Improving antibiotic use for complicated urinary tract infections
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General discussion
Main findings and recommendations

Antimicrobial resistance is a serious threat to human health worldwide [1-3]. There is a direct correlation between the use of antibiotics and selection of antimicrobial resistance [4,5]. Up to 50% of hospital antibiotic use is inappropriate [6-8], and efforts to reduce inappropriate antibiotic use have been shown to be beneficial with regard to resistance rates and costs, without an increase in clinical failures [6]. So, improvement is necessary, but how can we achieve this effectively?

The purpose of the studies presented in this thesis was to gain more insight into the process of improving antibiotic use, more specifically in patients with complicated urinary tract infections (UTIs). The urinary tract is a common source of infection. Together with lower respiratory tract infections, UTIs are the most prevalent infectious diseases in the hospital [9,10]. UTIs account for 9-31% of patients who present to the emergency department with severe sepsis or septic shock [11,12] and thirty percent of the health care-associated infections are UTIs [13,14]. Nearly all of them can be considered complicated UTIs, so treatment of complicated UTIs substantially contributes to overall antibiotic use in the hospital setting.

The studies described in this thesis were based on patient cohorts that were included for the QUality of Antibiotic use in uTI patients (QUANTI) trial (chapter 7). The QUANTI trial was performed at the Internal Medicine and Urology departments of 19 university and non-university hospitals located throughout the Netherlands. Retrospective baseline- and post-intervention measurements were performed in 50 patients per department, resulting in 1,964 and 2,027 patients respectively.

Adequacy of UTI guidelines

Appropriate antibiotic use is described in national and international treatment guidelines, which are increasingly being developed according to international quality criteria [15,16]. For recommendations on adequate empirical therapy, expected pathogens and local resistance data are important determinants. The dynamic nature of these determinants (i.e. continuously changing in time) [17,18] requires assessment of the adequacy of these recommendations in the real-life setting.

Adequacy of recommended empirical therapy in Dutch UTI guideline

Main findings

In chapter 2 we investigated the adequacy of the Dutch evidence-based guideline-recommended treatment options for patients with complicated UTIs
General discussion

[19], two years after guideline publication. A retrospective, observational multicentre study included 810 patients with a complicated UTI without special conditions and 174 patients with a urinary catheter. Susceptibility patterns of cultured uropathogens were compared with guideline-recommended treatment options, which included specific recommendations for patients with a catheter. We considered inadequate coverage rates (ICRs) below 10% as acceptable. Of the recommended antimicrobial therapy options for complicated UTIs in patients without other conditions, only the guideline-recommended combination of amoxicillin-gentamicin was adequate, with a ICR of 6%. For patients with a catheter, ICRs of recommended regimens ranged from 3-24%.

Additionally, we evaluated the adequacy of actually prescribed empirical therapy, for patients treated with guideline-adherent versus non-guideline-adherent therapy. Therefore, we compared the susceptibility patterns of cultured uropathogens with actually prescribed empirical therapy. We found that in patients with a UTI without other conditions actually prescribed guideline-adherent therapy resulted in less broad-spectrum, but not in less adequate therapy, i.e. no lower coverage rate, defined as the rate of susceptibility of the isolated pathogens to the prescribed empirical therapy.

In patients with a urinary catheter, actually prescribed guideline-adherent therapy had a higher coverage rate than prescribed non-guideline-adherent therapy. Our findings are supported by a recent study of Van der Velden et al. who evaluated adherence to antimicrobial treatment guidelines in patients with sepsis and concluded that non-adherence to the guidelines resulted in more broad-spectrum empirical therapy without a higher rate of susceptibility of the isolated pathogens to the prescribed empirical therapy [20].

**Conclusions and recommendations**

Overall, guideline adherence seems to be effective to increase coverage rates without prescribing unnecessary broad regimens. This is an important finding, because reducing the use of broad-spectrum antimicrobial therapy is an important strategy to prevent and control the emergence of resistant pathogens [21,22].

Concerning the relatively high inadequate coverage rates of many guideline-recommended treatment options, we concluded that due to continuously changing resistance rates and differences between the epidemiologies of uropathogens assumed in the guideline and those in real-life, regular real-life assessments of empirical treatment recommendations are necessary. We showed that, if such information would have been directly available, already 1 to 2 years after publication of the guideline for complicated UTIs [19] part of the treatment recommendations for these patients should have been changed. Although general consensus has been reached about methods for developing
evidence-based guidelines, less attention has been paid to the process for assessing when guidelines should be updated [23,24]. Some guidelines state that they should be updated when new information becomes available [24]. Bacterial resistance levels are continuously changing [17,18]. To keep antimicrobial treatment guidelines up to date the concept of ‘living guidelines’ should be introduced, i.e. electronically provided dynamic guidelines, based on the latest data about the prevalence of causative micro-organisms, their susceptibility patterns and the antibiotic prescription patterns of the treating physicians [25]. However, collection of these data is very time-consuming and requires resource-intensive studies as presented in chapter 2. As a consequence, the development of living antimicrobial treatment guidelines is complex. Alternative approaches, to estimate the adequacy of recommended treatment regimens in a more efficient way, should be introduced. One of them is presented in chapter 3.

**A novel approach to assess the effectiveness of antimicrobial treatment**

**Main findings**

**Chapter 3** focuses on an index-based method to estimate the effectiveness of recommended empirical treatment regimes. This index is based on three simple aggregated metrics: prevalence of causative micro-organisms, level of resistance and relative frequency of antibiotic use. Most of these metrics can be estimated from data routinely collected by existing surveillance programs, such as Nethmap in the Netherlands [17], or the European Antimicrobial Resistance Surveillance Network (EARS-Net) at the European level [18]. This is a clear advantage over the conventional estimation method, which involves complex resource-intensive studies that follow affected patient populations, culture the causative pathogens, assess their susceptibility and compare these results with the initiated empirical therapy.

We evaluated the usefulness of this novel approach by employing, as in chapter 2, the Dutch national guidelines for complicated UTIs [19]. We measured effectiveness by means of a drug effectiveness index, and showed that this metric agreed within 5% with results obtained with a more complex and resource-intensive conventional approach based on case-by-case ascertained treatment coverage.

Furthermore, we illustrated the feasibility of employing readily available antimicrobial resistance data in the calculation of the drug effectiveness index and show that, had prescription practices in the Netherlands remained unchanged since 2008, empirical treatment effectiveness would have decreased by up to 4% by year 2011.
Conclusions and recommendations

We have shown that it is possible to evaluate treatment effectiveness by employing the index-based approach, using routinely available antibiotic resistance data. A major advantage of the index-based method is the ability to describe, or even predict, the different scenarios when one or more of the necessary metrics (prevalence of causative micro-organisms, level of resistance or relative frequency of antibiotic use) changes in time. For example, the impact of future changes in resistance patterns and similar extrapolation of results to other theoretical scenarios, which are extremely difficult to evaluate with conventional approaches, could be easily assessed. This flexibility of the index-based approach facilitates the communication of the consequences of the resistance problem to the lay public and policymakers. For most of them antibiotic resistance is complex and theoretical, but the drug effectiveness index translates susceptibility patterns into metrics that they can understand and care about [26].

However, there are also some clear disadvantages compared to the conventional method described in chapter 2, of which the selection of patients is the most important one. Due to the complexity of including polybacterial cultures in the calculation, the index was restricted to patients for which a single bacterial species was identified in culture. Additionally, surveillance systems for antibiotic prescription data often do not discriminate between therapy initiated before (empiric) or after laboratory confirmation of in vitro susceptibility. Aiming to assess the empirical treatment effectiveness, the index-based method should exclusively use data about empirical antibiotic use. Such detailed information is not always provided by routinely collected data. Overall, to assess treatment effectiveness, the index-based approach cannot fully replace the accurate, but labour-intensive current approaches. Nevertheless, in resource-constrained settings, where empirical prescribing is most prevalent and complex studies to directly measure effectiveness may not be a practical proposition, the index-based approach could be useful. Furthermore, this approach could be extremely valuable as comprehensible tool for communicating trends in prevalence of resistance.

Adequacy of recommended diagnostic procedures in UTI guidelines

Main findings

In addition to empirical treatment recommendations, also other guideline recommendations (e.g. on diagnostic procedures) should be evaluated critically for their appropriateness. The objective of the study described in chapter 4 was to assess the additional value of blood cultures in patients with a complicated UTI, as UTI treatment guidelines differ in their recommendations whether to collect of blood cultures in those patients or not. Some authors advise collecting
of blood cultures from all patients with a complicated UTI [27,28]. They argue that bacteraemia is present in 15-25% of them [29] and that it is a useful clinical indicator of severe disease, which should influence patient management [28]. In contrast, others do not recommend collection of blood cultures at all, because it would provide little additional diagnostic value over urine cultures [19,30,31], or suggest to collect blood cultures only from patients at risk of discordant culture results (i.e. bacteraemia with uropathogens that could not be cultured from urine) [32,33]. The secondary aim of our study was therefore to identify for which group of patients collection of a blood culture seems useful.

In a retrospective observational cohort study, we evaluated 800 hospitalized patients with a complicated UTI in whom on the day of start of antibiotic treatment both a blood- and a urine culture were obtained. In 70% of patients urine cultures were positive and blood cultures in 29%. We found that in 7% of patients uropathogens caused bacteraemia with a pathogen that was not isolated from urine. Receiving antibiotic therapy at the moment of hospitalization was the only factor independently associated with discordant culture results (OR, 2.06; 95% CI, 1.18-3.61) and was associated with a 10.1% risk of having discordant culture results, compared with 5.4% without antimicrobial treatment (risk difference, 4.7%; 95% CI, 0.91-9.1%).

Conclusions and recommendations

Based on our results, we recommend collecting both blood and urine cultures in patients who receive antibiotics at the moment of hospitalization, because this appears to have a clear added diagnostic value. However, it can also be argued that ‘additional value’ should be defined as how often blood culture results changes initial empiric antimicrobial therapy, rather than how often there is bacteraemia with a uropathogen that could not be cultured from urine. In a prospective study Velasco et al explored this topic in women with uncomplicated acute pyelonephritis and found discordant culture results in 2.4% of patients, but no single case in which the antibiotic regimen was changed on the basis of blood culture results [34]. This low proportion of blood cultures that resulted in modification of the initial therapeutic approach was confirmed by other, mostly retrospective, studies, with rates (in which the antibiotic regimen was changed on the basis of blood culture results) varying between 0-1.9% [34-38]. Apparently, modification of empirical treatment, aiming at the most frequent uropathogens, on the basis of blood culture is not often required. However, culture results are also of importance in streamlining antibiotic therapy and guiding the iv-oral switch. So, although the risk of having discordant culture results is low and the proportion of blood culture results that changes initial therapy is even lower, in our opinion, routine performance of blood cultures is justified in those patients who have already received antibiotics at the moment of hospitalization.
Appropriate antibiotic use and quality indicators

In line with the critical appraisal of guideline recommendations in chapters 2-4 of this thesis, recently two analyses were performed of the quality of evidence of the Infectious Diseases Society of America (IDSA) guidelines. Both studies showed that approximately one-half of the IDSA guidelines were based on low-level evidence that was largely derived from expert opinion [39,40]. Concerning the IDSA guideline for complicated UTIs less than one-quarter of recommendations was supported by level I quality of evidence (i.e. evidence from $\geq 1$ properly randomized controlled trial) [40]. As being one of the most prevalent infectious diseases in the hospital, this can be considered as an urgent call for high-quality clinical research in the field of UTIs to strengthen evidence for treatment recommendations.

Nevertheless, the benefits of guideline adherence were confirmed in patients with a lower respiratory tract infection or sepsis, in whom guideline adherence was associated with improved clinical outcome, decreased bacterial resistance and reduced costs [41-45]. For patients with a complicated UTI, the evidence is limited [46,47], although in chapter 2 we demonstrated that guideline-adherence seems to be effective to increase coverage rates without prescribing unnecessary broad regimens. In an earlier study we developed a valid set of nine guideline-based quality indicators (QIs) that define appropriate antibiotic use in patients with a complicated UTI [48].

Appropriate antibiotic use for UTI patients and outcome

Main findings

The study described in chapter 5 aimed to evaluate for patients with a complicated UTI the association between appropriate antibiotic use (defined by these QIs) and length of hospital stay. Length of hospital stay (LOS) is an important outcome, because it reflects the recovery time of patients, affects the risk of in-hospital complications, and determines hospital costs. In the previous study, four out of nine indicators turned out to be applicable for both Internal Medicine and Urology departments [48] and therefore these indicators were identified as key indicators for appropriate antibiotic use in UTI patients: perform a urine culture before starting treatment, prescribe empirical treatment in accordance with the national guideline, switch from intravenous to oral treatment within 72 hours of starting treatment, and tailor antibiotic treatment on the basis of culture results.

To evaluate the association between appropriate antibiotic use (defined by these four key QIs) and length of hospital stay, we conducted a retrospective, observational multicenter study, including 1252 patients with a complicated UTI, hospitalized at Internal Medicine and Urology departments of 19
university and non-university Dutch hospitals. Data from the patients’ medical charts were used to calculate QI performance scores. Multilevel mixed model analyses were performed to relate LOS to QI performance (appropriate use or not).

We showed that prescribing therapy in accordance with local hospital guidelines was associated with a shorter LOS (7.3 days vs. 8.7 days; \( P = 0.02 \)), as was early intravenous-oral switching (4.8 days vs. 9.1 days; \( P < 0.001 \)). We also calculated in each patient the proportion of appropriate antibiotic use, defined as the patient’s QI sumscore divided by the number of QIs that applied to that specific patient. Interestingly, there was an inverse relationship between the proportion of appropriate use in a patient and LOS (9.3 days for lower tertile vs. 7.2 days for upper tertile; overall \( P < 0.05 \)).

**Conclusions and recommendations**

Although performance on the individual QIs in some cases lacked an association with LOS, performance on the total set of (applicable) QIs ultimately influenced this important outcome measure, in other words: following more steps in appropriate antibiotic use was associated with a shorter duration of hospital stay.

Using this approach has similarities with the concept of ‘care bundles’, recently introduced as a small set of practices (usually three to six elements) that each are considered to improve patient outcomes, but when implemented together are expected to result in better outcome than when implemented individually [49]. Examples are the bundles for the management of severe sepsis and septic shock. Extensive guidelines for these diseases have been condensed into the ‘Surviving Sepsis Campaign (SSC) care bundles’ including four recommendations that should be completed within 3 hours and another three recommendations that must be done within 6 hours [50]. Application of the SSC bundles led to sustained quality improvement in sepsis care and was associated with reduced mortality [50].

Characteristically, care bundles should be delivered by one healthcare team at one point in time [49]. Considering our QIs as a bundle would mean separating the QIs into two bundles: an early bundle (day 0) with the QIs ‘perform a urine culture before starting treatment’ and ‘prescribe empirical treatment in accordance with the national guideline’, followed by a bundle with the QIs ‘switch from intravenous to oral treatment’ and ‘tailor antibiotic treatment on the basis of culture results’, that must be completed within 72 hours.

In contrast to the proportional performance score used in our study, compliance with a bundle means completion of every component, with no score given for partial completion [49]. In our opinion, the “all or nothing” approach as used in bundles ignores the relevant information about performance of the single QIs. This information is crucial in improvement projects, e.g. to identify which QIs
are most in need of improvement. In addition to the individual QI performance scores, a total QI set performance score can be very useful to illustrate the ultimate effect of completing all elements of appropriate antibiotic use.

**Improving antibiotic use for complicated urinary tract infections**

Despite the illustrated benefits of appropriate antibiotic use, according to medical literature, up to 50% of hospital antibiotic use is inappropriate [6-8]. As already described in chapter 5 of this thesis, we defined appropriate antibiotic use for patients with a complicated UTI with a previously developed and validated set of nine guideline-based quality indicators [48].

**Appropriate antibiotic use in UTI patients: variation and determinants**

*Main findings*

The objective of the study presented in chapter 6 was to assess in a large group of hospitals the performance on these nine quality indicators. The departments Internal Medicine and Urology of 19 Dutch university and non-university hospitals participated. To assess the departments’ baseline performance on the QIs, a retrospective measurement was performed, including a minimum number of 50 patients per department. The study population consisted of 1,964 patients with a complicated UTI, which also served as study population for the studies presented in chapters 2-5. Previously constructed algorithms, in which data directly originating from the patient chart had to be inserted, were used to calculate the scores for each of the QIs. The secondary aim of the study was to identify which determinants influenced appropriate antibiotic use in patients with a complicated UTI. Various determinants are known to be of influence, resulting in large differences in appropriate antibiotic use between hospitals [7]. We distinguished patient, department and hospital characteristics, including organizational interventions aimed at improving the quality of antibiotic use (antibiotic stewardship elements).

Overall, a large variation was demonstrated between the departments in appropriateness of antibiotic use. Median QI performance of departments varied between 31% (“Treat UTI in men according to guideline”) and 77% (“Perform urine culture”). We found that in particular certain patient characteristics influenced the quality of antibiotic use. In patients with a febrile UTI for example, urine cultures were more likely to be performed and they also had better chances to receive the right antimicrobial agent and treatment duration, compared to patients with a non-febrile UTI. Furthermore, in patients with a urinary catheter empirical therapy was less common in accordance with the guideline.

Concerning department and hospital characteristics, including available antibiotic stewardship elements, the presence of an infectious disease (ID)
physician was positively associated with prescribing empirical therapy in accordance with the national guideline. This is in line with the growing evidence that ID physicians play an important role in patient care, infection control and antibiotic management [51]. Other stewardship elements associated with more appropriate antibiotic use were the presence of an antibiotic formulary, feedback on antibiotic resistance rates of the hospital and structural education on antibiotics for senior staff members. Overall, however, no hospital or departments characteristics, including antibiotic stewardship elements, were consistently associated with better performance on the QIs.

Conclusions and recommendations
The relatively poor rates of guideline adherence and the large inter-department variation confirm data from earlier reports in patients with pneumonia or uncomplicated UTIs [52,53]. For complicated UTIs, as far as we know, our study is the first evaluating the entire process of antibiotic use in these patients, from admission to discharge.

Additionally, determinants that influence the antibiotic treatment of complicated UTIs have never been studied before. The knowledge of which patient groups were at risk to receive less appropriate antibiotic treatment can very well be used in future studies to design effective and targeted interventions to improve antimicrobial prescribing. Furthermore, the poor associations between single stewardship elements and appropriate antibiotic use underline the need of careful evaluation of the effects of different clearly described stewardship elements, to assess their effect in daily clinical practice. Finally, it is difficult to translate the effects of single interventions to antibiotic stewardship programs, because they comprise a menu of different interventions, which effectiveness could be more or different than the sum of effects of single (available) stewardship elements.

A comparison of two strategies to improve antibiotic use in UTI patients

Main findings
Chapter 7 focuses on the results of the multicentre, cluster-randomized QUANTI trial in which we compared the effectiveness of two different strategies to improve the appropriateness of antibiotic use in patients with a complicated UTI: 1) a multi-faceted strategy, including feedback, education sessions, reminders and additional/optional improvement actions, based on an effective strategy to improve antibiotic use in patients with lower respiratory tract infections [54] and 2) a ‘competitive feedback strategy’, i.e. providing professionals with non-anonymous comparative feedback on the department’s appropriateness of antibiotic use in patients with complicated UTIs. Retrospective baseline and post-intervention measurements were performed in 2009 and 2012, including 1,964 and 2,027 patients respectively. The 19
participating Dutch hospitals (departments of Internal Medicine and Urology) were allocated to one of the improvement strategies. Primary endpoint of the study was the appropriateness of antibiotic use, defined by a set of nine validated guideline-based QIs. To summarize patients’ performance on the different QIs in one outcome measure, we also calculated – at baseline- and post-intervention measurement – for each patient a total QI set performance, defined as the patient’s QI sumscore divided by the number of QIs that applied to that specific patient. Secondly, we aimed to identify determinants of successful improvement.

We found that performance scores on several individual QIs showed a trend towards improvement from baseline to post-intervention measurements, but no significant differences were found between both strategies. Performing a urine culture improved significantly in both strategy groups and tailoring antibiotic treatment based on culture results and treating UTI in men in accordance with the national guideline improved only significantly in the competitive feedback group. The total QI set performance improved statistically significant in both strategy groups. However, all improvements were only modest, ranging from 3.3-7.4%.

The evaluation of determinants of successful improvement revealed that better compliance with the strategies was associated with more improvement on the total set of QIs. Low department’s baseline performance on the total set of QIs was associated with a larger effect of both improvement strategies.

**Conclusions and recommendations**

At first glance, the comparable effectiveness of both improvement strategies is quite unsettling. Hospitals that received the multi-faceted strategy performed not better than hospitals that received ‘only’ a competitive feedback report. The relatively poor effect of our multi-faceted strategy is in contrast to the original strategy by Schouten et al. [54], which was developed to improve antibiotic use in patients with lower respiratory tract infections. A possible explanation for this difference might be that in our strategy, after performing the standardized intervention elements (i.e. feedback reports, education sessions, an improvement plan and reminders), performance of the optional and additional improvement activities strongly depended on local professionals, whereas in the original strategy of Schouten et al. the study researcher and project quality improvement officer actively initiated and coordinated these flexible activities. We considered involvement of local professionals to be a crucial element of our strategy, as this showed to be successful in achieving sustainable improvement [6,55] and in general contributes to the local performance of improvement strategies. However, we probably overestimated the persuasive power of our strategy to involve local professionals. In this light, evaluation of departments’
compliance with the strategy was relevant [56], as it confirmed suboptimal compliance at many departments, and a trend towards more improvement with better compliance.

In the competitive feedback strategy arm, the relationship between better compliance and more improvement was even stronger. To our surprise, the compliance evaluation also showed that in both strategy arms 40% of departments performed additional improvement actions besides the standardized improvement elements (multi-faceted strategy) or the competitive feedback report (competitive feedback strategy). Apparently, the stimulus to engage local professionals was comparable for both strategies.

Our multi-faceted strategy consisted of multiple persuasive interventions, e.g. distributing educational material, reminders and feedback. For UTIs, other improvement studies evaluating one (or more) of these interventions were mainly performed in primary care patients with uncomplicated UTIs. The results of these studies showed broad ranges (0-42%) of effectiveness to increase appropriate GPs’ management [57-59]. Concerning antibiotic use for UTIs in the hospital setting, especially optimizing fluoroquinolone utilization has been studied [60,61]. Educational [60] and multiple targeted interventions [61] turned out to be very effective in these single-centre studies, evaluating one aspect of appropriate UTI care. Another single-centre study found that, in an emergency department setting, a multiple stewardship intervention including an electronic order set and audit and feedback was associated with increased adherence to uncomplicated UTI guidelines and reductions in unnecessary antibiotic therapy [62].

In a Cochrane systematic review, Davey et al. evaluated 45, sometimes multi-faceted, persuasive interventions for their change in antibiotic prescribing in all kinds of infectious diseases [6]. The median change in antibiotic prescribing varied between 42.3% and 3.5%. The lowest change was found in cluster-randomized trials, which is considered as the ‘gold standard’ study design in implementation research. It takes into account the clustering of patients within departments or hospitals and randomization at the department or hospital level protects against contamination from the intervention to the control arm. The disadvantage is that this design is not as statistically efficient as a patient randomized design: a large number of clusters (departments/hospitals) is needed, requiring expensive and time-consuming studies. Additionally, for an external researcher (as in our study) it may be difficult to involve local professionals of many different clusters to perform improvement interventions, limiting the effectiveness of this study design. On the contrary, in single-centre improvement studies the researcher is often someone from inside the hospital,
probably encouraging involvement of other local professionals or colleagues and therefore increasing effectiveness of this kind of studies.

The results of the QUANTI trial are highly relevant, given the current need to improve the quality of antibiotic use. First, the results suggest that, as described above, for improvement strategies initiated from outside the hospital it is difficult to actually engage professionals from the ‘inside’, resulting in less effectiveness of the strategy. This emphasizes the need for a locally initiated multidisciplinary team, as recommended in antimicrobial stewardship programs [63]. Secondly, we developed a novel feedback strategy, the so-called competitive feedback strategy, in which we combined the widely used approach of providing individual audit and feedback [64] with the increasingly common principle of releasing performance data into the public domain with the aim to improve quality by ranking performance of different providers [65-67]. As a result, we provided individual feedback to our professionals by non-anonymously ranking the various departments. This strategy turned out to be effective in improving antibiotic use, whereas a recent Cochrane review stated that there is no consistent evidence that the public release of performance data improves care [67]. Possibly, our competitive feedback strategy found the appropriate balance between being a stimulus by creating accountability [67] and ensuring enough confidentiality. This strategy deserves to be studied in further research.

Thirdly, the direct comparison of two different improvement interventions meets with the urgent need of head-to-head trials to extend the current evidence for effectively improving antibiotic prescribing [6,64]. Many simple and multifaceted interventions have been studied for their effectiveness, however, direct comparisons of two different interventions are scarce. This is probably because the ideal for those comparisons is a cluster-randomized study design, but, as explained before, such a design is quite complex and expensive [6].

With respect to the limited effectiveness of both of our strategies, it is important to realize that most improvement measures and programmes produce only modest effects (5-10%) [68]. In our opinion, these percentages would be much higher if compliance with improvement interventions would be better.

Finally, the question is: to what extent are our results generalizable to patients with other infectious diseases? Davey et al. evaluated interventions to improve antibiotic prescribing for hospital inpatients with all kind of infectious diseases, generalizing the effectiveness (defined by multiple outcome measures) of an intervention for one specific infection to all patients with an infection [6]. On one hand, we support this generic approach, because treatment guidelines for patients with different infectious diseases show many similarities, or, in other words, the definition of ‘appropriate antibiotic use’ is partly the same for
all patients. For example, for all patients with infectious diseases it is recommended to perform cultures before starting treatment, to prescribe empirical therapy in accordance with the guideline and to tailor treatment on the basis of culture results. Therefore, it is also possible to develop generic quality indicators to measure appropriate antibiotic use in all hospitalized adults with a bacterial infection, regardless the focus of infection [69]. Such generic QIs have been recently developed [69], enabling improvement projects involving patients with all kinds of bacterial infections.

On the other hand, we also know from our and other studies that interventions that have shown to be effective in a specific setting will not automatically be as effective in another setting [56]. In contrast to generic QIs, in our opinion, generic improvement interventions for patients with all kinds of bacterial infections do not exist. Improvement interventions should be evaluated in subgroups of patients (e.g. in patients with a complicated UTI) to extend the current evidence for effectively improving antibiotic prescribing.

Final conclusions

Guidelines for antimicrobial treatment play an important role in the process of improving antibiotic use, because they describe appropriate antibiotic use.

In this thesis, we demonstrated the value of appropriate antibiotic use (i.e. guideline adherence) in patients with a complicated urinary tract infection (UTI), one of the most prevalent infectious diseases in the hospital. Appropriate antibiotic use increases bacterial coverage rates without prescribing unnecessarily broad regimens, which is beneficial for the containment of bacterial resistance. Furthermore, appropriate antibiotic use seems to reduce length of hospital stay by more than 2 days and therefore favours patient outcome and health care costs. These links between guideline adherence and clinical outcome measures can be used to convince physicians to adhere to treatment guidelines.

In current practice, a large variation was shown between departments in the appropriateness of antibiotic use for patients with a complicated UTI. This was to some extent determined by patient characteristics, and only to a limited extent by department or hospital characteristics. No single antibiotic stewardship elements were consistently associated with appropriate antibiotic use. The effectiveness of antibiotic stewardship programs should also be evaluated as a result of their total menu of stewardship interventions, which could be more than the sum of effects of single stewardship elements.

We compared the effectiveness of two different strategies to improve the appropriateness antibiotic use in patients with a complicated UTI. We found that the effectiveness of both strategies was comparable and that better
compliance with the strategies was associated with more improvement. The results of our study emphasize the need for a locally multidisciplinary team of engaged professionals to initiate improvement interventions, as recommended in antimicrobial stewardship programs. They should not only focus on the QIs that were most in need of improvement, but also involve the total set of QIs, i.e. the entire process of appropriate antibiotic use, from admission until discharge. In addition, future improvement initiatives should aim to decrease inter-department variation in appropriateness of antibiotic use by focusing on departments with poor baseline performance, as low baseline performance was associated with a larger effect of improvement strategies.

Implications for further research
Many single interventions have been studied for their effectiveness to improve antibiotic prescribing in hospitals. Future studies should compare different interventions (or simple versus multi-faceted ones) to each other in subgroups of patients, e.g. UTI patients. For improvement strategies initiated from outside the hospital, the involvement of local professionals is the main priority. Our novel competitive feedback strategy, introducing a competitive element of public reporting in individual feedback, should be tested in a broader setting and compared to other forms of providing feedback to assess which strategy can be recommended, for example, in antibiotic stewardship programs. To answer this question trials with multiple arms are required, but these designs will only need more clusters to achieve sufficient statistical power. Other study designs, such as interrupted time interval analyses, should be considered.

To measure the appropriateness of antibiotic use, we used quality indicator performance. We collected data by retrospective chart review and inserted these data in previously constructed algorithms to minimalize variation in assessment due to personal preferences. Disadvantages of this method were that, although these algorithms have been rigorously constructed, assessment was retrospective and potentially rightful deviations from the guideline may be disregarded, especially in complex treatment decisions. In addition, this method is very time-consuming. Future studies should evaluate other methodologies to calculate quality indicators, because the introduction of the electronic patient file massively increases the possibilities to register ad hoc indicator performance, for example incorporating necessary data elements in the electronic file.
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69. Development of generic quality indicators for the optimalisation of antibiotic use in the hospital. The Netherlands Organisation for Health Research and Development, project number 50-51700-98-011. This study was presented, in part, as a poster presentation at the annual meeting of the Infectious Diseases Society of America, 2013 (40990).