Impact of medical microbiology
Dik, Jan-Willem

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Introduction

General introduction and research question

The Netherlands is cited to have “the best healthcare system in Europe”, but this comes at a price; the country also has one of the highest per capita spending in healthcare (Björnberg, 2015). Since 2013 there is a strong political focus on lowering healthcare costs; providing top quality healthcare in the most cost-effective way in order to keep the ever increasing expenditures under control (Schippers and van Rijn, 2013). This led to a drop in the total healthcare budget (as percentage of the gross domestic product) of the Netherlands in 2014 and 2015. Due to the healthcare system within the Netherlands, with an ‘open market’, politicians have a low influence on direct daily practice. In general, insurance companies and healthcare providers (e.g. the hospitals), together with medical specialists and patient groups, are the main players and decision makers in the system. Insurance companies can use this freedom, to negotiate lower prices with healthcare providers. This relatively open market will in general lead to a strategic trade-off for healthcare providers between (cost-)efficiency and quality, in order to be a competitive player. Ideally, the competitive healthcare system should encourage providers to spend money in the most cost-efficient manner, while at the same time improve the quality of healthcare on which providers are scored and judged. Concretely, this means that departments within a hospital (but also healthcare providers outside hospitals, such as commercial laboratories) will need to provide better, more transparent and more complete accountability of their activities to their boards of directors for the near future. There is thus a clear need for scientifically sound impact analyses, which evaluate clinical and financial effects of current practices, to support the policy makers and further improve quality (Brook, 2011; NZa, 2015; Ubbink, et al., 2014).

More and more, outcome measures such as mortality rates, waiting times, and patients’ ratings are used to define quality of healthcare. Also infection-related outcome measures such as the number of hospital-acquired infections (including surgical site infections) and antimicrobial resistance levels are often taken into account. Medical Microbiology and Infection Prevention is one of the departments that can influence those latter, infection-related outcome measures. In Europe, the Netherlands scores well on antimicrobial use and resistance levels; keeping both relatively low compared to other EU countries (European Centre for Disease Prevention and Control, 2013). The way microbiology is organized within hospitals in the Netherlands, with clinical microbiologists who are actively involved in patient care, is thought to have been a large contributor to these scores (Bonten, 2008). However, departments of Medical Microbiology within the Netherlands are under pressure of insurance companies and subsequently, also hospital boards of directors, to provide cheaper diagnostics (VGZ, 2013). In parallel, increasing levels of antimicrobial resistance are causing more infections and complications that are difficult to treat, leading to increasing healthcare costs (Review on
Antimicrobial Resistance, 2016). Germany is often mentioned as an example of a country where lower prices are being paid for the same microbiological diagnostic tests compared to other EU countries and especially the Netherlands (VGZ, 2013). The question is however, if such a comparison of diagnostic cost prices between Germany and the Netherlands is a fair one. Not everyone thinks so (Kusters, et al., 2014; Tersmette, et al., 2012). Germany and the Netherlands have different healthcare systems in place, making direct comparisons on cost price difficult (Müller, et al., 2015). In Germany, it is common to have the Medical Microbiology laboratory and their teams at distance of the patient and the majority of the hospitals do not have a medical microbiologist at their premises (Kaan, 2015).

Therefore, to better visualize effects of Medical Microbiology, also compared to other EU countries such as Germany, there have been debates how to better measure outcomes, besides just using process indicators (Bonten, et al., 2014; Bonten, et al., 2015). Furthermore, there has been a discussion on the overall position of Medical Microbiology and their focus. The Dutch Society of Medical Microbiology (Nederlandse Vereniging voor Medisch Microbiologie, NVMM) felt a need to act. They discussed their focus and the relevance and necessity of the Medical Microbiology, also regarding the finances (NVMM, 2012).

Within the University Medical Center Groningen (UMCG), Medical Microbiology is combined with an Infection Prevention unit into one hospital department. This was done to stimulate collaboration and integration of the two former departments, with as goal improvement of efficiency, patient safety and overall quality within the hospital. However, because Infection Prevention activities are not reimbursable on their own within the Dutch system, the UMCG has chosen to generate budget for Infection Prevention from the overhead of microbiological diagnostics. This makes the financial situation complex and is a relevant contributing factor when analyzing and evaluating such a department. Keeping in mind the before-mentioned need for impact analyses of healthcare practices, in order to create an objective and transparent overview of the work performed within the hospital, this research project and PhD thesis was therefore set out to answer the following question:

What is the clinical and financial impact of the combined activities of Medical Microbiology and Infection Prevention on relevant outcome measures, at an academic hospital such as the UMCG?

Theoretical framework

The department of Medical Microbiology and Infection Prevention in the UMCG comprises the broad spectrum of microbiology on clinical, teaching and research levels. For this research project, the focus will be mainly on (infection prevention-related) bacteriology (the virology aspect is covered by a second impact analysis and falls outside the scope of this thesis). To
adequately analyze and evaluate the department of Medical Microbiology, a model was developed which puts all activities into context. The development of this model is also part of this thesis (see chapter 3). In short, the model integrates all activities into three complementary so-called “stewardship programs”. An Antimicrobial Stewardship Program (ASP), Infection prevention Stewardship Program (ISP) and Diagnostic Stewardship Program (DSP); i.e. the AID Stewardship Program. It was developed keeping in mind that infection management should comprise of integrative actions focused on antimicrobial therapy, infection prevention/control, and diagnostics, as well as being more patient-centered. This thesis is also structured according this AID model.

**General background**

Medical Microbiology has a long history, starting with the Dutch scientist Antonie van Leeuwenhoek who in 1676 discovered “small animals”, that later became known as bacteria (van Leeuwenhoek, 1677). Besides Van Leeuwenhoek, Louis Pasteur, who worked on the principle of vaccination and the germ theory (Pasteur, 1881) and Robert Koch, who performed ground breaking work on multiple bacteria, including *Bacillus anthracis* and *Mycobacterium tuberculosis* (Koch, 1876) matured the field of Medical Microbiology. These three researchers are therefore considered to be the “fathers of the microbiology”. However, by the turn of the twentieth century, infections were still not treatable leading to high mortality rates. Patients infected, for example with tuberculosis, were isolated when possible to prevent further spread to others. All of this changed during the Second World War. In the years before, the Scottish biologist Alexander Fleming discovered penicillin (Fleming, 1929). During the war, his discovery was put into use for the wounded soldiers and became the first mass-produced antibiotic. Both Robert Koch and Alexander Fleming received a Nobel Prize for their respective work. During his acceptance lecture at the Nobel Prize ceremony, Fleming already warned for the negative side effects of antibiotics. He observed that bacteria can develop resistance quite easily *in vitro* when they are continuously exposed to low levels of penicillin. In his speech he foresaw a future where antibiotics are freely available for everyone and resistance could become a serious problem (Fleming, 1964). He could not have been more right…

Nowadays antimicrobial resistance has become a reality in modern medicine and is considered a worldwide health threat by the World Health Organization (WHO) (World Health Organization, 2012). The problems of resistance are mainly due to inappropriate use of antibiotics. As Fleming observed already in the 1940’s, bacteria will adapt to survive. Antibiotics are a unique treatment option, for the reason that they can eradicate the cause of the disease, e.g. the pathogenic bacteria. Bacteria in turn want to survive and have multiple ways of protecting themselves against antibiotics. By means of special resistant genes, either in the core genome of the bacterium itself or in exchangeable plasmids, they can for example
produce proteins to breakdown antibiotics. In a normal situation, when there are no antibiotics present, there is also no advantage in having these genes; it might even be a disadvantage (e.g. due to reduced fitness). However, if antibiotics are introduced, the bacteria that do have resistance genes now have an advantage and can thrive over the rest without them; a perfect example of Darwin’s survival of the fittest under given circumstances. Incorrect use of antibiotics can stimulate this even more. Subsequent suboptimal treatment, when antibiotics are given but in such a low doses that they cannot kill the bacteria, can lead to selection of resistance. Furthermore, therapy that is not finished completely can kill the bacteria without resistance, leaving room for more resistant bacteria that were not (yet) killed because therapy was cut short, to grow. The use of broad-spectrum antibiotics can have the same effect of killing non-resistant bacteria, creating room for the more resistant ones to grow and thrive. A next infection is then more likely to be caused by the more prevalent resistant bacteria for which antibiotic treatment is more likely to fail. This resistance development happened already to penicillin in the 1950’s.

The discovery of penicillin however, also led to a successful search for more antibiotics. These findings and ultimately general use of each new antibiotic however, also led to resistance development for these respective new antibiotics. This continued until the 1980’s. Around that time new discoveries of antibiotics became less frequent and some people began to see the destructive effects of 40 years of uncontrolled use. Last-resort antibiotics were defined and reserved specifically for highly resistant infections. But also against these more scarcely used antibiotics, resistance is developing and spreading. At the moment, no new classes of antibiotics are expected to become available and new types of antibiotics in the current classes are scarce, although there are some in the final clinical trials (Bettiol and Harbarth, 2015; Draenert, et al., 2015). Furthermore, there are some potential alternatives to antibiotics (e.g. antibodies, probiotics, lysins, bacteriophages and vaccination). However, it was estimated that at least another 10 years and 1.5 billion dollar is needed to finalize research on the top 10 most potential antimicrobials (Czaplewski, et al., 2016). The lack of research into new antibiotics by the pharmaceutical industry is partly financially driven, because the business-case is not interesting enough (EFPIA MID3 Workgroup, et al., 2016). Newly discovered antibiotics will inevitably be reserved as last-resort drugs, meaning that sales will be low and investments difficult to earn back. Several governmental programs by the FDA and the EU are therefore in place to stimulate research and development of antibiotics (see for example Harbarth, et al., 2015). However, a future where infections are untreatable once more, a so-called post-antibiotic era is a real risk (Fowler, et al., 2014; World Health Organization, 2014).

Vancomycin resistant *Entrococcus* spp. and carbapenem resistant gram-negative rods (e.g. *Klebsiella pneumonia* producing the NDM-1 enzyme) are just two examples of resistant microorganisms, of which the latter is considered the biggest threat right now. In November 2015, Chinese researchers discovered *Escherichia coli* carrying a plasmid coding for polymyxin resistance (Lui, et al., 2015). This was the first finding of such a plasmid, making them resistant
against the last group of available antibiotics (i.e. colistin) and more importantly, thanks to the plasmid, giving the bacteria the possibility to more easily exchange this resistance. In the following months, plasmids containing the gene for colistin resistance (mcr-1 gene) were found in human fecal samples on multiple continents suggesting worldwide spread (Arcilla, et al., 2016; Malhotra-Kumar, et al., 2016). Some saw these findings, as a final confirmation that a world with patients infected with effectively untreatable bacteria due to resistance against every single clinically available antibiotic, is imminent (Gallagher, 2015).

Implications of such a situation are severe. Clinically, patients would be at risk of dying again from manageable diseases such as tuberculosis and pneumonia. Financially, costs are estimated to be hundreds of billions of dollars worldwide (Review on Antimicrobial Resistance, 2016; Smith and Coast, 2013). These costs might seem as an exaggeration to some, but it is important to understand the huge (societal) consequences of a post-antibiotic world. There will for example, be a large impact on the workforce due to infections that become untreatable, thereby incapacitating those patients from functioning. Tuberculosis is one example that is often hailed as likely threat. Already, an alarming number of extensively drug-resistant tuberculosis cases (XDR-TB), where treatment options are highly limited, more toxic, and much more expensive, are reported around the world (Matteelli, et al., 2014). If this worrisome development continues, tuberculosis might once more become a highly dangerous and fatal disease that requires strict isolation in sanatoria, impacting our society (and our economy) tremendously (Review on Antimicrobial Resistance, 2016; Wilson and Tsukayama, 2016). Hospitals need more isolation rooms, patients are unable to work and at risk of dying, healthcare workers treating those patients are at risk, sanatoria need to be built again and the medication that is available is costly. It was estimated, that by 2050 an additional 10 million people worldwide would die every year from resistant infections alone (Review on Antimicrobial Resistance, 2016). This number not even takes into account the possible impact if prophylactic use of antibiotics in surgical procedures becomes ineffective. Post-operative wound infections will increase and certain operations (e.g. complex organ transplantations, intensive care, prosthetic implants, etc.) are most likely not safe to perform anymore, once again impacting our healthcare system and our economy hugely.

It is therefore not just the WHO, but also world leaders who advocate taking action. The G7 recognized the threat of antibiotic resistance and agreed on the need for a worldwide “one health” approach (G7 Germany, 2015). The Obama Administration made antibiotic resistance one of the focus points (Task Force for Combating Antibiotic-Resistance Bacteria, 2015) and the General Assembly of the United Nations discussed antibiotic resistance in September 2016. The Netherlands is one of the countries that is taking the lead in Europe. The Dutch Minister of Healthcare Mrs. Schippers is actively involved in promoting awareness and supporting research. As chair country of the European Union in the first half of 2016, antibiotic resistance was one of the topics put on the agenda by the Netherlands (Koenders,
2015), resulting in, among others, a European congress on antimicrobial resistance in Amsterdam in March 2016. This meeting aimed at focusing on the main problems leading towards the development of antimicrobial resistance.

Figure 1.1: Percentages of isolates that are classified as resistant as part of the total number of isolates of four different microorganisms in Europe. Data from the 2015 EARS-net report on antimicrobial resistance in Europe. Depicted are the percentages of methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* extended-spectrum beta-lactamase (ESBL), vancomycin resistant *Enterococcus faecium* (VRE), and *Klebsiella pneumonia* producing carbapenemase (KPC) in 2014 (except for Poland which is 2013 data) on a logarithmic scale. The Netherlands and Germany are highlighted in green.
Within the Netherlands the resistance threat was recognized quite early and already in 1980 the first interdisciplinary committee, the Working party Infection Prevention (Werkgroep Infectiepreventie, WIP) was established. This was followed by a specific Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid, SWAB) in 1996. Within these committees, specialists from Infectious Diseases, Internal Medicine, Pharmacy, Medical Microbiology and Infection Prevention are working together. Both committees are responsible for writing and maintaining binding national guidelines on infection prevention and antibiotic use.

Within healthcare centers, the first major problem of highly resistant bacteria was the emergence of outbreaks with methicillin-resistant *Staphylococcus aureus* (MRSA) in the USA in the late 60’s. Slowly MRSA started to become endemic to healthcare institutions worldwide. The Netherlands responded by implementing a strict search-and-destroy policy. This entails proactive surveillance to detect (“search”) and then isolate and if possible decolonize patients (“destroy”) that were found positive for MRSA. The search-and-destroy policy was a big success and nowadays the Netherlands is one of the few countries that continues to keep a low prevalence (besides the Scandinavian countries, which have similar policies) (see Figure 1.1). Within a large EUREGIO project (MRSA-Net, see also the info box), German border regions implemented a search-and-follow strategy for MRSA, adopting the Dutch principles. This has led to substantial and significant drop in MRSA incidence, once more showing the effectiveness of such a program (Jurke, et al., 2013). Next to a proactive screening policy, there is also a strong focus on appropriate antibiotic use. Also in this respect, the Netherlands performs exceptionally well compared to many neighboring countries (European Centre for Disease Prevention and Control, 2013).

A department of Medical Microbiology should stimulate compliance with the guidelines on correct antimicrobial use and infection prevention, as in both cases the results from microbiological cultures provide essential diagnostic information. Nowadays the department is often combined with an infection prevention and/or hospital hygiene unit. In that case, the department will consist of clinical microbiologists who actively work together with infection prevention specialists (Deskundige InfectiePreventie, DIP, in the Dutch system). They are supplemented with additional specialists depending on the hospital. Academic microbiology departments will most often also include molecular microbiologists and sometimes also infectious disease specialists. Together they are responsible for the microbiological diagnostics within the hospital. This includes among others bacterial cultures, virological assays and next-generation diagnostics such as whole genome sequencing tools.
With these diagnostics it is possible to identify as quickly as possible the microorganism(s) that might be responsible for the patient’s problem. Also part of the identification is a resistance pattern in order to advise the treating physicians on the correct antibiotic(s) for which the pathogen is susceptible. Something that is becoming more important with growing resistance levels.

Patients in academic hospitals, such as the University Medical Center Groningen, or other referral hospitals, are coming more frequently from further away (even from abroad), instead of from a small region surrounding the hospital. Also, patients are more often transferred from another general hospital to an academic center (Donker, et al., 2010). This means that the bacteria that patients are carrying are also coming from a much larger region compared to small hospitals, which directly influences the local resistance rates in the hospital. It is thus important to take this into account when thinking about antibiotic policies and infection prevention (Ciccolini, et al., 2013).

Especially with patients coming from a country with higher resistance rates as compared to the Netherlands (e.g. Germany). The risk of importing resistant bacteria becomes much higher and must be taken into account. Regional collaboration is therefore crucial (Donker, et al., 2015). The Medical Microbiology department of the UMCG works together in a regional collaboration of healthcare centers and microbiology laboratories (Regionaal Microbiologisch Infectiologisch Symposium, REMIS+). Furthermore it is part of a Euregional project, which is a large collaboration of Dutch and German healthcare centers and professionals within the border region. These Interreg-V projects, called health-i-care and EurHealth-1Health commenced in May 2016.

See for more information: http://www.eursafety.eu.
Scope of this thesis

Regional connectivity as mentioned above, has consequences for an antimicrobial stewardship and infection prevention measures within a hospital. For example, for a hospital like the UMCG, it means that they receive more patients from Germany than hospitals in the west of the Netherlands. Antimicrobial use and resistance data from Germany are thus important information to take into account and on some levels (such as MRSA) we know that there are large differences between the two countries (van Cleef, et al., 2012). Chapter 2 of the thesis is an example of a cross-border evaluation study of specific antimicrobial use between the two bordering regions. Such studies are important in order to detect and analyze antimicrobial resistance levels of patients. If needed, this information can be used to modify or update guidelines regarding antimicrobial stewardship and infection prevention, in order to provide optimal care within a hospital.

When a patient enters the hospital and is suspected of having an infection, many different medical disciplines will contribute to the care of this patient at one time or another. Most notably of course the department of Medical Microbiology, but also Infectious Diseases, the Pharmacy and a Surgical or Internal Medicine discipline. This integrative approach is laid out in more detail in Chapter 3. Here the process of different interventions is explained and described as a novel model that incorporates three complementary stewardship programs: Antimicrobial, Infection Prevention, and Diagnostic Stewardship (AID). The stewardship programs are a set of different interventions and actions initiated by the Department of Medical Microbiology. This model provides the theoretical framework and structure for the rest of this thesis.

Firstly the Antimicrobial Stewardship Program (ASP) is discussed. The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) gave a clear definition of an ASP in their 2012 position paper:

“… [it] refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration. The major objectives of antimicrobial stewardship are to achieve best clinical outcomes related to antimicrobial use while minimizing toxicity and other adverse events, thereby limiting the selective pressure on bacterial populations that drives the emergence of antimicrobial-resistant strains.” (Society for Healthcare Epidemiology of America, et al., 2012).

An ASP is effectively a catch-all for all kinds of interventions done to improve antimicrobial therapy. Although there are certain interventions that are often associated with an ASP (e.g. a switch program intravenous to oral, or an audit-and-feedback program), there is
no clear definition of the contents of an ASP. This is also strongly dependent on the setting in which an ASP will be implemented. Thus, before starting it is therefore important to make an assessment of the baseline situation (van den Bosch, et al., 2015). As stated, an ASP should focus on improving antimicrobial therapy by promoting the correct therapeutic in the correct dosage and route of administration for the correct duration. Different interventions can be necessary to achieve all these different goals. However, optimal therapy is not the only goal, but also a means to improve sustainability of patient care by reducing selective pressure that drives bacteria to become resistant.

As mentioned before, it is essential to evaluate practices within the hospital. Especially with an ASP, consisting of several interventions, it is important to know which interventions are effective and which not. This should be done not just by looking at clinical outcomes, but also by looking at the financial aspects of each intervention. The ASP section therefore starts with an overview of different methods to evaluate an ASP. Chapter 4 is an expert review that discusses ASP interventions and focuses mainly on the different methods to evaluate those interventions, clinically and financially. These financial evaluations are sometimes overlooked or underestimated evaluative analyses. This has consequences for the quality of these evaluations, because it is highly undesirable to draw conclusions on the effectiveness of an intervention if the costs and benefits are unknown or unclear (Drummond, et al., 2005). We systematically reviewed publications that included financial evaluations in Chapter 5.

At the UMCG, as part of the local ASP, an Antimicrobial Stewardship-Team or A-Team was implemented in 2012 (Lo-Ten-Foe, et al., 2014). The A-Team works following a consensus-based “day-2 bundle”. The evaluation is part of this thesis. Using a specially created email alert, antimicrobial therapy is evaluated by an A-Team member on the second day of therapy. The goal is to streamline therapy as quickly as possible using the first results of the microbiological diagnostics, together with other available data and the clinical course. By focusing on simple improvements, such as an early stop, or switch to oral administration, antimicrobial therapy should be optimized relatively uncomplicated (Goff, et al., 2012; Pulcini, et al., 2008). The effects of the implemented A-Team was first evaluated looking at clinical outcome measures (e.g. length of stay and antimicrobial use) (Chapter 6) and subsequently also financially (Chapter 7).

Regarding Infection Prevention Stewardship, two studies were performed to assess the impact on a subset of outcome measures (e.g. costs, number of patients colonized with resistant microorganisms per year, and number of outbreak patients per year). An important task of the Infection Prevention Division is recognizing, controlling and finally clearing outbreaks caused by resistant microorganisms. Actions performed to do so cost time, consumables, manpower, and revenue due to closed beds. Until now however, it was unclear what exactly is done when
the UMCG has an outbreak and what the costs are to control it. Seven different outbreaks that occurred between 2012 and 2014 were therefore retrospectively evaluated in Chapter 8. With rising resistance levels worldwide, but also in the Netherlands, there are more and more patients entering the hospital each year that carry (resistant) bacteria with them that can cause outbreaks. Prevention is therefore becoming more and more important as well. The hospital and department of Medical Microbiology invest each year extra money to keep up with the growing number of risk patients. Is it cost-beneficial to do these investments? Chapter 9 describes eight years of infection prevention in the UMCG looking at costs, control measures, utensil use, number of expected outbreak patients and the actual found number of patients, to make an estimation on the financial costs and benefits.

Finally, regarding Diagnostic Stewardship, the effect of taking blood for cultures was studied. Blood cultures take up a major part of (diagnostic) cultures that are performed. The UMCG performs over 10,000 every year, making it the second most frequent material for cultures after urine. Using the data of 5 years of admissions, a large dataset of (infectious) patients receiving broad-spectrum antibiotics from the start of their admission was constructed. Performing blood cultures is included in almost all guidelines for severe infections. The use of antibiotics can influence the result of a culture; so appropriate diagnostics should be performed before the start of therapy. Until now however, effects of performing these blood cultures remain unclear. Therefore, this evaluation in Chapter 10 focuses on several clinical outcome measures for patients receiving antimicrobial therapy with and without blood cultures.

Using all evaluations on the three different focus points of the department (on antimicrobial therapy, infection prevention and control, and diagnostics), a more wide-ranging and comprehensive impact analysis on relevant outcome measures can be performed leading to a general conclusion of this research as well as to some recommendations to improve the healthcare system and the overall quality of healthcare (Chapter 11).