Microbes that never sleep

– A multidisciplinary study of the antibiotic resistance management in Sweden.

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Abbreviations

CDA  Communicable Diseases Act
DDD  Daily Defined Doses
ESBL  Extended Spectrum Beta-lactamases
ESBL_{CARBA}  Extended Spectrum Beta-lactamases selecting for carbapenem-resistance
J01XX  Antibacterials for systemic use. A subgroup in the drug classification system: Anatomical Therapeutic Chemical Classification System (ATC)
MRSA  Methicillin-resistant Staphylococcus Aureus (MRSA)
SKL  Sveriges Kommuner och Landsting
Swedish Association of Local Authorities and Regions
Strama  Strategigruppen för rationell antibiotikaanvändning och minskad antibiotikaresistens
Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance
Abstract

The hypotheses of this study are that reduction and rational usage of antibiotics reduces development of antibiotic resistance. In Sweden, the trends do not follow this pattern. Despite a decrease in prescriptions of antibiotics, there is an increase in the number of patients infected with Methicillin-resistant Staphylococcus Aureus (MRSA), Extended Spectrum Beta-Lactamases (ESBL) and ESBL selecting for carbapenem-resistance (ESBL_CARBA). This study aims to study factors affecting antibiotic resistance management. An additional aim is to use a multidisciplinary approach for a subject that has mostly been studied with quantitative methods. First, linear regressions investigated any possible significant changes of prescription rates in outpatient care, hospital usage of antibiotic groups and antibiotic resistance. After this, nine interviews were conducted with physicians in outpatient care, hospital care and with representatives from the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (Strama), a network working for Swedish prevention against antibiotics resistance. There was a significant decrease in the number of prescriptions of antibiotics in outpatient care among all Swedish counties and a small, but significant increase of antibiotics used in hospitals. The number of patients infected with multidrug resistant bacteria also show a significant increase. The interviews revealed that health care workers in all counties follow the same guidelines and try to be as specific as possible in choosing antibiotics to hit specific bacteria. The respondents suggested migration and extended travelling as explanations to the growing number of cases of multidrug resistant bacteria. Further, two major factors emerged as important for an efficient antibiotic resistance management; Education/knowledge and Discussion. The results indicate a need for further research on rational usage of antibiotics and the use of broad-spectrum antibiotics in hospital care, rather than the reduction through prescriptions. The results indicate that rational usage has a bigger impact than reduction. Using a multidisciplinary approach gave a broader perspective on the issue and future studies should see the possibilities of mixing quantitative and qualitative studies.

Keywords: Antibiotic resistance, antibiotics, risk theory, infectious disease control
1. Introduction

1.1 Introduction
In the dawn of antibiotic development, as early as 1945, Sir Alexander Fleming, the man who made the discovery of penicillin, warned the world that an irresponsible use of antibiotics would lead to development of antibiotic resistance. Unfortunately, no one seemed to take him seriously. In the 1960s, cases of bacterial resistance against penicillin began to appear systematically and this was solved by research and development of new series of antibiotics. This pattern continued, with new types of antibiotics as a response to the development of resistance. Until today. Today new types of antibiotics are becoming scarce and at the same time more resistant bacterial strains appear. The need for a rational use of the antibiotics that still work is rising. In society, this is emerging into a growing crisis, but for the bacteria, the development of antibiotic resistance is just another evolutionary mechanism natural for all species. The two worlds seem difficult to combine, but perhaps it is a rational usage that will be the key for their coexistence.

1.2 Research area
The term antibiotics covers all drugs used for treating infections caused by bacteria. The drugs attack bacteria to get rid of infections while sparing human cells (Sköld, 2006). Since the first antibiotic substances were discovered in the 1920s, the development of new antibiotics have advanced into modern medicine’s most important weapon against microbes (Sköld, 2006). There are numerous working mechanisms among antibiotics, something that also has led to numerous types of antibiotic resistance. Looking at the number of techniques bacteria have developed in order to handle antibiotics, it is not hard to understand that antibiotic resistance is a growing problem. Most antibiotics affect only one type of bacteria, the narrow-spectrum antibiotics, while some interact with several bacterial strains, the broad-spectrum antibiotics. Broad-spectrum antibiotics also affect the natural bacterial flora in the body and select for resistance, and it is not recommended to use these too often, but instead choose those narrower in their approach (1177 Vårdguiden, 2016). In cases where the type of bacteria causing the infection is unknown, it is common to prescribe a broad-spectrum antibiotic to cover all sorts of bacteria or to combine several antibiotics (1177 Vårdguiden, 2016). This became popular during the 1960s and has since been a way of dealing with resistance (Rifkind & Freeman, 2005).
Since the first resistance against penicillin was noted, many types of bacteria have developed resistance against different antibiotics (Davies & Davies, 2010). The antibiotic resistance has a genetic character; it is a survival method that is selectively beneficial and mutations occur among bacteria to acquire protection from antibiotics (Tegmark-Wisell, 2011). When a patient is given an antibiotic treatment, bacteria protected with resistance mechanisms survive. The antibiotics thus select for resistance (Tegmark-Wisell, 2011). These bacteria in turn transmit the resistance to other bacteria and the resistance genes can become part of the normal flora. When the next course of treatment with antibiotics is initiated, it will have no effect. (Tegmark-Wisell, 2011). Apart from the resistance itself, the resistant bacteria can be transmitted between hosts, which is causing a growing problem in society.

The main resistant bacteria in Sweden are Methicillin-resistant Staphylococcus Aureus (MRSA), Extended Spectrum Beta-lactamases (ESBL) and ESBL\textsubscript{CARBA}. After an outbreak in Gothenburg in 2001, the problem of MRSA and a developing resistance was apparent. Since then, national precautions have been taken and programmes developed in order to reduce transmission (Struwe, 2008). ESBL and ESBL\textsubscript{CARBA} are enzymes that bacteria produce, making them resistant to beta-lactam antibiotics. The ESBL\textsubscript{CARBA} has also developed a resistance towards carbapenems, making it even more difficult to treat (Smittskydd Stockholm a, b, 2015).

1.3 Research problem
The mechanisms developed to create resistance towards antibiotics are spread and maintained by the microorganisms themselves. However, it has been shown that irresponsible use of antibiotics has accelerated the rate of this development (Spellberg et al., 2008). To reverse this, a reduction of the distribution of antibiotics is needed to decrease the selective pressure on the bacteria (Sköld, 2006 p. 133). In an article from 2013, Björkman et al. state that

"The level of antibiotic use correlates to the level of antibiotic resistance; therefore, infection treatment guidelines promote rational antibiotic prescribing." (2013 p. 51),

which further stress the possible positive results on antibiotic resistance by reducing the use of antibiotics. Further, Neumark et al. (2007) show in a study that a “wait and see”-policy, to postpone the prescribing of antibiotics and see if the infection is fought by the patient herself, has been an efficient alternative to an immediate prescribing. This means that there are possibilities to decrease the prescriptions on antibiotics without jeopardizing the patient care.
Rifkind and Freeman (2005) also show that the need for attenuation of prescriptions is apparent in order to reduce and slow down development of resistance. A German study shows a successful reduction of antibiotic consumption by 50% through information about rational use in a hospital ward. Together with the reduction, a reduced mortality and less drug resistance was seen, suggesting the positive correlation between the variables resistance and reduction (Scholze et al., 2015). This also implies that increasing knowledge and handing out information also affect the handling of the antibiotics consumption (Scholze et al., 2015).

The hypotheses are that a reduction of antibiotic distribution and a rational usage of antibiotics can reduce antibiotic resistance.

In Sweden, the process to tackle the antibiotic resistance problem has been ongoing the last fifteen years, since the problem of resistance development was noticed (Folkhälsomyndigheten, 2014). One way to manage antibiotic resistance has been to work for reducing the usage of antibiotics in all health care sectors and to set a national goal to 250 prescriptions of antibiotics per 1000 inhabitants per year in outpatient care (Folkhälsomyndigheten, 2014). The implementation of this goal have reduced the prescription rates (Swedres-Svarm, 2014). Work has also been done to favour a use of narrow-spectrum antibiotics in hospital care (Swedres-Svarm, 2014). This might seem as a “living happily ever after”-ending, where such a successful implementation is the starting point for reducing antibiotics resistance. However, this is not the case. Looking at the data of MRSA, ESBL and ESBL_{CARBA}, the number of reported cases have increased radically over the last years, despite the successful decrease of prescription rates (Swedres-Svarm, 2014).

Earlier studies have been focusing on the correlation between antibiotic resistance and irresponsible usage, but research is still missing on the mechanisms affecting the situation. There have been several reports that have initiated action plans, where the focus lies upon quantitative results (Swedres-Svarm, 2014, Folkhälsomyndigheten, 2014). However, qualitative studies on how the work is done and how the guidelines are implemented are still missing and there exists a research gap concerning the human factor of the mechanisms affecting the situation.
To understand the contradiction, this study will investigate some of the aspects affecting antibiotic resistance and its management in Sweden. Accordingly, the study wishes to fill in the knowledge gap on the human factors affecting the usage of antibiotics in Sweden.

1.4 Research objectives and aim
The antibiotic resistance development has been scrutinised from different angles and subject areas, but research on human factor is yet missing. The aim of the study is to contribute to the knowledge base concerning factors affecting the antibiotic resistance management. It aims to look upon the issue from a broader angle using a multidisciplinary approach.

1.5 Research questions
1. Can the previously observed trends in antibiotic usage and resistance in Sweden between 2010-2015 be verified?

2. What does the management of antibiotic resistance in Swedish counties look like?

3. How can the discrepancy between the decrease in prescriptions and increase in number of reported cases of multidrug resistant bacteria be explained? What is the perception among health care workers at three different organisational levels?

4. What factors do health care workers find important for an improved management of antibiotic resistance?

1.6 Scope
The thesis will be geographically limited to three Swedish counties; Blekinge, Stockholm and Västernorrland. It will be limited in time to the years 2010-2015. The antibiotic resistance and transmission of resistance will only concern humans. Neither environmental transmission, nor transmission through livestock food production will be treated. Three types of multidrug resistant bacteria will be mentioned; MRSA, ESBL and ESBL-CARBA.
2. Background & Theory

2.1 Antibiotics and antibiotic resistance

There are two types of antibiotics; *narrow-spectrum* and *broad-spectrum antibiotics*. The narrow-spectrum drugs are focused on one type of bacteria. Broad-spectrum destabilises several types of bacteria and have a stronger effect, both on the bacteria and on the patient. Recommendation is to use broad-spectrum antibiotics with care, as they affect not only the invasive bacteria but also the natural flora of the patient (1177 Vårdguiden, 2016). Studies have shown that using broad-spectrum antibiotics selects for multidrug resistance (Dancer, 2001).

Antibiotics use different ways to destabilise bacteria and disable their functions. The working mechanisms can be divided into four groups, giving rise to different types of treatment; Alteration of the cell envelope (1), Inhibition of the protein synthesis (2), Inhibition with the nucleic acid synthesis (3) and Inhibition of a metabolic pathway (4) (SCENIHR, 2009). To all these working mechanisms, a corresponding bacterial resistance development has been seen.

The first way of action of the antibiotics is to perturb the stability of the cell membrane of the bacteria through excretion of enzymes that depolarise or disturb the bacterium during the construction phase of its membrane (1). This weakens the bacterial cell wall and enables the antibiotics to enter. Among these the beta-lactam antibiotics are found. In this group penicillin, cephalosporins and carbapenems are the most common. There are several types of penicillin, among them; beta-lactamase sensitive, beta-lactamase resistant and extended spectrum penicillin (Internetmedicin, 2016). The beta-lactamase sensitive penicillin, a narrow-spectrum antibiotic, has a good effect on gram positive cocci and a low risk for stimulation of resistance development. Beta-lactamase resistant penicillin is used for skin lesions and infections in soft tissue and is efficient against non-Methicillin-resistant Staphylococcus Aureus, the mother strain to the Methicillin-resistant Staphylococcus Aureus. Extended spectrum penicillin is used to prevent development of resistance and often consists of a combination of penicillin and other active substances (Internetmedicin, 2016). When several agents are used together, it increases the effect and makes it difficult for the bacteria to both survive and develop resistance (Sköld, 2006). Cephalosporins is a type of broad-spectrum antibiotic that work on several types of bacteria. It is most often used to treat urinary tract infections and skin lesions (1177 Vårdguiden, 2016). There are several generations of cephalosporins, as the target bacteria have developed resistance over the years (Sköld, 2006). Today, the third and fourth generations of
cephalosporins are used for more severe infections and the first generations used for milder ones (*Farmacevtiska specialiteter i Sverige* [FASS] a, 2016). Another type of beta-lactams are the carbapenems, which are used on several multidrug resistant bacteria and severe infections because of their broad spectrum. (Internetmedicin, 2016, Tängdén, 2007-2008). The corresponding bacterial resistance to beta-lactam antibiotics is beta-lactamase, an enzyme produced by bacteria. The enzyme hydrolyses the beta-lactam of the antibiotic, which deactivates the antibacterial effect of the beta-lactam antibiotic (Sköld, 2006).

Antibiotics can also interfere with the protein synthesis (2) or the DNA synthesis (3) and supress the proteins from developing within the bacteria or disrupting the nucleic acid synthesis, by causing breaks in the DNA-chain and thus make the replication impossible. Examples are tetracyclines and quinolones. Tetracyclines hinder the protein synthesis of bacteria and has a broad-spectrum effect on both positive and negative cocci. The tetracyclines are especially efficient against airway pathogens (Internetmedicin, 2016). Bacteria develop resistance to tetracyclines by creating a protein, *efflux protein*, which expels tetracyclines through efflux before it has reached its specific target within the cell. Bacteria can also develop proteins that bind to ribosomes¹ to hinder tetracycline from working. Quinolones are a group of synthetic antibacterial drugs, interfering with the DNA synthesis (Sköld, 2006). It works as a bactericide and has the most effect on gram negative bacteria. Resistance mechanisms can be found in the bacterial DNA that reprograms the bacterial proteins and make the quinolones unable to bind to them. As with tetracyclines, resistance through efflux is found with quinolones. The resistance among quinolones has developed fast and the recommendation is to use this group with restriction (Internetmedicin, 2016).

Inhibition of a metabolic pathway (4) is done through blockage of the folic acid synthesis. Folic acid is needed in the cell for the synthesis of nucleic acid and the antibiotics work by inhibiting the enzymes controlling the process (Sköld, 2006). Sulphonamide and trimethoprim are antibiotics of this type and are often used together (SCENIHR, 2009). This combination efficiently blocks two steps of the folic acid synthesis and using them together obstructs the possible development of resistance in a more proficient way than separate usage (*Farmacevtiska specialiteter i Sverige* [FASS], b 2016). Sulphonamide and trimethoprim have showed a good efficiency and have been used extensively. However, today resistance is very

¹ A cell component that forms amino acids and is crucial for the cellular protein synthesis (Albers et al., 2002).
common and sulphonamide is rarely used. Trimethoprim is more widely used, though resistance is increasing and its usage is at risk (Sköld, 2006). Different resistance mechanisms have been observed towards these antibiotics. One is mutation of one of the enzymes controlling the folic acid synthesis, which makes it more difficult for the sulphonamide to bind (Sköld, 2006). Resistance to both sulphonamide and trimethoprim have been observed after bacteria have received plasmid genes from other bacteria that code enzymes to destroy the antimicrobial agent before it has effect (Sköld, 2006, Rifkind & Freeman, 2005).

There are also bacteria that have become resistant to several types of antibiotics, the so called *multidrug resistant bacteria*. These are not recognized by a particular aggressiveness, rather that it is difficult to initiate an efficient treatment after an infection (Vårdhandboken, 2014). The Communicable Diseases Act (CDA) in Sweden, that aims to prevent spreading of disease, include 60 notifiable diseases and when encountered, it is obligatory by law to inform the authorities of the case. Among these, infections caused by antibiotic resistant bacteria are found, such as MRSA, ESBL and ESBL\textsubscript{CARBA}. Below follows a description of the resistant bacteria in focus in this thesis.

2.1.1 Methicillin-resistant Staphylococcus Aureus (MRSA)

MRSA is a type of staphylococci that have developed resistance to beta-lactam antibiotics, mostly penicillin, through production of beta-lactamase (Smittskydd Stockholm, 2013). Staphylococci cause lesions in soft tissue and skin infections, but also sepsis and other more invasive infections. The bacteria are present in carriers, generally in nose, pharynx and perineum, without symptoms and are transmitted through contact (Smittskydd Stockholm, 2013). Staphylococci is the most common pathogen causing nosocomial infections (Otto, 2013). One type of MRSA is the health care-acquired MRSA. Studies show that it is transmitted in health care environments through catheters and penetration of the mucus membrane and epithelial barrier, but also through infected objects and unsatisfactory hand hygiene (Weiner et al., 2016; Struwe, 2008). Another type, the community-acquired MRSA is spread between humans. Earlier studies have found different ways of spread, among them sexual transmission, transmission through parental contact with infected children and transmission within households (Knox et al., 2015). Studies also show that health care personnel might acquire community-acquired MRSA and transmit this in health care units (Krishnamurty et al., 2014).
If carriergship is proven in a patient, follow up tests need to be executed and rules of conduct be given to the patient (Smittskydd Stockholm, 2013). A patient carrying MRSA is obliged to inform care givers, dental and medical, and if hospital care is needed there are special hygiene rules that need to be followed to ensure that the MRSA is not to be transmitted further (Smittskydd Stockholm, 2013). The number of transmitted MRSA cases has been increasing over the last years and from 2010 to 2015 it had more than doubled, from 1580 in 2010 to 3886 cases in 2015 (Folkhälsomyndigheten “MRSA statistik”, 2016).

2.1.2 Extended Spectrum Beta-lactamases (ESBL) and ESBL\textsubscript{CARBA}
ESBL is not a bacterium itself, but one of the enzymes breaking down beta-lactam antibiotics and it has an extended spectrum towards several types of antibiotics, which makes it more difficult to treat. The enzyme is present among intestinal bacteria, normally Escherichia coli. They cause no harm when in their natural habitat, but can cause sepsis and urinary tract infections if displaced to other parts of the body (Smittskydd Stockholm a, 2015). Asymptomatic carriergship is common, but the problem arises when infection occurs and treatment with traditional antibiotics has no effect. Then broader antibiotics are needed. Cause of transmission is fecal-oral and ESBL can be transmitted through food, water and contact (Smittskydd Stockholm a, 2015). Colonies of ESBL-producing bacteria can be present, apart from in the intestines, in lesions, the urinary tract and respiratory tract, which increases the risk of contagion. (Smittskydd Stockholm a, 2015). Careful hygiene routines have been shown to have a preventive effect (Pelat et al., 2016).

ESBL\textsubscript{CARBA} is another type of bacteria-produced enzyme and apart from the resistance towards beta-lactam antibiotics, this resistance has also been developed to carbapenems. With ESBL\textsubscript{CARBA} there are few treatment options left today (Smittskydd Stockholm b, 2015). A Swedish articles showed in 2015 that the treatment of ESBL with carbapenems selects for ESBL\textsubscript{CARBA} (Adler et al., 2016).

The procedure after a diagnosed case of ESBL is an obligatory report by the laboratory to the Public Health Agency. With findings of ESBL\textsubscript{CARBA}, further actions are taken, such as contact tracing of the case (Folkhälsomyndigheten “ESBL”, 2015). Patients carrying ESBL and ESBL\textsubscript{CARBA} are not obliged by law to inform relatives or working place, but they are strongly recommended to inform care givers when treatment with antibiotics and/or in hospital is
needed. There are no accepted test methods today to prove a carrierrship terminated (Smittskydd Stockholm a, 2015).

The trend of ESBL is pointing upwards. In the last five years the number of ESBL cases have doubled to 9587 cases reported in Sweden in 2015 (Folkhälsomyndigheten “ESBL statistik”, 2016) and the numbers keep on increasing. ESBL-CARBA have also increased, but it is difficult to compare the numbers as the disease became notifiable in 2012 and before that, information was gathered voluntarily (Swedres-Svarm, 2014). However, there is a visible trend that both these types of enzyme-producing bacteria is an increasing problem in Sweden.

2.2 Factors affecting occurrence and spread of antibiotic resistance

There are several possible causes for development of antibiotic resistance. Use of antibiotics have been shown to be the highest risk factor for development of antibiotic resistance (Harbarth et al., 2001). An irrational use accelerates the resistance process, but only using antibiotics is enough to stimulate development of resistance, due to the process of evolution (Tegmark-Wisell, 2011). In general, it takes two years before resistance is noted (Sköld, 2006) and studies have shown that resistance has significantly increased in all groups of antibiotics since they were released on the market (Rhomberg & Jones, 2009; Gupta et al., 2011).

In numerous situations, antibiotics are used to treat viral infections, which has no effect as antibiotics do not work on viruses. Instead, bacteria develop a resistance through this unnecessary exposure and stays latent in the patient. If the patient later is subject to an infection, the usage of the same antibiotics might not have effect on the now resistant bacteria (Sköld, 2006). The same mechanism is present if treatment dosage is too low or time of treatment is shortened (ECDC, 2016). In these cases, susceptible bacteria within the host can acquire resistance from other bacteria carrying the resistant gene: it is transmitted (SCENIHR, 2009, Rifkind & Freeman, 2005). The lack of knowledge of suitable treatment and unnecessary treatments have been shown to contribute to resistance development (Taha et al., 2016, Mouhieddine et al., 2015).

Another reason for development of antibiotics resistance is the use of broad-spectrum antibiotics (Sköld, 2006). A study from 2005 show that in all Europe, the usage of broad-spectrum antibiotics has taken over from the more narrow-spectrum types (Goossens et al., 2005). This is also the trend in Sweden (Swedres-Svarm, 2014). Antibiotics are often prescribed before a resistance test can inform about a suitable choice of antibiotics. To cover
all possible outcomes, treatment with broad-spectrum antibiotics is initiated. When the
diagnosis is received, it might become apparent that treatment with a narrow-spectrum
antibiotic had been sufficient. (Spellberg et al., 2008, Sköld, 2006).

After resistance is developed, it is easily spread to other bacteria in numerous ways (Spellberg
et al., 2008). Studies have shown that resistant bacteria are present among food animal
populations (Lalak et al., 2016), and that they are transmitted to humans through the food
production chain (Aitken et al., 2016). Further, livestock production contributes to the
development through waste water released from animal farms or through the air around the
farms (Aitken et al., 2016). Additionally, it has been demonstrated that manure contains
resistant bacteria (Baker et al., 2016). Where spread over fields, the resistant bacteria can be
found in the soil (Aitken et al., 2016). Crops growing in these fields absorb the resistant
bacteria, which in turn is transmitted to the human intestine through food consumption (Centres
for Disease Control and Prevention, 2013). Research has also shown that ground water and
rivers polluted with waste from the pharmaceutical industry and hospitals become reservoirs
for antibiotic resistance. This can then be transmitted to humans through the hydrological cycle
(Bengtsson-Palme et al., 2014; Hocquet et al., 2016). See figure 2.1 for a more detailed view
of the transmission scheme. Among the different transmission patterns, this thesis will be
limited only to human transmission of multidrug resistant bacteria.
In a review from 2015, Russotto et al. describe several studies that show the risks of transmission of multidrug resistant bacteria within hospital environment. They argue for the risks of bacterially contaminated surfaces in intensive care units causing bacterial spread. This is done by health care workers that come in contact with these surfaces and then spread multidrug resistant bacteria between patients (Russotto et al., 2015). Further, hand hygiene of health care workers is an important aspect when it comes to transmission. Incomplete hygiene regulations contribute substantially to the spread of resistance when bacteria are brought from one patient to another (Russotto et al., 2015). This has been noted to cause outbreaks in hospitals (Struwe, 2008).

In the last decades, antibiotic resistance has become an increasing problem, as the development of new antibiotics has slowed down and the industry has failed to provide the market with antibiotics replacing resistant types (Livermore, 2011). As it became apparent that antibiotics cannot be taken for granted any more, there has been an ontological shift in the paradigm of
antibiotics. Resistance is no longer approached with new types of antibiotics, instead alternative ways of dealing with preventing resistance has been the practice.

Several approaches are used to manage the increasing antibiotic resistance. Studies have shown that a well implemented hospital hygiene praxis, especially concerning improved hand hygiene among hospital staff, reduces the transmission of multidrug resistant bacteria (Austin et al., 1999) as well as the use of single rooms (de Cellès et al., 2013). Studies have also shown that the most efficient way of managing a spread of multidrug resistant bacteria is to combine different hygiene strategies (de Cellès et al., 2013). Vaccination is also used in some cases, though the types of bacteria that can be vaccinated against are limited. Research is performed to develop a vaccine against infections with Staphylococcus aureus, but has so far not been successful (Selle et al., 2016), thus this way of management is yet to be developed. Also, improvement of the process of culturing bacteria causing infections has been shown to facilitate the choice of proper antibiotics for the infection in question (Someshwaran et al., 2016). One of the most recognized factors of antibiotic resistance management is to use antibiotics rationally (Björkman et al., 2013). As mentioned in the introduction of this thesis, the reduced use of antibiotics has shown to decrease the antibiotic resistance (Scholze et al., 2015) and there is a strong connection between using antibiotics and the development of resistance (Björkman et al., 2013).

Concerning the attitude towards antibiotics, a common perception is and has been that the demands from patients increase the prescription rates, but studies have shown this to be a misunderstanding between the health care personnel and the patient (Davey et al., 2002). Studies show that healthcare workers play an important role in the rational usage of antibiotics. They are part of the education system for the public and can by their actions inform the general public on the situation and reduce the ignorance that contributes to the resistance development (Taha et al., 2016, Mouhieddine et al., 2015). Studies also show that the general public in Sweden have high trust in rational prescription and knowledge about the resistance development (André et al., 2010). Therefore, a joined effort from both sides is needed to further strengthen a rational use of antibiotics (Taha et al., 2016).

The research done so far encircles the problem, but studies are missing on what factors of the management of the rational usage of antibiotics are important and how the health care
personnel and educators perceive the situation. This study aims to fill this knowledge gap and contribute to a deeper qualitative understanding.

2.3 Administrative units
The responsibility for antibiotic use in Sweden lies upon the Public Health Agency (Folkhälsomyndigheten, 2016). Their mission is to work for the preservation of usage of antibiotics, provide information on antibiotics and antibiotics resistance and to encourage work to promote a more responsible usage of antibiotics in Sweden (Folkhälsomyndigheten, 2016).

The overall Swedish health care is the responsibility of the Swedish counties. There are 20 counties/regions that are responsible for the health care system within each geographic area (Sveriges Kommuner och Landsting [SKL], 2016). Since 2011 the Patient Safety Investment has been enrolled, an agreement between the Swedish State and the Swedish Association of Local Authorities and Regions (SKL), that was made to improve and guarantee safety for patients in all counties in Sweden (Folkhälsomyndigheten a, 2014). In this agreement, the Swedish counties were assigned to reduce the prescriptions of antibiotics and make sure to follow treatment recommendations concerning infections. This assignment remains with the counties, which are also helped by Strama; the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance, which operates the management of antibiotic usage in Sweden (Folkhälsomyndigheten a, 2014).

The Strama network was founded in 1995 to cover the need for a nationally coordinated initiative to work for prevention against antibiotics resistance (Strama, 2016). Strama has two levels; regional and national. At regional level, local Strama groups work within the counties in close collaboration with the County Medical Officers for Communicable Diseases Control. These local groups work closely with the Public Health Agency in Sweden and have also a well-developed network with each other for cooperation (Strama, 2016). On national level, Strama is working as a steering group, the “Strama Council”, incorporated in the Public health Agency and should work as advisory to the agency (Strama, 2016). The overall mission of Strama is to work for a multisectorial way to coordinate issues on keeping an efficient usage of antibiotics and to propose measures to protect human health in Sweden (Strama, 2016).

As mentioned above, studies have shown that education of health care personnel play an important part in using antibiotics responsibly (Taha et al., 2016, Mouhieddine et al., 2015).
Strama has embraced this in the management of antibiotic resistance as education of health care personnel and development of guidelines and praxis concerning the rational usage of antibiotics. Studies have also shown that the attitude of the general public affect a rational antibiotics usage (Taha et al., 2016), and Strama therefore also work on informing the general public about the issue of antibiotic resistance.

2.4 Risk theory
To the extent that it is relevant, the findings of this study will be connected to risk theory. Antibiotic resistance is a problem and means a risk; the risk of antibiotics not being an efficient treatment on harmful bacterial infections (Sköld, 2006, Centres for Disease Control and Prevention, 2013). Handling the development of antibiotic resistance is a form of risk management, which is a part of risk theory. This section will outline the theory, derived from the works of Ortwin Renn, who has developed the theory of risk governance and summarised risk analysis in the book Risk Governance (Renn, 2008). First the concept of risk management will be explained and then focus will be put on risk communication and risk perception. As the research questions of this thesis stress the human factors behind the management of antibiotic resistance and want to study the perception among health care personnel, these two themes were chosen due to their resembling role in risk theory.

Analysing the risks of a scenario is a helpful and necessary tool to reduce eventual damage and increase the chances of a positive outcome (Renn, 2008). Risk governance covers the process of handling risks, including communicating them to the public. Renn (2008) divides this into four phases; pre-assessment, appraisal, characterization/evaluation and management, all intertwined with communication, see figure 2.2 below.
Firstly, pre-assessment of risks consists of the identification of a potential risk, based on knowledge of the hazard, and also early warnings and monitoring. Second, the appraisal phase is where the risks are assessed scientifically to identify possible risks for human health or the environment. Research is important in this phase and the outcome is probability rates and modelled scenarios. In epidemiology, the probability is based on the correlation between exposure and effect, in this case, use of antibiotics leading to resistance. Characterization/evaluation calculates the tolerability and acceptability of the risk and last, management is the phase where strategies are developed to manage the calculated risk. The management have three starting points; the assessment on whether the risks are intolerable, tolerable or acceptable. From these points, the management is developed in different directions. The intolerable risks are those where most prevention is needed and the management can take on its course of action. Different risks generate different management strategies (Renn, 2008) and as antibiotic resistance is intolerable, this is the starting point for the management.

2.4.1 Risk communication
To coordinate the four phases, communication of the risks is a central part of risk assessment (Renn, 2008). The original aim of risk communication is to create a bridge between the public and the experts to reduce uncertainties and promote mutual understanding (Figure 2.2). As described in Risk Governance;
“[…] risk communication stresses a two-way communication process in which it is not only the members of the public who are expected to engage in a social learning process, but the risk managers as well. The objective of this communication effort is to build up mutual trust by responding to the concerns of the public and relevant stakeholders in understanding the rationale of risk assessment results and risk management decisions, and to help the arrive at a balanced judgement that reflects the factual evidence about the matter at hand in relation to their own interests and values.” (Renn, 2008, p.202).

There are four functions of risk communication listed by Renn;

1. **Education and Enlightenment:** Information to the audience on risk and management
2. **Risk training and inducement of behavioural changes:** Help to cope with risks
3. **Creation of confidence in institutions responsible for the assessment and management of risk:** Give the assurance that the structure is able to handle risk efficiently.
4. **Involvement in risk-related decisions and conflict resolution:** Include stakeholders in the risk management process. (Renn 2008, p. 203).

The communication process consists of two parts; first, the internal communication communicates risks to those involved in the governance framework. Here it is crucial that everyone who is involved understands the situation and their involvement and responsibilities. Secondly, in the external communication, those outside the direct involvement of the process need to be informed and involved in the process (Renn, 2008). Close communication is essential for an efficient risk governance. The efficiency of the external communication has a big impact on the general public’s perception on risk and the amount of knowledge in society is crucial for the whole risk governance framework. An insufficient risk communication can lead to big consequences in situations where correct information is crucial.

Communication can be done in different ways; four forms have been distinguished in earlier studies (Renn, 2008). **Documentation of risk information**, which opens for a transparency towards society, **Information**, clarification on the issue for the partner on the other side of the bridge, **Mutual dialogue**, implying two-way communication not only for education but also mutual understanding and dialog, and **Mutual decision-making**, inclusion of stakeholders from different parts on decisions concerning the risks (Renn, 2008).
2.4.2 Risk perception

Different groups have different concepts of risk, which poses a challenge in the risk governance process (Renn, 2008). Risk perception is not always connected to facts or very rational, rather it is based on personal experiences, fears, traditions and uncertainties. It is indeed a subjective factor. Knowledge and the feeling of control, increases the perception of a risk to be less threatening, whilst uncertainty and lack of control have the opposite effect (Renn, 2008). When receiving risk information, the ability and motivation to process the information plays a big part. Ability concerns the possibility of following a message and motivation concerns the interest to process the information. For these two conditions to be met, there is a need for the information to be available, there needs to be time for the receiver to process the information and it needs to be relevant and to concern the personal interests of the receiver. How these factors intertwine and are available, affect the way a person processes the information and what their perception will look like.

Perception and probability of risk are not necessarily the same, which highlights the “bridge”-function of risk communication even more as it is needed to balance the ideas and attitudes on the one hand and the actual probability for a risk occur on the other hand (Renn, 2008).
3. Methods and methodology

This thesis is a multidisciplinary study based on quantitative and qualitative data. The base was formed by statistics of antibiotic usage and resistance in Sweden. Data calculations with statistical analyses were executed to ensure significance and also served as take-off for interviews.

3.1 Methodology

The methodology for this thesis took off from a post-positivist approach and investigates the relationship between variables. Post-positivism is often applied by social scientists to investigate social values from a natural science perspective (Denscombe, 2009), which fits this thesis well. Post-positivism is a hypothetico-deductive method that through observations seeks to falsify the hypothesis (Hartman, 2004). The base is the standing possibility to falsify hypothesis and generate new ones in order to push science further (Hartman, 2004). This rational hypothesis testing with a deductive onset suited the method of this thesis and placed it in a multidisciplinary field. This methodology is applicable on both the quantitative and qualitative part.

3.2. Data calculations and statistical analyses

Data was taken from the Public Health Agency of Sweden and the network Strama. These organizations publish data on antibiotic resistance, prescriptions and hospital requisitions of antibiotics and the number of cases of infected patients with different multidrug resistant bacteria. The reported data on the cases of multidrug resistant bacteria was originally gathered from the database SmiNet. The Swedish pharmacies provide data on prescriptions and requisitions. The analyses were carried out on data ranging over five years, from 2010 to 2015, with exception of ESBL-CARBA, which only started to be reported in 2012, and therefore has data from fewer years.

All changes in number of prescriptions and incidence of multidrug resistant bacteria were analysed with linear regression (CI 95 %, p < 0.05) using the software R (R Core Team, 2016).
3.3 Interviews

The second part of the study was qualitative interviews, which were used as a research instrument rather than a social practice and the data was seen as a resource used in analysing the issue of antibiotic resistance (Brinkmann & Kvale, 2014). Dalen (2011) expresses the use of interviews as method as either being the main method to gather knowledge, or to use it together with other methods in order to complete the material, which motivates the choice of the quantitative and qualitative approaches.

Interviews were carried out in three Swedish counties, selected on grounds that appeared after calculations were done. The aim was to get a spread of conditions; one had the highest decrease of prescriptions, one was selected for its vast urban areas and one for its closeness to the national mean of decrease. In each county three interviews were conducted on two levels of health care; outpatient and hospital care, to get a deeper insight into the situation behind the data, and with three representatives from Strama. In total, nine interviews were executed.

As the professionals were few, there was no need for a particular selection strategy to find interviewees (Dalen, 2011). Instead, the Strama representatives were contacted and asked about participation. Then snowball sampling or random contact from the interviewer was used to find other respondents in the health care sector. The interviews were semi structured and conducted in person or over video link. The aim of the interviews was to reach a further understanding of the management of antibiotic resistance in the counties and shine light on the qualitative factors behind the data.

Adequate knowledge is needed to approach interviews from the onset of the thesis and valid questions are essential in order to get the sought answers (Brinkmann & Kvale, 2014). Therefore, the researcher did a thorough literature review and executed the quantitative analyses before carrying out the interviews. Another reason for this order was to create a conceptual framework before implementation (Brinkmann & Kvale, 2014).

Before the interviews, an interview guide was developed, based on the literature review. The questions were carefully scrutinised in order to avoid leading questions. There was a focus on an open introduction to the interviews, with questions about the professionals’ roles and perceptions. Further, the interviews were directed at the subject of antibiotics and the resistance work in the county. At the end, the interview was opened up for a more general view of the
subject, which hopefully served to fill eventual gaps (Dalen, 2011). The interviews were recorded and transcribed by the researcher for a better knowledge of the material, which gives a basis for a thorough analysis (Dalen, 2011). The interviews were executed in Swedish and the interview guides were translated to English before attached to the thesis, see Appendix 1. The quotes of interest were translated to English before included in the results section. For the analyses of the interviews, publications by Dalen (2011) and Brinkmann & Kvale (2014) were used for reference.

Concerning ethics, there was no need for applications concerning sensitive interviews, as the academic level of this thesis is not covered by the legislation around the need for ethical approval (Etikprövningsnämnden, 2016). However, it is still important to consider the ethical factor of the interviews. The Swedish Research Council has published a set of principles concerning research in the social science field. The aim of this publication is to support the researcher in making the appropriate decisions concerning ethics during the research process (Vetenskapsrådet, 2002). The Research Council summarises its principles into four requirements that are considered important during research; information requirement, consent requirement, confidentiality requirement and requirement of use (Vetenskapsrådet, 2002).

To fulfil the information requirement, the respondents were thoroughly informed about the study, both in the initial contact by e-mail or telephone and additionally at the actual interview situation. They were informed that their participation in the study was voluntary and reassignment from the interviews was possible at any time. Requirement of consent was reached when the respondents agreed to the interviews, either orally or in written. The importance of the confidentiality requirement is perhaps not as heavy as in more sensitive studies, though the records used by the researcher were treated with care. The result section of the thesis was coded and anonymised to hide the identities of the participants. The requirement of use means that the information received through the interviews will not be used in any other context but this study. All these requirements were communicated to the respondents (Vetenskapsrådet, 2002).
3.4 Method discussion

The validity and reliability of the interviews that are discussed in this section are based on frameworks found in the publications by Brinkmann & Kvale (2014) and Dalen (2011).

Interviews were used as method to get a deeper understanding of the factors behind the data. The statistical analyses provided the study with a baseline from which research questions could be formulated. Interviews were the next step to dig deeper and possibly find the influencing qualitative variables behind the data. Research questions were formulated before the execution of interviews, but during the interview procedure, other angles of the situation came forth. The study could then adjust its focus and encircle the problem. The choice of interviews showed to be a valid method, as for instance a sent out questionnaire would never recognise these changes and the interviews did prove to measure the actual focus.

A test interview was performed with a respondent in hospital care to clarify the interview guide. This lead to the adjustment and adding of some questions, to better encircle the aim of the interviews. Seven interviews were carried out in person and two interviews performed via video link. This is considered to have the same validity level as interviews carried out in person and there was no difference in quality between the different types of interviews. Choosing the three respondents from Strama needed no particular selection procedure and the bias to be dealt with is marginal. However, the snowball sampling in this case should be discussed, as some respondents in outpatient and hospital care were named by Strama representatives. This sampling method was chosen due to limited time, despite the risk of it giving a skewed sample. The respondents in outpatient and hospital care named by Strama representatives could have a bias in their opinions by favouring Strama. However, firstly, as the study did not investigate the attitudes towards Strama, but rather the local way of working, this is not a major error. Secondly, the answering pattern was the same with those chosen through snowball sampling and through personal contact made by the researcher. Thirdly, as this study is small and serves to enlighten the situation and open for further studies, the findings of this study should not be taken as proven truths, but rather a door-opener for future studies.

In all interview situations, there is a possible personal bias from the researcher, also in this case. To limit this, the interview guide was specifically designed to avoid leading questions, but in the cases where the respondent seemed confident in the situation, leading secondary questions were used to guide the respondent into the field intended by the initial question. This
was only used to help keep the respondent at the subject. Personal bias was also checked for in the test interview.

All interviews were recorded and the transcriptions were done continuously so that as little time as possible would pass between the event and the processing of the text and least memory bias of the researcher would occur. The interviews were then coded and read through systematically several times. The material was then color-coded to the different research questions and then analysed. For the last question, the themes were identified and then all quotes connected to the themes were put together.

3.5 Data discussion
The data constituting the first part of the thesis is based on reports received from SmiNet, the data base for national surveillance of communicable diseases under the Communicable Disease Act (CDA). Physicians and laboratories report to the database and the data is compiled by the Public Health Agency (SmiNet, 2016). Possible errors in the reporting rate can occur due to the human factor of missing to report cases. Still, SmiNet is the best option for surveillance and even if bias is present, the data from SmiNet is clear enough to show trends, which is what was needed for this thesis.

3.6 Source criticism
Denscombe (2009) stresses the importance of a continuous evaluation of the sources used in a literature review and emphasises the challenge to use secondary data as the original source is not always known. In the section the sources will be criticised by group and evaluated.

3.6.1 Printed material
The used publications are all published in the 21st century and several among them have upgraded editions, which is a good sign for the researcher as the potential faults are removed and deprecated. Several of the books on methods and methodology have been used in University education and approved for courses on advanced level. To get the most updated information from recent research, the articles used to frame the research problem and previous research are published in the last 20 years. All articles have been published in scientific journals and several are peer-reviewed.
3.6.2 Web based sources
Web-pages referred to have all been considered well and made sure to be recently updated (Denscombe, 2009). The web sources 1177 Vårdguiden, Folkhälsomyndigheten and Smittskydd Stockholm are organised by the authorities in Sweden to inform the general public and help health care personnel by publishing guidelines. Vårdhandboken is managed by the counties and regions in Sweden and publish health care guidelines. Centres for Disease Prevention and Control is the United States’ equivalent to the Swedish Public Health Agency and is an internationally renowned instance for issues on infectious diseases. It is always in the interest of governmental institutions and authorities to provide information that suits their interests (Leth & Thurén, 2000), which makes it important to check the quality of the information. The information provided on these pages can all be verified through other sources. The PDF-file on assessment of the antibiotic resistance is published by the European Commission and has a high credibility. Other PDF-files have been published by practitioners in the field of antibiotic resistance and are used as fact-base. One is a report on carbapenems and one a presentation on how antibiotics resistance is spread and both have been used in educational purposes. Leth & Thurén (2000) express that it is important to validate facts through two or more independent sources. What is written in these presentations can be confirmed on the websites Internetmedicin.se and FASS.se; two web portals developed for health practitioners in the Swedish Health care system.
4. Results

4.1 Research question 1

Can the previously observed trends in antibiotic usage and resistance in Sweden between 2010-2015 be verified?

In 2011 the national project Patient Safety Investment was initiated by the Swedish Association of Local Authorities and Regions (SKL) in order to decrease the number of prescriptions of antibiotics in Sweden. However, the problem of resistance remains and the number of cases of multidrug resistant bacteria are increasing. In this section, data trends and calculations of antibiotic usage and resistance will be presented and analysed statistically to answer the first research question.

The number of prescriptions of antibiotics has decreased significantly in Sweden over the last five years (b = -15.34, p = 0.001, R² = 0.946) (Figure 4.1, Figure 4.2). The numbers are lower in all counties in 2015 than in 2010.

![Number of prescriptions per 1000 inhabitants in Sweden 2010-2015](image)

**Figure 4.1** The number of prescriptions per 1000 inhabitants in Sweden.
The recognised decrease of prescriptions is a premise for testing one of the set hypotheses for this thesis; that a reduction of antibiotics distribution reduces the antibiotic resistance.

Looking closer at county level, the decrease in prescriptions per 1000 inhabitants between 2010 and 2015 was calculated in percent (Figure 4.3).

**Figure 4.2** The number of prescriptions per 1000 inhabitants in Sweden per county.

**Figure 4.3** The decrease of prescriptions per 1000 inhabitants in percent per county.
Västra Götaland and Blekinge show the biggest changes among the counties, where the prescriptions have decreased with more than 25% between 2010 and 2015 (Figure 4.3). On the other end of the figure, the counties of Örebro and Värmland show a decrease of less than 10% in the five years accounted for. The national mean shows a decrease of just above 20%.

The above data covers only antibiotics distributed by prescriptions in outpatient care. In Swedish hospitals the situation is different. Table 4.1 and figure 4.4 show the changes in use of a number of antibiotic groups often used within hospital care in daily defined doses (DDD)/100 patient-days in Swedish acute care hospitals. The use of all groups have increased, except for the cephalosporins, which show a small decrease, however not statistically significant. The use of combinations of penicillins has almost doubled, mainly due to the need for combining several antibiotics to tackle the rising resistance (Swedres-Svarm, 2014). This group, together with the carbapenems and the beta-lactamase resistant penicillins, is supposed to replace the cephalosporins. There is a significant increase of the antibiotic groups used in acute care hospitals ($b = 1.96$, $p = 0.001$, $R^2 = 0.975$) (Table 4.1, Figure 4.4).

### Table 4.1

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betalactamase resistant penicillins (J01CF)</td>
<td>10.9</td>
<td>11.3</td>
<td>12</td>
<td>13.1</td>
<td>13.5</td>
<td>**</td>
</tr>
<tr>
<td>Betalactamase sensitive penicillins (J01CE)</td>
<td>6.7</td>
<td>7.2</td>
<td>7.6</td>
<td>7.6</td>
<td>7.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Fluoroquinolones (J01MA)</td>
<td>6.1</td>
<td>6.2</td>
<td>6.3</td>
<td>6.6</td>
<td>6.9</td>
<td>**</td>
</tr>
<tr>
<td>Cephalosporins (J01DB-DE)</td>
<td>7.1</td>
<td>6.8</td>
<td>6.7</td>
<td>7.1</td>
<td>6.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Combinations of penicillins (J01CR)</td>
<td>3.3</td>
<td>3.8</td>
<td>4.4</td>
<td>5.5</td>
<td>5.9</td>
<td>**</td>
</tr>
<tr>
<td>Carbapenems (J01DH)</td>
<td>2.5</td>
<td>2.6</td>
<td>2.7</td>
<td>3.0</td>
<td>3.1</td>
<td>**</td>
</tr>
<tr>
<td>Aminoglycosides (J01GB)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
<td>N.S.</td>
</tr>
<tr>
<td>TOTAL</td>
<td>37.7</td>
<td>39.1</td>
<td>41</td>
<td>44.1</td>
<td>45</td>
<td>**</td>
</tr>
</tbody>
</table>
The other hypothesis concerns a few of the multidrug resistant bacteria in Sweden. The trends show that the number of patients infected with one of the three different types of multidrug resistant bacteria, MRSA, ESBL and ESBL-CARBA, are all increasing. In figure 4.5 the data on ESBL and MRSA are displayed: ESBL is reaching an incidence almost twice as high in 2015 as in 2010 and MRSA shows a more than doubled incidence in 2015 compared to 2010.
There was a significant increase for the number of MRSA cases \( (b = 4.196, p = 0.002, R^2 = 0.923) \) and for the number of ESBL cases \( (b = 9.388, p < 0.001, R^2 = 0.975) \), per 100 000 inhabitants 2010-2015.

Figure 4.6 shows the number of reported ESBL\textsubscript{CARBA} cases per inhabitants. There is a significant increase in the number of new cases \( (b = 0.491, p = 0.037, R^2 = 0.928) \) during the four years of given data.
In summary, the number of prescriptions of antibiotics in outpatient care in Sweden show signs of decrease in the last five years. Within hospital care, a significant increase of several groups of antibiotics could be observed. The use of combinations of penicillins, beta-lactamase resistant penicillins, fluoroquinolones and carbapenems have increased. Concerning multidrug resistant bacteria, the number of patients in Sweden infected with MRSA, ESBL and ESBL CARBA have all increased significantly.

The results in section 4.1 raise many questions. To further analyse some of them, three Swedish counties were chosen for closer study. Blekinge was chosen on the grounds that they had one of the highest decreases of prescriptions between 2010 and 2015 (see figure 4.3). The county of Västernorrland was chosen as they with their decrease of 17.33 % were fairly close to the national mean of a decrease of 20.74 %. The county of Stockholm was chosen because of its conurbation and being the county of the capital of Sweden. In the three counties, health care workers in three different levels were selected; from outpatient care to get a deeper insight into the prescription situation, from hospital care for a closer look at the changes in usage of antibiotics in inpatient care and lastly one person responsible for the national initiative Strama in the county.
4.2 Perceptions among health care workers concerning antibiotic usage and resistance
The respondents of the study are anonymous and the presentation of results is encoded (Table 4.2).

Table 4.2 Showing the coded respondents.

<table>
<thead>
<tr>
<th>County</th>
<th>Respondent Group</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>County 1</td>
<td>Outpatient care</td>
<td>R1, Outpatient care</td>
</tr>
<tr>
<td></td>
<td>Hospital care</td>
<td>R1, Hospital care</td>
</tr>
<tr>
<td></td>
<td>Strama</td>
<td>R1, Strama</td>
</tr>
<tr>
<td>County 2</td>
<td>Outpatient care</td>
<td>R2, Outpatient care</td>
</tr>
<tr>
<td></td>
<td>Hospital care</td>
<td>R2, Hospital care</td>
</tr>
<tr>
<td></td>
<td>Strama</td>
<td>R2, Strama</td>
</tr>
<tr>
<td>County 3</td>
<td>Outpatient care</td>
<td>R3, Outpatient care</td>
</tr>
<tr>
<td></td>
<td>Hospital care</td>
<td>R3, Hospital care</td>
</tr>
<tr>
<td></td>
<td>Strama</td>
<td>R3, Strama</td>
</tr>
</tbody>
</table>

4.2.1 Research question 2
What does the management of antibiotic resistance in Swedish counties look like?

In general, the counties are similar in that they all follow the national guidelines, at all three levels; hospital care, outpatient care and in the Strama groups.

The respondents from hospital care have similar comments concerning management. Notable parts are hospital hygiene and the usage of antibiotics in inpatient care. In terms of hospital hygiene, all respondents have an awareness around hygiene and follow the same praxis:

“For ESBL there’s a new update of the care programme [...] that says that you should have single rooms if you have catheter, skin lesions or diarrhoea” (R1, Hospital care)

“The access to single rooms and the personnel’s...well, the hygiene in general, matters” (R2, Hospital care)

“We work with infection control in all different levels, from how we dress to how the cleaning is done and how our facilities are built” (R3, Hospital care)
Another area is the usage of antibiotics and the struggle to use narrow-spectrum antibiotics, rather than broad-spectrum. One respondent says ironically that “our house wine is Claforan” (R2, Hospital care) and that it is important to use the narrow-spectrum antibiotics. “One has to think actively about using benzylpenicillin together with Gensumycin... I mean, it’s convenient to use Claforan instead”. Another respondent says that “Even though we still use Claforan to a too large extent, at least we are able to narrow it down” (R1, Hospital care).

The struggle to use narrow-spectrum antibiotics can be found in all three hospitals and has its base in the national guidelines from Strama, expressed by a Strama representative like this; “We have guidelines for inpatient care [...], guidelines that say; often narrow, narrow-spectrum antibiotics” (R3, Strama).

Several of the respondents in inpatient care connect the struggle to use narrow-spectrum antibiotics to the Infection tool. This is a plug-in included in the journal system in order to prevent nosocomial infections and reduce the use of broad-spectrum antibiotics. When physicians prescribe antibiotics, warning signs and questions for justification of prescribing that particular type of antibiotics appear on the computer screen to raise the awareness among health care personnel. The tool has been used in some counties; “The Infection tool was introduced a while ago and now we are working with it” (R3, Hospital care) and “then we have the Infection tool, which we were early to use” (R1, Hospital care).

The same similarities are found in the outpatient care. Here, the respondents describe that they have local strategies in their health care centres, which are all based on the national guidelines found in the Rainbow-brochure, published by Strama. They all answer that the reason for fewer prescriptions of antibiotics among children are the national guidelines about not prescribing penicillin for otitis (“if you look at general infections among children that demands antibiotics, otitis is one of them and there we have reduced the prescriptions” [R1, Outpatient care]). Further, the respondents are aware of the goal to reduce prescriptions of antibiotics to 250 per 1000 inhabitants and year and all work to reduce their own prescription patterns (“I prescribed too much of this and of that and I’ve had to learn and rethink a little”}

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2 A type of cephalosporin, a broad-spectrum antibiotic with high selectivity for antibiotic resistance.
3 A narrow-spectrum antibiotic mixed with an aminoglycocide. Not resistance selective as the cephalosporins.
4 National treatment guidelines on the most common bacterial infections in outpatient care.
5 Inflammation/infection of the ear
Another respondent says “It sounds like I think that I’m great at prescribing narrow antibiotics, but I really try to be narrow. And then of course, sometimes you have to prescribe something else, but then I think it’s important to motivate that choice in the patient’s journal, why you chose something that’s not recommended” (R3, Outpatient care).

The interviews with the Strama representatives show the same pattern and also stress the fact that since Strama is a national collaboration, the routines and guidelines should in fact coincide. The three respondents say individually “We are a part of the Strama network…and participate at the Strama day” (R3, Strama), “There was a need for a long-term plan and a need for a national gathering and so Strama was formed” (R2, Strama) and “those in the leading positions in the different Strama groups in Sweden are keeping this network together” (R1, Strama).

A quote from one of the respondents from Strama sums up the situation; “I mean, we work in a very similar way in the whole country, it’s just that we are at different stages. We need to adjust our way of working depending on the conditions, some have huge catchment areas that they can’t handle and some haven’t even started, or started too late and didn’t receive the necessary economic means and so on. So of course we are at different levels, but I think the tendency to work in the same way; paying visits to health care centres, present statistics, the feedback…I mean, everyone has realised that it is in this way we need to work.” (R3, Strama).

In summary of the second research question it can be said that the health care workers in all counties follow the same guidelines and national praxis concerning hygiene and antibiotics usage. The Strama representatives all report the same way of working and nothing substantial is deviating from this. All levels aim for the same goals; to choose narrow-spectrum antibiotics to the extent that it is possible and to reduce the number of prescriptions.

6 A conference for Strama representatives held each year to strengthen the bonds between the Strama groups
4.2.2 Research question 3

How can the discrepancy between the decrease in prescriptions and increase in number of reported cases of multidrug resistant bacteria be explained? What is the perception among health care workers at three different organisational levels?

All respondents explain the discrepancy between the decrease in prescriptions and increase in reported cases of multidrug resistant bacteria in similar ways, found in table 4.3.

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1, Outpatient care</td>
<td>“That has to be imported cases, we’re out travelling and pick up things.” “Then, if you think about the streams of refugees coming now, from areas where they’re very generous with prescriptions and there’s a problem with resistance.”</td>
</tr>
<tr>
<td>R2, Outpatient care</td>
<td>“This migration right now, we haven’t seen it before and a lot of people come from areas where antibiotics have been overused.” “A lot can be explained by import.”</td>
</tr>
<tr>
<td>R3 Outpatient care</td>
<td>“We haven’t been affected the most, but I think of all the refugees that have arrived.”</td>
</tr>
<tr>
<td>R1, Hospital care</td>
<td>“I feel quite convinced that the biggest reason by far is travelling and that the bacteria one picks up abroad today are resistant to a further extent”</td>
</tr>
<tr>
<td>R2, Hospital care</td>
<td>“We have a migration where we see that the immigrants bring with them multidrug resistant bacteria and specific infections.”</td>
</tr>
<tr>
<td>R3, Hospital care</td>
<td>“We have an inflow of migrants, that carry these contagions, then it doesn’t matter if we reduce our use of antibiotics.”</td>
</tr>
<tr>
<td>R1, Strama</td>
<td>“Of course, if you’re aware that you should take samples for these things, you might also take more samples.” “We import a lot of resistant bacteria, especially ESBL. A lot of people travel abroad and arrive home again as ESBL-carriers.”</td>
</tr>
<tr>
<td>R2, Strama</td>
<td>“There’s a pressure from the outside world that brings in... and asylum seekers that arrive, with tourism, even more with tourism than with asylum seekers.”</td>
</tr>
<tr>
<td>R3, Strama</td>
<td>“It’s about imported cases and Swedes going abroad and receive health care.” “But I also think that the reason to why the numbers are high is that we in the last two years have been trying to screen for multidrug resistant bacteria to a bigger extent.”</td>
</tr>
</tbody>
</table>

Table 4.3 Showing the different expressions from the respondents on the discrepancy between the decreasing prescriptions and increasing number of cases of multidrug resistant bacteria.

The quotes in table 4.3 show that all respondents indicate migration and immigration together with an extended travelling pattern among Swedes to be the reasons behind the increased number of multidrug resistant bacteria in Sweden. A few mention that they screen for these bacteria to a greater extent today and say that it might be another reason behind the increasing number.
Respondents from all counties report that they have noticed an increase in the number of reported cases of multidrug resistant bacteria, especially the extended spectrum beta-lactamase (ESBL). One respondent says that it is not a new phenomenon; “I think I’ve come across this regularly for quite many years now” (R1, Outpatient care). The rest affirm the increase with statements like “We have seen that ESBL has indeed increased” (R2, Hospital care) and “You come across ESBL and that’s something you didn’t before so in that way it’s an increase [...] I can’t say that I personally have noticed an evident increase of VRE and MRSA, a part from that they appear in more places nowadays, but concerning ESBL it’s an obvious increase” (R1, Hospital care). They also comment the discrepancy itself; “If we hadn’t decreased the prescription the problem would have been even bigger.” (R3, Hospital Care). The Strama representatives have another angle:

“It’s just a way to slow down the process [...] It’s a pity, there’s a lot of politicians and administrators and, well, the occasional colleague, that believe that we with these efforts will see decreasing resistance curves, but that’s not the case” (R2, Strama)

“We’re saying that this thing with decreasing the prescriptions of antibiotics will not decrease the resistance, I mean, it won’t decrease. It’s about slowing down the progression so to speak” (R3, Strama).

“We continue working [...] and we’re very aware of the problem.” (R1, Strama)

The respondents in the outpatient care-group all work for decreasing the usage of antibiotics at their respective health care centres. In hospital care, respondents agree on the importance of trying to stick to narrow-spectrum antibiotics in treatment; “I think we’re more directed towards trying to give less broad-spectrum treatments and put more focus on the results from the bacterial cultures and use them as guidelines in the course of treatment” (R2, Hospital care). They also describe the difficulties in trying to stick to the narrow-spectrum antibiotics. R1 in hospital care express it like this;

“Interviewer: Is it about a fear to make mistakes?
Respondent: Absolutely, I mean, it’s real safe to prescribe something that covers almost everything”

Another respondent has the same perception; “If you go in too narrow, you can miss your focus and then you’ve lost tempo and bed-days, so it’s not so easy” (R2, Hospital care). A respondent from Strama answers the question why broad-spectrum antibiotics have increased in hospital
care, whereas narrow-spectrum has decreased; “In hospitals they care for patients with worse infections. It’s easier to go narrow in the outpatient care where people come with trivial infections. It’s harder not to be broad in hospitals.” (R1, Strama).

In hospital care focus is upon trying to use the “right” antibiotics. Secondhandely, it is about decreasing the usage. One respondent says “You have to change the habits of the way people behave and not always prescribe Cefotaxim as a reflex” (R1, Hospital care). Another confirms and adds: “The only reasonable thing is to use less antibiotics and use directed antibiotics on the right infections.” (R2, Hospital care). The respondents at the hospitals also stress that their use of antibiotics is not included in the statistics of prescriptions, as they use antibiotics on requisition sales.

To summarise the base for answering question three; all respondents indicate migration and immigration together with an extended travelling pattern as explanations to the increasing number of patients infected with multidrug resistant bacteria in Sweden. They report consistently that they all have seen an increase in these bacteria, especially ESBL. Concerning the discrepancy, the Strama representatives express that the main goal is to reduce the pace of the rise in patients infected with multidrug resistant bacteria, not turning the trend around. All respondents agree that to keep the antibiotics usage rational is a difficult task and believe that the fear of using a narrow-spectrum antibiotic that might not cure the patient or not give patients care that is good enough, make them use more broad-spectrum antibiotics.

4.2.3 Research question 4
What factors do health care workers find important for an improved management of antibiotic resistance?

Two major factors were found among the respondents’ answers concerning the management of antibiotic resistance: Education/Knowledge and Discussion.

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7 The active substance in Claforan, a broad-spectrum cephalosporin.
8 The 250-goal for prescriptions only includes prescriptions from outpatient care. However, the data on the usage of antibiotics in Swedish healthcare does include all types of distribution.
“Education/Knowledge”

Respondents in outpatient care all testify that the attitude among patients towards antibiotics have changed to a more cautious view through more knowledge, which simplifies the process of a more rational usage of antibiotics. They express it like this;

“I think it’s more common today […] People can spontaneously mention the problems with resistance. It’s not good to prescribe antibiotics that you don’t need, because they might stop working. I think that’s something that has gone through, it’s not just health care personnel that are aware of this […] Sometimes it’s difficult for them (patients, author’s quote) to understand, but then I, with my knowledge and the guidelines we follow, try to explain to them and I think most of them get it.” (R1, Outpatient care)

“When I’m out lecturing, I usually ask that question (about changes in attitude among patients, author’s quote) and health care workers testify that it’s really the case. So, it’s not so difficult today to tell parents that this is an otitis and I think you won’t need antibiotics and then they usually just say oh, well. Before it was the other way around” (R2, Outpatient care)

“Most patients are very aware of the situation. Almost everyone has heard of the development of antibiotic resistance and that it’s important not to eat antibiotics if you don’t need them. I think that has changed from before.” (R3, Outpatient care)

Despite this, they also mention that patients can be persistent in demanding antibiotics, but with explanations and more knowledge, they almost always settle without a prescription; “One rarely prescribes antibiotics against one’s will […] I believe in explaining to people, tell them how the body works so they understand, and I think they do.” (R3, Outpatient care).

Education among professionals was also lifted as a major factor for addressing the management of antibiotic resistance. The main task of Strama is to educate about antibiotics and a rational use. As one Strama representative puts it “What works in hospitals and what works at health care centres – there’s a need to accumulate that knowledge and experience and use it. And that’s also the core of the work Strama does.” (R2, Strama). Education is performed on different levels. Either Strama representatives present data of prescriptions and cases of resistant bacteria to health care workers in hospital or outpatient care (“We hold a reflective meeting on the prescription of antibiotics and try to find areas of improvement.” [R1, Strama]), or there is an internal education within the health care centre or hospital. One of the respondents at a hospital explains that they have a consultant group at the infection ward that visits other wards and help them with prescriptions and choice of antibiotics (R1, Hospital care). All respondents in outpatient care testify that they either use knowledge they have received from Strama, for example through the Rainbow-brochure (R1, Outpatient care), or that they receive
education ongoing (“we usually invite hygiene nurses to our health care centre once a year to educate us and give us advice.” [R2, Outpatient care]).

“Discussion”

Respondents in the Strama group talk about their outreaching work to try to get discussions going in the different health care areas they visit to educate:

” The way of working is discussions in small groups with competent people in the same field that have a higher knowledge on the issues of antibiotics resistance and they try to mediate that knowledge […] to get a discussion going among colleagues.” (R2, Strama).

This work is meant to inspire discussions locally among professionals “I believe that to succeed with this, the discussions need to be made in the group that prescribes the antibiotics.” (R3, Strama).

The hospital care respondents mention discussions between wards on what types of antibiotics to use in what cases, and that the goal is to start discussions based on the education, see quote above about consultant work. No active discussions among colleagues in the same field were mentioned. Hospital hygiene however seems to be discussed, “We’re a small group that works with hospital hygiene and we meet once or twice a year to discuss these questions.” (R3, Hospital care).

Those in the outpatient care group report different types of discussions; with patients and with colleagues. Discussions with patients are described as possibly difficult “I think some physicians find it difficult to take a discussion with the parents about their children taking a medicine that tastes bad” (R3, Outpatient care). By this, the respondent refers to a narrow-spectrum antibiotic that tastes bad and that parents rather give their children a penicillin that tastes good, but happens to have a broad spectrum, than to force their children to take a medicine they do not like. Another respondent also describes the parental discussion to be difficult: “it’s often easier to prescribe antibiotics than to take the discussion” (R1, Outpatient care). However, the same respondent also implies that it is possible to have the discussion: “I think we’re good at taking the discussion with the parents and then we agree on waiting a couple of days to see if the infection gets better” (R1, Outpatient care).

The collegial discussions are frequent within the health care centres (“We have discussions in the medical group about our prescription patterns” [R3, Outpatient care]). Frequent
discussions can also be held with external contacts in educational purpose “we show them data, we talk about what it looks like and what we can do about it. We do it every year and then you can see that the work pays off, it gets better” (R2, Outpatient care). One respondent comments the discussions like this; “I think you receive an openness about the prescription patterns and you can continue in all areas and create a discussion climate and an openness where you dare to review each other and give each other feedback and support.” (R3, Outpatient care). One respondent, who is a local Strama agent in charge to keep the discussion ongoing at the health care centre, says that the work consists of both education and discussion.

The respondents on Strama level express their views on how physicians act in different situations, exemplified in this citation concerning the patient-physician discussion:

“We put together evidence for the use of antibiotics and get it out in the field to convince physicians that they should change […]. If you have this discussion in a patient forum or among the general public, it’s usually someone who says that the physicians throw prescriptions of antibiotics on them. And if you talk to the physicians, they say that the patients want the prescriptions and get angry if they don’t get them. It sounds like two different groups, blaming each other […]. Many physicians prescribe too much, probably because they think the patients want it.” (R2, Strama)

Concerning feedback on the physicians’ prescription patterns the comment is:

“Interviewer: How was it received?  
Respondent: In a good way actually. No one has felt accused and we didn’t come in with pointers. We’ve put it in their own hands, to discuss it themselves” (R3, Strama).

To summarise the last part of the results, the respondents agree that it is the themes of education, knowledge and discussion that play the biggest parts in improving the antibiotic resistance management and changing the perception on antibiotic usage among health care workers and patients. Education on rational antibiotic usage of both patients and health care personnel is seen as a major factor to help changing prescription patterns among physicians and to help patients from demanding unnecessary antibiotics. Also, education help to use narrow-spectrum antibiotics in hospital care, since increased knowledge can lead to further effects as it is spread. Discussion is lifted as an appreciated channel to reach consensus and further develop knowledge. The respondents think that the procedure of discussion rather than pointers beds for agreement and change.
5. Discussion

5.1 Discussion on risk theory
Antibiotic resistance management shares many similarities with risk management. The risks of antibiotic resistance have been identified and research has been done to appraise the hazard for human health. The understanding that using antibiotics lead to antibiotic resistance is part of the appraisal phase. The risk has been identified as intolerable and the probability of antibiotic resistance occurring is not the question anymore – it is a fact. The risk management is up and running and as seen in this thesis, there are many factors affecting this process, among them risk communication and risk perception.

Risk communication can be found in various ways in the management work. First and foremost, the first function of risk communication, mentioned by Renn (2008), is the Education and Enlightenment. The equivalent of this are the concepts of education and discussion, brought forth by the respondents in the interviews. Two of the other functions can also be exemplified; the help to cope with risk, achieved through intense education of physicians dealing with the risk, and the creation of confidence in the structure to be able to handle the risk, also through an increased base of knowledge on a suitable course of action to prevent resistance. These are three major examples of risk communication within the antibiotic resistance management. Internal communication is present between Strama and the personnel in both outpatient and hospital care and external communication is found between physicians and patients in their discussions on antibiotics. In these areas, communication has brought the message forward and facilitated the antibiotics resistance management.

There are however some parts of risk communication that has been less successful. The forth function, the involvement of stakeholders in risk-related decisions is absent in the antibiotic resistance management. The information goes out to physicians in outpatient and hospital care and remains internal within the health care sector. As respondents testify of discussions with patients demanding unnecessary antibiotics and difficulties in following the guidelines, there is an indication that a bigger inclusion of stakeholders in all of society could be beneficial for both health care personnel, patients and society as a whole. As Renn (2008) expresses it, an insufficient risk communication not being able to communicate the correct information leads to big consequences. This can be seen in the areas where the risk of antibiotic resistance is not clearly communicated to the stakeholders. In external communication it is seen among patients
demanding antibiotics even though they do not need it, which makes it more difficult for physicians to advocate an approach of narrow-spectrum antibiotics. This, in turn, complicates the goal of rational usage. A lack of internal communication might also lead to an irrational prescription pattern; if the different actors are unable to communicate and understand each other, the goal of a rational use is also jeopardised.

Renn (2008) also mentions four forms of risk communication; documentation of risk information, information, mutual dialogue and mutual decision-making, that are all important parts of the risk communication process. With these four points several weak spots can be found concerning antibiotic resistance management. In general, it seems that a transparency towards society is lacking in many ways. There is information and documentation, but most of the effort put into communicating it is focused within the group of physicians and the already informed Strama representatives. Material and efforts put into education is mostly focused in an area inaccessible for the general public. This might explain the difficulties physicians mention concerning patient discussions on unnecessary prescriptions of antibiotics. If more resources were put on the mutual dialogue, mainly concerning external communication, this would lead to a more informed civil society that is open to a behavioural change. Inclusion of more stakeholders outside Strama and physicians would have the same effect and facilitate a more extensive work against a developing antibiotic resistance. There are a number of ways to do this, but to depart from the concepts of mutual dialogue and mutual decision-making is a key-aspect for a successful management.

As of today, neither Strama nor physicians give any travelling recommendations for Swedes going abroad. They claim it would be impossible to stop people from travelling and that it would only have a startling effect. However, several respondents mention travelling as one of the reasons of increasing resistance as well as receiving health care abroad. To stop people from travelling might be a bit drastic, but there is a difference between intimidating and informing. More knowledge on possible scenarios and information on possible consequences of receiving health care abroad is a start, as well as a more extensive mutual dialogue. The goal might not be to stop people from travelling, but a first step is to provide the general public with information. The next step would then be to open for discussion on mutual decision-making and lead to behavioural changes, which would affect the risk perception of the general public.
The risk perception of antibiotic resistance plays a big part in how the antibiotic resistance management is shaped. Perception is formed by personal experience, fears and uncertainties and is individual. The Strama representatives have the perception that the risk is manageable and they signal a feeling of control that the risk can be handled. They seem confident in their work, which is more about decreasing the risk than exterminating it. Physicians in outpatient and hospital care are more inclined to reveal uncertainties concerning the management. They have all received the information, but traditions and uncertainties and their close patient contact give them a humbler view on how the management of antibiotics could be done. Physicians in hospital care are also notably concerned about the difficulties to stay specific and use narrow-spectrum antibiotics. Physicians in both organisational levels are, as the Strama representatives, confident that education and discussion are the most important factors in the management process, but they mention to a greater extent the possible problems of communicating this to patients and the general public.

A big part in forming perception of risk concerning antibiotic resistance seems to lie in the concern of the personal interest of the receiver. The respondents talk about the importance of rationalising the use of antibiotics for the common good, but what is stressed is the personal feedback; among physicians on their prescriptions, in the hospital environment the difficulties of when to use narrow- respectively broad-spectrum antibiotics and among patients in their concern for their own health. There might be more to develop on this part in order to find other ways of making the management process more efficient. To influence risk perception through knowledge is the type of approach that has been used so far. Further efforts could be put into stressing the personal responsibility of the health care workers in their prescription patterns and into emphasizing personal risks for the patients in their personal usage of antibiotics. Increased knowledge on personal hazard of using antibiotics would probably make the general public more inclined to think twice before insisting on treatment. In general, appealing to personal experiences of patients have effect on the risk perception of the individuals. The risk gets easier to handle as it becomes more substantial. Further studies on how the individual’s situation can be taken into account in risk communication and perception needs to be done, but this study indicates a possible positive outcome.

Ortwin Renn (2008) speaks of risk communication as a bridge, conjoining the different parts of risk governance. The results of this study shows the same pattern, where communication of knowledge is the factor connecting the different parts of antibiotic resistance management. The
discussion between actors is lifted by all respondents and communication can be labelled as one of the reasons behind the progress.

5.2 General discussion
The national goal of 250 prescriptions of antibiotics per 1000 inhabitants per year in outpatient care set in the Patient Safety Investment 2011-2014 seems to have had a certain effect on the prescription rate in Sweden. The decrease in prescriptions is significant. However, the increase of patients infected with multidrug resistant bacteria is also significant, which contradicts the anticipated correlation between prescriptions and antibiotic resistance. However, looking closer at data of antibiotic usage in hospital care, perhaps there are further insights to find. The trends show significant increases of several groups of broad-spectrum antibiotics in the latest years and the total usage also shows a significant increase. A moderate increase, but still pointing upwards. The national recommendation is to avoid using cephalosporins as it is very selective for resistance development. As a reaction to this, combinations of penicillins together with carbapenems and beta-lactamase resistant penicillins are supposed to replace cephalosporins. However, the decrease of cephalosporins is not significant. The changes are small within each group of antibiotics between 2010 and 2014, but the statistical analyses give a good indication on what the situation looks like: the usage of broad-spectrum antibiotics is increasing in hospital care. Further, physicians in hospitals testify that broad-spectrum antibiotics sometimes are ordered to cover all possible infections. Later, a test for resistance might show that using a narrow-spectrum antibiotic would have been sufficient. At the same time prescription rates are decreasing in outpatient care, where narrow-spectrum antibiotics are mostly used. This might indicate that an unnecessary usage of broad-spectrum antibiotics in hospital care is the reality behind the numbers. This might explain the discrepancy behind the decreasing prescription rates in outpatient care and the increasing number of cases of multidrug resistant bacteria, as the answers seems to be found in hospital care rather than in outpatient care. This leaves room for further studies on factors affecting the usage of antibiotics in hospital care and the resistance development in Sweden. In this line, a retrospective study in hospitals that gives information on how much of the hastily ordered broad-spectrum antibiotics that could have been more specific would raise the awareness on the situation and perhaps increase incentives on using narrow-spectrum antibiotics.

The question on how management of antibiotic resistance in Sweden look like showed the same picture in all counties. No specific similarities or differences were found between the three
chosen counties and this question did not point to any further need of additional studies. There are no major differences; the management is similar with the same guidelines, ideas and working routine in all three counties. This conclusion can help support future strategies and a choice was made to keep the research question. It turned out that the results did enlighten another part of the work towards rational antibiotic use; the recipients’ side, meaning those receiving the knowledge and the guidelines. The counties differ widely on several factors that can be enumerated as possible dependent variables concerning the reception of rational antibiotics usage. The size of county and number of inhabitants might affect the situation as a bigger county needs more resources to reach all residents. The distribution of urban and rural areas can also play a part as the possibility of reaching the general public is bigger in an urban area. Also resources put into the antibiotic resistance management in the county matters. This together with the attitude of the general public as well as the level of knowledge available can have impact on the reception of the message. In short, each county has its individual factors that play part in the reception of the message. If these can be identified and confirmed as variables influencing the success rate of the work, the management can be adjusted to this and lead to a more fruitful process. This thesis will not go more deeply into this, but stress that there is room for further research. Studies conducted in this field can have a big impact on the continuation of the work for a rational antibiotic usage and lead to new perspectives that can simplify the process. Further studies will also be a big contribution to a multidisciplinary approach and embed for additional inclusion of qualitative variables in the natural science field.

The hypotheses for this thesis were that a reduction of antibiotic distribution and a rational usage of antibiotics can reduce antibiotic resistance, which were studied deeper with the research question on decreased prescription and increased resistance in Sweden. The consistent explanation from the respondents was that the cause of this is migration and changed travelling patterns, without much comments. To achieve changes and reach a discourse open for variation, this is important to problematize. Thus, it is important not to stick to migration and extended travelling as the sole reasons for the increasing number of cases of multidrug resistant bacteria. These are known factors, but it could lead to a stagnation in the improvement process if they are considered the only explanations.

Furthermore, the results indicate that the answer is not as simple as the hypotheses and earlier research indicates. It seems that a decrease of the prescriptions is not the full answer, contrary, more focus should be put on rational usage. As the results indicate, the prescription rate has
decreased while the usage of antibiotics in hospitals have not shown any dramatic changes. Usage of antibiotics in itself causes resistance and the selective effect is increased by using broad-spectrum antibiotics. Thus, the increased usage of antibiotics in hospitals might be another reason to why there still is a selection for resistance in Swedish hospitals. Nosocomial infections are few in Sweden, but there are still the community-acquired infections. Selection is done in the hospital environment on MRSA, ESBL and ESBL-CARBA and even though they are not spread in hospitals, they might be in society. Future studies should look deeper into this and investigate the possible transmission paths of infections obtained in hospitals.

Measuring the number of prescriptions in outpatient care is easily done and it is also an easier goal to strive for; reduction of prescriptions. The goal to use more narrow-spectrum antibiotics is more difficult, as usage is dependent on infection and situation concerning time, space and possibilities. Economic resources are another factor that plays part here. Respondents mention the need for resources in the education and discussion process on all organizational levels. This affects the situation as well – without the means to improve, progress becomes more difficult to attain. Apart from the educational work, economic resources are important in terms of bed days and time at hospital. There is an interest in keeping the patients in hospital as short a time as possible to keep down the costs. A rational and efficient antibiotic usage would lessen the bed days and benefit the health care sector economically. It seems that if more resources and focus are put into antibiotic resistance management in general, it would give economic benefits and at the same time result in insights that could further enhance a rational antibiotics usage. Furthermore, concerning the use of broad-spectrum antibiotics in hospital care, the situation of economic resources should be discussed. If a lack of resources is a reason to why broad-spectrum antibiotics are used to the extent that it is, there is need for immediate change. This is not the time or place to be greedy, as the savings done in this case might turn out to be very expensive in the long run.

What also needs to be mentioned is that more tests for multidrug resistant bacteria are done today than before. The problem of these bacteria is acknowledged and screenings are done to a greater extent. This might be another factor behind the increasing number of cases of patients infected with multidrug resistant bacteria. However, few of the respondents mention this as a reason and it does not change the notion that the increasing number still is a problem. Furthermore, Strama mentions that the goal is not to reduce the number of cases of patients infected with multidrug resistant bacteria, it is to slow down the increase. This can be another
reason why resistance is going up and prescriptions are going down – there are no strategies to reduce the multidrug resistance. Here it seems important not to get stuck in old ruts and also obvious to raise a question on why it is considered so difficult to turn the rising trend of resistance around.

It is apparent in all interviews that the human factors behind guidelines and praxis seem to matter in the work on an improved management of antibiotic resistance. There is a wish that the education brought by Strama representatives and health care workers in their different educational contexts will stimulate to discussion. Even though the education is important, discussion seems to be the tool to reach to understanding, rather than the reports. As of today, the main part of education and discussion initiated by Strama is kept within the Swedish health care system, with few campaigns towards the general public. Some information is given on web sites, but not much focus has been put in this area. Connecting this to risk perception, where the apprehension of a risk to be personal affects a person’s behaviour, it seems that Strama could benefit much from this. Public information with focus on the personal risk of the Swedish citizens would raise the awareness among the general public. This would lead to reaction, simply because the risk suddenly becomes personal, which would facilitate the work of physicians in their patient discussions. In the long run it would hopefully affect the antibiotic usage in Sweden and open for the sought rational antibiotic usage.

Connecting to research objectives and aim, the research questions have with their qualitative angle helped to enlighten the area in a more multidisciplinary way. The study has filled a part of the knowledge gap concerning factors behind the discrepancy between the number of prescriptions and the antibiotics resistance, enlightened from both a quantitative and a qualitative perspective. However, there is still need for further research in this field in order to create a more comprehensive picture. The aim of investigating this issue using a multidisciplinary approach has highlighted the aspects of education and discussion in antibiotic resistance management as factors influencing the management process. The multidisciplinary approach has had a positive outcome and the use of qualitative methods revealed further understanding. This study can therefore serve as justification of using a continuous mix of methods in the field of infectious disease control and antibiotic resistance management. Hopefully other studies can pick up where this study ends and continue to contribute to the research area.
6. Conclusions

The trends of antibiotic usage in Sweden between 2010 and 2015 show a significant decrease in the number of prescriptions of antibiotics in outpatient care. Within hospital care a small, but significant increase of the usage of antibiotics is seen in several groups of antibiotics as well as in the total usage of these groups. The number of patients infected with MRSA, ESBL and ESBL\textsubscript{CARBA} have also increased significantly in the same period. Concerning management of antibiotic resistance, there are no notable differences between the three counties included in the study. The counties have the same praxis and follow the national guidelines in all three levels; hospital care, outpatient care and in the Strama groups.

Migration and an extended travelling pattern among Swedes are the explanations given in the study to the increasing number of multidrug resistant bacteria in Sweden. Health care workers do not perceive this as a major threat or problem. They report noticing the increase in multidrug resistant bacteria. There is an acceptance of the discrepancy and at the same time a positive view of the management of the antibiotics resistance and on the aim to use antibiotics in a rational way. In general, there is nothing dramatic on the issue.

The themes of education, knowledge and discussion are brought forward as important concerning how to improve management of antibiotic resistance. There is a strong will in educating and changing attitudes on antibiotic usage among health care workers and patients. Education and discussion on the aspects of the actual knowledge is agreed to be the best tool for reaching change and improvement of the management of antibiotic resistance in Sweden.

The results achieved through the study’s deductive approach are not enough to verify or falsify the hypotheses. Thus, the hypotheses that a reduction of antibiotic distribution and a rational usage of antibiotics can reduce antibiotic resistance cannot be rejected. The results of this study indicate that a rational usage of antibiotics might be more important to study than a reduction of use in order to reduce antibiotic resistance. This hypothesis could advantageously be investigated more deeply, but further studies are needed to strengthen the supposition.
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8. Appendix 1

8.1 Interview guides

Interview guide for physicians in outpatient care

– Presentation of the interviewer; name, background, education, aim of thesis. A moment for the respondent to ask questions before the interview starts.

1. For how long have you been a practicing physician?
2. When did you become a specialised doctor?

3. If we enter the field of antibiotic resistance; do you have any local guidelines for antibiotic resistance management in the health care centre where you work?

4. With the Patient Safety Investment 2011-2014, a national goal was set to decrease the prescriptions of antibiotics. If the informant seems to not recognise this, the interviewer will elaborate and explain. This has been successful and in your county there has been a decrease of X %.
   – Have you been working actively to decrease the prescriptions here at the health care centre?
   If YES – How? If NO– Why not?

5. The prescriptions have decreased especially in the group of children 0 - 4 years; why do you think that is?

6. In the group of patients 80 years and older, no decrease is seen. Do you have any ideas on possible explanations to this?

7. Despite the decrease of prescriptions, there is an increase in the number of cases of MRSA, ESBL and ESBL\_CARBA in all Swedish counties.
   – Have you noticed this? If YES – In what way?
   – What guidelines on multidrug resistant bacteria do you have?
   – The national guidelines are based on the concept of a decreasing rate of prescriptions leading to a reduced antibiotic resistance – but it seems that the results are the opposite. Why do you think that is?

8. MRSA is spread in both hospitals and in the community.
   – Do you have any strategies on handling community-acquired MRSA?
   Examples: Decreased prescription rates? Questions to patients about receiving health care abroad?

9. Looking closer, the prescriptions of narrow-spectrum antibiotics have decreased in your county, while those with a broad spectrum are increasing.
   – What types of antibiotics do you prescribe most often would you reckon?
   – What types of infections are most common?

10. What are your thoughts on your daily work of prescribing antibiotics?
11. What are your thoughts, more generally, on the situation with the developing antibiotic resistance?

*This should lead to a discussion on development of resistance and hopefully be an opening to a more general discussion on antibiotics.*

Assisting questions on this part:
– There is a lot of buzz around antibiotic resistance in the media right now, have you noticed that in the health care centre?
– Do you notice a change in attitude with patients and/or health care workers? How is the atmosphere around antibiotic resistance development?
– How should we reduce the development of antibiotic resistance? The current course of action does not seem to work; do you have any other ideas?
– Is there anything else you would like to add?

*The interview is concluded with an opportunity for the respondent to ask questions and a thank you for participation.*
Interview guide for physicians in hospital care

– Presentation of the interviewer; name, background, education, aim of thesis.
A moment for the respondent to ask questions before the interview starts.

1. For how long have you been a practicing physician?
2. How come you chose the specialty you are in?
3. What are your duties during a normal day at the hospital?

4. What does your work on antibiotic resistance look like, concretely? Do you follow any guidelines?
   If YES – What do they look like? If NO – Why not?

5. With the Patient Safety Investment 2011-2014, a national goal was set to decrease the prescriptions of antibiotics. If the informant seems to not recognise this, the interviewer will elaborate and explain. This has been successful and in your county there has been a decrease of X%.
   – Have you been working actively to decrease the prescriptions at your ward?
     If YES – How? If NO – Why not?

6. Despite the decrease of prescriptions, there is an increase in the number of cases of MRSA, ESBL and ESBL\textsc{carba} in all Swedish counties.
   – Have you noticed this? If YES – In what way?
   – What guidelines on multidrug resistant bacteria do you have?
   – The national guidelines are based on the concept of a decreasing rate of prescriptions leading to a reduced antibiotic resistance – but it seems that the results are the opposite. Why do you think that is?

7. What is the course of action for health care when a case of MRSA, ESBL and/or ESBL\textsc{carba} is identified?

8. Looking closer, the prescriptions of narrow-spectrum antibiotics have decreased in your county, while those with a broad spectrum are increasing.
   – What types of antibiotics are most common? Which ones do you prescribe most often?
   – What types of infections are most common?
   – Are there any special recommendations on what antibiotics that are to be used?
   – Have you noticed any consequences after some antibiotics are used more often than others?

9. What are your thoughts on usage of antibiotics and in your daily work of prescribing antibiotics?
10. What are your thoughts, more generally, on the situation with the developing antibiotic resistance?

This should lead to a discussion on development of resistance and hopefully be an opening to a more general discussion on antibiotics.

Assisting questions on this part:
– There is a lot of buzz around antibiotic resistance in the media right now, have you noticed that in the health care centre?
– Do you notice a change in attitude with patients and/or health care workers? How is the atmosphere around antibiotic resistance development?
– How should we reduce the development of antibiotic resistance? The current course of action does not seem to work; do you have any other ideas?
– Is there anything else you would like to add?

The interview is concluded with an opportunity for the respondent to ask questions and a thank you for participation.
Interview guide for Strama representatives

– Presentation of the interviewer; name, background, education, aim of thesis.
A moment for the respondent to ask questions before the interview starts.

1. What is your background?
2. How long have you been working with Strama?
3. What are your duties in Strama?

4. Tell me how you work. The goal of Strama is to increase the collaboration of the antibiotic question among the counties and to support the aim of a rational antibiotic usage – how do you do this more concrete?
5. For how long have your Strama group been active?
6. In what ways do you work with national Strama?

7. Let’s get into the statistics from this county. The national goal is to decrease the prescriptions of antibiotics.
   – What is your course of action on this?
   – Do you have the same ways of working in the different forms of care or does it differ between hospital care and outpatient care?

(8. You have succeeded in decreasing the prescription rate in this county with X %, how did you do it?) ← Depending on the answer to question 7.

9. The prescriptions have especially decreased in the group of children 0 - 4 years; why do you think that is?

10. In the group of patients 80 years and older, no decrease is seen. Do you have any ideas on possible explanations to this?

11. Despite the decrease of prescriptions, there is an increase in the number of cases of MRSA, ESBL and ESBLCARBA in all Swedish counties – why is that?
   – The starting point have been that a decreasing rate of prescriptions should lead to a reduced antibiotic resistance – but it seems that the results are the opposite. What possible explanations to that are there?

Depending on the talkativeness with the respondent, a follow-up question can be added:
   – ESBL is often imported, but is also increasing among Swedes in Sweden, what is done about this?

12. Do you have any strategies on handling community-acquired MRSA?
   – How can it be handled with decreased prescription rates? Do the prescriptions affect the increase of the number of cases?

13. The decrease in antibiotic usage should lead to a reduced antibiotic resistance. Despite this, there is an increase of MRSA and other multidrug resistant bacteria. How is this handled by Strama and the counties?
   – Are there any timetables or guidelines for this?
14. Looking closer, the prescriptions of narrow-spectrum antibiotics have decreased in your county, while those with a broad spectrum are increasing, especially in the acute hospital care – why is that?
   – What are your thoughts on this?

15. What are your thoughts, more generally, on the situation with the developing antibiotic resistance?

   *This should lead to a discussion on development of resistance and hopefully be an opening to a more general discussion on antibiotics.*

   **Assisting questions on this part:**
   – There is a lot of buzz around antibiotic resistance in the media right now, have you noticed that in the health care centre?
   – Do you notice a change in attitude with patients and/or health care workers? How is the atmosphere around the antibiotic resistance development?
   – How should we reduce the development of antibiotic resistance? The current course of action does not seem to work; do you have any other ideas?
   – Is there anything else you would like to add?

   *The interview is concluded with an opportunity for the respondent to ask questions and a thank you for participation.*