Empiric antibiotic prescribing in selected primary care settings: Identifying possible areas for improvement

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Contents

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2 List of Papers

Paper 1. Use of fluoroquinolones in nursing homes.
Fagan M, Skotheim SB. Tidsskrift for den Norske laegeforening : (Journal of the Norwegian Medical Society). 2010;130(20):2022-4.

Paper 2. Antibiotic prescribing in nursing homes in an area with low prevalence of antibiotic resistance: compliance with national guidelines.
Fagan M, Maehlen M, Lindbaek M, Berild D. Scandinavian journal of primary health care. 2012;30(1):10-5.

Paper 3. Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study. Fagan M, Grude N, Lindbaek M, Reiso H, Romøren M, Skaare D, Berild D. (Submitted)

Paper 4. A simple intervention to reduce inappropriate ciprofloxacin prescribing in the emergency department. Fagan M, Lindbaek M, Reiso H, Berild D. Scandinavian journal of infectious diseases. 2014;46(7):481-5.

3 Abbreviations

Abbreviation	Text
ADR	Adverse drug reaction
AGREE	Appraisal of Guidelines for Research and Evaluation
AOM	Acute otitis media
ASB	Asymptomatic bacteriuria
ASP	Antibiotic stewardship programs
ATC	Anatomic therapeutic code
CD	Community dwelling
CDSS	Clinical Decision Support Systems
CI	Confidence interval
CME	Continuing medical education
CRP	C-reactive protien
DDD	Defined daily dose
ECS	Emergency call service
ED	Emergency department
EPJ	Electronic patient journal system
ESBL	Extended β-lactamase
EUCAST	The European Committee on Antimicrobial Susceptibility Testing
GEE	Generalized Estimating Equations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICD	International Statistical Classification of Diseases
ICPC	The International Classification of Primary Care
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant Staphylococcus aureus
NGAPC	National guidelines for use of antibiotics in primary care
NH	Nursing home
OR	Odds ratio
PDR	Pan-drug resistant
REK	Regional ethics committee
RTI	Respiratory tract infections
SSTI	Skin and soft tissue infection
UTI	Urinary tract infections

4 Summary

Background. Two undeniable challenges facing modern medicine are the increasing problems of antimicrobial resistance and the lack of new antibiotics to combat infections. Alone these problems are serious, but the synergy of these two problems threatens to return us to the pre-antibiotic era. These problems are global and affect all levels of the health care system, from the rural family physician to the intensive care unit of tertiary hospitals. Rational antibiotic prescribing is paramount in meeting the challenges of antibacterial resistance. In Norway, approximately 90 % of all antibiotics are prescribed in primary care. The aim of this thesis is to elucidate antibiotic prescribing in selected primary care settings to identify possible areas for improvement.

Methods. Papers I and II are retrospective examinations of patient records at nursing homes over a one year period to identify the infection being treated with antibiotics and whether the choice of antibiotic was in line with the national guidelines for antibiotic treatment. In paper I the extent of microbiologic diagnostics ordered prior to empiric antibiotic therapy is registered.
Paper III examines positive urine cultures from patients 65 years and older living in 34 different nursing homes over a thirteen month period and compared etiology and resistance rates of uropathogens isolated from patients 65 years and older living at home.
Paper IV is a non-randomized controlled cluster intervention study comparing antibiotic prescribing for cystitis and pyelonephritis prior to and after an intervention

Results. Paper I. 94 infections were treated with ciprofloxacin. Urinary tract infection (UTI) was the most common infection both on the long-term (78 %) and the short-term wards (40 %). Respiratory tract infection was almost as common as UVI on short-term wards (37 %), but was uncommon on long-term wards (4 %). Specific bacterial etiology was identified in 44 infections (47 %), 12 of these by bacteria only susceptible for ciprofloxacin.
Paper II. 714 antibiotic courses were prescribed to 327 patients yielding a prevalence of patients treated with antibiotics of 6.6 %. Prescribing compliant with national guidelines was 77 % for UTI, 79 % for RTI, and 76 % for skin and soft tissue infections (SSTI). Ciprofloxacin was responsible for 63 % of non-compliant prescribing. On the short-term wards there was a higher rate of total prescribing, non-compliant prescribing, and prescribing by physicians employed at the local hospital
Paper III. In both the nursing home group and in the group living at home *Escherichia coli* (64 % both groups) was the most commonly cultured bacteria followed by *Enterococcus faecalis* (10 % vs 8 % respectively). *Escherichia coli* was also the most commonly cultured bacteria in females (70 %) and

males (39 %), but *Enterococcus faecalis* was significantly more common in males (18 %) than females (7 %) ($p < 0.05$). For males there was a significantly higher resistance rates to ciprofloxacin for *Escherichia coli* than for females (12 % vs 7 %; $p < 0.05$) and to mecillinam for *Proteus mirabilis* (12 % vs 3 %; $p < 0.05$).

Paper IV. In the targeted emergency department (ED), there was a significant ($p < 0.05$) reduction in ciprofloxacin prescribing and a significant increase in mecillinam prescribing for cystitis ($p = 0.042$). In the control ED, prescribing of ciprofloxacin doubled ($p < 0.05$). There were no significant changes in antibiotic prescribing for pyelonephritis in either ED.

Conclusion. The areas of improvement identified in this thesis include pre therapy microbiologic diagnostics, the need to consider restrictions on prescribing broad spectrum antibiotics, and the need for specific guidelines for the elderly based on gender for the treatment of UTI.

5 Sammenfatning på norsk

Bakgrunn. To store utfordringer moderne infeksjonsmedisin må forholde seg til er økende antibiotikaresistens og mangel på nye antibiotika. Hver for seg er disse utfordringer alvorlige, sammen truer de med å sende oss tilbake til tiden før antibiotika. Disse utfordringer er globale og påvirker alle nivåer i helsevesenet, fra fastleger, til sykehjem, til intensivavdelinger ved sykehus. Rasjonell antibiotikaforskrivning er avgjørende i kampen mot utvikling av resistens. I Norge blir omtrent 90 % av alle antibiotika foreskrevet i primærhelsetjenesten. Målet med denne oppgaven er å belyse antibiotikaforskrivning i deler av primærhelsetjenesten og identifisere mulige områder for forbedring.

Metode. Artikkel I og II er retrospektive undersøkelser av pasientjournaler ved sykehjem over en ett-års periode for å identifisere alle infeksjoner behandlet med antibiotika, og om valg av antibiotika var i tråd med de nasjonale retningslinjer for antibiotikabehandling. I artikkel I registrerte vi omfang og resultat av mikrobiologisk diagnostikk forut for antibiotikabehandling. I artikkel II undersøkte vi etterlevelsen (compliance) med de nasjonale retningslinjene for antibiotikaforskrivning i allmennpraksis
Artikkel III undersøkte positive urindyrkningssvar fra pasienter 65 år og eldre som bodde i 34 forskjellige sykehjem sammenlignet med dyrkningssvar fra pasienter 65 år og eldre som bodde hjemme i samme tidsperiode.
Artikkel IV var en ikke-randomisert kontrollert klynge-intervensjonstudie som sammenlignet antibiotikaforskrivning mot cystitt og pyelonefritt før og etter en intervensjon.

Resultater. Artikkel I. 94 ciprofloksacinkurer ble forskrevet til 78 pasienter ved sykehjem. Ingen pasienter fikk ofloksacin. Urinveisinfeksjon var den hyppigste indikasjon for pasienter på både langtids (78 %) og korttidsavdelinger (40 %). Luftveisinfeksjon var en nesten like hyppig indikasjon på kortidsavdelinger (37 %), men var det sjelden på langtidsavdelingene (4 %). 44 infeksjoner (47 %) ble verifisert med mikrobiologisk undersøkelse. 12 infeksjoner var forårsaket av en mikrobe som kun var følsom for ciprofloksacin.
Artikkel II. 714 antibiotikakurer ble foreskrevet til 327 pasienter ved sykehjem som ga en prevalens på 6,6 %. Forskrivningen var i tråd med antibiotika retningslinjer i 77 % av tilfellene for UVI, 79 % for LVI, og 76 % for hud- og bløtdelsinfeksjoner. Ciprofloxacin ble forskrevet i 63 % av forskrivninger som ikke var i tråd med retningslinjene. På korttidsavdelinger var det en høyere andel av forskrivning som ikke var i tråd med retningslinjer, og forskrivningen av de kurene var initiert av leger ansatt ved det lokale sykehuset.

Artikkel III. Hos både sykehjemspasienter og hjemmeboende pasienter var *Escherichia coli* (64 % begge gruppene) den vanligste bakterien fulgt av *Enterococcus faecalis* (10 % vs 8 %). *Escherichia coli* var også den vanligste bakterien dyrket hos kvinner (70 %) og menn (39 %), men *Enterococcus faecalis* var betydelig mer vanlig hos menn (18 %) enn hos kvinner (7 %) (p <0,05). Hos menn var en signifikant høyere andel *Escherichia coli* resistent mot ciprofloksacin enn hos kvinner (12 % vs 7 %, p <0,05), og høyere andel *Proteus mirabilis* resistent mot mecillinam (12 % vs 3 %, p <0,05).
Artikkel IV. Ved intervensjonslegevakten var det en signifikant reduksjon i ciprofloksacinforskrivning (p < 0,05), og en signifikant økning i mecillinamforskrivning for cystitt (p = 0.042). I kontroll-legevakten var det en signifikant økning i ciprofloksacinforskrivning i den samme perioden (p < 0,05). Det var ingen signifikante endringer i antibiotikaforskrivning for pyelonefritt ved begge legevakter.

Konklusjon. Områdene med forbedringspotensiale identifisert i denne avhandlingen inkluderer økt mikrobiologisk diagnostikk forut for behandling, behov for å vurdere restriksjoner på forskrivning av bredspektrede antibiotika, og behov for spesifikke retningslinjer for behandling av UVI hos eldre, basert på kjønn.

6 Introduction

Antibiotic: tending to prevent, inhibit, or destroy life [1](Webster's Dictionary)

In 2005, I started working at a nursing home in Arendal with both long-term patients and patients admitted for short-term rehabilitation. In the first weeks of work three patients transferred from the local hospital to my ward were being treated with ciprofloxacin. I called the microbiology laboratory for resistance results with the intention of changing to a narrower spectrum antibiotic if results allowed for this. There were, however, no culture results. I was left no option but to continue the ciprofloxacin treatment. Over the next year this situation reoccurred several times. I began to wonder about the extent of this problem, if it was indeed a problem. With this wondering the systematic evaluation which led to the first article about fluoroquinolone use in the nursing home was in swing, and the process culminating in this thesis began.

6.1 Historical Background

"Those who cannot remember the past are condemned to repeat it." George Satayana. The Life of Reason. 1905.

Evidence exists that both the ancient Chinese [2] and indigenous people of South America [3] knew of the antimicrobial effects of plant extracts. In the 1600's western Europeans benefited from this knowledge documented by the use of the quinine-containing bark of the cinchona tree for the symptomatic treatment of malaria.

By the late 1800's scientists were aware of substances demonstrating intermicrobic antagonism. In vitro observations gave hope that these substances could be used therapeutically, but serious toxicity limited their use [4]. There was a need for development of agents toxic to microbes yet safe for human cells. This quest for the "magic bullet" by Paul Ehrlich (1854 – 1915) led to the development of Salvarsan a synthetic arsenic-containing drug used successfully in the treatment of syphilis. Unfortunately, toxicity was again unacceptably high.

The term "antibiotic" was first used by Selman Waksman (1888-1973) in 1942 [5,6]. He defined antibiotics as chemotherapeutic agents produced by microorganisms to inhibit growth of other microorganisms. Although not an antibiotic by this definition, the synthetically produced sulfonamides preceded penicillin as the first therapeutically effective and relatively non-toxic antimicrobial agents. Alexander Fleming (1881-1955) discovered penicillin serendipitously in 1929 [7] but it was not until the late 1930's that Howard Florey (1898-1968) demonstrated penicillin's curative effects in mice [8]. In 1941 the first report of penicillin's curative effect in humans was published [9]. By the mid 1940's and for perhaps the first time in the history of man, the enormous rate of morbidity and mortality bacterial infections caused seemed to be overcome.

6.2 After penicillin: The golden age

'*One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases'*
Frank MacFarlane Burnet, Natural history of infectious disease.1962 [10]

From the early 1940's until the early 1960's over half of the antibiotics now in use were developed giving rise to antibiotic's "Golden Age» (figure 1) [11]. The pharmaceutical industry began playing a more important role in the discovery and development of new antibiotics. The same techniques of first screening biological material for evidence of antibacterial actions and thereafter isolating and purifying the agent for clinical use were utilized. In 1944 the first aminoglycoside and effective anti-tuberculosis drug, streptomycin, was developed. Soon thereafter this, the discovery of chloramphenicol, the first broad spectrum antibiotic, occurred. In the span of the next 15 years several new classes of antibacterial drugs were developed including the cephalosporins, tetracyclines, marcrolides, glycopeptides, and lincosamides. In addition to these drugs the semi-synthetic agent methicillin and the synthetic agents nitrofurantoin, isoniazid, metronidazole, trimethoprim and the quinolones were discovered in this time period.

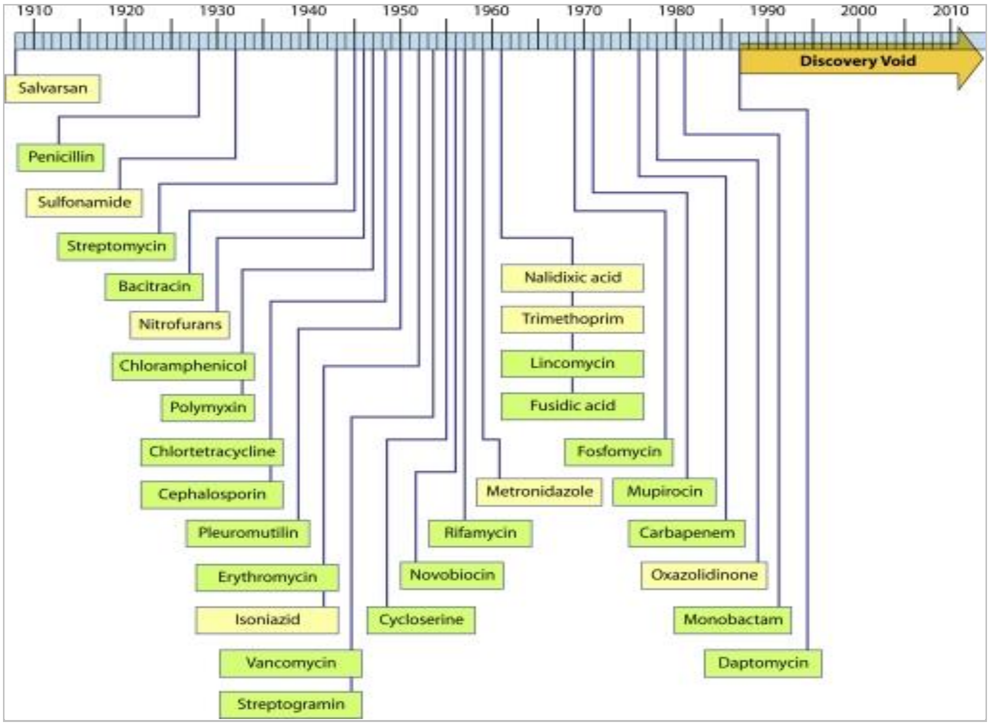

Figure 1. Antibiotic development 1900-2010. The tan boxes are synthetic antibiotics while the green boxes are antibiotics discovered by screening natural products. Methicillin (not shown in the figure) was developed in 1959 (reproduced with permission) [12]

6.3 Newer developments: "The innovation gap" or development void

From the early 1960's the development of new antibacterial agents has slowed significantly and no new classes of antibiotics have been discovered since 1987 [13]. There are several factors contributing to this hiatus. One of these is the limits of selective screening. After almost 20 years, it seems that the possibility of discovering new antibiotics by this technique is exhausted. The shift to techniques using genomics [14] developing new agents targeting known microbial structures like the bacterial cell wall, tRNA synthesis, transcription, and DNA-replication have not yet been as fruitful. Modifications in existing antimicrobial agents have resulted in new generations of agents within these classes. Unfortunately, these modest developments are dwarfed by the rapidly expanding problem of bacterial resistance to antibiotics.

Scientific challenges are not alone in explaining the development void and science alone cannot remedy the problem. Both the economics of the pharmaceutical industry and regulation barriers have a significant role contributing to the hiatus [15]. Antibiotics are used for short periods of time, and should be prescribed restrictively. Medications for chronic conditions like diabetes or hypertension are prescribed commonly and over long time periods. In terms of economic return for investment in development, it is clear that antibiotics cannot compete with medications for chronic illness [13]. Hinders to development due to regulations also contribute to the problem [15,16]. There are several areas of improvement. One example is setting reasonable requirements for non-inferiority for new antibiotics. Another regulatory issue is improving patent laws to ensure costly investments in antibiotic development are compensated by extending patents. Without addressing these issues to stimulate development the resulting lack of new agents coupled with increasing resistance problems will result in a return to the pre antibiotic era [17,18].

Novel approaches are necessary to solve the problem. Researchers need to think differently to discover new antimicrobial medications. Funding sources, both private and public, must coordinate efforts in order to share resources necessary for new development [19]. Finally, unnecessarily strict regulatory obstacles hindering use in patients must be modified [15].

6.4 Antibacterial Resistance

"*Although resistance is inevitable, the pace and extent of propagation of resistant organisms is governed by human behavior" Kieran Hand. Antibiotic Stewardship, 2013* [20]

In his acceptance speech at the Nobel Prize ceremony in 1945 Fleming warned of the problem of resistance to penicillin [21]. There are an enormous number (10^{15}) of bacteria in and on the human body. The replication time for many bacteria is less than one hour. Combining these two facts with the selection pressure antibiotics exert on bacteria make resistance development inevitable.

Antibiotic resistance is an all-encompassing term for a heterogeneous group of mechanisms. These mechanisms are defined by the action of the particular antibiotic and are intimately linked to the biology of the target microbe (figure 2). One can roughly divide antibiotics into those targeting the bacterial cell wall and those targeting cytoplasmic structures responsible for protein synthesis or cell replication. For example, β-lactam antibiotics like penicillin act on the cell wall. Bacteria have developed genes which are responsible for β-lactamases. These enzymes cleave the beta-lactam ring of the antibiotic rendering the antibiotic inactive. Another example is tetracycline which acts on the intracellular 30S portion of RNA inhibiting bacterial protein synthesis. Bacteria combat tetracycline by developing efflux pumps flushing tetracycline out of the bacteria before it can act on the bacterial RNA.

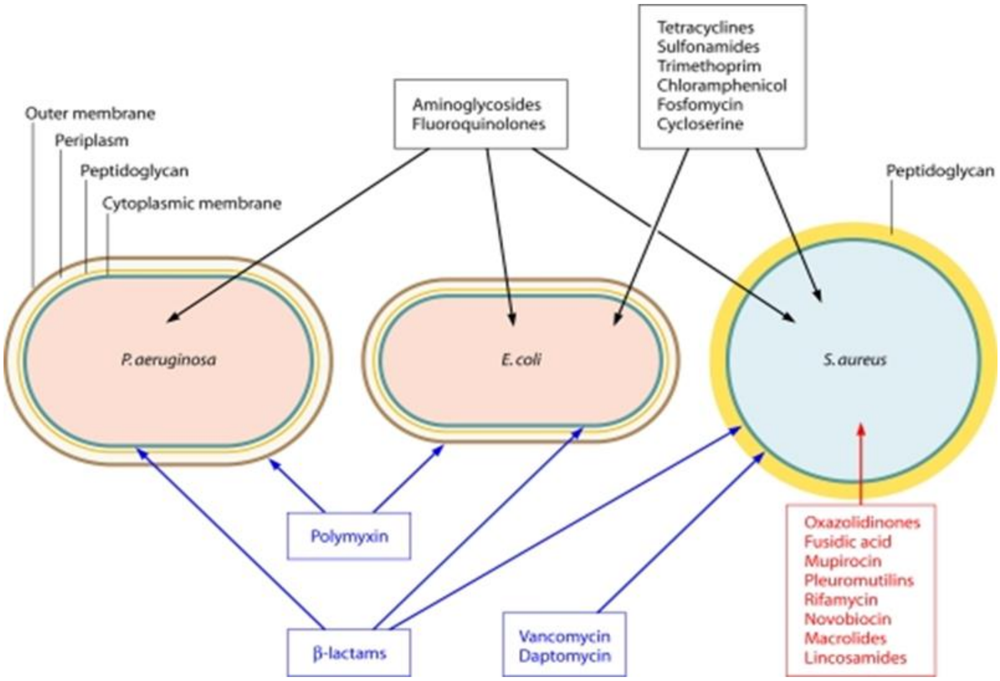

Figure 2. Target locations of antibacterial drugs. Arrows pointing into the cytoplasm indicates intracellular target while arrows pointing to the cell wall indicate extracellular target (reproduced with permission)[12]

There are pharmacologic strategies to combat these resistance mechanisms. B-lactamases can be counteracted with the antagonist clavulanic acid. Here, scientists have found a weapon to destroy the bacteria's "anti-antibiotic" weapon. A more common strategy to combat resistance development is to modify the core structure common in a specific antibiotic class [13]. This produces a new generation antibiotic with characteristics against which bacteria have not yet developed resistance. Examples of new generation antibiotics are found in the penicillin, cephalosporin, quinolone, macrolides and tetracycline classes. This has been responsible for the majority of "new" antibiotics developed after 1960.

Unfortunately bacterial biology has circumvented these pharmacological strategies giving rise to multi-drug resistant (MDR) and pan-drug resistant organisms (PDR). Transmission of resistance occurs vertically and horizontally. Vertical transmission occurs when a bacteria has developed resistance and passes on the genes responsible for the resistance phenotype to its progeny. Horizontal transmission, which is generally facilitated by extra-chromosomal genetic elements (plasmids), enables bacteria to "infect" other bacteria with resistance genes. Often these extra-chromosomal genetic elements code for several different forms of resistance and have been the culprits responsible for extended β-lactamase resistance (ESBL) and MDR/PDR.

There is a clear association between resistance prevalence and the use of antibiotics. European countries with the highest rates of outpatient use of penicillin (ATC code J01) had the highest rates of penicillin non-susceptible *Streptococcus pneumonia (S pneumonia)* (figure 3) [22]. Another study suggested that the observed higher rate of resistant *S pneumonia* in Atlanta was associated with a higher use of antibiotics in the same population [23]. Comparing data on total antibiotic prescription rates with antibiotic resistance rates for both *E coli* and *Klebsiella pneumoniae* (*K pneumoniae)* reveal a clear association; the countries with the highest prescription rates have the highest resistance rates [22,24].

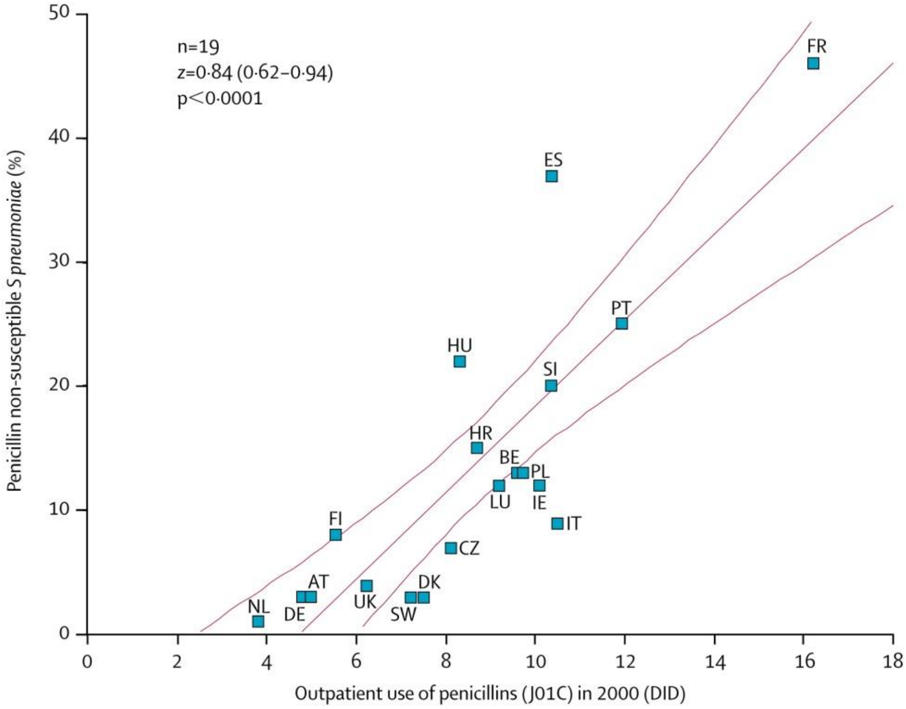

Figure 3. Correlation between outpatient use of penicillins and penicillin resistance in Streptococcus pneumoniae in Europe. (Reproduced with permission (Copyright © 2005 Elsevier Ltd. Goossens H, et al. The Lancet 2005 365, 579-587DO)[22]

The same correlation is seen on the individual patient level. Patients treated with antibiotics for respiratory tract (RTI) or urinary tract infections (UTI) have a higher rate of resistant microbes in their respiratory and urinary tracts after treatment [25,26]. Antibiotic use alters the normal flora of the patient's skin, oropharynx, vagina and gut. This microflora has a protective function for the individual patient and serves as a potential barrier for colonization of pathologic opportunistic MDR bacteria [27]. This is especially true for the gut flora. Once colonized, these patients serve as a reservoir for spread of MDR bacteria.

6.5 The situation in Norway

6.5.1 Antibiotics in Norway

Approximately 90 % of antibiotics are prescribed by primary care physicians in Norway [28]. Both the rate of prescribing and the relative predominance of narrow spectrum antibiotic prescribing is favorable in comparison to most other European countries [29]. Despite this relatively admirable situation, antibiotic prescribing has increased 56 % from 12.6 to 19.6 defined daily dose (DDD)/1000 inhabitants/day since 1974 [30] (figure 4). There has been a slight increase in the percentage of broad spectrum antibiotic prescribing but phenoxymethyl penicillin (Anatomic therapeutic code (ATC) J01CE02) is still the most commonly prescribed antibiotic [28,30,31]. Young children and the elderly over the age of 75 have the highest prevalence of antibiotic use and females use more antibiotics than men for all age groups [30].

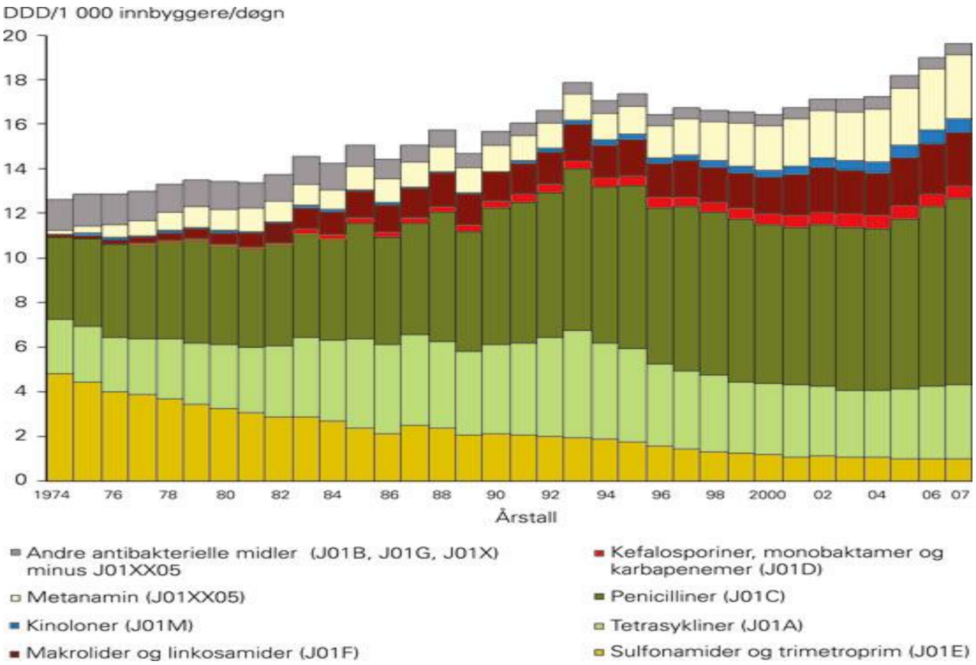

Figure 4. Antibiotic sales in Norway from 1974 by ATC group. (Reproduced with permission)[30]

6.5.2 Resistance in Norway

Along with the other Scandinavian countries, antibiotic resistance problems have been moderate in Norway compared to other European countries [24]. This is not to say that resistance problems are non-existent. Finland has had a problem with macrolide-resistant group A streptococci [32] and Iceland has had a serious problem with penicillin-resistant streptococci [33]. In Norway, the prevalence of ESBL producing *E coli* and *K pneumoniae* has increased and methicillin-resistant *Staphylococcus aureus* (MRSA) is also a problem. There is an association between antibiotic prescribing and resistance development clearly illustrated by *E coli* resistance to ciprofloxacin (figure 5) [34]. Whether resistance problems are a direct result of this practice is a subject of debate [35]. Central in the debate is whether the increase in resistant bacteria is due to selection pressure created by high use of antibiotics, or whether the resistance is due to imported clones which circulate in the environment periodically. Regardless of this debate, the need for prudent antibiotic prescribing is obvious.

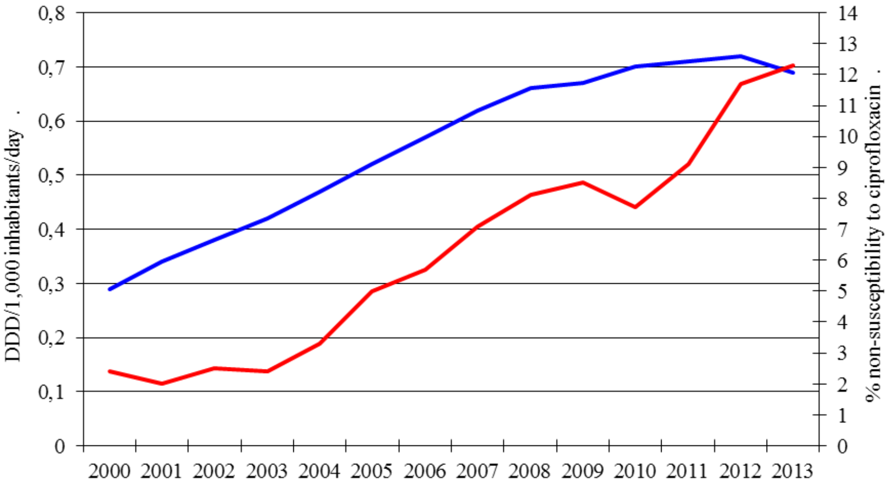

Figure 5. Ciprofloxacin usage (blue) and *E coli* non-susceptibility (red) (reproduced with permission, NORM/NORM-VET 2013. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway) [34]

6.6 More about ciprofloxacin

Ciprofloxacin (ATC J01MA02) is the broadest spectrum antibiotic available in Norway for per os administration. It is a member of the quinolone family of antibiotics, a second generation quinolone derived from nalidixic acid. These agents bind to bacterial DNA topoisomerase and DNA gyrase enzymes disrupting DNA replication and transcription leading to bacterial cell death. Before problems with resistance, ciprofloxacin was especially effective against gram negative organisms of the Enterobacteriacea family (e.g. *E coli, K pneumoniae, P mirabilis*) making it a popular choice for treating UTI.

Although its mechanism of action enables ciprofloxacin to be effective against gram positive organisms, its relatively high minimum inhibitory concentration (MIC-90) value (2-4 µg/ml) [36] makes it unsuitable for treating infections where aerobic gram positive organisms like S *pyogenes* and *S pneumonia* cause disease. This is supported by therapy failures in clinically important bacterial infections such as pneumonia and acute otitis media (AOM) [37,38].

Ciprofloxacin and ofloxacin were the first second-generation fluoroquinolones marketed in Norway. Initially and up until 2008, ciprofloxacin was only approved for empiric treatment of complicated UTI, serious Salmonella infections, and osteomyelitis [39]. Although ciprofloxacin has received approval for marketing its use in a wider range of infections [40], the national guidelines for use of antibiotics in primary care (NGAPC) [41] do not recommend ciprofloxacin as first choice empiric treatment for any infection.

Fluoroquinolone prescribing, primarily ciprofloxacin, has increased 74 % in the last decade from 0.43 DDD/1000 inhabitants in 2002 to 0.75 DDD/1000 inhabitants in 2012 [28]. In Norway, *E coli* resistance to ciprofloxacin has paralleled this trend increasing from 2.2 % in 2002 to 11.3 in 2012 (figure 5) [28] . Internationally, ciprofloxacin has been associated with other serious forms of resistance including ESBL [42] especially in the elderly. In addition to these resistance problems, ciprofloxacin has been linked to C*lostridium difficile* (*C difficile*) infections [43].

Ciprofloxacin can be administered both orally and intravenously. It is absorbed rapidly and has relatively good penetration in all tissues. Excretion occurs via both renal and hepatic pathways. From 10-30 % of orally administered drug appears in the gut. Approximately 40-50 % appears in the urine as unchanged drug. Ciprofloxacin is also excreted in sweat and contributes to resistance development in normal skin bacterial flora [44.]

In younger adults there are relatively few side effects. In the elderly, however, both side effects and interactions are more common [45 46]. Central nervous side effects are the most commonly reported side effects after gastrointestinal side effects making its use in the nursing home potentially problematic. Like several other antibiotics, ciprofloxacin can result in prolonged prothrombin time in patients using warfarin.

6.7 Untoward effects

"*Collateral damage: injury inflicted on something other than an intended target" Webster's Dictionary*[1]

Ecologic effects

The disadvantages of antibiotics are not limited to resistance problems. As mentioned previously, antibiotic use can have detrimental effects on patients' natural flora. The vacant ecological niche created by the disappearance of a patient's natural flora by antibiotics can be occupied by pathological opportunistic microbes. A serious example of this is antibiotic-induced pseudomembranous colitis caused by C*lostridium difficile*. This form of diarrhea is the most common heath care acquired infection in the USA, the most common cause of hospital-acquired diarrhea and the most common cause of gastroenteritis-associated death [47,48]. Other less serious examples of opportunistic infections occurring in the wake of antibiotic treatment are other forms of antibiotic associated diarrhea and Candida vaginitis.

Adverse reactions

Adverse drug reactions (ADR) to antibiotics range from life threatening conditions such as anaphylaxis, hepatic failure, bone marrow suppression and Steven's Johnson's syndrome to less serious but bothersome side effects like nausea and skin rashes. It is difficult to estimate the exact incidence of side effects of antibiotics in Norway. Registration of side effects is based on spontaneous reporting and therefore significantly underestimates the actual incidence. This is especially true for non-serious side effects as patients do not always seek medical care for these symptoms. Even when they do, there is a small and variable chance that the physician will report these side effects.

Studies from abroad indicate that side effects such as diarrhea [49] occur in 5-25 % and rash [50] in 2-4 % of patients. Though often self-limiting and uncomfortable, ADR are responsible for physician consultations, work absence and in some cases serious morbidity. In the USA approximately 20 % of emergency department visits for ADRs were due to antibiotics [51]. In the elderly antibiotics are the second most common class of drugs responsible for ADRs and have been implicated in fatalities [52,53].

Costs

There are both direct and indirect costs due to antibiotic prescribing. Used appropriately the direct cost of an antibiotic is both justified and appropriate. Total costs in Norway are 1.08 billion Norwegian crowns and accounts for 8.7 % of the annual costs of medications prescribed in Norway. How much of this is due to inappropriate prescribing is difficult to estimate and several factors make a calculation difficult. First, laws of confidentiality make it impossible for the national registry of prescriptions to know the diagnosis for which an antibiotic is prescribed. Secondly, it is impossible to know exactly which portion of the antibiotic prescribing was warranted and which was unwarranted. As respiratory tract infections are the most common infections treated in primary care, improving prescribing for these conditions can result in substantial savings. Studies from the USA [54] and England [55] suggest that direct costs of unnecessary antibiotic prescriptions are over US $ 700 million and US $ 35-70 million respectively. The costs of office visits come in addition. Another area contributing to high rates of unnecessary antibiotic prescribing occurs in nursing homes [56] for viral RTI and asymptomatic bacteriuria (ASB). Here, conservative estimates suggest that 22 % of prescribed antibiotics were unnecessary[57].

The indirect costs due to minor side effects and work absence due to these exist but are more difficult to estimate. Another indirect cost is the medicalizing of future episodes of self-limiting illnesses caused by the misunderstood belief held by patients treated with antibiotics that antibiotics are necessary[58].

6.8 Antibiotic stewardship

"*Stewardship: the conducting, supervising, or managing of something; especially: the careful and responsible management of something entrusted to one's care" Webster's Dictionary* [1]

6.8.1 Background

Antibiotic stewardship programs (ASP) are necessary because antibiotic resistance development is inevitable and the development of new antibiotics is stalled. The goals of ASP are to promote rational antibiotic prescribing without compromising patient safety. Antibiotic stewardship is a continuous process with three key elements;

1. Surveillance of antibiotic prescribing
2. Surveillance of resistance development

3. Availability and implementation of reliable guidelines

These elements are used in different strategies aimed at promoting rational drug prescribing. Rational empiric antibiotic prescribing entails choosing the most effective and safest antibiotic against the pathogenic microbe with the most limited impact on the normal flora. The most narrow-spectrum antibiotic should be given in a sufficient dosage over an adequate time period, long enough to eradicate the pathogenic bacterium and as short as possible to limit the impact on the normal flora. It is therefore important to streamline empirical broad-spectrum therapy if the bacterium is susceptible to a narrow-spectrum antibiotic.

The first step is to discern if the presenting complaint is due to an infectious etiology. Some of the most common presenting complaints in family medicine like cough, fever, or dysuria can be caused by non-infectious conditions. Secondly, if the etiology is presumably infectious, one needs to discern if the infectious agent is bacterial or viral. If it is bacterial, one needs to discern if it is necessary to treat with antibiotics. In some infections the etiology may be mixed viral/bacterial and in many cases it is not feasible to determine the putative bacterial etiology. Regardless of etiology, for many infections there is a high likelihood that the condition is self-limiting. Unfortunately, diagnoses like cough, purulent rhinitis, and bronchitis are too often treated with antibiotics despite clear evidence that antibiotics have no clinically relevant beneficial effects [59-61].

There are regional, institutional and individual differences in antibiotic prescribing with no obvious explanation for these differences. In Europe, this is illustrated by the marked differences in total antibiotic prescribing and the differences in the choice of antibiotics among countries [22]. In Norway, this is illustrated by both the difference in antibiotic prescribing in nursing homes [62] but also between individual physicians [63,64]. The use of rational antibiotic prescribing attempts to reduce these inexplicable differences. Surveillance of antibiotic use at the national, institutional and the individual levels generates the information necessary to identify areas for improvement.

Most ASPs are aimed at improving inpatient antibiotic prescribing [20,65,66]. While many of the components of ASP are relevant outside the hospital, they need to be tailored to address the unique characteristics of the nursing home and emergency department (ED) settings. Examples of these characteristics in the nursing home include multi-morbidity, polypharmacy, the role of non-physician initiated diagnosis, and the high rates of telephone prescribing [57]. In the ED, special considerations include consultation time constrain with high patient turnover, limited diagnostic resources and the challenge of patient follow-up. While there are some studies focusing on ASP in the nursing home setting, there are few studies specifically addressing the need for ASP in the ED [67].

6.8.2 Guidelines

Despite commonplace examples of unnecessary antibiotic prescribing, the most important goal of antibiotic stewardship is identifying patients having a clear indication for empiric antibiotic therapy. Indeed, antibiotics used properly have a crucial role in treating infections and are an integral part of ASP. In Norway, there are national guidelines for empiric antibiotic prescribing in both the hospital and in primary care [41,68] (table 1). The recommendations in these guidelines are tailored to Norwegian antibiotic resistance patterns and evidence-based when possible. In addition to therapy recommendations, and recommendation for when not to use antibiotics, the guidelines include information on the proper use of diagnostic testing. Examples of these include judicious use of point of care testing in respiratory tract infections, and appropriate techniques in acquiring material for microbiologic analysis.

Infection	Drug of choice
Acute Otitis Media (AOM)	Phenoxymethylpenicillin **Adults**:1.3 g x 3–4 x 5 d **Children**: 8–15 mg/kg 3–4 x 5 d
Streptococcal tonsillitis	Phenoxymethylpenicillin **Adults**: 660 mg x 4 x 10 d **Children**: 10mg/kg x 4 x 10 d
Acute sinusitis	Phenoxymethylpenicillin **Adults**: 0.66–1.3 g 3–4 x 7–10 d
Acute bronchitis	None
Pneumonia	Phenoxymethylpenicillin **Adults**: 1.3 g x 4 x 7–10 d **Children**: 15mg/kg x 4 x 7–10 d
Uncomplicated cystitis: Otherwise healthy, non-pregnant women 15–60 years of age	Trimethoprim 160 mg x 2 or 300 mg x 1 x 1–3 d Nitrofurantoin 50 mg x 3 x3 d Pivmecillinam 200 mg x 3 x 3 d
Complicated cystitis: Women > 60, men, children	**Adults:** Trimethoprim 160 mg x 2 or 300 mg x 1x 5–7 d Nitrofurantoin 50 mg x 3 x 5–7 d Pivmecillinam 200 mg x 3 x 5–7 d **Children:** Trimethoprim 3 mg/kg x2 x 3–7 d Nitrofurantoin 1.5 mg/kg x 2 x 3–7 d Pivmecillinam 7.5 mg/kg x 3 x 3–7 d
Pyelonephritis	**Adults:** Trimethoprim-sulfa 8/400 mg, 2 x 2 x 7–10 d Pivmecillinam 400 mg x 3 x 7–10 d (Amoxicillin 500 mg x 3 x 7–10 d) **Children :**Trimethoprim sulfa 0.5 ml/kg x 2 x 7–10 d Pivmecillinam 10–15 mg/kg x 3 x 7–10 d (Amoxicillin 15–20mg/kg x 3 x 7–10 d)
Pregnant women with cystitis or asymptomatic bacteriuria	Nitrofurantoin 50 mg x 3 x 7 d Pivmecillinam 200 mg x 3 x 7 d Trimethoprim 300 mg x 1 x 7 d

Table 1. Recommendations for treating respiratory and urinary tract infections. An excerpt from :Antibiotic treatment in primary care concise version (reproduced with permission The Antibiotic Centre for Primary Care and The Norwegian Directorate of Health)[41]

There are a several factors necessary for the development of high quality guidelines. The methodology behind the identification and evaluation of the studies providing the scientific basis for a guideline's recommendations must be both complete and transparent. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [69] system is an internationally accepted system for developing guidelines. This system addresses not only the quality of the evidence base of a guideline but also the advantages, disadvantages and feasibility of specific recommendations. Although important in guideline development, it is not sufficient to focus solely on the quality of the literature providing the basis of the guideline. This is especially relevant for infectious disease guidelines which cannot blindly adapt recommendations from other countries. Because the external validity of even high quality research abroad may be a serious limitation, the Norwegian guidelines have taken special consideration of Norwegian resistance data when preparing the guidelines.

A thorough evaluation of a guideline needs to consider transparency, user involvement, and an evaluation of implementation. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument [70] evaluates the process of practice guideline development including implementation and considers all these issues in scoring the overall quality of the guideline. It is divided into 23 criteria organized into 6 quality domains; scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The NGAPC have been evaluated with the AGREE instrument and received a relatively high score of 78/92 (personal communication, the Norwegian Electronic Health Library).

6.8.3 Interventions to improve antibiotic prescribing

Interventions to improve antibiotic prescribing aim to reduce inappropriate antibiotic prescribing and to encourage use of narrower spectrum antibiotics instead of broad spectrum antibiotics when possible. Interventions can be directed at the general public, patients, physicians or a combination of these groups [71]. Changing physicians' antibiotic prescribing behavior is, however, a challenge. Several modalities to attempt this task are available. Examples include printed guidelines issued by public health authorities, continued medical education (CME) courses, use of delayed prescribing, economic incentives and restrictions [66,72]. Several factors are important to improve physicians' antibiotic prescribing behavior [73]. In general, interventions such as academic detailing aimed at physician education appear effective [74]. However, no single type of intervention is universally effective and some interventions are relatively ineffective [75]. The best results are based on a combination of interventions [76].

Previous Norwegian interventions have demonstrated significant improvement in antibiotic prescribing in the ED [77,78] and in the hospital[79]. A recent Norwegian study showed that a peer-group based intervention reduced total antibiotic prescribing for respiratory tract infections and increased the proportion of first choice antibiotic penicillin G in favor of broad spectrum antibiotic prescribing[80].

Another type of intervention is the delayed prescription strategy. This approach utilizes a prescription given to a patient who does not need antibiotic treatment at the time of consultation but may need antibiotics if the condition worsens [81]. This enables the patient to initiate antibiotic treatment without the need for re-consultation. Critics have nonetheless pointed out that these reductions are disappointing low in comparison to simply not prescribing when there is no indication for antibiotics [81,82]. Restrictions on prescribing are another strategy employed in ASP [66,83]. Although not always popular among physicians, restrictions can reduce unnecessary antibiotic prescribing without increasing complications [84,85]. Restrictions have the added advantage of sustained improvement of antibiotic prescribing which can be a problem with other types of interventions [83,86].

For UTI there is less evidence that interventions reduce unnecessary treatment. This may be due to several factors. The majority of UTIs are uncomplicated cystitis for which antibiotic therapy is clearly effective and greatly appreciated by the patients. In addition the course of therapy for uncomplicated UTI is short making the contribution to total antibiotic usage less than infections requiring longer treatment duration. Studies therefore focus on improving the choice of antibiotic therapy [87]. In contrast to uncomplicated UTI, there is a clear need to improve diagnosis and therapy of UTI in the institutionalized elderly. UTI tract infections are the most commonly treated infection in nursing homes both in Norway and abroad[57,88-90]. Several factors including the high rate of cognitive impairment, misinterpretation of unspecific symptoms, and inappropriate use of diagnostic tests make the diagnosis of UTI in this patient group challenging and contributes to unwarranted antibiotic prescribing [56,91,92]. Overprescribing in the elderly is especially disconcerting due to increasing the risk of toxicity, drug interactions and antibiotic resistance in population [46].

6.9 The settings of these studies

Both the ED and the nursing home (NH) are arenas in which focus on rational antibiotic prescribing is important for several reasons. The rapidly expanding elderly population in the western world will result in an increasing need for assisted care institutions including NHs. During past 30 years the Norwegian population 80 years and older has more than doubled. There are approximately 900 NHs with over 40 000 beds in Norway, three times the number in 1970[93]. The average age of a patient in a Norwegian NH is 84 and approximately 75 % are women. Reduced cognitive function among Norwegian NH residents is approximately 60-75 % [94,95]. Morbidity in addition to dementia is a problem reflected by the high use of medications in these patients. Studies indicate that Norwegian NH patients use 6-12 medications daily with a substantial risk of adverse drug interactions[96,97].

The terminology referring to assisted care facilities is varied, reflecting the heterogeneity of the patients residing in these institutions. In this thesis the term nursing home refers to an institution where skilled nursing care is available 24 hours a day.

There is a growing use of ED services in Norway and abroad[98,99]. In Norway there are approximately 150,000 ED consultations annually with respiratory tract and urinary tract infections among the five most common registered diagnoses every year [99]. The ED service is integrated in primary care in Norway and is not hospital based. It is available from 3 PM-8 AM daily and 24 hours daily during the weekend throughout Norway. The unique characteristics of these two settings makes extrapolation of results from hospital based studies problematic.

This thesis aims to explore ways to improve antibiotic prescribing in these two Norwegian primary care settings.

7 This Thesis

7.1 Aim

The aim of this thesis is to examine specific target areas for improved antibiotic prescribing in selected primary care settings by:

1. Evaluating the indication for ciprofloxacin prescribing and the extent of microbiologic diagnostic work-up prior to prescribing.

2. Evaluating the degree to which antibiotic prescribing in the nursing home is in accordance with the national guidelines.

3. To see if differences in resistance rates of uropathogens isolated from nursing home patients compared to elderly patients living at home warrant separate empiric antibiotic therapy recommendations for urinary tract infections. To see if empiric antibiotic therapy recommendations for UTI in the elderly based on gender are warranted.

4. To see if a simple intervention can reduce ciprofloxacin prescribing in an emergency department.

7.2 Material and Methods

7.2.1 Paper I: Fluoroquinolone study [100]

Design: Cross-sectional retrospective study.

Population: Nursing home patients in Adrenal municipality prescribed a fluoroquinolone during a one year period.

Main outcome measures. The proportion of patients diagnosed with some form of microbiologic work up. Culture and resistance results for these patients.

Method: We identified all patients prescribed a fluoroquinolone by specifying the Anatomical Therapeutic Chemical Classification code (ATC) [101] in the Gerica® electronic patient record system (EPR) for the time period 1.12. 2006 to 30.11.2007. This generated a list of all patients prescribed ciprofloxacin (J01MA02) or ofloxacin (J01MA01). We searched the patients' records and recorded the following; patient age, gender, ward type (long-term or short term), indication, dosage, duration, and prescribing physician. Discharge summaries for patients initially treated at the local hospital were reviewed for all patients in whom initiation of antibiotic treatment occurred at the local hospital. We then contacted the microbiologic laboratory for culture and resistance results for all these patients.

Statistics. The data were published without formal statistical analysis.

Approval. The study was evaluated as a quality assurance project by the Regional Ethics Committee (6.2008.1602) and by the Norwegian Data Protection Authority.

7.2.2 Paper II: Compliance study [88]

Design. Descriptive cross-sectional retrospective study.

Population. Nursing home patients in Arendal municipality who were prescribed antibiotics in a one year period.

Main outcome measures. Choice of antibiotic in respect to the recommendations in the national guidelines for antibiotic prescribing.

Method. We used the ATC system to search Gerica® for all patients prescribed antibiotics during the 12 month period from 01.03.07-28.02.08. We searched the patients' medical records and recorded the following data; age, gender, ward (short-term vs. long-term), name of and indication for antibiotic, dose and duration of antibiotic treatment, the prescribing physician (nursing home, emergency call service (ECS), or hospital. Antibiotic use is measured as DDD per 1000 bed days. We calculated this by totaling DDD used in one year divided by the total number of nursing home beds x 365 and multiplying this by 1000.

Prevalence is calculated by the total number of days antibiotics were prescribed divided by the total number of beds x 365.

The national guidelines for antibiotic prescribing [102] have specific recommendations for empiric therapy for all common bacterial infections in the primary care setting. Deviation from the guidelines was defined as choice of antibiotics not in accordance with these recommendations.

Statistics. We used Pearson's chi-squared test to test for associations between the proportions of antibiotics prescribed according to national guidelines vs. proportion not in accordance with guidelines, and which ward patients were on (long-term vs. short-term). We calculated odds ratios (OR) and 95 % confidence intervals (95 % CI) to test for the association between type of prescribing physician, or type of ward with compliant prescribing.

Approval. The study was approved by the Regional Ethics Committee (2010/726a).

7.2.3 Paper III: Uropathogen resistance study

Design. Retrospective cross sectional study.

Population. Positive urine cultures from patients in nursing homes in a twelve month period were susceptibility tested and compared to positive urine cultures from non-hospitalized patients 65 years or older living at home.

Main outcome measures. Bacteria responsible for urinary tract infections and their antimicrobial resistance rates.

Method. Urine cultures fulfilling the criteria for significant bacteriuria (> 10,000 colony-forming units/ml urine) were included in the study. Appropriate antibiotics for resistance testing were selected for each bacterial species according to recommendations from the Norwegian Working Group on Antibiotics (NWGA). Results were interpreted according to clinical breakpoints from NWGA which are based on those from The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Resistance values were recorded either as susceptible (S), intermediate (I), or resistant (R).

Antibiotic resistance patterns from patients living in nursing homes were compared to resistance patterns from patients living at home. Resistance patterns from males were compared to results from females irrespective of where they lived.

Statistics. We used Pearson's chi-squared test to compare differences in gender distribution between the study group and the community dwelling (CD) group and the t-test for independent samples to compare the mean age in the two groups.

We used the Pearson's chi-squared test and the Fischer's exact test (when appropriate) to compare differences in resistance rates for relevant antibiotics between the study group and the CD group, and between males and females.

Approval. The study was approved by the Norwegian regional ethics committee (REK sør-øst 2013/2282).

7.2.4 Paper IV: Intervention study [103]

Design. Prospective non-randomized cluster control trial.

Population. Emergency department (ED) physicians prescribing antibiotics for urinary tract infections.

Main outcome measures. Antibiotic prescribing for UTIs.

Method. All antibiotic prescribing for UTIs was registered one year prior to and one year after the intervention in two different EDs. One ED received the intervention while the other ED served as control. Both EDs were located in southeast Norway, an area with similar resistance patterns, and served a demographically nearly identical population of approximately 100,000. Both EDs had approximately 40000 consultations annually.

The intervention had two components: Removing ciprofloxacin from the ED formulary and introducing a therapy suggestion list for antibiotic use accompanying all urine dipstick results.

Statistics. Frequencies of antibiotic prescribing were analyzed by means of a logistic regression model. Dependencies in the data, due to clustering at the physician level, were handled by Generalized Estimating Equations (GEE) with unstructured working correlation and robust variance estimation. 95 % confidence intervals were used.

Approval. The study was approved by the regional ethics committee (Project number REK:6.2008.1602).

8 Summary of results

8.1 Paper I: Fluoroquinolone study

78 nursing home patients received 94 ciprofloxacin prescriptions. Eleven of these patients were treated with ciprofloxacin more than once. No patients were treated with ofloxacin. 51 of the prescriptions were for patients on the long-term wards (315 beds) while 43 of the prescriptions were for patients on the short-term wards (45 beds). Of the 94 prescriptions 72 (77 %) were for women and 22 (23 %) for males. The mean age was 86 for women and 76 for men. There was no statistically significant difference in gender (73 % vs 81 %, p=0.31) or age (84.3 vs 83.6, p=0.68) between the patients treated on the long-term vs the short-term ward.

On the long-term wards the indication for ciprofloxacin prescription was UTI in 78 % of the cases, respiratory tract infection (RTI) in 4 %, mixed UTI/RTI in 6 %, and in 12 % for other infections. On the short-term wards the indication was UTI in 40 % of the cases, RTI in 37 %, mixed UTI/RTI in 7 %, and 14 % for other infections. There was a statistically significant difference in indication for ciprofloxacin prescribing between the two ward types ($p < 0.05$).

On the long-term ward nursing home physicians wrote 84 % of the prescriptions, hospital physicians wrote 10 % and physicians in the emergency department (ED) wrote 6 %. On the short-term ward nursing home physicians wrote 33 % of the prescriptions, hospital physicians wrote 62 % and physicians in the emergency department wrote 5 %. There was a statistically significant difference in prescribing physician affiliation between the two ward types ($p < 0.05$). Microbiologic diagnostics were performed in 51.8 % of treatments initiated by a nursing home physician, 51.5 % initiated by a hospital physician and in 20 % initiated by an ED physician. There were 36 positive cultures. Of these 36, twelve were caused by a bacterium which was solely susceptible to ciprofloxacin.

8.2 Paper II: Compliance study

The total antibiotic prescribing was for 714 infections in 327 NH patients which translates to 55 DDD/1000 bed days. The overall prevalence of patients receiving antibiotics was 6.6 %, with the long-term wards having a prevalence of 5.6 %, while the short-term wards having a prevalence of 11.2 %. UTI was responsible for 53 % of the infections, followed by RTI responsible for 21 %, and skin and soft tissue infections (SSTI) responsible for 14 %. Combined UTI/RTI or other infections were responsible for 5 %. In 8 % no documentation for the infection was found in the patients' records.

73 % of prescribing was by nursing home physicians, 17 % by physicians at the county hospital, 7 % by the doctor on call in the ED, and 3 % by the patients' family doctor. It was more likely that a non-nursing home physician was the prescribing physician for patients on the short-term ward than on the long-term ward (OR 4.39, 95 % CI 3.09- 6.24).

The most commonly prescribed antibiotics; trimethoprim, pivmecillinam, ciprofloxacin and penicillin V accounted for 61 % of total prescribing. 77 % of the prescriptions for UTI, 79 % for RTI, and 76 % for SSTI were in compliance with the guidelines. Ciprofloxacin and cephalexin accounted for 85 % (114/134) of the prescriptions not in compliance with the national guidelines. When comparing the proportion of antibiotics prescribed according to national guidelines, there was a tendency of higher non-compliant prescribing on the short-term as compared to the long-term ward (OR 1.41, 95 % CI 0.95 - 2.1, p= 0.09).

8.3 Paper III. Uropathogen resistance study

E coli was the most common bacteria in both the nursing home group and in the CD group (64 % vs. 64 %) followed by *E faecalis* (10 % vs. 8 %) with no significant difference between the two groups a whole (p = 0.454).

In the nursing home group there were significantly higher resistance rates to ciprofloxacin for *K pneumoniae* (18 % vs. 3 %; p = 0.016) and *P mirabilis* (25 % vs. 5 %; p = 0.011).

E coli was significantly more common in females than males (70 % vs. 39 %; p < 0.05), while *E faecalis* was significantly more common in males than females (18 % vs. 7 %; p < 0.05).

For males there was a significantly higher resistance rate to ciprofloxacin for *E coli* than for females (12 % vs. 7 %; p = 0.016) and to mecillinam for *P mirabilis* (12 % vs. 3 %; p = 0.036).

8.4 Paper IV Intervention study

Baseline demographics were nearly identical in the intervention ED and the control ED. The intervention ED had 14 % more UTI diagnoses than the control ED. The relative frequencies of cystitis and pyelonephritis before and after the intervention were similar in both EDs. In the intervention ED there were 1286 cystitis and 107 pyelonephritis diagnoses pre-intervention, with 1264 and 73 respectively post-intervention. In the control ED there were 1103 cystitis and 113 pyelonephritis diagnoses pre-intervention, with 1091 and 90 respectively post-intervention.

Between 86-89 % of cystitis diagnoses were treated in both the intervention and the control EDs both pre- and post-intervention. In the intervention ED ciprofloxacin prescribing decreased from 6.3 % of the cases pre-intervention to 3.4 % post intervention. In the control ED ciprofloxacin prescribing increased from 2.3 % pre-intervention to 4.7 % post-intervention. This significant decrease in prescribing of ciprofloxacin (p<0.05) in the intervention ED was accompanied by a significant increase in pivmecillinam prescribing (p=0.042).

There was no significant change in ciprofloxacin prescribing for pyelonephritis in either ED. Prescribing rates for pyelonephritis were higher in the intervention ED than in the control ED pre-intervention (15.9 % versus 8.0 % respectively) and remained higher post intervention (15.1 % versus 5.6 %).

9 Discussion

9.1 Summary

Adequate microbiologic diagnostic work up prior to empiric therapy with ciprofloxacin in the nursing home setting is often lacking. This is especially true when ciprofloxacin is prescribed off-hours by a physician in the ED. Pre-therapy diagnostic work up by nursing home physicians and by hospital physicians is better than ED physicians. Nonetheless, only half of nursing home patients treated with ciprofloxacin had their urine (or blood) cultured. The potential to reduce unnecessary ciprofloxacin treatment duration is substantial with adequate pre-therapy diagnostics.

Antibiotic prescribing in the nursing home often complies with the national guidelines. There are, however, certain aspects of the prescribing which need improvement. In terms of antibiotic choice, ciprofloxacin prescribing for RTI and UVI, cephalexin for UVI and SSTI, and doxycycline treatment for RTI are specific targets for improvement. It seems that prescribing on short-term wards comply less with the national guidelines than on long-term wards. As there is a higher percentage of non-nursing home physicians responsible for prescribing on the short-term wards, efforts to improve compliance must target the nursing home, the hospital and the ED.

Compared to elderly patients living at home, the elderly living in the nursing homes do not have significantly different bacteria responsible for their UTI, nor are these bacteria more resistant. There are, however, significant differences in the bacterial etiology and the resistance patterns of bacteria causing UTI in men compared to the bacteria causing UTI in women. These differences may need to be considered in national guidelines for treating infections in the elderly.

UTIs are one of the most common diagnoses made in the ED making it a target for optimizing empiric antibiotic therapy. A simple intervention combing a therapy suggestion list with removal of ciprofloxacin from the local formulary reduced unnecessary ciprofloxacin prescribing while increasing appropriate pivmecillinam prescribing. Potentially appropriate ciprofloxacin prescribing for pyelonephritis remained unchanged.

9.2 Internal validity of these studies

Success is going from failure to failure with no loss of enthusiasm. (Winston Churchill)

9.2.1 General considerations

A study's internal validity refers to how well a study avoids systematic bias, reflecting the quality of the study's methodology. There are a number of factors relevant when evaluating the internal validity of medical research. Internal validity is a prerequisite for a study's external validity which will be discussed later in this thesis.

The first three papers were retrospective cross sectional studies. There are inherent biases and strengths in retrospective studies. One weakness is the lack of randomization. The patient population is predefined. It is therefore difficult to know how representative the study population is for the problem one is researching. In three of these papers the nursing home was the setting of the study, and the patients were all treated with antibiotics. The gender distribution was 80 %, 73 %, and 79 % females in each of the studies respectively. This gender distribution is similar to other studies from European and North American NH studies [57,89,104] .

Papers I and II included all patients receiving an antibiotic while the third paper restricted inclusion to patients 65 years or older. Despite this, the ages in the studies are similar. In paper I, the mean age was reported by the ward on which the patient resided and was 84 years for both the long-term ward and the short-term ward. In paper II median age was 87 for females and 82 for males. In paper III the respective mean ages were 87 vs 83. Optimally we should have consistently used either the median or the mean to describe the midpoint of our populations' ages. The age range in our papers is also in line with studies from other European and North American NH studies [57,89,104].

9.2.2 Methodology: database generation

Recall bias is a problem in retrospective studies. These papers are based on what was documented and not necessarily what was actually done. In the three papers from the nursing homes, the defining inclusion-criteria was an antibiotic prescription. In the papers I and II, the nursing homes used the electronic patient journal system (EPJ) system Gerica®. The prescription module in Gerica® allowed us to generate a list of all patients receiving an antibiotic in a given time period. Gerica® does not, however, automatically require a physician designated diagnosis or diagnosis code (e.g. ICPC or ICD) before prescribing an antibiotic. If Gerica® had this function it would have been relatively easy to cross reference an antibiotic prescription with the diagnosis code generating a list in which each antibiotic prescription was linked to a specific diagnosis. This technique has been used in other studies and was used in paper IV in this thesis [80]. In paper IV the EPJ used in the participating EDs was WinMed®. In contrast to Gerica®, WinMed requires a physician to specify an ICPC diagnosis every time a physician writes an entry in a patients' journal.

While the relative ease in generating a diagnosis-prescription linked list is an apparent advantage, there are disadvantages with this approach also. The physician generated diagnostic ICPC code does not necessarily reflect the content of text in the actual EPJ entry. In certain cases it can be directly misleading. One example of this is seen in table II in paper IV where 33-41 % of patients with pyelonephritis and 11-14 % of patients with cystitis received no antibiotic treatment. This illogically high rate of no-treatment was seen in both EDs and in both observation periods. It also seemed illogical that a lower percentage of patients with pyelonephritis received antibiotics than patients with cystitis. To control for this we read all EPJ notes for patients not receiving antibiotics for both pyelonephritis and cystitis. Nearly all patients not receiving antibiotics for pyelonephritis were admitted to the hospital for treatment. This was the case in both EDs in both periods. For cystitis the majority of patients receiving no treatment were patients with questions about treatment, side effects, or advice about prophylaxis. This ancillary information would remain hidden in a database generated solely by an electronic extraction of ICPC diagnosis codes alone.

In papers I and II we had to read all journal entries for each antibiotic prescribed to determine the type of infection being treated because Gerica® could not generate a reliable diagnosis-prescription list. In these nursing homes there is no systematic use of diagnostic tools like the Loeb or McGeer criteria when evaluating patients having an infection [105,106]. Physicians' and nurses' written documentation was the basis for how we determined the type of infection. In the most extreme cases, there was so little information in the patients' records that it was impossible to specify the gross anatomical localization of the infection (RTI, UTI, SSTI, other). These cases were classified as unspecified infections and were responsible for about 8 % of the results in both papers. For the same reason we were not able to be more specific within an anatomical diagnostic group. Cystitis was grouped with pyelonephritis and asymptomatic bacteriuria (ASB) as UTI, bronchitis with pneumonia and COPD exacerbations as RTI, and cellulitis with decubitus as SSTI.

9.2.3 Selection bias urine sampling

Selection bias can influence the results of a study if the groups being compared are dissimilar. There are several possible dissimilarities in urine collection which may bias the results in paper III. The control group, though similar in gender distribution, was ten years younger than the NH group. The prevalence of resistant organisms in urine cultures increases with age [107-110]. We found no increase in resistance with age which may strengthen the validity of the observed results. In the control group we did not know the reason for urine culturing while in the NH group all urines were from patients treated for a suspected UTI. There were no post-therapy urine cultures in the NH group raising the potential for a difference in the contribution of post-therapy control urines in the two groups. Although Norwegian guidelines specifically dissuade urine culture for ASB [41], the relative contribution of ASB in the two groups is unknown. It is known than non-specific symptoms can result in inappropriate urine dipstick testing which is then inappropriately interpreted as a treatment requiring UTI. This type of misinterpretation may be more common in NH patients than in patients living at home. How inequities in the contribution of ASB and post-therapy controls would affect the validity of the observed results is difficult to know.

We did not know what percentage of the urine cultures were from patients with urinary catheters in either group. It is possible that there was an unequal prevalence of catheter specimens between the two groups. There is a higher prevalence of urinary catheter use in patients residing in NH [111] and urines cultured from patients with catheters have a higher rate of resistant organisms [112,113]. The potentially higher rate of catheters in the NH group would be expected to result in higher rates of resistant organisms in this group. Our results showed no higher resistance rates in the NH group.

Although there are guidelines for urine sampling in Norway [114], adherence to these guidelines may differ between the NH and the CD groups. As patients in the CD group were younger and living at home it is possible that the percentage of mid-stream urine sample was higher in the CD group. Again, it is difficult to know how this possible bias contributed to our results showing no difference between the two groups.

9.3 Inappropriate vs non-compliant prescribing

9.3.1 UTI

Antibiotics may be inappropriate to use even when the choice of antibiotic is in compliance with the national guidelines. This is exemplified by antibiotic prescribing for ASB. The problem of antibiotic treatment of ASB in the nursing home is both widespread and challenging. There is clear evidence that treating ASB is neither effective at eliminating bacteriuria nor improving clinical outcome of patients [115]. Furthermore, non-specific symptoms are often inappropriately interpreted as being due to a UTI [92]. As both ASB and non-specific symptoms are prevalent in nursing home patients this contributes to misleading urine dipstick testing and urine culture which in turn leads to inappropriate antibiotic prescribing. Antibiotic treatment of ASB contributes significantly to inappropriate antibiotic prescribing in the NH [56].

Unfortunately not being able to differentiate between the diagnoses within the anatomic diagnostic group makes it difficult to evaluate how much of the total prescribing was inappropriate. Nonetheless, total antibiotic prescribing is associated with increased resistance problems making reduction or elimination of antibiotic prescribing for ASB an important target for improvement. Unfortunately, incomplete and unsystematic documentation in patient records made it impossible to reliably determine how much of the total prescribing was due to ASB.

In contrast to ASB, antibiotics are indicated for both cystitis and pyelonephritis but the choice of antibiotic may be inappropriate. Neither ciprofloxacin nor cephalexin is recommended for empiric treatment of cystitis in the NGAPC (table 2). In the guidelines, ciprofloxacin is only recommended in definitive treatment based on a culture result in which the isolated bacteria is only susceptible to ciprofloxacin. It is possible that some of the ciprofloxacin prescribing in paper II was based on culture results and therefore may be appropriate. The database in paper II came from the same NHs as in paper I making it unlikely that treatment based on culture results are higher than they were in paper I. The results in paper I demonstrated that only 50 % of the patients treated with ciprofloxacin had a culture result, and only 12 % had a microbe solely susceptible to ciprofloxacin. Cephalexin is not listed in the national guidelines as a therapeutic option in the treatment for either cystitis or pyelonephritis. In addition, susceptibility determination for cephalosporins is not routinely reported by the microbiology laboratories used by the NHs in these papers.

Infection	Empirisk behandling	Duration
Uncomplicated lower urinary tract infection	Pivmecillinam 200 mg x 3 Trimethoprim 160 mg x 2 Nitrofurantoin 50 mg x 3 Amoxicillin 250 mg x 3* Cefalexin 250 mg x 3*	7 days for women 14 days for men
Upper urinary tract infection	Pivmecillinam 400 mg x 3 Trimethoprim-sulfamethoxazole 160+800 mg (2 tabl./20 ml mixture) x 2 Ciprofloxacin 500 mg x 2 Ofloxacin 400 mg x 2	7-14 days for both genders

Table 2. Recommendations for treating urinary tract infections.in nursing home patients. Adapted from: Antibiotic treatment in primary care (reproduced with permission The Antibiotic Centre for Primary Care and The Norwegian Directorate of Health[41])
***** Only when culture results show resistance to all other antibiotics

One interesting and arguably inappropriate finding in papers I and II was the low prescribing rates of nitrofurantoin for UTI. Cystitis is a much more common diagnosis in both the nursing home and in the emergency room than pyelonephritis. There is, therefore, no logical explanation for physicians prescribing nitrofurantoin so infrequently. In paper IV, *E coli* and *E faecalis* were the two most commonly isolated bacteria. Both bacteria are highly susceptible to nitrofurantoin in Norway [34]. The contraindications for use of nitrofurantoin are limited. The NGAPC dissuade use of nitrofurantoin in patients with renal insufficiency because the concentrations of nitrofurantoin in the bladder are dependent on renal excretion and decreased renal clearance may cause toxicity [41,116]. One might suspect that renal insufficiency with concomitant risk of toxicity in the elderly might be part of the reason for not prescribing nitrofurantoin in the NH setting. However, the prevalence of renal insufficiency in the elderly is not so high to explain that nitrofurantoin is used in only six percent of UTIs (table I in paper II). The low rates of nitrofurantoin prescribing for cystitis in the ED are clearly not due to the prevalence of renal insufficiency in this much younger and ostensibly healthier population (table II in paper IV). Previous randomized controlled studies show that nitrofurantoin is equally effective and no more toxic than other antibiotics in the treatment of cystitis [117]. Other countries report various rates of nitrofurantoin prescribing in both the NH setting and for uncomplicated UTI [104,118,119]. Dosing frequency alone doesn’t seem to be the explanation as mecillinam, the most frequently prescribed antibiotic, is also taken three times daily. It is not possible to explain why physicians in two completely different clinical settings had such low nitrofurantoin prescribing rates.

Why mecillinam and trimethoprim dominate prescribing practice in both the NH setting and in the two EDs is difficult to explain. The prescribing physicians' fear of resistance problems cannot explain this practice, especially in the case of trimethoprim. In Norway, both *E coli* and *E faecalis* have resistance rates for trimethoprim near or above 20 % [34] making trimethoprim a less logical choice than nitrofurantoin for the treatment of cystitis. That nitrofurantoin cannot be prescribed for pyelonephritis does not explain the low prescribing rates as cystitis is a much more common diagnosis than pyelonephritis.

9.3.2 RTI

As with UTI, there is a parallel situation with diagnostic imprecision of RTI in these papers. Differentiating a self-limiting RTI from a lower RTI that needs antibiotic treatment is challenging. In the outpatient population this contributes to a high rate of unnecessary antibiotic use for bronchitis despite clear evidence that antibiotics are not necessary [61,120,121]. Making this differentiation is more challenging in cognitively impaired elderly with a high rate of atypical presentations. Even the use of point of care testing with CRP and consistent documentation of the results would not provide irrefutable basis for a definitive diagnosis. Compounding this with a lack of specific diagnostic criteria prior to treatment resulted in our grouping several diagnoses together. In both papers I and II pneumonia, exacerbation of COPD, bronchitis and cough with fever were grouped as RTI when patients were treated with antibiotics.

While antibiotics can be indicated for both pneumonia and exacerbations of COPD they are not appropriate for bronchitis or unspecific cough with fever. Inappropriate antibiotic prescribing for viral RTI, like inappropriate antibiotic prescribing for ASB, contributes significantly to overuse of antibiotics [57] [18,122].

A unique and challenging assessment of appropriate antibiotic therapy arises when evaluating treatment of pneumonia in debilitated, severely cognitively impaired elderly, or in the elderly who develop a respiratory infection while terminally ill [123,124]. We did not systematically address antibiotic prescribing in the last days of patients' lives. The degree to which this practice contributes to resistance development is overshadowed by the ethical considerations in palliative treatment in these patients. Nonetheless, discussion with patients' relatives and good palliative routines on nursing home wards specifically addressing antibiotic use could avoid subjecting these patients to unwarranted antibiotic treatment.

Although these studies could not evaluate what proportion of the total antibiotics was prescribed inappropriately for viral RTI infections, we were able to evaluate whether the choice of the antibiotic was in line with NGAPC (table 3). Phenoxymethyl penicillin is the first line recommendation for pneumonia with doxycycline as an alternative in the case of penicillin allergy or difficulty swallowing. Despite this, doxycycline is prescribed 1.3 times more frequently than penicillin. Reports of the incidence of penicillin allergy in the general population vary, but true penicillin allergy (Type 1) is very rare and cannot explain why doxycycline is prescribed more often than penicillin[50,125]. While not inappropriate, the high prescribing rate of doxycycline may illustrate that guidelines alone will not dictate the choice of antibiotic. Issues such as convenience of administration may also play a role. Fortunately the macrolides with long half-lives, clarithromycin and azithromycin were rarely prescribed.

Empiric treatment	**Antibiotic dosage**	**Duration**
First Choice	Phenoxymethylpenicillin 660 mg -1,3 g x 4	7-10 days
Alternative choice	Doxycycline 100 mg x 1 Amoxicillin 500 mg x 3 Erythromycin enterocapsle 250 (500) mg x 4 Erythromycin ES 500 (1000) mg x 4 Clarithromycin 250-500 mg x 2	7-10 days
	Azithromycin 500 mg x1	3 days
Special indications*	Trimethoprim-sulfamethoxazole 160+800 mg (2 tabl/20 ml mixture) x 2	7-10 days
	Ciprofloxacin 500 mg x 2 + Phenoxymethylpenicillin 0,65-1.3 x 4	7-10 days

Table 3. Recommendations for treating pneumonia.in nursing home patients. Adapted from: Antibiotic treatment in primary care (reproduced with permission The Antibiotic Centre for Primary Care and The Norwegian Directorate of Health)[41].
***** Empiric treatment shortly after hospital discharge or when culture results show resistance to first and alternative choice antibiotics

As in the case with UTI, ciprofloxacin was the most frequently prescribed antibiotic not in compliance with the national guidelines. The use of ciprofloxacin in RTI is even less reasonable than in UTI. *S pneumoniae* is the most common bacterial etiology for RTI. In Norway at the time of this study, pneumococcal resistance to penicillin was < 1 % making the choice of ciprofloxacin for RTI indefensible [28].

Ciprofloxacin was also the most commonly prescribed antibiotic in patients with a presumed combined UTI/RTI and in patients with no specified infection. There are no specific recommendations for empiric therapy for infection of unknown etiology in the NGAPC. Although this makes evaluating compliance with guidelines a moot point, it does not make the issue of appropriate treatment in these cases irrelevant. Infections in the elderly often pose a diagnostic challenge. Delirium can be the presenting sign of an infection even in the cognitively well-functioning elderly. Even more challenging is the worsening of cognitive function in cognitively impaired patients with non-specific symptoms. Infection can be the cause, but localization of the cause may be less obvious. Both of these situations illustrate another potentially inappropriate aspect of antibiotic treatment not evaluated in these studies; missed diagnosis with inappropriate underuse of antibiotics. A systematic evaluation of these patients is necessary to discern infectious from non-infectious cause of their mental deterioration [126].

Acute deterioration due to a possible infection of unknown etiology in an otherwise well-functioning elderly patient is an example of an appropriate indication for antibiotic prescribing. It is, therefore, worth evaluating specific recommendations in the guidelines for the treatment of infections with unknown or uncertain etiology in the NH setting. The therapy suggestions need to cover UTI, RTI and more elusive and uncommon diagnoses such as cholecystitis and diverticulitis. Balancing effectiveness, toxicity, risk of interactions and contribution to resistance development in mind, possible alternatives include amoxicillin and trimethoprim-sulfa.

9.4 Advantages of the retrospective studies

An advantage of observational retrospective studies is that they often reflect routine clinical practice which is not necessarily the case with controlled prospective studies. This retrospective design was essential in the first two papers. Both studies aimed to evaluate the quality of real life clinical practice. Being observed would introduce bias as prescribing behavior is likely to be affected and often times improved by the observation process, the so called Hawthorne effect [127]. In paper I, it would be difficult to assess how prospective documentation and registration of diagnostic practice would affect physicians' diagnostic behavior prior to ciprofloxacin prescribing. Registering how often physicians ordered culturing prior to ciprofloxacin prescribing might lead them to increase the frequency of testing. Physicians might consciously or sub-consciously choose alternative antibiotics if even a slightly more time-consuming process was coupled to ciprofloxacin prescribing alone, especially when the study occurred over one year. Similarly, in the second paper, a prospective design would increase the possibility of physicians being aware that their antibiotic prescribing was being registered which could bias them to prescribe in accordance with guidelines.

One might circumvent the potential bias of being observed by blinding the physicians to the process. This raises the important issue of informed consent and cost. Both studies were evaluated by the regional ethics committee and deemed to be quality control studies. In paper I all nursing home physicians caring for the patients treated with ciprofloxacin have access to culture results (or the lack thereof) in the patients they are treating even when another physician ordered the culture (or neglected to do so). All nursing home physicians agreed to allow us to retrospectively register the indication, diagnosis and culture results of the patients receiving ciprofloxacin under their care. Doing this prospectively would raise the issues of informed consent to both physicians and patients in whom initiation of ciprofloxacin occurred outside the nursing home, e.g. in the ED or at the local hospital. The administrative challenge in these cases would be so considerable that many of these patients would not be included in the study. This would reduce the study material considerably in both studies, introduce bias and thus reduce the external validity of the studies. Performing the studies retrospectively allowed for a more complete, less time consuming database generation illustrating another advantage of retrospective observational studies; they cost less.

9.5 The non-randomized intervention cluster study

Paper IV was a prospective non-randomized cluster intervention study. The Cochrane collaboration has a specific set of criteria used to assess bias in interventions designed to improve healthcare practice [128,129]. Optimally, prospective studies should be double blinded and randomized to minimize bias. Randomizing minimizes selection bias, an essential criteria for RCTs evaluating the effect of a new medical treatment. In intervention studies, however, randomizing is possible but blinding is difficult and sometimes impossible. This study would have strengthened if it were a multi-center study including several ED's over the entire country. Having many participating EDs would allow us to randomize the ED's into intervention vs control with several ED's in each arm. It would have also given a larger material strengthening the power of the study. Unfortunately, economic and time restraints made a larger study infeasible.

Blinding of the physicians in the intervention ED was not possible in this study. The administrations in the participating EDs were aware of the study but individual ED physicians were not specifically informed that the therapy suggestion list or the removal of ciprofloxacin from the formulary was part of a study. Nonetheless, their not being informed cannot be viewed as blinding. To what degree physician suspicions of being part of a study contributed to the observed reduction of ciprofloxacin prescribing is a possible bias contributing to the lower rates of ciprofloxacin prescribing in the intervention ED.

A reasonable criticism of this study is its inability to determine which of the two components of the intervention or if the combination of them was responsible for the observed results. To determine this we would have to evaluate each component individually. This would require more time, in essence one more year, and resources to have the same power as this study. This does not seem necessary. Both components required little effort. Delivery of a printout of the urinalysis to the physician is already standard practice. One component involved simply stapling a preprinted list located right next to the urinalysis apparatus to the urinalysis output. The other component involved removing ciprofloxacin from the formulary for a year. The combination of the two components in the intervention could easily be incorporated in the standard practice of a Norwegian ED. This makes the clinical relevance of a theoretical but time consuming optimization of the study to determine which component was most important questionable. We did not systematically question the nurses or physicians about whether this was a burden or whether they were inconvenienced by the intervention. This should have been done at the conclusion of the study and would clearly strengthen the grounds for the assumption that this intervention was acceptable. Nurses, physicians and administration were however informally asked after the intervention about their views, and the feed-back was positive.

9.6 External validity

External validity refers to the relevance of a study in a broader context than the setting in which the study was performed. A prerequisite for the external validity of any study is the study's internal validity. Serious bias or a flawed methodology makes a study's external validity irrelevant. Unfortunately even a well-designed study with little bias does not guarantee the study's external validity. This is an especially important consideration in studies focused on antibiotic resistance due to the substantial geographic variation in resistance problems and antibiotic prescribing practice.

Paper I addresses diagnostic practice when prescribing empiric therapy with a specific broad-spectrum antibiotic, ciprofloxacin. Nursing home and hospital physicians initiated pre-therapy diagnostics for only 51.7 % and 51.5 % of the patients who received ciprofloxacin. This is unacceptably low but better than the ED physicians where merely 20 % (1/5) of these elderly patients had their urine cultured prior to ciprofloxacin treatment. Both Norwegian and international guidelines explicitly recommend urine culture for elderly patients with a suspected UTI [41,130,131].

In this paper we did not publish whether there was a statistically significant difference in diagnostic or prescribing practice between the two wards or the physicians' workplace. Neither did we evaluate the contribution of individual physicians to the results. There are several reasons for this. The aim of this observational study was to document the indication for ciprofloxacin prescribing and the extent of microbiologic diagnostics prior to prescribing. If the aim was to demonstrate a statistically significant difference between the physicians workplace or between individual physicians a much larger sample size would be necessary to have the power to demonstrate this difference. This may have generated interesting findings as other studies show that individual physician prescribing and physician specialty can contribute to non-compliant antibiotic prescribing [64,132,133].

The clinically relevant findings in paper I was the very poor rate of microbiologic diagnostics regardless of the physician's workplace and high levels of non-compliant prescribing of ciprofloxacin for RTI on the short-term wards. A culture rate of urine 50-80 % below national and international guidelines demonstrates substantial room for improvement not only for NH physicians but for hospital and ED physicians as well. The study also demonstrates that hospital physicians are responsible for much of the prescribing on short-term wards illustrating the need for interventions aimed beyond the NH to improve guideline adherence for NH patients. Finally, the very low rate of pre-therapy microbiologic diagnostics initiated by the ED physicians gives reason to consider a separate NH physician based off-hours emergency service for NH patients.

One can also question the external validity of studies done in municipalities in southeastern Norway in other geographical areas. Are the results generalizable domestically not to mention abroad? Let us begin at home. There are no significant regional differences in antimicrobial resistance within Norway. This would make the external validity of studies done in Arendal potentially relevant for the rest of the country seen from a resistance perspective. When it comes to prescribing behavior and pre-therapy diagnostics one has to assume that behavior of physicians in Arendal does not differ significantly from other parts of the country. None of these studies can address this assumption and there is evidence of significant differences in prescribing in both the NH, the ED and among family physicians in routine practice settings in Norway [62-64].

The next issue to address is whether the findings in these studies are generalizable outside Norway. International variation in the culture of prescribing and use of microbiologic diagnostic testing are relevant in gauging the external validity of these papers. The greater the difference in resistance problems, the greater the concerns about the external validity of these papers will be. Similar resistance patterns and similar cultures in Scandinavia can make the external validity of these studies relevant in these countries. The lack of a clinically relevant difference in uropathogens between NH patients and the elderly living at home shown in paper III contrast with similar studies from countries outside Scandinavia [134,135]. This may appear to weaken the external validity of our study but the opposite is true. The contrasting conclusions illustrates the need for local/national evaluation of resistance prevalence (or lack thereof) between the NH patients and the elderly living at home when defining empiric therapy recommendations.

9.7 Potential for reduction of inappropriate ciprofloxacin prescribing

Reduction of inappropriate ciprofloxacin prescribing is a theme in all four papers in this thesis. Paper IV addresses the issue of reducing unnecessary ciprofloxacin prescribing directly and the other three papers address this indirectly. One can ask: What's the fuss about ciprofloxacin? It's paradoxical, but one reason for reducing unnecessary ciprofloxacin prescribing is to preserve the possibility for prescribing ciprofloxacin when it is necessary. Another and perhaps equally important reason is to avoid adverse ecological effects caused by ciprofloxacin. These untoward effects such as *C difficile* infection and development of resistance to other classes of antibiotics exemplified by quinolone linked MRSA emergence affect not only the patient being treated, but create problems in the institutions where the patients are treated [136,137]. These concerns are central in the practice of rational antibiotic prescribing which emphasizes prescribing an appropriate antibiotic with the narrowest spectrum when necessary.

9.7.1 Potential for improving antibiotic use with improved diagnostics

Obtaining a culture specimen prior to prescribing enhances the potential to reduce total broad spectrum antibiotics like ciprofloxacin. Although culture results cannot blindly be equated with the etiology behind a patient's presentation, they can provide valuable clinical information. This information can be used to shorten therapy duration in selected patients. Knowledge of the bacterial etiology enables switching to a narrower spectrum antibiotic when this is possible. In the first paper this information was available in only 52 % of the patients. In these patients ciprofloxacin could have been replaced with a narrower spectrum antibiotic in 24/50 patients (48 %) of the cases. In 15/50 patients (33 %), culture yielded either no growth or was contaminated. Rapid clinical improvement in these patients may indicate that an infection was not responsible for the patients' symptoms allowing physicians to discontinue ciprofloxacin. In 48 % of the patients no culture results were available. Without culture results, changing from broad spectrum antibiotic therapy or discontinuing therapy is more difficult and potentially places a patient at risk for undertreatment.

Paper III challenges the assumption that resistance prevalence among uropathogens from elderly in NHs is higher than among the elderly living at home. Studies from other countries have supported this assumption [134,135]. For the two most common bacteria *E coli* and *E faecalis,* our study showed no significantly higher resistance rate for any of the five antibiotics used for UTIs (table II in paper III). Although paper III demonstrated a significantly higher resistance rate for ciprofloxacin among *K pneumoniae* and *P mirabilis*, the clinical relevance of these findings is less important for several reasons. Combined, these two bacteria were only responsible for 9.6 % of the bacteria isolated while *E coli* and *E faecalis* were responsible for 73.5 %. Furthermore, there was no significant difference in resistance rates for mecillinam, nitrofurantoin, or trimethoprim for any of these bacteria between the two groups.

9.7.2 Potential for reduction of non-compliant prescribing

Ciprofloxacin is no more effective than other antibiotics in the treatment of uncomplicated UTI [117]. In paper IV the aim was to see if it was possible to reduce inappropriate ciprofloxacin prescribing in the ED. There was a significant reduction in ciprofloxacin prescribing for cystitis but prescribing for pyelonephritis showed no such change. This reduction occurred despite a national increase in the sale of ciprofloxacin during the same time period strengthening the evidence that the intervention was responsible for the observed reduction in ciprofloxacin prescribing [138].

There are concerns that interventions to reduce broad spectrum antibiotic prescribing may result in a shift to another inappropriate antibiotic associated with other resistance problems [139]. In paper IV the opposite of this concern occurred. The decrease in ciprofloxacin prescribing seems to have been offset by a significant increase in appropriate pivmecillinam prescribing. There was a non-significant increase in cephalexin prescribing in the intervention ED for both cystitis and pyelonephritis. However cephalexin was responsible for less than three percent of the antibiotics prescribed making the insignificant increase clinically unimportant.

One criticism of this study is its inability to evaluate precisely how much of the ciprofloxacin prescribing was actually indicated and therefore appropriate. The potential that reduced appropriate ciprofloxacin prescribing resulted in increased rates of therapy failure though possible, seems unlikely. The decrease in ciprofloxacin prescribing occurred concomitantly with a rise in pivmecillinam prescribing. Acute uncomplicated UTI (U71) is the second most common diagnosis made in the ED setting in Norway [99]. As in other countries, *E coli* is the bacteria isolated in 75-90 % of the cases of uncomplicated UTI [140-143]. In Norway, the resistance rates for *E coli* are lower for mecillinam than ciprofloxacin (5.0 % vs 7.2 %) [34] making the theoretic risk of therapy failure actually less when physicians prescribe pivmecillinam instead of ciprofloxacin.

Another situation in which ciprofloxacin may be appropriate is in patients contacting the ED due to failure of therapy with another antibiotic. We were unable to know precisely how this patient group contributed to the use of ciprofloxacin. Nonetheless, it is unlikely that there are many of this type of patient in Norway. Pivmecillinam and trimethoprim are responsible for approximately 70 % of the antibiotic prescribing for UTI in the ED (table I in paper IV). Resistance rates for *E coli* in urine samples for pivmecillinam (7.2 %) and trimethoprim (20.4 %) [34] remains less or close to the 20 % level international guidelines recommend for empiric therapy for uncomplicated UVI [144]. In addition, there is evidence that therapy with trimethoprim is clinically effective in about half the cases of uncomplicated UVI even when culture results demonstrate trimethoprim resistance illustrating that in vitro testing does not always reflect in vivo effect in UVI [145-147]. High urine concentrations of antibiotic may result in clinical cure despite in vitro resistance. Also, placebo studies indicate that at least 25 % of patients with an uncomplicated UVI will experience spontaneous resolution of their symptoms [148-150]. The high prescribing rates of these effective antibiotics makes the probability of a patient seeking treatment for therapy failure no higher than 20.4 % (the resistance rate of *E Coli* for trimethoprim) and in all probability nearer ten percent.

Even in the case of therapy failure with these antibiotics, ciprofloxacin is not the sole alternative. On the contrary, nitrofurantoin is available and a better alternative than ciprofloxacin in uncomplicated UTI. In Norway, *E coli* resistance to nitrofurantoin is substantially lower than ciprofloxacin (1.0 % vs 7.2 %) [34]. E coli resistance to nitrofurantoin is also shown to be low in other European and North American studies [146,151]. In addition, *E faecalis*, the second most commonly cultured uropathogen in paper III is always susceptible to nitrofurantoin in Norway. Ciprofloxacin on the other hand, is not recommended for use in infections caused by *E faecalis*. *S saprophyticus* is often cited as the second most common etiology of uncomplicated UTI [143,152] and has generally higher susceptibility rates to nitrofurantoin than to ciprofloxacin. These resistance considerations make nitrofurantoin a better choice than ciprofloxacin for the treatment of uncomplicated UTI not only in Norway but in other countries with ciprofloxacin resistance problems.

9.8 Antibiotic stewardship in primary care: How these studies fit in

Whether they are designed for the use in the hospital, the nursing home, the ED or the outpatient clinic antibiotic stewardship programs (ASP) have common features several of which are addressed in this thesis (table 4). Regardless of the clinical setting, there are two approaches which roughly divide ASP into either a restrictive or persuasive category [20,66]. The restrictive approach employs strategies prior to prescribing and relies on either limiting the antibiotics in the formulary or requiring some form of approval before specified antibiotics can be dispensed. In contrast, the persuasive approach employs a diverse range of strategies after antibiotics have been prescribed. One group of persuasive strategies is based on education and includes guideline development, guideline implementation, academic detailing, and auditing prescribing practice. Another group of persuasive strategies aims at modifying therapy based on optimal pharmacologic and microbiologic considerations. It is not possible to clearly identify which approach, strategy or combination is superior, either in general or in the nursing home [153,154]. The heterogeneous combination of strategies in different ASPs makes it difficult to compare which ASP is most effective in achieving its goals. In addition, the goals of ASP are also heterogeneous and include reduction of total antibiotic prescribing, broad spectrum antibiotic prescribing, guideline adherence, expenditure reduction or reducing antibiotic resistance. This heterogeneity in mind, many different interventions reach their goals in the short term but long term improvement is more challenging [83,86,155,156].

Table 4. Approaches used in antibiotic stewardship programs and which approaches are addressed in this thesis. R Restrictive approach. P Permissive approach. NA Not Addressed in this thesis

Approach	Type	Description	Examples	Ref	Addressed
Limiting the formulary	R	Having only certain antibiotics available in the clinical location where patients are treated	Removing ciprofloxacin from the emergency room	103,157	Paper IV
Antimicrobial order forms	R	Requiring prescribers to document the indication for using certain specified antibiotics	Mandatory forms for fluoroquinolones, cephalosporins and long half-life macrolides	158	NA
Education	P	Providing information to physicians, nursing staff and patients on resistance developments, appropriate antibiotic treatment.	Continuing medical education, academic detailing, internet sites aimed at educating the general public	80,159	NA
Guidelines	P	Actively updated and implemented guidelines	National guidelines on diagnosis and empiric therapy recommendations	41,160	Paper I,II,III,IV
Audit	P	Surveillance of antibiotic resistance and prescribing trends with feedback to physicians.	NORM, Feedback to individual physicians on their prescribing practice	34,80,161	Paper I,II,III
Antibiogram development	P	Use of local resistance prevalence to determine likelihood of adequate therapy to tailor relevant local empiric antibiotic recommendations	Specific recommendations based on gender in nursing home patients with UTI	162,163	Paper III
Rapid diagnostic testing	P	Preferably point of care testing while waiting for microbiology results.	Non-specific testing such as CRP, specific molecular based (PCR) tests for identification of virus and bacteria	164,165	NA
Clinical Decision Support Systems	P	Point of care physician prompting to aid guideline-compliant prescription.	Computer based reminders integrated in EPJS a Paper based algorithm accompanying lab results	120,166	Paper IV
Delayed prescribing	P	Prescription accompanied by information on when to wait and when to use antibiotics	Wait and see prescriptions for RTI	167,168	NA
Post-prescription modification	P	Optimizing dosage, duration and administration based on PK/PD principles	Reducing unnecessarily high dosage of mecillinam for cystitis, or unnecessarily long duration of therapy for CAP	169,170	NA
De-escalation of therapy	P	Switching from broad spectrum to narrow spectrum antibiotics based on culture results	Use of amoxicillin in UTI caused by susceptible bacteria	171	Paper I

9.8.1 The Norwegian guidelines: Adherence and revision suggestions

A guideline without implementation is like a symphony orchestra without an audience. They may be of high quality and they are certainly expensive to develop, but if they have no effect then it's a waste of resources. Implementation is necessary if the resources invested in guideline development are to yield results. There are numerous stumbling blocks hindering physician adherence to guidelines. Physicians need to know that the guidelines exist, they must have confidence that the guidelines are reliable, and they must be willing to follow them [172]. Effective implementation circumvents these stumbling blocks.

Systematically examining physician prescribing behavior is a way to evaluate adherence to antibiotic guidelines. Papers I and II did this in the nursing home setting, the latter demonstrating high rates of compliance (77-79 %) for UTI, RTI and SSTI in comparison to studies abroad [173-175]. These compliance rates are similar to findings from a Norwegian NH study from 1998 [90]. The results of our study seen in the light of this previous study may indicate a tradition of compliance to antibiotic guidelines in Norway. However, a different Norwegian study demonstrated significant variation in antibiotic prescribing between 133 NHs. This study did not examine the indication for antibiotic prescribing making evaluation of guideline compliance impossible [62]. Paper IV demonstrated similarly high guideline adherence for cystitis (83-88 %) in both EDs both pre and post intervention. For pyelonephritis guideline adherence in the intervention ED was 56-59 % while it was 79-85 % in the control ED. The design of this paper did not allow us to explain the baseline differences between these two EDs.

The high level of compliance demonstrated in these papers may imply that guidelines are successfully implemented. The first national guidelines for antibiotic prescribing in primary care (NGAPC) in Norway were published in 2000 and distributed to all medical students and family practice physicians [102]. Since then, the NGAPCs have been revised in 2008 and in 2013. They are available in both book form and electronically [41,176]. In addition the NGAPCs have been harmonized with two of the most frequently used reference resources in Norwegian primary care, the Norwegian electronic physician handbook and the Norwegian emergency department handbook [177,178]. As discussed previously, drawing conclusions about the entire country from these studies is not possible. Regardless of the uncertainty the NGAPC's implementation has in explaining the high levels of compliance, implementation is not a static process. Other studies clearly demonstrate the ephemeral effects of interventions when they are not part of a continuous process [83,86].

Updating the NGAPC is a continuous process and is part of the Norwegian government's strategy for prevention of antibiotic resistance [179]. Papers II and III address issues which can be considered in future versions of the NGAPC. Paper II broaches the issue of empiric therapy for infections with an unclear etiology. It is possible that physicians' uncertainty explains why they prescribe ciprofloxacin in this situation. Specific antibiotic recommendations for treating infections of unclear etiology may reduce broad spectrum prescribing. These recommendations must be consensus based as there is little evidence documenting the optimal antibiotic for this condition in the NH population.

Paper III challenges the findings in other studies showing that NH patients have infections due to microbes with higher rates of antibiotic resistance. Our findings do not give grounds to alter the recommendations for UVI therapy in Norwegian NHs in this respect. These divergent findings support the often cited need to consider local resistance problems when tailoring guidelines. Paper III did however demonstrate significant differences in bacterial etiology and resistance prevalence between uropathogens isolated from men and women. It also launched a model calculating the risk of empiric therapy failure based on these differences. Studies from the intensive care units have calculated the likelihood of inadequate treatment using the same principles as in Paper III, demonstrating the need to adapt unit specific recommendations to local resistance prevalence [162,163]. Paper III may indicate different risks of empiric antibiotic failure for UTI in men vs women suggesting the need for separate recommendations.

9.8.2 Use of restrictions

Paper IV demonstrates that a combination of formulary restrictions and the use of a clinical decision support system (CDSS) based on a therapy suggestion list significantly reduced ciprofloxacin prescribing for cystitis. The relative reduction of 46 % though significant was due to a seeming less impressive absolute reduction of 2.9 % (from 6.3 % to 3.4 %). However, this reduction occurred despite a simultaneous national increase in ciprofloxacin prescribing. This is reflected by increased ciprofloxacin prescribing observed in the control ED. A clear advantage of this combination intervention was its ease of implementation and minimal use of resources. Costs and the time required to establish and maintain an ASP are often cited as their biggest obstacles [65,180].

Restriction based interventions may be unpopular among physicians indicated by concerns about infringement on prescribing autonomy and ethically inappropriate undertreatment. It is undeniable that restrictions are an infringement on prescribing autonomy, but physicians may exaggerate the degree of that infringement [181]. The potential for unethical undertreatment has clear relevance when treating critically ill inpatients and when cost containment is a primary impetus for the ASP [182,183]. These are important concerns but do not seem to be relevant in our study. Though not specifically stated, the aim of the study in paper IV was not to reduce potentially appropriate antibiotic prescribing for pyelonephritis. The observed reduction of only 0.9 % was insignificant. Furthermore, the overwhelming majority of patients had cystitis, an uncomfortable but non-serious infection. There were three other antibiotics available all equally effective as ciprofloxacin [117]. In a broader perspective than the individual patient, there are obvious ethical issues raised by the overuse of broad-spectrum antibiotics. Every prescribing physician has an ethical responsibility to avoid or at least delay resistance problems. This is accomplished through rational antibiotic prescribing.

9.8. 3 Use of clinical decision support systems (CDSS)

The therapy suggestion list accompanying urine dipstick results in paper IV is an example of a CDSS. The aim of CDSS is to improve prescribing by automatically providing physicians with evidence based suggestions to optimize therapy choice. CDSS can be employed in many clinical situations and are not limited to antibiotic prescribing. The format of CDSS can be either paper or data based. In general CDSS seem to improve adherence to guidelines[166]. More specifically, recent study dealing with RTI in the ED demonstrated that CDSS was effective in improving antibiotic prescribing and that a paper based CDSS was equally effective as a data based CDSS[120].

One criticism of the CDSS portion of our intervention is that symptoms alone are sufficient to diagnose uncomplicated cystitis. This would circumvent the need for dipstick testing. In the intervention ED there is a tradition but no clear policy that patients with symptoms suggestive of an UTI deliver urine for dipstick testing prior to consultation with a physician. Nonetheless, we cannot be certain that all the patients were diagnosed with dip-stick testing. The physicians evaluating these patients would not have been exposed to the paper based CDSS. This could indicate that the other component of the intervention (removing ciprofloxacin from the formulary) had a greater role in reducing ciprofloxacin prescribing.

9.8.4 Post-prescription modification

There are several strategies in ASPs which use post prescription modification. De-escalation is one form of post-prescription modification which entails switching empiric broad-spectrum therapy to narrower spectrum therapy once culture results allow for this. Studies from both abroad and from Norway show reduced antibiotic prescribing while reducing costs [65,171]. The issue of post-prescription modification without securing a culture specimen prior to empiric therapy was an important theme in Paper I and has been discussed previously in this thesis. Other forms of post-prescription modification aim to optimize antibiotic dose, duration, and form of administration. In paper I the average daily dose of ciprofloxacin was 887 mg on the short-term wards and 882 on the long-term wards. The national guidelines recommend a daily dose of 500 mg for cystitis and 1000 mg for pyelonephritis. This indicates that pyelonephritis dosing was more common than cystitis dosing. It is unlikely that pyelonephritis is more common than cystitis suggesting an inappropriately high ciprofloxacin dose in cystitis treatment. An added concern is the increased risk of adverse drug reactions in the elderly due to unnecessarily high antibiotic dosage. Unfortunately a limit of Paper I was its inability to precisely determine how many UTIs were due to cystitis and how many were due to pyelonephritis.

Another example of post-prescribing modification is shortening the length of antibiotic prescribing. The importance of keeping the course of treatment as short as necessary is twofold. First, reducing total amount of antibiotics prescribed will contribute less to resistance development. The second reason is giving a patient adequate, not excessive treatment. This is especially important in elderly patients due to an increased risk of adverse drug reactions. Optimal length of treatment for uncomplicated UTI is well documented [117,144,184]. For other infections including both community and nosocomial RTI and UTI in the elderly the optimal duration of therapy is more controversial and based on consensus [185-189]. Results on therapy duration were not reported in Paper II due to the uncertainty of therapy duration on the short-term wards. Initiation of antibiotic therapy on these wards occurred in the hospital in 41 % of these patients. The discharge summary rarely specified the date the patient began treatment making reliable calculation of therapy duration impossible. A final example of post therapy modification is switching from intravenous to oral administration. There was only one patient treated with intravenous cefuroxime in study II. At the time of the study intravenous therapy was not a routine function in the NH in Arendal. This has since changed. Intravenous therapy of NH patients to avoid hospital admission is increasing in Norway, making this form of post-prescription modification relevant.

9.8.5 Is there a need for Antibiotic Stewardship in Norway?

"To gild refined gold, to paint the lily ... is wasteful and ridiculous excess. (William Shakespeare)

Or

“There is always room for improvement”(axiom)

Seen in a global perspective, Norway along with other Scandinavian countries has relatively modest bacterial resistance problems. There is also low total use of antibiotics and low use of broad spectrum antibiotics [22]. ASPs are both time consuming and require economic resources. The Norwegian healthcare system, like healthcare systems the world over are forced to prioritize resources making it reasonable to question the need for ASPs.

The need for ASPs is obvious, both from an economic standpoint but more importantly from an ethical standpoint. The threat posed by antibiotic resistance has been compared to the threat of global warming [18]. Both threats are due to excesses in human behavior. Remedies to both threats require fundamental changes in human behavior globally. With the lack of new antibiotic development coupled with relentless resistance development we need to administer the existing antibiotics as if they were a non-renewable resource [17]. Despite modest resistance problems, Norway needs to continue doing everything possible to hinder a further escalation of bacterial resistance and thereby prolong the life of existing antibiotics.

It is difficult to find reasons not to prioritize ASPs in Norway or elsewhere. Antibiotic stewardship advocates appropriate treatment for patients who need it and avoidance of unnecessary treatment for patients who do not. It advocates conservation of valuable resources. Antibiotic stewardship can be effective in reversing resistance problems both at the individual patient level, the institutional level and the national level. It is simply good medical practice.

10 Conclusion

The areas of improvement identified in this thesis include pre therapy microbiologic diagnostics, the need to consider restrictions on prescribing broad spectrum antibiotics and the need for specific guidelines for the elderly based on gender for the treatment of UTI. There was relatively high compliance with the national guidelines by nursing home physicians. This suggests that resources necessary for interventions to improve antibiotic prescribing be used in other settings.

11 Further research

Nitrofurantoin underuse. It is paradoxical that an effective, inexpensive antibiotic which has low rates of resistance isn't used more frequently. The results of the studies in this thesis seen in the light of national prescribing trends indicate that this is a national phenomenon. A literature study to systematically evaluate the extent of harmful side effects is warranted. A qualitative study to elucidate physicians' attitudes towards nitrofurantoin is necessary to understand possible explanations for this prescribing practice.

Better national surveillance of compliance with guideline recommendations. Norway has a national prescription registry documenting all prescriptions delivered to pharmacies. Presently there is no system for assigning a diagnosis to the prescription. Having the diagnosis consistently registered with the antibiotic prescription would provide invaluable information about prescribing trends. In turn, this information could fuel further research on improving antibiotic prescribing.

13 References

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13 Appendix 1: Errata

1. Side 5. Borchgrevinck er feil . Borchgrevink er riktig
2. Side 16. contributes er feil . contribute er riktig
3. Side 20.
    a. Feil: Along with the other Scandinavian countries antibiotic resistance problems have been moderate in Norway compared to other European countries.
    b. Riktig: Along with the other Scandinavian countries, antibiotic resistance problems have been moderate in Norway compared to other European countries.
4. Side 20. Figure 5 tekst er skjev. Ordet “Figure” henger ut til hø men bør være rett foran “5”
5. Side 21.
    a. Feil : Fluoroquinolone prescribing, primarily ciprofloxacin has increased 74 % in the last decade from 0.43 DDD/1000 inhabitants in 2002 to 0.75 DDD/1000 inhabitants in 2012
    b. Riktig : Fluoroquinolone prescribing, primarily ciprofloxacin, has increased 74 % in the last decade from 0.43 DDD/1000 inhabitants in 2002 to 0.75 DDD/1000 inhabitants in 2012
6. Side 21.
    a. Feil: Ciprofloxacin is also excreted in sweat and contributes to resistance development in normal skin bacterial flora 44
    b. Riktig: Ciprofloxacin is also excreted in sweat and contributes to resistance development in normal skin bacterial flora 44.
7. Side 27
    a. Feil: In general, it appears that interventions such as academic detailing aimed at physician education appear effective
    b. Riktig : In general, interventions such as academic detailing aimed at physician education appear effective
8. Side 30
    a. Feil : We searched the patients’ record
    b. Riktig: We searched the patients’ records
9. Side 32
    a. Feil: population of approximately 100000
    b. Riktig: population of approximately 100,000