The quest for optimal antimicrobial therapy
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Chapter 1
Introduction

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To be submitted
Since the discovery of sulphonamides and penicillin in the 1930’s, and their widespread use in clinical practice during World War II a plethora of new antimicrobial agents have entered the market. Antimicrobial agents changed health care in the twentieth century enormously making infectious diseases curable. They are considered one of the greatest public health achievements of that era; saving the lives of persons with infectious diseases such as syphilis, tuberculosis, typhoid fever, streptococcal and staphylococcal infections. Initial optimism has faded that these new drugs would eliminate infectious diseases as killer diseases, at least in the Western World. Infectious diseases are still among the leading causes of death worldwide, accounting for 11.1 million deaths (20% of all deaths) in 2002. Indeed the death rate from infectious diseases in the USA increased again from 1980 to 1992 by 58%. This increase was not only caused by new infectious diseases such as AIDS but also by pneumonia and septicemia. So, where did it go wrong?

A major factor has been the unrestricted use of antibiotics leading to increasing emergence of resistance. Therapy failure, because of insensitive pathogens to commonly used antimicrobial agents has led physicians to prescribe newer and more broad-spectrum antimicrobial agents. This in return leads pathogens to become resistant to these drugs as well. Thus, introduction of new antimicrobial agents in the past decennia has been rapidly followed by bacterial resistance to these compounds. For example, resistance to the antimicrobial agents most commonly used to treat Streptococcus pneumoniae infections emerged within a decade of their introduction to the market. This is reflected by papers related to antimicrobial agents in the last 10 – 15 years featuring more and more aspects of drug-resistance (Figure 1). We searched the SilverPlatter Medline database on-line from 1966 to 2003 for papers related to antimicrobial agents and microbial drug-resistance using appropriate key-words (appendix 1). Total number of papers covered by SilverPlatter Medline, number of papers related to antimicrobial agents, and papers referring related to microbial drug-resistance, were identified.

Complicating matters is that antimicrobial agents are not only used in humans. They are also used in (food) animals, not only to treat or prevent infection but also as a growth promoter. In the European Community in 1997 an estimated 10,493 tons of antimicrobial substance were used of which 52% was used for humans, 35% for therapeutic veterinary use and 15% as a growth–promoter for food animals. In spite of the large consumption of antimicrobial agents in animals and some reports of veterinary use being responsible for resistance in humans, it is accepted by experts that the main contribution to resistance in human pathogens is clinical use of human antimicrobial agents in humans. In hospital care where antimicrobial pressure is most
intense, the consequences of antimicrobial resistance are strongly felt. To safeguard the effectiveness of antimicrobial agents, antimicrobial policies have been developed by various hospitals. These policies consist of infection control measures and strategies to manage prudent antimicrobial prescribing. This thesis will focus on optimizing prudent prescribing of antimicrobial agents in hospital care.

In the following paragraphs we will describe the general background of the various chapters of this thesis.

Figure 1. Publications in Medline on antibiotics and drug-resistance. 1966 – 2003

Legend: The small graph (insert) covers all publications by SilverPlatter Medline from 1966 – 2003, from 174,641 in 1996 to 496,986 in 2003. Absolute number of papers on antimicrobial agents (gray bars), and on antimicrobial agents and drug-resistance (black), are shown as bars in the large figure. Percentage of papers on antimicrobial agents that address microbial drug-resistance of all publications is represented by the black line.
Scope of the problem
Rational use of antimicrobial agents is relevant because of three key issues: economics (use and costs), bacterial resistance and clinical outcomes.

Economics (use and costs)
Up to a third of patients admitted in hospital are prescribed at least one antimicrobial agent, leading up to 30% of a hospital’s drug budget in the Western World.\textsuperscript{12,13} Overuse and inappropriate use of antimicrobial agents is a widely recognized problem that has been addressed widely in the scientific literature. Unnecessary use of antimicrobial agents and use of the newest broad-spectrum agents where more narrow-spectrum and older agents would suffice leads to unnecessary high treatment costs.\textsuperscript{14-16} Antibiotic-resistance too will have a considerable economic impact, not only because of a need of more expensive second-line drugs but also because of longer hospital stay associated with treatment failure.\textsuperscript{17}

Antimicrobial use in the context of this thesis
Surveys consistently show consumption of antimicrobial agents to be low in ambulatory care in the Netherlands. Ten DDD/1000 inhabitant-days were used from 1997 – 2001, which was the lowest in Europe.\textsuperscript{18,20} Nevertheless, also in the Netherlands in ambulatory care an increase in unnecessary use of broad-spectrum more expensive newer antibiotics is seen at the expense of older and narrow-spectrum, still appropriate penicillins.\textsuperscript{21}

Use in hospital care in the Netherlands is not only much more intense it also increased in the same period; from 47 to 52 DDD per 100 patient-days. In the university hospitals use was relatively higher. Co-amoxiclav was the most commonly used antibiotic in Dutch hospitals, 14 – 17 DDD/100 patient-days in this period. Shifts in use took place with especially the use of newer broad-spectrum antibiotics increasing; e.g. co-amoxiclav, third-generation cephalosporins, ciprofloxacin, and vancomycin.\textsuperscript{18}

In the University Hospital Groningen the expenditure on antimicrobial agents increased from 1.97 to 2.67 million Euros from 1997 – 2000, almost a quarter (23%) of total drug expenditure in the hospital during that period.\textsuperscript{22,23} In the department of Internal Medicine in the period 1998 – 2001 use was relatively high 81 (SD 13) DDD/100 patient-days compared to the 63 DDD/100 patient-days reported in Nethmap 2003. (Figure 2)\textsuperscript{18}
**Bacterial resistance**

Emergence of resistance is a multi-factorial problem. Of particular importance is the use and misuse of antimicrobial agents. Stimulating prudent use of antimicrobial agents is therefore one of the cornerstones to control development of antimicrobial resistance as identified at the Copenhagen Conference in 1998; “the Microbial Threat”

After raising awareness in Europe about the seriousness of the problem of antimicrobial resistance, surveillance of resistance, monitoring antimicrobial use, research into understanding development of resistance and a rigorous evaluation of interventions to reduce the harm of bacterial resistance are the other main recommendations of that Milestone conference. On a European level the European Antimicrobial Resistance Surveillance System (EARSS) and European Surveillance of Antimicrobial Consumption (ESAC) initiatives have been instrumental in collecting high quality data on microbial resistance and antimicrobial consumption respectively. Currently, a European study

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1 With thanks to P.V. Nannan Panday for calculating the consumption data and the pharmacy department and the hospital for making the data available.
named Self medication with Antibiotics and Resistance (SAR) explores the uncharted, but much feared territory of use of antibiotics by the public without interference of a licensed prescriber 29.

A striking example of correlation in use of antimicrobial agents and resistance based on sales data from IMS Health Global Services and EARS surveillance data is shown by Bronzwaer et al 30. This study shows an almost perfect linear relationship between use and resistance at the country level but the authors are the first to describe some important limitations of their findings. This is an ecologic study analyzing aggregated data thus no causal inferences can be made to the individual level. Socio-economic and behavioral aspects are possible confounders. Resistance rates are for some countries based on limited number of isolates. Thirdly, there may have been sampling bias, with possibly more frequently taking blood cultures by Northern European physicians. Bias and confounding may have an impact on the association generally reported between antimicrobial prescribing and resistance. Nevertheless, the evidence is mounting that prescribing volume is linked to resistance even despite the possible publication bias that studies showing no impact of use on resistance are less likely to be published 31. Several examples show that within a hospital (abundant) use of specific antimicrobial agents can lead to emerging resistance of pathogens to those specific agents 32-34.

The finding that after a nationwide campaign in Finland the resulting reduction in the use of macrolides led to a decreased erythromycin resistance in group A Streptococci supports efforts to optimize antimicrobial therapy 35. Resistance, also in the hospital setting is shown to diminish after interventions to optimize antimicrobial use, but in the study of Khan et al. it took six months before an impact on resistance was seen 36. Sometimes no impact of a decrease in antibiotic use on resistance is reported 37. A more theoretical approach combined population genetic models and epidemiological observations to study the impact of drug use on changes in resistance. From the analyses it became clear that emergence of resistance under selective antimicrobial pressure was much faster, than the decay after a similar decline or cessation of drug consumption 38. The authors conclude that these results highlight that as soon as resistance is detected an intervention should be initiated. Clearly many underlying mechanisms affecting development or reduction of bacterial resistance are suggested to exist: e.g. antibiotics with high- or low-resistance inducing potential have been described, cross-resistance to other antibiotics, wide-spread resistance versus clonal resistance, veterinary antibiotic use, optimal dosing and even population density 39-40.

In hospitals the situation is aggravated by high antimicrobial pressure, close vicinity of other patients who often have invasive devices that allow for an easy “porte d’entrée”,

6
and health-care workers moving from patient to patient. These factors contribute to transmission of resistant bacterial strains. Prevention of infection, prudent use of antibiotics, surveillance of antimicrobial resistance and improving hygiene practices in hospital care are considered major aspects of controlling emergence and spread of resistance in hospital care.\textsuperscript{31-41}

The bacterial resistance problem in the Netherlands still favorably compares with that of other or neighboring countries. However, also here shifts and increases in resistance patterns following antimicrobial consumption patterns are observed in ambulatory and hospital care.\textsuperscript{44,45}

**Clinical outcomes**

Stimulating rational prescribing of antimicrobial agents is expected not only to reduce the development of bacterial resistance at acceptable costs but also to improve quality of care and patient outcome.\textsuperscript{2,46} Treatment with antimicrobial agents balances between prescribing to narrow and to broad spectrum drugs. Prescribing to narrow-spectrum drugs not covering the causative pathogens leads to treatment failure. To broad-spectrum prescribing leads to super-infections e.g. of Fungi and development of resistance.\textsuperscript{16} Physicians tend to be on the safe side preferring to cure their current patients even if this might mean a loss of efficacy of an antimicrobial treatment in future patients. Therapy with to narrow-spectrum agents; i.e. not effectively treating a causative pathogen, is linked with both emergence of resistant bacteria and increased mortality due to treatment failure.\textsuperscript{47,48}

In summary we can conclude that antimicrobial use strongly contributes to emergence and spread of antimicrobial resistance. To prevent resistance from becoming an incurable problem timely and lasting attention to rational antimicrobial use is needed.

**Antimicrobial policies and guidelines**

To curb spending on antimicrobial agents and other drugs hospitals have often restricted the number of drugs that are readily available in a hospital. Restricted lists of drugs or drug-formularies are usually developed and made available to all prescribers within a hospital.\textsuperscript{49} In the Netherlands nearly all hospitals have additionally developed local antimicrobial treatment guidelines, consisting of disease specific therapeutic treatment recommendations.\textsuperscript{49} Those guidelines often embody a hospital’s antimicrobial policy that includes hygienic measures as well. Such antimicrobial policies and their reflection in the guideline are usually based on existing evidence, adapted where necessary to local resistance patterns, and economical considerations.\textsuperscript{50}

Nevertheless, adherence to guideline-recommendations is only moderate, also in the Netherlands.\textsuperscript{15,50-55}
Barriers to adherence to guidelines in general

So why do physicians not follow those clinical practice guidelines? Two provocative statements from opposing views trying to answer this question are: “free us from this confetti of interference” 56, and “specialists are easily offended and defend their autonomy” 57. The first statement is the title from an editorial in the BMJ, reflecting on the numerous guidelines physicians’ have to deal with in daily clinical practice. The second statement comes from an interview with the former chief inspector of health care in the Netherlands who states that especially in university hospitals it is difficult to change specialists’ viewpoints.

Autonomy of physicians, in ambulatory and hospital settings, is found by several authors to impede physicians’ willingness to change their prescribing behavior 58-61. Lack of ownership of a guideline; i.e. the target group being not (sufficiently) involved in drawing up the guideline, has been identified as an important barrier in general practice too 58,62.

Attributes of the guidelines themselves too have an impact on their use in general practice. Guidelines that are based on evidence based recommendations are better followed than recommendations that are not having a firm evidence base. More explicit recommendations that are not too controversial and are compatible with existing routine are better accepted 63.

In general there are thus different barriers that impede physicians to adopt guideline-recommendations into routine practice. In a practical model Cabana et al describe knowledge, attitudes and behavior as consecutive steps physicians have to go through when changing their (prescribing) behavior 64. Lack of familiarity and awareness of a guideline impede physicians’ knowledge of the contents of such a guideline. The “confetti of interference” statement falls in this category as time-constraints might inhibit general practitioners to stay aware of all new relevant available guidelines and their contents. Several attitudinal issues are described that make it less likely a physician will follow guideline-recommendations:

- Lack of agreement with specific guidelines and guidelines in general;
- Lack of outcome expectancy, i.e. following a guideline might not lead to improved care;
- Physicians may lack self-efficacy, believing he or she cannot perform the guideline recommendations;
- Physicians may not be motivated to follow a guideline-recommendation from routine or habitual considerations;
- Existing external barriers, such as patient preferences contradictory to guideline-recommendations, may keep physicians from changing their prescribing behavior.
Guideline characteristics or opposing guidelines, and environmental factors: e.g. lack of time, resources or organizational constraints may also inhibit physicians to change their actual prescribing behavior 64.

Cabana’s barriers are illustrated by a U.S. a survey into interns’ attitudes towards clinical practice guidelines was performed. This study showed that physicians considered guidelines to much aimed at reducing health care costs. Guidelines were considered to rigid and decreased satisfaction with clinical practice. Guidelines that were issued by an insurer were looked upon with more suspicion as opposed to guidelines issued by their own (medical specialty) professional group (=ownership). A perceived loss of autonomy was identified as a barrier too 60. In that same survey recently graduated physicians were more positive towards guidelines. They considered guidelines to have an educational value, to be a convenient source of advice, and especially, as this was an American study, to be a safeguard against malpractice suits.

In the Netherlands specialists were not very motivated to use joint treatment guidelines; i.e. guidelines for both specialists and general practitioners. They were afraid of a loss of autonomy, increased workload, and a decreased possibility to attract industry-sponsorship for research or conference-visits. The specialists had reservations regarding the development process, they felt not enough involved. However, they perceived the guidelines as positive as a supportive tool for specialists in training, for general practitioners and for areas outside their own expertise 61.

**Barriers to antimicrobial treatment guidelines**

Prescribing of antimicrobial agents is not based on microbiological considerations only. Cultural and economic factors influence therapeutic decisions as well. Patient expectations and financial gain may stimulate physicians to prescribe antimicrobial agents for e.g. upper respiratory infections with a probable viral cause 65. Similarly, antibiotics were unnecessarily prescribed for acute otitis media in general practice when patients were more severely ill when first contacting a physician or had (non-relevant) co-morbidity. In this Dutch study e.g. patients’ disease behavior, patients’ demand and physicians’ habit were important reasons to prescribe antibiotics 66. Physicians’ prescribing of unnecessary antibiotics to institutionalized elderly was influenced by range of nonspecific symptoms, e.g. “a patient not being herself”. Physicians relied heavily on nurses subjective reporting of such changed patient behavior 67.

In hospital care in Australia a lack of awareness of a hospital’s antibiotic policy may be causing physicians not to follow guideline recommendations 68. However, these Australian hospital physicians perceived antimicrobial policies in general to be useful
Differences in prescribing behavior exist between intensive care specialists and infectious disease specialists. These may be explained by differing diseases managed but also by different training, culture and cognitive styles of physicians. A survey in the United States showed that most physicians are aware of antibiotic resistance as a serious (inter)national problem. However, they perceived the problem less relevant for their daily clinical practice and did not feel a need to reduce broad-spectrum antimicrobial prescribing to any great extent.

Halm et al showed that non-adherence with a pneumonia practice guideline to stimulate out-patient treatment of low-risk pneumonia cases was contributable to a variety of patient, system, and physician factors. Patients with additional comorbidities were more likely to be admitted to hospital. They were also more likely to be admitted when they were elder, male, and employed. Also, involvement of a primary care physician in the admission decision led to less adherence with this guideline recommendation. Finally, hospital physicians with more experience in treating pneumonia were less inclined to treat identified low-risk patients as outpatients.

De Gans et al. showed adherence to a national guideline for bacterial meningitis in the Netherlands to be extremely poor (33%). Not following guidelines was suggested to be caused possibly by existence of contradicting local guidelines, poor dissemination of the national guideline, fear of missing all possible causative pathogens for this serious illness, and a possible lack of evidence-base. Guidelines cannot be so specific that they apply to all clinical situations. Clinically relevant considerations may lead to “rational non-adherence”. Allergies to antimicrobial agents might be such a reason to deviate from a first choice guideline recommendation. Sometimes, non-adherence to guidelines is caused by purely logistical aspects of care, interfering with keeping to dosing intervals and timely administration of surgical prophylaxis.

Thus, we know that certain physician-characteristics, guideline attributes and organizational (system) features have an impact on how physicians follow guideline recommendations. However, patient-characteristics, that influence physicians prescribing behavior in the clinical setting, are still largely uncharted territory. The barriers described above are context specific. Appropriately addressing these barriers in a targeted intervention will increase the chance of success of interventions aimed at optimizing antimicrobial therapy. Unfortunately, we have only a sketchy knowledge of those barriers to using local antimicrobial treatment guidelines, especially in European settings.
Interventions to optimize therapy

There is ample evidence that changing physicians’ behavior in general is possible, intervention strategies have to consider barriers at different levels as described before and should be adapted to specific settings and target group. Various approaches have been used of which the majority was effective to at least a certain extent. [table 1] Interestingly, combined interventions that addressed specific barriers, were not consistently shown to be more effective than single interventions. Most of the evidence is available for professional-oriented interventions (education, reminders and feedback), less for interventions targeting the patient or an organization. Limited data is available of the impact of an intervention on patient outcomes. [74,75]

In antimicrobial control programs different intervention strategies are used. Many interventions in optimizing antimicrobial therapy combine or employ the following intervention strategies: dissemination of guidelines involving multidisciplinary teams, restricted lists of available antibiotics, or authorization-requiring prescribing of certain antibiotics, reminders to streamline or switch intravenous to oral therapy, etceteras. In an American survey of 47 hospitals all used a restricted list of available antibiotics, and 43 used it with at least one of the following control measures: automatic stop-orders (60%), antimicrobial agents requiring previous authorization before they can be used in the clinic (40%), and antimicrobial treatment guidelines (70%) [76].

In table 1 an overview is given of most commonly employed interventions to improve antimicrobial use arranged to the type of intervention employed. The work of Bearden and Allen, and that of Avorn and Solomon serve as a basis for this classification [65,77]. Additional examples are referred to without trying to be complete. The impact of the intervention strategies used in these studies is described for those studies that employed a rigorous study design. Table 1 provides merely a sketch of the impact of intervention studies that have been performed; a rigorous Cochrane review is currently being undertaken [78].

Different outcomes are studied in interventions aimed at optimizing antimicrobial prescribing: e.g. amount of specific antimicrobial agents used, appropriateness of therapy (e.g. covering targeted / cultured pathogens), adherence to guidelines, treatment costs, impact on bacterial resistance, and patient outcomes as length of hospital stay, readmission rates or mortality [77,79,80].

Historically in the Netherlands much attention has been paid to controlling antimicrobial prescribing. On a national level the Dutch Working Party on Antibiotic Policy (Dutch acronym is SWAB) catalyzes efforts in hospitals to optimize the use of antibiotics through guideline development, education and antibiotic resistance surveillance. (http://www.swab.nl) In recent years several studies addressed optimal
antimicrobial care in the Netherlands, they focused at the use of national guidelines on
treatment of meningitis ⁵⁴, timely initiation of antimicrobial therapy ⁸¹,², adherence to
hospital treatment guidelines ⁵¹,²,³, empirical therapy at a neonatal intensive care unit
⁸⁴, and switch protocols of intravenous to oral antibiotic therapy ⁸²,⁸⁵.

Table 1. Strategies to implement changes in general medicine and interventions used especially targeting antimicrobial prescribing in hospital care.

<table>
<thead>
<tr>
<th>Professional oriented interventions</th>
<th>General ⁷⁴</th>
<th>Antimicrobial agents ⁶⁵,⁷⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of educational materials</td>
<td>Limited effect</td>
<td>Clinical guidelines are available in most hospital settings ⁴⁹,⁷⁶, though impact is generally considered limited ⁶⁵,⁷⁷(-)*, study ⁸⁴(?)</td>
</tr>
<tr>
<td>Educational meetings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Large conferences / courses</td>
<td>Mixed effects</td>
<td></td>
</tr>
<tr>
<td>- Small interactive courses</td>
<td>Mostly effective (often combined with feedback)</td>
<td></td>
</tr>
<tr>
<td>Educational outreach</td>
<td>Especially effective at changing prescribing behavior</td>
<td>Academic detailing ⁸⁷(+)</td>
</tr>
<tr>
<td>Local opinion leaders</td>
<td>Often difficult to identify and mixed effects</td>
<td></td>
</tr>
<tr>
<td>Patient mediated interventions</td>
<td>Mixed effects</td>
<td></td>
</tr>
<tr>
<td>Audit and feedback</td>
<td>Limited impact but when combined with educational outreach or reminders it showed more promise.</td>
<td></td>
</tr>
<tr>
<td>Reminders</td>
<td>especially effective for prevention (vaccination or cancer screening)</td>
<td>-Reminders aimed at appropriate use ⁸⁸,⁸⁹(+) streamlining ⁸⁰(?), switch intravenous to oral conversion ⁸⁵,⁹¹ (?) ⁸²(+-), or combination of streamlining, switching ⁹⁰(+) -Clinical pathways ⁵³ (?) ⁸⁴(+) -Computerized support ⁹⁵,⁹⁶ (?)</td>
</tr>
<tr>
<td>- Computerized decision support</td>
<td>mostly effective</td>
<td></td>
</tr>
<tr>
<td>Mass media campaigns</td>
<td>Mostly effective</td>
<td></td>
</tr>
</tbody>
</table>
## Table 1. Strategies to implement changes in general medicine and interventions used especially targeting antimicrobial prescribing in hospital care.

<table>
<thead>
<tr>
<th>General 74</th>
<th>Antimicrobial agents 48,77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-mediated interventions</td>
<td>Mixed effects</td>
</tr>
<tr>
<td>Combination of interventions</td>
<td>More effective than single interventions is most reviews, but not in recent reviews</td>
</tr>
<tr>
<td></td>
<td>Combining an educational program with guidelines 81(?) feedback, reminders 85,97 (?) restricted access 98(?), antibiotic order form 99(+), or combinations of these strategies 12,100-102 82 (?)</td>
</tr>
</tbody>
</table>

### Organizational interventions

<table>
<thead>
<tr>
<th>Substitution of tasks</th>
<th>Pharmacists had an impact on prescribing, delegation of tasks to nurses showed had a limited impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-professional collaboration</td>
<td>Effective for a range of chronic diseases</td>
</tr>
<tr>
<td>Antimicrobial Management Team (AMT)/ infectious disease consultant service 16,104,105 (?)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structural interventions</th>
<th>Limited effects, mostly single site non-controlled studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. total quality management / continuous quality improvement</td>
<td>-Antimicrobial order forms 106-108 (?)</td>
</tr>
<tr>
<td></td>
<td>-Routine cycling of antimicrobial agents 109(?) 84(?) may be promising but more studies needed 110</td>
</tr>
<tr>
<td></td>
<td>-No study identified looking at restricted access to antimicrobials was rigorously evaluated or had an appropriate study design, 111-117 (?)</td>
</tr>
</tbody>
</table>

| Financial interventions | Fundholding and budgets had an impact on prescribing |

Adapted from Grol and Grimshaw9. (+) positive effect; (+/-) unclear or limited effect; (-) no effect (all rigorously evaluated; e.g. RCT, CCT or ITS design and appropriate analysis according EPOC criteria118); (?) not clear due to inadequate evaluation or study design.
A large number of studies have been done to optimize antimicrobial therapy. Still no single strategy has proven to be most effective. Most of the strategies use professional oriented approaches, e.g. educational outreach, educational conferences, or organizational interventions, e.g. antibiotic order forms, infectious disease consultant support or antimicrobial management teams. As in medical care in general 46, the impact on changing antimicrobial prescribing in a hospital setting varies and seems to depend on the local situation 40. An important problem identified in the earlier mentioned Cochrane review is that the majority of published interventions showed major shortcomings in the design of the study. Of 306 identified papers only 91 (30%) met the EPOC quality criteria 15. Inappropriate study-designs were especially uncontrolled before and after designs and inappropriate interrupted time series designs. Therefore, the impact of many interventions cannot be reliably interpreted and the impact of much cited intervention studies may be grossly over- or underestimated. Table 1 clearly reflects these findings of Ramsay et al., only 10 of 39 papers identified used an adequate study design. Bearden 77 and Avorn 85 might therefore have shown a too simplified picture in their papers.

In conclusion, we know that different interventions strategies have been used to improve antimicrobial prescribing. Unfortunately, we also know that success rates of interventions differ and that rigorousness of evaluations of impact of interventions leaves much to be desired. Various outcome measures to evaluate antimicrobial prescribing have been used, but reliability of those outcome measures is not always clear. It is also not clear for which intervention is best suited for what setting. Barriers related to institutional, physician, patient, and guideline characteristics may all have an impact on how successful an intervention will work out but need to be identified before embarking upon an intervention program.

This thesis
In this study an interventional program to implement an existing local hospital antimicrobial treatment guideline in the University Hospital Groningen was developed, performed, and evaluated. A major goal was to measure the impact of that intervention on physicians' prescribing behavior reliably.

We used a stepwise approach or implementation model to change physicians' behavior that is based on theoretical models of change 119. Three phases in the study are identified. In a first phase: a) existing barriers to following guideline recommendations are identified, b) reliability of assessing adherence to a guideline is investigated, c) case characteristics that may explain guideline adherence are explored and d) how good is the guideline itself? Then in the second phase an intervention strategy is selected and
worked out. Finally in the third phase the impact of the intervention on prescribing behavior and prescribing costs is assessed. (Figure 3)
Research questions

In chapter II, the reliability of the assessment of physicians’ adherence to guideline recommendations is addressed. Case characteristics and assessors’ professional background are considered in relation to agreement on assessment. Assessment of adherence is aided by an algorithm developed by Kunin and Gyssens to assess appropriateness of antimicrobial therapy. Chapter III employs a qualitative approach; i.e. interviews, to probe into existing barriers for physicians to follow a local antimicrobial policy in a university hospital setting. The quality of the university hospital guideline recommendations are analyzed in chapter IV. The adequateness of guideline recommended antimicrobial agents for empirical therapy at covering finally cultured pathogens is compared to that of the frequently prescribed broad-spectrum agent ciprofloxacin. Chapter V explores, in a quantitative cross-sectional study, the extent to which patient and case characteristics have an impact on following specific guideline recommendations for three frequently observed infections; sepsis, urinary tract infections (UTI) and lower respiratory tract infections (RTI).

Based on the findings of chapter III – V a combined intervention strategy to improve antimicrobial prescribing is developed. The total impact and that of the different components of that intervention strategy on prescribing behavior and costs are rigorously analyzed in chapter VI of this thesis.

In the general discussion the study-findings and implications are put into perspective for targeted clinicians and antimicrobial policy makers at hospital and national level.
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INTRODUCTION


Appendix 1.

Papers featuring antimicrobial agents and microbial resistance

Bacterial resistance has become a topic of increased concern in the field of infectious diseases. A quick search in Medline was performed to identify whether this increased concern was indeed reflected by an increased publication frequency of papers related to bacterial resistance.

Methods

The SilverPlatter™ Medline database was searched on-line from 1966 to 2003 for papers related to antimicrobial agents and microbial drug-resistance using appropriate keywords.

The following thesaurus SilverPlatter™ medline key-words were used for retrieving papers related to antimicrobial agents: “Anti-Bacterial-Agents, Antibiotics-Antifungal, Antibiotics-Antitubercular Carbapenems, Cephalosporins, Cephamycins, Antibiotics-Combined, Antibiotics-Glycopeptide, Monobactams, Penicillins, Antibiotics-Peptide, Thienamycins, Aminoglycosides, Cephalosporins, Quinolones, Lincomycin, Macrolides, Penicillins, Antibiotics-Peptide, Rifamycins, Sulfanilamides, Tetracyclines,” Additionally the free text terms: antibiotic and antibact were used.


Articles containing any of these key-words were included in the overview and all MESH-terms were “exploded” and searched in all subheadings

Number of papers covered by SilverPlatter™ Medline, number of papers including free-text or key-words related to antimicrobial agents, and those last papers referring to free-text or key-words related to microbial drug-resistance, was identified.
Results (figure 1)
Papers covered by SilverPlatter Medline increased from 174,641 in 1996 to 496,986 in 2003. (Access date June 9, 2004). Absolute numbers of papers featuring antibiotics increased in the same period, but relative number of these publications (2 – 3%) kept at pace with the overall increase of covered papers in the database. Papers on antimicrobials featuring drug-resistance fluctuated, 15% to 12% from 1966 to 1990 of all papers on antimicrobial agents, but that proportion started to increase in the early 1990’s to 19% in 2003.

Conclusion
Papers related to antimicrobial agents in the last 10 – 15 years feature more and more aspects of drug-resistance.