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Master Thesis

Feasibility of using a sequence- based method (AMR-Diag) for detection of antibiotic resistance in Humans

Applied and Commercial Biotechnology

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Abbreviations

ABR - Antibiotic/antibacterial resistance

AMR – antimicrobial resistance

AST - Antimicrobial Susceptibility Testing

CRP - C- Reactive Protein

DDD - Defined Daily Dose

ESBL - Extended Spectrum Beta Lactamase

EUCAST - European Committee for Antimicrobial Susceptibility Testing

GP - General Practitioner

MIC - Minimum Inhibitory Concentration

MRSA - Methicillin-Resistant Staphylococcus aureus

NIPH - National Institute of Public Health

OECD - Organization for Economic Cooperation and Development

PCR - Polymerase Chain Reaction

POCT - Point of Care Test

ROI - Return on Investment

SWOT - Strengths Weaknesses Threats Opportunities

WHO - World Health Organization

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Abstract

Antibiotic resistance has become a global problem and the need to hinder its continuous spread due to inappropriate prescribing of antibiotics, overuse of antibiotics in livestock, and insufficient hygiene practices in hospital, global trade and travel is of utmost concern. Treating resistant infections have an effect on both the hospital and society. The absence of accurate diagnosis of clinical infections is a call for rapid evidence-based diagnostic tests to help clinicians better identify and target bacteria causing infections. The proposed tool, AMR-Diag seeks to fulfil the need in the reduction of AMR spread with faster and more accurate diagnostics.

In order to validate the need and establish early feasibility for the development of ABR-Diag, we used primary data from exploratory discussions from both representatives from microbiology lab and team with proposed tool, secondary data from articles amd databases. We used the Business model canvas to create value for the company and the Value Proposition Canvas to create value for customers.

Norway adopts the EUCAST guidelines whose diagnostic workflow takes up to 3-4 days before a patient can get appropriate treatment with antibiotics. However, the sequence-based diagnostic workflow on ABR differs from the current standard EUCAST disk testing. AMR-Diag has a competitive advantage over other diagnostic methods. Length of patient stay in hospital is a serious cost element.

The cost of DNA sequencing is a major obstacle for the proposed tool, AMR-Diag, to become implemented. However, the cost of DNA sequencing is expected to continue to reduce. The proposed tool AMR-Diag is a leap forward in the fight against AMR and therefore should be given a chance to prove what it can do in this course. We therefore propose that the company uses Norway as its beachhead market, and joins forces with its partners and do political lobbying for Norway to take a leading role in combating AMR.

1. Introduction

The World Health Organization (WHO) defines antibiotics as medicines used to prevent and treat bacterial infections. According to WHO, antimicrobial resistance (AMR) spread is a principal threat to global health, food security, and development. It is worldwide and can affect anyone of any age from less developed to developed countries. Although antibacterial resistance occurs naturally, antibiotic resistant bacteria increasingly emerge and spread due to inappropriate prescribing of antibiotics, their overuse in the livestock sector, and insufficient hygiene practices in hospital. Global trade and travel are also accelerating the spread misuse and overuse of antibiotics (D'Costa et al., 2011; WHO, 2017). It is worth noting that it is the bacteria and not the individual that becomes resistant to the antibiotic (WHO, 2015a). While there is a widely recognized need for new antibiotics to address AMR, the number of companies undertaking Research and Development (R&D) in this area has decreased substantially with a corresponding decrease in both the development pipeline and number of approvals for new antibacterial medicines (Payne, Miller, Findlay, Anderson, & Marks, 2015). Several point-of-care diagnostic tests provide results within a shorter time frame of 1-4 hours but are not able to provide information about the antibiotic resistance profile of the infection (Dubouix-Bourandy et al., 2011; Poritz et al., 2011; Zumla et al., 2014).

The burden of deaths from antimicrobial resistance is estimated to sky rocket to 10 million lives each year by 2050, at a cumulative cost to global economic output of $100 trillion (O'Neill, 2016) and losses of $2.9 trillion (~0.16% of their GDP) in Organization for Economic Cooperation and Development (OECD) countries (OECD,2016) . In order to tackle antibiotic resistance, the World Health Assembly, adopts a global action plan on antimicrobial resistance, which outlines five objectives to achieve continual ability to treat and prevent infectious diseases with effective and safe, high quality medicines, used in a responsible way and available to all in need:

- To improve awareness and understanding of antimicrobial resistance through communication, education and training;
- To strengthen surveillance and research;
- To reduce the incidence of infection through effective sanitation and hygiene;
- To optimize the use of antimicrobial medicines in both human and animal health;

- To ensure sustainable investment in contesting antimicrobial resistance (WHO, 2015b)

In Norway, resistance to antibiotics is monitored by 3 systems; Norwegian Surveillance System for Communicable Diseases (MSIS), Norwegian Surveillance System for antimicrobial drug resistance (NORM), Norwegian Surveillance System for antimicrobial drug resistance - Veterinary Medicine (NORM-VET) (NORM, 2017). In accordance with WHO to fight antibiotic resistance, the Norwegian Ministry of Health and Care Services outlines the National Strategy against Antibiotic Resistance 2015-2020 (Service, 2015) whose principal goals are: to reduce the total use of antibiotics, to use antibiotics appropriately (only when needed), to increase knowledge of what motivates the development and spread of antibiotic resistance, to be a driving force in international and normative work to increase availability, appropriate use, and development of new antibiotics, vaccines and better diagnostic tools. Among the sector specific goals, the health sector has to ensure that by 2020: Antibiotic use in the total inhabitants is reduced by 30 percent, measured in DDD/1000 inhabitants/day, as compared with 2012; Norway will be one of the three European countries that uses the least antibiotics on humans, measured in DDD/1000 inhabitants/day; Prescription of antibiotics will be reduced from an average of 450 prescriptions per 1000 inhabitants per year to 250 prescriptions per 1000 inhabitants per year; Prescription of antibiotics for respiratory infections will be reduced by 20 percent, measured in DDD/1000 inhabitants/day, compared to 2012; and finally, studies will be carried out on the burden of disease as a consequence of antibiotic resistance, as a consequence of possibly too little antibiotic use, and the effect of infection control measures (Service, 2015).

Norway has a National system for surveillance, officially nominated National Reference Laboratories and a National recommendation or obligation for reporting to health authorities (Prevention & Control, 2013). The prevalence of antibiotic-resistant bacteria in Norway is quite low, relative to the rest of Europe. *Staphylococcus aureus* resistance to Methicillin is the most common type of antibiotic resistance predominantly in hospital patients, people with weak immune systems and the elderly. Bacteria with the resistance mechanism Extended Spectrum β-lactamase carbapenemases ($ESBL_{CARBA}$) and bacteria resistant to all available antibiotics has been detected in Europe and there is fear that these infections might spread into the Norwegian Health Care System (NORM, 2017). IMP carbapenemase, *Klebsiella pneumonia*e carbapenemases (KPC), New Delhi metallo-beta lactamase, Oxacillinase (OXA-

48) and Verona integron-encoded metallo-beta lactamase (VIM), are the five most common carbapenemases in *Enterobacteriaceae* (Prevention & Control, 2013). This form of ESBL-resistance is the most concerning and there are few treatment options for these patients. However, factors such as; increased antibiotic use, travel, importation of food and spread of resistant bacteria in food production can change the situation in Norway (NORM, 2017).

It is therefore of utmost importance to estimate the disease burden and associated costs relating to antibiotic resistance in Norway (Service, 2015). Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality. In many clinical situations infections are not accurately diagnosed and, in the absence of an accurate diagnosis, clinicians prescribe antibiotics just to be on the safe side. This leads to increasing rates of AMR. There is therefore, a crucial need to provide rapid evidence-based diagnostic tests to help clinicians better identify and target bacteria causing infections. Treatment should therefore only commence in patients when a bacterial infection has been accurately identified. The correct antibiotic should be prescribed following rapid identification of the micro-organism alongside its antibiotic susceptibility (Plüddemann et al., 2015).

1.1 Priority Pathogens

According to the WHO priority pathogens list for Research and Development (R&D) of new antibiotics, ***Acinetobacter baumannii***, carbapenem-resistant; ***Pseudomonas aeruginosa***, carbapenem-resistant and **Enterobacteriaceae** (*Klebsiella pneumoniae, Escherichia coli*, *Enterobacter spp., Serratia spp., Proteus spp., and Providencia spp, Morganella spp*), carbapenem-resistant, 3rd generation cephalosporin-resistant, have been placed into the 1st of 3 priority groups: critical, high and low (WHO, 2017). Incidence of bacterial infections caused by ESBL producing bacteria are increasing in Norway (NORM, 2017). Resistance of *S. aureus* to methicilin (MRSA) remains a public health priority in Europe with some countries recording above 25% MRSA cases in 2016. Resistance is also seen in Vancomycin resistant *enterococci* (VRE) with 77 cases of VRE reported to MSIS in 2015, Multidrug resistance (MDR) as seen in tuberculosis with 3-12 cases treated annually in Norway (NORM, 2017) (ECDC, 2017).

Klebsiella pneumoniae

Klebsiella pneumoniae is common in urinary tract, respiratory tract, skin and bloodstream infections. It easily spreads between patients in healthcare settings through hands of hospital personnel and is a frequent cause of hospital outbreaks, if proper prevention and control measures are not taken. Resistance traits are often acquired through plasmids. *Klebsiella. pneumoniae* has a chromosomally encoded class A beta-lactamase which makes it resistant to aminopenicillins. Carbapenem resistance in *K. pneumoniae* by a range of carbapenemases, which may confer resistance to virtually all available beta-lactam antibacterial drugs is an emerging public health threat.

More than one third of the *K. pneumoniae* isolates reported are resistant to at least one of the antibiotic groups under surveillance (fluoroquinolones, third-generation cephalosporins, aminoglycosides and carbapenems) (ECDC, 2017). Although carbapenemase resistance was low in 2016, the majority of carbapenem-resistant isolates had additional resistance to the antibiotic groups under surveillance. Patients infected with multi-drug resistant *K. pneumoniae* with carbapenemase resistance have limited treatment options including combined therapy and use of antibiotics like colistin and others from polymixins group (ECDC, 2017).

E. coli

Although *Escherichia coli* is part of the normal intestinal flora in humans, it is commonly associated with bloodstream and urinary tract infections of community and healthcare origins in Europe. *Escherichia coli* resistance is either as a result of mutations or acquisition of mobile genetic elements encoding resistance mechanisms such as production of ESBLs. *Escherichia coli* resistance is continually increasing in Europe with increased resistance to commonly used antibiotics. Isolates are reportedly resistant to at least one of the antibiotic groups under surveillance. Resistance to carbapenems in *E. coli* remains low (<0.1%) in the EU/EEA (ECDC, 2017).

Acinetobacter species

Acinetobacter species mainly cause healthcare-associated infections, such as pneumonia and bloodstream infections, and often result in hospital outbreaks if appropriate prevention and control measures are not implemented. *Acinetobacter* species can persist in the healthcare environment and are difficult to eradicate once established. The Baltic countries, Southern and

South-eastern European countries show a high resistance level of *Acinetobacter* species. In 2016, most of the reported isolates indicated combined resistance to fluoroquinolones, aminoglycosides and carbapenems (ECDC, 2017).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a non-fermenting gram-negative bacterium commonly found in aquatic environments in nature. It is an opportunistic pathogen and a major cause of infection in hospitalised patients with localised or impaired immune systems. It is a common cause of hospital acquired pneumonia, bloodstream and urinary tract infections.

Carbapenem resistance and resistance to fluoroquinolones, aminoglycosides, some beta lactams and polymyxins is common in *P. aeruginosa* in many European countries. As *P. aeruginosa* is intrinsically resistant to the majority of antimicrobial agents, combined resistance to multiple antimicrobial groups is further complicating treatment of serious infections. Resistance occurs through modified antimicrobial targets, exclusion of antibiotic if they enter the cell and reduced permeability and degrading enzymes preventing antibiotics from penetrating its outer membrane (ECDC, 2017).

Methicillin Resistant *Staphylococcus aureus* (MRSA)

In addition to health-care associated infections, increasing levels of community-associated MRSA are being reported worldwide. In 2016, as in previous years, large inter-country variations in MRSA percentages among invasive isolates of *S. aureus* were observed across Europe. Based on consistent laboratory reports between 2013-2016, the EU/EEA population-weighted mean MRSA percentage has significantly declined (ECDC, 2017). In Norway, MRSA infections are registered as healthcare-associated (HA) for healthcare personnel or cases diagnosed due to a stay in hospital or nursing home without reported infection abroad, community-associated (CA) for cases diagnosed in the primary health care without hospitalisation or having worked in in a healthcare unit or reported infection from abroad, or Imported infection based on cases where infection acquired abroad or from unknown sources are reported. Between 20 and 40 per cent of the Norwegian population are colonised with *S. aureus* without symptoms. MRSA are resistant to all penicillin-derived antibiotics making treatment of MRSA infectionis difficult. *Staphylococcus aureus* is one of the most common causes of infection in healthcare institutions (NORM, 2017).

1.1.1 Susceptibility Testing

Upon administration of an antibiotic, resistant bacteria are able to thrive and multiply over susceptible bacteria which are killed or inhibited. This process of influence by an antibiotic is called selective pressure for the survival of resistant bacterial strains. Although some bacteria may be naturally resistant, others may become resistant through genetic mutation or acquired resistance from another bacterium (Gallo & Puglia, 2013).

Currently, bacterial susceptibility can be measured by both phenotypic and/or genotypic methods. Phenotypic methods including disk diffusion or MIC determinants in which the minimum inhibitory concentration (MIC) value of an antibacterial agent of an organism is determined, predict measurable susceptibility and resistance, while genotypic methods predict resistance only. Zone inhibition by a very low concentration of the agent is considered more sensitive than one which is not inhibited even by a high concentration. The clinical criteria are based on pre-established breakpoints which objectively classify an organism as either resistant or susceptible (sensitive). The S-breakpoint is a concentration that separates sensitive from non-sensitive micro-organisms. It is expressed as $S \leq X$ mg/L (where X is a MIC value), and the concentration which separates resistant organisms from non-resistant (e.g. sensitive or intermediately sensitive) organisms is called the R-breakpoint and is expressed as $R > Y$ mg/L (where Y may be the same or a higher MIC value than X). Bacteria are classified as resistant when their MICs are above the predefined threshold. Antimicrobial susceptibility testing in the European Union is harmonised through EUCAST which decided to develop a disk diffusion test built on the Mueller Hinton medium with a confluent McFarland 0.5 inoculum (EUCAST, 2017; Kahlmeter, 2014).

ESBL producing organisms have become multidrug resistant and their detection is not always evident in routine susceptibility tests. The difficulty in detecting such complex resistant phenotypes is a serious challenge facing clinical laboratories and have contributed to the uncontrolled spread of ESBL producing organisms and related treatment failures. Hence, there is a need for better detection of ESBLs in the clinical laboratory (Mohanty, Gaind, Ranjan, & Deb, 2010).

The **ESBL E-test method** using the cefepime-clavulanate strip is confirmed to be the best method so far, especially in AmpC beta-lactamase producing organisms (Mohanty et al., 2010), with sensitivity of 98%, better than 83% sensitivity using cefotaxime-clavulanate strip, and 74% sensitivity using ceftazidime clavulanate strip (Stürenburg, Sobottka, Noor, Laufs, & Mack, 2004).

The **Vitek ESBL test** has proven to be more reliable than the 2-disk test for the detection of ESBLs in E. coli and K. pneumoniae, the two species in which ESBLs are most common. The test also detects hyperproduction of the K. oxytoca beta-lactamase, a situation which leads to similar resistance levels to that in ESBLs (Sanders et al., 1996).

However, these currently used routine methodologies are still associated with time delays and economic cost, especially for organisms that are difficult to grow. They are often accompanied by a need for further genetic characterization of isolates such as sub-typing and identification of resistance genes, often requiring the involvement of specialized or reference laboratories. This further adds to the cost and time delays, reducing the possibility of a timely response. Whole genome sequencing (WGS) methods have proven to be feasible for surveillance purposes, with high concordance when compared to phenotypic susceptibility testing for the prediction of antimicrobial susceptibility (Tyson et al., 2015; Zankari et al., 2013). Other genotypic methods include Single PCR, multiplex PCR, Realtime PCR and Ligation techniques (Prevention & Control, 2013). Previous feasibility studies to identify antimicrobial resistant genes have developed a web-based method, **ResFinder** that uses BLAST for identification of acquired antimicrobial resistance genes in whole-genome data with 100% identity to 1862 GenBank files (Zankari et al., 2012). Spectrometric identification uses MALDI-TOF for analysis (Prevention & Control, 2013).

1.2 Description of “The Proposed Tool” (AMR-Diag)

The continuous spread of antibiotic resistance is a global problem with incidence of infections with ESBL-resistant bacteria increasing in Norway in particular and worldwide in general. The dire need for accurate and real-time diagnosis of patients to minimize AMR spread has greatly motivated Associate Professor, Dr. Rafi Ahmad and his team who are working on

developing a sequence-based method to detect antibacterial resistance. The project AMR-Diag, which has been recently funded by the Research Council of Norway (RCN), Better Health and Quality of Life (BEDREHELSE) programme. AMR-Diag is a joint Indo-Norwegian researcher project on antimicrobial resistance, following up the bilateral agreement of Science and Technology between India and Norway, and the Memorandum of Understanding on health research between the Indian Council of Medical Research (ICMR) and the Research Council of Norway (RCN). This project got research funding from Norway and India of 11 million NOK. and feasibility studies are ongoing to see to its realization. The proposed tool is a real-time sequencing-based method for detection of antimicrobial resistance in humans. The plan is blood and/or urine samples of patient is sent from hospital or primary health care to a microbiology (MCB) lab for DNA extraction, followed by a culture dependent/culture independent DNA sequencing. Based on a machine learning approach, microbial sequences will be matched in real time with sequences in the customized in-house database to detect bacterial species and resistance type and feedback is sent to the Physician (discussion with Dr Rafi).

1.3 Aim of the study

As its main objective, this project sets to validate the need and establish early feasibility for the development of antimicrobial resistant (AMR)- Diagnosis.

Secondary objectives:

- How practical is it for the primary (municipal e.g. GPs, Old people's home) and hospital health care professionals to use the proposed tool (AMR-Diag)?
- Is AMR-Diag advantageous from a cost and time over current detection methods?
- Determine the value potential of AMR-Diagnosis.

2. THEORY/BACKGROUND

2.1 Competition

The sequence-based method for detection of antibacterial resistance may face a lot of competition as there are already existing techniques (Pulido, García-Quintanilla, Martín-Peña, Cisneros, & McConnell, 2013) to detect antibiotic resistance as summarized in the table below.

Table 1: methods used to detect ABR

Methods	**Description/characteristics**
Culture media (EUCAST, 2017; Sanders et al., 1996; Stürenburg et al., 2004)	-Phenotypic methods used to determine both antibacterial resistance and susceptibility -Results take 3-4 days -High sensitivity for detecting antibiotic resistance -Highly standardized by CLSI and EUCAST -These methods usually require pure cultures for susceptibility testing to be performed -Examples; broth dilution, E-test, Disk Diffusion and Commercial systems (Vitek from BioMerieux, Microsan WalkAway from Siemens)
PCR-based techniques (Bogaerts et al., 2013; Monteiro, Widen, Pignatari, Kubasek, & Silbert, 2012)	-Genotypic method to determine resistance only -Carried out in a relatively short period of time -Rapidly provides information on antibiotic resistance -The presence of resistance genes may not always compare with phenotypic resistance **Examples;** -single multiplex real-time - Real-time Array-PCR for Infectious Diseases technology
MALDI-TOF MS	-The use of MALDI-TOF MS for the identification of resistant strains based on differences in spectra is extremely rapid and highly automated

(Hrabák et al., 2012)	-The results obtained using MALDI-TOF MS may not always directly compare with phenotypic resistance and differences between strains that are not related to resistance complicate the explanation of results.
Microarray (Cohen Stuart et al., 2010)	-Identify the presence of specific nucleic acid sequences using complementary oligonucleotides - Can detect thousands of different resistant genes in a single assay -Highly sensitive and specific -Results obtained may not always correlate with phenotypic resistance as there is no data on MIC values -Microarray technique may have limited ability to detect resistance in isolates harboring novel or uncharacterized mechanisms of resistance -Method no longer in use but is being implemented in Illumina's Hi-Seq genome sequencers
Microfluidics (Choi et al., 2013)	-Make use of extremely small volumes of reagent and analyte for detection of antibiotic resistance -MIC values can be obtained -Automated with the potential for providing results extremely rapidly (3-4hours) -Due to their small size, the chips used in these assays can be fused into portable devices, which may facilitate antimicrobial susceptibility testing at the point of care
Whole Genome Sequencing (Snitkin et al., 2013)	-Has the potential to predict resistant phenotypes -when used alone, sequencing may fail to predict resistance pattern if it has not been genetically characterized -Rapid sequencing of an entire bacterial genome -High cost of sequencing relative to other methods

2.2 Evolution of DNA sequencing costs

The cost of sequencing a genome has witnessed great improvement over the years, with the evolution of sequencing technologies. The initial cost of sequencing at $100 million in the early 2000s using the Sanger sequencing was brought down to $10,000 later in the decade following the introduction of next generation sequencing methods like Illumina, Pyrosequencing, and SOLiD in the market. This cost evolution (Figure 1) is as a result of acquisition of more sophisticated instrumentation and it continues to decrease as more and more sequencing methods (third generation technologies) are introduced into the market (Wetterstrand, 2018).

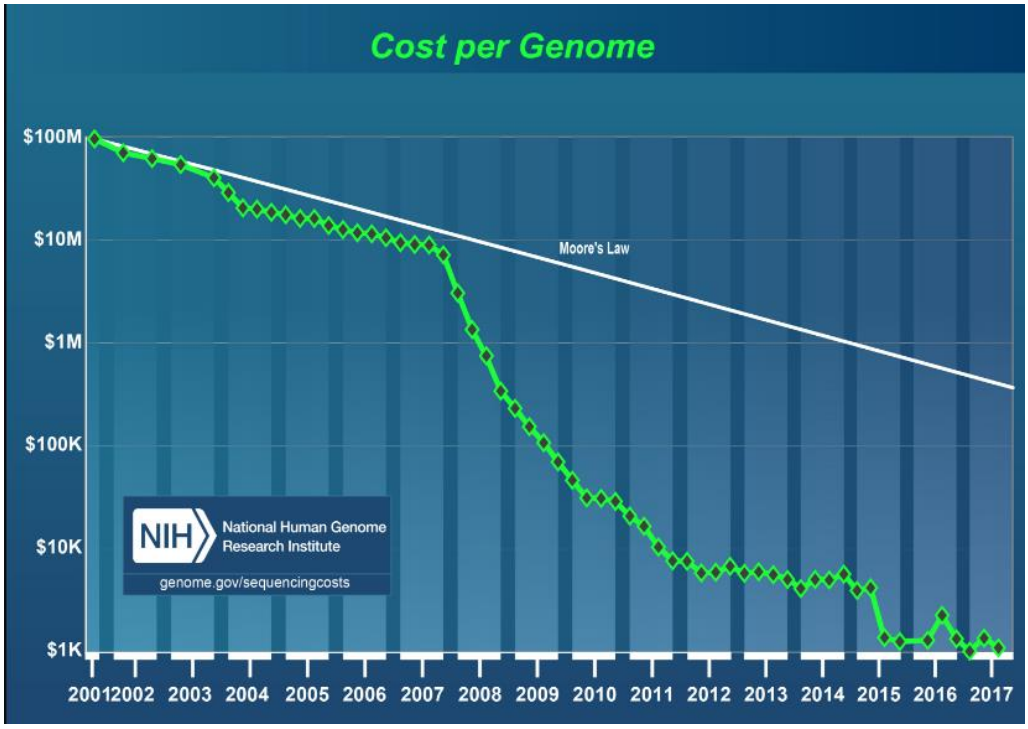


Figure 1: cost per genome (Wetterstrand, 2018)

2.3 Business Model

A business model describes the rationale of how an organization creates, delivers and captures value. It can be best described through 9 basic blocks which are; key company partners, key activities, key resources, channels, value proposition, customer relationships, customer segments, cost structure, and revenue streams. These 9 basic blocks which form the business model canvas, cover four main areas of the business: the customers, the offers, the infrastructures, and the financial viability (Osterwalder & Pigneur, 2010). The success of any business idea is determined from both investor and customer perspectives. The entrepreneur must set out to answer the following questions:

- Who are the customers to be satisfied?
- What is the market size and trend?
- What competition is there in the market already and what about newcomers?
- What is the competitive advantage of the product or service?
- How much financial funding is needed and how will the business idea generate profit?

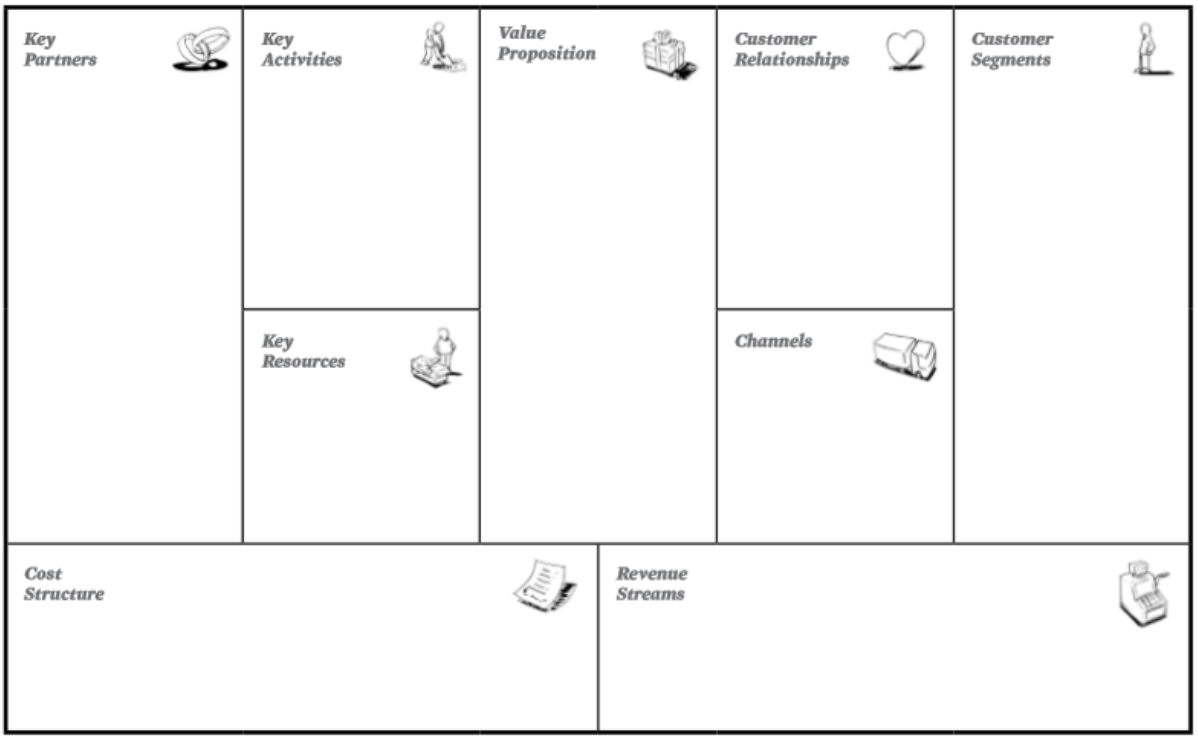


Figure 2: the Osterwalder business model canvas (Osterwalder & Pigneur, 2010)

Customer segments

The customer segment block defines the diverse groups of people or organizations a company seeks to satisfy. Customers are an important component of any business. Lack of profitable customers will crumble a company in no time. The different types of customer segments include; the mass market, the niche market, the segmented, the diversified market, and multi-sided platforms. In the mass market, the business model focuses on large group of customers with similar needs and problems. The niche market requires the value propositions to be delivered to the distinct needs of specific customer segments. The segmented market distinguishes market segments with slightly different needs and problems. The diversified market serves more than two unrelated customer segments with very different needs and problems. Lastly, the multi-sides markets concentrate on two or more interdependent customer groups. Both customer groups are important for the success of the business (Osterwalder & Pigneur, 2010).

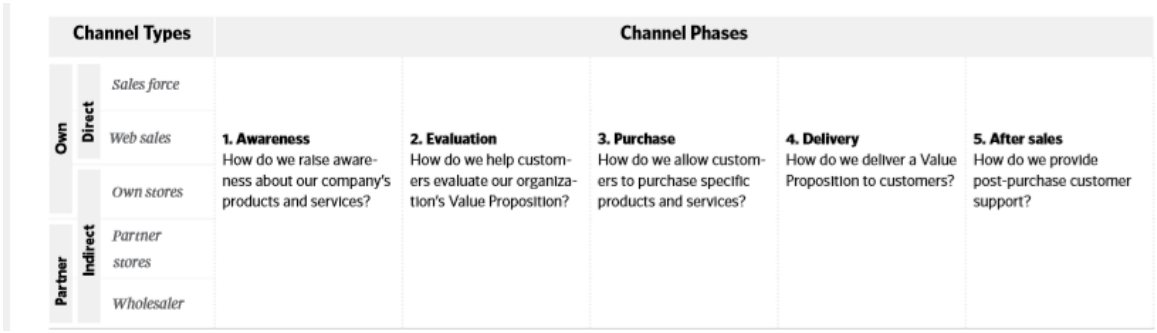
Value proposition

The value proposition explains how a product or service solves customer's problems or improves their solution. It gives reason why a customer should patronize a particular product and not another i.e benefits a company offers to customers. Value Propositions may be Innovative, representing a new offer or Habitual, comparable to an existing market offer, but with added features. Creating value for customers may involve one or several of the following; customization in which the customer has several options to choose from, price of product or service, newness, accessibility, performance, convenience/usability, design, status/brand, getting the job done and reducing the cost of product or service (Osterwalder & Pigneur, 2010).

Channels

This block describes how a company reaches out to its customers to deliver its value proposition. Distinguishing between Direct (Own) and Indirect (Partner) channels, any channel must cover 5 phases as illustrated in the table below; raising awareness among customers about a company's products and services which could be through adverts, promotions, evaluation whereby customers are able to evaluate a company's Value Proposition over its competitors, allowing customers to purchase specific products and services, delivering a Value Proposition to customers and finally, depending on the product, providing post-purchase customer support.

Table 2: types and phases of channels (Osterwalder & Pigneur, 2010)



Channel Types			Channel Phases				
Own	Direct	*Sales force*	**1. Awareness** How do we raise awareness about our company's products and services?	**2. Evaluation** How do we help customers evaluate our organization's Value Proposition?	**3. Purchase** How do we allow customers to purchase specific products and services?	**4. Delivery** How do we deliver a Value Proposition to customers?	**5. After sales** How do we provide post-purchase customer support?
		Web sales					
		Own stores					
Partner	Indirect	*Partner stores*					
		Wholesaler					

As shown in the table above, an organization can choose between its own channels, partner channels, or both of them when reaching its customers. The different channels must be integrated in such a way to create a great customer experience while making profit. Partner Channels lead to lower margins, but they allow an organization to expand its reach and benefit from partner strengths. Owned Channels and particularly direct ones create both higher margins and operating costs (Osterwalder & Pigneur, 2010).

Customer Relationships

This block describes how a company communicates with specific customer groups. It must be clear what kind of relationship the company wants to establish with a particular customer segment ranging from personal to automated. Customer relationships are motivated by customer acquisition, retention and boosting sales. Amongst others, we have customer relationships including; personal assistance, self-service, automated services, co-creation and communities (Osterwalder & Pigneur, 2010).

Revenue Streams

This block describes the various ways a company makes money from the different customer segments. The revenue could either result from one-time customer payments called Transaction revenues, or Recurring revenues resulting from an ongoing payment to deliver a Value Proposition or provide post sales customer support. Revenue streams can be generated from asset sales, usage fee, licensing, subscription fee, brokerage fee, advertising and leasing or renting. The revenue created from each revenue stream depends on the pricing mechanism used; Fixed menu pricing; predefined prices based on static variables and dynamic pricing; Prices change based on market conditions (Osterwalder & Pigneur, 2010).

Key Resources

The Key Resources block describes the most important assets required to make a business model work. It describes what is needed by a company to make value propositions. These resources can be classified into Physical, Intellectual, Financial and Capital resources.

Physical resources include physical assets such as manufacturing facilities, buildings, vehicles, machines, systems, point-of-sales systems, and distribution networks. Intellectual resources like brands, proprietary knowledge, patents and copyrights, partnerships, and customer databases are difficult to develop but offer substantial value when fully created. Financial resources represent the monetary needs required to run the business. Human resources are critical in knowledge-intensive and creative companies. Every enterprise requires human resources (Osterwalder & Pigneur, 2010).

Key Activities

The Key activity building block describes the most important things a company must do to make its business model work. Key activities are required to create and offer solutions to customer problems, reach markets, sustain communication with customers, and yield revenues. Like Key Resources, Key Activities vary according to business model types. They are grouped into Production, Problem solving and Platform/network. Production activities relate to designing, creating and distributing products in significant amounts and of great quality. Problem solving activities seek to find new solutions to customer problems. Platfrom activities relate to platform management, service provisioning, and platform promotion (Osterwalder & Pigneur, 2010).

Key Partnership

Many companies build up a network of suppliers and partners to optimize their business, reduce business risks and acquire resources. Four types of partnerships can be identified; strategic alliance between non-competitors, strategic partnership between competitors. Joint ventures to develop a new business and buyer supplier relationships to ensure reliable supplies (Osterwalder & Pigneur, 2010).

Cost structure

Cost structure describes all relevant costs incurred to make a business model work. Costs can be incurred from creating and delivering a Value Proposition, sustaining Customer Relationships, and generating revenue, which are easily calculated from proper well defined Key Resources, Key Activities, and Key Partnerships. Every business model seeks to minimize cost and we can distinguish 2 classes of business model Cost Structures: cost-driven and value-driven. Cost-driven business models focus on minimizing costs wherever possible. This approach aims at creating and maintaining the leanest possible Cost Structure, using low price Value Propositions, maximum automation, and extensive outsourcing. Value driven business models are more focused on creating value that cost implications. They create Premium Value Propositions with highly personalized services (Osterwalder & Pigneur, 2010).

Cost structures are characterized by fixed costs, variable cost, economies of scale and economies of scope. Fixed costs remain unchanged despite the amount of goods or services produced. Variable costs differ proportionally with the amount of goods or services produced. Economies of scale are cost advantages a business enjoys due to increasing productivity. Economies of scope are cost advantages a business enjoys due to a larger scope of operations (Osterwalder & Pigneur, 2010).

2.4 Value Proposition Canvas

The Value Proposition Canvas zooms into the details of two of the building blocks of the Business Model Canvas; Value Proposition and Customer Segment and helps in creating value for customers. The Value Proposition Canvas has two sides, with the Customer Profile which clarifies customer understanding. The particular customer segment from our business model is broken down into its jobs, pains, and gains and the Value Map which describes how we intend to create value for our customer(s). It breaks down our value proposition into products and services, pain relievers, and gain creators. A Fit is achieved between the two when one meets the other. Three kids of fit that can be identified; Problem-solution Fit, Product-Market Fit and Business Model Fit (Osterwalder et al., 2015).

- **Value Map**

Products and Services: provides a list of propositions the company intends to offer its customers. Products and services could be tangible, intangible, digital or financial with relevance ranging from “nice to have” to “essential” (Osterwalder et al., 2015).

Pain relievers: describes how the value proposition alleviate specific customer groups out of their pain. These could be things that annoy customers before, during, or after they are trying to complete a job or that prevent them from doing so (Osterwalder et al., 2015).

Gain Creators: describes how products and services create gain for customers. Gain creators focus on those gains relevant to customers and where our products and services can make a difference (Osterwalder et al., 2015).

- **Customer Profile**

Customer jobs: describe what customers are trying to get done in their work and in their lives, as expressed in their own words. We distinguish 3 different jobs including functional jobs, social jobs and emotional jobs which range from insignificant to important depending on customer preference (Osterwalder et al., 2015).

Pains: describe bad outcomes, risks, and obstacles related to customer jobs. Severity of the pain ranges from moderate to extreme (Osterwalder et al., 2015).

Gains: describe the outcomes customers want to achieve or the concrete benefits they are seeking. Four types of customer gains can be identified including; required, expected, desired and unexpected gains. their relevance ranges from nice to have to essential (Osterwalder et al., 2015).

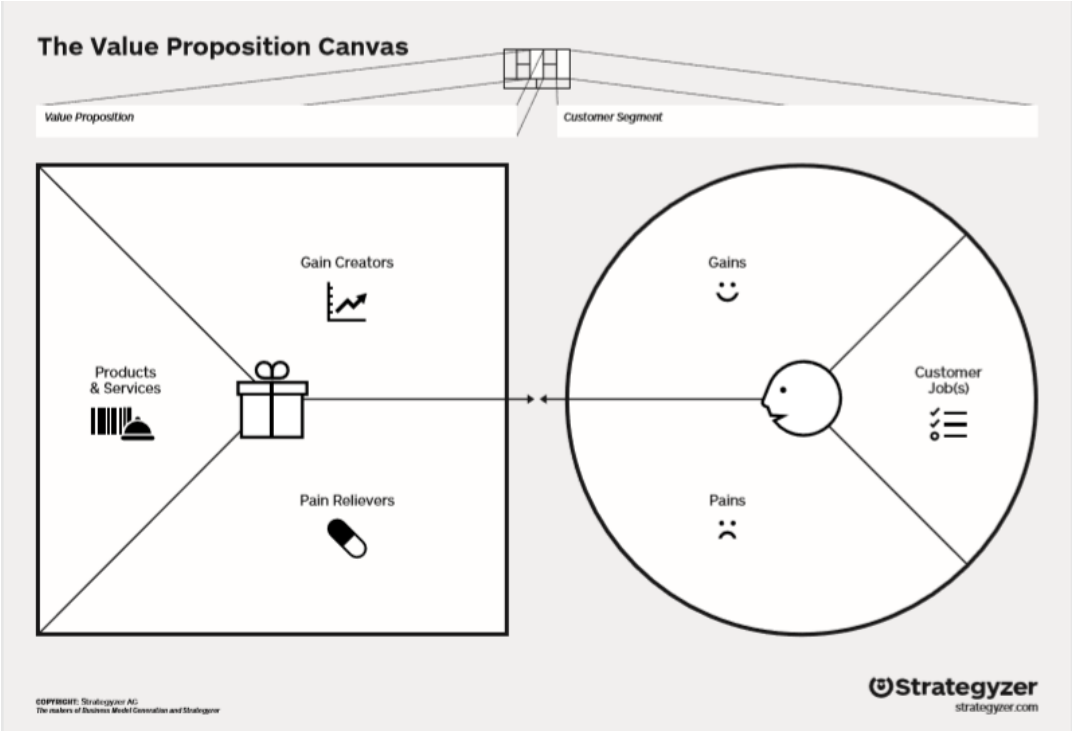


Figure 3: Value Porposition canvas (Osterwalder et al., 2015)

2.5 Market Segmentation

Market segmentation is the process of splitting customers, or potential customers, in a market into different groups, or smaller subsets of consumers with similar taste, demand and preference. This means that, given the various needs of consumers, a strategic company is one which positions itself based on the abilities to serve the best and most profitable market segment; and different market segments require different market strategies. Considering the fact that not all individuals have similar needs, the overall aim of segmentation is to identify growth potential segments which can become target markets (Armstrong, Adam, Denize, & Kotler, 2014; McDonald, 2012).

In a segmentation process, the build-up approach sees customers as different and then proceeds to identify possible similarities between them. The break down approach on the other hand is mostly used to segment consumer markets and sees customers to be identical and targets to identify groups which share particular differences. Segments are developed in the interaction between two or more parties. The segmentation model should be able to identify risk factors in a market and be able to adjust to these by being dynamic (Freytag & Clarke, 2001).

A Dynamic Interaction Segmentation model in Figure 4 regards the buyer's perception of their own needs and wants as an important variable of segment identification. Needs and wants are developed through interaction between buyer and seller with influence from the activities of the competitors and environmental changes.

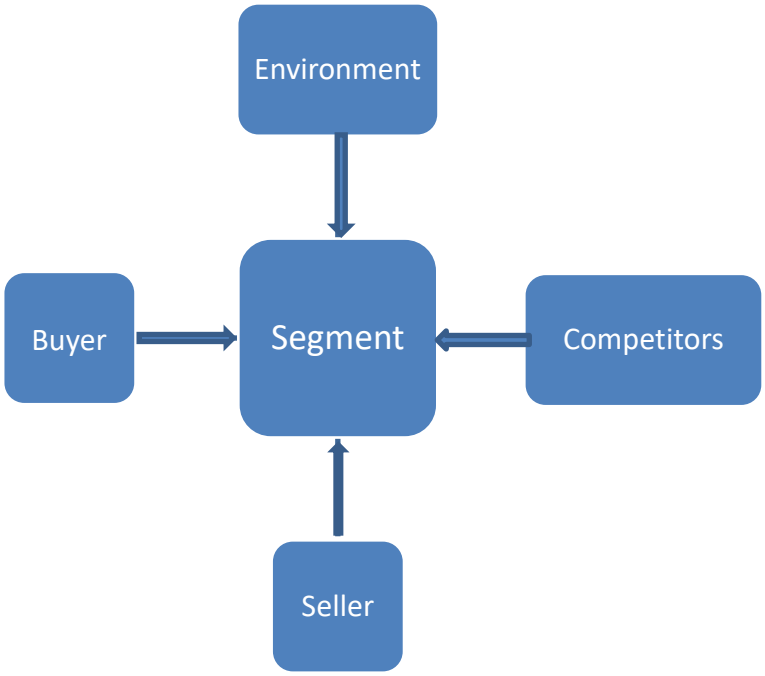


Figure 4: Dynamic interaction segmentation model (Freytag & Clarke, 2001)

In order to segment a market:

- customers in the different segments must have different preferences and needs
- customers must have different ability and willingness to pay
- the company must be able to reach out to the different customer groups

Table 3: market segmentation

Segmentation base	**Brief description**
Business to business (B2B)	
➢ Stakeholders	This segment involves customers such as the government, owners (shareholders), suppliers etc.
➢ Geographics	Physical location or region
Business to customers (B2C)	
➢ Demographics	Segments defined by measurable description of customers such as age, sex, socio-economics etc.
➢ Geographics	Segment with identifiable location to customers such as country, state, region, city etc.
➢ Psychographic	This segment is classified by a customer's inner feelings and the tendency to behave in certain ways. It includes lifestyle, social or personal characteristics
➢ Behavioral	Segment classified by purchasing or consumption behaviour of the consumer

2.5.1 Burden of antibiotic resistance

Although antibacterial resistant infections are costlier to treat than susceptible infections, there is a scarcity of definitive cost evidence available to allow for a comprehensive study of the economic burden of this resistance (WHO, 2014). From a medical, social, and economical viewpoint, bacterial resistance is of great concern, becoming common in healthcare institutions and often resulting in treatment failure, thereby, implying an added burden on healthcare costs. Assuming an average antibiotic cost of $20, the total societal cost of antibiotic resistance (SCAR) attributable to each ambulatory antibiotic prescription in the US would increase antibiotic costs by 65 % (with hospitalization cost contributing the highest) when combined with antibiotic costs paid by patients or payers (Michaelidis et al., 2016).

In the event of an outbreak, fatal infectious diseases are both scary and expensive to deal with. Countries can choose one of three following options to pay for ABR; first, wait until there is a problem and then try to solve it as in the case of disease outbreaks. Second, recognize that prevention is better than cure and individually invest in the tools needed to fight resistance. Or third, by working together and jointly paying for global public goods to efficiently and effectively avoid large-scale outbreak of untreatable infections (Resistance, 2016). In order to help policy makers and healthcare professionals to make appropriate health decisions, there is a need to measure the economic burden of ABR which is directly linked to disease burden. Some factors affecting the quantification of economic burden of ABR include; increasing prevalence of antibiotic resistance, effects of unavailability of effective antibiotics in common medicines such as surgery, transplant and chemotherapy, and Effect of antibiotics on national income, labor supply and economic growth (Gandra, Barter, & Laxminarayan, 2014).

The business model for antibiotics is not balanced by the opportunity to make attractive profit. The developer gets a very low return for creating something which greatly benefits the society. Without more attractive returns for investors, the number of new antibiotics reaching the market will continue to decrease and antibacterial resistance will continue to spread. There needs to be a rebalancing between the value to society and the value to investors, as without that, investment will continue to decline, and the long-term impact will be a huge societal cost. Empiric therapy results in needless courses of antibiotics prescribed to patients who do not even have a bacterial infection. This model has led to increasing resistance, unnecessary side effects and negative impact on the human microbiome. The development and use of simple, cheap, efficient and accurate rapid diagnostics to identify the infecting pathogen and its susceptibility profile could hinder resistance worsened by empirical therapy. Low cost, simple or no instrumentation and ease of use are crucial to global utilization of diagnostic tests (Payne et al., 2015). Some tests include: Influenza Breath POCT; a Community-Associated Lower Respiratory Tract Infection test, a Nucleic Acid-Based Ventilator-Associated Pneumonia test, The Xpert® Carba-R, Cepheid Xpert MRSA/SA SST, Curetis Unyvero Pneumonia P50 Test and Biofire Filmarray Respiratory Panel (Dubouix-Bourandy et al., 2011; Payne et al., 2015; Poritz et al., 2011; Zumla et al., 2014).

The antibacterial drug market is forecast to rise from about $27.1 billion in 2015 to $35.6 billion in 2022. This is as a result of market drivers including growing use of new diagnostic tests, increased geriatric population; challenges including high RnD cost, uncertain regulatory policies, and rapid emergence of antibacterial resistant strains; market trend is an increase in

the demand for antibiotics. Increasing incidence of pneumonia, blood stream infections, and urinary tract infections (UTI) are anticipated to foster the usage of carbapenems class of antibiotics (Research & Markets, 2015). The impact the present diagnostic model (sequence-based method) has on development and spread of resistance (on bacteria type) will be important for such estimations. The cost incurred by such diagnosis resulting in fewer sick individuals and a reduction in the spread of infection will therefore, be a good investment. Diagnostic testing helps physicians or GPs to differentiate viral from bacterial infections and determine the susceptibility of agents involved (Cecchini & Lee, 2017) in order to decide what antibiotic works best for what infection as shown in the diagram below:

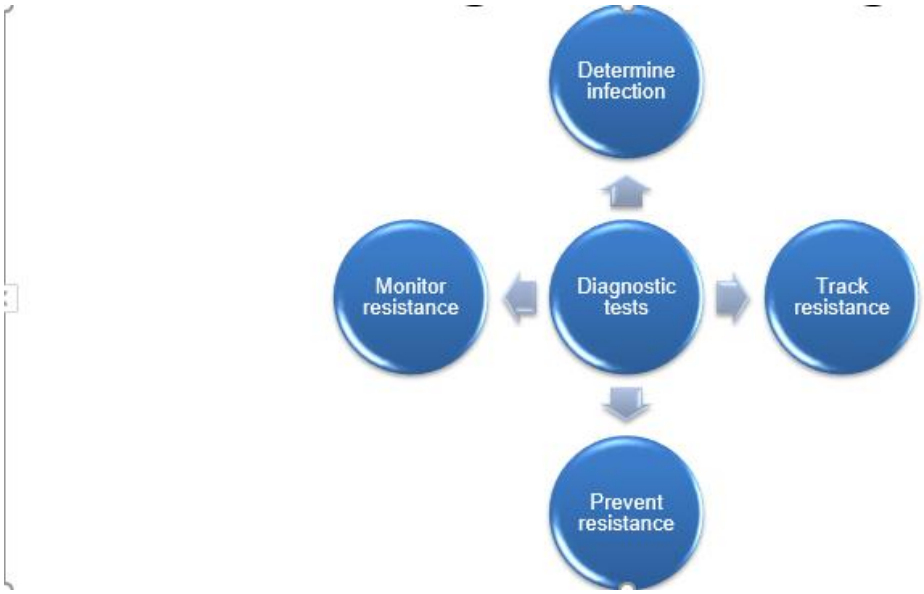


Figure 2: Use of diagnostic tests

2.6 SWOT Analysis

This is a tool used to analyse a business or project with reference to its internal factors (strengths and weaknesses) and external factors (opportunities and threats. It is aimed at determining whether a business or project should continue, stop or be redesigned. or not a project or business should be established.

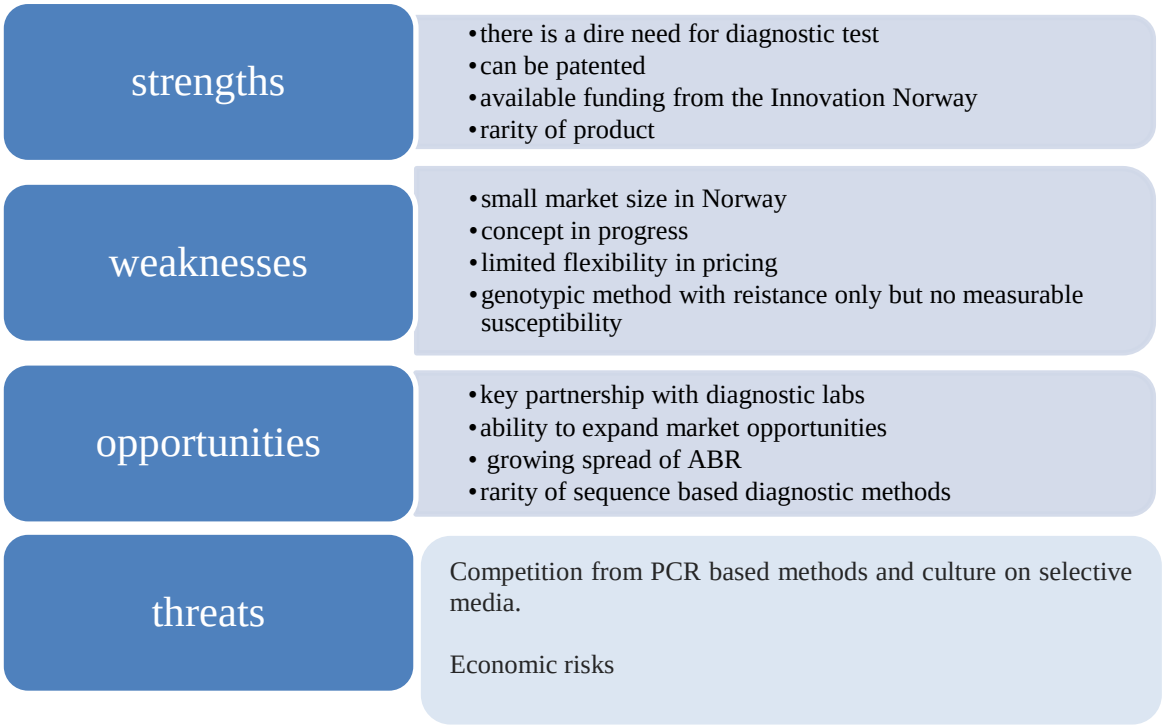


Figure 5: SWOT Analysis for sequence-based method

3. Materials and Method

Data Collection: using a deductive inductive approach (Greener & Martelli, 2015), we conducted primary data from an exploratory interview with Dr Anders Bredberg of the Sykehuset Innlandet, Microbiology Department at Lillehammer who gave us an insight on the common hospital infections and the antibiotic resistance workflow, explaining what happens at each stage when a patient in down with an infection. A discussion with Dr Rafi Ahmad gave us the description of the proposed tool. We also collected secondary data by article search from the internet and the Library. We also used the Osterwalder business model canvas to formulate a business plan for our sequence-based technology.

Search strategy: We searched for review articles published in English in PubMed, Google Scholar and WHO publications with the terms "antibacterial resistance", "antibiotic resistance in humans" "cost of antibiotic resistance" "burden of antibiotic resistance", etc for the period of 2013-present. From the review article references, we were able to get primary articles of importance which were then used in our study.

In order to determine carbapenemases in Enterobacteriaeceas, a search was done on NCBI. Using SRA database to search for "carbapenemase", *E. coli* and *Klebsiella* were each selected from top organisms. Results were sent to the RunSelector and viewed as an expanded interactive table. By clicking on each of the Biosamples, we were able to determine which contained carbapenemase or not. The tables (for each of the bacteria) were then downloaded to Excel. Search was performed on 21/01/2018. From the excel file (appendix2), highlighted samples are non-carbapenemases.

Using NCBI and "Nucleotide" database, search words used for the number of nucleotide sequence for *E. coli, Acinetobacter, Klebsiella* and *Psuedomonas* in ESBLs classes B and C on included "IMP carbapenemase, VIM (metallo-β-lactamase), NDM-1 (New Delhi metallo-β-lactamase) and CMY beta-lactamase". For each of these classes of ESBL, four groups of bacteria (*E. coli, Klebsiella, Psudomonas and Acinetobacter spp*) were used for the nucleotide sequence by clicking the "top organisms" on the right-hand side of the searches. Also, GenBank information given was used to determine the source or host of the bacteria by searching up indicated articles on PubMed. Search was performed on 25/01/2018 (appendix 1).

4. RESULTS AND DISCUSSION

4.1 Diagnostic Workflow

From our onsite visit and interview, we noticed the following workflow for the diagnosis and treatment of ABR from when patients engage General Practitioners/hospitals to when patients are treated as shown in the figure below.

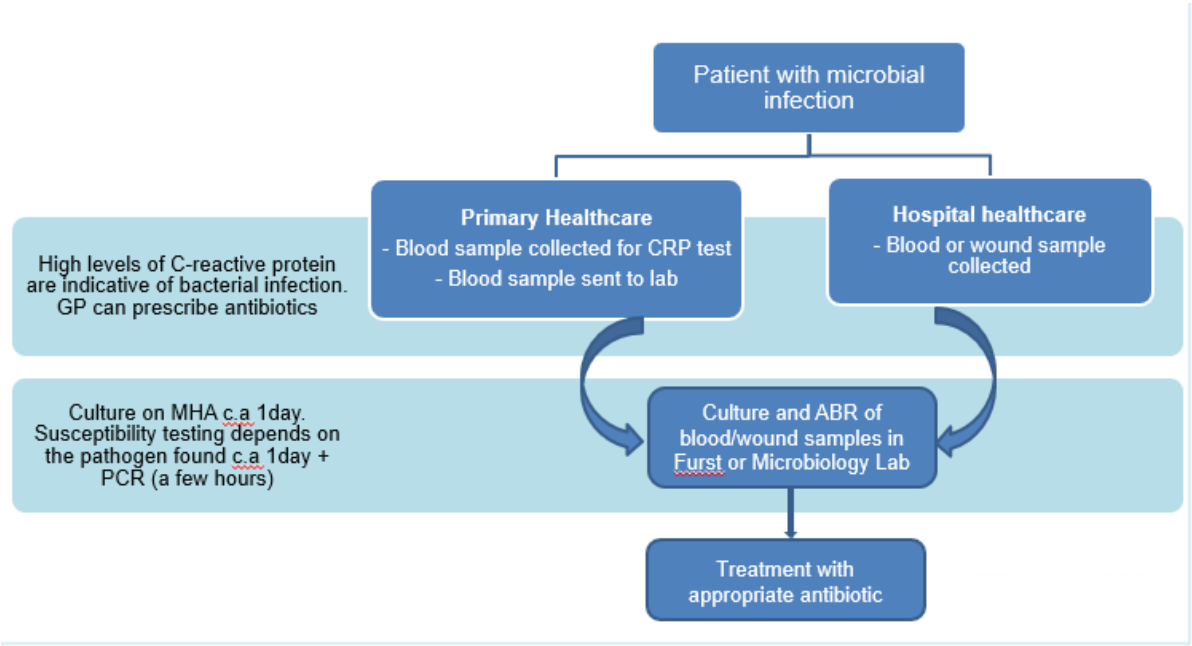


Figure 6: Antibiotic resistance diagnostic workflow

In Primary Health Care, when a patient visits the General practitioner (GP), their blood sample is collected and rapidly a C-reactive protein (CRP) test is run to differentiate bacterial from viral infections. High levels of CRP are indicative of bacterial infection and patient could be prescribed with antibiotics in case ABR is suspected. The blood and/or wound samples from the GP and hospital healthcare are sent to the Microbiology Laboratory or Fürst Lab for culture and resistance testing. Following EUCAST guidelines, samples are cultured on Mueller Hinton Agar with horse blood. Culture takes about a day and then susceptibility testing is done, depending on the type of pathogen found, which also takes one day. PCR-based technology is then used to determine resistance within a few hours. Depending on ABR test results, the patient is then treated with appropriate antibiotics (interview with Dr. Anders). This just goes to show the long waiting times involved in using the standard EUCAST

antibacterial susceptibility testing methodology taking at least three days to have results. The standard process of culture and susceptibility testing generally takes 3-4 days and sometimes even more than a week, meanwhile, many patients are empirically treated with antibiotics. Although it is faster, cheaper and more clinically effective for an individual patient to be treated with antibiotics empirically. However, for the community and future populations, targeted therapy which reduces the potential of resistance may ultimately cure more infections and save more lives (Cecchini & Lee, 2017; Payne et al., 2015). Norway like most European countries adopt the EUCAST guidelines for susceptibility test. Use of rapid diagnostic tests is limited. Rapid diagnostic tests are only available nationwide in 40% of OECD countries (OECD, 2016).

4.2 Workflow of sequence-based diagnostics of antibiotic-resistance

1. Primary health care or hospital to take blood sample/swabs from patient with infection

2. DNA isolation by molecular biology lab

3. DNA sequencing done by a molecular biology lab

4. DNA sequence continuously sent by internet to the company´s server

5. Sequence analysis by the company´s algorithms and database

6. Feedback of the results to the health care professional (or patient)

7. Possible continuous feedback to NIPH for surveillance purpose

With the current diagnostic workflow following EUCAST guidelines, the AMR-Diag sequence-based method still fits in as it involves Primary health care or hospital collecting blood/urine/swabs from patients and sending to the microbiology lab for DNA extraction followed by sequencing. Samples can also be sent to the a molecular lab for DNA extraction and sequencing analysis. This means less work for the MCB lab since the sequencing is culture free and will only take a couple of hours. Unlike the EUCAST guideline method, AMR-Diag will provide digital results which can be stored and used further analysed. Although we expect the cost of sequencing to become cheaper with time, AMR-Diag in routine laboratories is

expensive knowing that the cost of sequencing is more than that of EUCAST disk diffusion test.

4.3 Future implications of a sequence-based approach for diagnostics

The method has a potential for being a disruptive innovation. Today we operate the good old workflow with doctors/nurses taking blood samples/swabs and sending them to a diagnostic lab (private or public) for diagnosis. It is possible to see this set into a more distributed system contrary to the todays centralised system. DNA isolation has been automated and can in the future be part of the DNA sequencing instrument or closely integrated with such an instrument. This is what is called the “black box principle”, patient sample in and result out. It may be possible to do the testing without lab expertise. This can open up the possibility for primary health care to do the operation without the help of a centralised lab, although the primary health care professional will need to send the data to the company for analysis. But this will in practise be just linking up to internet and feeding the digital data automatically to the company and getting the digital result back. The feeling will be of a local diagnostic procedure.

The consequence of this thinking is that hospital healthcare will be important especially in the beginning to get the method implemented in the current workflow. However, primary health care will be crucial for the future success of the company. Most likely, the future revenue stream will mainly come from primary health care professionals. It is even possible to see a private market opening up, where the patient or relatives use a “drive-in” test center to get a quick diagnosis, a second opinion or monitor the treatment of the disease.

4.4 Can sequence-based testing be reliable?

The nucleotide sequence search gave the following results summarised in *Table 4* (from appendix 1) which are indicative of the total number of sequences that have been studied up till the point when search was conducted. This shows only a small number of sequences *Enterobacteriaeceae, Acinetobacter and Pseudomonas species* in ESBLs and therefore require more sequences yet to be studied or identified.

Table 4: Number of nucleotide sequence for E. coli, Acinetobacter, Klebsiella & Psuedomonas in ESBLs (B&C).

IMP carbapenemase	**NDM-1 (New Delhi metallo β lactamase)**
- *Klebsiella spp* 931	- *E coli* 337
- *E coli* 49	- *Klebsiella spp*. 81
- *Pseudomonas spp* 73	- *Pseudomonas spp*. 41
- *Acinetobacter spp*. 21	- *Acinetobacter spp*. 31

VIM (Verona integron metallo β lactamase)	**CMY (cephamycin hydrolysing)**
- *Pseudomonas spp*. 793	*E coli* 168
- *Klebsiella spp*. 89	*Klebsiella spp*. 44
- *Acinetobacter spp*. 27	
- *E coli* 14	

Summarising the data on appendix 2, we were able to determine the number of carbapenemase Biosamples from the 2 *Enterobacteriaeceae* (*E. coli* and *Klebsiella*) as shown in Table 5 below. Out of a total of 235 runs from 218 *E. coli* sequences and 179 runs from 141 *Klebsiella species,* 166 and 153 are carbapenemase producing organisms respectively while only a 69 *E. coli* and 26 *Klebsiella species* and non carbapenemases. This therefore implies an increase in carbapenemases resistance which is a call for concern needing action. This is also indicative of the fact that the sequence based method has the ability to precisely identify the infectious

bacteria and possible resistance genes since it will be compared to already known sequences in the database in real time.

Table 5: carbapenemase in Enterobacteriaeciae

Enterobacteriaeciae	Nº of sequences	Nº of runs	Carbapenemase	Non-carba
E. coli	218	235	**166**	69
Klebsiella	141	179	**153**	26

In order to make the business idea sustainable therefore, there is a need for NIPH to incentivise this method in order to make it affordable for the common populations. Although kick starting in Norway, after evaluating the performance of the method, it could extend its market to neighbouring countries and worldwide. Continuous search in the public database since new genomes are constantly being sequenced and published, and updating the proposed sequence tool will enable the sustainability of this business idea.

4.5 Creating value for the business

Table 6: Osterwalder format business plan for sequence-based for detection of AMR

<table>
<tr>
<td rowspan="2">Key Partners

-Research Council of Norway (RCN)

-Bedrehelse

-Indian Council of Medical Research (ICMR)

-Fürst Lab

-Lillehammer Microbiology lab

-Inland Norway University of Applied Sciences</td>
<td>Key Activities

-Detection of antibiotic resistance

-Storage of results

-Provide education and training on use of the technology

-Sharing results with health units

-Development of sequence-based method

-Research and Development</td>
<td rowspan="2">Value Proposition

-Faster method for ABR detection (culture-free sequence-based)

-Affordable ABR diagnostic method

-Convenient method to be used by primary health care and hospital health care professionals

-Data storage and sharing</td>
<td>Customer Relationship

-E-mails

-Direct contact

-Personal assistance

-Automated service

-Reference labs/groups</td>
<td rowspan="2">Customer segments

-NIPH

-Primary health care

-Hospitals acute dept.

-Diagnostic labs

-Nursing Homes

-General Practitioners</td>
</tr>
<tr>
<td>Key Resources

-Infrastructure

-Sequence database

-Search algorithms

-Competence in sequence-based diagnostics</td>
<td>Channels

Direct Channel

-own sales force

Indirect channel

-through partners (GPs and diagnostic labs)</td>
</tr>
<tr>
<td colspan="3">Cost Structure

Investment cost

Research and development cost

Labour cost

Cost of storage of results</td>
<td colspan="2">Revenue Streams

Cost of sequencing

Sharing of results in the database</td>
</tr>
</table>

We segmented our market using business to business (B2B) as follows:

Geographical

Since the company setup for the sequence-based technology is in Norway, it will be beneficial to the company to first gain the market here in Norway and easily correct functional errors in the methodology before expanding it to other Scandinavian countries, rest of Europe and the rest of the world. Therefore, in order not to risk drowning the product through lack of differentiation or go too narrow and end up with few numbers we could use the beachhead strategy. Norway can be the beachhead to reach international markets. Norway due to its position of having few AMR cases can also be a leading star in developing new strategies to combat AMR.

Stakeholders

- **Norwegian Institute of Public Health (NIPH):** these are the policy makers responsible for knowledge production and regular evaluations for the health sector, providing knowledge about the health status in the population, influencing factors and how it can be improved. The NIPH has amongst its four divisions, the division of Health Services which provides a knowledge base for decision makers at all levels in the health care services, from central government to the municipal health service (NIPH, 2017). They can easily influence the implementation of the sequence-based method in use.
- **Diagnostic Laboratories**: these are designated laboratories to carry out antimicrobial resistance test. This group of customers need to be convinced of the efficiency and convenience the sequence-based method has over the standard culture media.

4.6 Creating value for customers

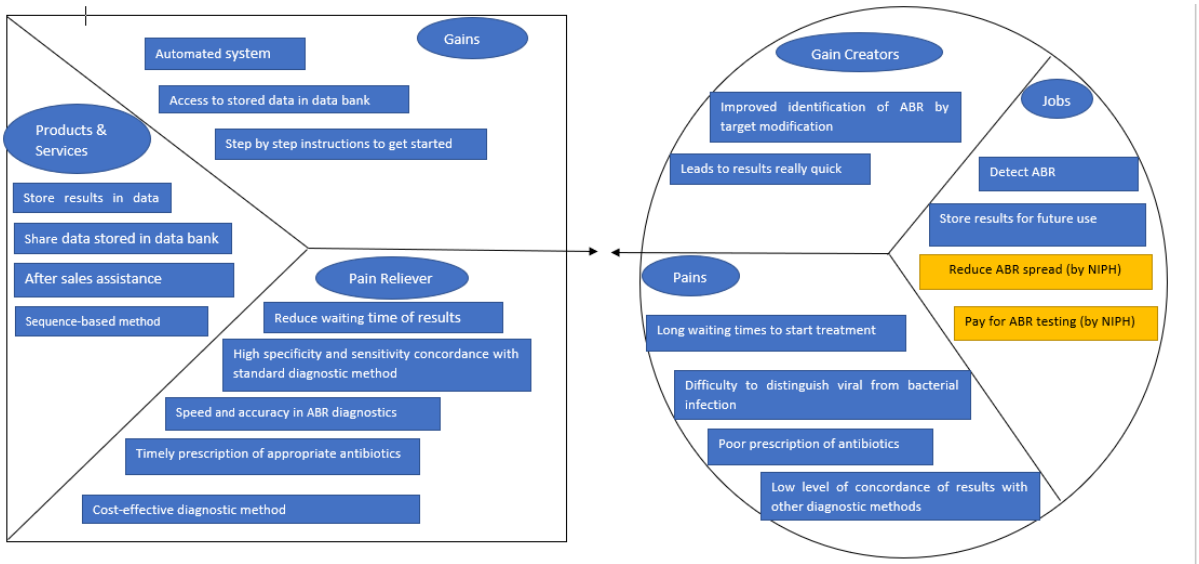


Figure 7: Value proposition canvas for sequence-based method

The value proposition above targets 2 customer groups; Diagnostic Laboratories and NIPH (with different customer jobs where indicated). If we focus on one customer group only which is the NIPH, we can prove that the customer has certain jobs, pains and gains which our value proposition addresses, therefore we have a Problem-Solution fit (Osterwalder et al., 2015). Their job is to pay for and cover the cost of AMR testing in order to reduce its spread among the populations. They work together with selected laboratories that carry out this AMR testing hence they seek to alleviate the pain of having to wait up to 3days for standard culture test and poor prescription of antibiotics to patients. They are in need for rapid diagnostic methods that will distinguish bacterial from viral infections with results similar to that of standard tests or other diagnostic tests. The proposed tool, which is a sequence-based diagnostic method AMR-Diag, therefore targets to provide a convenient method to detect AMR with accurate results within a short time frame at an affordable cost. While providing the ability to store data in a data bank that can be used for future analysis.

4.7 Estimating the cost of ABR

ABR poses a significant burden on healthcare systems and national budgets (OECD, 2016). In all of 2017 there were 24,199 resistance testings in the Lillehammer Microbiology Lab. Half of these tests were done in the Vitek II machine, other half manually with either disk diffusion or E-test MIC strips. It takes a technician about 10 mins to carry out a resistance test, and Petri dishes with solid agar media cost about 20 NOK each. We can therefore estimate that in Lillehammer the cost of ABR testing in the year 2017 was as follows:

10 mins/test → 241,990 mins → 4033 hours or about 2,5 full time positions

Assuming a lab technian wage to 400,000 NOK x 1,3 social cost this amounts to 1,5 mill. NOK

Assuming 1sample = 1test and 1 petri dish is used per test, → 20NOK x 12100 = 242,000 NOK

Cost of Mueller hinton agar ranges from 187 NOK (100g) – 2,652 NOK (2.5Kg) (Sigma-aldrich, 2018)
Cost of Antibiotic disks ranges from 148 NOK – 700 NOK (vgdusa, 2018)

Hospitals spend $10,000-$40,000 on treatment for a patient infected with multidrug resistant organism. ABR influences the burden of disease management by increasing Intensive Care Unit (ICU) and hospital stays with an additional cost on nursing and medical care. Services like food and laundry make up for 13%, lab tests and imaging make up 12%, and pharmacy services correspond to <2% of additional costs (OECD, 2016).

It is easy to see that the days in the hospital treating the patient is the serious cost element. For every day saved in hospital care a good and improved test is paid back many times. Even one day saved in hospital treatment will be a fantastic saving for the society. The problem is that the hospitals get the big bill and diagnostic labs/the primary health care can reduce the cost. How can this be insentivised? Simply by the rate paid from the National Health Care system to the labs and the health care professionals.

The implication of this is that NIPH is a crucial decision maker for getting a new method being developed and used. They can set a policy that will make this a success for the company. This is also a good argument for implementing this first in Norway and then taking it from country to country in the western world first.

4.8 Competitive analysis

Considering that sequencing costs about 1000 NOK per sample, and exploiting other factors such as speed, convenienc, data storage and sharing, automation and nature of sequencing could be some of the factors that make the proposed tool stand out in comparison with standard culture and PCR-based methods as shown below. Sequencing prices are continously dropping and the proposed tool though expensive when compared to PCR-based and standard culture methods, could be affordable upon incentivisation. The proposed tool therefore, stands out interms of data storage and sharing, automation and speed since its sequencing is culture-free thereby saving the 3-4 days or more of culturing the bacteria. This could be seen as a competitive advantage that makes the proposed tool stand out from other methods thereby, reducint the risk of immediate competition.

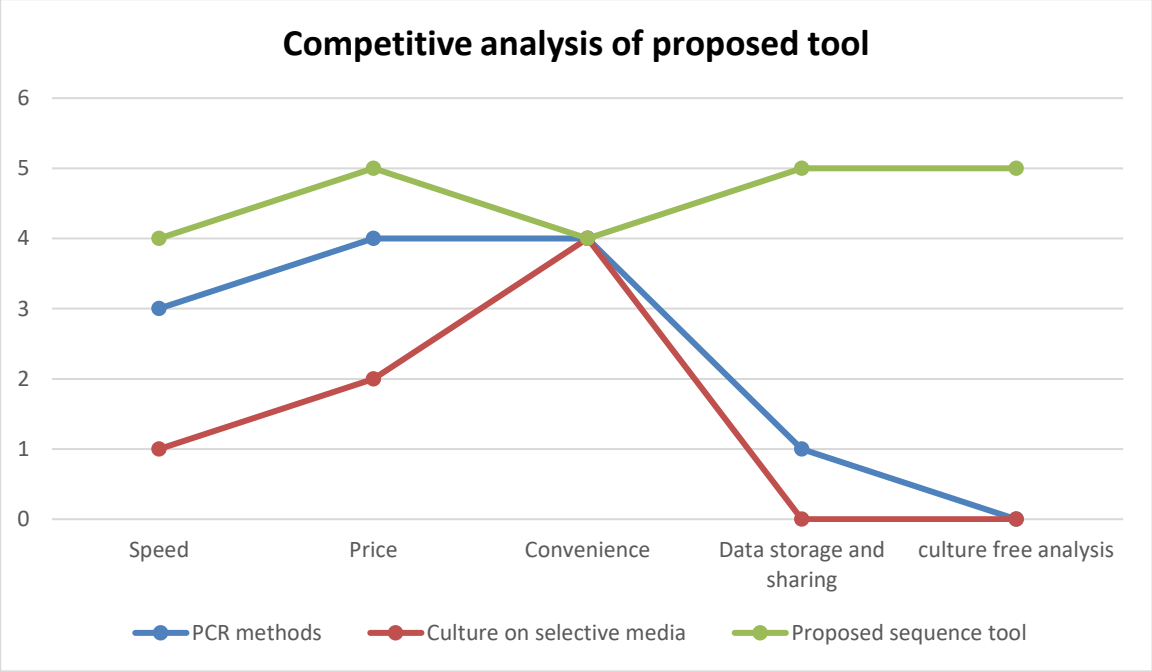


Figure 8: competitive analysis of proposed tool

The AMR-Diag method is a rapid method and it also generates digital data that can be stored in a biobank for later use or continuous monitoring. This means that the method in a way has two possible customers, first the doctor/hospital that treats a patient and secondly NIPH that has a desired need for continuous monitoring of AMR in Norway. This means that payment for the test could be a shared cost between those treating the patient and NIPH monitoring and setting guidelines for AMR in Norway.

From the SWOT analysis, the following suggestions on how the company can take advantage of it strengths and the opportunities in the market to grow and succeed, how it can improve its weaknesses and tackle the threats is shown in the confrontational mix below.

Table 7: confrontational mix

	Strengths -there is a dire need for diagnostic test -AMR-Diag can be patented -available funding from Innovation Norway -competent team	Weaknesses -start up with no brand yet -small market size in Norway -concept in progress -limited flexibility in pricing -genotypic method with no measurable susceptibility
Opportunities -key partnership with diagnostic labs -ability to expand market opportunities - growing spread of ABR -rarity of sequence-based methods for ABR diagnostics	***SO strategies*** • Collaborate with NIPH to implement method in use • Contract with well know laboratories and policy makers to raise awareness on the importance of diagnostic tests • Expand facility for greater output	***WO strategies*** • Partner with other market leaders to gain market recognition • Organise conferences, seminars and workshops to create awareness in the population on the need for diagnostic testing
Threats -competition from other diagnostic tests -economic risks	***ST strategies*** • Use customer loyalty and superior quality to outperform competitors	***WT strategies*** • Develop a detection method to provide results in the shortest timeframe possible

	• Secure a strong customer base in Norway before going to international markets	• Convince laboratories to use alongside current detection methods to provide reliable results

5. CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

Our study set out to validate the need and establish early feasibility for the development of AMR- Diagnosis. Considering the increasing number and spread on antibiotic resistance, there is a need to develop a technology that is fast, cost effective, convenient to use and at an affordable price. Considering the fact that clinicians may be conservative to adopting a new method which hasn't been standardized yet, and also the fact that most genotypic methods predict resistance only and not susceptibility as well, makes it a little harder for new methods to be introduced in routine microbiological laboratories.

Despite the advances so far, a great need for rapid, point-of-care pathogen-specific, sensitive, and affordable diagnostic test still remains in the lookout for the advancement of clinical management, infection control, and improved public health response to emerging pathogens and antibacterial resistance. The proposed tool AMR-Diag is a leap forward in the fight against AMR and therefore should be given a chance to prove what it can do in this course.

Current Norwegian policy makes use of the EUCAST system for diagnosis which could be a hindrance to the proposed tool. Therefore, future policies need to integrate new and innovative diagnostic methods for AMR. The true cost of ABR does not only rely on morbidity and mortality, but also involves the social perspective. In the event of an outbreak, fatal infectious diseases are both scary and expensive to deal with. Countries can choose one of three following options to pay for AMR; first, wait until there is a problem and then try to solve it as in the case of disease outbreaks. Second, recognize that prevention is better than cure and individually invest in the tools needed to fight resistance. Or third, by working together and jointly paying for global public goods to efficiently and effectively avoid large-scale outbreak of untreatable infections (Resistance, 2016).

The cost of DNA sequencing is a major obstacle for the proposed tool, AMR-Diag, to become implemented. However, the cost of DNA sequencing is expected to continue to be reduced. New methods are being implemented that will speed up the use of sequencing as a core tool in diagnostics and other fields. As for many important changes in society, a political decision is needed for implementing a publically funded monitoring program for AMR.

5.2 Recommendations

Upon completion of our study, we came up with the following proposals to the company with proposed tool (AMR-Diag) for further research:

1. The company with its partners e.g. Hedmark Kunnskapspark, Innlandsykehuset and maybe Helse Sørøst should join forces and do political lobbying for Norway to take a leading role in combating AMR. This could both benefit the Norwegian health care and put Norway in a leading role internationally. We would argue for a 10 year program to build up an AMR biobank and a novel diagnostic procedure that can be implemented both in human and veterinary medicine. This program could cover at least 60-70% of the testing cost in the initial 10-years period, the other cost (30-40%) should be covered by the patient treatment refund system. It may even be possible to think 80-20. Our prediction is that sequencing over this period of 10 yrs will become affordable for the diagnostic test to be paid for by the health care systems around the world, and after these 10 yrs Norway will sit on a unique biobank that can be commercially exploited.
2. The company should use Norway as its starting market (beachhead) and then later expand the business idea to other countries.
3. More research on the true cost estimates of antibacterial resistance should be carried out in collaboratioin with “Helsedirektorat” for access to country data.
4. To create awareness in potential customers through organization of seminars, symposiums and workshops on the usage, importance and efficiency of the proposed tool, AMR-Diag.

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Appendices

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