Development of quality indicators for appropriate antibiotic use in daily hospital practice
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Chapter 1

General introduction
Emergence of antibiotic resistance
The breakthrough of antibiotics in the 1930s led to a dramatic decline in illness and death from infectious diseases. Antibiotics, often described as 'wonder drugs', fundamentally altered health care in the twentieth century by creating curable bacterial infectious diseases. Today antibiotics are indispensable in practically all health care systems. Achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies, and cancer chemotherapy would be impossible without an effective treatment for bacterial infections.

However, the extensive use of antibiotics is also the most important driving force in the emergence of resistant microorganisms, threatening the effectiveness of these 'wonder drugs'. Antibiotic consumption is high in human medicine, but antibiotic use for growth promotion and prevention of diseases in veterinary medicine, agriculture, aquaculture, and horticulture are also significant contributing factors. Worldwide, antibiotic consumption and antibiotic resistance are still on the rise, which, together with the steady decline in the discovery of new antibiotics, creates one of the greatest current threats to human health. With the arrival of untreatable strains of carbapenem-resistant Enterobacteriaceae, we are at the break of a post-antibiotic era.

Antibiotic stewardship programs
The reasons for resistance to antibiotics are complex, and also comprises human behavior at many levels of society. To help curbing antibiotic resistance in hospitals, better use of current agents is warranted and a decrease of inappropriate antibiotic use is imperative. Antibiotic stewardship programs are developed to optimize antibiotic selection, dosing, route, and duration of therapy, in order to maximize the chance of clinical cure or prevention of infection. At the same time, they aim to limit the unintended consequences of antibiotic use, such as the emergence of resistance, adverse drug events, and costs. Antibiotic stewardship programs have been shown to be effective and financially self-supporting. Multidisciplinary local stewardship teams are now established across the world, with the task to design programs in their own hospitals. In the Netherlands, the development of an Antibiotic-team (A-team) is mandatory in every hospital since 2014. This so-called A-team (antibiotic team) comprises infectious diseases specialists, microbiologists, hospital pharmacists and quality assurance experts and focuses on authorization of antibiotics for special indications, measuring and monitoring antibiotic use, the organization of special improvement projects, and the provision of education, training, and consultations. In order to set priorities and focus improvement, an essential tool for an effective stewardship program is the ability to measure the appropriateness of antibiotic use in individual patients.

Antibiotic guidelines
Appropriate antibiotic use is described in the recommendations of guidelines. International, national and local guidelines on the management of various infections have been developed and are updated regularly. The Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) are important collaborations that develop guidelines for infectious diseases. In the Netherlands, the SWAB, the Dutch Working Party on Antibiotic Policy, develops national antibiotic guidelines. Previous studies have shown that adherence to guidelines improves clinical outcome, is correlated with less development of resistance and lowers costs. The aim for guidelines is to support clinical decision making, and to increase effectiveness of antibiotic care by preventing under-, over- and misuse of antibiotic therapy. Moreover, adherence to these guidelines will result into a decrease of unwanted variability in practice.

In summary, guidelines aim to improve the appropriateness of antibiotic therapy by bridging the gap between what is already known from scientific studies and what is performed in daily clinical practice.

Nonetheless, not always are patients receiving care as recommended in guidelines: the publication and dissemination of guidelines do not directly ensure appropriate antibiotic use in daily clinical practice. For inpatients receiving antibiotics, studies have shown that guideline adherence is often suboptimal, up to 50% of hospital antibiotic use is inappropriate, and adherence varies considerably between hospitals and between care providers.

Measuring appropriate antibiotic use
After developing guidelines, the next step to improve the appropriateness of antibiotic use is to gain insight into the quality of antibiotic use in daily clinical practice. Quality indicators (QIs) are measurable elements of practice
performance for which there is evidence or consensus that they can be used to assess and change the quality of antibiotic care provided. They consist of a numerator and denominator. The denominator describes the patients to whom the care should be applied to and the numerator the patients who have actually received the care as recommended. Table 1 shows an example of a QI; the quotient between the numerator and denominator is the indicator score. A well-known classification to categorize QIs is: structure-, process- and outcome indicators. Structure indicators measure requirements and attributes of settings in which antibiotic care occurs. Process indicators measure the process around antibiotic care at the patient level. Outcome indicators measure the effects of antibiotic care on the health status of patients and populations.

Table 1. Example of a quality indicator

<table>
<thead>
<tr>
<th>Numerator</th>
<th>Denominator</th>
<th>Indicator score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients who started with empirical systemic antibiotic therapy according to the national guideline</td>
<td>Total number of patients who started with empirical systemic antibiotic therapy</td>
<td>75%</td>
</tr>
</tbody>
</table>

Indicator development

During the past decade quality indicators have been developed and implemented in many healthcare settings to measure, compare and improve appropriateness of care. Many governmental- and professional associations have developed QIs. To obtain the information needed to develop QIs, a systematic or non-systematic method can be used. Systematic methods rely on available scientific evidence complemented when necessary with expert opinion. The method used for the development of QIs in this thesis is the well-known RAND modified Delphi procedure. This consensus method is also a rigorous systematic process where QIs are developed based on scientific evidence combined with expert opinions. There were no universally accepted requirements for using the Delphi technique, which led to considerable variability across studies in the characteristics and the reporting of the Delphi procedure. Boulkedid et al. developed a practical guidance on the use and reporting of the Delphi method in QI research.

When the study of this thesis started in 2011, a couple of indicator sets were already developed for antibiotic care in the hospital using a systematic method like the RAND modified Delphi procedure. More precisely, in previous studies we developed QIs for the treatment of the two most prevalent infections in the hospital: lower respiratory tract infections and urinary tract infections. The Surviving Sepsis Campaign developed a care bundle for optimal start of treatment in the first 24 hours. The European Surveillance of Antimicrobial Consumption (ESAC) developed QIs to measure appropriate antibiotic use in outpatients in Europe. What was missing was a set of generic indicators covering all steps in the process of antibiotic use, applicable to all hospitalized adult patients with a suspected bacterial infection.

In 2011 we initiated the ‘Development of Reliable generic quality indicators for the optimisation of ANTibiotic use in the hospital (RIANT)’ study, with the aim to develop reliable generic quality indicators which define appropriate antibiotic use in the treatment of all bacterial infections in hospitalized adult patients. This set of QIs was intended to measure and monitor the various steps in the process of antibiotic use on the patient level, along the entire antibiotic pathway.

Indicator validation

For an optimal and reliable use of the developed QIs, their clinimetric properties have first to be tested in clinical practice. However, few study groups have tested their QIs in daily clinical practice before using them for example in improvement projects. Registration of data is different in every country and varies over time, which has an effect on applicability, validity and reliability of data collection. Therefore it is mandatory to locally test the clinimetric properties of the QIs, in order to discriminate between indicators that are feasible, valid and reliable in a specific setting and those that are not. There are several criteria to consider when assessing the QIs. These important clinimetric characteristics are described below.

Measurability. Is defined as the availability of administrative data required to evaluate the indicator. Too much missing data may bias the results and therefore, the number of missing data should be reported.

Applicability. An indicator should be applicable to a substantial proportion of the reviewed patient records.
Inter-observer reliability. When two different registration employees are extracting data or data is collected by two different methods, this may affect the indicators scores by subjective interpretation of information in the medical records. Therefore, the level of agreement between employees or methods should be assessed after performing duplicate registration.\textsuperscript{38, 39}

Room for improvement. QIs must be capable of detecting variability in quality of care between and within hospitals. High QI scores with little variation between hospitals make indicators less sensitive and therefore less useful in daily practice.\textsuperscript{27}

Case mix stability. The QI scores may be influenced by characteristics of the underlying population (case mix).\textsuperscript{21} More specifically, patient factors such as comorbidity or severity of illness may influence the performance on process- and outcome indicators.\textsuperscript{39} This should be evaluated.

Outline of this thesis
This thesis describes the development and validation of QIs that can be used to assess and improve appropriateness of antibiotic use in the hospital. Secondly, it focuses on measuring antibiotic use in the Netherlands and its effect on clinical outcome. Each of the studies contributes to answering the question: What is appropriate antibiotic use and how can we measure it?

In 2006 the Dutch Working Party on Antibiotic Policy (SWAB) introduced an online national antimicrobial guide (SWAB-ID) for the treatment and prophylaxis of common infectious diseases in hospitals. Every hospital in the Netherlands was offered the opportunity to get a local copy of the national version, and to edit this version for local use. Customizing (national) guidelines for local use is necessary to meet local circumstances, resource constraints and barriers to implementation. By the end of 2012, approximately 40% of Dutch hospitals used a local, customized version of SWAB-ID. In \textbf{Chapter 2} we compared two approaches, the local SWAB-ID based and local non-SWAB-ID based antimicrobial guides, and described the relative comprehensiveness and compliance with the national SWAB-ID antimicrobial guideline. To determine the impact of this online tool in providing comprehensive antibiotic treatment guidelines.

The RIANT-study was performed at 4 university and 18 non-university hospitals located throughout the Netherlands. PREZIES (prevention of nosocomial infections by surveillance) is a department of the RIVM (National Institute for Public Health and the Environment, the Netherlands) and organizes biannual point prevalence measurements primarily aimed at identifying nosocomial infections. This point prevalence measurement was used to include 1890 adult patients using antibiotics for a suspected bacterial infection.

\textbf{In Chapter 4} we answered the question ‘what is appropriate antibiotic use’ by performing a literature search and asking an international expert panel which potential QIs are the most important when considering good antibiotic therapy. We developed a set of generic evidence-based QIs to measure and monitor appropriate antibiotic use in hospitalized adult patients with a suspected bacterial infection, using a RAND modified Delphi method.

In Chapter 6 we validated the QIs we systematically developed in Chapter 3, by assessing their clinimetric characteristics in daily clinical practice in the 1890 patients treated with antibiotics for a suspected bacterial infection.

\textbf{Chapter 5} evaluates the association between appropriate antibiotic use for patients with a suspected bacterial infection and their length of hospital stay. Appropriate antibiotic use was defined by the previous developed and validated set of generic indicators. The study group was again the group of patients enrolled in the RIANT study.

In the general discussion, \textbf{Chapter 7}, the main results of this thesis are summarized and discussed, followed by final conclusions and implications for further research.
Chapter 1

Reference List