered during admission, antibiotics prescribed at discharge, length of antibiotic therapy, indication for treatment and discharge diagnoses, estimated glomerular filtration rate (eGFR) on admission, antibiotic allergies, place of initiation of therapy, admittance from an institution, patient demographics and outcome data. Primary outcome measure was antibiotic use throughout the hospital stay, analysed by WHO AWaRe-categories and adherence to guideline. Secondary outcome measures were a) antibiotic prescribing patterns by groups of diagnoses, which were analysed using descriptive statistics and b) non-adherence to the national antibiotic guidelines, analysed using multivariable logistic regression.

Results: Through analysis of 1235 patient admissions, we identified five key targets for antibiotic stewardship interventions in our population of hospital inpatients; 1) adherence to guideline on initiation of treatment, as this increases the use of WHO Access-group antibiotics, 2) antibiotic prescribing in the emergency room (ER), as 83.6% of antibiotic therapy was initiated there, 3) prescribing for patients admitted from other institutions, as this was significantly associated with non-adherence to guideline (OR=1.44 95% CI 1.04, 2.00), 4) understanding cultural and contextual drives of antibiotic prescribing, as non-adherent prescribing differed significantly between the sites of initiation of therapy (between hospitals and ER versus ward) and 5) length of therapy, as days of antibiotic therapy was similar across a wide range of diagnoses and with prolonged therapy after discharge.

Conclusions: Analysing the process of antibiotic prescribing in hospitals with patient-level data identified important targets for antibiotic stewardship interventions in hospitals.

Background

Suboptimal use of antibiotics is a key driver of antibiotic resistance [1]. In order to improve the antibiotic prescribing process, we need to understand it. Historically, antibiotic sales statistics have been easy to collect, and are therefore widely used as a proxy indicator to monitor antibiotic prescribing [2-5]. Although analyses of antibiotic sales data are useful at an aggregated level, they do not specify patient level use or outcomes. Whilst providing a baseline, such data cannot be used to assess the appropriateness of antibiotic prescribing, limiting opportunities for optimising antibiotic stewardship interventions. Accurate, patient level assessment of antibiotic prescribing is an essential step in optimising antibiotic use. Audit and prevalence studies with manual data collection are time-consuming, but often necessary to retrieve this information. Many hospitals still lack electronic medical records that allow automated extraction of antibiotic prescription data with accompanying indications for treatment [6-8]. The introduction of WHO Access, Watch and Reserve (AWaRe) categories have provided a framework for analysing antibiotic consumption, focusing on limiting unnecessary use of watch and reserve antibiotics [9, 10]. We present the findings of an observational multicentre cohort study aiming to identify targets for antibiotic stewardship interventions by analysing the antibiotic prescribing process from admission to discharge for individual patients.

Methods:

Study design and setting

This was an observational, multicentre cohort study across the wards of infectious diseases, pulmonary medicine and gastroenterology at three teaching hospitals in Western Norway [11]. The largest hospitals (denoted A and B hereafter) are emergency care, university hospitals with 1100 and 600 beds, respectively, covering most specialities, except transplant surgery. Hospital C is an emergency care, teaching hospital with 160 beds, which is in close collaboration with Hospital A.

Data collection

The cohort included patients recruited to an antibiotic stewardship intervention study and consisted of adult patients discharged from study wards between the 10th of February and the 11th of July 2014 with a hospital stay ≥ 24 hours and ≤ 21 days, receiving antibiotics during admission for an indication within guideline recommendations [11, 12]. If a patient was readmitted during the study period, only the first stay was included. Patients with the following indications were included in the analysis: 1) lower respiratory tract infections (LRTI) 2) exacerbation of Chronic Obstructive Pulmonary Disease (COPD ex) 3) urinary tract infections (UTI) 4) skin- and soft tissue infections (SSTI) and 5) sepsis. Patients were excluded if: a) they were admitted to intervention wards in the post-intervention period; and b) comorbidity and patient outcome data were missing.

Data were collected manually from electronic medical records, including admission notes from the emergency room, medical charts, physicians' clinical notes, discharge letters and laboratory test results. Data included patient demographics, indication for antibiotic treatment, antibiotic use throughout the hospital stay, discharge diagnoses, estimated glomerular filtration rate (eGFR) on admission, length of stay, 30-day readmission, in-hospital and 30-day mortality, comorbidity and admittance from institution. Coded data on discharge diagnoses were retrieved from the hospital administrative system.

Outcomes

The primary outcome measure was antibiotic regimens used throughout the hospital stay, grouped by AWaRe-categories and guidelines adherence on initiation of treatment and analysed at initiation of treatment, after first modification of regimen, and at discharge. Secondary outcome measures were antibiotic prescribing patterns by groups of diagnoses and non-adherence to the national antibiotic guidelines, analysed as association with study variables.

Patient characteristics and diagnoses

To assess comorbidity, the Charlson Comorbidity Index (CCI) was calculated based on ICD-10 diagnoses at discharge [13, 14]. CCI was categorised as CCI equal to 0, 1, 2, 3, 4 or >4, with zero being no registered comorbidity and >4 substantial comorbidity.

The initial working diagnosis, documented in the electronic medical record for prescribed antibiotics, was used as the principal indication. Patients and treatment regimens were grouped by indications according to Supplement 1, Table 1. For patients having several diagnoses, all diagnoses were documented and a variable indicating multiple working diagnosis was created. Co-author BS (Infectious diseases (ID)-physician) assessed patients with multiple working diagnoses and assigned a primary indication for treatment based on the expectation that the treating physicians were likely to choose antibiotic treatment covering the most severe working diagnosis. Accuracy of diagnoses was defined as the percentage of patients for whom the initial indication for antibiotic treatment matched the discharge diagnosis (group level), defined as the infectious disease diagnosis coded or written in free text in the discharge letter.

Antibiotic prescribing

Antibiotic regimens could include single or multiple antibiotics. Initially prescribed antibiotic regimens were assessed for adherence according to the Norwegian national antibiotic guidelines, as all hospitals included the national guidelines in their local antibiotic policy. Only first-choice empirical regimen for a given indication was regarded adherent. Assessment of adherence was performed using automated syntax in SPSS for Windows (IBM SPSS Statistics, version 24, USA). Indication for treatment was combined with prescribed active substance(s) to generate the adherence variable and adherence was thereafter adjusted manually for patients with kidney failure or antibiotic allergies.

Anti-infectives for systemic use (ATC-group J01), metronidazole tablets (ATC code P01AB01) and vancomycin tablets (A07AA09) were defined as antibiotics in this study. The prescribed antibiotic regimens were assigned to WHO AWaRe categories [9, 15]. For overview of AWaRe categories and included antibiotics, see Supplement 1, Table 2. Antibiotics belonging only to the "key access" category were included in the "access" category, while antibiotics belonging to "access-watch" and "watch" were included in the watch category. Since the use of antibiotics in the "reserve" category was minimal, the groups of "watch" and "reserve" were combined for analysis. Several antibiotics frequently used in Norway are not included in WHO AWaRe categories. To be able to include these patients in analysis, a modified version of AWaRe categories was prepared (Supplement 1, Table 2). Of the antibiotics not included in the original AWaRe categories, mecillinam, pivmecillinam, metenamin and tobramycin were added to the "access" category and cefuroxime was added to the "watch" category. If an antibiotic regimen contained both access and watch/reserve-group antibiotics, the regimen was classified as watch/reserve.

Modification of antibiotic therapy

Modifications that prescribing physicians made to the first antibiotic regimen were defined in four categories: escalation, de-escalation, change within same level or unchanged. Day 1 was the day antibiotic therapy was initiated. Patients with regimens in the unchanged category were not included in analysis of time to change. Definitions of modifications are given in Table 1. Assessment of antimicrobial spectrum and categorisation of change were performed and checked by ID-physicians (authors BS and IS, respectively). Examples are given in Supplement 1, Table 3.

Table 1: Modifications of antibiotic regimens

Process measures	Definition
Modification of therapy	
Escalation	Change from oral to intravenous (i.v.) antibiotic treatment within the same antibacterial spectrum, change to more broad-spectrum treatment, adding an antibiotic to a combination.
De-escalation	Change from i.v. to oral antibiotic treatment within the same antibacterial spectrum or change to more narrow-spectrum treatment.
Change same level	Change to a regimen within the same antibacterial spectrum and form of administration (i.v./oral).
Unchanged	Regimens where first change of therapy was discontinuation of antibiotics, either during admission or after discharge.
Time to first modification of AB regimen	Time to first escalation/de-escalation/change within same antibacterial spectrum and dosage form (change of active substance(s), i.v. to oral switch, stopping or adding an antibiotic).
Number of treatment regimens	The number of treatment regimens from initiation of treatment until antibiotics prescribed at discharge
Day of oral antibiotics	The first day that one or more oral antibiotics were given.

Duration of antibiotic therapy

Duration of antibiotic therapy was measured in days from the first to the last day of therapy and reported as: 1) mean total days of treatment, including prescribed treatment after discharge, 2) mean days of in-hospital antibiotic therapy and 3) mean days of therapy after discharge. When antibiotic treatment continued after discharge, the day of discharge was counted as in-hospital therapy. Information about antibiotic therapy after discharge was retrieved from the discharge letter and also reported as percentage of patients where post-discharge antibiotics were described.

Data analysis

Descriptive statistics were applied to describe the prescription patterns. To examine which factors were associated with non-adherence, we used univariable and multivariable logistic regression. A targeted selection of factors were evaluated for the multivariable logistic regression model: place of antibiotic therapy initiation, indication for treatment, hospital site, admission from institution, accuracy between indication for treatment and discharge infection diagnosis, sex, age group,

comorbidity measured by CCI, multiple working diagnoses, antibiotic allergies and eGFR. Variables that in univariable analysis had a p-value of less than 0.2 were included in the final model. Only the first four variables were associated with non-adherence in univariable analysis and included in the final multivariable model. P-values below 0.05 were considered statistically significant for all analysis. Stata SE version 15 (Stata Statistical Software, College Station, TX, USA) was used for all statistical analysis, while SPSS for Windows (IBM SPSS Statistics, version 24, USA) was used for assessment of adherence.

Results

During the study period, 1544 patients with available comorbidity and outcome data met inclusion criteria. Of these patients, 309 were admitted in the post-intervention period at intervention wards and was therefore excluded, leaving 1235 unique patients included in analysis for this study.

Diagnoses and patient characteristics

The characteristics of the patients are given in Table 2. The most frequent diagnosis was LRTI (33.4%), followed by COPD exacerbations (22.7%), sepsis (20.1%), SSTI (12.2%) and UTI (11.7%) (not shown in tables). In the group of patients with SSTI, 6.0 % of patients were admitted from an institution, compared to 20.7% for patients with UTI. When investigating accuracy between the groups of indications for empirical antibiotic treatment and discharge infection diagnoses, there was substantial variation with a range from 41.5% accuracy for patients initially diagnosed with sepsis, to 95.3% for patients diagnosed with SSTI.

>Table 2<

Empirical antibiotic prescribing

Prescribed antibiotic regimens were adherent to guidelines for 63% of patients (Table 3). Antibiotics belonging to the WHO AWaRe “Access” category were prescribed as initial regimen for 74% of patients

in total, while the remaining 26.0% of antibiotic regimens were from the "Watch/Reserve" category. Where initial antibiotic regimens were adherent to guidelines, 89% of regimens were in the WHO AWaRe access category (Figure 1). Second regimens included more antibiotics from the watch/reserve categories and 71% of regimens were now in the access category. At discharge, 85% of regimens from the adherent group were in the access category. Where initial antibiotic regimens were non-adherent to guidelines, only 49% of the regimens were in the access category. This increased to 61% for the second regimen and then again to 74% at discharge.

> Table 3<

>Figure 1<

The majority (83.6%) of antibiotic prescriptions were initiated in the emergency room, ranging from 64.8% of prescriptions for UTI to 96.8% for sepsis (Table 3). Initiating antibiotic therapy at the ward increased the likelihood for non-adherence to guidelines, compared to prescribing in the emergency room, with an odds-ratio (OR) of 1.7, 95% CI (1.24, 2.36) (Table 4). When compared to LRTI, all groups of diagnoses were associated with a higher likelihood of non-adherence, ranging from OR = 1.42, 95% CI (1.03, 1.98) for COPD ex to OR =1.62, 95% CI (1.09, 2.41) for UTI (all $p<0.05$). Being admitted to hospital B was associated with reduced OR of non-adherence compared to hospital A, with an OR=0.63, 95% CI (0.46, 0.86), p=0.004. Patients admitted from an institution had increased risk of receiving non-adherent antibiotic treatment, OR=1.44, 95% CI (1.04, 2.00), p=0.029. Other factors tested were not associated with prescriptions being non-adherent to guidelines.

>Table 4<

Modification of antibiotic therapy

The initial antibiotic regimen was modified during admission for 61.4% of the patients, and 20.6% of initial regimens was continued until discharge and then changed (Table 3). For the remaining patients, the initial antibiotic regimen was either stopped (9.7%) or continued after discharge (8.3%). This pattern varied between diagnoses. For patients with sepsis, 82.7% of initial antibiotic regimens were changed during admission, in contrast to 54.7% and 50.3% of regimens for SSTI and UTI patients, respectively.

De-escalation was the most frequent first modification of antibiotic regimens and in total, 56.4% of first modifications were de-escalations, across all diagnoses (Table 3). For patients whose therapy was modified, the mean day of change was 3.6 days with 95% CI (3.5, 3.8). The time from start of antibiotic therapy to first change varied from patients with sepsis where day 3.0 with 95% CI (2.7, 3.3) was the mean day of change to patients with LRTI where change occurred on day 4.0 with 95% CI (3.7, 4.2).

In total, 84.5% of patients received oral antibiotics during the course of treatment (Table 3). Time to oral treatment differed substantially between diagnoses, from 2.7 days, 95% CI (2.3, 3.1) for UTI's to 5.1 days, 95% CI (4.6, 5.5) for sepsis.

Duration of antibiotic therapy

The mean duration (in-house and post-discharge) of antibiotic therapy was 10.6 days, 95% CI (10.3, 10.9) (Table 3). Mean days of in-house and post-discharge therapy was similar across all diagnosis. Patients diagnosed with sepsis had the highest mean number of in-house antibiotic days at 6.6 days, 95% CI (6.1, 7.1), while patients with SSTI had the highest mean days of therapy after discharge and total days of antibiotics with 7.1 , 95% CI (6.4, 7.7) and 12.5 days 95% CI (11.6, 13.4), respectively. After discharge, 77.4% of patients continued with antibiotic therapy.

Discussion

This study has identified key gaps and potential targets in the antibiotic prescribing process in hospitals for antibiotic stewardship interventions:

Table 5: Identified gaps and potential targets for antibiotic stewardship interventions

Gaps identified	Potential targets
Guideline adherence increased the use of narrow spectrum WHO Access group antibiotics in this study setting	Promoting adherence to guidelines when prescribing empirical antibiotic therapy
Antibiotic therapy was initiated in the emergency room for 83.6% of patients	Targeting antibiotic prescribing in the emergency room, focusing on first line clinical staff
Non-adherence to antibiotic guideline was associated with admittance from another institution	Understanding the drivers for non-adherence in patients admitted from institutions and focusing on antibiotic prescribing for this group of patients
Non-adherence to antibiotic guideline was associated with the place of initiation of therapy, both regarding hospital site and wards compared to emergency room	Understanding the cultural and contextual drivers for antibiotic prescribing across institutions and specialties
Mean length of antibiotic therapy was similar across very different groups of diagnosis. Antibiotics prescribed upon discharge contributed significantly to the total days of antibiotic therapy and the appropriateness of this practice is often not clear	Focusing on reducing the duration of antibiotic therapy safely, in accordance with emerging evidence on duration of antibiotic treatment

One of the main aims of antibiotic stewardship programs is to reduce unnecessary use of broad-spectrum antibiotics. We applied WHO AWaRe categories to describe the categories of antibiotics prescribed and found that when initial antibiotic treatment were according to Norwegian national guidelines, the majority of regimens (89%) consisted of only access group antibiotics. Non-adherent empirical regimens however, included several antibiotics from the watch/reserve category, but these regimens were often switched to regimens within the access categories upon first modification of treatment. At discharge, a greater number of regimens were from the access category, both suggestive

of clinical microsystems that tried to adhere to guidelines and antibiotic stewardship principles, but also likely related to the restricted availability of oral broad-spectrum antibiotics in Norway.

In an American study from 2014, Braykov et al ranked antibiotics in categories of narrow-spectrum, broad-spectum, extended spectrum and restricted antibiotics [16]. Although there are some differences between the studies regarding the categories used to classify antibiotics, the results show that the prescription pattern is very different between the hospitals in the two studies. While 74% of patients in our study initially received antibiotics belonging only to the access group, most patients (78%) had broad-spectrum and extended spectrum antibiotics prescribed as empirical therapy in the Braykov-study. This reflects the nature of the Norwegian national antibiotic guidelines, which mainly have antibiotics from the access group as first-line empirical treatment recommendations.

Initiating empirical antibiotic therapy is a crucial step in the treatment of infections and an important target for antibiotic stewardship interventions, as recently outlined by Tamma et al in their paper describing the four moments of antibiotic decision making [17]. In our study, antibiotics were mainly prescribed in the emergency departments. The physicians responsible for prescribing are usually interns and residents and in Norwegian hospitals, junior doctors rely heavily on guidelines for antibiotic prescribing [18]. From a separate study by Skodvin et al, including patients from the same intervention study cohort, we also know that mean compliance with guidelines recommendations for microbiology testing practices was 89% [19]. Most patients (83.6%) started antibiotic treatment in the emergency departments and non-adherence to guidelines was higher when treatment was initiated at the wards, compared to the emergency departments (OR=1.7, 95% CI (1.24-2.36), p=0.001). Other studies report reluctance from other medical teams to change therapy further down the line and together this highlights the need to focus on first-line clinical staff when planning antibiotic stewardship interventions [20].

Non-adherence to guidelines was also associated with hospital site and whether patients were admitted from an institution or not. Patients admitted from nursing homes or other institutions may have had treatment prior to hospital admission. A combination of age, frailty, comorbidity and increased fear of resistant bacteria as cause of infection could have caused physicians to prescribe more broad-spectrum antibiotics for these patients. There is however, a need for a more thorough understanding of prescribing practices in this particular group of patients. Studies show that organisational culture influence antibiotic prescribing [20-22]. This could potentially explain why the odds ratio for non-adherent prescribing was significantly lower at hospital B than the two other included hospitals (OR=0.63 95% CI (0.46, 0.86), p=0.004). It also signals that a thorough understanding of organisational culture with barriers and facilitators for prudent antibiotic prescribing is an important part of planning for antibiotic stewardship interventions.

Empirical antibiotic regimens were usually modified during admission (61.5%) and oral antibiotics were prescribed for 84.5% of patients. Other studies looking at the process of antibiotic prescribing in hospitals have focused on review of empirical therapy in relation to patient outcome or effect of interventions on prescribing process measures [23-25]. Braykov et al found that by the 5th day of therapy, 21,5% of empirical antibiotics were narrowed or discontinued, while Aillet et al found that antibiotic review was performed in 69% of patients with bacteraemia [16, 24]. In comparison, although we did not measure all patients at one specific day, 74,5% of empirical antibiotics were de-escalated (56,4%) and stopped (18,1%) as first modification of therapy in our study. Modifications happened between day 3 and 4 when initiation of therapy was defined as day 1. This is in agreement with recommendations stating that review of therapy should take place 48-72 hours after initiation of antibiotic therapy [26-28]. Upon discharge, 77.4% of patients continued antibiotic treatment and the mean length of post-discharge therapy was similar to the mean length of in-house treatment. This could mean either that most patients were not fully recovered upon discharge or that antibiotics were continued “just in case,” justifying an earlier discharge and giving the physician reassurance for the

patients' well-being. The lack of documentation regarding length of antibiotic therapy has been heavily debated and studies suggest shorter antibiotic courses are safe and effective for an increasing number of diagnoses [29-33]. In our study, there was a remarkable similarity in duration of antibiotic therapy between the various groups of diagnoses, both in-hospital and post-discharge. For all patients, the mean number of days of antibiotic therapy were 10.6 days and the range for the various groups were narrow (9.3 to 12.5 days) when post-discharge therapy was included. There is a need for more studies, informing policymakers and clinicians about the optimal duration of antibiotic therapy for individual diagnosis, both in-hospital and for post-discharge use.

This study has some limitations. When assessing adherence to guidelines on initiation of treatment, we used the indication for treatment stated in the electronic medical record, and this was usually a working diagnosis on admission. The diagnosis may change with more data and results available. To check whether this constituted a major issue for interpretation of data, we looked at the coherence between indication for treatment and the infection discharge diagnosis (if present) in the discharge letter. The group of diagnoses for which this might be an issue, is sepsis, where accuracy between indication for treatment and discharge diagnosis was low. During the study period, SIRS-criteria were used to screen patients for sepsis. SIRS identify more patients as suspected sepsis than the qSOFA score, which is currently in use. The low accuracy in this group could be due to lack of documentation of sepsis at discharge, with only the original focus of the infection often documented in discharge papers. It is possible that review of therapy took place without modifications to the patient's antibiotic regimen. Such reviews were not identified during data collection and represents a limitation to this study. We also did not take dosing into consideration when assessing adherence to guidelines and modification of therapy. Appropriateness of antibiotic therapy was not evaluated after initial assessment of adherence to guidelines for empirical antibiotic treatment. It is therefore unknown whether escalation, de-escalation, stop or change was the best option for each individual patient. From the study by Skodvin et al, with patients derived from the same intervention study cohort, we do

however know that only 18% of patients had applicable microbiology test results and for only half of these patients (9% of the total cohort), these findings were used to guide therapy [19].

The Nordic countries and the Netherlands are currently in a more favourable position regarding antimicrobial resistance and are still able to utilize the most ecologically friendly antibiotics in empirical regimens. Exploring different ways of aggregating and analysing data to understand hospital antibiotic prescribing processes are however important in all countries and institutions, aiming to identify targets for stewardship interventions.

Future studies should include assessment of appropriateness of therapy throughout the hospital stay to have a more comprehensive review of prescribing quality at every step of the process. Identifying and studying contributions from other healthcare professionals, like nurses and pharmacist and the team effort in antibiotic stewardship would also be valuable. As patient involvement and empowerment is increasing, the contribution of patients in antibiotic stewardship in hospital settings should also be investigated. Such studies could contribute to the identification of more targets for antibiotic stewardship interventions.

Conclusions

Analysis of patient level antibiotic prescribing and the use of WHO AWaRe to categorise antibiotic regimens throughout the hospital stay, identified relevant targets for antibiotic stewardship interventions in our population of hospital inpatients. Identified targets included 1) adherence to guidelines 2) focus on prescribing physicians in the emergency room 3) prescribing for patients admitted from an institution 4) organisational culture and 5) duration of antibiotic therapy.

List of abbreviations

AB: Antibiotic

AWaRe: Access, Watch, Reserve

CCI: Charlson Comorbidity Index

COPD ex: Exacerbation of Chronic Obstructive Pulmonary Disease

eGFR: estimated Glomerular Filtration Rate

UTI: Urinary Tract Infection

LRTI: Lower Respiratory Tract Infection

SIRS: Systemic Inflammatory Response Syndrome

SSTI: Skin- and Soft Tissue Infections

qSOFA: quick Sequential [Sepsis-related] Organ Failure Assessment score

WHO: World Health Organization

Declarations

Ethics

The study was performed in accordance with the Declaration of Helsinki [34]. The study was approved by the local data protection officer (2013/9352) and the regional ethical committee of Western Norway approved the waiver of informed consent (2013/1305). All patients treated with antibiotics received an information leaflet at the ward about the study and provided the opportunity to withdraw from the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due in concordance with the approval from the Data Protection Officer (2013/9352), but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JSW, BS and IS designed the study and data was collected by JSW, IS, LKSK, BS, MIN and TV. JSW, IS, LKSK and BS validated data and JSW, RMN, BS and IS did the data analysis. All authors performed data interpretation, while JSW, BS, ES and IS wrote the manuscript. All authors critically assessed the manuscript throughout the writing process and also read and approved the final version.

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Table 2: Patient characteristics

	LRTI (n=412) n (%)	COPD ex (n=280) n (%)	Sepsis (n=248) n (%)	SSTI (n=150) n (%)	UTI (n=145) n (%)	Total (N=1235) n (%)
Sex						
Male	196 (47.6)	149 (53.2)	148 (59.7)	101 (67.3)	62 (42.8)	656 (53.1)
Female	216 (52.4)	131 (46.8)	100 (40.3)	49 (32.7)	83 (57.2)	579 (46.9)
Agegroup						
<= 45	43 (10.4)	2 (0.7)	51 (20.6)	52 (34.7)	16 (11.0)	164 (13.3)
46-65	88 (23.4)	70 (25.0)	50 (20.2)	48 (32.0)	21 (14.5)	277 (22.4)
66-85	192 (46.6)	179 (63.9)	106 (42.7)	37 (24.7)	71 (49.0)	585 (47.4)
>85	89 (21.6)	29 (10.4)	41 (16.4)	13 (8.7)	37 (25.5)	209 (16.9)
Charlson Comorbidity Index						
CCI = 0	163 (39.6)	8 (2.9)	111 (44.8)	108 (72.0)	72 (49.7)	462 (37.4)
CCI = 1	109 (26.5)	178 (63.6)	73 (29.4)	23 (15.3)	37 (25.5)	420 (34.0)
CCI = 2	58 (14.1)	47 (16.8)	41 (16.5)	9 (6.0)	21 (14.5)	176 (14.3)
CCI = 3	32 (7.8)	24 (8.6)	9 (3.6)	5 (3.3)	9 (6.2)	79 (6.4)
CCI = 4	14 (3.4)	18 (6.4)	6 (2.4)	3 (2.0)	1 (0.7)	42 (3.4)
CCI > 4	36 (8.7)	5 (1.8)	8 (3.2)	2 (1.3)	5 (3.5)	56 (4.5)
Admitted from institution						
No	341 (82.8)	255 (91.1)	203 (81.9)	141 (94.0)	115 (79.3)	1055 (85.4)
Yes	71 (17.2)	25 (8.9)	45 (18.1)	9 (6.0)	30 (20.7)	180 (14.6)
AB allergies						
Yes	43 (10.5)	38 (13.6)	19 (7.7)	13 (8.7)	9 (6.2)	122 (9.9)
No	367 (89.3) 1 missing	242 (86.4)	229 (92.3)	137 (91.3)	136 (93.8)	1111 (90.0) 1 missing
eGFR on admission						
>50	308 (74.8)	230 (82.1)	187 (75.4)	129 (86.0)	101 (69.7)	955 (77.3)
10-50	103 (25.0)	49 (17.5)	59 (23.8)	21 (14.0)	43 (29.7)	275 (22.3)
<10	1 (0.24)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.7)	4 (0.32)
Dialysis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.08)
30-day mortality	55 (13.4)	19 (6.8)	22 (8.9)	2 (1.3)	6 (4.1)	104 (8.4)
30-day readmission	78 (18.9)	76 (27.1)	39 (15.7)	26 (17.3)	37 (25.5)	256 (20.7)
Mean LOS (95% CI)	7.3 (6.8, 7.7)	6.8 (6.3, 7.2)	7.1 (6.6, 7.6)	6.3 (5.6, 7.0)	7.0 (6.3, 7.7)	7.0 (6.7, 7.2)

Figure 1: Antibiotic regimens prescribed from admission to discharge, by AWaRe categories and adherence to guideline on initiation of therapy

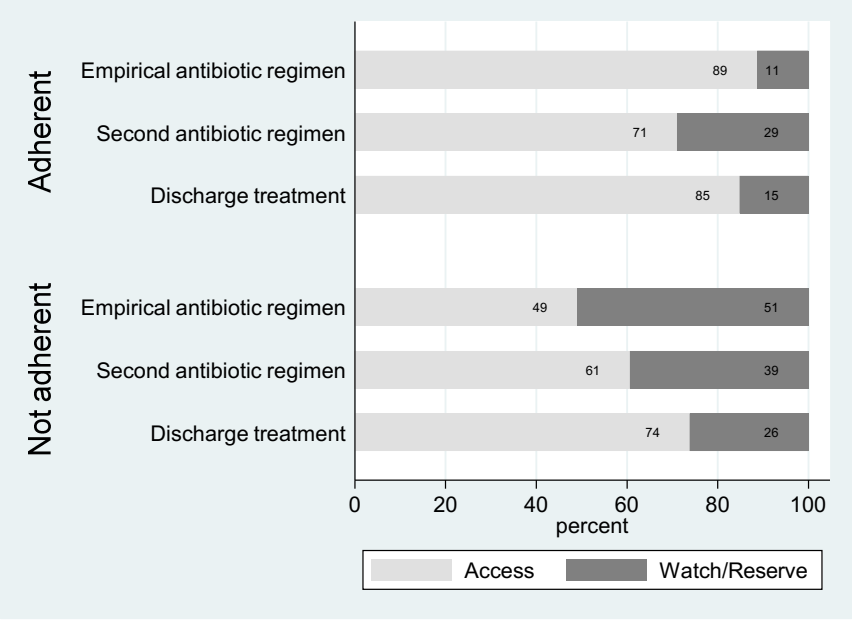

Table 3: Antibiotic (AB) prescribing in hospitals – process measures

	LRTI (n=412) n (%)	COPD ex (n=280) n (%)	Sepsis (n=248) n (%)	SSTI (n=150) n (%)	UTI (n=145) n (%)	Total (N=1235) n (%)
AB initiated						
Emergency room	320 (77.7)	244 (87.1)	240 (96.8)	135 (90.0)	94 (64.8)	1033 (83.6)
Ward	92 (22.3)	36 (12.9)	8 (3.2)	15 (10.0)	51 (35.2)	202 (16.4)
Adherence to guideline						
Yes	280 (68.0)	177 (63.2)	151 (60.9)	90 (60.0)	80 (55.2)	778 (63.0)
No	132 (32.0)	103 (36.8)	97 (39.1)	60 (40.0)	65 (44.8)	457 (37.0)
Accuracy between indication for AB-treatment and discharge infection diagnoses[⌂]						
Yes	331 (80.3)	255 (91.1)	103 (41.5)	143 (95.3)	122 (84.1)	954 (77.3)
No	81 (19.7)	25 (8.9)	145 (58.5)	7 (4.7)	23 (15.9)	281 (22.8)
Empirical AB regimen was						
Changed during admission	232 (56.3)	167 (59.6)	205 (82.7)	82 (54.7)	73 (50.3)	759 (61.4)
Changed at discharge	99 (24.0)	57 (20.4)	22 (8.9)	57 (38.0)	19 (13.1)	254 (20.6)
Continued at discharge	32 (7.8)	29 (10.4)	2 (0.8)	5 (3.3)	34 (23.5)	102 (8.3)
Stopped	49 (11.9)	27 (9.6)	19 (7.7)	6 (4.0)	19 (13.1)	120 (9.7)
Empirical AB regimen was						
Deescalated	227 (55.1)	176 (62.9)	142 (57.3)	95 (63.3)	56 (38.6)	696 (56.4)
Escalated	84 (20.4)	45 (16.1)	43 (17.3)	29 (19.3)	24 (16.5)	225 (18.2)
Changed – equal spectrum	19 (4.6)	3 (1.1)	41 (16.5)	15 (10.0)	12 (8.3)	90 (7.3)
Unchanged▪	82 (19.9)	56 (20.0)	22 (8.9)	11 (7.3)	53 (36.6)	224 (18.1)
Time to change of first AB regimen (n=1011)						
Mean (95% CI)*	4.0 (3.7, 4.2)	3.9 (3.7, 4.1)	3.0 (2.7, 3.3)	3.4 (3.1, 3.8)	3.5 (3.1, 3.9)	3.6 (3.5, 3.8)
Number of treatment regimens through admission						
1	41 (9.9)	33 (11.8)	5 (2.0)	6 (4.0)	34 (23.5)	119 (9.6)
2	245 (59.5)	187 (66.8)	86 (34.7)	77 (51.3)	75 (51.7)	670 (54.3)
3	92 (22.3)	43 (15.4)	122 (49.2)	44 (29.3)	29 (20.0)	330 (26.7)
>3	34 (8.3)	17 (6.1)	35 (14.1)	23 (15.3)	7 (4.8)	116 (9.4)
Oral AB given						
Yes	326 (79.1)	243 (86.8)	204 (82.3)	136 (90.7)	135 (93.1)	1044 (84.5)
No	86 (20.9)	37 (13.2)	44 (17.7)	14 (9.3)	10 (6.9)	191 (15.5)
Mean first day (95% CI)	4.2 (3.9, 4.5)	3.6 (3.3, 3.8)	5.1 (4.6, 5.5)	4.8 (4.3, 5.3)	2.7 (2.3, 3.1)	4.1 (3.9, 4.3)
First change of AB regimen						
During admission	232 (56.3)	167 (59.6)	205 (82.7)	82 (54.7)	73 (50.3)	759 (61.5)
At discharge	99 (24.0)	57 (20.4)	22 (8.9)	57 (38.0)	19 (13.1)	254 (20.6)
Continued at discharge	32 (7.8)	29 (10.4)	2 (0.8)	5 (3.3)	34 (23.5)	102 (8.3)
Stopped	49 (11.9)	27 (9.6)	19 (7.7)	6 (4.0)	19 (13.1)	120 (9.7)
Antibiotics prescribed at discharge						
Yes	296 (71.8)	214 (76.4)	193 (77.8)	139 (92.7)	114 (78.6)	956 (77.4)
No	116 (28.2)	66 (23.6)	55 (22.2)	11 (7.3)	31 (21.4)	279 (22.6)
Days of AB treatment						
Mean (95% CI)[Δ]	10.2 (9.7, 10.6)	10.0 (9.6, 10.5)	11.5 (10.8, 12.2)	12.5 (11.6, 13.4)	9.3 (8.6, 10.1)	10.6 (10.3, 10.9)
In-hospital	6.3 (5.9, 6.7)	6.0 (5.7, 6.4)	6.6 (6.1, 7.1)	6.0 (5.3, 6.6)	5.3 (4.8, 5.8)	6.2 (5.9, 6.4)
After discharge▪	5.5 (5.2, 5.8)	5.2 (4.9, 5.6)	6.3 (5.8, 6.8)	7.1 (6.4, 7.7)	4.9 (4.5, 5.3)	5.8 (5.6, 6.0)

*Does not include patients who did not change initial antibiotic regimen (stop was only change)
⌂ Measured as match between initial grouped indication for treatment and grouped discharge diagnosis
● Unchanged includes patients where discontinuation of antibiotics was the only change
Δ Does not include 40 patients where length of prescription treatment after discharge was not stated in discharge letter.
▪ Does not include 40 patients where length of prescripton treatment after discharge was not stated in discharge letter and 5 patients where length of prescription treatment was longer than 30 days.

Table 4: Factors associated with non-adherence to antibiotic guideline

	Adherence (n=778) n (%)	Non-adherence (n=457) n (%)	Univariate analysis OR (95% CI)	p-value	Adjusted analysis* OR (95% CI)	p-value
AB initiated						
Emergency room	670 (64.9)	363 (35.1)	1		1	
Ward	108 (53.5)	94 (46.5)	1.6 (1.18, 2.18)	**0.002**	1.7 (1.24, 2.36)	**0.001**
Indication for treatment						
LRTI	280 (68.0)	132 (32.0)	1		1	
COPD ex	177 (63.2)	103 (36.8)	1.23 (0.90, 1.70)	0.196	1.42 (1.03, 1.98)	**0.035**
Sepsis	151 (60.9)	97 (39.1)	1.36 (0.98, 1.89)	0.065	1.44 (1.02, 2.02)	**0.037**
SSTI	90 (60.0)	60 (40.0)	1.41 (0.96, 2.10)	0.079	1.56 (1.05, 2.31)	**0.028**
UTI	80 (55.2)	65 (44.8)	1.72 (1.17, 2.54)	**0.006**	1.62 (1.09, 2.41)	**0.017**
Hospital						
Hospital A	376 (60.8)	242 (39.2)	1		1	
Hospital B	203 (70.7)	84 (29.3)	0.64 (0.48, 0.87)	**0.004**	0.63 (0.46, 0.86)	**0.004**
Hospital C	199 (60.3)	131 (39.7)	1.02 (0.78, 1.34)	0.872	0.95 (0.71, 1.26)	0.712
Admitted from institution						
No	678 (64.3)	377 (35.7)	1			
Yes	100 (55.6)	80 (44.4)	1.44 (1.04, 1.98)	**0.026**	1.44 (1.04, 2.00)	**0.029**
Accuracy between indication for AB-treatment and discharge infection diagnoses⌂						
Yes	604 (63.3)	350 (36.7)	1		1	
No	174 (61.9)	107 (38.1)	1.06 (0.81, 1.40)	0.671	0.99 (0.72, 1.35)	0.936
Sex						
Male	411 (62.7)	245 (37.3)	1		1	
Female	367 (63.4)	212 (36.6)	0.97 (0.77. 1.22)	0.790	0.98 (0.77, 1.24)	0.857
Agegroup						
<45	106 (64.6)	58 (35.4)	1		1	
46-65	168 (60.7)	109 (39.3)	1.19 (0.79, 1.77)	0.405	1.26 (0.83, 1.91)	0.277
66-85	367 (62.7)	218 (37.3)	1.09 (0.76, 1.56)	0.656	1.08 (0.73, 1.60)	0.695
>85	137 (65.6)	72 (34.4)	0.96 (0.63, 1.47)	0.854	0.87 (0.54, 1.37)	0.540
Charlson Comorbidity Index						
CCI=0	304 (65.8)	158 (34.2)	1		1	
CCI=1	265 (63.1)	155 (36.9)	1.13 (0.85, 1.48)	0.402	1.14 (0.83, 1.56)	0.421
CCI=2	102 (57.9)	74 (42.1)	1.40 (0.98, 1.99)	0.066	1.35 (0.93, 1.97)	0.115
CCI=3	48 (60.8)	31 (39.2)	1.24 (0.76, 2.10)	0.386	1.20 (0.72, 2.02)	0.482
CCI=4	26 (61.9)	16 (38.1)	1.18 (0.62, 2.27)	0.611	1.18 (0.60, 2.33)	0.626
CCI>4	33 (58.9)	23 (41.1)	1.34 (0.76, 2.36)	0.310	1.39 (0.77, 2.51)	0.279
Multiple working diagnoses						
1	493 (64.6)	270 (35.4)	1		1	
2	238 (60.7)	154 (39.3)	1.18 (0.92, 1.52)	0.193	1.12 (0.87, 1.46)	0.381
3	47 (58.8)	33 (41.2)	1.28 (0.80, 2.05)	0.299	1.18 (0.73, 1.92)	0.491
Antibiotic allergies◊						
No	708 (63.7)	403 (36.3)	1		1	
Yes	69 (56.6)	53 (43.4)	1.35 (0.92, 1.97)	0.120	1.40 (0.95, 2.06)	0.088
eGFR						
eGFR >50	598 (62.6)	357 (37.4)	1		1	
eGFR <50	180 (64.3)	100 (35.7)	0.93 (0.71, 1.23)	0.611	0.88 (0.66, 1.17)	0.378

* All factors are adjusted for where AB was initiated, indication for AB treatment, hospital and admittance from institution
⌂ Measured as match between initial grouped indication for treatment and grouped discharge diagnosis
◊1 data missing

SUPPLEMENT 1

Table 1: Grouping of indication for treatment

	Indication for treatment*
Lower respiratory tract infections (LRTI)	Community acquired pneumonia (normal and severe), healthcare associated pneumonia (normal and severe), unspecified lower respiratory tract infections, unknown – suspected pneumonia, aspiration pneumonia, atypical pneumonia, lung abscess, empyema.
Chronic obstructive pulmonary disease exacerbation (COPD ex)	Patients with COPD, presenting with LRTI (community and healthcare associated).
Sepsis	Suspected cases of sepsis originating from; lower respiratory tract, urinary tract, unknown focus, soft tissue, abdomen and catheter.
Skin and soft tissue infections (SSTI)	Erysipelas, cellulitis, abscess, other skin and soft tissue infections, mastitis, necrotising soft tissue infections, postoperative wound infection.
Urinary tract infections (UTI)	UTI – unspecified, pyelonephritis, lower UTI/cystitis, unknown-suspected UTI, catheter associated UTI.

*Indications are given in decreasing order of frequency

Table 2:

Overview of AWaRe categories with study modifications

AWaRe Category	AWaRe antibiotic	Active substances	Study antibiotics added to category
Access*	Beta-lactam antibiotics	Amoxicillin, amoxicillin + clavulanic acid, ampicillin, benzathine benzylpenicillin, benzylpenicillin, cefalexin, cefazolin, cloxacillin, phenoxymetylpenicillin, procain benzyl penicillin	Pivmecillinam Mecillinam Cefalotin Dicloxacillin
	Other antibiotics	amikacin, chloramphenicol, clindamycin, doxycycline, gentamicin, metronidazole, nitrofurantoin, spectinomycin (EML only), sulfamethoxazole+trimethoprim	Tobramycin Metenamine
Watch	Quinolones and fluoroquinolones	e.g. Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin	
			2nd gen cephalosporins: Cefuroxime
	3rd generation cephalosporins (with or without beta-lactamase inhibitor)	e.g. Cefixime, ceftriaxone, cefotaxime, ceftazidime	
	Macrolides	e.g. Azithromycin, clarithromycin, erythromycin	
	Glycopeptides	e.g. teicoplanin, vancomycin	
	Antipseudomonal penicilins + beta-lactamase inhibitor	e.g. piperacillin - tazobactam	
	Carbapenems	e.g. meropenem, imipenem + cilastatin	
	Penems	e.g. faropenem	
Reserve	Aztreonam		
	4th generation cephalosporins	e.g. cefepime	
	5th generation cephalosporins	e.g. ceftaroline	
	Polymyxins	e.g. polymyxin B, colistin	
	Oxazolidinones	e.g. linezolid	
	Fosfomycin (IV)		
	Tigecyclin		
	Daptomycin		

* Antibiotics included in the access category only

Table 3: Evaluation of antimicrobial spectrum and categorization of change

ESCALATION	Added spectrum in new regime
Cipro →Ampi/genta	Gram positives (Enterococci)
Erytro→ Ceftriaxon	Gram negatives
Cefotax→ Pip-taz	Anaerobes, enterococci
Ampi/genta→ Pip-taz	Anaerobes
Pc iv →TXS	Gram neg
Ampi→Doxy	Atypicals (Intracellular)
Pc→Clinda	Anaerobes and staphylococci
Genta→TXS	Streptococci
Cefotax→ Cipro/Metron	Anaerobes
Cefurox→Cefotax	Gram negatives
Pip-taz→Meropenems	ESBLs
Pc/Azitro→Cefotax	Gram negatives
Cefotaxime/Metron→Merop	ESBLs
Kloxa→Pc/Clinda	Anaerobes
Cefurox→ Pip-taz	Anaerobes, enterococci
Fenoxypc→Claritromycin	Atypicals (Intracellular)
Kloxa→Pc/Metro	Anaerobes
Cefotax/Metron→Meropenems	ESBLs
Pc/metro→Pc/genta	Gram negatives
Cefotaxime/Ampi→PipTazo	Anarobes
Pc→Doxy	Atypicals (Intracellular)
Cefurox→ TXS	Gram negatives
Cipro/genta→ TXS	Gram positives
Vanco/Clinda→ TXS	Gram negatives
DE- ESCALATION	**Reduced spectrum in new regime**
Pc/genta→Ampi	Gram negatives
Ampi/genta→ Cefuroxime	Enterococci, some gram negatives
Pip-taz→ Fenoxypc+cipro	Anaerobes
Cefotax→ Cipro	Gram positives
Clinda →Dicloxa	Anaerobes and ↓streptocci
Cefotaxime/Metron→Cipro/TXS	Anaerobes
Pip-taz→Cipro	Anaerobes and gram positives
Pc/genta→ Fenoxypc	Gram negatives, S aureus
Pc/genta→Amoxi	S aureus, Several gram negs
Cefurox→Cipro	Gram positives
TXS→Mecillinam	Gram positives, Several gram negs
Kloxa/Genta/Clinda→Pc	Gram negatives, S aureus, Anaerobes
Pc/clinda→Kloxa	Anaerobes
Cefurox/metro→Cefotax	Anaerobes
Pc/genta/metro→Ampi/genta	Anaerobes
Pc/genta→Pc/metro	Gram negatives
Kloxa /Clinda→Pc	S aureus, some anaerobes
Cefurox→Cipro	Gram positives
Ampi/genta→Amoxi	S aureus, Several gram negs
PipTaz→Cipro/Azitro	Anaerobes, enterococci
Ampi/genta→TXS	Enterococci
Kloxa/genta→Cipro	Gram positives
Pc/Kloxa→Fenoxypc	S aureus
Pc/genta→Fenoxypc	Gram neg, S aureus
Pc/genta/metro→Cipro/metro	Gram positives
Amoxi/Pivmecill→Cipro	Gram positives, enterococci
Ampi/genta→Cipro	Gram positives, incl enterococci

UNCHANGED	
Cefotax↔ Pc/genta	
Cefotax↔TXS	
Pc/Cipro ↔ Pc/genta	
Ampi/genta↔ Ceftriaxon/Pc	
Pc/Cefotax↔Cefotax	
Pc/Clinda/genta↔ Clinda/genta	
Ampi/genta/Cefurox↔ Ampi/genta	
Cefotax /genta↔Cefotax	
Pip-Taz/Clinda↔Pip Taz	Increased penetration, but not broader antimicrobial spectrum

IV

Seksjon 1. GENERELLE OPPLYSNINGER

Del 1.1. Personen som registrerer		
Navn	☐ Lars Kåre Kleppe ☐ Ingrid Smith ☐ Marion Neteland ☐ Jannicke Slettli Wathne ☐ Trude Cecilie Mellingsæter ☐ Brita Skodvin	☐ Ottar Hope ☐ Eli Hoem ☐ Torbjørn Smith ☐ Dagfinn Lunde Markussen ☐ Per Espen Akselsen ☐ Torhild Vedeler
Dato		

Del 1.2. HF, sykehus, avdeling, post (navn)	
☐ 11: SUS - Infeksjon ☐ 12: SUS - Gastro ☐ 13: SUS - Lunge	☐ 31: HUS – Infeksjon (Med 6) ☐ 32: HUS – Infeksjon (Med 5 V) ☐ 33: HUS – Gastro (Med 1 V) ☐ 34: HUS – Lunge post 1 ☐ 35: HUS – Lunge post 3
☐ 21: HDS - Infeksjon ☐ 22: HDS - Gastro ☐ 23: HDS – Lunge	

Seksjon 2. PASIENT

Del 2.1. Pasientdata			
Fødselsdato:		Kjønn:	☐Mann ☐ Kvinne
Studie ID-nr:		NPR-ID:	
Inndato:		Utdato:	
Relevante allergier mot antibiotika?	☐Ja ☐Nei	Ja - beskriv:	
Innlagt institusjon siste 48 timer (pleiepersonell 24/7)	☐ Ja ☐Nei	Utskrevet til institusjon	☐ Ja ☐Nei ☐ Ikke rel.
Død under aktuell innleggelse:	☐Ja ☐Nei	Død innen 30 dager etter utskrivning	☐Ja ☐Nei ☐ Ikke rel.
Reinlagt innen 30 dager etter utskrivning	☐Ja ☐Nei ☐ Ikke relevant		
Kommentar:			

Del 2.2 Komorbiditet:

☐ Kreft ☐Hjertesvikt ☐ Diabetes ☐ Nyresvikt ☐ Apopleksi ☐Rusmisbruk ☐ Annet: ☐ KOLS

Del 2.3. Indikasjon for antibiotikabehandling (TD=Tentativ diagnose, ED =Endelig diagnose)

Profylakse (eksklusjonskriterium) ☐			Indikasjon ikke angitt i journal ☐	
TD (nr)	**ED (nr)**	**Generell diagnose**	**Spesifikk diagnose**	
		☐Annet (**ingen infeksjon**) – beskriv:		
		☐ CNS Infeksjon	☐ Hjerneabscess	☐ Meningitt
		☐ Endokarditt	☐ Nativ klaff ☐ Biologisk klaff ☐ Mekanisk klaff	
		☐ Abdominal infeksjon	☐ Gastroenteritt ☐ Clost. difficile ☐ Intraabd. Abscess ☐ Peritonitt	☐ Divertikulitt ☐ Colitt ☐ H.pylori ☐ Cholecystitt/ cholangitt
		☐ Gynekologisk infeksjon		
		☐ Hud- og bløtdelsinfeksjon	☐ Erysipelas ☐ Cellulitt ☐ Nekrot. fascitt ☐ Postop. sårinfeksjon	☐ Mastitt ☐ Abscess ☐ Annet – beskriv*
		☐ Infeksjon uten kjent fokus	Evt. hva mistenkes? ☐ Pneumoni ☐ UVI ☐ Abdominal infeksjon	
		☐ Infiserte intravasale katetre		
		☐ Neutropen feber	☐ Samfunnservervet ☐ Nosokomial	Utgangspkt^:
		☐ Ortopediske infeksjoner	☐ Proteseinfeksjon (eksklusjon!) ☐ Osteomyelitt	☐ Artritt
		☐ Nedreluftveisinfeksjon (NLI) ☐ Konfus ☐ Resp. >30 ☐ Age>65 ☐ BT syst < 90 el. diast. ≤ 65mmHg	☐ Pneumoni ☐ Samf. ervervet ☐ Nosokomial ☐ Aspirasjon ☐ Atypisk ☐ Uspesifisert NLI	☐ KOLS eksaserbasj. ☐ Bronkitt ☐ Lungeabscess ☐ Empyem ☐ CRB-65 score 3-4 el. behandlingssvikt
		☐ Sepsis	☐ Samf.ervervet ☐ Nosokomial	Utgangspkt^:
		☐ Urinveisinfeksjoner (UVI)	☐ Kateterass. UVI ☐ Pyelonefritt	☐ Nedre UVI/ cystitt ☐ Uspesifisert
		☐ Øvre luftveisinfeksjon (ØLI)	☐ Sinusitt / otitt ☐ Tonsilitt	☐ Uspesifisert

* Inkl. bitt, diabetisk fotsår ^Hvor mistenkes infeksjonen å utgå fra; urinveiene, lungene,..

Kommentar:

Utgangspkt^:

Del 2.4. Antibiotika									
Behandling startet (sted)	**Ind.**	**Start-dato**	**Legemiddelnavn**	**Styrke**	**Adm. form**	**Doserings-intervall**	**Antall doser gitt**	**Behandling kontinuert (sted)**	**Antall doser gitt**
AKM									
AKM									

Kommentarer:

Resept: *Legemiddelnavn Dose Intervall Adm.måte Behandlingslengde (sluttdato og antall dager)*

2.5 Labprøver		Kommentar:
Nyrefunksjon	☐ GFR >50 ☐ GFR 10-50 ☐ GFR <10 ☐ Dialyse	

2.5	Mikrobe	Materiale (til dyrkning)								
		Blod	Urin	Feces	Luft-veier	Sår	Puss	Andre	Resistens (S,I,R)	
1	Prøve tatt – ingen vekst									
2	Prøve tatt - normalflora									
3	Prøve tatt – ÷ klinisk bet.									
4	Acinetobacter									
5	Chlamydia trach.									
6	Clostridium diff.									
7	E. coli									
8	Enterobacteriacae -									
9	Enterokokker (gr D)									
10	H.influenzae									
11	H.pylori									
12	Klebsiella									
13	MRSA									
14	Mycoplasma pn.									
15	Proteus									
16	Pseudomonas									
17	S. gr A									
18	S. gr B									
19	S. gr G									
20	S. pneumoniae									
21	S.gr C									
22	Staph. aur									
23	Staph. KNS									
24	Annet:									

Kommentar:

2.6	Mikrobe	Test (antigentest, mikroskopering osv)					
L-PCR	Bordetella pertussis	☐Pos	☐Neg	Annet	Pneumokokk antigen	☐Pos	☐Neg
	Bordetella parapertussis	☐Pos	☐Neg		Legionella pneumophilia	☐Pos	☐Neg
	Mycoplasma pneum.	☐Pos	☐Neg		Clostridium difficile toxin	☐Pos	☐Neg
	Chlamydophilia pneum.	☐Pos	☐Neg		VRE – screening	☐Pos	☐Neg
	Influensavirus A	☐Pos	☐Neg		Mycobacterium tuberculosis	☐Pos	☐Neg
	Influensavirus B	☐Pos	☐Neg		Mycoplasma pneum. antistf	☐Pos	☐Neg
	Humant metapneu. virus	☐Pos	☐Neg		Borrelia antistoff	☐Pos	☐Neg
	Parainfluensavirus 1-2-3	☐Pos	☐Neg				

Annet funn/kommentar:

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