Master thesis in Pharmacy

IS THE PRESCRIBING OG ANTIBIOTICS AMONG NORWEGIAN INTERNAL MEDICINE RESIDENTS IN COMPLIANCE WITH THE TREATMENT GUIDELINES?

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COLLABORATIVE PROJECT

In the period between August 2013 and May 2014 the master thesis in Pharmacy within the field of clinical pharmacy and pharmacoepidemiology was carried out at the Norwegian Advisory Unit on Antibiotic use in hospitals, Department of Research and development, Haukeland University Hospital. This was a collaborative project between Center for Pharmacy, Department of Clinical Science, University of Bergen and the Norwegian Advisory Unit on Antibiotic use in hospitals. The advisory unit provides information to hospitals about prudent antibiotic prescribing including the use of antibiotic guidelines, and develops methods for surveillance and monitoring of antibiotic consumption. The writing of the master thesis was carried out under the supervision of the following advisers at the unit:

1. Infectious disease specialist and associate professor at the University of Bergen

   Ingrid Smith

2. Cand pharm and employee at the Hospital Pharmacy in Bergen

   Marion Neteland

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SUMMARY

Antibiotic resistance is increasing in Norway, though the situation is less severe than in other parts of Europe. Suboptimal prescribing of antibiotics leads to increase in resistance. In Norway, national treatment guidelines exist for prudent prescribing of antibiotics, but little is known about Norwegian hospital doctors' compliance with the treatment guidelines. The master thesis investigated if the prescribing of antibiotics by internal medicine residents is in compliance with the treatment guidelines.

Internal medicine residents were given a questionnaire about antibiotic dosage for predefined diagnoses, to see if their answers were in compliance with the guidelines. By use of an audit, data was collected for the same diagnoses at Voss hospital and Haukeland University Hospital, in order to validate the results from the questionnaire.

The results from the questionnaire indicate that the internal medicine residents have good knowledge about the dosage regimes suggested in the guidelines. Given the small number of patients registered at the hospitals for predefined diagnoses, the results from the clinical setting cannot validate the results from the questionnaire. The findings from the wards suggest that the doctors are familiar with the guidelines though there is also room for improvement for more prudent antibiotic prescribing. For instance, whereas few respondents answered they would prescribe 4 mill IE x 4 (4%) or 5 mill IE x 4 (18%), on the wards (32%) of the doctors prescribed 4 mill IE x 4 and (27%) 5 mill IE x 4, indicating that higher dosage of penicillin G are actually used than what is recommended in the current national guidelines, for pneumonia without sepsis.

However, more research, by use of an audit as it was done in this project, is needed to answer if internal medicine residents prescribe antibiotics in compliance with the guidelines. Monitoring of antibiotic prescribing can for instance be done by clinical pharmacist.

ABBREVIATIONS

AMR	Antimicrobial resistance
ASP	Antimicrobial stewardship program
ATC	Anatomical Therapeutic Chemical Classification System
CAP	Community Acquired Pneumonia
DDD	Defined Daily Doses
DNA	Deoxyribonucleic acid
DRP	Drug related problems
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Agreement
EU	European Union
ESBL	Extended-spectrum beta-lactamases
GI	Gastrointestinal
HAP	Hospital acquired pneumonia
HUH	Haukeland University Hospital
IDSA	Infectious Diseases Society of America
MIC	Minimum inhibitory concentration
MRSA	Methicillin Resistant *Staphylococcus aureus*
UTI	Urinary tract infection
SHEA	Society for Healthcare Epidemiology of America
WHO	World Health Organization

1 INTRODUCTION

1.1 Infectious diseases and antibiotics

Through ages infectious diseases have had substantial impact on human development. In the past 150 years, important developments have contributed to the decreased occurrence of infectious diseases in many parts of the world, such as infection control practice developed, as a result of knowledge about organisms causing infection and the understanding of the way these pathogens spread in the environment. Routes of transmission of infectious diseases have declined with the improvement in living standards, better nutrition, development of vaccines, clean water, and improvement in hand hygiene. Many serious infections with high morbidity and mortality sharply declined with the discovery of antibiotics in the middle of 20th century (1).

Antibiotics are drugs with the ability to kill bacteria, and as a result they cure people of potentially fatal infectious diseases (2). One of the most important developments of modern medicine is the discovery of these effective agents to prevent and treat infections caused by bacteria and other pathogenic microorganisms (3). It is no exaggeration to say that antibiotics have revolutionized medicine. Several fields of modern medicine such as transplantation, cancer treatment, the care of premature babies and several forms of surgery would not be possible without these agents (4).

1.2 Short history of antibiotics and their characteristics

For thousands of years substances with anti-infective potential have been applied medically. Both Chinese and ancient Greek physicians used substances with antimicrobial activity. However, the therapy for infections remained strictly empirical until the discovery of the microbiological basis of infections in the 19th century. Heavy metals were found to be useful against a number of infections in the early 1900s (3). It was Alexander Fleming who revolutionized the concept of antimicrobial treatment by discovering penicillin in 1928 (5, 6).

Though the modern era of chemotherapy really began with the discovery and clinical use of the sulfonamides in 1936 (3), it was with the onset of the Second World War and the support of American pharmaceutical industry that penicillin was converted into a medicine that could be manufactured on a grand scale (4). By 1950s the golden age of antimicrobial chemotherapy was well under way (3).

Antibiotics were first defined as a substance made by a microbe that inhibits the growth of other microorganisms (4, 7). As the chemical structure of the antibiotic substances became known, it was possible to synthesize new drugs in the laboratory. This could be done by either modifying the structure of older molecules or by synthesizing new structures that do not exist in nature (8). In this paper the term antibiotics will be used to denote both natural occurring antibiotics and synthetic agents.

Antibiotics are unique drugs (2). These agents have few side effects except for allergic reactions in some individuals, and in majority of cases antimicrobials have low toxicity (9). Most importantly, these drugs act both on bacteria that cause the infection but also on other bacteria in the environment creating a reservoir of potentially resistant organisms (2). Anti-infectives are the only class of drugs where inappropriate use in one patient can jeopardize the efficacy of treatment in other individuals (4).

1.3 Antimicrobial resistance

As early as 1945 Alexander Fleming warned about the threat of bacteria developing resistance (10). Resistance is the microorganism's ability to counteract the action of antibiotics (1). Antibiotics were mostly used in hospitals, which was also where drug-resistant strains initially appeared. In the late 1950s resistance to multiple drugs first occurred (4). The resistant bacteria spread in hospitals and in communities once resistance had emerged (11).

Resistance to antibiotics is not new (12). Antimicrobial resistance (AMR) has been around for as long as antibiotics have been used to treat infections (4). But the number of resistant organisms, the geographic location affected and the extent of resistance is increasing. Resistance is also evident in other microorganisms such as fungi, viruses and parasites (12).

Today we are facing a situation where most pathogenic bacteria are resistant to one or more of the antibiotics commonly used to treat them (10). Millions of metric tons of antibiotics have been produced and employed for a variety of purposes since their introduction (6). Important and unhelpful contribution also stems from the use of antibiotics in the agricultural and veterinary field (4).

1.3.1 Epidemiology of resistance

There is a strong association between the usage of antimicrobial agents and the occurrence of resistance (13). Antibiotics have been used excessively and with little attention to the inevitable consequences of resistance (2). Mostly, antibiotics are used unnecessarily by physicians uncertain of a diagnosis or when largely self-limited bacterial and viral infections are treated with antibiotics (10).

Use of antimicrobial agents cause selective pressure on bacteria and is a key issue in understanding the epidemiology of resistance [12]. Several studies have shown association between the degree of antibiotic exposure and the occurrence of resistance. Bacteria dominate in all ecosystems, have developed over a period of 3, 5 billion years and have adapted to the most extreme living conditions. Bacteria's adaptive characteristics are based on the ability to reproduce fast and produce many daughter cells during a short period of time. Bacteria can also duplify amplified genes under stressful conditions, as a mechanism to create genetic variation and phenotypic diversity. Natural occurring mutations in chromosomal genes in a bacterial population is an advantage, that will be selected under certain environmental conditions, for example under exposure of antibiotics (14).

1.3.2 Mechanisms of resistance

Resistance can expand either through the spread of resistant pathogenic bacteria or by transfer of resistance genes from one type of bacteria to another (13). Bacteria share its DNA with other bacteria through three distinct forms of horizontal gene transfer; conjugation, transduction and transformation (14). The most important mechanism is conjugation.

Chromosomal or extrachromosomal DNA is transferred from one bacterium to another through cell-to-cell contact. When plasmid DNA is enclosed in a bacterial virus and transferred to another bacterium of the same species this called transduction. Transformation is uptake of DNA from the environment and incorporating it into the genome by normal homologous recombination (15). Increased efflux, reduced cellular uptake, alteration of the target and inactivation of the drug are typical mechanisms of resistance (4).

Transfer of resistance genes is not limited to closely related bacteria but can take place between bacteria of different evolutionary origin and ecological sources (13). There is substantial evidence that heavy use of one antibiotic may be a risk factor for the acquisition of infections by organisms resistant to other unrelated antibiotics. The use of one antibiotic will

create selective pressure in other bacteria, because plasmids within the bacterial cell may carry resistance genes for multiple antibiotics from different chemical groups (10). In addition, some antibiotic groups seem to be stronger associated with selection of resistant clones than others. For instance broad-spectrum antibiotics are little specific for the disease causing pathogens, while pharmacokinetic parameters of some antibiotics lead to extended antibiotic-exposure of the bacteria florae in the GI-tract (14).

1.4 Development of new antibiotics

Antibiotic discovery and development has almost stopped (2). Almost all antibiotics that are in use today belong to the classes of antimicrobial agents discovered before 1970 (16). Antibiotics developed during the period 1970-2000 were mostly structural modifications of existing ones (4). Several reasons exist for the current situation.

Firstly, it is challenging to find antibiotics that enter Gram-negative bacteria and evade endogenous efflux. In addition, burden of licensing regulation has increased the size, complexity and cost of clinical trials, creating a barrier to all but the biggest and richest pharmaceutical companies. More importantly, antibiotics are less profitable than treatments of chronic diseases (17). Likelihood of eventual resistance coupled with the short duration of therapy and falling sales, mean that the commercial incentive to develop new antibiotics is still lower than for drugs treating chronic diseases such as diabetes or hypertension. As a result, the supply of new antibiotics is likely to remain limited, and the use and distribution of those that are developed needs to be carefully managed to avoid their unnecessary use which predisposes for development of resistance (4).

1.5 Antibiotic use in animals

It is interesting to note that the use of antibiotics in healthy food-producing animals is greater than in the treatment of diseases in human patients. It is well documented that food animals are reservoirs of resistant human pathogens. Antibiotics are used extensively for disease prevention and as growth promoters usually involving mass administration to many animals at the same time (11). How these substances lead to increased growth rate is uncertain, but the prevention of diseases probably plays an important role. Such practices intensify modern food production, and suboptimal growth in unsanitary conditions is compensated with addition of antibiotics to feed (10), (18). Since the same antibiotics are used in food animals and in human medicine, there is a risk of emergence and spread of resistance, including those

capable of causing infection in both animals and people. In many countries, antimicrobials are authorized and widely used as growth promoters. Restricted authorization of antimicrobial types began several decades ago in the EU while Norway abounded all such use in the late 1990s (18).

1.6 Resistance patterns for some common bacteria species in Europe and Norway

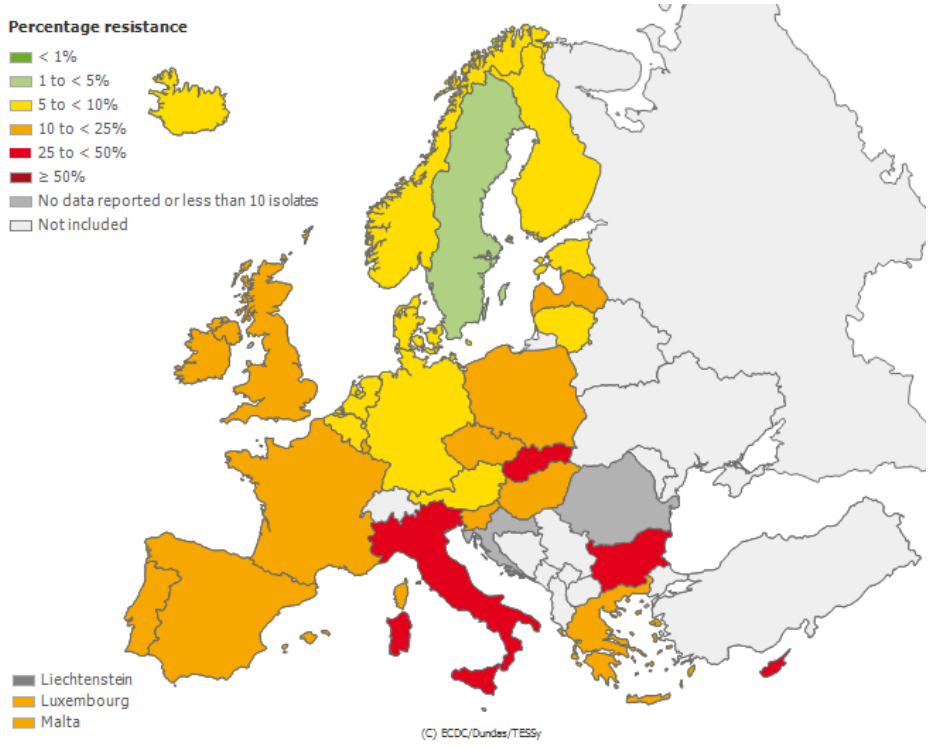
According to the latest annual epidemiological report issued by European Centre for Disease Prevention and Control (ECDC), the percentages of AMR continued to increase in Europe, especially multidrug Gram-negative resistance. AMR in Europe varies by microorganism, antimicrobial agent and geographical region. The burden of antibiotic resistance from Gram-positive to Gram-negative pathogens will likely outweigh recent achievements in the control of Gram-positive pathogens (11). For several combinations of antimicrobial agents and microorganisms, resistance percentages reported are generally lower in northern Europe compared with southern Europe. Differences in antimicrobial use and infection control practices in the reporting countries may in part explain these variations (19).

1.6.1 *Escherichia coli* and *Klebsiella pneumoniae*

Escherichia coli and *Klebsiella pneumoniae* are among the most prevalent Gram-negative pathogens which cause a variety of diseases both in humans and animals (6). Increasing antimicrobial- resistance among *K. pneumoniae* isolates is a growing public health concern in Europe and worldwide (19). The emergence of extended-spectrum beta-lactamases (ESBL) is a significant clinical problem also in Norway. Though *Klebsiella* spp. blood culture isolates remain generally susceptible to broad-spectrum antimicrobials in Norway, the prevalence of ESBL production in *Klebsiella* spp. is generally increasing (13). ESBL are enzymes that have resistance to most beta-lactam antibiotics, including penicillin and cephalosporins (20).

E.coli is a major cause of urinary tract infections. In the period between 2008 and 2011, the percentages of *E.coli* isolates resistant to 3rd generation cephalosporin's significantly increased in 18 of 28 reporting European countries, and no country showed a decreasing trend during this period. The ECDC report emphasizes that AMR in *E.coli* requires close monitoring as the percentages of isolates resistant to commonly used antibiotics continue to increase (19). Map 1 shows proportion of 3rd generation cephalosporins resistant and

intermediary susceptibility *Escherichia coli* isolates in participating countries in 2012 (21). According to the NORM/NORM-VET report, the resistance rates for *E.coli* in Norway are slowly drifting upwards for most antibiotics, even though the resistance rates among urinary tract isolates have remained relatively stable over the last 10 years (13). The prevalence of ESBL producing *E.coli* significantly increased from 3, 3% in 2011 to 5, 5% in 2012.



Map 1: Proportion of 3rd generation cephalosporins resistant (R+I) Escherichia coli isolates in Participating Countries in 2012 (21)

1.6.2 *Staphylococcus aureus*

Gram-positive *Staphylococcus aureus* has in recent years emerged as a multidrug-resistant pathogen and a major cause of nosocomial infections (6). The NORM/NORM-VET report from 2012 (13) supports the findings published by ECDC (19) that MRSA resistance remains low in Norway. What is interesting however, is that while the prevalence of invasive diseases caused by MRSA infections has until now remained stable at a low level, the latest results indicate an increasing number of MRSA infections and colonizations (13).

1.6.3 Consumption trends of antibiotics in Europe and Norway

The issue of AMR in general is still a limited problem in Norway (13). Figure 1 shows that Norway is among the EU/EEA with lowest distribution of consumption of antibacterial agents in hospital sector in 2011 (22). This is good news as the development and spread of antimicrobial resistance is associated with overuse of antimicrobials (19).

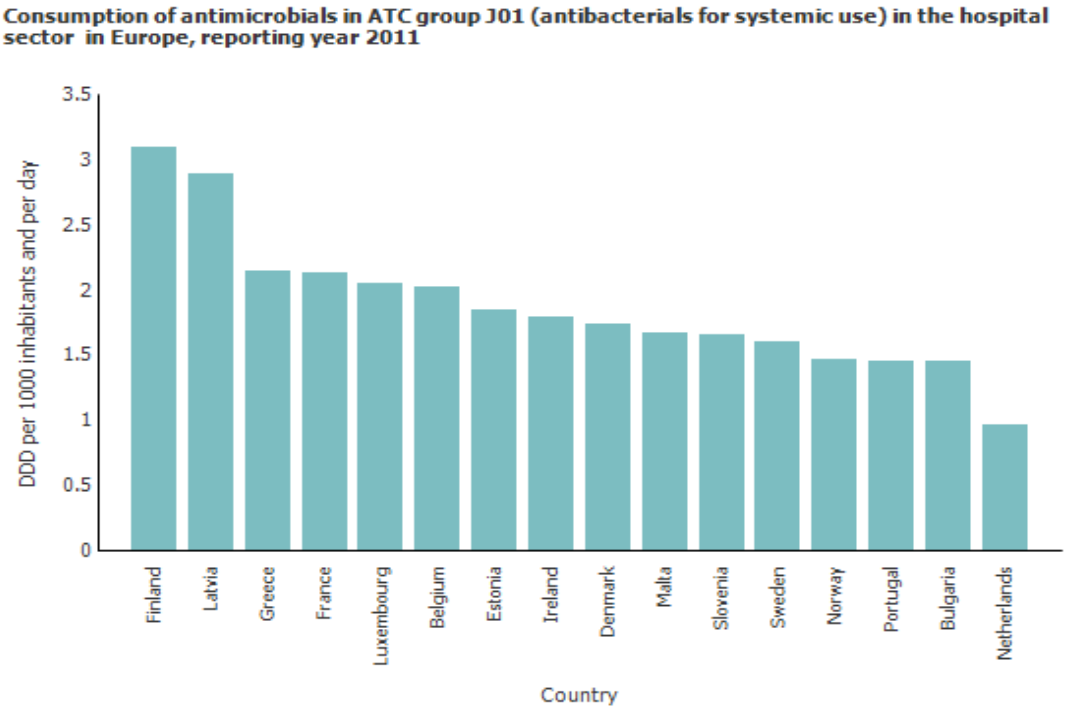
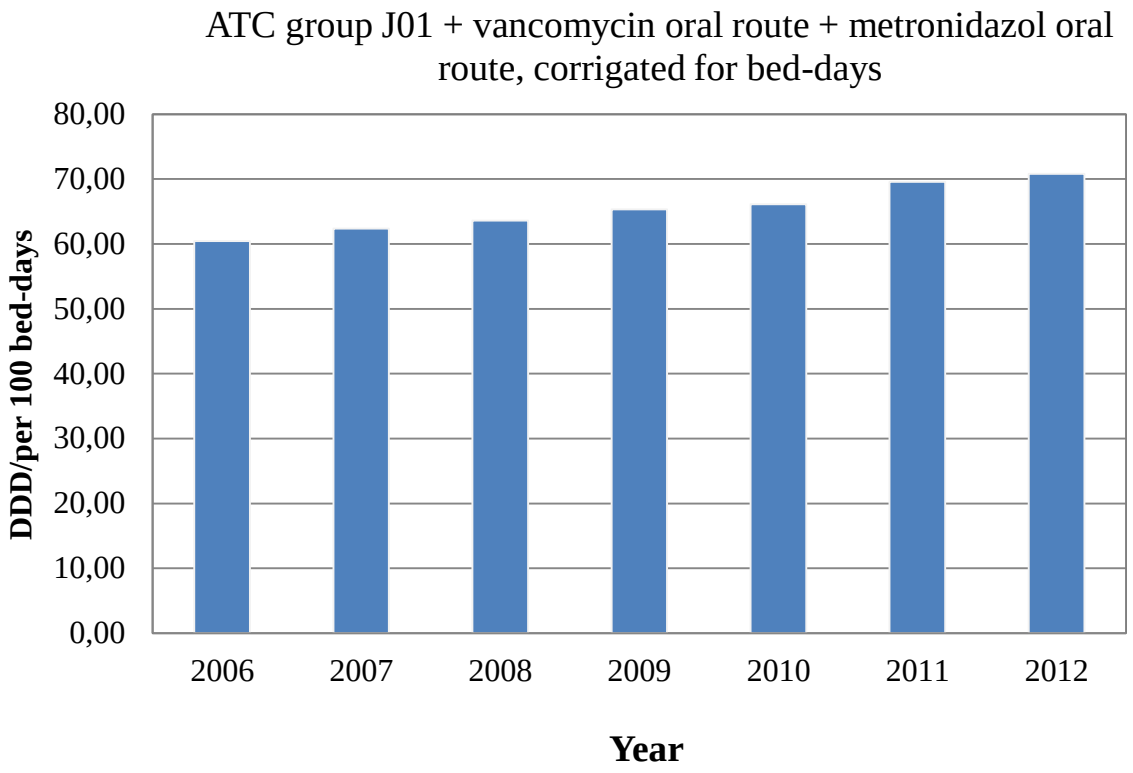


Figure 1: Consumption of antimicrobials in the hospital sector in Europe in 2011 (22).

Although there has been a gradual increase in the consumption, and a shift among the various subgroups, the total consumption of antimicrobial agents in Norway has remained relatively stable over many years (13). If the use of antimicrobial agents in Norway increases, or resistant clones are imported from abroad, the situation may rapidly change (13). According to the latest report published by the Norwegian Advisory Unit on Antibiotic use in hospitals, the use of antimicrobial agents in Norwegian hospitals is increasing. Figure 2 illustrates these trends for the period 2006-2012 (23). In addition, the sales of narrow spectrum penicillin in Norway are reduced, while the sales of penicillin with extended spectrum are steadily increasing (13). Such development is highly unfortunate as excessive use of broad-spectrum agents contribute to the development and selection of drug-resistant organisms (4).

Figure 2: Consumption of antimicrobials in Norwegian hospital in the period 2006-2012 (23)



1.7 Prudent antibiotic prescribing and ASP

Infection control practice and prudent antibiotic prescribing combined with fast diagnostics are essential to prevent the emergence and spread of antibiotic resistance [14]. Prudent antibiotic prescribing implies safe and effective antibiotic treatment against disease-causing pathogens with minimum effect on the normal bacteria florae in the body (24). Given bacteria's adapting abilities it is important to stress that resistance developing cannot be avoided in environments which have been exposed to antibiotics. Antibiotic resistance is easy to acquire but more difficult to get rid of.

Due to the increasing resistance rate of bacteria and the slow development of new antimicrobials, implementation of (ASP) have been recommended for more than 20 years in Northern America and more recently in Europe, as one of the main effective approaches to improve antibiotic use (25). The overall aim of ASP is to improve patient outcomes, ensure cost-effective therapy and reduce adverse effects associated with antimicrobial use, including

antimicrobial resistance, through optimization of antimicrobial use among hospitalized patients.

The strategies employed in ASPs include prospective audit with intervention and feedback, formulary restriction and preauthorization requirements for specific agents, education of prescribers, use of computer decision support, and implementation of guidelines and clinical pathways (25). With increasing frequency, clinical guidelines are being produced with the overall aim to ensure high-quality care (26). The impact of clinical guidelines on provider behavior and improved clinical outcomes has been difficult to measure.

Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have developed a guideline with the elements needed to structure ASP (25, 26). The guidelines suggest a multidisciplinary approach with an infectious diseases physician and a clinical pharmacist with training in infectious diseases as core members of the team with close collaboration of a clinical microbiologist, information system specialist, infection control professional and hospital epidemiologist.

1.8 Strategies to combat antimicrobial resistance in Norway and the introduction of the research question

Several nations, international agencies, and organizations worldwide have recognized the public health crisis and taken action to combat AMR through strategies applied in the relevant sectors. In 2001 WHO published its global strategy to contain AMR (11). This year it was supplemented by the Antimicrobial resistance: global report on surveillance 2014 (27).

In 1998 the Norwegian Ministry of Health and Social Affairs issued a national action plan against antimicrobial resistance due to the growing concern about antimicrobial resistance (13), which was replaced by a new plan in 2004 (28). These actions plans were substituted by a national strategy for the prevention of healthcare associated infections and antimicrobial resistance in 2008 (13). This latest strategy called for continued surveillance of both antimicrobial resistance and antibiotic use.

By continued surveillance of drug use, it is possible to follow trends over time concerning doctors' prescribing profile (29). Antibiotic surveillance implies the systematic collection and analysis of data about the use of antibiotic in humans and animals. These data can then be

used to plan, implement and evaluate strategies for optimal use of antibiotics. The strategy emphasizes the necessity of surveying the use of antibiotics within health institutions (1).

The national strategy also states that infection control and prudent antibiotic use are two sides of the same coin. It emphasizes the importance of developing and implementing national antibiotic guidelines and to evaluate effects of their use (1). In addition, the infection control plan for westerner Norway Regional Health Enterprise 2012-2015 urges that basic infection control guidelines need to be followed, in order to succeed with infection prevention (30).

In Norway, national guidelines exist for antibiotic use in hospitals (31). In the period prior to 2013 almost every Regional Health- Enterprise had their own local guides (1), but from 2013 new national guidelines were published by the Norwegian Directorate of Health (31). Since clinical guidelines are an essential part of ASP in general (26), and the Norwegian latest national strategy states the importance of their use, the overall aim of this master thesis is to investigate Norwegian hospital doctors' compliance with the antimicrobial treatment guidelines. Currently, little knowledge exists about what antibiotic dosage Norwegian doctors prescribe in the hospital sector and if these dosage are in compliance with the treatment guidelines.

It is important to know how the antimicrobials are used in the clinical setting, since incorrect drug choice is one of the main problems in relation to development of resistance (32). Stepwise selection of resistance is facilitated by suboptimal antibiotic dosage (10).Thus, the research question is as follows: *Is the prescribing of antibiotics among Norwegian internal medicine residents in compliance with the treatment guidelines?*

The research question is two folded. The first part investigates if the dosage internal medicine residents answered in a questionnaire with specific diagnoses and predefined antibiotics are in compliance with the guidelines. In order to validate the answers from the questionnaire, the second part looks into what dosage residents at wards, prescribe for the same diagnoses by comparing these results with the treatment guidelines. In addition, the master thesis will shortly discuss how pharmacists can contribute to reduce the overall consumption of antibiotics in a hospital setting.

In this context, compliance implies correct medicine in correct dosage in accordance with guidelines recommendations. When assessing the antibiotics prescriptions at the wards, one looked only at the choice of antibiotic and dosage regime, in order to be able to validate the

findings from the questionnaire. The focus of the investigation at the wards has been on antibiotics prescribed and in what dosage at the time of admission to hospital. In other words, when a diagnosis is proposed but not confirmed by the responsible physician. Duration of the treatment, change of treatment from intravenous to oral route, and assessment if modification of therapy has taken place due to microbiological results, have been excluded from this master thesis, although these are important element of prudent antibiotic prescribing. Recommendations from previous regional guidelines for Helse-Bergen Health Enterprise are taken into consideration, since some of the data collected, stems from before the new national treatment guidelines were introduced.

The questionnaire was developed by an infectious disease specialist working at the Medical department, HUH, who expected that the doctors would give incidental answers about dosage regimes that are not in compliance with the guidelines. It was expected to observe discrepancy between the guidelines and how antibiotics were prescribed at the wards. In addition, it was expected to observe discrepancy between what doctors answered they would prescribe and what was actually prescribed in the clinical setting for predefined diagnoses.

Research suggests that physicians might find it difficult to comply with the national guidelines (10). The IDSA's and SHEA's guidelines strengthen this argument by stating that although physicians usually agree in principle with national guidelines, the barriers exist for complying with the guidelines in practice (26). Given the recent trends in higher antimicrobial consumption in Norwegian hospitals, it was also expected to see more broad-spectrum antibiotics prescribed than the guidelines suggest.

1.9 Indications and antibiotics studied

The subsequent section introduces the diseases and the antibiotics studied in this project. It was decided to focus mainly on infectious diseases that usually occur in the hospital setting. According to a report issued by the Research-and development department, Section for patient safety, Health-Bergen from 2010 on hospital infections and infection control, urinary tract infections, lower respiratory infections and sepsis are among the most occurring infectious diseases at the HUH (29).

The active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties, the so called Anatomical Therapeutic Chemical (ATC) classification system. Five different levels are

assigned in order to classify drugs into groups. Fourteen main groups of drugs represent the (1st level), therapeutic/pharmacological subgroups are the 2nd level. While the chemical/pharmacological/therapeutic subgroups represent the 3rd and 4th levels. The 5th level is the chemical substance (33). To illustrate the structure of the code the complete classification of penicillin can be used as an example (34) . The table 1 summarizes the antibacterial agents investigated in this project.

J Anti-infective agents for systemic use

(1st level, anatomical main group)

J01 Antimicrobial agents for systemic use

(2nd level, therapeutic subgroup)

J01C β-lactam antimicrobial agents, penicillin's

(3rd level, pharmacological subgroup)

J01C E β-lactam sensitive penicillin

(4th level, chemical subgroup)

J01C E01 Benzylpenicillin (Penicillin G)

(5th level, chemical substance)

Table 1: an overview over ATC subgroups studied

ATC code:	**Chemical subgroup:**	**Chemical substance:**
J01C E01	β-lactam sensitive penicillin	Penicillin G
J01D D01	Other β-lactam agents	Cefotaxime
J01C A01	Broad spectrum penicillin	Ampicillin
J01C F02	β-lactam resistant penicillin	Cloxacillin

1.9.1 Pneumonia with and without sepsis and clinical treatment

Inflammation of the alveoli rather than the bronchi or bronchioles is defined as pneumonia. It is characterized by an inflammatory process, bacteria and white blood cells that on the chest X-ray appears as shadows in the normally clear lungs (35). Both viruses, bacteria and, in the immunocompromised host, parasites and fungi, can cause acute pneumonia (4). The nature of pneumonia acquisition is the most practical way of classifying pneumonia. Pneumonias are classified as community acquired (CAP) and hospital-acquired pneumonia (HAP), respectively.

A variety of organisms can cause CAP, while the most common bacteria are *S. pneumoniae*. Clinical features of CAP are cough, initially dry, later purulent or blood-stained, rust- colored sputum, in addition to fever and chest pain. In three subsets of patients pneumococcal infections usually occur. Risk factors for acquiring pneumonia are diabetes, decreased or absent splenic function and patients with either congenital or acquired immunoglobulin deficiencies (36).

If the bacteria spread to the blood the patient is said to have bacteremia (35). Systemic consequences of infection develop in patients with bacteremia. In one study of 270 blood cultures, the majority of positive blood cultures were associated with sepsis, severe sepsis or septic shock. Clinical syndrome that complicates severe infection is defined as sepsis. Sepsis is characterized by clinical signs such as vasodilation, increased microvascular permeability and leukocyte accumulation in tissues that are remote from the infection (37). Lower respiratory tract is in majority of cases the origin site of the infection (38).

According to the regional guidelines 2004-2013(39) empirical treatment for pneumonia without sepsis was penicillin G 2-5 mill IE x 4, given as an intravenous infusion. The latest national guidelines from 2013 also recommend penicillin G as an intravenous infusion given 2 mill IE (1,2 g) x 4 (40). Prescribing of penicillin G was previously denoted in international units, (IE: internasjonale enheter in Norwegian). One million IE is the same as approximately 0,6 g penicillin G (41). Since the previous guidelines denoted amount of penicillin to be given in IE and because doctors at the wards still prescribe in IE, the unit will be used throughout this paper.

Treatment regime for pneumonia with sepsis, according to the previous regional guidelines was penicillin G 5mill IE x 4-6, given intravenously in a combination with an aminoglycoside

(39). The 2013 national guidelines recommend the same antibiotics but penicillin G should be given 4 times a day (40).

1.9.2 J01C E01 benzylpenicillin- penicillin G

Of total antibiotics sales in Norway in 2012, hospitals sales accounted for 7% (13). Penicillins accounted for around 45 % of the sales to Norwegian hospitals in 2012 (13). The penicillins can be either naturally occurring or semisynthetic. The most important examples which are produced by fermentation of moulds from *Penicillinum notatum* and *P.chrysogenum,* are benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V). Penicillin G is primarily active against Gram-positive bacteria and is also β- lactamase sensitive. Many bacteria produce β- lactamases, which can inactivate penicillin's β-lactam ring, an integral part of its structure (4). In general, when prescribing β-lactams, it is essential to administrate dosages frequently enough. High maximal concentrations of β-lactams have little influence on the bactericide effect. The most important factor is the time over minimum inhibitory concentration T>MIC. Increased in dose will lead to a small extension of T>MIC, since most of β-lactam antibiotics have short t ½ (42).

Several antibiotics, among others penicillin G, inhibit the synthesis of peptidoglycan. This is a substance that does not occur in eukaryotes and is an essential part of the bacteria's cell wall. (15). Through the interaction of the common β-lactam ring with the transpeptidase enzymes, penicillin G inhibits peptidoglycan cross-linking. Penicillin's generally have low toxicity with allergic reactions being the main problem (4). According to the latest NORM/NORM-VET report, there was an increasing prevalence of penicillin non-susceptibility in Norway from 3,8 % in 2009 to 6,2 % in 2012 for *S. pneumonia* isolates from respiratory tract specimens (13). Reduced susceptibility and resistance to penicillin for *S. pneumoniae* isolates, is much higher in countries outside Scandinavia and in the Netherlands. In South-Europe, resistance in systemic isolates has shown to be up to 50% (14).

1.9.3 Upper urinary tract infection (UTI) without sepsis and J01D D01 ampicillin

UTI usually refers to the presence of organisms in the urinary tract together with symptoms, and clinical symptoms of infection (35). In community and hospital practice, UTI is a common problem. Factors that impair urine flow predispose for infection, such as reflux of urine from the bladder into the ureter, congenital abnormalities and enlargement of the prostate gland (4). In 5-10% of the cases of sepsis, urinary tract is the site origin of infection (38). *Escherichia coli* are by far the most common causative bacterium of acute uncomplicated UTI acquired in the community. There are many serotypes of this organism, but only a few are responsible for the majority of infections. The remaining part is caused by other Gram-negative enteric bacteria, such as *Klesiella* and *Proteus* species, and by Gram-positive cocci, particularly enterococci (35).

For UTI with sepsis, two drugs were investigated, J01C A01 ampicillin and J01D D01 cefotaxime. According to previous regional guidelines, ampicillin 2g x 4 given as an intravenous infusion, is the first-line recommendation, in combination with an aminoglycoside (39). Current national guidelines also recommend ampicillin, but with the dosage regime 1-2g x 4 in combination with an aminoglycoside (43). Ampicillin is a broad-spectrum penicillin (44), effective against many Gram-negative bacteria, including *Haemophilus influenza*, *Escherichia coli*, *Salmonella*, and among others *Shigella* (4). According to the NORM/NORM-VET report, the resistance rates among urinary tract isolates have drifted upward for most antibiotics, though they have remained relatively stable over the last ten years. Resistance to ampicillin has gradually increased from approximately 25% to 35% (13).

1.9.4 J01D D01 cefotaxime

Cefotaxime belongs to the group of β-lactam antibiotics, called cephalosporins. Cephalosporins also inhibit the synthesis of peptidoglycan, as penicillin G (15). In 2012 cephalosporins accounted for 18% of the total hospital sales of antibiotics in Norway (13). Several similarities exist between cephalosporins and penicillins. Cephalosporins have been classified into generations, and cefotaxime belongs to the 3rd generation. The pharmacological activity has been towards an increase in activity towards Gram-negative species, and increased resistances to β-lactamase as the development of cephalosporins has progressed

through the generations. Over the years, the usefulness of the 3rd drugs has diminished, as a result of the spread of strains capable of producing ESBLs (4). The dosage regime recommended by previous regional guidelines for cefotaxime in the treatment of UTI with signs of sepsis, was 2g x 3 (39). The national guidelines advice 1g x 3(43).

1.9.5 Bacterial arthritis and J01F02 cloxacillin

A number of diverse microorganisms can cause infectious arthritis of single or multiple joints. Bacterial arthritis is the most common, and the most commonly caused by *staphylococcus* specie. The knee is the most frequent site of infection in adults, followed by the hip, shoulder, wrist and ankle. Typical symptoms are pain and loss of function of one or more joints over a 1-2 week period. Other symptoms include swelling, redness and increased warmth of the infected joint. (3). According to the previous regional guidelines, the recommended treatment for bacterial arthritis was cloxacillin 2 g x 4 given as an intravenous infusion in a combination with an aminoglycoside (39). The current national guidelines, recommend only cloxacillin with the same dosage regime as before (45).

J01F02 cloxacillin is an β-lactamase-stable penicillin, meaning stable against β-lactamase from *Staphylococcus aureus* and thus an effective agents in the treatment of infections caused by these bacteria. Majority of the β-lactamases from other microbes degrade the drug (46). Table 2 summarizes the similarities and differences between regional and national guidelines for the antibiotics studied in this project.

Table 2: an overview over recommendations for antibiotic treatment for specific diagnoses from both the previous regional- and the current national antibiotic guidelines

Diagnoses	**Antibiotics**	**Regional guidelines 2004-2013**	**National guidelines 2013-**
Pneumonia without sepsis	Penicillin G	2-5 mill IE x 4	2 mill IE (1,2 g) x 4
Pneumonia with sepsis	Penicillin G	5 mill IE x 4-6 + aminoglycoside	5 mill IE (3 g) x 4 + aminoglycoside
UTI with sepsis	Ampicillin	2 g x 4 + aminoglycoside	1- 2 g x 4 + aminoglycoside
Bacterial arthritis	Cloxacillin	2 g x 4 + aminoglycoside	2 g x 4 + aminoglycoside
UTI with sepsis	Cefotaxime	2 g x 3	1 g x 3

2 MATERIALS AND METHODS

WHO defines drug utilization research as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences." Over the years, a number of terms have come into use, and it is important to understand the relationship between different domains. Application of epidemiological methods to studies of the clinical use of drugs in populations, is called pharmacoepidemiology. An essential part of pharmacoepidemiology is drug utilization research, as it describes the extent, nature and determinants of drug exposure.

Together, drug utilization research and pharmacoepidemiology provide insight into patterns and quality of drug use. Quality of use can be determined using audits to compare actual use to national prescription guidelines or local drug formularies(47). Audit is a method used to investigate if an institution is following a set of regulations and guidelines (30). The WHO document on drug utilization research, points out that " an audit in drug use was defined by Crooks (1979) as an examination of the way in which drugs are used in clinical practice carried out at intervals frequent enough to maintain a generally accepted standard of prescribing"(47).

2.1 Part one: the questionnaire about antibiotic dosages

2.1.1 Doctors in internal medicine

Internal medicine residents were chosen as a sample population for the investigation on how the doctors prescribe antibiotics. Internal medicine residents are a representative sample of different Norwegian internal medicine departments. These physicians work and specialize in different hospitals. The residents were given a questionnaire at a seminar about infectious diseases held in Bergen once a year, which they all only attended once. The questionnaire contained questions about common infections that usually occur in hospitals. The residents were asked to assign appropriate dosage regimes for predefined antibiotics used to treat specific diagnoses. The data was collected in the years 2007-2010, 2013 and 2014.

2.2 Part two: antibiotics prescribed at the hospitals

2.2.1 Haukeland University Hospital and Voss hospital

Medical departments at Haukeland University Hospital (HUH) and Voss hospital and Respiratory unit at HUH, were chosen to investigate how ward doctors actually prescribe antibiotics. The reason for choosing these departments stems from the fact that patients with infectious diseases are usually admitted to one of these departments.

Public hospitals in Norway are organized in regional and local health trusts. Western Norway Regional Health Authority is one of four regional health trusts that owns and runs five local health trusts. Helse-Bergen Health Enterprise is one of them, and HUH and Voss hospital both belong to that Health Enterprise (48).

HUH serves as the central hospital of Hordaland county, the regional hospital of Hordaland, Rogaland and Sogn and Fjordane counties, and as a local hospital of Bergen, Midthordland and Nordhordland. Haukeland has approximately 11000 employees, almost 600.000 patients are treated at the hospital each year, and around 2000 health workers receive part of their tuition and practical training at the hospital (48, 49).

HUH is the second largest hospital in Norway in terms of medical research. The hospital is a national specialist hospital and resource center for burn injuries, air-pressure injuries, Cornea-protesises and treatment of intercranial tumors. In addition, the hospital runs several Advisory Units, for instance Center for Tropical Medicine and Imported Diseases (48, 49), and the National Advisory Unit for antibiotic use in hospitals.

Voss hospital has a close cooperation with departments at HUH as Voss hospital is part of Health-Bergen Health Enterprise (50). Voss hospital has 400 employees and is a local hospital for habitants in Hordaland, Bergen and counties in Sogn. The Medical ward at Voss is a part of a general internal medicine department which treats mostly patients in need of immediate medical attendants. Patients with different diagnosis are treated at this ward, some examples are disease of the GI-tractus, endocrinology diseases and infectious diseases (51).

2.2.2 Respiratory unit: Lung ward 3 at HUH

The Lung department diagnoses, treats and prevents diseases of the respiratory system (52). Lung post 3 serves as a treatment facility for lung cancer, lung infections and tuberculosis (53).

2.2.3 Medical department at HUH

The Medical Department, including Endocrinology, Gastroenterology, Hematology, Nephrology with dialysis and Infectious diseases at the HUH, covers the field of internal medicine. Table 3 provides an overview over sections at the department and the respective names of the wards.

Table 3: an overview over medical sections and wards at the Medical department, HUH

Section	Wards
Endocrinology	Medical ward 8
Gastroenterology	Medical ward 1 West
Hematology	Medical ward 5 North
Infectious diseases	Medical ward 5 West and- ward 6
Nephrology including dialysis	Medical ward 1 North and- ward 2

Medical ward 2 and -ward 5 North were excluded from the investigation, due to that these wards have severely ill patients with multiple diagnoses. The ward 2 treats patients in need of dialysis, while ward 5 North takes care of patients with severe blood diseases such as leukemia (54), (55).

2.2.4 Endocrinology- Medical ward 8

Medical ward 8 has responsibility for treating patients with endocrinological diseases, such as diabetes mellitus, as well as treating patients with other general internal medicine diseases. Through interdisciplinary cooperation ward 8 also treats psychiatric patients as well as patients admitted to the hospital due to overdose of narcotics and other substances (56).

2.2.5 Gastroenterology- Medical ward 1 West

Diseases of gastro- intestinal tractus are treated at Medical ward 1 West, in addition to general internal medicine diseases. This includes diagnosis and treatment of GI-bleeding, cancer and

liver diseases, and investigation of pancreas and bile diseases. Inflammatory diseases, such as Ulcerous colitis and Morbus Crohn are also treated at this ward (57).

2.2.6 Infectious diseases -Medical ward West 5 and-6

Medical ward 6 (infectious disease ward 1) treats among others tropical diseases, sepsis, HIV and AIDS patients, in addition to patients with other internal medicine conditions (58). Medical ward 5 West (infectious disease ward 2), primarily treats patients with infectious diseases, including pneumonia, urinary tract infections, tuberculosis and wound infections (59).

2.2.7 Nephrology -Medical ward 1 North

As other Medical wards at the hospital, ward 1 North also treats general internal medicine conditions while it specializes in the treatment of renal diseases. Severe hypertension, glomerulonephritis and pyelonephritis are some of the diseases treated at this ward (60).

2. 3 Data collection at HUH and Voss hospital

The information on prescription trends from different Medical departments by looking into medication charts was collected two times a week from mid-November 2013 until mid-January 2014. Data on diagnosis and the name of the antibiotic with its ordered dosage regime was registered on a case report form prepared beforehand. The same procedure was initiated for the Lung department. The data collection lasted from mid-December 2013 until mid-January 2014 for this department. Nevertheless, other antibiotics not mentioned in the questionnaire given to residents were also registered when appropriate. Antibiotics prescription trends at Voss hospital were collected once a week from January- March 2014.

2.4 Data processing and statistical analysis

The data collected from the questionnaire given to the residents, was processed by importing the antibiotic dosages according to the year registered and indication given, into a Microsoft Excel (2010) spreadsheet. The data was subsequently coded and transferred to IBM® SPSS® statistics (2012) for further analyses by generating appropriate frequency tables and graphs.

Results from the questionnaire were analyze by using IBM® SPSS® statistics (2012) to see if there was any difference in compliance with the guidelines according to the year questionnaire was given.

The data collected at different wards at HUH and Voss hospital was processed by transferring the data registered on case report form to Microsoft Excel (2010) spreadsheet. The data contained information about diagnosis registered from the medication chart, antibiotic chosen and the dose given either as intravenous infusion or oral tablet. Sometimes the given diagnosis was not written down, in order to confirm the diagnosis and the rationale behind the antibiotics given, data from the patients' medical records in DIPS HBE Prod 7.3.1.1 was used.

DIPS is an electronic database for medical records used in Health - Bergen (61). By entering the date of birth and the Norwegian personal number from patients that were on antibiotics, it was possible to read the medical history of that given patient, diagnosis suspected at the time of admission to the hospital and the rationale behind prescribed antibiotics. The data was then coded and transferred to IBM® SPSS® statistics (2012) in order to make frequency tables and graphs.

2.5 Ethical considerations:

In order to assess hospital doctor's prescription trends, sensitive patient data had to be retrieved. Regional Committee for medical and health research ethics allowed dispensation from professional confidentiality in order to retrieve the necessary information. All patients had to be informed about the study beforehand and had the possibility to withdraw. Patients admitted at the study wards received information brochure about the study. Data was stored safely and paper data was deleted after it had been registered electronically.

3 RESULTS

3.1 Part one: results from the questionnaire

The total number of respondents of the questionnaire was (*n*=272). Four questions were excluded from future analysis as the questions were ambiguously formulated, and the data could not provide satisfactory information for further interpretation. The graphs mostly present prescription trends independent of the year questionnaire was given. In order to illustrate change over time, some results will be presented by year. All dosages presented refer to intravenous administration.

3.1.2 Penicillin G in the treatment of pneumonia without sepsis

Table 4 shows the respondents' answers to how they would prescribe penicillin G, when treating pneumonia without signs of sepsis, by year the questionnaire was given. In total *n*: 188 doctors (69%) would prescribe 2 mill IE x 4, whereas (*n*=49), (18%) would prescribe 5 mill IE x 4.Very few of the residents (0, 4- 1%), would prescribe a dosage lower than 2 mill IE x4. The same holds true for the dosages that are higher than 2 mill IE x 4 but lower than 5 mill IE x 4, (0, 4- 4 %). None of the respondents answered that they would need to look up the dosage while, 1% would use another dosage than one of the alternatives provided.

Table 5 illustrates compliance with the guidelines for pneumonia without sepsis, according to year. The total study population was (*n*=265) and not (*n*=272) because some of the respondents did not answer this question. Compliance with the guidelines before 2014 refers to 2 – 5 mill IE x 4, while for 2014 it implies 2 mill IE x 4. If the respondents answered "wood look up" it was coded as compliant to the guidelines. This implies for all diagnoses. In 2007, compliance was (91%), whereas in 2014, (79%). In the period 2008-2010 it was between (89-98%), whereas in 2013, 93%. In total, independent of the year questionnaire was given; compliance was (9 %). Table 10 shows (*p*=0, 07) by use of Ficher's exact test.

Figure 3 and 4 present the results from table 4 graphically. Figure 3 illustrates the most typical dosages the respondents would prescribe, independently of the year the questionnaire was given. The term "other" in the description of possible graphical alternatives refers to dosage alternative that did not receive many answers. This refers for instance to, another dosage or 1

mill IE x 3. The term "other" would be used for other graphical presentations as well; tough meaning of it may vary according to the diagnosis.

Figure 4 shows how the prescribing of the dosage 5 mill IE x 4 varies over the years the questionnaire was given.

Table 4: dosages of penicillin G in the treatment of pneumonia without signs of sepsis, **(*n*=272)**

Dosage	Year						
	2007	**2008**	**2009**	**2010**	**2013**	**2014**	**Sum**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1 mill IE x 3	-	-	1 (3)	-	-	-	1 (0,4)
1 mill IE x 4	1 (2)	-	2 (6)	3 (6)	1 (2)	-	7 (2)
2 mill IE x 3	2 (4)	-	1 (3)	-	-	-	3 (1)
2 mill IE x 4	31(69)	33 (67)	20 (56)	34 (68)	35 (76)	35 (76)	188 (69)
4 mill IE x 3	1 (2)	-	-	-	-	-	1 (0,4)
4 mill IE x 4	-	-	3 (8)	4 (8)	1 (2)	2 (4)	10 (4)
5 mill IE x 3	-	1 (2)	-	-	-	1 (2)	2 (0,7)
5 mill IE x 4	8 (18)	14 (29)	8 (22)	8 (16)	7 (15)	4 (9)	49 (18)
another dose	-	-	-	-	2 (4)	2 (4)	4 (1)
would look up	-	-	-	-	-	-	-
did not answer	2 (4)	1 (2)	1 (3)	1(2)	-	2 (4)	7 (3)
Total	45	49	36	50	46	46	272

Table 5: compliance with the guidelines for pneumonia without sepsis, according to year **(*n*=265)**

Year	**Penicillin G-pneumonia without sepsis**		
	Compliance with the guidelines		
	No	**Yes**	**Total**
	***n* %**	***n* %**	***n***
2007	4 (9)	39 (91)	43
2008	1 (2)	47 (98)	48
2009	4 (11)	31 (89)	35
2010	3 (6)	46 (94)	49
2013	3 (7)	43 (93)	46
2014	9 (21)	35 (79)	44
Total	24 (9)	241 (91)	265

Figure 3: dosage of penicillin G that respondents answered they would prescribe in the treatment of pneumonia without sepsis, independent of year **(*n*=272)**

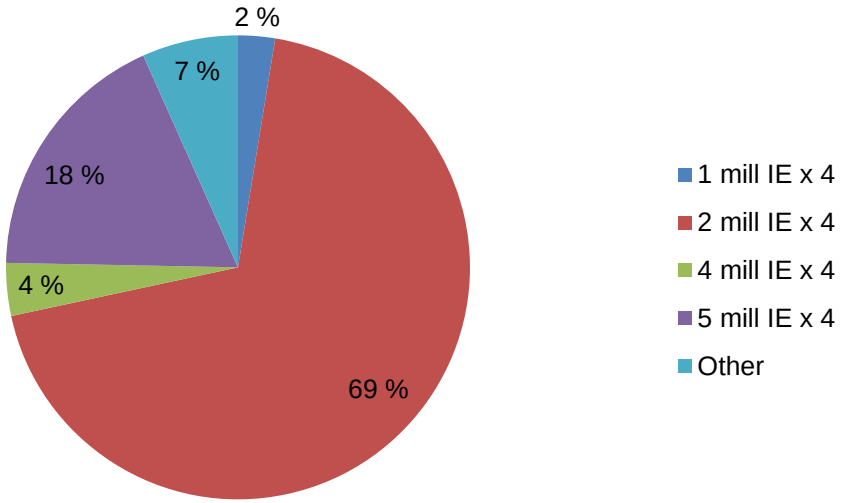
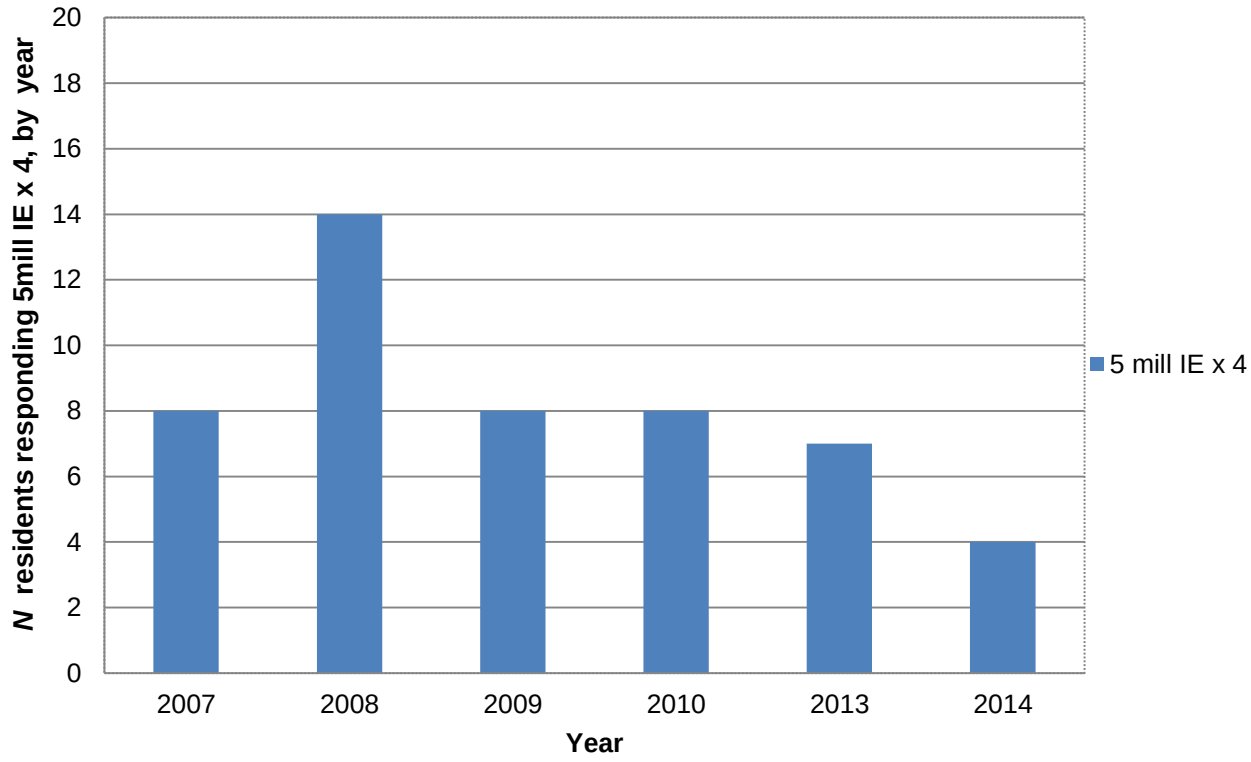


Figure 4: prescription of penicillin G, 5mill IE x 4, by year **(*n*=49)**



3.1.3 Penicillin G in the treatment of pneumonia with sepsis

Table 6 illustrates how the doctors answered they would treat pneumonia with signs of sepsis, with penicillin G. The majority of the residents' (*n*= 200), (73%) would prescribe 5 mill IE x 4, followed by (*n*= 20), (7%) who would prescribe 5 mill IE x 6, independent of year. Eighteen, (7%) would prescribe 4 mill IE x 4, while only (5%) said they would prescribe penicillin G 2 mill IE x 4. None of the doctors said they would need to look up the dosage, whereas (3%) answered they would use another dosage than suggested in the questionnaire.

Table 7 shows compliance with the guidelines, according the year questionnaire was. Total study population was (*n*= 266) since some of the respondents returned blank sheets. Compliance to the guidelines between 2007-2013 referred to 5 mill IE x 4-6, whereas for 2014, it implied 5 mill IE x 4. In total, (*n*: 218), (82%) complied with the guidelines. In 2007, (81%) of the respondents answered in compliance with the guidelines, whereas in 2014, (84%) of the respondents had complied with the guidelines. In the period 2008-2010 compliance was between (74-90%), whereas in 2013, (83%). The use of Fisher's exact test generated (*p*=0, 54), table 10.

In Figure 5, the results are shown graphically, independent of year. Figure 6 illustrates how many residents answered they would prescribe 5 mill IE x 6, by year.

Table 6: dosage of penicillin G in the treatment of pneumonia with signs of sepsis **(*n*=272)**

Dosage	Year						
	2007	**2008**	**2009**	**2010**	**2013**	**2014**	**Sum**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1 mill IE x 3	-	-	-	-	-	-	-
1 mill IE x 4	-	-	1 (3)	-	-	-	1 (0,4)
2 mill IE x 3	-	-	-	-	-	-	-
2 mill IE x 4	1 (2)	-	4 (11)	2 (4)	4 (9)	2 (4)	13 (5)
4 mill IE x 3	-	-	1 (3)	-	-	-	1 (0,4)
4 mill IE x 4	3 (7)	4 (8)	1 (3)	8 (16)	1 (2)	1 (2)	18 (7)
5 mill IE x 3	-	-	1 (3)	1 (2)	1 (2)	1 (2)	4 (2)
5 mill IE x 4	32 (71)	35 (71)	24 (67)	37 (74)	35 (76)	37 (80)	200 (73)
5 mill IE x 6	3 (7)	8 (16)	2 (6)	2 (4)	3 (7)	2 (4)	20 (7)
another dose	4 (9)	1 (2)	1 (3)	-	2 (4)	1 (2)	9 (3)
would look up	-	-	-	-	-	-	-
did not answer	2 (4)	1 (2)	1 (3)	-	-	2 (4)	6 (2)
Total	45	49	36	50	46	46	272

Table 7: compliance with the guidelines for pneumonia with sepsis, according to year **(*n*=266)**

Year	Penicillin G-pneumonia with sepsis Compliance with the guidelines		
	No	**Yes**	**Total**
	***n* %**	***n* %**	***n***
2007	8 (19)	35 (81)	43
2008	5 (10)	43 (90)	48
2009	9 (26)	26 (74)	35
2010	11 (22)	39 (78)	50
2013	8 (17)	38 (83)	46
2014	7 (16)	37 (84)	44
Total	48 (18)	218 (82)	266

Figure 5: dosage of penicillin G, independent of year **(*n*=272)**

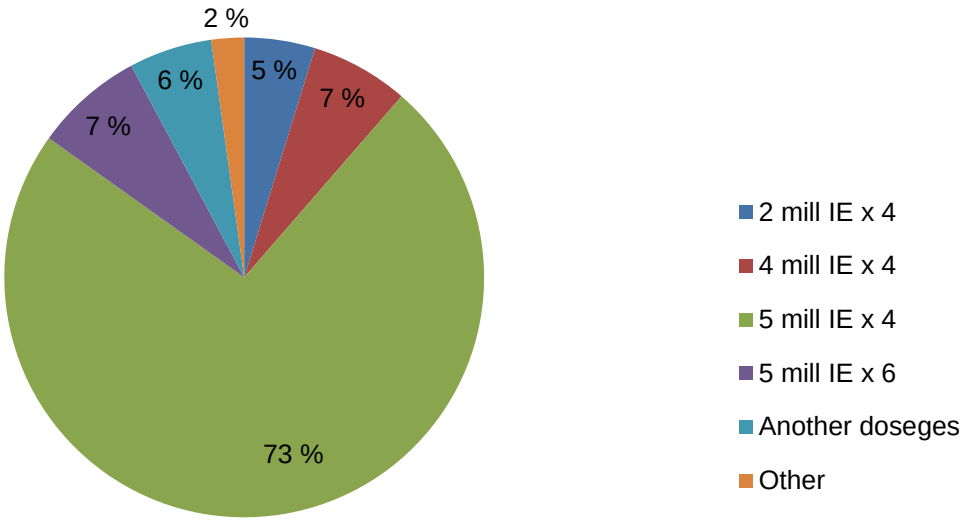
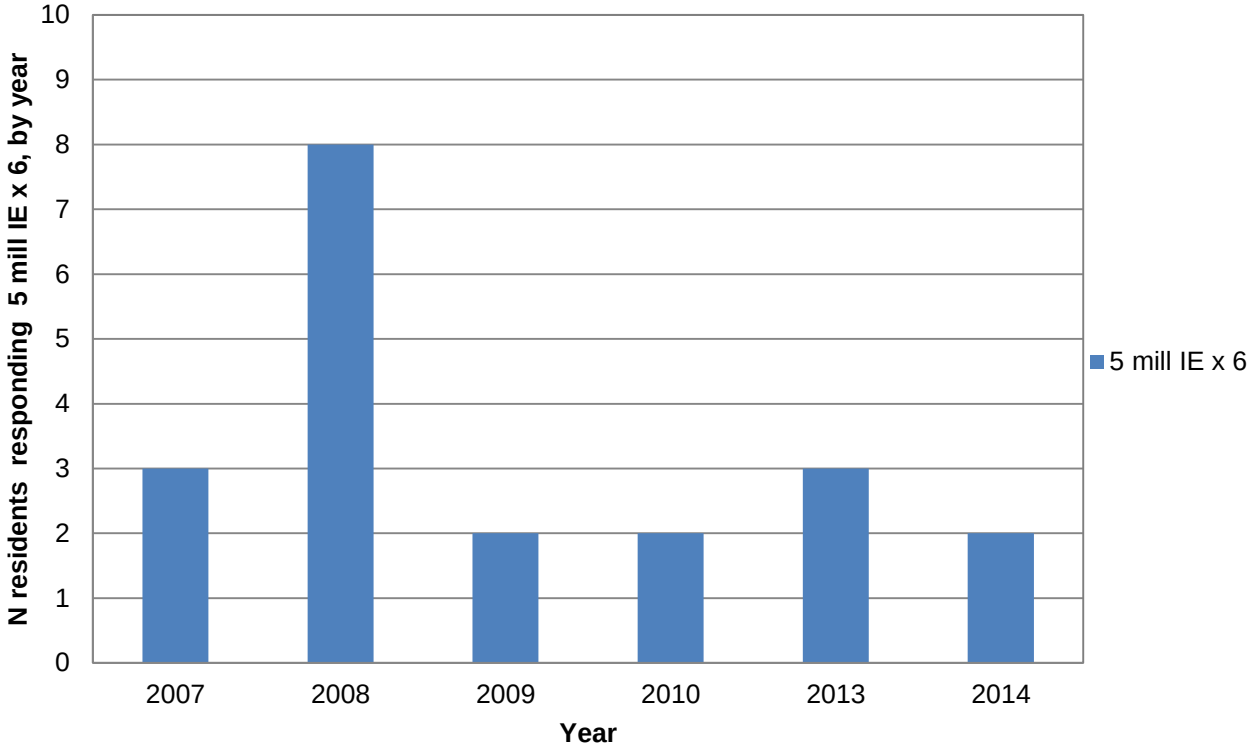


Figure 6: prescription of penicillin G, 5mill IE x 6, by year **(*n*=20)**



3.1.4 Ampicillin in the treatment of UTI with signs of sepsis

Table 8 shows how the residents would prescribe ampicillin in treatment of UTI with signs of sepsis. The biggest proportion, (48%) of doctors, answered they would use 2 g x 4. Around (20%) would prescribe 2g x 3, while (18%) would look up the dosage. Between (4- 6%) said they would prescribe in the range between 1g x 3 and- 1g x 4. Figure 7 shows the most common dosage independent of year the questionnaire was given.

Table 9 illustrates compliance to the guidelines, according to year. The study population was (*n*= 264) since all respondents did not answer this question. In the period 2007-2010 and 2013 compliance referred to 2 g x 4, whereas for 2014 it implied 1-2 g x 4. In total, (69%) of the respondents answered in compliance with the guidelines. In the period 2007-2010, compliance was between (64-79%), whereas in 2013 it was (74%). In 2014, (66%) of the respondents gave an answer in compliance with the guidelines. Table 10 shows (p=0,41) generated, by Fischer's exact test.

Table 8: dosage of ampicillin in the treatment of UTI with signs of sepsis **(*n*=272)**

	Year						
Dosage	**2007**	**2008**	**2009**	**2010**	**2013**	**2014**	**Sum**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1g x 3	-	2 (4)	3 (8)	3 (6)	1 (2)	1 (2)	10 (4)
1g x 4	3 (7)	2 (4)	4 (11)	3 (6)	3 (7)	1 (2)	16 (6)
2g x 3	14 (31)	5 (10)	6 (17)	10 (20)	8 (17)	13 (28)	56 (21)
2g x 4	19 (42)	24 (49)	21 (58)	22 (44)	26 (57)	20 (44)	132 (48)
another dose	-	1 (2)	-	-	-	-	1 (0,4)
would look up	6 (13)	13 (27)	2 (6)	11 (22)	8 (17)	9 (20)	49 (18)
did not answer	3 (7)	2 (4)	-	1 (2)	-	2 (4)	8 (3)
Total	45	49	36	50	46	46	272

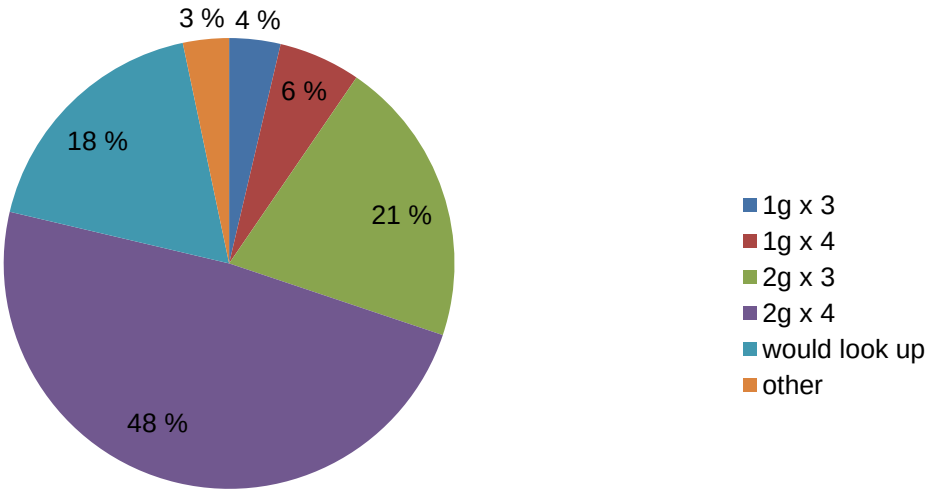
Table 9: compliance with the guidelines for UTI with sepsis, according to year **(*n*=264)**

Year	Ampicillin-UTI with sepsis Compliance with the guidelines		
	No	**Yes**	**Total**
	***n* %**	***n* %**	***n***
2007	17 (40)	25 (60)	42
2008	10 (21)	37 (79)	47
2009	13 (36)	23 (64)	36
2010	16 (33)	33 (67)	49
2013	12 (26)	34 (74)	46
2014	15 (34)	29 (66)	44
Total	83 (31)	181 (69)	264

Table 10: Fischer's exact values for antibiotics studied, except for cefotaxime

	Penicillin G pneumonia without sepsis	**Penicillin G pneumonia with sepsis**	**Ampicillin UTI with sepsis**
	p value	*p value*	*p value*
Fischer's exact test	0,07	0,54	0,41

Figure 7: the most common dosage of ampicillin in the treatment of UTI with signs of sepsis **(*n*=272)**



3.1.5 Cefotaxime in the treatment of UTI with signs of sepsis

Table 11 illustrates how the doctors said they would prescribe cefotaxime when treating UTI with signs of sepsis. This question was not given in 2007 and 2013, thus the study population was (*n*= 181) and not (*n*= 272). Most doctors, (78%) would use 2g x 3, whereas (*n*= 18), (10%) would look up the dosage for this particular diagnosis. Only (*n*= 7), (4%) and – (*n*= 8), (4%) of the asked respondents would prescribe 1g x 3 – and 2g x 2, respectively.

Table 12 shows compliance to the guidelines, according to the year the questionnaire was given. They study population was (*n*= 175) give that all respondents did not answer all questions. Compliance for the years 2008-2010 referred to 2 g x 3, while for 2014, it implied 1 g x 3. In total, (73%) of the respondents answered in compliance with the guidelines. In the period 2008-2010 compliance was between (89-94 %). In 2014, compliance was (19%). It was not possible to generate *p*-value by use of Fisher's exact test for this diagnosis. Figure 8 illustrates graphically the most common dosage of cefotaxime prescribed for UTI with signs of sepsis.

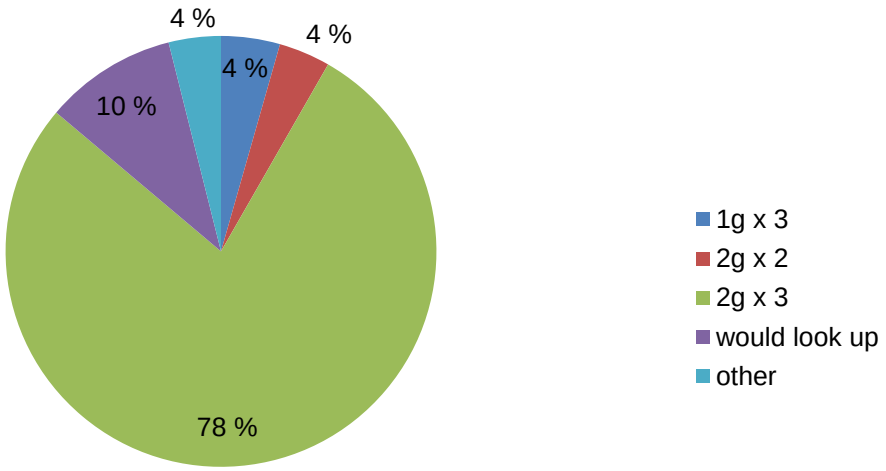
Table 11: dosage of cefotaxime in the treatment of UTI with signs of sepsis **(*n*=181)**

	Year				
Dosage	**2008**	**2009**	**2010**	**2014**	**Sum**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1g x 3	-	2 (6)	3 (6)	3 (6)	8 (4)
2g x 2	4 (8,)	2 (6)	-	1 (2)	7 (4)
2g x 3	37 (75)	29 (81)	41 (82)	34 (74)	141 (78)
another dose	1 (2)	-	-	-	1 (0,6)
would look up	6 (12)	3 (8)	4 (8)	5 (11)	18 (10)
did not answer	1 (2)	-	2 (4)	3 (6)	6 (3)
Total	49	36	50	46	181

Table 12: compliance with the guidelines for UTI with sepsis, according to year **(*n*=175)**

	Cefotaxime-UTI with sepsis		
	Compliance with the guidelines		
Year	**No**	**Yes**	**Total**
	***n* %**	***n* %**	***n***
2008	5 (10)	43 (90)	48
2009	4 (11)	32 (89)	36
2010	3 (6)	45 (94)	48
2014	35 (81)	8 (19)	43
Total	47 (27)	128 (73)	175

Figure 8: the most common dosage of cefotaxime in the treatment of UTI with signs of sepsis (***n*=181**)



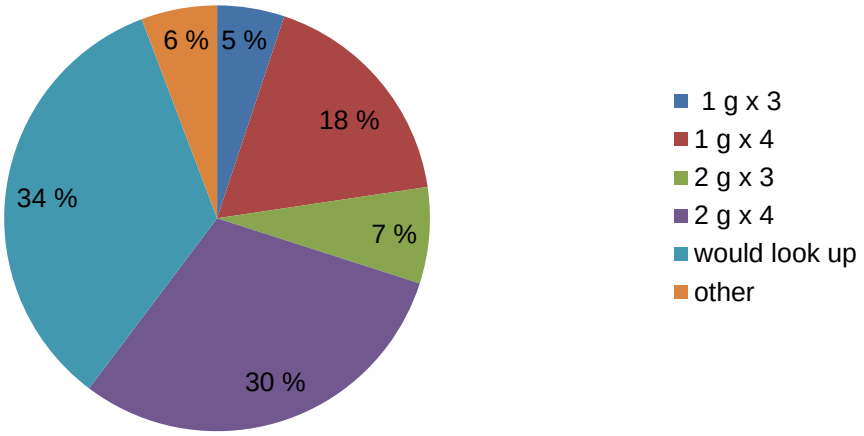
3.1.6 Cloxacillin in the treatment of bacterial arthritis

The dosages of cloxacillin that the respondents would use in the treatment of bacterial arthritis are illustrated in table 13. The two most frequent answers are that they would prescribe 2g x 4 (30%) or look up the dosage (34%). Forty eight, (18%) said they would prescribe 1 g x 4, while less than (10%) would prescribe 1g x 3 or 2g x 2. Figure 9 illustrates the most common dosage in the treatment of bacterial arthritis the respondents' would prescribe, independent of year the questionnaire was given.

Table 13: dosage of cloxacillin in the treatment of bacterial arthritis **(*n*=272)**

Dosage	Year						
	2007	**2008**	**2009**	**2010**	**2013**	**2014**	**Sum**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1g x 3	-	3 (6)	2 (6)	5 (10)	3 (6)	1 (2)	14 (5)
1g x 4	8 (18)	5 (10)	7 (19)	14 (28)	5 (11)	9 (20)	48 (18)
2g x 2	2 (4)	-	1 (3)	1 (2)	1 (2)	-	5 (2)
2g x 3	7 (16)	3 (6)	2 (6)	4 (8)	4 (9)	-	20 (7)
2g x 4	12 (27)	16 (33)	18 (50)	15 (30)	12 (26)	10 (22)	83 (30)
another dose	-	-	-	-	-	-	-
would look up	13 (29)	19 (39)	5 (14)	11 (22)	21 (46)	24 (52)	93 (34)
did not answer	3 (7)	3 (6)	1 (3)	-	-	2 (4)	9 (3)
Total	45	49	36	50	46	46	272

Figure 9: the most common dosage of cloxacillin in the treatment of bacteria arthritis **(*n*=272)**



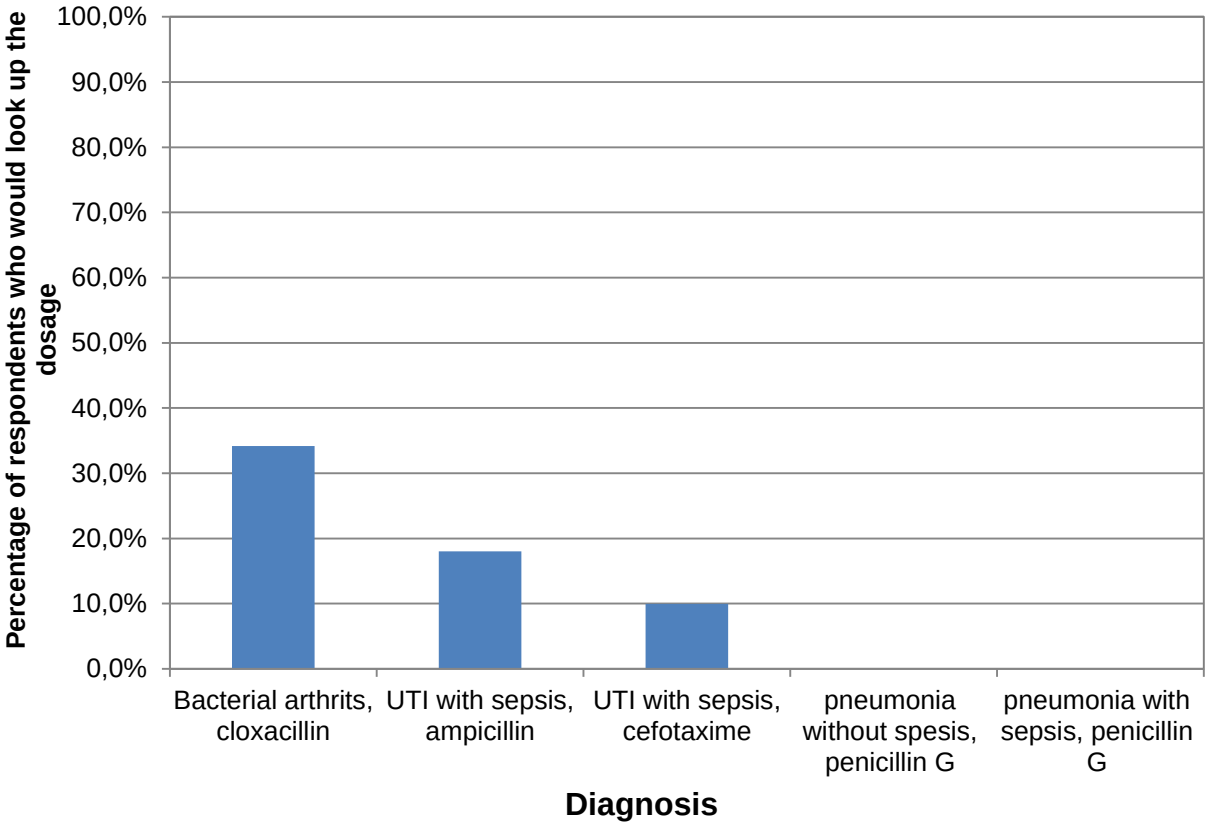
3.1.7 Respondents who would look up the dosage according to diagnosis

Table 14 shows the respondents' answers if they would look up the dosage for diagnosis' and antibiotics in the questionnaire. In total, (*n*=98) respondents (34%) would look up the dosage in the treatment of bacterial arthritis with cloxacillin. Forty nine respondents, (18%), would look up the dosage of ampicillin in the treatment of UTI with sepsis, whereas (*n*: 18), (10%) would look up the dosage in the treatment of the same diagnosis with cefotaxime. None of the doctors would look up the dosage of penicillin G in the treatment of pneumonia with and without signs of sepsis. Figure 10 illustrates these trends graphically.

Table 14: respondents who would look up the dosage according to diagnosis, independent of year **(*n*=160)**

Would look up the dosage	
Diagnosis and antibiotic	***n (%)***
Bacterial arthritis, cloxacillin	93 (34)
UTI with sepsis, ampicillin	49 (18)
UTI with sepsis, cefotaxime	18 (10)
Pneumonia without signs sepsis, penicillin G	-
Pneumonia with signs sepsis, penicillin G	-
Total	160

Figure 10: percentage of doctors who would look up the dosage according to diagnosis, independent of year **(*n*=160)**



3. 2 Part two: results from the wards

In total, (*n*=380) patients were registered having received antibiotics at Voss hospital and HUH. Since antibiotics were studied in relation to specific diagnoses, (*n*=271) patients were excluded from further analysis due to their diagnosis. Orthopedic –and surgical infections are examples of diagnosis excluded from the study.

3.2.1 Number of antibiotics received per patient at the wards

Table 15 summarizes number of antibiotics received per patient at the wards. The most common number of antibiotics per patient varied between 1 or 2 antibiotics. Only infectious disease department 1 and 2 had patients that received up to 5 different antibiotics during the time of study. Three patients, (5%) at infectious disease department 1 and – (*n*=1) patient, (1%) at department 2, respectively received 5 antibiotics. Gastroenterological department and medical department at Voss had 3 antibiotics per patient as the highest number.

Table 15: number of antibiotics per patient **(*n*=380)**

Antibiotics per patient	**Infect dis.1**	**Infect dis.2**	**Gastro-enteral**	**Medical + Endo**	**Nephro -logy**	**Medical dpt, Voss**	**Respt. unit**
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
1	16 (26)	37 (42)	24 (50)	17 (45)	36 (55)	27 (66)	21 (55)
2	26 (43)	36 (40)	21 (44)	17 (45)	22 (34)	8 (19)	11 (29)
3	11 (18)	12 (13)	3 (6)	3 (8)	6 (9)	6 (15)	5 (13)
4	5 (8)	3 (3)	-	1 (3)	1 (1)	-	1 (3)
5	3 (5)	1 (1)	-	-	-	-	-
Total	61	89	48	38	65	41	38

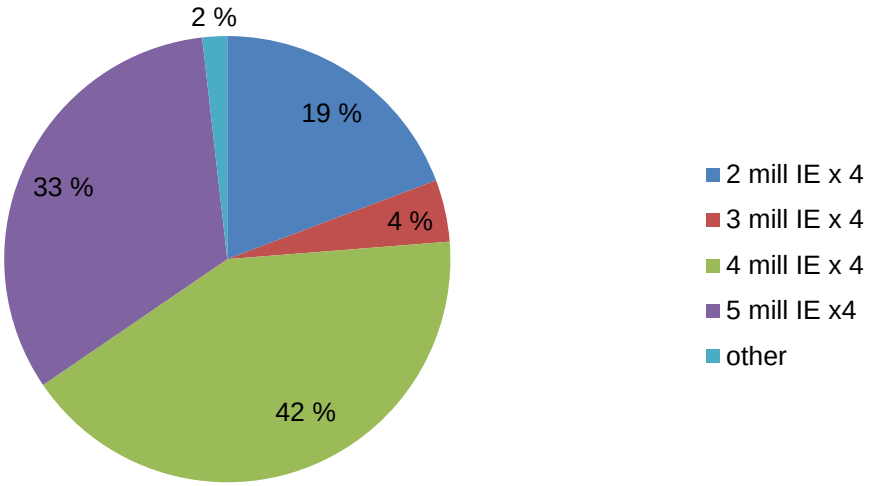
3.2.2 Penicillin G prescribed independently of the diagnosis

Table 16 illustrates the most common dosage prescribed of penicillin G, independently of the wards patients were admitted at, and the diagnosis given. In total, (*n*= 156) patients were prescribed penicillin G of whom (*n*= 65), (42%) were prescribed 4 mill IE x 4, (*n*= 51), (33%) were rescribed 5mill IE x 4 and (*n*= 30), (19%) received 2mill IE x 4. Figure 11 presents graphically the most common dosage prescribed of penicillin G at the wards.

Table 16: dosage of penicillin G prescribed independently of the diagnosis **(*n*=156)**

Dosage	***n* (%)**
2 mill IE x 4	30 (19)
2 mill IE x 6	1 (0,6)
3 mill IE x 4	7 (4)
3 mill IE x 6	1 (0,6)
4 mill IE x 3	1 (0,6)
4 mill IE x 4	65 (42)
5 mill IE x 4	51 (33)
Total	156

Figure 11: the most common dosage of penicillin G at the wards **(*n*=156)**



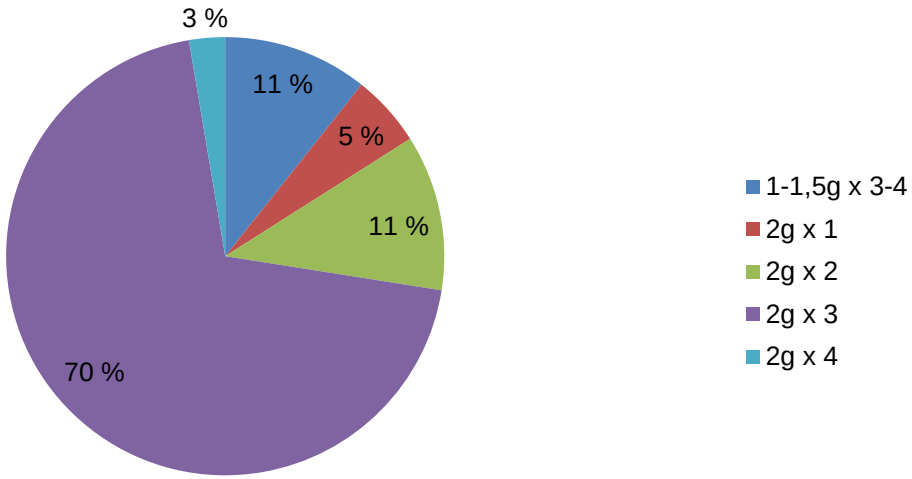
3.2.3 Cefotaxime prescribed independently of the diagnosis

Table 17 illustrates the most common dosages of cefotaxime prescribed at the wards, independently of the diagnosis given. The most common dosage prescribed was 2g x 3, (70%), whereas (11%) of the doctors prescribed 2g x 2. Figure 12 presents these results graphically.

Table 17: dosage of cefotaxime given independently of the diagnosis **(*n*=113)**

Dosage	***n* (%)**
1g x 3	9 (8)
1,5 g x 3	1 (0,9)
1g x 4	2 (2)
2g x 1	6 (5)
2g x 2	13 (11)
2g x 3	79 (70)
2g x 4	3 (3)
Total	113

Figure 12: the most common dosage prescribed of cefotaxime independently of the diagnosis given **(*n*=113)**



3.2.4 Penicillin G in the treatment of pneumonia without signs of sepsis

Table 18 illustrates the most common dosage prescribed of penicillin G at the wards in treatment of pneumonia without signs of sepsis. In total, (*n*= 44) patients were registered having pneumonia. The most frequent prescribed dosage was 2mill IE x 4, (34%), whereas (*n*= 14) doctors (32%) prescribed 4mill IE x 4. Twelve doctors, (27%) prescribed 5mill IE x 4. Two patients (4%) received a dosage of 3mill IE x 4, whereas one patient, (2%) was prescribed 4mill IE x 3.

Table 18: dosage of penicillin G in the treatment of pneumonia without signs of sepsis **(*n*=44)**

Dosage	***n* (%)**
2 mill IE x 4	15 (34)
3 mill IE x 4	2 (4)
4 mill IE x 3	1 (2)
4 mill IE x 4	14 (32)
5 mil IE x 4	12 (27)
Total	44

3.2.5 Penicillin G in treatment of pneumonia with signs of sepsis

Table 19 shows how the doctors at the wards prescribed penicillin G in treatment of pneumonia with signs of sepsis. In total, (*n*= 24) patients were diagnosed with this particular disease. Twelve doctors, (50%) prescribed 5 mill IE x 4, whereas (37%) of the doctors prescribed 4 mill IE x 4. Only (*n*=3) doctors, (12%) prescribed 2mill IE x 4.

Table 19: dosage of penicillin G in treatment of pneumonia with signs of sepsis **(*n*=24)**

Dosage	***n* (%)**
2 mill IE x 4	3 (12)
4 mill IE x 4	9 (37)
5 mil IE x 4	12 (50)
Total	24

3.2.6 Ampicillin in treatment of UTI with signs of sepsis

Table 20 illustrates how the doctors at the wards prescribed ampicillin in treatment of UTI with signs of sepsis. In total, (*n*= 16) patients were diagnosed. Fifteen doctors (94%) prescribed 2g x 4. One doctor prescribed 1g x 3.

Table 20: dosage of ampicillin in treatment of UTI with signs of sepsis **(*n*=16)**

Dosage	***n* (%)**
1g x 3	1 (6)
2g x 4	15 (94)
Total	16

3.2.7 Cefotaxime in treatment of UTI with signs of sepsis

Table 21 illustrates the prescription of cefotaxime in the treatment of UTI with signs of sepsis at the wards. Six patients were diagnosed with the disease. Three patients, (50%) were prescribed 2g x 3, two patients, received 1g x 3, while one patient, was prescribed 2g x 2.

Table 21: dosage of cefotaxime in treatment of UTI with signs of sepsis **(*n*=6)**

Dosage	***n* (%)**
1g x 3	2 (33)
2g x 3	3 (50)
2g x 2	1 (17)
Total	6

3.2.8 Cefotaxime in the treatment pneumonia without signs of sepsis

Table 22 illustrates the number of patients who received cefotaxime in the treatment of pneumonia without signs of sepsis. In total, 11 patients were prescribed cefotaxime, of whom (*n*=7) patients, (64%), were prescribed 2g x 3, (*n*=2) (18%) 1g x 3 and 1 patient received 1g x 4 –and 2g x 2 respectively.

Table 22: dosage of cefotaxime in the treatment pneumonia without signs of sepsis **(*n*=11)**

Dosage	***n* (%)**
1g x 3	2 (18)
1g x 4	1 (9)
2g x 2	1 (9)
2g x 3	7 (64)
Total	**11**

3.2.9 Cefotaxime in the treatment of UTI without signs of sepsis

Eight patients who were diagnosed with UTI without signs of sepsis, received treatment with cefotaxime as illustrated in table 23. Six patients, (75%), were prescribed 2g x 3, whereas 1 patient received 1g x 3 – and 2g x 3, respectively.

Table 23: dosage of cefotaxime in the treatment of UTI without signs of sepsis **(*n*=8)**

Dosage	***n* (%)**
1g x 3	1 (12)
2g x 2	1 (12)
2g x 3	6 (75)
Total	**8**

4 DISCUSSION

4.1 Main findings from the questionnaire

The rationale behind the questionnaire was to prove the hypothesis proposed by an infectious disease specialist working at the Medical department, HUH, that antibiotics are to some extent prescribed incidentally and not in accordance with the regional and later national guidelines.

4.1.2 Penicillin G in the treatment of pneumonia with and without sepsis

Our results show that this is not the case, as the dosage of the antibiotics studied is mostly in accordance with both previous local and current national guidelines. As an illustration, in treatment of pneumonia without sepsis, (69 %) of the respondents answered that they would prescribe penicillin G, 2 mill IE x 4, which is in compliance with the national guidelines. The previous regional guidelines recommended penicillin G to be prescribed in the range between 2 mill IE x 4 and – 5 mill IE x 4. However, also prior to the introduction of the new guidelines in 2013, most of respondents answered they would prescribe 2mill IE x 4, table 4.

The hypothesis put forward by the infectious disease specialist was that the doctors for this diagnosis would prescribe higher doses of penicillin G, for instance 4 mill IE x 4, and 5 mill IE x 3, rather than 2mill IE x 4. Figure 3 shows that only (4%) of the respondents answered they would prescribe 4 mill IE x 4, whereas (0, 7%) would prescribe 5 mill IE x 3, table 4. Such results may suggest that doctors are inclined to use the lowest dose of penicillin G as possible, contrary to what was assumed. Since regional guidelines recommended for this diagnosis penicillin G to be prescribed in the range between 2 mill IE x 4 and – 5 mill IE x 4, it would still be in compliance with the regional guidelines, even though the doctors had answered 4 - or 5 mill IE x 4.

Another observation that strengthens the argument that the doctors do follow the guidelines, stems from analyzing the prescription of penicillin G, 5 mill IE x 4 by year, figure 4. During a time period between 2007-2010 and 2013-2014 only 4-14 respondents would prescribe 5 mill IE x 4. This observation may suggest that doctors are careful to prescribe higher doses of penicillin G even if local guidelines suggested that penicillin G could be prescribed up to 5 mill IE x 4.

The results for penicillin G in the treatment of pneumonia with sepsis, figure 5, also suggest that the respondents would prescribe according to the guidelines. Regional guidelines recommended 5 mill IE x 4-6, while the current national guidelines recommend 5 mill IE x 4. In total, (73%) of the doctors answered that they would prescribe 5 mill IE x 4. The infectious diseases specialist proposed that the most common answers would be 4 mill IE x 4 and 5 mill x 3. However, only (7%)- and (2%) answered they would prescribe 4 mill IE x 4 and 5 mill IE x 3, respectively, table 6. Such results suggest that the internal medicine residence have good knowledge about the correct dosage of penicillin G.

One qualitative study from a teaching hospital in the Netherlands discovered that residents and supervisors had different attitudes towards the guidelines. For instance, residents were more receptive to using the guidelines than the supervisors who considered guidelines as a threat to their personal autonomy (62). Since respondents from the questionnaire were internal medicine residents, it could be that their knowledge of the correct dosage in relation to the guidelines is better than that of more experienced specialists. Norway is among the countries in Europe with lowest antibiotic consumption as the Netherlands, figure 1. Thus, it can be that some of the challenges in compliance to guidelines are similar in Norway as well. On the other hand, since this master thesis did not investigate any adherence barriers to antimicrobial treatment, nor compared attitudes to guidelines between senior doctors and residents, it cannot answer to such questions.

4.1.3 The treatment of UTI with sepsis and bacterial arthritis

The argument that the residents do follow the guidelines is also strengthened by looking into the results for ampicillin in treatment of UTI with signs of sepsis, figure 7. In total, (n= 132) respondents (48%) would prescribe ampicillin 2 g x 4, which is in compliance with both the regional and national guidelines, though the new guidelines recommend 1-2 g x 4.

For treatment of bacterial arthritis with cloxacillin, figure 9 (n= 83), (30%) of respondents answered they would prescribe 2g x 4, which is in compliance with both regional and national guidelines. This low figure could be due to the fact that this is not among the most common infections at the hospitals. This is supported by the observation that more doctors, (n= 93), (34%) would look up the dosage as opposed to the (30%) who would prescribe 2 g x 4. The fact that the doctors would look up the dosage, indirectly means that they would prescribe the correct dosage in the end.

When looking at percentage of doctors who would look up the dosage according to diagnoses figure 10, bacterial arthritis with (34%), is the diagnosis with the highest number of respondents who would look up the dosage. These results, thus confirm the suggestion that the respondents have good knowledge of the dosage regimes for the common diagnoses studied.

Over all these results suggest that the hypothesis proposed, that the doctors would use antibiotics incidentally and that the dosages are not in compliance with the guidelines is not confirmed.

The results do suggest that there is greater compliance with the regional guidelines than the national guidelines. For instance, in treatment of UTI with signs of sepsis, figure 8, (78%) of the doctors answered they would adhere to previous regional guidelines by prescribing cefotaxime 2g x 3, whereas only (4%) would comply with national guidelines by prescribing 1g x 3. Table 11 shows that the number of respondents who would prescribe cefotaxime, 1 g x 3 has remained stable from 2010 to 2014, (n= 3). The argument that the respondents are more familiar with the regional guidelines is supported by looking closely into suggested prescription of ampicillin, 1g x 4, by year, table 8. The current guidelines suggest that ampicillin can be prescribed in the range between 1 g x 4 and 2 g x 4, respectively. It is interesting to note that there has been a decrease from 2013 to 2014 in number of doctors who would prescribe ampicillin, 1g x 4. In 2014, only one respondent would prescribe 1g x 4.

Stronger familiarity with the regional guidelines is strengthened when analyzing compliance with the guidelines according to year, for the diagnoses studied. For penicillin G in the treatment of pneumonia without sepsis there was near significant difference (p=0,07) between years in compliance with the guidelines. Lowest compliance was observed in 2014, when guidelines recommended 2 mill IE x 4, table 5. For other diagnoses studied, there was not observed any significant difference but the compliance with the guidelines seemed to vary to some extent over the years. In the treatment of UTI with sepsis with cefotaxime, table12, the lowest compliance was observed in 2014 with (19 %) when the guidelines recommended 1g x 3 instead of 2 g x 3.

On the other hand it is not surprising that the doctors are more familiar with the regional guidelines. These recommendations have been in use since 2004, while the national guidelines were first published in July 2013. Since the time of publication, the national

guidelines have only been available in full electronic version. The Norwegian Advisory Unit on Antibiotic use in hospitals has received information about the electronic version not being practical enough for common use in a clinical setting. Thus, limited accessibility to the guidelines can be one reason as to why small adaptation to the new guidelines has been observed for some diagnosis. At the time of writing, a pocket version of the guidelines is soon to be distributed in the hospitals, which will hopefully increase familiarity with the new guidelines.

4.2 Main findings from the wards

The hypothesis proposed, that there would be discrepancy between the guidelines and how antibiotics were prescribed at the wards, is not confirmed, though there are some interesting observations which could indicate that there is room for more prudent antibiotics prescribing.

Expected deviation between what doctors answered they would prescribe and what is actually prescribed in the clinical setting for predefined diagnoses, is to some extent confirmed. Overall, results from the wards could not validate the findings from the questionnaire.

It was not confirmed that more broad-spectrum antibiotics are prescribed than the guidelines suggest though results indicate that broad-spectrum antibiotics are sometimes prescribed unnecessarily.

4.2.1 Penicillin G in the treatment of pneumonia with and without sepsis

In treatment of pneumonia without signs of sepsis with penicillin G, altogether (*n*= 15), (34%) prescribed 2 mill IE x 4, table 18. When comparing the results from the wards with the results from the respondents' questionnaire, the majority of doctors in both studies would prescribe 2 mill IE x 4. It is however interesting to note that few respondents answered they would prescribe 4 mill IE x 4, (4 %), or 5 mill IE x 4, (18 %), whereas on the wards however, (32%) of the doctors prescribed 4 mill IE x 4 and (27 %) 5 mill IE x 4, indicating that higher doses of penicillin G are used than what is recommended in the current national guidelines. These results are in line with observations of infectious disease specialist working at the medical department that 4 mill IE x 4 and 5 mill IE x 4 are commonly prescribed dosages of penicillin G.

When looking at the prescription trends for treatment of pneumonia with sepsis with penicillin G, in total, (*n*= 12), (50%) of doctors prescribed 5mill IE x 4, table 19, which is in compliance

with the guidelines. Nine doctors, (38%) prescribed 4mill IE x 4, which is lower than what the guidelines recommended. In contrast, (7%) of the respondents from the questionnaire answered they would prescribe 4mill IE x 4. Therefore, the infectious specialists' assumption how 4mill IE x 4 is common dosage prescribed, seems to be confirmed.

These results can be an indirect measure of common dosages for penicillin G, though more research is needed with bigger populations to be able to generalize the results. To some extent, it seems that 4-5 mill IE x 4 are the common dosages prescribed both for pneumonia with and without sepsis This argument is strengthened by the fact that 4-5 mill IE x 4 are the common dosages prescribed for penicillin G at the wards independent of the diagnosis given, figure 11.

An interesting observation however, is that none of the doctors working at the wards prescribed 5mill IE x 6 for pneumonia with sepsis. The previous guidelines recommended prescribing penicillin G until 6 times daily (39), and some respondents, (7%) from the questionnaire answered they would prescribe this dosage, yet at the wards no one prescribed penicillin G x 6 daily.

It is important to note that the current guidelines are not consistent in their recommendation whether to prescribe penicillin G 5mill IE x 4 or x-6 times daily. In one chapter about antibiotics alternatives for treatment of pneumonia with sepsis, it is recommended to prescribe penicillin G x 4 daily (40), while another chapter recommends that penicillin G can be prescribed up till 6 times daily (63) . Such a recommendation relies on the fact that high doses of beta-lactam antibiotics do not kill more bacteria than lower doses, as the effect of these antibiotics is dependent on the time the concentration is over minimum inhibitory concentration (MIC) (42).

Suboptimal doses of antibiotics predispose for limited eradication of bacteria, reoccurrence of infection and development of resistance (63). All antibiotic treatments increase the risk of developing resistance if the dose is not optimal (64). Thus, when treating pneumonia with sepsis more doctors should prescribe penicillin up till 6 times a day.

4.2.2 Ampicillin and cefotaxime in the treatment of UTI with sepsis

It is interesting to note that ampicillin in the treatment of UTI with signs of sepsis is prescribed at the wards, in adherence to the highest dose recommended, 2 g x 4, but none of the doctors prescribed a lower dose of ampicillin, 1 g x 4. In relation to treatment of UTI with signs of sepsis with cefotaxime, the majority of doctors prescribe 2 g x 3, which is in compliance with the regional guidelines, while (*n*= 2) prescribed 1g x 3 which is in compliance with the current guidelines. These results can support the findings from the questionnaire that doctors have better knowledge of the regional- than the national guidelines. Furthermore, doctors are more inclined to use higher dosages when prescribing antibiotics, than what was assumed from the result from the questionnaire. The fact that the most common dosage of cefotaxime, independently of diagnosis, is 2g x 3, figure 12 can support this argument. On the other hand, the number of patients' registered with these diseases on the wards amounted to (*n*=16) and (*n*= 6) patients respectively, making it difficult to generalize these results.

Inconsistency in the new guidelines can also be a reason as to why doctors prescribe higher dosages of ampicillin and cefotaxime. In the chapter about sepsis in the new guidelines, the recommended dose of ampicillin is 2 g x 4 (65), while in the chapter about UTI treatment with signs of sepsis, ampicillin dosage is recommended in the range of 1-2 g x 4 (43). The same inconsistency is evident in the recommendation of the treatment with cefotaxime. Lower dose is recommended in the chapter about UTI treatment with signs of sepsis (43), while chapter on sepsis recommends 2 g x 3 (65). Thus, where the clinicians look up the recommended dose may influence their prescription trends.

4.2.3 Cefotaxime in the treatment of pneumonia and UTI without sepsis

The registration of antibiotics at the wards did not confirm the hypothesis that more broad-spectrum antibiotics are prescribed than the guidelines suggest, though two interesting observations were discovered, concerning prescription of cefotaxime as initial treatment of pneumonia and UTI without sepsis, table 22 and 23.

Being a broad-spectrum antibiotic, cefotaxime is an unfortunate drug to prescribe as a first alternative, and is not recommended in the guidelines as such. In total, (*n*=11) patients received ceftoaxime in the treatment of pneumonia and 8 in the treatment of UTI. It is a good

thing that only few of the patients who were registered with these diseases received cefotaxime as initial treatment.

However, as broad-spectrum antibiotics lead to increased resistance among microorganism (4), it is essential that such practice is not a standard prescribing procedure at the hospitals. Broad-spectrum antibiotics do not lead to better clinical outcomes than small spectrum antibiotics when the disease causing bacteria is known (24). Especially, when the pathogen is unknown, empirical treatment for pneumonia without sepsis is penicillin G 2 mill IE x 4(40). Cephalosporins lead easier to resistance development than penicillin's. In addition these antibiotics have greater effect on bacteria in the GI-tract than penicillin's (66). More research is needed to understand why some patients were prescribed cefotaxime and how common this practice is.

4.2.4 Number of antibiotics per patient

Our final observation was that majority of the patients at the wards received one or two antibiotics during the registration period, though 4 and 5 antibiotics per patient could also occur, table 15. The reason behind switch between several different antibiotics can be due to the fact that the patient is not responding to the original treatment regime or that microbiologically test results in relation to disease causing pathogen prompt a shift of antibiotic treatment to a more sensitive antibiotic. It could also be that the doctors too easily switch between different antibiotics. Such practice is not recommended as unnecessary antibiotic use increases number of resistant organisms. On the other hand more research is needed in order give concrete reasons as to why patients could receive up to 5 different antibiotics.

4.3 Findings from the questionnaire - strengths and limitations

The result from the questionnaire did not confirm the proposed hypothesis, that the doctors would prescribe either incidentally or higher doses than recommended. On the contrary, the results seem to suggest that doctors have good knowledge about dosages recommended for predefined diagnoses. It is important to discuss whether the questionnaire was made in an appropriate way to address the questions it was meant to answer.

4.3.1 Reliability

The biggest strength of the questionnaire is that the similar population was tested over a period of 6 years. By giving specific dosage alternatives for each diagnosis one could test the doctors' knowledge about the correct dosage regimes for chosen antibiotics.

However, in order to assess doctors' compliance with the guidelines, it would have been better if the questions were formulated in such a way that the respondents had an opportunity to write down their own propositions for treatment with antibiotics for given diagnoses, rather than to be given suggestions beforehand. In that way, one could get clearer picture of doctors' knowledge of the guidelines and their prescription trends.

For instance, the term "*would look up*" that was one of the choices given in the questionnaire, was not properly defined. The term could mean using guidelines to look up the dosage, but it could also imply using some other manual, for instance *Felleskatalogen*. It is probably assumed that the respondents would consult the guidelines, but assuming that they would do so does not mean that they do so in a clinical setting. It would have been better if the question was formulated in another way, for instance "if you need to look up the dosage which manual would you consult?" Then, one would get information if the doctors were familiar with the guidelines rather than assuming that they are.

4.3.2 Validity

Even though the results from the questionnaire give an overall impression that the respondents are familiar with the guidelines for the diagnoses studied, it cannot provide information about doctors' attitudes toward the guidelines in general.

The questionnaire did not contain any questions about, age, sex, how far the doctors had progressed in their specialty program, which hospital they were working at, in order to control for the effects these variables could have on respondents' knowledge about correct dosage regimes.

The antibiotics studied in the questionnaire evolved around beta-lactam and cephalosporin antibiotics. Though it is important to address the use of these agents, it would have been better if other antibiotics were included in the questionnaire in order to have more information about doctors' knowledge and attitudes towards the guidelines in general.

The greatest limitation of the questionnaire is that the questionnaire was not validated beforehand, or under the process of collecting the data. The data was not collected in 2011-2012 and even the questionnaire did not ask exact questions from year to year, which unfortunately undermines its quality.

4.4 Findings from the wards- strengths and limitations

4.4.1 Reliability

The strength of the findings from the wards is that the data was collected from a real clinical setting by registering relevant information about antibiotics from patients' medication chart– and clinical records. In addition the same person collected the data making it less likely for big variations in the registration process.

Information bias could occur when checking the medical records for proposed diagnosis, since they are incomplete. My tutor, an infectious diseases specialist, assessed the diagnoses assigned by the student and some differences were registered and adjusted before further analysis.

Greater cooperation with the clinical staff at the wards could have helped clear up the undefined aspects in patients' journals, in relation to at what point of the treatment the antibiotics were prescribed. On the other hand, it is questionable if the busy time schedule at the wards would allow for a through data analysis with the clinical staff.

4.4.2Validity

One of the biggest limitations of this study design is the short timespan for the data collection. Short registration period did not generate big study populations in order to be able to validate answers from the questionnaire by use of statistical correlation. It was not possible to correlate data from the wards with the data from the questionnaire given the small study population. For instance the number of patients registered at the wards in the treatment of UTI with sepsis with ampicillin was (n=16), whereas only (n=6) patients were registered who received cefotaxime. On the other hand, total number of respondents who answered the questions about treatment of UTI with sepsis was (n=272).

It is a limitation that the same doctors are not included in both studies. It can, however be assumed that some of the previous and current internal medicine residents are working either at Voss or HUH.

A longer time period with inclusion of other antibiotics than for instance penicillin G and cefotaxime, would also be necessary to be able to generalize the findings from the wards. It would have been interesting if other substances belonging to 3rd generation cephalosporins were investigated, in addition to carbapenems. According to the NORM/NORM-VET report the use of these broad spectrum agents has steadily increased in Norwegian hospitals in recent years (13).

With bigger study populations it would also have been possible to observe trends in prescription practice between hospitals. No evident differences were observed between the wards or hospitals in terms of antibiotic prescription, except for the number of antibiotics received per patient.

4.5 Key findings in relation to similar studies in Norway

Majority of literature on antibiotics comes from countries with a much higher antimicrobial resistance than Norway, making that knowledge difficult to generalize to the Norwegian setting (24).

Four studies conducted in Norway, investigated if the prescription of antibiotics among Norwegian doctors is in compliance with the guidelines. It was not checked for similar studies in other countries, as different resistance patterns across Europe may influence the recommendations in national guidelines making the comparison between countries difficult.

Berild et al investigated appropriate antibiotic use according to diagnoses and bacteriological findings at a University Hospital in Oslo. The compliance with the guidelines was (> 90 %). High compliance with the guidelines is similar to this study, though the results from Berild et al studies have greater strength as they were collected over a period of three years. On the other hand, the data stems from 1990s (67), making it difficult to compare with the prescription trends in hospitals from Western Norway, 18 years later. A study by Harthug et al pointed out that therapeutic choice of antibacterial agents in Norway differs according to hospital size and hospital type, and that it is also unclear whether strong local opinion leaders

have an impact on individual hospital tradition (68). Thus this master thesis and the results from Berild et al are difficult to compare.

Blix et al, found in a study about risk of drug related problems for various antibiotics in hospitals that there is a positive pattern for antibiotic use in accordance with the Norwegian treatment guidelines (32). Since their study included six different internal medicine departments at four hospitals in Norway, had a study population of 283 patients and also explored drug related problems (DRP), to antibiotics, it is difficult to compare these results with the findings from this master thesis.

It is nevertheless positive that even though the studies by Blix et al and Berild et al were conducted in different settings than this study, compliance with the antibiotic treatment guidelines was observed. Nonetheless, little is known about the process and factors responsible for how physicians change their practice methods when they become aware of a guideline. It is assumed that physician adherence to guidelines may be hindered by a variety of barriers and that factors improving physician guideline adherence may not be generalizable, since barriers in one setting may not be present in another (69).

In a study from 2003, Agdestein et al looked at whether general practitioners in Norway adhere to guidelines in the treatment of urinary tract infections. The study showed that the Norwegian general practitioners usually comply with the guidelines in the choice of antibiotics (70). Eriksen et al showed that prescription trends at 5 nursing homes in Oslo were also in compliance with the guidelines for general practitioners (71). It is difficult to compare these findings with this study as the general practitioners work in a different setting than hospital doctors and treat less severe patients.

4.5 ASP and clinical pharmacists

Since more research is needed to assess doctors' compliance to the guidelines it is interesting to discuss which role pharmacist could have in such projects. Adherence to guidelines is essential in order to ensure prudent antibiotic prescribing (26). Clinical pharmacists may have a role to play in this (72).

In the UK, clinical pharmacists have an established role within hospitals. Pharmacists are also an important part of ASP worldwide, with multidisciplinary working models described in the

USA, France and Ireland (73). The typical clinical pharmacy service includes prescription monitoring, taking accurate medication histories, provisions of medicines information, patient counselling and regular cooperation with the medical and surgical team. Key services for antibiotic pharmacists include among others audit of local practices, monitoring of antibiotic consumption, participation in infection control, formulary development and appraisal of new antimicrobials (72).

Given the non- prescribing of penicillin G x 6, and the requirement for more knowledge about prescription trends, it seems that there is potential for a clinical pharmacists in Norwegian hospitals as well. In addition, a study by Blix et al showed that a wide range of drug-related problems to prescription of antibiotics existed among hospitalized patients at medical departments (32). For instance, by use of an audit, as it was done in this project, clinical pharmacists could monitor local practices and antibiotic consumption. In addition, in hospitals where there are no employed pharmacists, nursing staff could be trained in doing some tasks usually assigned to pharmacists, for example, use of an audit.

Even though the latest national strategy for prevention of healthcare associated infections and antimicrobial resistance states the importance of inclusion of pharmacists in infection control (1), the strategy does not give any clear recommendations as to how clinical pharmacists can contribute to reduce antibiotics prescribing. The educational institutions must also provide opportunities for specialization for Norwegian pharmacists, within the field of infection control if pharmacists should play a more active role to reduce antibiotics prescribing in hospitals. In Norway there is currently no specific postgraduate course for clinical pharmacists. University of Oslo at one point offered postgraduate degree in clinical pharmacy, but this program is currently not admitting any new students (74).

For instance, in the UK, specific postgraduate courses exist for pharmacists, for example MSc in infection control and management (72).Weller at al also discuss that despite training in infectious diseases, the clinical/,-antibiotic pharmacist will have to work hard to gain the respect of medial colleagues who may not appreciate comments and suggestions from non-medical staff. The authors stress requirement for good working relationship and trust to develop within clinical teams. Even in the UK where clinical pharmacists have been involved for some time as participants of ASP, Wickens et al point out that opportunity exists to expand pharmacists role further and to ensure greater multidisciplinary engagement (73).

Weller et al argue how an clinical/,-antibiotic pharmacist ability to be effective could be reduced by lack of specialist knowledge or by lack of support from clinical colleagues.
If clinical pharmacists should play a greater role in the implementation of treatment guidelines in Norway, they face challenges as the use of clinical guidelines is disputed among physicians themselves. The strongest disagreement has evolved around use of aminoglycoside it the treatment of pneumonia and sepsis. Some have called guidelines to be even fundamentalistic (75) while others have characterized them as unjustifiable (76).

Use of an audit seems to be a good way of monitoring prescription trends. However, it is necessary that through prescription monitoring one is able to distinguish between patients that do not receive optimal antibiotic prescribing due to wrong choice of drug and dosage regime, and those that do not receive antibiotics according to treatment guidelines on the grounds of patients' clinical situation that will make it necessary to deviate from the guidelines. In that way one would be able to improve and ensure credibility of the guidelines. Laxminarayan et al point out that guidelines need to be updated regularly and be well implemented in order to be productive, in combination with sufficient leadership, commitment and funding (18).

It is also important to note that ASP by itself cannot remove the problem of antimicrobial resistance. Chung et al point out that ASP is a small, but necessary part of a larger whole that includes regulatory policies and interventions to control antibiotic use in live-stock, educational measures and interventions to stimulate the research and nonetheless development of new classes of safe and effective antibiotics (77).

5 CONCLUSION

The results from the questionnaire suggest that Norwegian internal medicine residents' are familiar with the dosages recommended in the guidelines for the diagnoses studied, contrarily to what was assumed.

Given the small study population at the wards, the prescription trends could not validate the results from the questionnaire. Data from the wards seem to suggest that residents prescribe in accordance with the guidelines, though some discrepancies have been observed, indicating that there is room for more prudent antibiotic prescribing. Expected deviations between the answers from the questionnaire and dosages prescribed at the wards, were to some extent confirmed. In addition, broad spectrum antibiotics are sometimes prescribed unnecessarily.

More research, by use of an audit as it was done in this project, conducted by a clinical pharmacist for instance, coupled with a longer data collection period, can be an appropriate way of understanding doctors' compliance with the guidelines. ASP alone cannot reduce the problem of antimicrobial resistance, but is an important part of a greater multidisciplinary initiative.

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