General conclusion, discussion and recommendations
Conclusions and discussion

With a strong political focus in the Netherlands on controlling healthcare costs and providing efficient healthcare, as well as the competitive pressure for healthcare institutions to be more cost-efficient due to the relatively open market in the Dutch healthcare system, there is a clear need for more impact analyses on provided healthcare (Brook, 2011; NZa, 2015; Schippers and van Rijn, 2013; Ubbink, et al., 2014). Studies that evaluate current practices, compare them, and make recommendations. Only with such studies, it will be possible to make (financially and clinically) founded decisions on new and current interventions, but also create the justification towards insurance companies, patients, and hospital boards of directors/managers. The research described in this thesis looked at the current and new practices of the Department of Medical Microbiology and Infection Prevention of the University Medical Center Groningen (UMCG). Data from these studies and the resulting publications provide a comprehensive overview and evaluation on a clinical and a financial level. In this final chapter, findings and conclusions from the previous chapters will be brought forward leading to a general conclusion and answer to the main 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?* followed by some recommendations for the future.

For a healthcare institution and especially for a Medical Microbiology laboratory, it is important to know the patient population, their pattern of transfer(s) between healthcare providers and the antimicrobial resistance rates in the healthcare region (Ciccolini, et al., 2013; Donker, et al., 2015). Data on antimicrobial use (that directly affects resistance development (Goossens, 2009)) is therefore also of importance. Previously performed studies showed that antimicrobial use in Germany is higher than in the Netherlands (European Centre for Disease Prevention and Control, 2013; Holstiege and Garbe, 2013; Holstiege, et al., 2014). However, these were always studies done on a national level with incomplete data. Due to the large, cross-border catchment area of the UMCG, it is especially important to know antimicrobial use among patients along the border region. These German patients living in the border region can visit Dutch hospitals in accordance with the new EU directive 2011/24/EU on cross-border patient care (The European Parliament and the Council of the European Union, 2011). They are therefore also part of the healthcare region of the UMCG. It is therefore wise to take these cross-border patients into account as UMCG and to be prepared for a possible increase in numbers for the coming years. With regard to infection prevention it is therefore highly valuable to have more in-depth information on these patients, their antimicrobial use and local antimicrobial resistance patterns. Data like this can be used to adapt local UMCG guidelines in the best-fitting manner. In Chapter 2, for the first time, data is shown on antimicrobial use of patients across the Dutch-German border. And indeed, also in the border region antimicrobial use among pediatric outpatients is higher in Germany compared to the Dutch border region.
Especially the differences in second-generation cephalosporin use in the first line are something to take into account when looking at infection prevention. The Euregio can and should work together on this topic to improve the usage of antimicrobials. Dutch experiences and guidelines can be of great help to German health care professionals and Dutch health care professionals should take these baseline differences into account when German patients are visiting a Dutch hospital. Indeed, this is one of the factors that we propose to be part of a more integral infection management approach within Chapter 3.

When patients with an infectious problem are visiting the hospital, it is vital that all involved specialists from different medical disciplines work together in an integrated, interdisciplinary manner. The work of the Department of Medical Microbiology is structured into three different, but integrative focus points and we translated that into three stewardships aspects: Antimicrobial, Infection Prevention and Diagnostic (AID) Stewardships (see figure 11.1). It is of no use to implement interventions to improve antimicrobial use, if there are no appropriate diagnostics performed or if they are performed too late (i.e. after starting of empirical therapy). Without diagnostics it is impossible to know what the causative pathogen of the patient is, making guided therapy in the correct form and dosage also impossible. Similarly, without infection prevention, uncontrolled spread of resistant microorganisms will impact antimicrobial use and consequently also resistance development. Thus all three aspects should be in place within a healthcare institution and within the healthcare region, to complement each other, thereby providing an integrative infection management approach. This focuses on the correct diagnostics to adequately identify the pathogenic microorganism(s) in a timely manner, correct therapy using the results from the diagnostics and finally infection prevention measures to ensure that colonized patients are not transferring their microorganisms to other patients and resistance development is curbed.

It also recognizes that different patients require different attention, with more complex patients requiring the input and experience of several more experienced specialists that should work together on infection management. These specialists are supported by a network of specially trained doctors and nurses (i.e. link-docs and link-nurses). Less complex patients can be covered for a large part by this network; thereby making sure that the limited time of the more experienced specialists is used in the most efficient manner. This patient-specific approach should lead in the near future to a so-called theragnostic approach where therapy and diagnostics are integrated, limiting the use of broad empiric substances further and improving quality of healthcare. Finally, the model matches supply and demand of numbers of patients and available staff.

Antimicrobial Stewardship Programs (ASPs) target antimicrobial therapy to make sure that patients are most effectively treated (thereby also limiting possible side-effects) and at the same
time resistance development is kept at an as low as possible level. Many different interventions are implemented worldwide to ensure those goals and it is important to evaluate these interventions because results and effects depend on the setting (Davey, et al., 2013). There is no universal approach and continuous evaluation is thus necessary. We provide some ways and methods to measure ASP interventions in Chapter 4 and evaluate the quality of financial outcomes and methods in Chapter 5. Different methods exist to evaluate an ASP and these evaluations can be difficult due to missing negative controls or bundle interventions. It is therefore important to think about the method of evaluation that one choses and the specific pros and cons of each approach. Regarding financial evaluations that are published, improvements can and should be made. In general, not all (relevant) costs and benefits are looked at, giving an incomplete picture, which also leads to possible erroneous conclusions to be drawn. Also, methods are often not explained properly making it difficult or even impossible to generalize conclusions to other settings or to repeat the analysis. Results that were found, mainly focus on direct costs of antimicrobials and the conclusion seem to be that (especially in high use countries) costs can be saved due to an ASP. These conclusions were also drawn in a similar review published at the same time, strengthening our own findings and conclusions (Coulter, et al., 2015).

Figure 11.1: Multi Stakeholder Platform of the AID Stewardship model. Pyramid platform showing the interdisciplinary stakeholder connections between the Antimicrobial Stewardship Program (ASP), Infection Prevention Stewardship Program (ISP) and Diagnostic Stewardship Program (DSP) as was presented in Chapter 3 of this thesis.
Keeping these results in mind, we set out to evaluate the ASP in the UMCG. Chapter 6 describes the clinical outcomes and Chapter 7 the financial outcomes of an ASP on a urology ward within the UMCG. The program consisted of an Antimicrobial Stewardship-Team (A-Team) that visited the ward after a patient received 48 hours of antimicrobial therapy. The A-Team member discussed the patient’s therapy with the attending physician. Based on the available diagnostics and present guidelines, a decision was made regarding continuation of antimicrobial therapy. Such an audit and feedback intervention was described earlier, although focused on 72 hours of therapy instead of the 48 hours that was chosen at the UMCG (Pulcini, et al., 2008). Due to the presence of the microbiological laboratory on the premises of the hospital leading to relatively fast turn-around-times of the diagnostics, it was chosen to perform the intervention after 48 hours instead of 72 hours. We show that the audit and feedback led to an increased switch from intravenous administered antimicrobials to oral antimicrobials in one out of four patients. Furthermore, in one out of four patients therapy could be stopped after 48 hours, because there was no (longer) an indication to warrant the prescription of antimicrobials. This led to a substantial and significant decrease in length of stay for a subgroup of the intervened patients. Finally, a decrease in the overall numbers of patients receiving antimicrobial therapy was observed, indicating that the intervention also had a more systemic effect beyond the patients that were consulted by the A-Team. These results not only show the large effects of an audit and feedback program, but also that this is possible to perform successfully after 48 hours instead of 72 hours. In the separate economic evaluation (Chapter 7), all costs and benefits of the A-Team were calculated for the same two cohorts as the clinical evaluation. Considering all outcomes from a hospital perspective, this intervention was considered (highly) cost-efficient, primarily due to the decreased length of stay of the intervened patients. The quality of the intervention and its financial evaluation was recognized and therefore chosen as one of the three best practices in Dutch hospitals as presented at the European Ministerial Conference on Antibiotic Resistance organized by the Dutch government and published in the European best practice report (Oberjé, et al., 2016).

The Infection Prevention Stewardship Program (ISP) of the Department of Medical Microbiology and Infection Prevention is the overarching name for all infection prevention and infection control related activities. The unit of Infection Prevention mainly coordinates these. Examples are the screening of (risk) patients within the hospital; educating and promoting hygiene measures such as hand hygiene; auditing, reporting and improving current practices; and actions to control events with colonized patients. All actions are done to ensure a safe environment and to minimize the deleterious effects that infections due to (resistant) microorganisms can have on patients but also on hospital staff and visitors. All these actions are done in close collaboration with regional partners, and this collaboration should intensify even more in the nearby future (Donker, et al., 2015). For the impact analysis as was performed for this thesis, two projects were undertaken.
Firstly, it was investigated which costs are associated with a nosocomial outbreak within and the hospital and how high these costs are. In general, there is little data published on costs and infection prevention. As with antimicrobial stewardship, the same difficulties are present when performing research. Because an outbreak within the hospital is the biggest impact that (nosocomial) pathogens can have, this was chosen to be the main topic. In 2011, the Netherlands saw the enormous impact of uncontrolled spread of resistant bacteria. From 2010 to 2011, the Maasstad Hospital in Rotterdam had one of the biggest nosocomial outbreaks ever seen in the Netherlands (Externe onderzoekscommissie MSZ, 2012). This outbreak exemplifies two important aspects: the devastating effect of a not correctly functioning ISP (and ASP and DSP); and the subsequent impact this has on patients and costs. Costs were reported to be millions of Euros and several patients died directly due to their infection with the highly resistant \textit{Klebsiella pneumonia} (van den Brink, 2013). The UMCG never had an outbreak of this magnitude, but outbreaks do occur. Chapter 8 describes the different actions and measures that were undertaken during seven different outbreaks that occurred between 2012 and 2014. By using different databases and performing interviews with the, at that time, involved professionals, it was possible to collect a complete overview of all the different actions that were performed in order to control the respective outbreak. All these actions could then be quantified into Euros, making it possible to calculate the average cost per patient per day for the UMCG during such an event. Depending on the type of organism, ward, number and characteristics of affected patients, these costs will differ. Unfortunately the dataset was too small to determine the different effects of these variables precisely and conclusively. However, the average daily cost of \texteuro{}546 per patient is a good indication of the large financial impact and the first time that a figure was calculated in this comparable manner.

Using this number, it was also possible to do further research into the financial effects of Infection Prevention. Because there was never situation without infection prevention in the past, it is also debatable if such a situation should be taken as a baseline level when looking at costs (Graves, 2004). We therefore choose to do an incremental cost-analysis, looking at the extra investments done each year and the effects of those investments to see if they would be financially beneficial or not. Thus, effectively comparing each year with the previous year. As with an ASP, it is of course patient safety that should be the main driver to invest in infection prevention, but when there are multiple ways to achieve that goal, it is important to know which is the most cost-efficient to keep healthcare costs under control. In Chapter 9, we describe this incremental cost-analysis over a time-period of eight years within the UMCG (2007-2014). It was observed that the number of patients colonized with high-risk microorganisms that are known to cause outbreaks is rising each year (e.g. MRSA, ESBL \textit{K. pneumoniae} and VRE). With more colonized patients, the risk of spread to other patients thus increases and with that the risk on outbreaks increases as well. To keep up with this growing risk, more money is spent each year on infection prevention personnel. The effects of these extra infection prevention facilities were measured by looking at a subset of indirect indicators to confirm that the investments had an effect. And indeed, an increase in the use of utensils, hand disinfection and surveillance cultures was observed over the eight years. Based on the increased number of high-risk patients, it was calculated how many outbreak patients were to
be expected and these number were compared to the actual found numbers of patients. These found numbers were lower than the expected ones. This entails that savings were achieved, because less money had to be spent on the control of outbreaks. These savings were higher than the yearly investments, giving a return on investment (ROI) of 1.9. This is just one aspect where infection prevention has an effect and the beneficial financial effects are therefore expected to be even higher.

Regarding the Diagnostic Stewardship Program (DSP), it was chosen to look at one of the most frequently performed diagnostic tools by the department: the blood cultures. With a database of five years of UMCG admissions, it was determined what the differences in outcomes were when looking at antimicrobial users with blood cultures during start of therapy and those without. The results presented in Chapter 10 suggest a beneficial effect of performing blood cultures for patients receiving multiple days of IV antimicrobials (i.e. with infectious problems). Of all investigated patients, almost half of the patients that received IV therapy started at admission, did so without having blood cultures taken at the same time (ideally prior to start). This was also seen in a nearby community hospital. These numbers alone are worrisome, because these patients are in a sense treated ‘blindly’. Without proper diagnostics, the causative agent will remain unknown, and adjustment of therapy therefore will be impossible. This not only affects the patient due to potentially suboptimal and toxic therapy, but also the general population because unnecessary broad-spectrum use drives antimicrobial resistance. Furthermore, the group with blood cultures had also a positive correlation with a reduced LOS, suggesting that therapy might have been more effective, and/or physicians felt more confident to stop therapy earlier. In parallel, duration of antimicrobial therapy was also shorter in the group with blood cultures. Due to the high correlation of performing blood cultures and performing other clinical chemical diagnostics (i.e. CRP, eGFR and leucocyte counts), we assume a bundle effect in which patients who received an integral approach of diagnostics have the better outcomes. An ASP (or DSP) should therefore also focus on timely performing diagnostics in patients who receive antimicrobials.

All these studies done on the three focus points of the department finally come together in a single conclusion and an answer to the question posed in the beginning of the thesis: *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?* Impact is defined here as clinical and financial effects of different interventions done by the department and the outcome measures are defined depending on the interventions as described in the previous 9 chapters. We can conclude that all interventions that were looked at, improved patient care in one way or another. The A-Team as implemented within the hospital improved antimicrobial therapy (less antimicrobial usage and users, less IV antimicrobials, shorter duration) and
reduced length of stay and therefore also costs for a subgroup of patients, earning back the investments. Infection prevention measures improved patient safety by lowering the risk for outbreaks and thereby preventing outbreak patients and again saving enough money to earn back more than the yearly investments. Finally, looking at the diagnostic interventions, effects of blood cultures are also found on length of stay, improving patient care and safety and earning back the costs of the diagnostics. Overall, all these interventions came to a potential of yearly savings of €538,931. This figure takes into account an A-Team on just one ward as described in Chapter 6 and 7. If the A-Team were to be implemented hospital-wide an extrapolation can be calculated keeping in mind the different wards and patients, their respective antimicrobial use and the costs to visit them. Per year, another €1,212,016 could be saved due to more than 3400 saved bed days, making the hospital more efficient, more competitive and creating a huge potential to increase revenue (or reduce capacity of the hospital). Freeing up beds also means waiting times will be reduced. Waiting times is one of the main healthcare quality outcome measures that is looked at nowadays and especially from a patient perspective an important aspect. Complications, readmissions and effects from a societal perspective are not even (fully) included in these analyses, making the potential benefits even greater.

The importance of knowing the impact of Medical Microbiology is partly driven by an imperfect financial system within this hospital. Cost prices for microbiological diagnostics are higher than the actual cost for performing them. This is due to an overhead of almost 25%, which covers, among others, the cost for infection prevention. It makes the department less competitive in an open healthcare market of the Netherlands that is based on unit cost prices for diagnostics. Therefore, diagnostics can be an easy target for budget cuts and they are subject of discussions if they should be priced lower (because for example, competitors in Germany are much cheaper) (VGZ, 2013). This thesis concludes that both diagnostics and infection prevention paid for by the diagnostics’ overhead have a highly positive impact both clinically and financially. Consequently, cutting back globally on diagnostics in general (and thus on the budget of the whole department as well) is not advisable. Out-sourcing laboratory-based diagnostic work to cheaper competitors in for example Germany or Belgium could be an option, and promises to save the hospital money on the short term. The question is however, what these diagnostics cover. Is for example consulting included (on appropriate diagnostics, antimicrobial therapy and/or infection prevention)? Furthermore, what will be the turn-around-time to deliver results? With a laboratory located further away from the premises of the hospital, turn-around-time until results will be longer due to transportation time. Furthermore, it is important to take into account that cutting back on diagnostics, in the case of the UMCG also means cutting back on the budget of infection prevention and consulting. These tasks will need to be covered either by the selected cheaper competitors (which does not match reality), or by the hospital itself. If costs within the hospital organization and especially within the Department of Medical Microbiology were more transparent, it would most likely also lead to a better understanding and a more sustainable situation with less quick, unfounded cut backs.
Because this thesis shows quite clearly that interventions performed by the department are highly cost-beneficial on the long term, we would also advise highly against such cutbacks.

We propose therefore a more transparent financial system for Medical Microbiology and Infection Prevention, whereby diagnostics, consulting and infection prevention are disconnected from each other financially and infection prevention is paid for by departments through an insurance-based system. This system should prevent such quick, unfounded budget cuts on diagnostics (and at the same time on infection prevention), secondly it should provide a financial incentive for the rest of the hospital to improve their infection prevention and thirdly it should make the diagnostics of the department more competitive on a financial level.

Under the current Dutch system of reimbursed bundle payments, the DBC/DOT system, infection prevention and control procedures are not covered within the bundles as specific actions that can be reimbursed. Hospitals are therefore left to finance these units or departments as they see fit, independently of reimbursement by insurance companies or other external revenues. This makes these budgets easy targets for cutbacks, even though in general they compose just 1-2% of the total hospitals’ budgets. One solution is to make infection prevention part of the overhead of microbiological diagnostics (which are covered as reimbursable actions within some bundles). The UMCG has chosen for this solution as discussed before. A consequence is, that these diagnostics become more expensive, making it more difficult to compete with commercial laboratories (this is similar for some Dutch commercial laboratories that also perform infection prevention and need to compete with foreign [e.g. German] commercial laboratories). These higher prices also fuel the discussion that microbiological diagnostics are too expensive and that they can be cheaper, as the case is in Germany. Again, important to note is that the unit cost price comparison usually purely comprises technical diagnostics (i.e. technical analysis and reports), but no consulting/Stewardship.

A more sustainable solution proposed here, would be an insurance-based finance system for Infection Prevention. This system entails that each ward/specialty/department becomes more financially responsible for their infection prevention and control measures. Proper infection prevention starts at the ward itself. Actions of physicians and nurses that see patients on a daily basis are the key components within the whole healthcare process. These are completed by actions performed by an infection prevention team, such as identification of risk patients. Correct hand hygiene for example is a vital part of infection prevention. If wards are performing suboptimal, microorganisms can spread among patients and outbreaks can occur. And when an outbreak indeed occurs, it costs hundreds of Euros per patient per day to control and eradicate the outbreak (as we clearly demonstrated in chapter 9). Part of these costs during outbreak situations, fall upon the unit of infection prevention who has to free up people, perform environmental surveillance and start to follow-up all patients at risk (up to 26% of the total outbreak costs). A more fair solution would be that all wards and specialties
bear the costs for infection prevention together. Through a monthly insurance policy for example. This fee will cover all infection prevention and control measures that are needed when an event occurs that requires actions and can cover the daily work of the infection prevention department. To provide a financial incentive and stimulate wards to improve their infection prevention, wards pay according to their relative risk, meaning that those that are performing better will pay less than the suboptimal performing wards. Such a system would make the cash flows more transparent and creates a ‘polluter-pays’ principle.

Based upon the infection prevention databases and using the results from the study described in chapter 9, an estimate can be made on the total cost per year that fell upon the UMCG because of outbreaks and smaller isolated events (“epi events”). This total amount should be at least be covered by newly implemented insurance fees, but needs to account for possible extra costs due to unforeseeably bigger outbreaks or other situation (e.g. events like the 2015 Ebola outbreak or the 2010 H1N1 pandemic), we would advise to include an extra margin for emergency coverage. If this extra coverage has not been used, it could for example be applied to implement innovative tools for the hospital, cover extra educational courses or it can be returned to the wards in the form of a discount/cash back on next year’s fee. This would correspond to the payment models implemented for classic insurances (e.g. liability, health care, life insurance). Using a set of transparent quality indicators such as number of events during the last years, total scores on the different quality audits (e.g. on adherence to dress code protocols), and antibiotic use, a relative risk of each ward can be calculated to score them objectively. By publishing these scoring lists and updating these on a regular basis, wards can follow their performance, compare their score to other wards and try to improve it. Wards that score the best are generally assumed to have fewer problems with spread of microorganisms and will consequently also bear less of the infection prevention costs. Eventually this should stimulate all healthcare professionals to actively improve infection prevention, making the whole hospital a safer environment for patients and a more cost-efficient institution creating therefore a win-win situation.

Concluding, we show here that investments lead to improved quality of care, and it thus pays off to invest in Medical Microbiology and Infection Prevention. Interventions performed by a department such as the UMCG Medical Microbiology and Infection Prevention, improve patient care and overall healthcare quality. By reducing LOS, it creates potential to increase revenue by making healthcare processes more efficient and at the same time lowering potential waiting lists. We recommend a proactive ASP, ISP and DSP for each healthcare institute to prevent, diagnose, and treat infectious problems in an integrated way. We recommend evaluating antimicrobial therapy after 48 hours, as this will lead to improvement of therapy and will save costs. It should however be noted that these results are highly depended on the patient’s characteristics. A general evaluation of practices without adjusting outcomes to specific patient groups is therefore not recommended. Infection Prevention departments or units should have enough funds to keep up with the growing resistance problem and the risks
that this brings with it. Outbreaks are costly events and prevention or quicker control of these can easily be cost-efficient. Focus should therefore be on a preventative approach from a regional perspective. Blood cultures (and other diagnostics) are still not performed for all indicated patients and this should be a focus for A-Teams. Patients with blood cultures taken can be treated more effectively, thereby creating again potential improve patient care, reduce length of stay, and save costs. ASPs or DSPs should focus on these aspects. Finally, the current financial system is not adequate anymore to address the urgent challenges that we face. Growing antimicrobial resistance rates creates more risks of difficult to treat nosocomial infections. Prevention and control therefore requires a sustainable budget. An insurance-like financial system following the ‘polluter-pays’ principle could be a solution to tackle this issue. Ultimately, implementing these recommendations should lead to situation where antimicrobial resistance and the increasing risk on nosocomial outbreaks is tackled, the importance of correct and timely diagnostics is recognized and most importantly: patient care and overall healthcare quality is improved in a sustainable manner.