Inland Norway University of Applied Sciences

Faculty of Applied Ecology, Agricultural Sciences and Biotechnology

Ajay Kumar Shah

Master Thesis

Price sensitivity in the clinical testing market for Extended-Spectrum Beta-Lactamase

Master's Degree in Applied and Commercial Biotechnology

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Ajay Kumar Shah

Abbreviations

Bla: Beta-Lactamase

COGS: Cost of Goods Sold

CPOs: Carbapenemase Producing Organisms

CTX-M: Cefotaxime-Munich

ESBL: Extended Spectrum Beta Lactamase

EUCAST: European Committee on Antimicrobial Susceptibility Testing

GBP: Great Britain Pound

HRI: Health Related Infection

IVD: In Vitro Diagnostic

LAMP: Loop Mediated Isothermal Amplification

MALDI-TOF: Matrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry

MICs: Minimum Inhibitory Concentrations

MRSA: Methicillin Resistant *Staphylococcus aureus*

NGS: Next Generation sequencing

NICE: National Institute for Health and care Excellence

NOK: Norwegian Kroner

PBP: Penicillin Binding Protein

PCR: Polymerase Chain Reactions

PEoD: Price Elasticity of Demand

RT-PCR: Real Time PCR

SHV: Sulphydryl Variable

TEM: Temoniera

VAT: Value Added Tax

WHO: World Health Organization

Table of Contents

Abstract

This thesis studies the potential for using molecular testing for ESBL in Norwegian hospitals. Background material was obtained by checking the prices of existing kits, doing an interview with one of Norway's foremost experts on ESBL testing and performing calculations based on public statistics.

A survey was then performed that was expected to form the basis of a price sensitivity analysis. The number of respondents was too low for statistical analysis, but a very rough estimate for the kit prices that microbiological hospital labs are willing to pay was obtained. The realism of this price level is discussed.

All responses were from medium sized hospitals. They also stated that the throughput they needed would be 8 to 24 samples per run. This confirms theoretical estimates of the throughput needed for Norwegian hospitals of medium size.

Keywords: ESBL detection; Price sensitivity; Prices of kits and instruments

1. Introduction

1.1 ß-lactam antibiotics

These are a class of antibiotics which contains all those antibiotics agents whose molecular structure carry beta lactam and this is essential for the function of all the antibiotics in this group. The beta-lactam ring is shown in figure 1. This class of antibiotics have 3-carbon and 1-nitrogen in their molecular structure which is highly reactive. This antibiotic inhibit the formation of bacterial cell wall, by interfering with the protein necessary for cell wall formation where later bacteria get either killed or growth inhibition. Some bacterial enzymes named as penicillin binding protein (PBP) have major role in peptidoglycan synthesis and these antibiotics bind to these PBP which later leads to lysis and cell death (Etebu & Arikekpar, 2016).

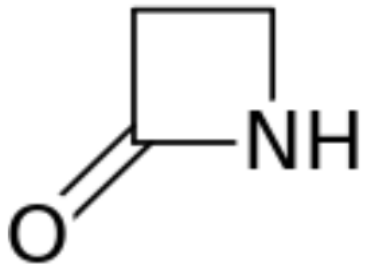

Figure 1: Structure of Beta-lactam ring (Etebu & Arikekpar, 2016).

The ß-lactam antibiotics are mainly classified into four groups namely: Penicillins, Cephalosporins, Monobactams and Carbapenems. The frequency of their use in the USA is shown in the table 1.

Table 1: The use of different ß-lactam antibiotics in the USA in the decade from 2004 to 2014 (Bush & Bradford, 2016).

Class of ß-lactam	**Percentage of prescriptions**
Narrow spectrum penicillins	3.12
Broad spectrum penicillins	36.54
Cephalosporins	47.49
Monobactams	1.66
Carbapenems	11.20

Table 1 reflects the fact that penicillins and cephalosporins are general purpose antibiotics whereas carbapenems are antibiotics of last resort. Only one monobactam is in common use, and it share of the market is marginal (Arne Deggerdal, personal communication).

1.1.1 Penicillins

This class contains beta lactam compounds where 6-aminopenipenicillanic acid ring are centred and other rings are in side chains, as is shown in the figure 2, part 1 (Etebu & Arikekpar, 2016). The penicillin get their potency from 6-aminopenipenicillanic acid nucleus and mainly work against gram positive bacteria (Berendsen et al., 2013).

1.1.2 Cephalosporins

This class is similar to penicillin both in structure and function. It contains 7-aminocephalosporanic acid in the nucleus and 3,6-dihydro-2 H-1,3 thiazane rings. The general structure of cephalosporins is shown in figure 2, part 2. There has been developed several generations of cephalosporins, which is mentioned in table 2. Their latest generations are more effective against gram negative bacteria (Pegler & Healy, 2007). This is summarized in table 3.

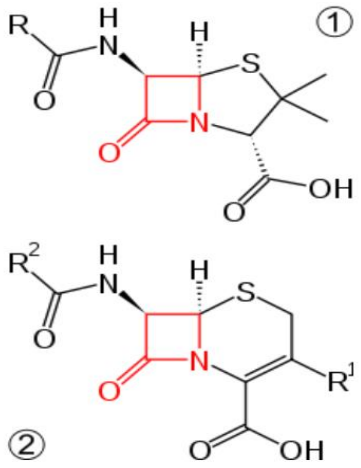

Figure 2: Structure of Penicillin (top) and cephalosporin (bottom), red color indicates the beta lactam ring (Etebu & Arikekpar, 2016).

Table 2: Cephalosporin family (TulaneUniversity, 2016).

Category	**Parental agents**	**Oral agents**
First generation	Cefazolin	Cephalexin
Second generation	Cefotetan, Cefoxitin, Cefuroxime	Cefuroxime axetil, Cefaclor
Third generation	Cefotaxime, Ceftazidime, Ceftriaxone	Cefixime, Cefdinir
Fourth generation	Cefepime	
Fifth generation	Ceftaroline	

Table 3: Generational coverage (TulaneUniversity, 2016).

Generation	**Gram Negatives**	**Gram Positives**	**ß-Lactamase Stability**
1st	+	+ + +	+/-
2nd	+ +	+ +	+
3rd	+ + +	+	+ +
4th	+ + +	+ +	+ + +
5th	+ + +	+ + +	+ + +

1.1.3 Monobactams

These antibiotics are part of beta lactam compounds but are different from other beta lactams, in monobactams beta lactam ring remain in one side and is not attached to any other ring. Aztreonam is a monobactam that is commercially available having narrow spectrum activity and act mostly against gram negative pathogens (Etebu & Arikekpar, 2016). The structure of Aztreonam is shown in figure 3.

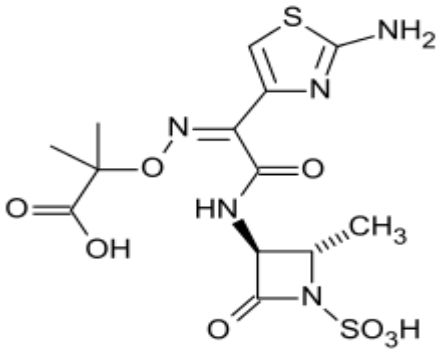

Figure 3: Structure of the Monobactam Aztreonam (Etebu & Arikekpar, 2016).

1.1.4 Carbapenems

Carbapenems have the property of wide spectrum antibiotic which gives potency to this antibiotic to fight against ESBL and Metallo beta lactamase. Because of this reason this antibiotic is considered to be trustworthy and with rise in resistant to this antimicrobial agent is considered to be main people health related problems. Due to its wide spectrum property, it gives detrimental effect to all Gram-positive bacteria and gram-negative bacteria as well as anaerobic bacteria (Codjoe & Donkor, 2017). The general structure of carbapenems is shown in figure 4.

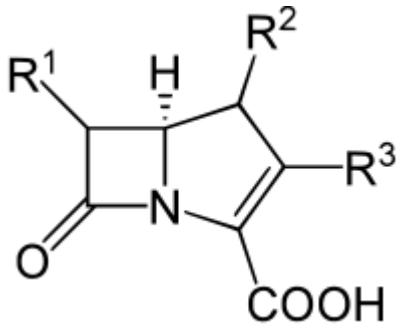

Figure 4: Structure of Carbapenem (Etebu & Arikekpar, 2016).

1.2 Extended Spectrum ß-lactamases (ESBL)

ß-lactamases are enzymes that hydrolyze the ß-lactam ring and it can be chromosomal or plasmid borne. The plasmid borne enzymes can be transferred from one bacterial species to another (Bush & Bradford, 2016). ESBL are ß-lactamases that will hydrolyze ß-lactam compounds which will not normally be broken down by ß-lactamases, and are plasmid borne. When one talks about ESBL the subject is an enzyme carried on a plasmid, not an organism. Bacteria most likely to harbour the ESBL plasmids are members of the Enterobacteriaceae family, for instance *E.coli* or *Klebsiella pneumoniae* (Wintermans et al., 2013). There are several classes of ESBL among which some of them are mentioned below.

1.2.1 Temoniera (TEM)

TEM-1 is most easily experienced beta-lactamase in Gram-negative microbes and because of this production the resistance against ampicillin and ampicillin is increased up to 90% (Cooksey et al., 1990). The change in the position of amino acid around the active site of the enzyme is responsible for change in its configuration which gives entry to oxyimino beta

lactam substances. Because of these changes in amino acid positions 140 types of TEM have been described (Bradford, 2001; Jacoby & Munoz-Price, 2005).

1.2.2 Sulfhydrylvariable (SHV)

The enzyme SHV become prominent in Enterobacteriaceae in last decade of 20th century but now found in different epidemiological condition of human, animal and environment. SHV have evolved from narrow to extended-spectrum of hydrolysis, due to change in the amino acid which alter the position at the active site of beta-lactamases (Liakopoulos, Mevius, & Ceccarelli, 2016). Till now because of this substitution mechanism 50 Types of SHV have been recognized (Jacoby & Munoz-Price, 2005).

1.2.3 Cefotaxime-munich (CTX-M)

Those common ESBL which do not come into TEM and SHV family is categorized in to this to focus the greater effect against cefotaxime than to ceftazidime. There are nearly 40 CTX-M have been recognized and some of them more easily hydrolyze the ceftazidime than cefotaxime. The more commonly found are CTX-M-14, CTX-M-3 and CTX-M-2 (Bradford, 2001; Jacoby & Munoz-Price, 2005).

1.2.4 OXA

This group of enzyme is characterized by hydrolysing activity against oxacillin and cloxacillin and on this basis it has been named as OXA. This group of enzyme also gives resistance to ampicillin and cephalothin. There is very little similarity among the members of this group enzymes (Bradford, 2001).

1.2.5 Carbapenemases

Carbapenemases belong to a diverse group of ß-lactamases that can break down carbapenems. This is a serious problem since carbapenems are antibiotics of last resort (Komatsu et al., 2018). Carbapenemases can be serine ß-lactamases (class A or D) or metallo ß-lactameases (class B) (Queenan & Bush, 2007).

New ESBLs are detected at regular intervals, but that it takes time before they become clinically relevant. Carbapenemases are not considered ESBLs, but this is more a matter of definition than a real difference. Anyway, they both pose the same type of problem. An example is OXA-48, which sometimes has carbapenemase activity (Arne Deggerdal, personal communication).

1.3 Clinical Significance of ESBL

Most of the bacteria carrying ESBL are not necessarily pathogens. There are two aspects of the clinical significance of ESBL.

1. To prevent the spread of bacteria carrying the plasmid between patients or between patients and staff, even when the bacteria carrying the plasmid do not cause disease. To safeguard against this, the hospitals perform screening of patients, relatives and staff that may have been in contact with such bacteria. Samples for this is referred to as screening samples. Bacteria negative for ESBL are not picked up in screening.

2. If a patient has a disease caused by a bacterium that carries ESBL, this has implication for the treatment as well as for the prognosis. Samples from these patients are referred to as clinical samples. From these tests the hospital will know how frequent ESBL is in the population of bacteria that causes the specific disease in the patient, since they already have registered infection with that type of bacteria before they test for the presence of ESBL.

In the Scandinavian countries the routines are as follows:

If ESBL is indicated in a screening, steps are taken to avoid spread. If a patient and the presence of ESBL is not related to his disease, he will be isolated, treated for his disease in the normal way, but nothing will be done about the ESBL. If it is relatives or staff, their access to the hospital will be restricted, but nothing will be done about the ESBL status. Over time the ESBL status will spontaneously change to negative (Arne Deggerdal, personal communication).

If ESBL is indicated in bacteria causing the disease of a patient, the patient will be isolated and the treatment will be modified to use antibiotics that are not inactivated by the ESBL. Usually this involves the use of carbapenems, but if the ESBL is a carbapenemase it is more complicated (Lingaas, 2016).

Table 4: The cost per day of the stay at hospitals without treatment (Helsedirektoratet, 2019).

Year	Price (NOK)
2019	4,885
2018	4,747
2017	4,622
2016	4,505
2015	4,387
2014	4,255

The additional cost per day of keeping a patient in contact isolation (keeping the patient shielded from fellow patients) was between NOK 4953 and NOK 6532 in 2014 according to a lecture given by Petter Elstrøm, from Folkehelseinstituttet (The Norwegian Institute of Public Health) (Elstrøm, 2016).

1.4 Testing for ESBL

Norwegian hospitals in general follow NordiCAST and EUCAST rules (Parajuli, 2018). According to EUCAST, the recommended strategy for the detection of ESBLs in Enterobacteriaceae is based on non-susceptibility to indicator oxyimino-cephalosporins, followed by phenotypic (and in some cases genotypic) confirmation tests. The recommended methods for ESBL screening in group 1 Enterobacteriaceae are broth dilution, agar dilution or disk diffusion. It is necessary that both cefotaxime (or ceftriaxone) and ceftazidime are used as indicator cephalosporins, as there can be large differences in Minimum Inhibitory Concentrations (MICs) of cefotaxime (or ceftriaxone) and ceftazidime for different ESBL producing isolates. After screening, ESBL confirmation is done by different phenotypic test (EUCAST, 2013).

The NordiCAST rules generally recommend using the tests described by EUCAST, but also opens up for PCR based tests and in all cases will be PCR reactions with primers against the ESBL gene. Depending of the test setup this can theoretically be a set of reactions against different ESBLs or a multiplex PCR detecting several ESBLs in one reaction. Tests can either be in-house, meaning that the hospital has designed primer sets and/or probes and then bought a general purpose PCR kit (everything except primers/probes) or it can be a commercial ESBL kit, meaning that the manufacturer has designed primer sets, probes (if they are used) and

supply them with the general PCR components. This also means that the kit has been IVD CE approved. In practical use there is no difference between the two types of PCR based kits (Arne Deggerdal, personal communication).

There are two large weaknesses of the PCR based methods as well as two important strengths. The weaknesses are:

- Only ESBLs that have been previously described can be detected. According to a survey carried out in 2018, some of the largest hospitals in Norway do not consider this a problem (Parajuli, 2018).
- It is difficult to find commercial kits that will even detect all of the well known ESBL variants (Parajuli, 2018).

The strengths are:

- The time to results is short, only a matter of a couple of hours, as low as 90 minutes in some cases (Parajuli, 2018).
- There are cases where ESBLs are inducible and the process is too slow for the strain to show up as resistant in a traditional phenotypic test. Then the molecular test will be correct and the traditional one will be a false negative (Rawat & Nair, 2010).

Other types of tests for ESBL

Sequencing: One of the molecular diagnostic method is amplicon based Next Generation Sequencing (NGS) and has been used in Hospital Acquired Infection Bio Detection system, which is used to detect the pathogenic organisms and the genes which is resistant to antimicrobial agents. This bio detection system removes the negative samples and detect the positive sample directly from the raw material and helps in the easy and fast detection process (Peker et al., 2018).

MALDI-TOF: The molecular detection technique like Matrix Assisted Laser Desorption Ionization time of flight Mass Spectrometry (MALDI-TOF MS), detects the genes which are responsible for ESBL activity and its limiting factor is that it cannot detect all of the ESBL encoding gene and is expensive. A kit named Rapid ESBL Screen kit 98022 is commercially available and gives the result within 2 hours but have some limitations too (Poirel, Fernandez, & Nordmann, 2016).

*Loop Mediated Isothermal Amplification (LAMP)***:** This method amplifies the DNA in fast pace with high specificity and efficiency under isothermal conditions. In addition, along with reverse transcription, it can amplify RNA sequences with greater efficiency (Notomi et al., 2000). The principle of LAMP is shown in figure 5.

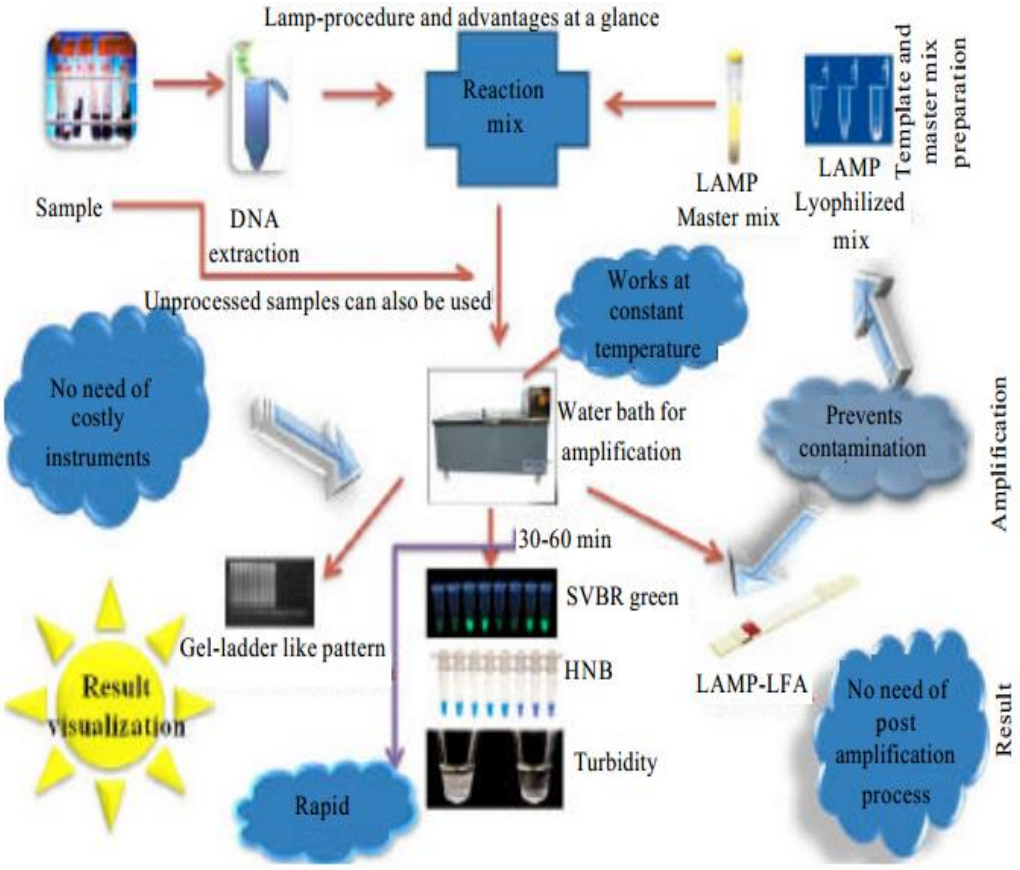

Figure 5: The LAMP process (Dhama et al., 2014).

1.4.1 Commercial ESBL detection kits

eazyplex® SuperBug

The principal of LAMP was described above. On the basis of this principle a device named Genie II has been designed which uses a set of kits named eazyplex® SuperBug from Amplex Diagnostics GmbH, for the detection of pathogens as mentioned in the report of NICE-2017 (NICE stands for National Institute for Health and Care Excellence), the time duration for complete result is 30 minutes (NICE, 2017).

Gene Proof ESBL PCR Kit

The ESBL PCR kit is designed by GeneProof biotechnological company. This kit is especially designed for the detection of *bla* $_{SHV}$ and *bla* $_{CTX-M}$ genes by RT-PCR (Real Time- Polymerase Chain reaction) method. The kit has been internally standardised which is included in the reaction mixture that enables the identification of all the five known variants of CTX-M (CTX-M 1, CTX-M 2, CTX-M 8, CTX-M 9 and CTX-M 25). The kit takes the advantage of hot-start technology which reduces the non-specific reactions. The Specificity is 100% and Sensitivity is 95% for both CTX-M and SHV (GeneProof, 2016).

Allplex™ Entero-DR Assay

Allplex™ Entero-DR Assay is a multiplex real time PCR assay which can detect and identify 8 antibiotic resistant genes simultaneously. Its' important aspect is it can monitor three major resistance of antibiotics namely carbapenem, vancomycin and extended spectrum of beta lactam in a single reaction within 3 hours. It uses rectal swab or bacterial colony for sample (Seegene, 2019).

1.5 Spread of ESBL

The first time ESBL was reported was in 1983 and plasmid borne AmpC beta-lactamases was reported in 1988. Usually, ESBLs are a mutant form, plasmid borne beta-lactamases originated from older beta-lactamases (such as TEM-1, TEM-2, SHV), which have an extended substrate profile which hydrolyse the all cephalosporins, penicillins and aztreonam (Thomson, 2001).

ESBLs when reported in 1983, it was described in Enterobacteriaceae and Pseudomonadaceae in different parts of world mainly in *Klebsiella pneumoniae* and *Escherichia coli*. The majority of ESBLs found in clinical sample are TEM and SHV types which have evolved from narrow spectrum beta-lactamases like TEM-1, TEM-2 and SHV-1. The CTX-M enzyme have originated from *Kluyvera spp*.,being noticed in Enterobacteriaceae and reported from Asia, Africa, Europe, South America and North America (Pitout, Nordmann, Laupland, & Poirel, 2005).

During 80s and 90s, the ESBL producers were mainly found in Hospital environment and mainly in ICU (Intensive care Unit), and the responsible hosts for this enzyme production were *Klebsiella* and *Enterobacter spp*. In one of the surveys it is found that the percentage of *E. coli*

associated with ESBL production is rising and is 3.6% in 2005 rises to 4.8% in 2008. This number is mainly found in USA, Canada or Israel but it is less in Europe (Schoevaerdts et al., 2011).

With the passes of time hospital acquired infections is rising and is becoming top ranked problem on the globe and the responsible pathogen is *Klebsiella spp*., which produces ESBLs. This is the main concern because of few numbers of antibiotic for its treatment and also its transmission rate is fast to other Gram-negative bacilli or Enterobacter (Bellíssimo-Rodrigues et al., 2006).

Until the nineties, there were two types of ESBL active globally, namely Temoniera (TEM) and Sulfhydrylvariable (SHV) types associated mainly with hospital outbreaks and the bacteria which produced this enzyme was predominantly *Klebsiella pneumoniae.* But after 2000 there erupted another type of ESBL enzymes called Cefotaxime-munich (CTX-M) and the bacteria responsible for this enzyme was mainly *Escherichia coli*. Also, some of the study was done in the clinical samples of the hospital and they found that other than *E. coli*, *K. oxytoca* and *K. pneumoniae* also have the capacity to produce CTX-M enzyme and mostly because of gram negative bacteria, resistance has been occurred. So one of the mode of transmission of ESBL to human is either by physical contact or taking of contaminated food infected with ESBL producing strains. The food which is of animal origin have higher chances of accumulating ESBL and the wide spectrum antibiotic Cephalosporin inactivated because of enzymes produced by these bacteria (Vásquez-Jaramillo, Ramírez, Akineden, & Fernández-Silva, 2017).

In 2011, WHO (World Health Organization), has a statement where it is mentioned that Healthcare Related Infections are more in low and middle income countries and it is 10.1% where as its number is less in high income country and is 7.6%. When the number of staying days in hospital is more, it is directly linked to more antibiotic resistant, more chance of increased Health Related Infections (HRI) (Hendrik, Voor In 't Holt, & Vos, 2015).

1.6 MRSA For cost comparison

Methicillin resistant *Staphylococcus aureus* (MRSA) is pathogen which is resistant to many drugs and its infection is related to hospital acquired, length of stay in the hospital may be longer and may leads to mortality. As mentioned earlier patient infected with this pathogen

also have to be kept in contact isolation and the cost is also extra like for nursing time, protective materials, cleaning stuff, hygienic things and so on (Hubner et al., 2014).

It is seen that MRSA screening itself is expensive and if the patient has to stay for longer then it is another increase in expenses. In order to reduce the cost burden, quick detection test has to be implemented. And factor which increases the cost burden are longer stay in hospital, cost from microbiological analysis of the swab, cost from the disposable items, clothing, nursing time , laundry, and cost related to contact isolation and so on (Goldsack et al., 2014).

The fast and accurate detection of the pathogen which carry MRSA genes help in reduction of hospital infection and unwanted contact isolations as well as costs associated to it. When the sample (swabs from nose, groin, axilla, wounds) is collected, it should go through the PCR method which is one of the genotypic methods to detect the *Staphylococcus* which is resistant to methicillin. Though the traditional culture method can also be used to identify the pathogen but this culture technique some time give the false positive result and creates further problems in treatment mechanisms. On the other hand, PCR method give accurate result and also the method is fast in detection and hence reduces the costs, which also states that genotypic method is necessary before the culture technique (Andrea Tübbicke, 2013; Gidengil et al., 2015; McKinnell et al., 2015).

Though the number of MRSA cases is rising globally, its rate is still low in Scandinavian countries, which is due to strict control measures. In Norway, the proportion of *S. aureus* isolates which are resistant to methicillin has been less than 1% for nearly 10 years but the reported occurrence rate of MRSA in general population has raised from 0.5 per 100,000 populations per year in 1995 to 19 per 100,000 population per year in 2010 (Li, Ulvin, Biboh, & Kristiansen, 2012).

Norwegian guidelines for MRSA require the following patients to be tested at admittance:

- Patients who have previously tested positive and have not had at least three negative tests after that.
- Patients who have previously tested positive during the last 12 months.
- Patients who have been living with someone that are MRSA positive.
- Patients who have been in contact with someone that are MRSA positive without using protective gear.

- Patients that during the last 12 months have been admitted to a hospital, been extensively treated or examined by health staff or worked in a health institution, refugee camp or orphanage outside the Nordic countries.

New staff are tested according to the same criteria (Arne Deggerdal, personal communication).

Accute patients are kept in isolation during tests and the traditional culture test take about 48 hour, which increases extra costs. But the new method based on PCR called Xpert MRSA assay which take only 75 minutes to give result. Even though this method is expensive but studies suggest PCR based method is more sensitive and more specific (Li et al., 2012). The Xpert MRSA PCR method combines the three steps for complete rapid testing, purification of sample, amplification of nucleic acid and detection (Andersen et al., 2010).

Price for MRSA detection kit

Price is from the site of the distributor Medac Diagnostica GmbH.
Price for an MRSA detection kit for 25 reactions is 515 EURO and for 50 reactions is 935 EURO,
Here, if 1 EURO= 10 NOK (Approximately)
Then for 50 reactions, price is 935 EURO.
For 1 reaction 935/50 =18.7 EURO
Therefore, for 1 reaction price is 18.7*10 = 187 NOK.
But for 25 reactions price is 515 EURO and for unit reaction 515/25=20.6, which is 206 NOK (MedacGmbHDiagnostika, 2017).

1.7 Price Sensitivity

Price sensitivity is the degree to which consumers are affected by the change in the price of product or services. Price elasticity of demand is a calculated measure for price sensitivity. Price sensitivity, when properly calculated, can predict changes in customer purchase behavior in response to a certain change in product price. This helps the manufacturer to go for better decision in price setting.

There are several pricing strategies that suppliers of medical tests could possibly use, but the two most common are:

1. Cost plus pricing. This means that the selling price is the sum of the cost price plus a mark-up. The mark-up is basically the profit, cost price is the sum of the COGS and the products part of the company's overhead. Note that if competing products have lower cost price, they will with this system also have a selling price advantage.
2. Competitive pricing is based on the selling price of competing products. It will usually mean that a company will have to accept smaller profit margins when a new product is introduced. It is a strategy which is usually deemed necessary if the product is price sensitive.

Some products which do not show any reaction on change in price are said to be price inelastic and these products are used on daily basis.

Price elasticity of demand (PEoD) measures the sensitivity of quantity demanded if there is change in the price of the product.

PEoD = (% Change in the Quantity Demanded) / (% Change in the price).

PEoD is expressed on the following conditions.

- If PEoD >1, price is elastic and it is sensitive to change the price.
- If PEoD = 1, Demand is unit elastic.
- If PEoD < 1, Demand is price inelastic (Fiona, 2016).

1.8 Aim of the study

There were mainly two aims for this study namely:

1. To estimate a price where molecular tests are competitive with traditional techniques.
2. To perform a price sensitivity analysis.

2. Material and Methods

2.1 Literature survey methods

The literature search was done online and the databases accessed was Google Scholar, Web of Science, Oria (University online library) and Science Direct. In addition information was obtained by looking directly in official Norwegian statistics and checking the web-sites of relevant hospitals and the Norwegian "Folkehelseinstituttet".

2.2 Interview techniques

The interview with ESBL specialist professor Rafi Ahmad was performed as an open-ended, exploratory interview.

2.3 Questionnaire

The questionnaire was prepared based on the information from the literature review focusing on a price where molecular tests are competitive with traditional techniques. The questionnaire was aimed for different hospitals in Norway and it contains 8 questions in total. Among which some questions have Yes-No answers, some multiple choice answers and one open ended questions where participants can express their views.

2.4 Survey method

The electronic questionnaire was sent to different hospitals with microbiology department in Norway by e-mail address provided by University. The questionnaire was in fillable PDF forms where it can be fill, save and send back by e-mail. The Email addresses of different hospital in Norway was obtained from their website tracking through online web pages. The mail was addressed to the person responsible for ESBL testing in hospitals. Before placing the questionnaire in email short introduction about the project was mentioned. The questionnaire is attached as appendix 1.

2.5 Analysis methods

Data analysis is a process of inspecting, cleansing, transforming and modelling data in order to have useful information, informing conclusions and supporting decision making process (Selene Xia & Gong, 2014). The main analysis activity was expected to be construction of price elasticity profile and calculation of confidence intervals. Unfortunately, it is clear that data are too limited for any such analysis. Instead, analysis will just be based on comparison of what can be estimated as realistic sales price compared to what the responding hospitals are willing to pay.

3. Results

The results in this thesis can be grouped in three. First there is the information obtained by interviewing one of the foremost Norwegian experts on ESBL testing, professor Rafi Ahmad. Second, there is the results from the survey described under Materials and Methods. Finally some results are calculations based on official statistics or data from suppliers. It important to stress that whereas the data obtained from literature search cannot be considered results, any information obtained by analysis, calculations or cross-tabulation of such data can be considered results. All prices referred to in this thesis is without VAT.

3.1 Interview

The summary of the interview done with professor Rafi Ahmad is mentioned as, at first he said that he is working on ESBL using sequencing technology, so he can answer anything only about sequencing related to ESBL. And about the kits use and its pricing, he suggested to visit hospitals to get further information as he is not using any kits and related technology method, so he cannot say anything related to kits method.

He mentioned, to go for the detection of ESBL, certain steps have to be followed as mentioned below.

First, we need to check whether the sickness is due to bacteria or virus. If its bacteria then we need to go for go for the culture of this bacteria from clinical sample, it may take 24 to 48 hours or even more in some cases, then we need to look for which bacteria is this, after that whether the bacteria is resistant or not, then we need to check for bacterial species.

So, for this detection method traditional culture is necessary and he don't fully support that kits use method can be the better than traditional culture (Phenotypic test) technique. Also, he mentioned that detection of ESBL directly from the clinical sample without going through microbiological culture is not possible. Also, he said that even if you use kits, you have to go through microbiology test and the kits method do not detect new strain. So his overall saying was traditional detection method is the best till now.

3.2 Survey

Four of the contacted hospitals gave a response, three of them by filling in the forms and the last one by stating that they felt that it was wrong to focus on economic alone. The responses are anonymized, the three hospitals referred to as hospitals A, B and C, respectively. Very few numbers of response have been obtained from the targeted hospitals and most of them did not reply the email. The hospitals that gave a meaningful response provide health coverage for roughly 701 000 individuals as of 2017 according to their own annual reports. That constituted some 13% of the Norwegian population at the time.

The results from the survey are tabulated below.

The first question in the survey was: Provided that PCR based ESBL detection is as sensitive and as precise as the traditional methods and has 24 hours shorter time to results, would you consider changing from the traditional methods if the price was low enough? All three responding hospitals answered that they would, but one hospital (C) answered that if possible they would prefer a fast method that would also detect new ESBL varieties. Although the questionnaire specifically asks for PCR based methods, it must be assumed that the answer will also cover LAMP based methods, as they have the same strengths and weaknesses as PCR based tests.

The second question was: Which price per test would make you switch to PCR based ESBL detection for screening?

Table 5: Price that hospitals will pay for fast molecular ESBL screening tests.

Price per test in NOK	**Hospitals**
50	A
150	B, C
450	-
1000	-
2500	-

As seen from the table 5, two of the hospitals was found to be ready to pay 150 NOK and one hospital was interested to pay 50 NOK for PCR based ESBL detection for screening per test. None of the hospitals were interested to go for higher price as mentioned in the table.

The third question was: Which price per test would make you switch to PCR based ESBL detection for clinical sample?

Table 6: Price that hospitals will pay for fast molecular ESBL tests (clinical samples).

Price per test in NOK	Hospitals
50	A, C
150	B
450	-
1000	-
2500	-

As seen from table 6, for clinical samples testing, two hospitals are found to be interested to pay 50 NOK and only one hospital is ready to pay 150 NOK.

Question number 4 was: Would you prefer to have a kit that uses your current PCR instruments? All of the hospitals who have responded to survey are interested to go for kit method which uses their current PCR instrument.

Question number 5 was: If you should buy an instrument dedicated to fast ESBL testing, what would you deem to be sufficient maximum number of samples per run?

Table 7: Test capacity deemed sufficient by the different hospitals.

Number of samples per run	Hospitals
8	A
24	B, C
48	-
96	-
>96	-

From table 7 it is seen that, hospitals B and C wants 24 samples to be run at a time but hospital A want only 8 sample to be run in one time.

Question number 6 was: Based on your answer to Q5, what would you consider a reasonable price for the instrument that can handle the analysis (PCR) part of fast ESBL testing?

Table 8: Price considered reasonable for an ESBL test analysis instrument.

Price in NOK	Hospitals
5000	-
15 000	A
45 000	C
100 000	B
300 000	-

From table 8 it can be seen that there is a relatively wide range of what the hospitals are willing to pay for test instruments, in this case qPCR or LAMP instruments. It is also important to note that hospital A is the respondent that feels that the price should be lowest. It is also this respondent that only needs a throughput of eight samples per run.

Question number 7 was: Based on your answer to Q5, what would you consider a reasonable price for the instrument that can handle nucleic acid extraction and PCR setup as well as the analysis (PCR) part of fast ESBL testing?

Table 9: Price considered reasonable for an ESBL test sample prep + analysis instrument.

Price in NOK	Hospitals
10 000	-
30 000	C
100 000	A
250 000	B
500 000	-

As can be seen from table 9, hospitals A and B are willing to pay a premium for a system that includes sample preparation. This does not seem to be the case for hospital C.

Question number 8 was: What would you consider an acceptable price for a kit used by the instrument described in question 7, including reagents for nucleic acid extraction as well as for analysis (PCR or similar)?

Table 10: Price that hospitals will pay for fast molecular ESBL tests including sample prep.

Price per test in NOK	Hospitals
50	A, C
150	B
450	-
1000	-
2500	-

From the above table it was seen that none of the hospitals were interested in paying a significant premium for a kit that includes sample preparation.

3.3 Derived data

None of the responding hospitals have published their resistance testing data in recent years. However, in "Resistensrapport for Sykehuset Innlandet 2018" (Sykehuset Innlandet 2018) it is stated that in general the incidence of antibiotic resistance at Sykehuset Innlandet is close to the national average. The number of performed ESBL tests from Sykehuset Innlandet are therefore considered representative for the number of ESBL tests needed for a population of the size served by Sykehuset Innlandet HF (408 051 inhabitants as of 31st December 2017; Sykehuset Innlandet HF Annual Report 2017).

"Resistensrapport for Sykehuset Innlandet 2018" (Sykehuset Innlandet 2019) is an official report which is basically an automatic report from the database tool Crystal reports 2018, with an unsigned introduction. It can be found on the hospital's website and the link is given in the reference list (SykehusetInnlandet, 2018).

The relevant ESBL test data extracted from the tables of the resistance report is:

Blood culture

E.coli: 349 tests from 324 patients. 14 tests positive for ESBL A.

Klebsiella pneumonia: 82 tests from 72 patients. 3 tests positive for ESBL A.

Urine (both from hospital and outpatients)

E.coli: 7322 tests from 5377 patients. 165 tests positive for ESBL A + 1 positive for ESBL M.

Klebsiella pneumonia: 2041 tests from 1697 patients. 65 positive for ESBL A + 1 positive for ESBL M.

Screening

A total of 425 patients were tested. 84 were positive.

This adds up to 10 219 tests, or roughly 25 tests per 100 individuals that the hospital provides health care for.

The hospital labs responding to the survey are all of a similar size, so it seems to be logical to use average numbers for estimating the number of test per laboratory per year. The labs on the average provide tests for 234 000 inhabitants, which means 5853 tests per year. A large proportion of these would be performed in connection with planned admission. To get an upper estimate of the PCR capacity requirement for these laboratories, the number of samples per year was divided by the number of working days in 2017 (251) to get 23.3 samples per day. This is clearly an overestimate of samples per run. Running one PCR reaction per working day would waste the time to result advantage that molecular testing offer. It does, however align well with the numbers obtained from the survey in that more than 24 samples are not needed.

Price per test calculations for eazyplex superbug kits:

According to the UK based National Institute for Health and Care Excellence (NICE), the cost of the Genie II device described in the introduction is GBP (£) 9,000.

The cost of Kits: GBP 1542, which contains 48 single use test kits,
Therefore, for single time use, we have 1542/48=32.13

Also, according to the institute, unit cost for traditional microbiological culture is GBP 7.00
So roughly if I take, 1 GBP = 11 NOK.

Then, we have Unit cost by using kits is 32.13*11=353.43 NOK.
And unit cost by using microbiological culture is 7*11=77 NOK.

From the above figure though it looks, by using kits it becomes so much expensive but if we see the time duration of the result and efficiency in detection of the CPO and ESBLs genes, it

can be justifiable that using kits is better than traditional microbiological culture technique (NICE, 2017).

Price per test calculations for ESBL PCR kit from manufacturer company Gene Proof:

Price is from the site of the distributor Medac Diagnostica GmbH.

We have ESBL PCR kit for 25 reactions for 490 EURO and 50 reactions for 890 EURO,
Here, if 1 EURO= 10 NOK (Approximately)
Then we have for 50 reactions, on 890 EURO.
For 1 reaction 890/50 =17.8 EURO
Therefore for 1 reaction we have, 17.8*10 = 178 NOK (MedacDiagnostics, 2016).
While this thesis was written, the Gene Proof ESBL PCR kit was withdrawn from the market.

4. Discussion

This thesis with an intention to know the price sensitivity in the clinical testing market for ESBL, its evaluation cannot be conclusive due to limited number of respondents. If there would have been more response, then better explanation could have been obtained about pricing of the instruments and its kits. The hospitals who do not answer the survey, may be because of their privacy issues or they do not want to be in public about their systems.

In the questionnaire there seems to have some limitations, the upper limit of pricing scale of the kits and instruments have been set much higher, it would have been better to have more pricing points in the lower end of the scale. When asking for the reasonable price for analysis plus extraction instrument, it would have been better to ask how much they would be willing to pay in addition to the price of analysis instrument. The question related to extraction of nucleic acid and analysis of the clinical sample could have been separately mentioned.

The prices about the kits is not possible to achieve as what the customers are expecting and it seems lower than the range mentioned by the diagnostic company and health care excellence. None of the customers go above 150 NOK, as the pricing mentioned by diagnostic company and health care excellence are 178 NOK and 353.43 NOK respectively (MedacDiagnostics, 2016; NICE, 2017). Also, the kits available for MRSA detection from Medac diagnostica, its pricing is 187 NOK per sample, so its not possible to have ESBL detection kits in lower prices than as mentioned above (MedacGmbHDiagnostika, 2017). However, the next step on the price "ladder" of the questionnaire is 450 NOK/sample, so it is not unrealistic that the respondents that answered 150 NOK would be willing to prices comparable to that of Gene Proof kit (178 NOK/sample). On the other hand, the fact that the kit is no longer on the market may mean that the price was either too high to achieve sales or too low to make a profit.

When question about whether or not they preferred kits that could utilize their existing analysis equipment, all the respondents answered yes. This seems to be in contrast to the results of Parajuli (Parajuli, 2018). One of the obstacles to using PCR based ESBL detection that appeared in the responses to his survey was that the existing PCR equipment was either old or overloaded with other tests. One possible explanation for this difference is that the hospitals responding to Parajuli's survey were the largest ones in Norway, whereas the respondents to this survey are medium size. Another possibility is that the difference is just due to small sample size.

The respondents also were very reluctant to pay much for a pure analysis instrument. This may be related to the fact that they preferred to use their existing equipment. Only one of the respondents (B) was willing to pay what is a realistic price for a qPCR or a LAMP instruments. There is a range of small qPCR instruments available for less than 100 000 NOK and the LAMP instrument Genie II will come in at around 100 000 NOK. Another respondent might be able to find a small capacity qPCR instrument at a slightly higher price than they are willing to pay 45 000 NOK. For instance there is a dual channel 16 sample qPCR instrument available at 6500 USD, which is equal to 56 500 NOK approximately (Chai, 2019). There is no qPCR solution currently available at 15 000 NOK, which is the price range that hospital A wants. The only way to achieve something like this price would have to be using end-point PCR.

Respondents A and B were more willing to pay for a combined instrument for sample prep and analysis. B was willing to add 150 000 NOK for the extraction part and A was willing to add 85 000 NOK. These are both realistic prices, but since A was unwilling to pay a realistic price for the analysis part, it is only respondent B that is interested in paying a realistic price for a combination instrument. Respondent C requires a special comment. Apparently, they seem to, willing to pay less for a combination instrument than for a stand-alone analysis instrument. This may be an artefact of the questionnaire. The hospital has answered 30 000 NOK for the combination instrument, which is closer to the 45 000 NOK they have answered for the analysis instrument than the next step up the "ladder" (100 000 NOK). What this really mean is that respondent C is not interested in paying much of a premium for adding sample prep.

When the patients are admitted in the hospitals and if ESBLs are detected from patients' sample by chance then such patients are kept in isolation (Lingaas, 2016). Also, when patients admitted and screened by culture technique then patients are kept in isolation for 5 days till result of the culture comes. The duration of the positive patients which are kept in isolation varies depending on the techniques used for detection. If culture technique is followed then isolation is done for 20 days, and isolation ended when the three successive cultures comes negative and if PCR technique is followed then isolation is done for 7 days. Also, culture screening costs 7 EURO and PCR screening costs 19 EURO (190 NOK) but survey result shows only two of the customer willing to pay 150 NOK and one customer willing to pay 50 NOK for screening by PCR, which is not achievable (Van der Zee et al., 2013).

The respondents all want a relatively low throughput from their dedicated analysis instruments, either 8 or 24. This fits with customer need calculation performed in the results section based on public numbers from Sykehuset Innlandet.

Finally, there are two surprising results from the survey. One is that hospital C is willing to pay more for screening than for clinical samples. This seems counter-intuitive, since one would expect clinical samples to be more time critical. Also, none of the respondents seem to be willing to pay anything extra for the inclusion of sample prep in the kits. This may be due that the steps of the price "ladder" are too far apart. As mentioned earlier in the discussion, it might have been better to ask how much added value they considered sample prep to be, and then have a range from 5 NOK to maybe 50 or 100 NOK.

5. Conclusion

This thesis had two main objects:

1. To estimate a price where molecular tests are competitive with traditional techniques.

2. To perform a price sensitivity analysis.

Due to the low number of respondents it was not possible to perform a price sensitivity analysis, since this is a statistical procedure requiring large numbers.

Data obtained from the performed survey gave some indication of the price that microbiology labs of medium sized hospitals are willing to pay for molecular testing for ESBL. At least in some circumstances some hospitals were willing to pay close to a realistic price for the reagent kits. One out of three hospitals was willing to pay realistic price for instrumentation.

Two minor pieces of fact should also be mentioned here. First, one out of three hospitals was willing to pay higher prices for screening than for clinical samples. Second, the analytic instruments that these hospitals wanted should ideally have a quite low capacity, only 8 to 24 samples per run.

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Appendix 1-Survey Questions

The answers to the questions below will contribute to the master thesis "Price sensitivity in the market for Extended-Spectrum ß-Lactamase (ESBL) testing"

Question 1: Provided that PCR based ESBL detection is as sensitive and as precise as the traditional methods and has 24 hours shorter time to results, would you consider changing from the traditional methods if the price was low enough?
Yes No

If yes, continue with Question 2, if no, please specify why.

Note: all prices mentioned below is in Norwegian kroner.
Question 2: Which price per test would make you switch to PCR based ESBL detection for screening?
50 150 450 1000 2500

Question 3: Which price per test would make you switch to PCR based ESBL detection for clinical samples?
50 150 450 1000 2500

Question 4: Would you prefer to have a kit that uses you current PCR instruments.
Yes No

Question 5: If you should buy an instrument dedicated to fast ESBL testing, what would you deem to be sufficient maximum number of samples per run.
8 24 48 96 >96

Question 6: Based on your answer to Q5, what would you consider a reasonable price for the instrument that can handle the analysis (PCR) part of fast ESBL testing
5000 15 000 45 000 100 000 300 000

Question 7: Based on your answer to Q5, what would you consider a reasonable price for the instrument that can handle nucleic acid extraction and PCR setup as well as the analysis (PCR) part of fast ESBL testing
10 000 30 000 100 000 250 000 500 000

Question 8: What would you consider an acceptable price for a kit used by the instrument described in question 7, including reagents for nucleic acid extraction as well as for analysis (PCR or similar).
50 150 450 1000 2500