Appropriate antimicrobial prescribing has significant clinical benefits (ie, reduced THE mortality) and ROLE reduces development OF of antimicrobial resistance and health care costs. Antimicrobial stewardship programs aim to improve antimicrobial prescribing but sometimes fail to acknowledge BEHAVIOUR that improving IN antimicrobial prescribing actually means changing human behaviour. Human behaviour is not based on a fully rational process but depends on a complex interplay between several behavioural ANTIMICROBIAL PRESCRIBING: determinants and social norms. Despite its rational theoretical foundation, stewardship programs are known to persistently encounter prescriber resistance. This resistance is generated by the tension between the governance of the stewardship team and the autonomy of individual prescribers. Behavioural and social ARE theory seem underused in WE antimicrobial stewardship intervention programs, contrary to more common use in other scientific fields. Previous studies using interventions based on behavioural theory have ONLY found promising HUMAN results in improving antibiotic prescribing. Most of these studies focused on antibiotic prescribing for respiratory tract infections in primary care. We used behavioural theory to design and implement an AFTER intervention approach ALL? to improve appropriateness of hospital antimicrobial prescribing for all indications. Our approach was inspired by the participatory action research paradigm, which focuses on collaboration and empowerment of the stakeholders in the change process and is effective in other complex health JONNE care situations. JOCHUM In our SIKKENS approach, prescribers were invited to choose and co-develop 1 or more interventions to improve their own prescribing, whereby they were stimulated to base their choice on conclusions of a prior root cause analysis of their prescribing patterns. The approach is therefore designed to benefit from tailoring to local determinants and draws on 3 behavioural principles: (1) respect for the prescribers' autonomy to avoid feelings of resistance; (2) the inclination of people to value a product higher and feel more ownership for it if they made it themselves, which is referred to as the IKEA effect; and (3) the tendency of people to follow up on an active and public commitment. We aimed to test the approach's effectiveness in improving appropriateness of antimicrobial prescribing in hospitals. Appropriate on a fully rational process but depends on a complex interplay between

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The role of behaviour in antimicrobial prescribing; are we only human after all?

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	Dr. J. Schouten
	Dr. E. Charani

"Resistance is useless"
from *The hitchhikers guide to the galaxy* by Douglas Adams

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narrow spectrum amoxicillin would be preferable because it would stimulate development of antimicrobial resistance less. The resistance of bacteria caused by the moxifloxacin treatment could then spread from our patient to others and cause infections. One of the difficulties in finding a balance between these needs is that the doctor who chooses the antibiotic is responsible for the individual patient in front of him/her, and the other persons who may also be impacted by these decisions in the future are unidentified and they are not yet his/her patients. An interesting article about the ethical side of AMS and how to deal with patient autonomy in this dilemma was written by Leibovici et al.8 It entails a discussion about whether a doctor needs to inform the patient about treating him/her sub maximally in order to protect future patients. It is also important to mention that the exact relation between the broadness of an antimicrobial's spectrum of effectiveness and impact on the microbiome and resistance has not yet been fully elucidated.9 Finally, unnecessary antibiotic use can be driven by the practice of defensive medicine, in which a doctor aims to minimize chances of treatment failure

This thesis comprises seven chapters that were published in scientific journals, precluded by this general introduction and concluded by the general discussion. In this chapter, I will introduce the subjects of this thesis for the reader without previous knowledge on the subject of antimicrobial stewardship and its related concepts. This chapter consists of short paragraphs answering core questions to allow the more knowledgeable reader to skip paragraphs on subjects they are already familiar with.

Why is antimicrobial prescribing different from prescribing other drugs?

Antimicrobial drugs are drugs that aim to kill or slow the growth of microorganisms present in a human being or other animal. The most well known type of an antimicrobial drug is the antibiotic, which works against bacteria. Antimicrobial drug prescribing differs from prescribing many other types of drugs in that the effectiveness of the antimicrobial drug can diminish over time due to the effect of the drug itself. This phenomenon of diminishing effectiveness can be explained by the development of antimicrobial resistance, which is the tendency of microorganisms to become less susceptible to a specific antimicrobial drug or a group of antimicrobial drugs. The main driver of antimicrobial resistance is the selection pressure caused by antimicrobial prescribing, which grows as antimicrobial prescribing increases. This means that prescribing an antimicrobial drug not only affects the patient receiving the drug at that time, but it also impacts success of antimicrobial treatment in the future.[1] Moreover, and this makes antimicrobial prescribing really unique, is that antimicrobial prescribing may also affect other patients that did not receive the drug itself (more on this below). However, as a side note, a recent study has suggested that causing antimicrobial resistance may not be a unique feature of antimicrobial drugs after all, as drugs of various (non-infectious disease) therapeutic classes may promote antimicrobial resistance.[2]

Why is antimicrobial resistance a problem?

Antimicrobial resistance is rising globally. In many settings, multi-drug resistance is common, meaning that these microorganisms are not susceptible to a whole range of antimicrobial drugs.[3] This is a very serious problem for several reasons. *First,* many infectious diseases (e.g. pneumonia, sepsis) are serious diseases, and can be fatal when untreated. Antimicrobials are usually very effective drugs that are able to significantly improve the clinical course of an infectious disease. When microorganisms become resistant, patients will receive less effective treatment or the effective treatment can be delayed, leading to increased morbidity and mortality. *Second*, when first-line antimicrobials are made ineffective by antimicrobial resistance, physicians try to use second-line antimicrobials instead. However, these drug are often more expensive, less effective or associated with more side effects. In case of multi-drug resistance, even these second- or even third-line antimicrobials may be ineffective. This would not be a big problem if there were a steady development of new, effective antimicrobial drugs, but that has not been the case recently. In contrary, in the last decades there was a relative lack of investments in the

development of new antibiotics,[4] for instance because it is less lucrative to invest in antibiotics, because they tend to be used sparingly and in short courses compared to other drugs for chronic diseases such as HIV or hypertension. Moreover, due to financial reasons, some older and mostly narrow-spectrum antibiotics suffer from a lack of availability.[5]

Third, antimicrobial resistance can spread from one microorganism to another, for instance by means of mobile genetic elements named plasmids.[1] Resistant microorganisms also spread between humans and other animals, even in health-care settings, despite the continuous efforts for infection prevention practices like hand hygiene.[2,6] This leads to the unique situation that the prescription of an antimicrobial drug not only impacts the person it is prescribed to, but also the society as a whole.

How can we prevent the rise of antimicrobial resistance?

The main driver of development of antimicrobial resistance is the selection pressure caused by the presence of an antimicrobial drug.[1,3] By reducing the amount of antimicrobial drugs that are prescribed, this pressure can be reduced. Examples of ways to reduce prescribing are to prescribe antimicrobials only when indicated, by using shorter courses, and prescribing more narrow spectrum antimicrobials when appropriate. The coordinated efforts of health-care workers and others to stimulate the appropriate use of antimicrobial drugs is called antimicrobial stewardship (also called antibiotic stewardship),[4,7] which is the subject of this thesis.

A second important way to prevent the rise of antimicrobial resistance is to prevent the spread of resistant microorganisms from one patient to another, by using practices like optimal hand hygiene, isolation, the use of appropriate dress codes for health-care workers etc. These practices should preferably be conducted in tandem with AMS programs. However, this subject falls outside the scope of this thesis.

What is antimicrobial stewardship (AMS)?

Antimicrobial stewardship (AMS) comprises the coordinated efforts of health care workers and others to improve antimicrobial prescribing, and it comes with a need to balance individual and societal needs.[5,7] This balance is necessary because the needs of an individual patient may not always align with the needs of society.

For example, when a young and otherwise healthy patient develops a lung infection (pneumonia), antibiotic choices may vary between a narrow spectrum antibiotic (amoxicillin) specifically targeting the most common and deadly bacterium (which is *Streptococcus pneumonia*) and a broad spectrum antibiotic (moxifloxacin) which is effective against virtually all bacteria causing a pneumonia in the Netherlands. For the individual patient in this case, there may be no significant disadvantages associated with the

treatment with moxifloxacin instead of amoxicillin, because the probability of serious side effects is low for both drugs; and because the patient is young and otherwise healthy, the chance is small that he or she will need another antibiotic in the near future in which case resistance may become relevant. The advantage of moxifloxacin instead of amoxicillin treatment for this patient would be clear, as the chance of treatment success is probably (slightly) higher. However, from a societal point of view, the more narrow spectrum amoxicillin would be preferable because it would stimulate development of antimicrobial resistance less. The resistance of bacteria caused by the moxifloxacin treatment could then spread from our patient to others and cause infections. One of the difficulties in finding a balance between these needs is that the doctor who chooses the antibiotic is responsible for the individual patient in front of him/her, and the other persons who may also be impacted by these decisions in the future are unidentified and they are not yet his/her patients. An interesting article about the ethical side of AMS and how to deal with patient autonomy in this dilemma was written by Leibovici et al.[8] It entails a discussion about whether a doctor needs to inform the patient about treating him/her sub maximally in order to protect future patients.

It is also important to mention that the exact relation between the broadness of an antimicrobial's spectrum of effectiveness and impact on the microbiome and resistance has not yet been fully elucidated.[9] Finally, unnecessary antibiotic use can be driven by the practice of defensive medicine, in which a doctor aims to minimize chances of treatment failure in fear of making mistakes, for instance because of overestimation of treatment failure risks or because he/she is afraid of patient complaints or insurance claims.

What are the aims of AMS?

Commonly, the aims of AMS are to curb development of antimicrobial resistance, to reduce costs and to improve patient outcomes including prevention of drug side effects.[10]

What is 'improved antimicrobial prescribing'?

As all AMS programs focus to improve antimicrobial prescribing, it is important to know what 'improved prescribing' exactly means. There are many adjectives used in the scientific literature trying to describe this elusive phenomenon of high quality prescribing, for example 'appropriate', 'prudent', 'optimal', 'rational', 'good' or 'adequate' prescribing. For clarity, I will only use the term appropriate prescribing in this thesis. Although the meaning of all used terms vary in literature, the common denominator is that antimicrobial prescribing is appropriate when it is used only when really needed, using an effective antimicrobial with a spectrum as narrow as possible, using the least invasive and least costly route of administration, in a course as short as possible, and using an optimal dose; all this while preserving patient outcomes and avoiding side effects as much as possible. Often, adherence

to guidelines is added to these criteria. As this definition suggests, and also reflecting the difficulty of the balance described above, the judgment of whether an antimicrobial prescription is appropriate is subjective. However, in order to assess the impact of AMS programs on antimicrobial prescribing, a valid and reliable method to assess appropriateness is paramount. We used and subsequently validated a method that used the judgment of an infectious disease physician to assess appropriateness. The results of this study are described in **Chapter 2**.

What are the effects of appropriate prescribing?

A recent series of systematic reviews has showed that the attainment of several of the aforementioned aspects of appropriate prescribing, for instance empirical therapy according to guidelines, de-escalation of therapy (resulting in therapy as narrow as possible), and switch from intravenous to oral therapy are associated with better clinical outcomes (including reduced mortality), reduced number of adverse events and lower costs, although evidence quality was low.[11,12] It is also clear that antimicrobial use leads to development of resistance, and reduced use may decrease resistance. Moreover, studies have shown that AMS programs decrease antimicrobial resistance and decrease *Clostridium difficile* infection incidence (which can also be induced by antimicrobial use).[13,14]However, the evidence so far remains inconsistent and of low quality,[14-16] what can be explained by the fact that the relationship between AMS interventions and resistance development is indirect, and studies on this relationship are hindered by the many confounding and complicating factors that are present in research in health care practice. Another complicating factor is that we sometimes do not know which drug is best when looked at its effect on antimicrobial resistance.[9]

How do AMS programs try to improve antimicrobial prescribing?

AMS have used a great variety of interventions to influence prescribing doctors. The recently updated Cochrane review about AMS in hospitals acknowledged two main intervention types: restrictive or enabling interventions.[14] *Restrictive* interventions aim to reduce the freedom of handling of doctors to prevent unwanted prescriptions. Examples include the use of a list of restricted antibiotics, i.e. some antibiotics cannot be prescribed in certain situations; authorization, i.e. antibiotics can only be prescribed after authorization by a certain authority (e.g. microbiologist); and automatic stop orders, i.e. a prescription is automatically discontinued after a certain period. *Enabling* interventions comprise all actions that facilitate appropriateness of prescribing without reducing the doctor's freedom of handling, for instance by removing barriers for appropriate prescribing or by increasing means and/or competence of health care workers. Examples include education, audit & feedback including consultations by infectious disease experts, (optimizing) access to information resources, and creating/optimizing guidelines. The Cochrane review concluded that interventions are effective in changing antimicrobial prescribing despite not always using the most effective behaviour change techniques

and that lower use of antibiotics probably does not increase mortality. Furthermore, enablement interventions consistently increased the effect interventions. It concluded, future research should focus on, among others, exploring the barriers and facilitators to implementation.[14]

What are the current problems with AMS interventions?

Due to the vast array of stewardship interventions I will not be able to describe all (potential) drawbacks of all intervention types. However, in general, AMS activities are often critically received by hospital doctors. One important reason is that many doctors perceive the top-down governance of AMS programs as a threat to their autonomy.[17-25] This may lead to reduced uptake of interventions or even overt opposition to AMS programs. It is often feared that restrictive interventions lead to greater opposition because they actually do reduce doctor autonomy. This problem of prescriber opposition is perhaps best illustrated by the 'boomerang effect' - i.e. intervention effects reverse when they are discontinued - that was shown to be associated with (mostly restrictive) AMS interventions.[14] Moreover, even when restrictive AMS interventions are not discontinued, effects may diminish over time.[14]

Another important problem to mention is that research into the effectiveness of specific AMS strategies is hampered by studies with insufficient methodological quality. Many past studies incorporated an uncontrolled before-after design, which is a design that is vulnerable to confounding by external influences (e.g. national campaign to combat antimicrobial resistance), regression to the mean (which is always a problem but can be most salient when AMS is initiated after outbreak of a resistant strain) or pre-existing trends (e.g. the outcome length of hospital stay, that over the last years showed a downward trend for many patient categories). Due to the often multifaceted nature of AMS interventions, and the complicated environment of hospital practice, these concerns may lead to serious questions about study validity.

What are credible AMS research designs?

The randomized controlled trial (RCT), which has been described as the 'holy grail of medical research', is not really suited to AMS research because it comprises individual randomization, meaning it generally used patients as unit of randomization.[26] In AMS, the target of intervention is the prescribing doctor, not the patient. Moreover, contamination of the intervention is difficult to prevent, e.g. doctors exposed to an educational intervention will probably discuss its contents with unexposed doctors during their work. The cluster-randomized controlled trial design offers an interesting and strong methodological solution. In these trials, clusters of individuals (often departments of hospitals) rather than individuals are randomized to a certain intervention or control arm. However, because of financial and logistic constraints, this trial design remains underused.[14,26] Interrupted time series (ITS) or stepped wedge trial (SWT) designs offer a more feasible and also methodologically sound option.

In ITS, intervention deployment is preceded by numerous (often >3) longitudinal measurements of the outcome of interest. These measurements are then continued after intervention deployment for another series of longitudinal measurements. In SWT, the exact moment of intervention deployment is varied using randomization between randomization units (e.g. departments or hospitals). ITS, and also SWT depending on the number of measurements, are generally robust to problems like regression to the mean and pre-existing trends. ITS can be vulnerable to external influences (i.e. time-dependent confounding), but this can be minimized by including a control group,[26] and probably also when using a combination of ITS and SWT, see for an example the Dutch Unique Method for Antimicrobial Stewardship (DUMAS) study in **Chapter 4**.

What is missing in current AMS strategies?

Let's get back to the 'how' of AMS.[12] The most glaring omission in AMS strategies is the lack of use of insights from behavioural science. Many previous AMS studies seemingly failed to acknowledge that AMS really means changing doctor behaviour. This while a recent overview paper on AMS concluded: "an inventory of barriers and facilitators and behavioural theories should guide the stewardship team's choice of potential interventions to change current antibiotic use".[12]But so far, this has not been the case for most AMS programs.[14,27-31] As infectious disease specialists, pharmacists and clinical microbiologists are relatively new to the intricacies of behavioural change, they may perhaps be excused for this oversight. However, it is interesting to know that even experts in the field of economy - which fundamentally deals with human behaviour and how to change it – have only relatively recently acknowledged the importance of behavioural science for their subject.[32,33] I will elaborate on this in the next paragraph.

Are doctors human?

One of the most game-changing scientists in the subject of economy and behavioural change (although he is a psychologist) is Daniel Kahneman. He and others challenged the widely accepted concept of humans being so-called Econs, i.e. people always choose what is in their best interest, and think about choices in life without making systematic mistakes (i.e. they behave and think rationally).[32,33] In several experiments that often concerned gambling dilemmas, Kahneman and colleagues showed that people often do not behave like Econs, but more like the so-called Humans. Humans are different from Econs in many ways because their behaviour is guided by several behavioural determinants, and influenced by several cognitive biases, which violates what most people see as rationality.[32-34] For instance, Humans: fear losses more than they value wins ('loss-aversion bias'), are influenced by what the majority of their group has done ('bandwagon effect') or by previously considered values ('anchoring bias'), and value things they own or made themselves higher than other things ('endownment effect' and 'IKEA-effect' respectively), etc.[32,34,35] To illustrate, I will discuss the example of the anchoring bias in more detail,

because it is a beautiful example of what some may call the irrationality of the human brain (more on irrationality later). Kahneman et al. performed an experiment that went as follows: several groups of students were asked to write down the number at which a wheel of fortune stopped, and were subsequently asked to answer the following questions: 1. "Is the percentage of African nations among UN members larger or smaller than the number you just wrote?" and 2. "What is your best estimation of the percentage of African nations among UN members?". Unknown to the students, the wheel of fortune was rigged so that it only stopped at the number 10 or the number 65. Comparing students where the wheel stopped at 10 with students where it stopped at 65, the average estimates from the students in response to the second question were 25% and 45% respectively. This showed that the students were clearly influenced by the wheel of fortune (the 'anchor')! Although the students should have known that information from a wheel of fortune is in no way informative for answering the question, they used it nevertheless.[32]

Does this mean that human beings are in fact irrational? No, because many of our cognitive biases help us to deal with the world. In these cases, they present themselves in the form of heuristics, which simplify things to help us judge situations, and they generally work well. [34,36] In this perspective, the very presence of heuristics in our thinking can be seen as rational. However, the most important problem with this question is that it is unclear what irrationality actually is, which is the reason this term is frowned upon in behavioural economist spheres.[36] We can better say that due to the fact we have to deal with a complicated world where information is not always completely available, and that our human brain has limited computational power; we have to use heuristics because they often work well. This can also lead to mistakes sometimes, and it is important to realize this when trying to change human behaviour.

And, yes, doctors are humans, so their rationality has limits too, as has been shown in several studies.[34] For example, psychiatrists having to judge whether a patient could safely be discharged were far less likely to agree to discharge when the chance of violent behaviour by the patient was presented as 10 out of 100 compared to a chance of 10%.[32]Another, and more specific AMS example of doctors who are influenced by other things than purely rational reasoning was the qualitative study by Charani et al. They showed that antimicrobial prescribing is influenced by 'the prescribing etiquette', a set of unwritten cultural rules around prescribing in the hospital.[37]

What do we know about behavioural interventions in AMS?

Previous studies using behaviourally-founded theory to improve antimicrobial prescribing have shown good results, but most of these studies were performed in primary care and on the subject of respiratory tract infections.[38-44]A simple but illustrative example was the vignette-study by Tannenbaum et al, showing that presenting broad-spectrum antibiotics as one group in the electronic prescription system reduced prescriptions of these drugs compared to when these drugs were presented as individual

options.[40] What this study did was to compare optimal versus suboptimal choice architecture, which can serve as a nudge towards preferred behaviour (in case of optimal designed choice architecture that is).[33] More on nudges and choice architecture in the General Discussion, **Chapter 9**.

What is participatory action research? (PAR)

Participatory action research (PAR) is a research paradigm that differs from the more standard scientific approach in that it means researching *with* people, not *on* people, and is an attractive method from a behavioural science point of view.[45,46] In PAR the interventions that will be implemented are not determined beforehand. PAR is in fact a hybrid of science and improving practice, which makes it suited to the practical challenges of AMS.[47] The essence of PAR is to collaborate with relevant stakeholders among the persons under study and adapt the study based on their input and findings as the project proceeds. One of the main advantages of the bottom-up approach of PAR is that due to the important role of these stakeholders and the openness of the approach, the chance of opposition from the persons under study would be reduced. See **Chapter 3** for an extensive introduction into PAR and its suitability for AMS. PAR can be a successful approach because it is shaped to benefit from several mechanisms from behavioural science. For more information on these mechanisms and how PAR and behavioural science was used to improve antimicrobial prescribing in hospitals in the DUMAS-study including its results, see **Chapter 4**.

Does context matter when prescribing antimicrobial drugs?

As would be expected when reading the previous paragraphs, yes, it does. Doctors' decisions are influenced by several other factors besides pure rational reasoning. Therefore, and as was mentioned before, AMS programs should start with an assessment of relevant barriers and facilitators in the target environment.[12] The DUMAS-study included such an assessment for specific departments, see **Chapter 4.** It would also be interesting to see how several specific factors like gender or experience of a doctor, time of prescribing and expert consultation are associated with appropriateness of prescribing in a hospital-wide setting, to allow us further insights into the determinants of antimicrobial prescribing. For instance, it has been suggested that appropriateness of antibiotic prescribing for respiratory infections in primary care drops as clinical sessions progress. This resulted in the interesting hypothesis that doctors may suffer from decision fatigue, i.e. they increasingly lose the ability to resist prescribing inappropriately as the day goes on.[48] We decided to test the effect of time of day and other factors on antimicrobial appropriateness in the hospital clinic, see **Chapter 5**.

Another perspective on the context of prescribing is the speed of which information about the infection is available for the prescribing doctor, and whether he or she acts on this in time. This is especially important for severe infections like bloodstream infections because of their high

mortality. For these infections it is paramount that blood culture results are processed quickly, independent of factors like time of day.[49,50] We show in **Chapter 6** how the speed of blood culture varies depending time of day that the culture is signalled positive, and how this affects time to prescription change.

What is the role of education in AMS?

Educational interventions are commonly used in AMS, which is important because barriers to appropriate prescribing often include a lack of knowledge or understanding of the problem of antimicrobial resistance. [51-53] Although education seems also a logical choice to try to change behaviour of an unwilling prescriber, it remains important to realize that doctors are not Econs, who would be expected to immediately change their behaviour when they for instance received knowledge that their longstanding practice of extended post-surgical prophylaxis was not evidence-based.[32,33] Instead, because doctors are Humans, other behavioural factors (like the opinion to 'never change a winning team')[54] may play a role in ensuring that behaviour is not changed in the preferred manner, despite the educational session that provided the latest theoretical evidence. Nevertheless, education remains an important tool in stewardship,[10] and is one of the few available tools to shape the prescribing of future doctors during medical study. As resources and space in the medical curriculum are often scarce, [55] it is paramount to identify resource-effective educational interventions that can change students' prescribing. Electronic learning (E-learning) may provide a unique opportunity for this, also due to its capacity for interactivity and progress monitoring, and its flexibility when or where to learn. We designed and performed a controlled E-learning intervention study in fourth year medical students, which is described in **Chapter 7**.

How can we get doctors to participate in voluntary E-learning?

One of the major challenges of facultative education is to get people to participate. This applies especially for E-learning, because there generally is no specific place or time to do it, so the students' motivation must be high enough, which turns out it often isn't. Previous studies have shown that autonomous motivation (i.e. motivation that comes from within, for instance due to interest in the subject or an understanding of its importance, as opposed to controlled motivation which is determined by outside rewards) is associated with higher study efforts and better achievements,[56-58] but its role in E-learning participation is thus far unknown. Thus, to better understand how participation in AMS educational interventions is determined, it is important to elucidate whether autonomous motivation is associated with E-learning participation. We hope this knowledge will enable us to raise participation rates in the future. We therefore performed a study testing the association between autonomous motivation and participation in an E-learning about antimicrobial prescribing among medical residents, which is described in **Chapter 8**.

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Clinical microbiol (all internists), and residents of from the index hospital ar e in the study by emai contact. We asked cialist who had a iously assessed all 56 case using the case he assessments of this doctor mpared wit ier assessments (intrarater agreeme sments of agues (interrater agreement); this doc index ex he previous assessments were perfor onths ea prevent the influence of a recall eff were supplied with a set of 28 case forms and an i ecause each expert only assessed one set of cases, pa formed so that all cases were judged once (see Figure on the maximum possible similarity between experts, , hospital, and experience (in order of priority) to enable ese factors. The in-study assessment procedure and the nt procedure were identical, except that the latter comp e meeting with the research doctor, whereas the latter paper. All experts were instructed to classify the followi ns as appropriate: 1. The prescription followed the relev mpletely, in which case the prescription was classified as . The prescription deviated from the guideline on one or m which case the ward doctor's arguments for deviating were rationality; if found rational then the prescription was classif priate, otherwise the deviating aspects were classified as inappr ., the indication was not or only partially covered by a relevant n this case, the expert assessed the case for rationality, define ective antimicrobial regimen covering it pathogens with xcessive (i.e., unnecessary combination or broad spectr a more narrow spectrum is available); if he prescripti nsidered appropriate. The instructions in ch guideli ital guid ion as and iate, e of

Experts agreed in 80% of cases with the reference standard, which may seem reasonable but still leaves some room for improvement. For example, if data for the sensitivity and specificity of specialist assessments are applied to a situation with a prior probability of appropriateness of 50%,1 which is reported in literature, the positive and negative predictive value would be only 82% and 77%, respectively. On the one hand, the assessment of the appropriateness of antimicrobial prescriptions is usually done to guide antimicrobial stewardship interventions at a clinical ward/group level rather than at an individual/patient

Assessment of appropriate antimicrobial prescribing: do experts agree?

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among residents and specialists, and also among specialists with varying experience. This result is encouraging to change the culture of prescribing, recently described as the "prescribing etiquette', in which senior doctors' antimicrobial prescribing is rarely questioned by others.20 Although previous studies have suggested that ID specialists and clinical microbiologists have different standards for assessing appropriateness, we found no differences.11 Although antimicrobial guidelines and practices often differ between hospitals, hospital of employment had no clear impact on validity. The agreement between the experts ranged from 70% to 90%, and Cohen's kappa's ranged from 0.35 to 0.72 (Figure 3). According to a commonly used classification system, these values can be described as fair to substantial, with most values falling into the moderate category.21 Previous studies reported various levels of interrater agreement with Cohen's kappa's ranging from 0 to 0.8,5-9,11,12 one study reported an overall agreement of 71%.6 We found an intrarater agreement of 71%, which was lower than the interrater agreement but similar to one earlier study,7 and lower than a study of pharmacists'

Abstract

Objectives: Little is known about the validity and reliability of expert assessments of the quality of antimicrobial prescribing, despite its importance in antimicrobial stewardship. We investigated how infectious disease doctors' assessments compared with a reference standard (modal expert opinion) and with the assessments of their colleagues.

Methods: Twenty-four doctors specialized in infectious diseases or clinical microbiology (16 specialists and 8 residents) from five hospitals were asked to assess the appropriateness of antimicrobial agents prescribed for a broad spectrum of indications in 56 paper cases. They were instructed how to handle guideline applicability and deviations. We created a reference standard of antimicrobial appropriateness using the modal assessment of 16 specialists. We calculated criterion validity, and interrater and intrarater overall and specific agreement with an index expert (senior infectious disease physician), and analysed the influence of doctor characteristics on validity.

Results: Specialists agreed with the reference standard in 80% of cases (range 75-86), with a sensitivity and specificity of 75% and 84%, respectively. This did not differ by clinical speciality, hospital, or years of experience, and residents had similar results. Specialists agreed with the index expert in 76% of cases and the index expert agreed with his previous assessments in 71% of cases.

Conclusion: Doctors specialized in infectious diseases and clinical microbiology assess the appropriateness of antimicrobials prescribed for a broad spectrum of indications with an acceptable agreement and validity, regardless of their experience or hospital of employment. However, there is room for improvement, which merits attention in multidisciplinary discussions and education.

Introduction

Assessing the quality of antimicrobial prescribing is an important part of antimicrobial stewardship programmes.[1-3] This can be done by assessing patient outcomes, such as mortality or length of stay, in relation to different antimicrobial regimens,[4] but the heterogeneous population of patients admitted with infectious diseases can make the interpretation of these important outcome data difficult. For this reason, many antimicrobial stewardship programmes assess the quality of antimicrobial prescribing by using outcomes directly related to the prescription itself, such as guideline adherence and antimicrobial appropriateness. But are these measures valid and reliable: does one doctor's assessment of prescribing quality compare with a reference standard (validity) and does it compare with a colleague's assessment (reliability)? In other words, can these measures be used as primary outcome in antimicrobial stewardship research and practice? To the best of our knowledge, while a few studies have evaluated the reliability of assessing antimicrobial prescribing quality,[5-12] none have included measures of validity. Moreover, what is considered appropriate prescribing in one hospital might be considered inappropriate in another,[13] and may even differ between clinical specialties (e.g., infectious disease specialists and clinical microbiologists).[11] It is therefore important to find out whether clinical specialty and other doctor characteristics, such as hospital in which the doctor is employed or years of experience are determinants of appropriate prescribing. It would be instructive and helpful if residents rather than clinical specialists could perform these assessments.

Previous reliability studies used different definitions of quality of antimicrobial prescribing, which varied from strict guideline adherence (with the exclusion of prescriptions not covered by guidelines),[11,12] to appropriateness of therapy based on expert opinion.[5-10] However, guideline adherence might not be an appropriate 'gold standard' because in clinical practice there are often good reasons to deviate from guideline recommendations. Moreover, in our experience guidelines do not cover all individual clinical situations, it is sometimes unclear which guideline is applicable, and national and international guidelines may offer conflicting advice. When assessing the appropriateness of antimicrobial prescribing, it is important to provide guidelines on how these specific problems should be addressed. Lack of clear and unambiguous assessment guidelines may lead to low estimates of reliability and validity. Importantly, earlier studies investigated prescribing in specific populations, often excluding surgical or ICU wards,[5-7,12] which limits the generalizability of findings.

We evaluated the validity and reliability of assessments of antimicrobial appropriateness by comparing how specialists (clinical microbiologists and infectious diseases specialists) and residents in these specialties from different hospitals assessed the prescribing of antimicrobial agents in paper cases based on patients on the adult wards of an academic hospital. We created a reference standard by combining the assessments of specialists.

Methods

Case selection

Figure 1 gives an overview of the case selection and assessment procedure. Important terms used in this article are defined in the Box below. We accessed a database of antimicrobial agents prescribed from 2011 to 2013 in the VU University Medical Centre, a 700-bed tertiary care academic hospital in Amsterdam, the Netherlands (index hospital). The hospital antimicrobial stewardship team assembled all clinical data as part of standard health care quality measurements. Patient cases were eligible for selection if the patient was staying on any adult clinical ward, and had an active prescription of a systemic antimicrobial agent at the time of the survey. Prescriptions with anatomic therapeutic chemical classification codes beginning with J01, J02, J04AB02 and J05AB were included.[14] The database contained relevant patient data, including the indication for the prescription and reasons for deviating from appropriate guidelines, taken from medical files or provided by the responsible ward doctor.

All prescriptions in the database had already been assessed for appropriateness by an infectious disease specialist, during a face-to-face discussion with the research doctor (see Assessment procedure). Prescriptions were selected at random from the database using the random number generator in SPSS. If multiple antimicrobials had been prescribed, only one was selected per case. To optimize statistical power, we included 28 cases initially assessed by the index expert as appropriate and 28 cases assessed as inappropriate (maximally heterogeneous). To reduce participant workload, the 56 cases were subsequently randomly divided into two sets of 28 cases, each with 14 assessments of appropriate and inappropriate prescribing. The case sample size was based on calculations assuming maximal heterogeneity, α of 5%, and a power of 80% to detect a kappa of 0.4 or higher, including a margin of six cases to account for case exclusion.[15]

Ethics

The hospital medical ethical committee granted permission for the collection and use of patient data (reference 2011/315). After assembly, the data were coded and stripped from any identifying information, and then made available for research. Members of the research team could not access the original medical records.

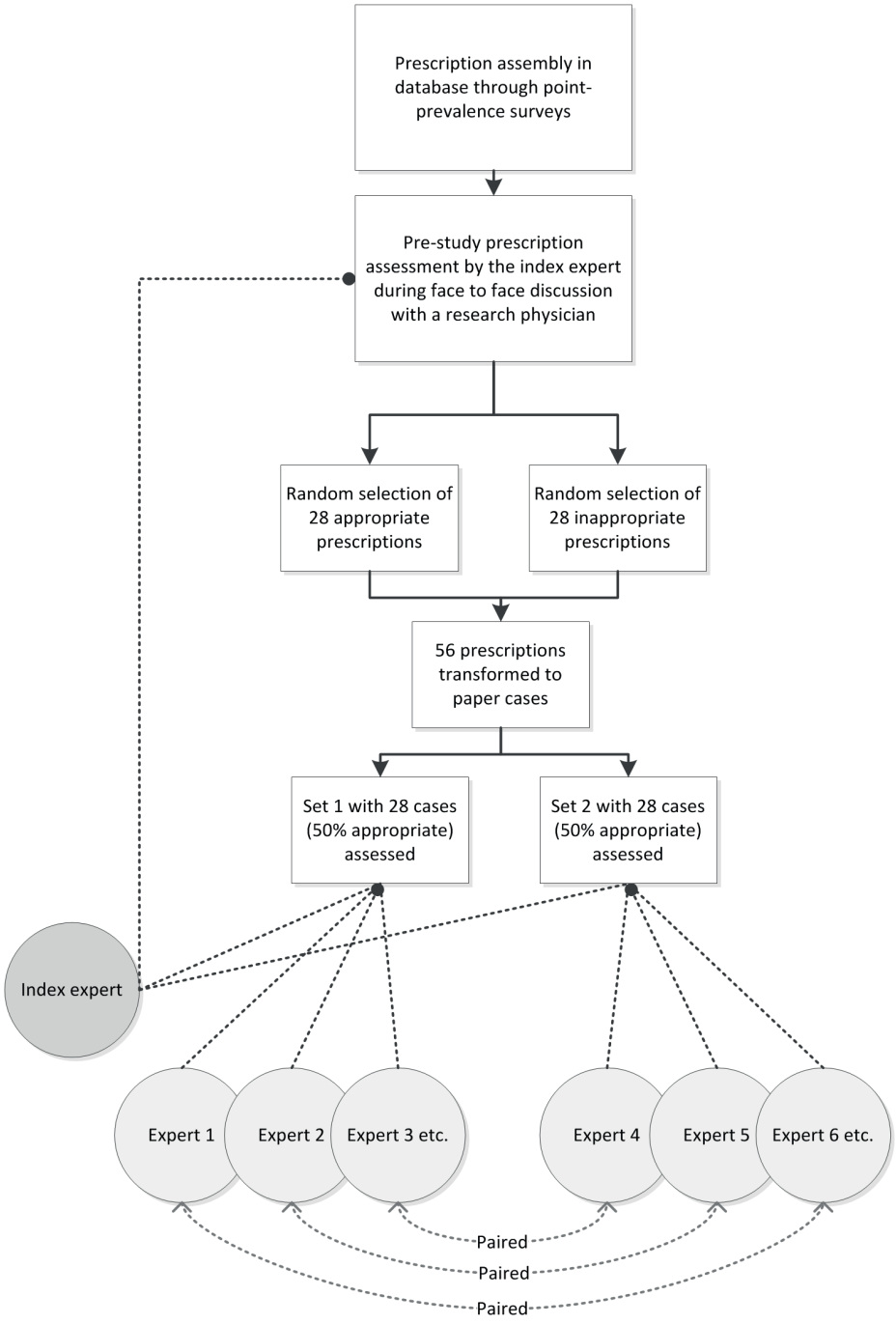

Figure 1
Overview of case selection and assessment procedures. Experts were paired to enable comparison of the full 56 cases between pairs. For illustrative purposes, only a small number of participants is shown.

Box: definition of terms used in this article

- Agreement or overall agreement: absolute measure of reliability; a head-to-head comparison of two assessments, expressed as a percentage reflecting the number of cases for which two experts agreed relative to the number of cases assessed
    - Interrater agreement: comparison of agreement between two experts
    - Intrarater agreement: comparison of the agreement between two assessments made by the same expert at least 12 months apart
    - Appropriateness agreement: type of agreement, commonly referred to as specific or positive agreement, comprising a percentage reflecting the probability that either one of the experts classifies a case as appropriate given that the other did so too.
    - Inappropriateness agreement: type of agreement, commonly referred to as specific or negative agreement, comprising a percentage reflecting the probability that either one of the experts classifies a case as inappropriate given that the other did so too.
- Antimicrobial appropriateness: dichotomous measure of antimicrobial prescribing quality whereby the assessing expert bases his/her judgment on a systematic consideration of guideline adherence, potential reasons for deviating from guidelines, and rational prescribing.
    - Rational prescribing: prescribing an effective antimicrobial regimen covering relevant pathogens without being excessive.
- Criterion validity: type of validity based on the agreement of a measurement instrument with a reference standard, which is divided into:
    - Sensitivity: measure of criterion validity; percentage reflecting the proportion of cases classified appropriate by an expert among cases classified appropriate by the reference standard.
    - Specificity: measure of criterion validity; percentage reflecting the proportion of cases classified inappropriate by an expert among cases classified inappropriate by the reference standard.
- Cohen's kappa: relative measure of reliability adjusting the observed agreement for the agreement expected by chance; values range from -1 to 1; negative values indicate less agreement than expected by chance, a value of 0 indicates the observed agreement is equal to that expected by chance, and a value of 1 indicates maximal agreement.
- Experts: clinical microbiologists, infectious disease specialists (internists), and residents from either specialty who participated in the study to assess appropriateness of antimicrobial prescription cases.
    - Index expert: infectious disease specialist who performed both pre-study and in-study assessments of all 56 cases; served as comparison for interrater agreement and served as only source for intrarater agreement
- Reference standard of antimicrobial appropriateness: best available indicator of antimicrobial appropriateness; created by combining all specialist experts' assessments (excluding resident assessments) and taking the most frequent response per case as reference standard.

Case forms

The two selected case sets were printed out, in Dutch. Each case report contained all relevant patient data (including culture results), any co-prescribed antimicrobial drugs, the ward doctor's reason for prescribing with possible reasons for deviating from a guideline, each relevant guideline, and comments made by the research doctor about appropriateness (e.g., antimicrobial indication is consistent with the guideline, but the dosage is not consistent with guideline recommendations for a patient with poor renal function). A checkbox form was included to register participants' assessment. The form also included room for any possible remarks. As example, one case has been translated into English (Figure 2).

Case number: X	Specialty: X	Gender:F	Age: X
Drug: amoxicillin/clavulanate oral	Dose: 625mg	Frequency: 3/day	Current length of therapy: 5d

Previous or current antimicrobial co-medication: none

Reason for admittance: minor surgery (details omitted in this supplement to preserve anonymity of hospital ward)

Relevant medical history: none

Reason for prescription according to ward physician/patient record: "after surgery, the operation wound at location X became warm and swollen. There is no infection yet but we gave the amoxicillin/clavulanate preventively. Drains are still inserted and functioning. Patient is getting better."

Relevant microbiological diagnostic results: no cultures taken

Relevant radiologic results: none performed

Other information: no inflammation parameters determined (CRP etc), no fever present.

Case summary: fifth day of amoxicillin/clavulanate 625mg TID orally "preventively" for warm and swollen operation wound after minor surgery 6 days ago with drains still inserted and functioning, no fever and no infection diagnostics.

Relevant guideline: hospital guideline. Surgical site infections: primary intervention: surgical. If antimicrobial treatment necessary: 1. flucloxacillin 1000mg 6/day iv for 7 days, 2. In case of penicillin-allergy: clindamycin 600mg 3/day iv for 7 days.	Other guidelines: none

Discussion remarks: The ward physician says this is preventive and that there is no infection present. There is no fever and they did not determine any inflammation parameters. The question rises whether this is an infection and whether antimicrobial therapy is indicated. Second, the choice for amoxicillin/clavulanate is broader than advised by the relevant guideline, is this deviation from the guidelines rational for this specific anatomic location of infection?	**Indication:** appropriate / no indication for antimicrobial prescription* **If chosen no indication, skip all judgments below on this page*
	Choice of antimicrobial: appropriate / too broad / too narrow / other fault(s)
	Dose: appropriate / too high / too low
	Frequency: appropriate/ too high / too low / should be continuous infusion
Room for remarks from expert:	**Administration route:** appropriate / should be oral / should be IV
	Duration: appropriate / too long

Figure 2
Case form example translated to English from Dutch

Participant recruitment

Clinical microbiologists, infectious disease specialists (all internists), and residents of either specialty (all hereafter called experts) from the index hospital and from four other hospitals were asked to participate in the study by email or personal contact. We asked the infectious diseases specialist who had already previously assessed all 56 cases to assess these again, using the case forms. The assessments of this doctor could therefore be compared with his earlier assessments (intrarater agreement) and with the assessments of his colleagues (interrater agreement); this doctor is referred to as the index expert. The previous assessments were performed more than 12 months earlier to prevent the influence of a recall effect. All other experts were supplied with a set of 28 case forms and an instruction manual. Because each expert only assessed one set of cases, pairs of experts were formed so that all cases were judged once (see Figure 1). Pairs were based on the maximum possible similarity between experts, based on speciality, hospital, and experience (in order of priority) to enable comparisons of these factors.

Assessment procedure

The in-study assessment procedure and the pre-study assessment procedure were identical, except that the latter comprised a face-to-face meeting with the research doctor, whereas the latter former done on paper. All experts were instructed to classify the following three situations as appropriate: 1. The prescription followed the relevant guideline completely, in which case the prescription was classified as appropriate. 2. The prescription deviated from the guideline on one or more aspects, in which case the ward doctor's arguments for deviating were assessed for rationality; if found rational then the prescription was classified as appropriate, otherwise the deviating aspects were classified as inappropriate. And 3., the indication was not or only partially covered by a relevant guideline. In this case, the expert assessed the case for rationality, defined as an effective antimicrobial regimen covering relevant pathogens without being excessive (i.e., unnecessary combination therapy or broad spectrum when a more narrow spectrum is available); if rational, the prescription was considered appropriate. The instructions indicated which guideline was the relevant guideline, which in most cases was the hospital guideline. This procedure was applied to each of the following prescription aspects: indication, choice of antimicrobial, dosage, administration route, and duration.[16] If at least one of the above aspects was assessed as inappropriate, prescribing was considered inappropriate. No expert had knowledge of clinical outcomes or the previous assessment of a case.

Validity

A reference standard of antimicrobial appropriateness was compiled, based on the modal response of all specialist expert pairs (excluding residents) per case. In the few cases where the number of specialist experts that considered a prescription appropriate or inappropriate was equal, the modal response of the residents was used to decide appropriateness. We defined criterion validity as agreement with the reference standard; sensitivity and specificity were

calculated as main outcome measures. For each comparison, the responses of the individual expert were not included in the reference standard, in order to avoid incorporation bias.[17] To this end, we compiled the reference standard for each comparison separately. We tested whether criterion validity differed by clinical specialty, experience, position (specialists versus resident) and hospital of employment.

Agreement

Interrater agreement was determined by comparing each expert pair's assessments with the index expert's assessments. Intrarater agreement was determined by comparing the two assessments of the index expert. Agreement was chosen as primary outcome instead of Cohen's kappa because it is an absolute measure with clear interpretability;[18,19] however, Cohen's kappa values are given to enable comparison with results in the literature. Specific and overall agreement was calculated.[18]

Statistical analysis

Confidence intervals were calculated using the 2.5th and 97.5th percentile of 10,000 bootstrapping samples as interval limits. Validity between different expert groups was compared using logistic generalized estimating equations with an exchangeable correlation matrix to account for clustering within cases (first level) and experts (second level). Agreement with the reference standard was used as dependent variable. We also report p-values from a multivariable model containing all three expert characteristic variables. All analyses were performed with SPSS (version 22.0) and R (version 3.1.2). P-values <0.05 were considered significant.

Results

Patient case and expert characteristics

Case characteristics are presented in Table 1. One case in which vancomycin was used included a therapeutic drug monitoring guideline that was out of date at time of the study and the case was therefore excluded. Besides the index expert, 23 experts (15 specialists, 8 residents) from five hospitals (three academic) participated in the validation procedure. We created ten expert pairs. Two infectious disease residents from the same hospital mistakenly completed the same set of cases so could not be paired. Because of the odd number of participants, one clinical microbiologist could not be paired with another expert. Expert characteristics and mean agreement about prescribing appropriateness are presented in Table 2.

Table 1
Characteristics of selected patient cases

	Set 1 (n=28)	Set 2 (n=27)	Total (n=55)
male patient (%)	13 (46)	14 (52)	27 (49)
median age (range)	58 (25-86)	61 (23-90)	59 (23-90)
type of ward			
intensive care	3 (11)	5 (19)	8 (15)
medical	13 (46)	9 (33)	22 (40)
surgical	12 (43)	13 (48)	25 (46)
indication for antimicrobial (%)			
prophylaxis			
immunodeficiency	3 (11)	2 (7)	5 (9)
post-surgical	2 (7)	3 (11)	5 (9)
recurrent infections	1 (4)	2 (7)	3 (5)
therapy			
bone/joint infection	1 (4)	4 (15)	5 (9)
ear-nose-throat infection	1 (4)	2 (7)	3 (5)
endovascular infection	4 (14)	0 (0)	4 (7)
pneumonia	6 (21)	4 (15)	10 (18)
sepsis without anatomic site	3 (11)	2 (7)	5 (9)
skin/soft tissue infection	3 (11)	5 (19)	8 (15)
urinary tract infection	1 (4)	0 (0)	1 (2)
other	3 (11)	3 (11)	6 (11)
antimicrobial agent group (%)			
penicillin	7 (25)	7 (26)	14 (26)
cephalosporin	5 (18)	5 (19)	10 (18)
carbapenem	3 (11)	0 (0)	3 (6)
glycopeptide	2 (7)	4 (15)	6 (11)
quinolone	1 (4)	1 (4)	2 (4)
other antibiotic	5 (18)	10 (37)	15 (27)
antimycotic	3 (11)	0 (0)	3 (6)
antiviral	2 (7)	0 (0)	2 (4)
median number of co-prescribed antimicrobial agents (range)	1 (0-4)	0 (0-2)	1 (0-4)

Table 2
Characteristics of the experts who assessed the appropriateness of antimicrobial prescribing

Expert	Experience in years in current role (averaged for pairs)	Mean appriopriateness	# assessed cases
Index hospital			
Index IDS	8	31%	55
IDS pair 1	31	45%	53
IDS pair 2	3	47%	53
IDS in training pair 1	6	31%	52
CMB pair 1	8	39%	54
CMB pair 2	1	42%	55
CMB in training pair 1	6	41%	54
CMB in training pair 2	3	36%	55
Other hospital			
IDS pair 3	21	40%	53
IDS pair 4	3	29%	55
IDS in training 1	6	11%	27
IDS in training 2	6	38%	26
CMB pair 3	25	38%	53
CMB 7	3	50%	28

IDS; infectious disease specialist. CMB; clinical microbiologist. Cases assessed as 'not enough information' by the expert were excluded if present in the comparison. IDS's in training 3 & 4 and CMB 7 could not be paired so are presented alone.

Validity

In 20 (36%) cases, all specialist experts agreed about the appropriateness or inappropriateness of prescribing; in four (7%) cases, the specialist experts were equally divided about the appropriateness of prescribing. According to the reference standard, 38% of the prescriptions were appropriate. The specialist experts agreed with the reference standard in 80% of cases (range 75-86), with a mean sensitivity and specificity of 75% (range 65-86) and 84% (range 75-97), respectively. The index expert agreed with the reference standard in 84% of cases, with a sensitivity and specificity of 68% and 94%, respectively. Residents agreed with the reference standard in 81% of cases (range 77-86), with a mean sensitivity and specificity of 71% (range 60-100) and 87% (range 79-100), respectively. The difference in agreement with the reference standard between resident and specialist experts was not significant (crude p=0.72, adjusted p=0.63). Agreement with the reference standard was similar among specialist experts with minimally or maximally six years of experience (81% versus 80%, crude p=0.50, adjusted p=0.45), among clinical microbiologists and infectious diseases specialists (80% versus 81%, crude p=0.50, adjusted p=0.44), and among experts employed in the index hospital and other hospitals (80% versus 82%, crude p=0.67, adjusted p=0.58). There was no significant interaction between these expert characteristics.

Agreement

Intrarater and interrater specific and overall agreement for all experts is presented in Figure 3. The mean overall agreement between the index expert and the specialists as a group, other ID specialists, clinical microbiologists, ID residents, and clinical microbiology residents was 76%, 77%, 77%, 85%, and 82%, respectively. The mean overall agreement between the index expert and the specialists from the index hospital and the other hospitals was 75% and 78%, respectively. The index expert agreed with his previous assessments in 71% of cases. There was greater agreement about inappropriate prescribing than about appropriate prescribing.

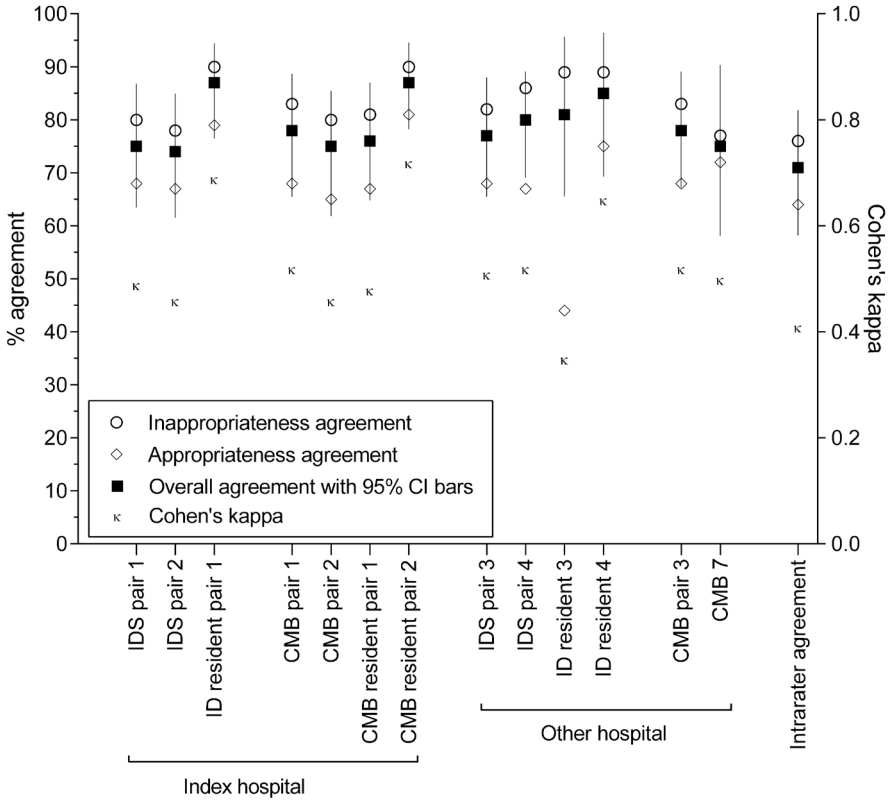

Figure 3

Specific and overall agreement, and Cohen's k of experts compared with the index expert. ID, infectious disease; IDS, infectious disease specialist; CMB, clinical microbiologist. ID resident 3, ID resident 4 and CMB 7 could not be paired so are presented alone. The interrater agreement shown is the comparison between the index expert's pre-study and in-study assessments.

Cases with minimal or maximal agreement

In 13 cases, all experts agreed that the antimicrobial therapy was inappropriate. Six of these cases concerned post-surgical prophylaxis longer than 24 hours (i.e. vancomycin prophylaxis after cardiac

valve replacement), two cases where therapy was continued after infection was ruled out, and two cases where empirical therapy was not streamlined when culture results were available.

In three cases, all experts agreed that the antimicrobial therapy was appropriate: ciprofloxacin prophylaxis during high-risk neutropenia, imipenem/cilastatin for fever during high-risk neutropenia, and fluconazole for oral candidiasis.

In four cases, the specialist experts were divided in their opinion about the appropriateness of the prescription. These cases concerned a patient treated for severe community-acquired pneumonia without coverage for atypical pathogens while the Legionella urinary antigen test was negative; intravenous amoxicillin/clavulanate for a nasal septum abscess after failure of oral therapy with the same drug; Pneumocystis jirovecii pneumonia prophylaxis during eculizumab therapy; and 5 weeks of empiric flucloxacillin for chronic osteomyelitis with cultures positive for Pseudomonas aeruginosa but not for Gram-positive organisms (ceftazidime was co-prescribed).

In three cases, several experts thought that there was not enough information available to make a judgement about appropriateness, even though this was not a possible response in the form. Two of these cases concerned the prescription of ceftriaxone for which neither the responsible ward doctor nor the medical record provided an indication for antimicrobial treatment; this led the experts to classify the case as 'not enough information' or as inappropriate. The third case concerned the long-term use (>6 weeks) of imipenem/cilastatin for an inoperable patient with a persistent duodenal fistula and an infection of an aortic prosthesis by multiresistant bacteria.

Discussion

In this study, we determined the extent of agreement among clinicians about the appropriateness of prescribing antimicrobial agents. Specialist experts agreed with the reference standard in 80% of cases (range 75-86; sensitivity 75%, specificity 84%). This level of agreement was similar among residents, clinical microbiologists and ID specialists, experts with different levels of experience, and experts employed in different hospitals. The specialist experts agreed with the index expert in 76% of cases, with better agreement about inappropriate prescribing than about appropriate prescribing. The index expert, who had assessed the cases before, agreed with his previous assessments in 71% of cases.

Our approach was unique in several aspects. First, a relatively large group of experts, including ID specialists, clinical microbiologists, and residents in either specialty from different hospitals, assessed the cases. This allowed us to create a reference standard, and permitted us to evaluate criterion validity, which has not been done before.[5-12] Secondly, we explicitly explained in advance the experts how to deal with guideline applicability, what were legitimate reasons for guideline deviations, and

how to deal with antimicrobial prescribing in the absence of guidelines. Thirdly, a broad variety of cases was included, including cases where no guideline can be applied.

Experts agreed in 80% of cases with the reference standard, which may seem reasonable but still leaves some room for improvement. For example, if data for the sensitivity and specificity of specialist assessments are applied to a situation with a prior probability of appropriateness of 50%,[1] which is reported in literature, the positive and negative predictive value would be only 82% and 77%, respectively. On the one hand, the assessment of the appropriateness of antimicrobial prescriptions is usually done to guide antimicrobial stewardship interventions at a clinical ward/group level rather than at an individual/patient level. Therefore these moderate predictive values may be acceptable because the result does not have consequences for the individual patient. Moreover, assessments are often repeated before conclusions are drawn, so this suggests antimicrobial appropriateness can be a valid and reliable outcome in both stewardship practice and stewardship studies. On the other hand, the suboptimal consensus among the specialists about appropriate antimicrobial prescribing makes it difficult to formulate clear stewardship recommendations. Therefore, we feel this last aspect merits attention in training programmes and multidisciplinary discussions. Local or preferably national guidelines about what constitutes appropriate prescribing may help to strengthen the message.

We found that agreement with the reference standard was similar among residents and specialists, and also among specialists with varying experience. This result is encouraging to change the culture of prescribing, recently described as the "prescribing etiquette', in which senior doctors' antimicrobial prescribing is rarely questioned by others.[20] Although previous studies have suggested that ID specialists and clinical microbiologists have different standards for assessing appropriateness, we found no differences.[11] Although antimicrobial guidelines and practices often differ between hospitals, hospital of employment had no clear impact on validity.

The agreement between the experts ranged from 70% to 90%, and Cohen's kappa's ranged from 0.35 to 0.72 (Figure 3). According to a commonly used classification system, these values can be described as fair to substantial, with most values falling into the moderate category.[21] Previous studies reported various levels of interrater agreement with Cohen's kappa's ranging from 0 to 0.8,[5-9,11,12] one study reported an overall agreement of 71%.[6] We found an intrarater agreement of 71%, which was lower than the interrater agreement but similar to one earlier study,[7] and lower than a study of pharmacists' assessments.[10] However, intrarater agreement may have been underestimated because the two assessments procedures were not entirely identical (face-to-face versus paper). Moreover, the index expert assessed more prescriptions as inappropriate at the second, paper assessment. It may illustrate that face-to-face decisions are taken differently than on paper. It also suggests that specialists' opinions on appropriate prescribing may be inconsistent over time. It underlines that individual expert opinion is not equal to a reference standard and that intrarater agreement deserves more attention.

The experts appeared to find it easier to decide whether a prescription is inappropriate than whether it is appropriate. It is important to note that when the prevalence of a response category rises above 50%, the probability of agreeing on that category purely by chance increases. We aimed to minimalize this by using a group of cases in which the prevalence of appropriate prescribing was 50%. However, the percentage of what was considered appropriate prescribing was lower than 50% among many experts. Consequently, experts were more likely to agree on inappropriateness compared with appropriateness based on chance alone. Interestingly, the experts disagreed about how to assess the appropriateness of antimicrobial prescriptions when neither the responsible ward doctor nor the medical record provided information on the indication: some experts assessed the prescription as inappropriate, and others that there was 'not enough information'. Instructions on how to classify cases with missing information would have helped to create a more uniform assessment with higher agreement.

Our study had some weaknesses. Ideally, all experts should have assessed all 56 cases instead of only 28. However, we felt that the higher workload would reduce the number of experts willing to take part in the study. Therefore we chose to use pairs of experts, to share the workload. Although we matched pairs on their characteristics, this may have diminished the variability of outcomes. For instance, if an expert had an 'extreme' opinion about prescribing appropriateness in the cases reviewed, his/her results would be combined with those of another expert, who would probably have had a more moderate opinion about prescribing appropriateness. Some experts could not be paired, so their results are less comparable than those of pairs of experts.

In conclusion, we found that infectious diseases specialists, clinical microbiologists, and residents with a different number of years of experience and working in different hospitals assess the appropriateness of antimicrobials prescribed for a broad spectrum of indications with an acceptable agreement and validity. However, there is room for improvement as full consensus about the appropriateness of antimicrobial prescribing is lacking. This aspect of appropriateness evaluation merits attention in multidisciplinary discussions and training programmes on antimicrobial stewardship.

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Whereas PAR has been d ciences since the 1940s, hardly any PA hcare until the late 1990s.22 Sinc sed.21,25,26 PAR differs in ls (RCTs), which are co e gold standard 27 This is based on th us that the highest level e derived from setti re influences on the outcom tervention are controlled.25 As PAR is an approach th le factors, interventions and stakeholders, it is not feasible single aspect of the research situation. Consequently, outc attributed to a single intervention: it is the process as a w gs about change. An advantage of this multifactorial and ary involvement is that PAR produces evidence that is of to the local setting for which it is intended. The latter is rue for evidence produced by RCTs, as real-life situations to the controlled situation. This is especially people with older age, comorbidities tion and physical impairment are excluded Ts, the potential to generalize trial findings to this p can therefore be argued that the context and research ich research approach delivers the best-quality eviden ns where multidisciplinary teams work with complex p s or whole systems, PAR may be an appropriate appr e complex and multidisciplinary character of anti p programmes, PAR seems a suitable approach for dev g and evaluating these programmes. However, we are n es describing the use of PAR in the development of an nip programmes. We did, however, identify two studies t dies on prescribing drugs other than antimicrobials. Do ribed a PA h that was effective in reducing b in the m somnia in a rural community. n shown t proving medication use ce by first e ng of patient barrier cation use and sub d interve on, PAR has been reporte care situations other than

drug prescribing. Examples include the development and implementation of a critical pathway for patients with symptoms suggestive of an acute coronary syndrome,31 the development and implementation of a model of care for older acutely ill hospitalized patients,32 and the identification of potentially feasible interventions for the improvement of dietary habits and physical activity.33 A PAR design for antimicrobial stewardship Although to date PAR has not been used to improve antimicrobial prescribing, we hypothesize that this approach is suitable for the

Participatory action research in antimicrobial stewardship: a novel approach to improving antimicrobial prescribing in hospitals and long-term care facilities

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symptoms of infections, and taking routine urine cultures to determine local resistance patterns. The selected intervention types differed by long-term care facility, and if similar intervention types were selected the focus often differed (e.g. optimizing diagnostic protocols for urinary tract infections in one facility and for respiratory tract infections in another). In both projects, several participants expressed their appreciation of being involved in the development and implementation of the antimicrobial stewardship programme. A surgeon participating in the DUMAS project stated: 'the approach appeals to me because people are more involved instead of getting an assignment. I think that giving people the initiative will lead to more effect. New projects are generally critically received because we are already overloaded with things we must do, and people can project.

Abstract

It is challenging to change physicians' antimicrobial prescribing behaviour. Although antimicrobial prescribing is determined by contextual (e.g. a lack of guidelines), cultural (e.g. peer practice) and behavioural (e.g. perceived decision making autonomy) factors, most antimicrobial stewardship programmes fail to consider these factors in their approach. This may lead to suboptimal intervention effectiveness. We present a new approach in antimicrobial stewardship programme development that addresses relevant determinants of antimicrobial prescribing: participatory action research (PAR). PAR is a collaborative process that aims to bring about change in social situations by producing practical knowledge that is useful in local practice. It requires substantial involvement of relevant stakeholders to address determinants of the studied behaviour and to facilitate empowerment. PAR is well suited for complex problems in multidisciplinary settings as it adapts to local needs, delivering a tailored approach to improving local practice. We describe how PAR can be applied to antimicrobial stewardship, and describe the PAR design of two on-going multicentre antimicrobial stewardship projects, in the acute care setting and the long-term care setting, respectively.

Introduction

Antimicrobial stewardship programmes aim to improve antimicrobial prescribing to reduce antimicrobial resistance development, reduce costs and improve clinical outcomes. Antimicrobial prescribing is determined by contextual but also cultural and behavioural factors.[1 – 4] Examples of contextual factors include a lack of guidelines or access to guidelines, a lack of diagnostic resources, patient characteristics (e.g. clinical features, comorbidities, communication possibilities), patient expectations, nursing staff expectations, a lack of time or workforce and frequent staff turnover.[1,5 – 10] An example of a cultural factor is 'prescribing etiquette', a term describing the set of unwritten but widely accepted cultural rules around prescribing.[4] Examples of behavioural factors include a lack of awareness of guidelines, a lack of agreement with guidelines, physicians' perceived decision-making autonomy, fear of withholding or adjusting treatment and resistance to change current practice ('never change a winning team').[1,5,11 – 18]

Although many antimicrobial stewardship strategies are available,[11,12,19] changing physicians' prescribing behaviour is challenging,[13,14] due to the combination of the aforementioned influencing factors and the variety of possible interventions, disciplines, healthcare professionals and healthcare settings involved. Most antimicrobial stewardship strategies fail to consider contextual, cultural and behavioural factors in their approach, which may lead to suboptimal intervention effectiveness.[12,15,16] Antimicrobial prescribing improvement programmes should therefore include a proper analysis of relevant determinants.[1 – 4] We present an approach that addresses these determinants: participatory action research (PAR). To illustrate the use of PAR in antimicrobial stewardship programme development, we describe a study design that has been applied in two different healthcare settings (i.e. the acute care setting and the long-term care setting).

PAR

A research approach that is well suited to addressing complex problems in healthcare settings is PAR. This approach always uses qualitative research methods, often combined with quantitative methods.[20,21] A primary aim of PAR is to produce practical knowledge that is useful in local practice.[22] Several definitions of action research have been developed over the years.[20,22 – 24] We incorporated these definitions into the following description of PAR:

> Participatory action research aims to bring about change in social situations by both improving practice (i.e. taking action) and creating knowledge or theory (i.e. reflecting on action). In other words, it bridges the gap between theory and practice. It works through a cyclical process of planning, action and reflection. This process is collaborative: it requires substantial involvement of relevant stakeholders, which facilitates empowerment. The persons under study are considered 'co-researchers' who test practices and gather evidence in action phases, and evaluate this action and plan further action in reflection phases. In other words, participatory action research is working with people, not on people.

Whereas PAR has been described and applied in social sciences since the 1940s, hardly any PAR was published in the context of healthcare until the late 1990s.[22] Since then, the use of PAR in healthcare has increased.[21,25,26] PAR differs in several aspects from randomized controlled trials (RCTs), which are considered the gold standard in healthcare research.[27] This is based on the consensus that the highest level of evidence can only be derived from settings where influences on the outcome other than the intervention are controlled.[25] As PAR is an approach that involves multiple factors, interventions and stakeholders, it is not feasible to control every single aspect of the research situation. Consequently, outcomes cannot be attributed to a single intervention: it is the process as a whole that brings about change. An advantage of this multifactorial and multidisciplinary involvement is that PAR produces evidence that is of practical use to the local setting for which it is intended. The latter is not always true for evidence produced by RCTs, as real-life situations may not be comparable to the controlled situation. This is especially a concern in geriatric medicine: as people with older age, comorbidities, polypharmacy, decreased cognitive function and physical impairment are often excluded from participation in RCTs, the potential to generalize trial findings to this population is limited.[28] It can therefore be argued that the context and research question determines which research approach delivers the best-quality evidence. In clinical situations where multidisciplinary teams work with complex problems, new situations or whole systems, PAR may be an appropriate approach.[25,26]

Due to the complex and multidisciplinary character of antimicrobial stewardship programmes, PAR seems a suitable approach for developing, implementing and evaluating these programmes. However, we are not aware of any studies describing the use of PAR in the development of antimicrobial stewardship programmes. We did, however, identify two studies that used PAR in studies on prescribing drugs other than antimicrobials. Dollman et al.[29] described a PAR approach that was effective in reducing benzodiazepine use in the management of insomnia in a rural community. PAR has also been shown to be effective in improving medication use in general practice by first enabling the understanding of patient barriers to optimal medication use and subsequently offering tailored interventions.[30] In addition, PAR has been reported as an effective approach in complex healthcare situations other than drug prescribing. Examples include the development and implementation of a critical pathway for patients with symptoms suggestive of an acute coronary syndrome,[31] the development and implementation of a model of care for older acutely ill hospitalized patients,[32] and the identification of potentially feasible interventions for the improvement of dietary habits and physical activity.[33]

A PAR design for antimicrobial stewardship

Although to date PAR has not been used to improve antimicrobial prescribing, we hypothesize that this approach is suitable for the development, implementation and evaluation of antimicrobial stewardship programmes, as it is for other complex healthcare situations. Below we describe a research design that uses PAR to develop, implement and evaluate antimicrobial stewardship programmes. The design consists of nine phases, each representing an element of the cyclical process of planning, action and reflection that is typical of PAR (**Figure 1**).

Furthermore, in Table 1 we present two applications of the design in two different healthcare settings: the DUMAS project (acute care) and the IMPACT project (long-term care).

Phase 1: preparation (planning)
Identifying and contacting participating centres and their relevant stakeholders (e.g. physicians, nursing staff, pharmacists, microbiologists, infectious disease consultants and managerial staff), initiating partnership development, determining objectives and key outcomes, and planning data collection.

Phase 2: data collection (action)
Researchers collect local quantitative and qualitative data on (appropriateness of) antimicrobial use, factors that influence antimicrobial prescribing and potential areas for improvement.

Phase 3: data evaluation (reflection)
The data collected in Phase 2 are analysed by the researchers and presented to relevant stakeholders of the involved healthcare setting. The data are subsequently discussed.

Phase 4: data uptake (action)
Relevant stakeholders and researchers collaboratively identify facilitators and barriers with regard to antimicrobial use, and determine opportunities to improve appropriate antimicrobial use.

Phase 5: intervention selection (action)
Based on the analysis of facilitators and barriers in Phase 4, the stakeholders discuss intervention types that suit their preferences and their identified opportunities. Subsequently, they select existing interventions, or interventions that need to be adjusted or developed, for implementation in collaboration with the researchers.

Phase 6: intervention planning (planning)
In collaboration with the researchers, the stakeholders create a plan for development, adjustment and implementation of the interventions selected in Phase 5, including elements to ensure sustainability of the interventions.

Phase 7: intervention implementation (action)
The interventions described in Phase 6 are developed, adjusted and implemented by the researchers and stakeholders collaboratively.

Phase 8: data collection (action)
Researchers collect local quantitative and qualitative data on (appropriateness of) antimicrobial use and the implementation of the interventions.

Phase 9: data and intervention evaluation (reflection)

The data collected in Phase 8 are analysed by the researchers, compared with the data collected in Phase 2 and presented to all relevant stakeholders of the involved healthcare setting. The stakeholders reflect on the data and the implemented interventions. Where necessary, adjustments are made to the intervention plan or new opportunities are determined, in which case another cycle of planning, action and reflection follows.

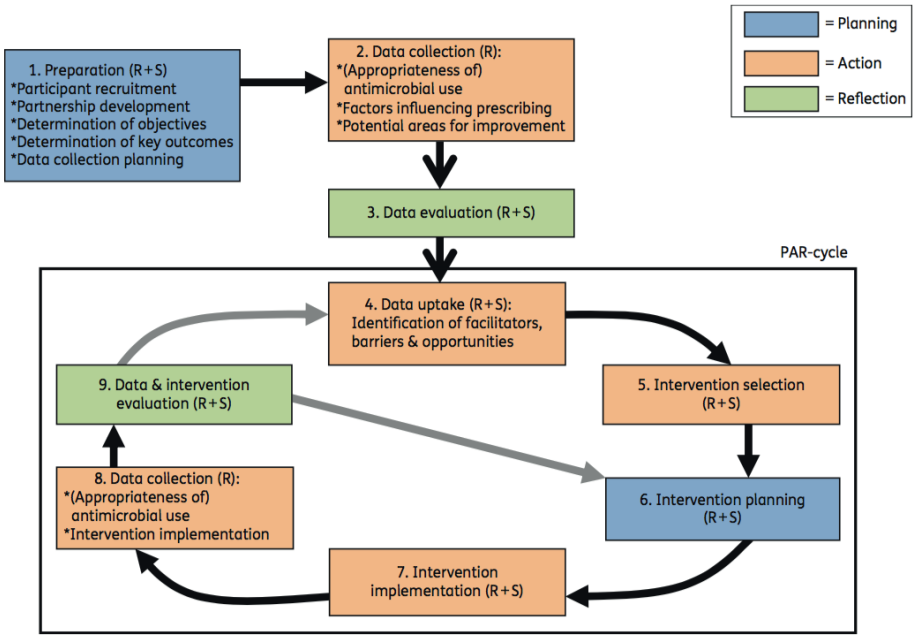

Figure 1
Visualization of the PAR design for the development, implementation and evaluation of antimicrobial stewardship programmes. R, researchers; S, (relevant) stakeholders.

Table 1
Design of DUMAS (acute care) and IMPACT (long term care), two multicenter projects that apply PAR to develop, implement and evaluate an antimicrobial stewardship programme.

	Dutch Unique Method for Antimicrobial Stewardship (DUMAS)	**Improving Rational Prescribing of Antibiotics in Long Term Care Facilities (IMPACT)** (The Netherlands National Trial Register ID: NTR3106)
Population	Hospital inpatients (1 tertiary care centre and 2 community hospitals) in the Netherlands.	Residents of 10 nursing homes (NHs) and 4 residential care facilities (RCFs) in the Netherlands.
Design	Initiation of PAR approach varies per participating clinical ward according to a stepped wedge design.	Facilities are allocated to an intervention or a control group (5 NHs and 2 RCFs each). The control group proceeds through the phases in a different order: 1,2,8,3,4,5,6,7 (phase 9 skipped).
Analysis	Intervention effect evaluated using segmented regression analysis of antimicrobial consumption and appropriateness, combined with qualitative data analysis. Levels and slopes of appropriateness in the period prior to phase 3 are used as control data within en between departments.	Intervention effect evaluated using multilevel regression analysis (intervention group vs. control group), combined with qualitative data analysis.
Time schedule	October 2011 – Spring 2015	March 2011 – Spring 2014
PAR phases		
Preparation	Determine objectives and target hospitals. Invite hospitals and all wards to participate. Identify and contact coordinating ward specialists. Determine key outcomes and collaboratively prepare data collection.	Determine objectives and randomly invite facilities to participate. Allocate facilities to the intervention or control group. Identify and contact relevant stakeholders. Determine key outcomes and collaboratively prepare data collection.
Data collection	Researchers conduct 2-monthly point-prevalence surveys of antimicrobial prescribing and retrieve pharmacy data. Appropriateness of prescribing is judged by local hospital guidelines using a standardized algorithm.[34] (Duration: phase 3 starts after 12 months but the surveys are continued until the end of the project.)	Quantitative data collection: recording of infection diagnosis and treatment by physicians, chart review by researchers, and retrieval of pharmacy data. Physicians' recorded data are used to judge appropriateness of antibiotic prescribing with a guideline-based algorithm developed by an expert panel. Qualitative data collection: semi-structured interviews with physicians and nursing staff on antibiotic prescribing and resistance.
Data evaluation	In individual semi-structured interviews, ward members react to phase 2 data and discuss potential interventions. These ward members are selected in collaboration with the local "ward-team" (coordinating medical specialist + specialist in training + nurse), which is established at each ward as the first point of contact. Researchers present survey and interview results to all ward members, followed by a discussion.	Researchers present the local study results to the facilities in the intervention group and discuss them in a multidisciplinary team meeting with relevant stakeholders, including physicians, nursing staff, pharmacists, microbiologists, and managerial staff.
Data uptake	Collaboratively identify local facilitators and barriers to appropriate antimicrobial prescribing and opted interventions. Example: the surveys may reveal that a ward frequently uses amoxicillin/clavulanate to treat surgical site infections (SSIs), whereas flucloxacillin or even no antibiotic treatment is recommended by the guidelines. The interviews may show that this can be explained by a combination of concerns for consequences of SSIs, custom, convenience (eg amoxicillin/clavulanate generally covers most pathogens for most infections), and lack of knowledge of alternatives and the guidelines recommending them.	Relevant stakeholders identify local facilitators and barriers to appropriate antibiotic prescribing in focus group discussions facilitated by the researchers, and prioritize opportunities to improve antibiotic prescribing. Example: the study results may reveal a substantial level of inappropriate antibiotic prescribing for urinary tract infections. Potential barriers to appropriate prescribing that may be identified are suboptimal communication between nursing staff and physicians, perceived patient pressure to prescribe antibiotics and lack of local therapeutic guidelines.[1,5,7,8]

Continued Table 1

Intervention selection	The local ward-team and the researchers collaboratively select the definite bundle of interventions. The choice of interventions is unrestricted but inclusion of at least an educational, a structural, an organisational, and a cultural intervention is promoted.[16]	Relevant stakeholders select interventions that suit the opportunities prioritized in phase 4, in collaboration with the researchers.
Intervention planning	Collaboratively plan development, adjustment, and implementation of the selected intervention(s).	Collaboratively plan development, adjustment, and implementation of the selected intervention(s).
Intervention implementation	Collaboratively develop, adjust, and implement interventions. Example: for the ward in the above described example, the bundle may comprise E-learning for physicians and nurses on the therapy of SSIs and the effects of overuse of amoxicillin/clavulanate on resistance (educational intervention), automatic stop orders for antibiotics (structural intervention), rewriting local SSI therapy guidelines and handing out pocket summaries (organisational intervention), and appointing a staff member as antibiotic "champion" who encourages colleagues to prescribe appropriately during regular clinical meetings (cultural intervention).	Collaboratively develop, adjust, and implement interventions. Example: in case of the above described example, stakeholders may decide to implement a protocol for nursing staff to improve communication with physicians about symptoms of urinary tract infections, physician training in coping with external pressure, and physician-pharmacist meetings aimed at developing therapeutic guidelines applicable to the local setting.
Data collection	Ongoing point-prevalence surveys of antimicrobial appropriateness (see phase 2) combined with frequent contacts with each local ward team.	Data collection (see phase 2) is repeated, combined with a questionnaire survey on perceptions of the activities that occurred in phase 3 to 7.
Evaluation	Evaluate the effectiveness of the selecting interventions by using phase 8 data. Adjust the intervention bundle where necessary (repeat the procedure from phase 6 to 9). If the desired effect is not achieved according to both the researchers and the ward (*for example: there are continued signs of inappropriate amoxicillin/clavulanate use*), repeat the PAR procedure starting at phase 4 (the researchers will be involved in at least one repeated cycle if needed).	Evaluate the effectiveness of the selected interventions by comparing pre- and post-intervention data. In case of the above described example, the selected interventions are judged successful if the level of inappropriate prescribing for urinary tract infections has decreased to an acceptable level (as determined collaboratively by researchers and relevant stakeholders based on the literature and overall findings in the facilities participating in the study). Report the results to each facility, which allows them to reflect on their and other facilities' performance. Where necessary, adjust interventions or develop new interventions, in which case the PAR procedure is repeated starting at phase 4 (by the relevant stakeholders themselves; researchers are involved in the PAR cycle up to this point).

First experiences with PAR in antimicrobial stewardship

Examples of interventions selected in the PAR process in acute care settings (DUMAS project) include interactive education of physicians, guideline optimization, optimization of guideline accessibility, E-learning, work process restructuring and publicity campaigns on guideline importance. The selected intervention types differed by medical specialty and ward, due to the identification of different barriers and variable preferences. For example, ear – nose – throat

surgeons preferred the development of a concise pocket guideline card with the most common infections in their practice, whereas internists preferred education and a comprehensive guideline app for smartphones. In long-term care settings (IMPACT project), examples of selected interventions include optimization of local therapeutic guidelines, optimization of diagnostic protocols, physician education, nursing staff education, the development of standardized checklists on which the nursing staff register signs and symptoms of infections, and taking routine urine cultures to determine local resistance patterns. The selected intervention types differed by long-term care facility, and if similar intervention types were selected the focus often differed (e.g. optimizing diagnostic protocols for urinary tract infections in one facility and for respiratory tract infections in another).

In both projects, several participants expressed their appreciation of being involved in the development and implementation of the antimicrobial stewardship programme. A surgeon participating in the DUMAS project stated: 'the approach appeals to me because people are more involved instead of getting an assignment. I think that giving people the initiative will lead to more effect. New projects are generally critically received because we are already overloaded with things we must do, and people can be rigid, making change difficult. So they will love being in charge themselves.' Regarding the multidisciplinary nature of the approach, DUMAS participants indicated that this intensifies and improves mutual understanding and collaboration between different medical specialties. For example, the approach enables infectious disease consultants to better promote appropriate prescribing across hospital wards ('management by walking around'). The appeal of the PAR approach is also reflected in the high participation rate of the IMPACT project: 11 of 12 invited nursing homes wanted to participate in the project. A general practitioner stated: 'The thing I like about IMPACT is that you do not only get insight into how you are doing [with regard to antibiotic pre- scribing], you can also actually do something about it, and you can decide with all those involved what should be good to do.'

A challenge experienced throughout the PAR process in both projects is time pressure on relevant stakeholders. As the involvement of relevant stakeholders is crucial for the process, it is important to prioritize intervention development and implementation by first focusing on the most important barriers to be addressed. It can also be challenging to keep relevant stakeholders motivated and involved. Two important conditions are needed to achieve this. First, regular contact between the researcher and relevant stakeholders ensures that relevant stakeholders remain well informed about the antimicrobial stewardship programme development process, and in turn that researchers remain well informed about local practice. The second condition is the appointment of a 'champion', a stakeholder who promotes exemplary prescribing behaviour and is responsible for ensuring involvement of colleagues in the PAR process.

Discussion

We propose PAR as a new approach to the development of anti- microbial stewardship programmes in local healthcare settings. This approach systematically analyses and accounts for the many contextual, cultural and behavioural factors involved in local antimicrobial prescribing, to optimize intervention effective- ness. We show how a PAR design has been applied to antimicrobial stewardship using the example of two Dutch multicentre antimicrobial stewardship projects, in the hospital setting (DUMAS) and long-term care setting (IMPACT), respectively. Key to these projects is the participation of physicians, nursing staff and other relevant stakeholders, who are motivated for and actively involved in changing their own practice.

The first experiences of the DUMAS and IMPACT projects show that the selected intervention types differ between care settings (acute care versus long-term care) but also within care settings (e.g. between different locations or departments), which strengthens the assumption that complex clinical settings need a tailored approach to antimicrobial stewardship programme development rather than a 'one size fits all' approach. Some differences between and within care settings may be attributed to variation in patient population. For example, in the acute care set- ting, appropriate antimicrobial prescribing may be more challenging in the intensive care unit or the emergency department as there may be insufficient time to check local guidelines in urgent situations.[35 – 37] In long-term care facilities, decision making on antimicrobial prescribing is different for residents with limited life expectancy, where medical considerations are often accompanied by ethical and legal considerations.[38] Other differences between and within care settings may be attributed to practical considerations. For example, availability of diagnostic resources in long-term care facilities is limited compared with acute care settings.[6,7] Practical considerations may play an even more important role in low-income countries, where resources may be scarce (e.g. limited access to web-based interventions or diagnostic resources). PAR does not depend upon the availability of specific interventions, and accounts for diversity in local facilitators and barriers. Therefore, we expect this approach to be broadly applicable to antimicrobial stewardship in a wide variety of local settings.

The applicability of PAR to antimicrobial stewardship programmes depends on the motivation and involvement of relevant stakeholders. Our first experiences indicate that this can be sup- ported by ensuring close collaboration between researchers and local stakeholders, and the appointment of an exemplary relevant stakeholder as 'champion'. In addition, participants in the DUMAS and IMPACT projects indicated that the collaborative nature of PAR results in greater engagement compared with top-down approaches. Indeed, top-down approaches can result in prescribers' resistance to antimicrobial stewardship programmes, explained by some as due to perceived threat to physicians' autonomy.[39]

A concern of the applicability of PAR in antimicrobial steward- ship is that the involvement of physicians, nursing staff and other relevant stakeholders in intervention selection and development

may lead to the selection of the easiest, least invasive and there- fore possibly least effective interventions. This is in line with several studies showing that interventions directed at behaviour or attitudes are difficult to implement, whereas these are generally more effective in changing clinical practice.[40,41] However, first addressing facilitators, barriers and opportunities with regard to appropriate antimicrobial prescribing, and selecting interventions thereafter, encourages the selection of interventions that take these facilitators and barriers into account. In addition, we believe that confronting participants with their prescribing behaviour motivates increased effort to improve, especially in these times of increasing transparency of healthcare quality.

A limitation of the PAR approach is that it does not enable the determination of which interventions in a bundle are (the most) effective and which are not, because it is the approach as a whole that is evaluated rather than its individual components. Nevertheless, the aim of PAR in the context of antimicrobial stewardship is not to produce successful interventions that are generalizable to other settings, but to produce an antimicrobial stewardship programme that is applicable to an individual setting. Consequently, results of a PAR approach cannot be directly extrapolated to other (local) settings. Nevertheless, the experience of previous PAR in antimicrobial stewardship will yield practical knowledge about specific situations, which may accelerate the application of the methodology in new settings.

In conclusion, we presented two multicentre antimicrobial stewardship projects to show how PAR can be applied to antimicrobial stewardship in different healthcare settings. This approach includes an analysis of determinants of complex problems in local, multidisciplinary situations to generate tailor-made solutions. Based on the literature and first experiences of the projects, PAR is a new and promising approach in the challenging field of changing physician behaviour in antimicrobial prescribing.

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The study was performed from October 1, 2011 mber 31, 2015. Seven departments from 2 hospitals partici were surgical, 2 were medical, and 2 were pediatric depa was a 700-bed tertiary care medical center with salari ospital 2 was a 550-bed teaching general medical cent pecialists, both located in Amsterdam, the Netherl iod, hospital 1 used a pre-existing preauthorizatio f antimicrobials, whereas hospital 2 performed a bial k interventions but only in departments not pating local antibiotic formulary committee selec artments ation based on the need for change (low iateness ar h antimicrobial consumption), for whi esults of 12 e antimicrobial appropriateness and ption measur lable. We then approached depart eads or the depa disease expert with a participa uest. Participation nd we offered no financial c ation. Seven of 8 a al departments agreed to p ; 1 department head ecified reasons. Timing of t of the intervention ph tment was not randomi use of expected availabili nt department stakeh ducation schedules, and pot elays of ethical revie s. Intervention start sequence a wn in eFigure 1 in lement. Our primary outcome v ppropriateness, m 41 C .) a gy p or a od (baseline or intervention). Data were collec out assessments were performed retrospectively to enable f the following antimicrobial prescription factors was assess ness: indication, choice of antimicrobial, dosage, admini d duration. A prescription was only deemed to be appr f the following criteria applied for each of the above facto eline adherence or guideline deviation or no guideline b nal reasons, as judged by the assessing infectious diseases ology specialist,

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Behavioral Approach to Appropriate Antimicrobial Prescribing in Hospitals: The Dutch Unique Method for Antimicrobial Stewardship (DUMAS) Participatory Intervention Study

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design and implement an intervention approach to improve appropriateness of hospital antimicrobial prescribing for all indications. Our approach was inspired by the participatory action research paradigm,28 which focuses on collaboration and empowerment of the stakeholders in the change process and is effective in other complex health care situations.28 In our approach, prescribers were invited to choose and co-develop 1 or more interventions to improve their own prescribing, whereby they were stimulated to base their choice on conclusions of a prior root cause analysis of their prescribing patterns. The approach is therefore designed to benefit from tailoring to local determinants7,29- 33 and draws on 3 behavioral principles: (1) respect for the prescribers' autonomy to avoid feelings of resistance11- 19; (2) the inclination of people to value a product higher and feel more ownership for New projects

Abstract

Importance: Inappropriate antimicrobial prescribing leads to antimicrobial resistance and suboptimal clinical outcomes. Changing antimicrobial prescribing is a complex behavioral process that is not often taken into account in antimicrobial stewardship programs.

Objective: To examine whether an antimicrobial stewardship approach grounded in behavioral theory and focusing on preserving prescriber autonomy and participation is effective in improving appropriateness of antimicrobial prescribing in hospitals.

Design, Setting, and Participants: The Dutch Unique Method for Antimicrobial Stewardship (DUMAS) study was a prospective, stepped-wedge, participatory intervention study performed from October 1, 2011, through December 31, 2015. Outcomes were measured during a baseline period of 16 months and an intervention period of 12 months. The study was performed at 7 clinical departments (2 medical, 3 surgical, and 2 pediatric) in a tertiary care medical center and a general teaching hospital in the Netherlands. Physicians prescribing systemic antimicrobial drugs for any indication for patients admitted to the participating departments during the study period were included in the study.

Interventions: We offered prescribers a free choice of how to improve their antimicrobial prescribing. Prescribers were stimulated to choose interventions with higher potential for success based on a root cause analysis of inappropriate prescribing.

Main Outcomes and Measures: Appropriateness of antimicrobial prescriptions was determined using a validated approach based on guideline adherence and motivated guideline deviation and measured with repeated point prevalence surveys (6 per year). Appropriateness judgment was masked for the study period. Antimicrobial consumption was extracted from pharmacy records and measured as days of therapy per admission. We used linear and logistic mixed-model regression analysis to model outcomes over time.

Results: A total of 1121 patient cases with 700 antimicrobial prescriptions were assessed during the baseline period and 882 patient cases with 531 antimicrobial prescriptions during the intervention period. The mean antimicrobial appropriateness increased from 64.1% at intervention start to 77.4% at 12-month follow-up (+13.3%; relative risk, 1.17; 95% CI, 1.04-1.27), without a change in slope. No decrease in antimicrobial consumption was found.

Conclusions and Relevance: Use of a behavioral approach preserving prescriber autonomy resulted in an increase in antimicrobial appropriateness sustained for at least 12 months. The approach is inexpensive and could be easily transferable to various health care environments.

Introduction

Appropriate antimicrobial prescribing has significant clinical benefits (ie, reduced mortality) and reduces development of antimicrobial resistance and health care costs.[1,2] Antimicrobial stewardship programs aim to improve antimicrobial prescribing but sometimes fail to acknowledge that improving antimicrobial prescribing actually means changing human behavior.[3,4] Human behavior is not based on a fully rational process but depends on a complex interplay between several behavioral determinants and social norms.[5-10] Despite its rational theoretical foundation, stewardship programs are known to persistently encounter prescriber resistance. This resistance is generated by the tension between the governance of the stewardship team and the autonomy of individual prescribers.[11-19] Behavioral and social theory seem underused in antimicrobial stewardship intervention programs, contrary to more common use in other scientific fields.[3-8,10,20,21] Previous studies[8,22-27] using interventions based on behavioral theory have found promising results in improving antibiotic prescribing. Most of these studies focused on antibiotic prescribing for respiratory tract infections in primary care.

We used behavioral theory to design and implement an intervention approach to improve appropriateness of hospital antimicrobial prescribing for all indications. Our approach was inspired by the participatory action research paradigm,[28] which focuses on collaboration and empowerment of the stakeholders in the change process and is effective in other complex health care situations.[28] In our approach, prescribers were invited to choose and co-develop 1 or more interventions to improve their own prescribing, whereby they were stimulated to base their choice on conclusions of a prior root cause analysis of their prescribing patterns. The approach is therefore designed to benefit from tailoring to local determinants[7,29-33] and draws on 3 behavioral principles: (1) respect for the prescribers' autonomy to avoid feelings of resistance[11-19]; (2) the inclination of people to value a product higher and feel more ownership for it if they made it themselves, which is referred to as the IKEA effect[34-36]; and (3) the tendency of people to follow up on an active and public commitment.[8,37-40] We aimed to test the approach's effectiveness in improving appropriateness of antimicrobial prescribing in hospitals.

Methods

Study design

The Dutch Unique Method for Stewardship (DUMAS) study was a prospective, stepped-wedge, participatory intervention study aimed to improve antimicrobial prescribing. The institutional medical ethics review boards of the VU University Medical Center, Amsterdam, the Netherlands, and OLVG, Amsterdam, the Netherlands, approved all study procedures and waived informed consent for patients.

Setting

The study was performed from October 1, 2011, through December 31, 2015. Seven departments from 2 hospitals participated, of which 3 were surgical, 2 were medical, and 2 were pediatric departments. Hospital 1 was a 700-bed tertiary care medical center with salaried specialists, and hospital 2 was a 550-bed teaching general medical center with self-employed specialists, both located in Amsterdam, the Netherlands. During the study period, hospital 1 used a pre-existing preauthorization system for broad-spectrum antimicrobials, whereas hospital 2 performed antimicrobial audit and feedback interventions but only in departments not participating in the study.

Enrollment

The local antibiotic formulary committee selected departments for study participation based on the need for change (low appropriateness and moderate to high antimicrobial consumption), for which the results of 12 months of baseline antimicrobial appropriateness and consumption measurements were available. We then approached department heads or the department's infectious disease expert with a participation request. Participation was voluntary, and we offered no financial compensation. Seven of 8 approached medical departments agreed to participate; 1 department head refused for unspecified reasons. Timing of the start of the intervention phase for each department was not randomized because of expected availability issues of relevant department stakeholders, education schedules, and potential approval delays of ethical review boards. Intervention start sequence and timing are shown in eFigure 1 in the Supplement.

Outcome measures

Our primary outcome was antimicrobial appropriateness, measured with a validated appropriateness assessment instrument.[41] One of 3 infectious diseases specialists (including M.A.v.A. and E.J.G.P.) assessed the adult prescriptions, and 1 of 3 infectious diseases/immunology pediatricians (including M.v.d.K.) assessed the pediatric prescriptions for appropriateness. They were masked for clinical outcomes and study period (baseline or intervention). Data were collected prospectively, but assessments were performed retrospectively to enable masking. Each of the following antimicrobial prescription factors was assessed for appropriateness: indication, choice of antimicrobial, dosage, administration route, and duration. A prescription was only deemed to be appropriate if one of the following criteria applied for each of the above factors: complete guideline adherence or guideline deviation or no guideline but based on rational reasons, as judged by the assessing infectious diseases specialist, immunology specialist, or pediatrician. Rationality was defined as an effective antimicrobial regimen that covered relevant pathogens without being excessive (ie, unnecessary combination therapy or broad spectrum when a more narrow spectrum is available). If present, drug allergies, oral intake, and previous culture results were taken into account. Cases that could not be assessed because of missing information were excluded. We notified clinical staff of both hospitals by email before the start of the baseline measurements.

Antimicrobial consumption was a secondary outcome, reported in days of therapy per 100 admissions per month. Antimicrobial appropriateness and consumption measurements only included prescriptions with Anatomical Therapeutic Chemical codes beginning with J01, J02, J04AB02, and J05AB.[42] Other outcomes were changes in specific appropriateness categories, intravenous antimicrobial consumption, consumption of specific antimicrobial subgroups, and length of hospital stay.

Data collection

Antimicrobial appropriateness was measured through point prevalence surveys at a rate of 6 times per year. Local antimicrobial stewardship teams performed the surveys as part of standard quality measurements. All team members were trained and supervised by the coordinating investigator (J.J.S.) using standard operating procedure documents. An antimicrobial case was included in the survey if the patient was admitted to a clinical ward of a participating department and had a prescription for a systemic antimicrobial agent at 0.00 hours on the day of the survey. Relevant clinical data needed for assessment, including prescription indication and reasons for guideline deviations, were collected by contacting the responsible ward physician or were retrieved from medical files. Antimicrobials prescribed for prokinetic reasons (erythromycin) were excluded. Data were then coded and stripped from any identifying information. To prevent anticipatory behavior, we did not notify the clinical wards of the exact survey dates.

Data on antimicrobial consumption, admission rates, admission diagnoses, and length of stay were derived from pharmacy systems and administrative records. Only data on patients with a length of stay of at least 24 hours were included. Two pediatric critical care units were not included because of lack of electronic data. Baseline and intervention periods were at least 12 months, but more data were collected whenever possible.

Root cause analysis

An analysis of local root causes of inappropriate prescribing was performed after 12 months of baseline measurements for the baseline phase of each department separately. The analysis was based on interviews of a purposive sample of department members. Sample size depended on department size but included at least 2 medical specialists, 2 junior physicians, and 2 nurses per department. Interviews were audio recorded. The interviewer (J.J.S.) was a psychologist and physician trained in qualitative research. Interviewees supplied written informed consent before the interview start. The interviews were guided by a topic list that consisted of standard questions that focused on the cause categories of the Eindhoven Classification Model: technical, organizational, human, and patient (see eTable 1 in the Supplement for a translated topic list).[43,44] The interviewer asked additional questions on potential causes for inappropriate prescribing using the 5 whys method, which entails repeatedly asking for a cause underlying each cause of a certain event as supplied by the interviewee.[45] For additional validity, the conclusions of the analysis were discussed with department members during the intervention approach.

Intervention approach

Figure 1 summarizes the intervention approach. The approach was performed for each department separately and started with a plenary introduction and discussion with department physicians. Participation was voluntary for each department and physician. Department members were stimulated to choose interventions with higher potential for success based on the root cause analysis, which would result in one set of interventions per department. Intervention choice was not predefined, was free, and was only restricted by practical feasibility. Essential to the approach was the appointment of 1 or more antibiotic ambassadors chosen by their peers, which defined the start of the intervention period. We also informed nurses from each department of the baseline results. The ambassador team contained at least 1 medical specialist per department, but participation of junior physicians, nurses, and quality-of-care personnel was encouraged. Department ambassadors were asked to represent their department during subsequent intervention discussions, to champion good antibiotic policy and the chosen interventions,[3,29] and to help develop and implement the interventions. Support and involvement of study personnel with each department's intervention approach were determined by the preferences of the antibiotic ambassador(s) and limited to a maximum of 12 months after the start of the intervention period.

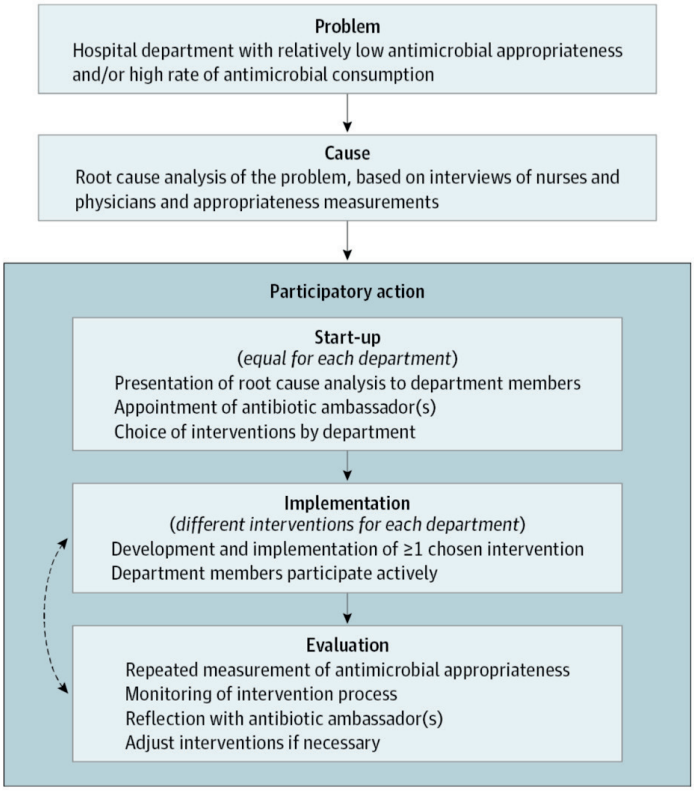

Figure 1
Intervention approach used in the study

Statistical analysis

We used logistic mixed regression analysis to model antimicrobial appropriateness time trajectories and linear mixed regression analysis to model monthly antimicrobial consumption and length-of-stay time trajectories. Each model contained the fixed-effects variables of time, study period, and the interaction term, which allowed the baseline period to function as control for the intervention period. The intervention period was considered to have started with the first plenary department meeting. Odds ratios were converted to relative risks for better interpretability.[46] We included random effects for department and clinical ward in each model. Antimicrobial consumption analyses contained a random effect for month of the year to account for season effects. All continuous outcomes were log transformed before analysis. To be able to report outcomes on the original scale of measurement, we calculated predicted means per time point, which were then back-transformed in case of continuous outcomes. Regression coefficients from these models were back transformed and then transformed to change percentages for optimal interpretability.

The CIs were calculated with 10 000 bootstraps while accounting for the clustered nature of the data. Significance level was .05 (2-sided). Main analyses were limited to the period when data were available for all departments: 16 months before and 12 months after the start of the intervention period.

We performed a sensitivity analysis for both primary outcomes: a mixed-model analysis with only study period as the fixed effect, ignoring slopes. We performed the analyses of the antimicrobial appropriateness and consumption subgroups using the same single fixed-effect method because we assumed time trend estimations were more vulnerable to chance events in these small groups. We used R statistical software, version 3.2.3 with package lme4, version 1.1-11, for all analyses (R Development Core Team).

Results

Population and point prevalence survey characteristics

There were 21 306 clinical admissions during the baseline period and 15 394 clinical admission during the intervention period. The appropriateness surveys included 1121 patients during the baseline period and 882 patients during the intervention period. Detailed characteristics are given in Table 1.

Table 1
Patient and Point Prevalence Survey Characteristics During the Baseline (16 Months) and Intervention Periods (12 Months)[a]

	Baseline period	Intervention period
Number of patients admitted to participating departments (range of totals per department)	21 306 (726 to 7 501)	15 934 (505 to 5 741)
Number of patients included in point-prevalence surveys	1 121	882
- with at least 1 antimicrobial prescription (%)	459 (40.9)	346 (39.2)
Prescriptions in point-prevalence surveys	700	531
Exclusion due to incomplete information or used as prokinetic (%)	12 (1.7)	7 (1.3)
Prophylactic indication (%)	114 (16.6)	67 (12.8)
- medical (%)	84 (12.2)	47 (9.0)
- surgical (%)	30 (4.4)	20 (3.8)
Therapeutic indication (%)	574 (83.5)	456 (87.2)
- respiratory infection (%)	143 (24.9)	145 (31.8)
- urinary tract infection (%)	32 (5.6)	35 (7.7)
- soft tissue infection (%)	79 (13.8)	59 (12.9)
- intra-abdominal infection (%)	48 (8.4)	54 (11.8)
- intravascular infection (%)	19 (3.3)	20 (4.4)
- sepsis due to other cause (%)	146 (25.4)	76 (16.7)
- other indication (%)	107 (18.6)	67 (14.7)

[a] Data are presented as number (percentage) of patients unless otherwise indicated

Root cause analyses and chosen interventions

The root cause analyses identified causes in 4 themes: physician (eg, lack of knowledge), culture (eg, rejection of interference), organization (eg, infectious diseases experts set wrong example), and guidelines (eg, hard to find and use). Between 2 and 4 interventions per department were chosen, each connected to 1 or 2 of the above themes; for example, participatory education sessions (physician and culture), presence of infectious diseases physicians during ward round (organization), and guideline revision (guidelines). Detailed characteristics are given in Figure 2 and eTable 1 in the Supplement. Time from the first plenary meeting to the implementation of the first intervention varied between immediate (supervisors' promise to improve) to 6 months for the first pediatrics department, where the antibiotic ambassadors team was formed 4 months after the plenary meeting because of logistical problems.

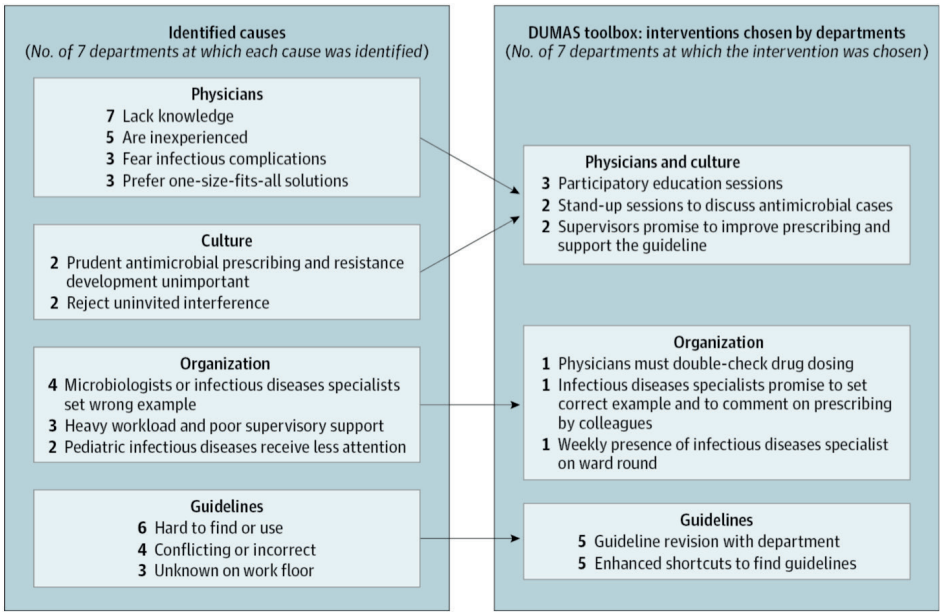

Figure 2
Summary of the Root Cause Analyses and Interventions Chosen by the Departments to Improve Their Prescribing. DUMAS indicates Dutch Unique Method for Antimicrobial Stewardship.

Antimicrobial appropriateness

The intervention approach was associated with a significant 13.3% (95% CI, 64.1%-77.4%) increase in antimicrobial appropriateness (relative risk, 1.17; 95% CI, 1.04-1.27), without any significant changes in time trends (Figure 3A). Results of the analyses per appropriateness subgroup are given in Table 2 and per department in eFigure 2 and eTable 2 in the Supplement.

A, Antimicrobial appropriateness relative to the start of the intervention phase and logistic mixed-model regression analysis. Mean antimicrobial appropriateness increased 13.3%, from 64.1% at intervention start to 77.4% at 12-month follow-up. B, Antimicrobial consumption in days of therapy per admission relative to the start of the intervention phase and logistic mixed-model regression analysis. Points represent results from the point prevalence surveys; lines, predicted means from the regression analysis; and shaded area, 95% CIs around these predicted means. RR indicates relative risk.

[a] The RR was significantly different from 1 at the .05 level.

Antimicrobial consumption

Antimicrobial consumption did not decrease significantly during the intervention phase, and there were no changes in time trends (Figure 3B). Results of the analyses per antimicrobial drug group are given in Table 2 and per department in eTable 2 in the Supplement.

Figure 3
Antimicrobial Appropriateness and Consumption

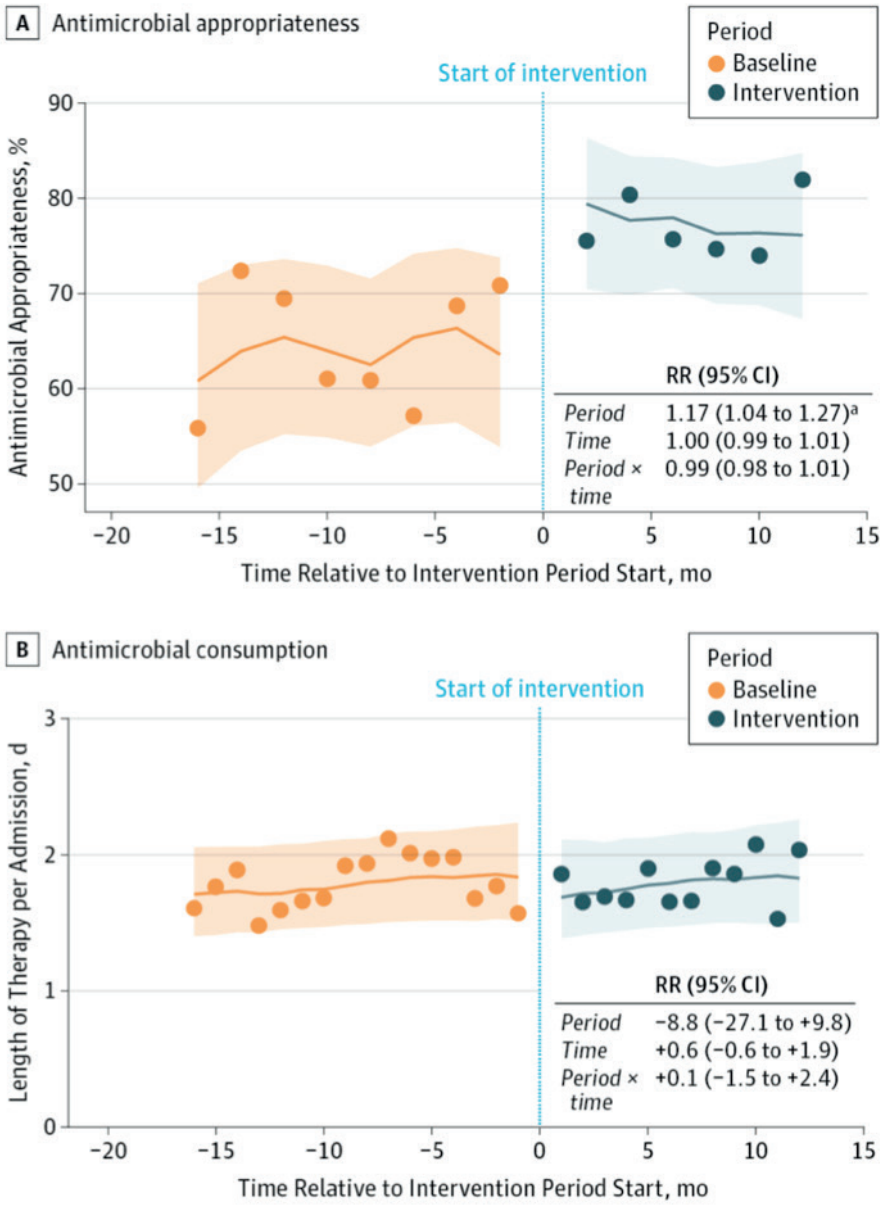

Table 2
Point Prevalence Survey Outcomes During Baseline (16 Months) and Intervention Periods (12 Months)

	Total Within Period, %			
Outcome	**Baseline period**	**Intervention period**	**Absolute difference**	**RR for appropriateness (95% CI)**
Appropriate overall	64.1	77.4	+13.3	1.16 (1.11 to 1.23)
Inappropriate, per category:				
- antimicrobial unnecessary	6.6	1.5	-5.2	0.24 (0.08 to 0.45)
- inappropriate choice	11.2	8.0	-3.2	0.62 (0.42 to 0.90)
- inappropriate dose	11.4	6.1	-5.4	0.56 (0.35 to 0.80)
- inappropriate administration	1.8	2.0	+0.2	1.19 (0.43 to 2.57)
- excessive duration	4.4	4.9	+0.5	1.11 (0.64 to 1.83)
Antimicrobial consumption in days of therapy/admission	baseline period	intervention period	absolute difference	relative difference, % (95% CI)
Overall	2.00	2.02	+0.03	+1.2 (-14.7 to +19.9)
- intravenous only	1.21	1.28	+0.07	+5.8 (-8.4 to +22.7)
By antimicrobial group:				
- penicillin without BL inhibitor	0.38	0.41	+0.03	+8.4 (-13.8 to +36.6)
- penicillin with BL inhibitor	0.50	0.37	-0.13	-26.3 (-41.1 to -8.4)
- cephalosporin (1st or 2nd gen.)	0.01	0.01	-0.00	-15 (-56.5 to +66.5)
- cephalosporin (3rd gen.)	0.25	0.31	+0.06	+22.7 (+4.8 to +43.2)
- carbapenem	0.00	0.01	+0.00	+24.2 (-74.8 to +519.1)
- quinolone	0.09	0.07	-0.02	-22.8 (-49.3 to +17.3)
- clindamycin	0.01	0.01	-0.00	-11.8 (-51.8 to +62.4)
- aminoglycoside	0.03	0.03	-0.00	-12.3 (-49.7 to +51.1)
- trimethoprim +- sulphonamide	0.02	0.02	+0.00	+11.2 (-47.8 to +137)
- other antibiotic	0.21	0.24	+0.02	+11.8 (-22.6 to +59.9)
- antifungal or antiviral	0.05	0.02	-0.03	-57.2 (-81.3 to -1.6)

Abbreviations: CI, confidence interval; BL, betalactamase; gen., generation; RR, relative risk.

Other results

Length of hospital stay did not change relative to the start of the intervention approach (eFigure 3 in the Supplement). The single fixed-effect sensitivity analysis supported the primary analysis showing similar results (Table 2).

Discussion

To our knowledge, this is the first hospital antimicrobial stewardship study grounded in behavioral science and allowing physicians a free choice in how to improve their own prescribing.[28] In our

multicenter study in 7 departments divided between 2 hospitals (a teaching and an academic hospital), we found that our approach was associated with a significant 13.3% increase in antimicrobial appropriateness during a period of 12 months after the intervention start. We found no reduction in antimicrobial consumption.

We believe the observed increase in antimicrobial appropriateness is clinically relevant because our definition of appropriateness specifically focused on unwanted prescriptions from a stewardship point of view. Attainment of underlying goals, such as empirical therapy according to guidelines and de-escalation of therapy improves mortality and other clinical outcomes.[2] The potential drawback of such a method is that it is based on expert opinion. However, in a recent validation study,[41] the used appropriateness instrument had 80% agreement with a reference standard that consisted of the modal assessment of 15 medical specialists (infectious diseases specialists and clinical microbiologists). Of importance, the persistence of the effect during the relatively long follow-up period of 12 months suggests good sustainability.[20,47] The trend back to baseline in Figure 3 is suggestive but too small and the CI is too wide to interpret this as such. The true effect of our approach can be estimated by extrapolating the results from our point prevalence surveys to all antimicrobial days of therapy prescribed at participating departments during the first 12 months of the intervention period (37 046 days). This would mean that the 13.3% increase in appropriateness equaled 4927 improved days of therapy.

Our study design incorporated an extensive number of repeated measurements, which allowed us to control intervention effects for baseline levels and trajectories. This way we could discern between the effects of our intervention approach and previous events or interventions. By starting the intervention approach at a different time for each department (stepped-wedge design), we minimized the chance that the overall effect was influenced by external events (eg, national campaigns for prudent antimicrobial use).

The effectiveness of our approach is explained by the advantages of using methods from behavioral science. We hypothesize that participating department members felt relatively nonthreatened by our approach because of their freedom in choosing a personal solution, which is an important theme in antimicrobial stewardship.[11- 17,19] Moreover, by committing to the project and choosing and developing their own intervention set, they may have felt more inclined to support the project and change their own prescribing behavior.[8,34- 40] This may have been an important intervention in itself. Finally, giving prescribers a free intervention choice could have led to them choosing an easy way out, for instance, choosing education as the only intervention. However, because our approach incorporated a root causes analysis of prescribing, a recommended strategy in stewardship,[7,30- 33] prescribers were gently nudged toward using interventions that were likely to be more effective.[48] An approach similar to ours has been unsuccessful in improving antimicrobial prescribing in nursing homes.[49] However, among other differences, that study used a predetermined list of possible interventions, which may have limited prescribers' feeling of freedom and diminished support of the aforementioned IKEA effect.[34- 36]

We found no reduction of antimicrobial consumption in our study. This finding may reflect that overall antimicrobial use is a nonspecific measure without information on appropriateness of therapy. Moreover, an increase in antimicrobial prescribing quality can be reached without a reduction in days of therapy, for instance, by increasing streamlining, better dosing, and using more narrow-spectrum therapy empirically (Table 2).[2] In line with this, we found a significant 26% reduction in the consumption of penicillins with β-lactamase inhibitors, which was the most prescribed type of antibiotic in our population. Alternatively, that finding could suggest that prescribers find it harder to stop or refrain from starting than to narrow antibiotic prescribing because these situations may be more dependent on individual clinical reasoning than on evidence-based guidelines.

The patient safety of our approach was based on the preserved full autonomy of prescribers at all times during the study, which would make a worsening of patient safety unlikely. Our focus on appropriateness had the advantage that it stimulated adherence to multidisciplinary and generally evidence-based guidelines, even when this would lead to more instead of fewer days of therapy. The absence of an increase in length of hospital stay can be seen as circumstantial evidence in this regard.

Limitations and strengths

Our study has limitations. First, prescribers' awareness of being monitored could have led to a change in behavior (Hawthorne effect). Because they were informed of the study before the start of the baseline measurements, this could have led to diminished intervention effects. Of importance, the department received even more attention from the research team during the start of the intervention phase; thus, the Hawthorne effect would then be even bigger. However, this behavioral phenomenon (ie, personal attention for commitment leads to behavioral change) is in fact a feature not a bug of the intervention approach mechanism.

Second, the stepped-wedge enrollment order was nonrandomized because the approach was dependent on practical circumstances, such as department preferences, room in the educational roster, or availability of department heads and opinion leaders. We believed that adapting to these circumstances superseded the advantages of randomization, especially because this adaption will also be necessary when implementing our approach in practice. Still, although we found no evidence of this, departments could have stalled their participation in the study until they improved their antibiotic prescribing on their own just before intervention start.

Third, the earlier validation study of the antimicrobial appropriateness method was limited to prescriptions for adult patients. However, there was no procedural difference with the method used for the assessment of pediatric prescriptions.

Fourth, execution of our approach in one pediatric department was less fluent, with delayed implementation of some interventions. This was caused by time constraints of the antibiotic

ambassador and the department's extensive size. The local effect of the approach on appropriateness mirrored this (eTable 2 in the Supplement), perhaps reflecting the importance of the ambassador on the effect.

Fifth, the Dutch health care system differs from other systems, which may limit generalizability. However, our results were achieved regardless of specialists' payment structure because we included both salaried (hospital 1) and self-employed specialists (hospital 2).

Sixth, a potential weakness of a stepped-wedge design is contamination of the intervention; thus, information or effects of departments in the intervention period could have influenced departments still in the baseline period. Although this effect cannot be excluded, to our knowledge, there were no physicians who transferred between participating departments in this period.

Our approach offers good potential for implementation in other hospitals, even in resource-challenged circumstances, because it adapts to local possibilities, requires no expensive investments, and is successful in surgical, medical, and pediatric settings. The root cause analysis method was relatively simple and pragmatic and was performed without help from quality improvement personnel. Our study was performed with a minimal budget, comprising the salary of 1 research physician and an estimated 3 hours per week of infectious diseases specialist efforts for 3 years. Of importance, for practical implementation without research objectives, many (but not all) of our time-consuming appropriateness measurements may then be omitted. On the other hand, a bigger financial budget may increase effectiveness because more expensive desired interventions, such as mobile applications, could then be implemented.

Conclusions

Use of a participatory approach based on behavioral theory with a central focus on prescriber autonomy resulted in an increase in antimicrobial appropriateness sustained for at least 12 months. The approach is unique, inexpensive, and suited to different types of hospital departments.

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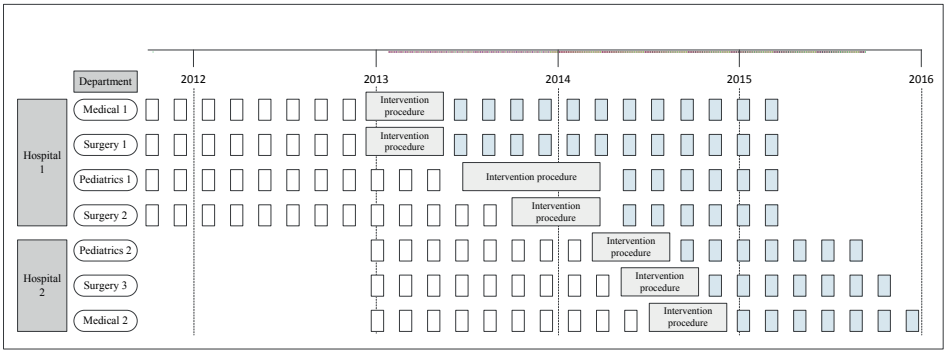
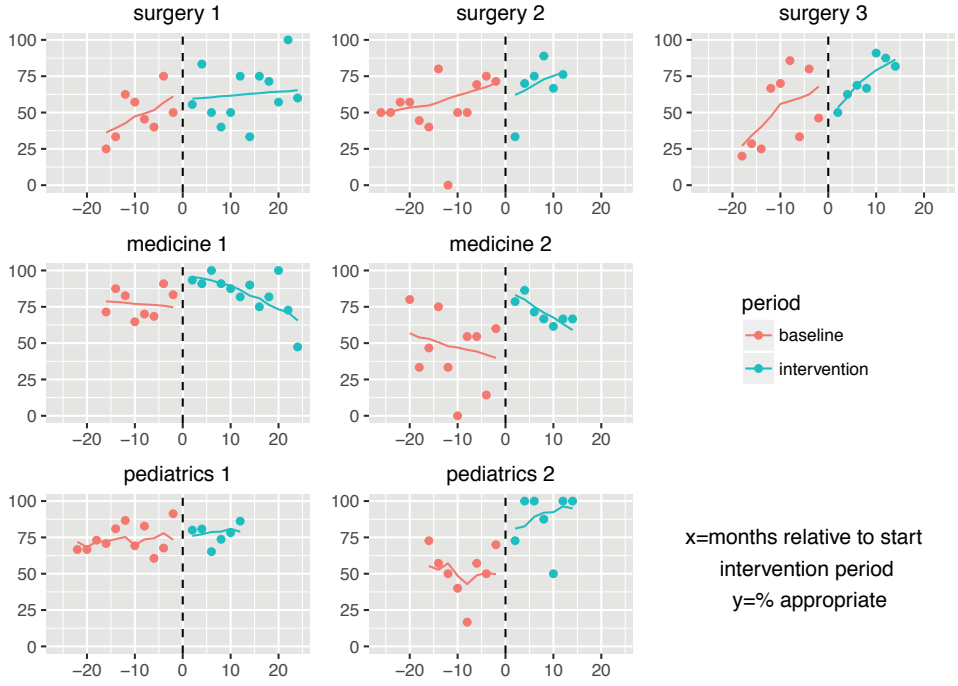
Supplement

eFigure 1
Schematic overview of DUMAS-study department-enrollment order and timing. Grey boxes represent the period starting with the first plenary session and ending with the installment of the local antibiotic ambassadors.

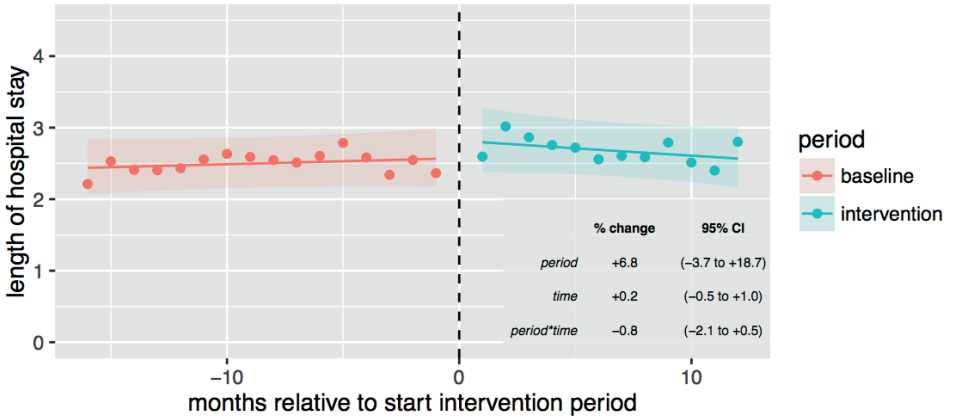


eFigure 2
Antimicrobial appropriateness relative to start of the intervention phase per department with all available data.



Points represent results from the point-prevalence surveys, and lines represent predicted means from the regression analysis.

eFigure 3
Length of hospital stay in days of therapy relative to start of the intervention phase per department and linear mixed regression analysis.



Points represent uncorrected data, and lines represent predicted means from the regression analysis.

eTable 1
Interview guide (translated from the original Dutch version)

Introduction:
The goal of this interview is to perform a root cause analysis and to discuss ideas for interventions to improve antimicrobial use. This interview is voluntary and everything discussed will be used while preserving your anonimity. It is possible that we use fragments of this interview in the future plenary discussion, or in scientific publications, but this will be done without using your name or in any way that the statements can be redirected to you. This interview will be audiorecorded. Do you consent to participate according to these conditions?
[if the interviewee mentions a reason/cause for suboptimal antimicrobial use, keep on questioning (5x why) for underlying causes until the interviewee cannot continue naming another underlying cause]
General questions:
1. What is your opinion on the clinical antimicrobial use within your department? What goes well, what can be improved? if suboptimal situations are mentioned-> are these systematic or incidental? Can you relate these to technical (i.e. elektronic prescription system down-time), organizational (i.e. local rules, guidelines, training of new staff, management priorities, culture, etc), human (knowledge, competence), or patient related factors? Are there any differences to other departments, for instance department (name other surgery/medicine department)
2. How do physicians on your department usually choose the right antimicrobial drug? What is your experience of working with external consultants (ID physicians, clinical microbiologists)? What is their influence? Do you notice any difference between thee advices of these specialties? Do you undergo training in antimicrobial prescribing?
3. Is there any situation or antimicrobial drug indication that you find especially difficult?
4. How important is the prevention of development of antimicrobial resistance for you when considering antimicrobial prescribing?
5. What is your opinion of the hospital antimicrobial guideline-system? Which version do you use, on paper or the digital version? How can the system and the guidelines be improved?

Continued eTable 1

Results of your department
The baseline measurement of the DUMAS study shows that your department's antimicrobial appropriateness is xx%. Most inappropriate prescriptions where for indication X/ deviated from appropriate use because they were too long/ too much IV / no streamlining etc. (include department-specific information). For instance: (name at least 5 examples of frequent inappropriate prescriptions).
What is your first reaction to these findings?
What is your explanation? (discuss each type of frequent inappropriate prescription and use 5xWhy)

Improvement?
1. What is in your opinion the best way to improve antimicrobial prescribing in this hospital? And for your department? What is your personal role in this? Is your department different from other departments? Which interventions to improve antimicrobial use would you like for your department?
2. On a scale of 1 (not confident at all) to 10 (totally confident), how confident are usually you of prescribing an appropriate antimicrobial prescription?
3. Any remaining questions, topics for discussion or advice?

eTable 2
Results of the root cause analysis and chosen interventions

Department	Baseline appropriateness	Intervention period appropriateness	Main problems	Identified causes	Interventions
Surgery 1	48%	60%	Unnecessary and/or prolonged treatment and prophylaxis with amoxicillin-clavulanate for soft tissue infections. No/late IV-oral switch.	Fear for post-surgical complications. Physicians seldom encounter clinical problems caused by antimicrobial resistance, therefore low priority for prudent antimicrobial use. Residents consider clinical ward work less important. Automatic prescribing habits make work easier (one-size-fits-all)	Physician-led revision of guidelines followed by presentation of new guideline. Weekly stand-up sessions (nurses & physicians) to discuss resident-generated iv-oral switch reports (for four months).
Surgery 2	60%	73%	Prolonged IV treatment with broad-spectrum antibiotics for complicated soft tissue infections. Antibiotic choice deviated from guidelines.	Inexperienced residents facing complicated infections with relatively low availability of supervisory support. Supervisors do not know or support use of hospital guideline.	Infectious disease specialist presence during weekly grand ward round (continuous). Improvement of digital guideline availability.
Surgery 3	53%	70%	Inappropriate antibiotic choice & duration for various indications. No/late IV-oral switch and streamlining.	Guidelines unknown and hard to find. Consulting microbiologists set wrong example by deviating from guidelines.	Creation of top 10 of antimicrobial prescription indications, followed by place links to the corresponding guidelines on the department homepage. Education session on antibiotic use by microbiologist.
Medicine 1	77%	91%	Inappropriate antibiotic choice for respiratory and soft tissue infections. Prolonged treatment for various infections. Late IV-oral switch.	Guidelines not user-friendly and hard to find. Infectious disease specialists set wrong example by deviating from guidelines. Nurses and physicians not familiar with advantages and prerequisites of early IV-oral switch.	Guideline revisions. Infectious disease specialists promise to give correct example and to comment on prescribing of colleagues. Daily stand-up sessions (nurses & physicians) to discuss resident-generated iv-oral switch reports (for three months). Monthly education sessions on resident-generated antibiotic subjects (continuous).

Continued eTable 2

Medicine 2	49%	75%	Unecessary and/or prolonged broadspectrum treatment of respiratory infections. Late IV-oral switch and inappropriate dosing.	Automatic prescribing habits make work easier. Guideline unclear. Inexperienced residents with relatively low availability of supervisory support due to high work load. Prefer no interference from other specialties.	Guideline revision. Supervisors promise to improve prescribing, increase focus on antibiotics during ward rounds, and adhere to guideline. Improvement of digital guideline availability.
Pediatrics 1	73%	78%	Prolonged post-surgical IV prophylaxis. Inappropriate dosing. Prophylaxis not discontinued during treatment. No deescalation of carbapenems in the presence of culture results.	Large department with many subspecialties without uniform policies. Fear for complications with immunocompromised patients and post-surgery. Prefer no interference from other specialties. Pediatric policy gets relative scarce attention in hospital antibiotic committee.	Double physician check of all drug prescriptions. Physician-led guideline revision (not yet finished at study end). Deal with pediatric surgeon on reducing post-surgical prophylaxis.
Pediatrics 2	51%	86%	Unnecessary combination therapy for neonatal infections. Inappropriate dosing.	Relatively few attention of infectious diseases and antibiotic guideline committee for pediatrics department and vice versa. No uniformity in supervisors opinions.	Physician-led guideline revision. Supervisors promise to adhere to the new guideline.

Abbreviation: IV, intravenous.

eTable 3
Antimicrobial appropriateness and consumption per department over baseline period (16 months) and intervention periods (per year)

Antimicrobial appropriateness, %	**baseline**	**intervention year 1**	**difference with baseline**	**relative risk for appropriateness**	**95% CI**	**intervention year 2**	**difference with baseline**	**relative risk for appropriateness**	**95% CI**
Surgery 1	48	60	+12	1.20	(0.82 to 1.54)	65	+16	1.28	(0.91 to 1.59)
Surgery 2	64	73	+9	1.13	(0.89 to 1.31)	-	-	-	-
Surgery 3	57	70	+13	1.18	(0.96 to 1.36)	-	-	-	-
Medicine 1	77	91	+14	1.15	(1.05 to 1.23)	75	-2	0.98	(0.80 to 1.10)
Medicine 2	49	75	+25	1.34	(1.14 to 1.53)	-	-	-	-
Pediatrics 1	74	78	+4	1.02	(0.91 to 1.13)	-	-	-	-
Pediatrics 2	51	86	+35	1.43	(1.25 to 1.64)	-	-	-	-
Antimicrobial consumption, days of therapy per admission	**baseline**	**intervention year 1**	**difference with baseline**	**relative difference, %**	**95% CI**	**intervention year 2**	**difference with baseline**	**relative difference, %**	**95% CI**
Surgery 1	1.7	1.5	-0.2	-11.9	(-33.4 to +16.9)	2.1	+0.3	+19.7	(-9.5 to +57.5)
Surgery 2	4.7	3.6	-1.2	-24.5	(-44.9 to +2.7)	-	-	-	-
Surgery 3	0.9	1.0	+0.1	+13.2	(-1.2 to +29.9)	-	-	-	-
Medicine 1	8.7	8.0	-0.7	-7.6	(-28.9 to +20.7)	8.0	-0.6	-7.5	(-28.8 to +19.9)
Medicine 2	1.0	1.3	+0.3	+22.2	(-3.2 to +53.2)	-	-	-	-
Pediatrics 1	4.6	6.4	+1.7	+36.8	(+16.8 to +59.2)	6.3	+1.6	+34.5	(+15.3 to +56.5)
Pediatrics 2	0.9	0.9	-0.1	-6.3	(-18.2 to +7.5)	-	-	-	-

The study was performed from October 1, 2011, through D[illegible] r 31, 2015. Seven departmen[illegible] re surgical, 2 were medical, a[illegible] s a 700-bed tertiary care med[illegible] ital 2 was a 550-bed teaching [illegible] ecialists, both located in Amste[illegible] od, hospital 1 used a pre-existin[illegible] nonlization system for broad-spectrum antimicrobials, whereas hospital [illegible] rmed antimicrobial audit and feedback interventions but only in depa[illegible] s not participating in the study. The local antibiotic formulary comm[illegible] lected departments for study participation based on the need for cha[illegible] y appropriateness and moderate to high antimicrobial consumption), f[illegible] h the results of 12 months of baseline antimicrobial appropriateness [illegible] onsumption measurements were available. We then approached dep[illegible] infectious disease expert with a particip[illegible] y, and we offered no financial co[illegible] l departments agreed to parti[illegible] ed reasons. Timing of the [illegible] t was not randomized be[illegible] artment stakeholders, e[illegible] nedules, and poten[illegible] ethical review boards. [illegible] ntion start sequence and tim[illegible] ure 1 in the Supplement. Our primary outcome was antimi[illegible] ness, measured with a validated appropriateness asses[illegible] nt.41 One of 3 infectious diseases specialists (including M.[illegible] G.P.) assessed the adult prescriptions, and 1 of 3 infectious di[illegible] ology pediatricians (including M.v.d.K.) assessed the pediatri[illegible] s for appropriateness. They were masked for clinical outcom[illegible] period (baseline or intervention). Data were collected prospecti[illegible] sments were perf[illegible] retrospectively to enable masking. E[illegible] ollowing antimi[illegible] tion factors was assessed for appr[illegible] ndication, choi[illegible] , dosage, administration [illegible] duration. A pres[illegible] med to be appropriat[illegible] the following criter[illegible] above factor[illegible] deline adherence or guid[illegible] rational reasons, as judged by the [illegible] alist, immunology specialist,

or pediatrician. Rationality was defined as an effective antimicrobial regimen that covered relevant pathogens without being excessive (ie, unnecessary combination therapy or broad spectrum when a more narrow spectrum is available). If present, drug allergies, oral intake, and previous culture results were taken into account. Cases that could not be assessed because of missing information were excluded. We notified clinical staff of both hospitals by email before the start of the baseline measurements.Antimicrobial consumption was a secondary outcome, reported in days of therapy per 100 admissions per

The 'morning dip' in antimicrobial appropriateness: circumstances determining appropriateness of antimicrobial prescribing

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design and implement an intervention approach to improve appropriateness of hospital antimicrobial prescribing for all indications. Our approach was inspired by the participatory action research paradigm,28 which focuses on collaboration and empowerment of the stakeholders in the change process and is effective in other complex health care situations.28 In our approach, prescribers were invited to choose and co-develop 1 or more interventions to improve their own prescribing, whereby they were stimulated to base their choice on conclusions of a prior root cause analysis of their prescribing patterns. The approach is therefore designed to benefit from tailoring to local determinants7,29- 33 and draws on 3 behavioral principles: (1) respect for the prescribers' autonomy to avoid feelings of resistance11- 19; (2) the inclination of people to value a product higher and feel more ownership for New projects

Abstract

Objectives: Quality of care has been shown to vary depending on the time of day or day of the week and depending on caregivers' gender and experience. We aimed to study how these factors influence quality of antimicrobial prescribing.

Methods: Prospective point-prevalence surveys were performed to determine the association between the above-mentioned prescription factors and antimicrobial appropriateness. Surveys included cases of patients admitted to a tertiary care hospital with a prescribed systemic antimicrobial drug and its prescribers. The main outcome was appropriateness of antimicrobial prescriptions. A post hoc qualitative survey among hospital physicians asked physicians to reflect on the results.

Results: The study included 351 antimicrobial prescriptions by 150 physicians prescribed for 276 patients. Appropriateness of antimicrobial prescribing in the morning was significantly lower compared with the afternoon and evening/night [43% versus 68% versus 70%, crude OR afternoon versus morning = 3.00 (95% CI " 1.60–5.48), crude OR evening/night versus morning = 3.40 (95% CI " 1.64–6.69)]. First-year residents performed significantly worse than their more experienced colleagues [51% versus 69%, crude OR = 2.09 (95% CI = 1.26–3.38)]. Infectious disease expert consultation improved appropriateness [54% versus 81%, crude OR = 3.71 (95% CI = 2.05–6.23)]. No significant effects for gender or office hours versus non-office hours were found. Post hoc survey results suggest creating room to improve prescribing circumstances during mornings and for inexperienced physicians.

Conclusions: Antimicrobial prescribing was less appropriate in the mornings and when prescribed by inexperienced physicians. Appropriateness may be increased by improving prescribing circumstances.

Introduction

In-hospital prescribing of antimicrobial agents is inappropriate in up to 50% of cases and an important cause of rising antimicrobial resistance.[1–4] Many hospitals therefore run antimicrobial stewardship programmes to improve their antimicrobial prescription quality. To improve the efficiency of these programmes and to improve understanding of antimicrobial misuse it is important to know which factors surrounding antimicrobial prescribing are associated with a lack of antimicrobial appropriateness.[1]

Quality of hospital care has been shown to vary depending on the time of day. Hospital admissions at night-time are associated with higher mortality and more complications than during week- days and office hours.[5–8] Mortality and complication rates are higher, even for electively admitted patients, at weekends.[6–8]

Working in shifts disturbs our circadian rhythm with its complex sleep regulation, leading to a detrimental decline in cognitive functioning.[9] Irrespective of sleep deprivation, our functional capacity is lowest between 02:00 and 07:00 and between 14:00 and 17:00.[10] A qualitative study on antimicrobial prescribing in hospitals suggested that physicians feel more pressure and make more errors when working after-hour shifts.[11] Antibiotic use has already been shown to be less appropriate on emergency wards at the weekend in comparison with weekdays.[12] Interestingly, a recent study showed that primary care physicians show 'decision fatigue' more often at the end of their shift, and this was reflected by a progressive decrease in clinicians' ability to resist prescribing antimicrobial treatment.[13] The authors hypothesized that due to the 'cumulative cognitive demand' of medical decision-making during the day, clinicians may gradually be less able to prescribe appropriately.

Medical residents are responsible for the majority of antimicrobial prescriptions in medical clinics, despite the fact that they are generally the least experienced members of staff. Generally, this responsibility is shared with a supervisor.[14] A study of the factors influencing the drug choices made by medical students and their teachers showed that final-year medical students rely more on their supervisors' opinion than on drug effectiveness, side effects and guidelines when making prescribing decisions.[15] It is thought that more prescribing experience leads to better prescriptions, but little is known about the influence of clinical experience on the appropriateness of antimicrobial prescribing in practice.[4,15–17]

As we generally assume that knowledge comes with experience, one would expect senior doctors to know more about antimicrobial drugs. A study on the relative experience of residents found no difference in their antimicrobial knowledge scores,[3] a possible reason for this being the more recent education on the topic enjoyed by the younger residents. However, the knowledge test may have ignored the more practical or pragmatic knowledge of experienced doctors, which may be a better predictor of good prescribing. For instance, experienced physicians are probably more capable of

finding relevant information and have better knowledge of when to consult an antimicrobial expert like a clinical microbiologist or an infectious disease (ID) specialist. Finally, the sex of the prescriber could also be a factor in determining antimicrobial appropriateness, as some studies show that better adherence to guidelines, and direct patient outcomes such as decreased mortality, are associated with female physicians.[18–22]

The factors mentioned above can potentially influence antimicrobial appropriateness and knowledge of these relationships can guide antimicrobial stewardship programme efforts. We investigated a number of factors associated with appropriateness of antimicrobial prescribing: the time of day the prescription is written, the prescribers' clinical experience and gender, and ID expert consultation. We performed prospective point-prevalence surveys of antimicrobial appropriateness on all clinical wards in a tertiary care hospital in the Netherlands to measure the associations of these factors with antimicrobial appropriateness.

Methods

Study design

Prospective repeated point-prevalence surveys of antimicrobial appropriateness.

Ethics

There was no active patient involvement. We used patient data collected for regular care. The hospital medical ethical review committee approved the study (reference 2011/315).

Collection of antimicrobial prescriptions

We performed seven point-prevalence surveys of antimicrobial appropriateness between October 2011 and September 2012 on all clinical wards of a 700-bed tertiary care hospital in Amsterdam, including paediatric and ICU wards. Dutch hospitals run a different employment system for pharmacists than many other countries do, as they do not monitor or advise on choice or duration of antimicrobial therapy, and their role in antimicrobial dosing is often limited to therapeutic drug monitoring and adjustments to renal function. At the time of the study, there were no on-going antimicrobial stewardship interventions, except for a list of restricted antimicrobials requiring pre-authorization by an ID expert. Surveys were performed without advance notice every two months on a weekday. All admitted patients with an active antimicrobial prescription at 00:00 on the day of the survey were included. No surveys took place on Mondays, as we feared it would lead to a different indication mix, e.g. less surgical prophylaxis taking the weekend into account. A research physician or medical student performed all surveys. Prescriptions older than 72h at the time of inclusion were excluded to minimize the influence of later events (e.g. availability of culture results) and to minimize recall bias. Information on patient cases was extracted from electronic and paper medical records and completed with information from a discussion with the ward physician.

Determination of appropriateness

We defined appropriate antimicrobial therapy as prescription of an antimicrobial agent satisfying any one of the following three conditions on the day of the survey: (i) it followed relevant guidelines; (ii) it deviated from the relevant guidelines but rational arguments for deviation were documented in the patient file or supplied by the ward physician; and (iii) there was no relevant guideline but the prescription was considered a rational choice. A rational choice was defined as an effective antimicrobial drug covering relevant pathogens without an excessively broad antimicrobial spectrum, long duration, high or low dosage or incorrect route of administration (e.g. omission to switch to oral therapy if adequate or possible). An ID specialist (internist) judged all adult prescriptions and an ID paediatrician judged all paediatric prescriptions. These specialists were blinded for prescription time, prescriber characteristics and any advice from other ID physicians. We judged each prescription for appropriateness of indication, antimicrobial choice, dosage, administration route and duration.[23] If one of the above factors was determined inappropriate the prescription was coded as inappropriate. Prescriptions lacking in information (e.g. prescribed by general practitioner so indication unknown) and thus preventing good judgement were excluded from analysis. This method has an acceptable validity and reliability for prescriptions for adult patients.[24]

Prescription factors

Prescription times were derived from the electronic prescribing system. We constructed a time of prescription variable comprising three categories: morning (08:00–12:59), afternoon (13:00–18:59) and evening-night (19:00–07:59). The morning category included the extra hour after noon because we assumed that most physicians would take lunch around 13:00. Although evening shifts start at 17:00, the evening shift in this timeline started at 19:00 because in our experience physicians working on the day shift are often still present until that time. Additionally, we created a dichotomous office hours variable comprising the category 'office hours' (09:00–18:59 on weekdays, excluding national holidays) and the category 'non-office hours' (including all other prescriptions). We assembled information on physicians' clinical experience and gender during contact with the ward physician. The starting point for experience was considered to be the date of first clinical work. Clinical experience was divided into inexperienced (<1 year experience) and experienced (>1 year experience) because we expected the learning curve to be steepest during the first year. Finally, we also asked the ward physician whether an ID expert (clinical microbiologist or ID specialist) had been consulted at the time of prescribing.

Statistical analysis

We used logistic regression analysis to examine the influence of all prescription factors on the antimicrobial appropriateness variable while controlling for clustering within the data (e.g. physicians within one department prescribe more similarly compared with physicians in different departments). We used multiple imputation to account for missing data.[25] We reported the results of a complete case analysis as a sensitivity analysis.[26] Both crude and adjusted OR were reported, with ORs>1 representing higher odds of prescribing an appropriate antimicrobial agent. The significance level was 0.05 (two-sided).

We assessed whether ID expert consultation served as a mediating variable for each other prescription factor by adding this variable to each statistical model. When this addition resulted in a reduction of the original effect, we concluded that mediation was present.[27,28] Effect reductions were expressed as percentages, and in the absence of any guiding literature, we arbitrarily considered percentages above 20% to be relevant.

We controlled for potential confounding using a forward stepwise procedure to determine each adjusted model. All prescription factors and a dichotomous variable indicating prescriber specialty (surgical versus medical or ICU) were considered, excluding ID expert consultation in cases in which a mediation effect of this variable was demonstrated. We used R statistical software, version 3.2.3 for all analyses (R Development Core Team).

Post hoc survey

The above study was followed up by a short online survey about our results among residents and specialists of the two most frequently prescribing surgical specialties, the most frequently prescribing medical specialty and clinical microbiology. The survey was performed in September 2015. It contained multiple-choice and open-ended questions about the results of the first part of our study. Two researchers (J. J. S. and S. L. G.) independently identified and then combined recurring themes within the open-ended question responses. More detailed information on the methods is supplied in the Supplementary Methods section (available as Supplementary data at JAC Online). The contents of the survey could only be finalized after the results of the first part of the study became known, so these are described in the results section.

Results

Prescriptions and patients

We included 351 antimicrobial prescriptions prescribed by 150 physicians for 276 patients. The complete inclusion procedure is shown in Figure 1. The median number of prescriptions per physician was 2 (range 1–11). The antimicrobial agent was prescribed less than 24 h previously in 54% of cases, between 24 and 48 h previously in 30% of cases and between 48 and 72 h previously in 16% of cases. The three most frequently prescribed antimicrobial agents were amoxicillin/clavulanate (19%), ceftriaxone (13%) and vancomycin (7%). Overall appropriateness was 65%. We included only 25 specialist prescriptions so no separate specialist category was made.

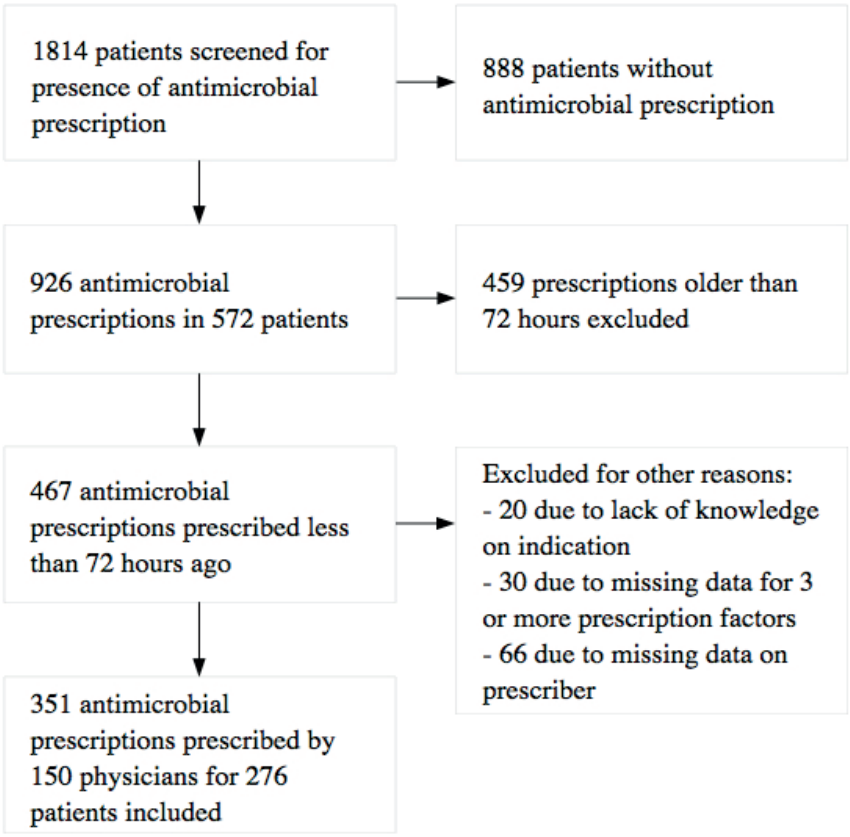

Figure 1
Overview of the inclusion procedure.

Association between prescription factors and appropriateness

Antimicrobial prescribing in the morning proved significantly less appropriate than in the afternoon and evening/night. Physicians consulting an ID expert prescribed more appropriately, as did more experienced physicians. The latter effect included a 24% mediation effect of expert consultation (Table 1). Physician specialty, which was used as potential confounder for these associations, was also related to appropriateness [medical specialty 74.9%, n = 187 versus surgery 48.8%, CI = 0.21–0.53)].

Table 1
Regression analysis of the associations between prescription factors and antimicrobial appropriateness.

Prescription factor	prescriptions (n)	mean appropriateness (%)	crude OR (95% CI)	adjusted OR (95% CI)	mediation effect of ID expert consultation (%)
time of day					
morning	78	43.3	1	1	-
afternoon	180	67.8	3.00 (1.60-5.48)	3.12 (1.64-5.62)[a]	5
evening/night	93	70.3	3.40 (1.64-6.69)	2.99 (1.44-5.69)[a]	5
office hours					
office hours	226	61.5	1	1	-
non-office hours	125	66.2	1.23 (0.75-2.00)	1.06 (0.64-1.72)[a]	-
clinical experience					
< one year	114	50.8	1	1	-
> one year	237	68.9	2.09 (1.26-3.38)	1.53 (0.91-2.52)[b]	24
gender					
female	241	66.3	1	[c]	-
male	110	61.8	0.86 (0.51-1.45)	[c]	-
ID expert consultation					
no ID expert consulted	226	53.7	1	1	-
ID expert consulted	125	81.1	3.71 (2.05-6.23)	3.17 (1.74-5.18)[b]	-

ID, infectious disease; [a] adjusted for clinical experience; [b] adjusted for physician specialty; [c] no relevant confounding. All results based on the imputed dataset.

Sensitivity analysis

Table 2 shows the number of complete cases and the results of the complete case analysis.

Post hoc survey contents and participation

The survey focused on the associations of time of day and experience with appropriateness. A strict order of questioning was enforced to ensure that participants could not go back and forth between questions to prevent influence of later questions in the survey. Initially, the survey queried respondents' expectations of these associations, after which results were revealed and the survey continued with open-ended questions about possible explanations for the results. Finally, respondents were asked to judge the plausibility of explanations formed by the research team. We invited 195 physicians with four specialties to participate. After one email reminder, 66 physicians opened the survey, 61 of whom completed the survey (31% response rate). Respondents who did not complete the survey were excluded. During the theme identification process of the open-ended questions, two independently identified themes were mentioned by fewer than 10% of the participants and were consequently excluded from the final theme list.

Table 2
Sensitivity analysis using complete cases only, regression analysis of the associations between prescription factors and antimicrobial appropriateness.

Prescription factor	prescriptions (n)	mean appropriateness (%)	crude OR (95% CI)	adjusted OR (95% CI)
time of day				
morning	66	43.9	1	1
afternoon	148	66.2	2.75 (1.41-5.20)	2.25 (0.88-5.23)[a]
evening/night	71	66.2	2.72 (1.23-5.54)	1.86 (0.63-4.94)[a]
office hours				
office hours	200	60	1	1
non-office hours	110	66.4	1.33 (0.78-2.22)	1.02 (0.48-2.08)[a]
clinical experience				
< one year	61	49.2	1	1
> one year	125	67.2	2.12 (0.99-4.21)	1.55 (0.63-3.77)[b]
gender				
female	196	65.9	1	[c]
male	85	61.2	0.84 (0.46-1.57)	[c]
ID expert consultation				
no ID expert consulted	74	52.7	1	1
ID expert consulted	42	83.3	8.03 (1.30-25.56)	5.64 (0.95-16.2)[d]

ID, infectious disease; [a] adjusted for clinical experience; [b] adjusted for time of day; [c] no relevant confounding, [d] adjusted for prescriber's sex.

Post hoc survey results

The majority of respondents (98%) did not expect appropriateness to be worse in the morning than at other times of the day. After revealing that appropriateness was lowest during mornings, theme analysis showed the most prevalent explanations for these results were the morning rush, reduced support from consulting specialties and supervisors, and reduced availability of diagnostic results during this period. Suggestions to improve prescribing in the morning focused on improvement of antimicrobial prescribing overall (e.g. the improvement of guidelines, education), an in- crease in time available to prescribe, a reduction in unsupervised prescribing and an improvement in the speed at which microbiological results and advice are made available. When asked to react to the association between reduced appropriateness and inexperience, the predominant indication given by respondents was lack of practical knowledge. Complete results of the survey are presented in Tables S1 to S3.

Discussion

In this prospective observational study, we found that appropriateness of antimicrobial prescribing was significantly lower in the morning than in the afternoon or evening/night. Consultation with an ID expert increased the appropriateness. Experienced physicians performed significantly better than their less experienced colleagues, which may partially be explained by the increased ID expert consultation. We found no significant effects regarding gender or office hours versus non-office hours. The follow-up survey of work-floor physicians showed that the 'morning dip' was an unexpected finding. When confronted with our results, most physicians suggested that prescribing in the morning is less ideal owing to the morning rush, reduced access to diagnostic results and reduced presence of supervisors or consulting specialties. Suggestions to improve morning prescribing included a reduction of workload and integration of a prescribing moment into the ward round routines. When asked to explain why inexperience leads to lower appropriateness, a lack of practical skills was offered as a plausible explanation. Improved education in the field of antimicrobial prescribing was recommended.

Our research uniquely combined a primary quantitative analysis with a follow-up survey including qualitative data, allowing direct reflection on our results by the study population. Other study strengths include the duration of one year that minimized seasonal effects, and its unique combination of assembled prescription factors that enabled assessing the mediating effect of ID expert consultation. The main study limitations included a lower inclusion rate than expected owing to a more uneven distribution within groups and use of a subjective primary outcome. However, the specific method of measuring appropriateness used has been shown to have good validity and inter-rater agreement.[24] The specialist who determined the appropriateness could not be blinded for knowledge about ID expert consultation in all cases, which left some room for bias. The study was single centre so results may be context specific. Our list of factors was not exhaustive—other factors not measured may also be important. Finally, prescriptions were included when present at midnight, so antimicrobials prescribed just after midnight were exposed to more time in which the circumstances could possibly change (e.g. culture results become available) than antimicrobials prescribed just before midnight. On the other hand, the prescriber or supervisor had more time in which to correct any mistakes.

Our study is the first to show a 'morning dip' in antimicrobial prescribing when compared with the rest of the day, despite a higher rate of ID expert consultation. The result was unexpected and in contradiction with previous literature on quality of care during non-office hours,[6–8,12,29] and contrasted with a previous study describing decision fatigue in primary care prescribing for respiratory infections.[13] However, in a qualitative study on antimicrobial prescribing, morning ward rounds were described as 'fraught, . . .with little time for note making'.[11] Communication during ward rounds has been shown to often be interrupted which can disrupt clinical activities.[30] Environmental factors such as heavy workloads are well-known contributors to prescribing errors.[31] Moreover, it has been shown that many prescribing errors in hospitals result from attention lapses which are partially attributable to frequent interruptions and heavy workloads.[16] Our follow-up survey results corroborate these findings, with

one resident stating: 'There may be more time in the afternoon and night to consider patient policies, due to the morning chaos/ward rounds'. The overriding conclusion may be that due to busy ward rounds and reduced supervisory support and advice from other specialties, the already difficult job of appropriate antimicrobial prescribing in hospitals is significantly harder in the morning.

First-year residents prescribe less appropriately than their more experienced colleagues do. Education in antimicrobial prescribing is suggested by many physicians as a means to improve prescribing by junior doctors, including those working in antimicrobial stewardship.[1,16,32] However, results of our research and previous studies emphasize the importance of a significant focus on practical knowledge during such education programmes, rather than only a pharmacological focus.[31] For instance, our survey results suggest that junior doctors feel unprepared regarding use of guidelines, and that they lack knowledge of common dosing schemes and use of intravenous catheters. Physicians with poor practical knowledge may underperform as their common tasks take more time leaving less time for medical decision-making.

ID expert consultation is associated with higher appropriateness, and its mediating effect on the relationship of experience to appropriateness suggests that experienced physicians use these consultations more often. It can be hypothesized that knowing when and how to ask for help is an essential part of the practical knowledge of prescribing.

Survey recommendations to improve antimicrobial prescribing in the morning mainly focus on improving the physicians' prescribing environment, while recommendations to help inexperienced physicians often suggest education on how to handle this environment. A logical next step would be to combine these two suggestions. As an example, we suggest hospital steward- ship programmes could analyse the prescribing environment of a clinical ward, especially during morning activities in order to identify and possibly remove any barriers to good prescribing. Any barriers that cannot be removed can then be attended to in an introductory course for new physicians. Although the 'morning dip' in our study was not caused by too little ID expert consultation, more consultations would probably be advantageous as well. Other suggestions in the survey focus on supervisory support, suggesting delaying prescribing until a supervisor is available for support. However, this may be problematic in the case of acute problems, as supervisors are not always available— especially surgeons.[11] Increasing supervisory efforts seems a worthy goal but would probably also increase costs or decrease productivity elsewhere.

Conclusions

In this prospective hospital-wide study, we found a surprising and unexpected 'morning dip' in appropriateness of antimicrobial prescribing compared with the rest of the day. Inexperienced physicians also prescribed less appropriately than their more experienced colleagues. Our follow-up qualitative survey showed that work-floor physicians relate these findings to a suboptimal pre-scribing environment, especially during ward rounds, and they suggest improving this environment and improving supervisory support and education of physicians in antimicrobial prescribing and stewardship.

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Supplement

Additional details on the collection of antimicrobial prescriptions

Only antimicrobial drugs in WHO's Anatomical Therapeutic Chemical Classification codes J01, J02, J04AB02 and J05AB were included.[1] Prescriptions on the adult haematology ward were not included because they prescribed a large volume of antimicrobials following strict standard protocols and we assumed that the influence of prescribers on the prescription quality would be low. Antimicrobial prescription details collected including prescription time and the name of the prescribing physician together with patient demographics, medical history, relevant laboratory, microbiological, and radiological results were extracted from the electronic patient system. We acquired the indication for the prescription by consulting the paper medical records and by contacting the responsible ward physician on the day of the survey.

Additional details on determination of appropriateness

In the appropriateness determination process, the relevant guideline used was the hospital guideline, unless the indication was not covered in the local guideline, in which case first the national guideline and then specialist branch guidelines were taken as the relevant guideline, if possible and available.

Additional details on statistics

We accounted for clustering within patients, survey date, physicians, and departments using generalized estimating equations with an exchangeable correlation matrix. We used multiple imputation with chained equations to impute 100 datasets to account for missing data.

We used a pragmatic approach to determine mediation effects, because the otherwise most optimal bootstrap approach for estimating indirect effects in mediation analysis is not available for generalized estimating equations. The following approach was used: in cases where the resulting prescription factor coefficient was closer to 0 than the crude coefficient and the crude coefficient was significantly different from 0, we reported the coefficient percentage change to reflect the size of the mediation effect.

In all cases without any mediation, ID expert consultation was considered a potential confounder and was eligible for inclusion in the adjusted model. All other prescription factors and a dichotomous variable dividing prescribers into surgical or medical (including intensive care) could be included in the adjusted model. For each prescription factor, the composition of the adjusted model was determined in a forward stepwise procedure using a 10% coefficient change threshold. Variables office hours and time of prescribing were considered too similar to be included in any model simultaneously, so the variable with the highest coefficient change would be included in situations where both were eligible for inclusion. We used R statistical software, version 3.2.3 with packages lme4 (version 1.1-11), and mice (version 2.30), for all analyses (R Development Core Team).

Sample size calculation

We estimated the required sample sizes using standard sample size calculations that were then corrected for clustered data, using the design effect correction factor.[2] We assumed an intra-class correlation coefficient of 0.2, on average three prescriptions per physician, and an average appropriateness of 60%. Using a power of 80%, significance level of 5% and a minimal relevant OR of 2.0 or 0.5 this resulted in a minimal required sample size of 121 prescriptions for each level of each prescribing factor. Based on our experience with previous point prevalence surveys we estimated to reach these numbers using seven surveys, elapsing a full year to even out potential influences of seasonal effects.

Additional post-hoc survey details

Besides questions reflecting on study results, the survey contained question asking for informed consent and questions about the respondents' background. The final composition of the survey was determined after analysis of the quantitative part of the study was completed. The survey was performed with the online tool SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA). Responses to all open-ended questions were independently analysed for recurring themes by two researchers (JJS & SLG). They made a list of two to five themes per question including quote examples that they felt represented the theme. We then combined the two resulting lists of themes into a final theme list during a discussion with a third member of our research team (MAA). Only themes mentioned by at least 10% of participants were included. We scored the mentioning of each theme by each participant.

Supplementary data

Table S1
Results of the post-hoc survey: multiple-choice questions

	n (%)
Total number of respondents included	61
Specialty	
surgery	19 (23)
medical (non-ID)	31 (51)
ID & clinical microbiology	11 (18)
Specialist	22 (36)
On which part of the day would you expect antimicrobial appropriateness to be the lowest?	
morning	1 (2)
afternoon	7 (12)
evening/night	53 (87)
We found lower antimicrobial appropriateness in the morning compared to other parts of the day. Do you think the following hypothesis is a relevant explanation for this finding?	
morning rush	
yes	46 (75)
neutral/no idea	7 (12)
less supervision	
yes	31 (51)
neutral/no idea	13 (21)
less cognitive functioning	
yes	4 (7)
neutral/no idea	21 (34)
different indications for prescribing	
yes	7 (12)
neutral/no idea	33 (54)
different influence of microbiology results/advice	
yes	40 (66)
neutral/no idea	13 (20)

ID, infectious disease; IV, intravenous.

Table S2

Results of the post-hoc survey: theme-analysis of open-ended questions about time of day.

We found lower antimicrobial appropriateness in the morning compared to other parts of the day. What is your best explanation for this?	**Mentioned n (%)**	**Description**	**Example quote**
Morning rush	30 (49)	Residents are very busy in the mornings (e.g. ward round, surgery) which leaves less time for consideration and discussion of antimicrobial prescriptions.	"There may be more time in the afternoon and night to consider patient policies, due to the morning chaos/ward rounds"
Consultation of ward supervisor	19 (31)	Specialists are not always available for supervision of residents in the morning. Some residents are too busy to consult them in the morning.	"In the morning, the least experienced residents often prescribe unsupervised"
Consultation of other specialities	18 (30)	Advice from consultations of other specialities (including ID specialists and clinical microbiologists) is generally delivered in the afternoon.	"Consulting physicians first have to consult their own supervisor so advice is generally delivered in the afternoon"
Diagnostic results	16 (26)	Results of diagnostic procedures (radiology, microbiology, laboratory) become available as the day progresses, generally after noon.	"Culture results become available at the end of the day so prescribing becomes more directed and is often improved by advice from a microbiologist"
What do you think could be done to improve antimicrobial prescribing in the morning?			
Suggestions to improve antimicrobial prescribing overall	23 (38)	Create/promote guidelines. Increase accessibility of guidelines. More education about antimicrobial prescribing, inappropriateness and the use of protocols.	"More antibiotic education for residents. A clear-cut discussion of the sepsis-protocol"
Take more time to prescribe antibiotics in the morning	17 (28)	Reduce work-load of residents. Implement an antimicrobial prescription step in each ward round. Increase awareness of this problem so residents will pay more attention.	"Create moments where you cannot be interrupted by nurse questions, to prevent being distracted"
Reduce unsupervised prescribing	14 (23)	Advance the supervision moment to an earlier time. Never prescribe without supervisor consent. Check every prescription during the moment of supervision.	"Increase awareness of antibiotic prescribing during ward rounds and make sure supervisors are directly accessible for consultation"
Improve and speed up microbiological results and advice	8 (13)	The earlier results are available the better. Some respondents suggest that result communications are sometimes unnecessarily delayed.	"Many residents are afraid to make an IV to oral switch in improving patients in the absence of culture-results"

ID, infectious disease; IV, intravenous.

Table S3

Results of the post-hoc survey: theme-analysis of open-ended questions about experience.

We found that inexperienced physicians prescibe antimicrobials less appropriately. What is your best explanation for this?	**Mentioned n (%)**	**Description**	**Quote example**
Practical knowledge	28 (46)	Inexperienced physicians have more difficulty finding guidelines/protocols and relevant sources to guide them. They do not know how to handle common ward matters such as dosing schemes and IV drips.	"Inexperience with all ward matters (for example: care for IV catheters) is more important than pharmacological knowledge alone"
Pharmacological knowledge	24 (39)	Knowledge about antimicrobial drugs, indications, which drug for which bug etc. increases with experience	"In my experience as inexperienced resident, I need to look up more information because of missing knowledge"
Fear and insecurity	8 (13)	Fear for adverse consequences of de-escalation or IV to oral switch. Fear to ask for advice or clarification from supervisors/ consulting physicians. General insecurity leading to mistakes.	"Not speaking up about doubts over antibiotic choices or when the supervisor says something that may be incorrect, but rather prescribing a wrong dose"
High workload	11 (18)	Inexperienced physicians are very busy because they have many duties and work less efficiently.	"Due to inexperience and a high workload during ward rounds their view of the overall picture is worse"
What do you think could be done to improve antimicrobial prescribing of inexperienced physicians?			
Teach practical skills	20 (33)	Physicians should be taught why adhering to guidelines is important, where they can be found and how to manage a clinical ward. Each relevant physician should be notified of new or revised guidelines.	"At the start, teach about use of (local) antibiotic protocol, the importance of cultures, switching etc."
Teach general knowledge	24 (39)	Increase and improve education about antibiotics and antimicrobial stewardship. Most importantly during medical school and first year residency.	"Antibiotic prescribing should only be allowed after passing an antibiotic course successfully"
Reduce unsupervised prescribing	21 (34)	Inexperienced physicians to receive more support from supervisors. Supervisors should emphasize the importance of guideline adherence. Always consult supervisor before prescribing an antimicrobial agent.	"Give a lot of feedback to diminish the insecurityfactor"

ID, infectious disease; IV, intravenous.

Supplement references

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Because the variable depended on the moment of n the hospital and not time of arrival in the offsite ' n time point rather than 19.30h (actual labora demarcate the end of regular office hours. To zoom laboratory closing times in our data, we constructed a amed 'alternative office hours' that divided the 24h day (which was between 2 and 14h) and least optimal (1 regard to timely culture processing. Primary outcome he duration of each culture-processing step between in n and the administration of the first dose of the change men. We assessed the influence of the time of day of c culture transport and gram stain duration and all subseq ing steps using the two office hours variables introduc whether severity of the infection impacted culture- also had a specific focus on the processing of Staphy eraemia cases admitted on the ICU.21 Addit disea bouring hospital judg d antim ate coverage for n the blood culture. fter gram stai rapy with high expectatio against the coverage after full deter ed as the hogen was susceptible in vit ents wit with insufficient pharmacokin ere alw , e.g. nitrofurantoin for Esche ia. In quate therapy, whether or not a te is in stance guideline adherence, e.g n- susc coli with ceftriaxone constitut ge, despi lack of streamlining may be ate from t imicrobial stewardship.22 Jud ific infectio ist on the related concept s of antimicr e been shown valid and r pared to colleagu also report data on trea erence. Linear regres to compare durations ours. All time variables w transformed prior dditionally, a variable denoting coverage of roorganism(s) was added to each crud ding. Confounding

was considered relevant if the regression coefficient from the univariable analysis differed from the coefficient in the multivariable model (containing the potential confounder) by more than 10%. We compared antimicrobial coverage percentages of the cultured microorganism(s) between the empiric phase, after gram stain completion, and after final determination/susceptibility using logistic generalized estimating equations to adjust for clustering within patient cases. All analyses were performed using Stata 13 (StataCorp, USA). $P<0.05$ was considered significant for all analyses.

The impact of laboratory closing times on delay of adequate therapy in blood stream infections

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Staphylococcus aureus were highlighted to illustrate that processing times for this finding, which indicates a serious infection with high mortality,21 were similar to those of cultures with other microorganisms. The same applied to patients admitted to the ICU. Based on the pattern of Figure 2, we constructed an alternative office hours variable denoting 02:00h-14:00h as the optimal period for speedy culture processing, results of which are also shown in Figure 1. Adding a variable denoting adequacy of empiric treatment to the model did not change the above findings substantially. or pediatrician. Rationality was defined as an effective antimicrobial regimen that covered relevant pathogens without being excessive (ie, unnecessary combination therapy or broad spectrum when a more narrow spectrum is available). If present, drug allergies, oral intake, and previous culture results

Abstract

Background: Patients with blood stream infections need early adequate antimicrobial treatment to reduce mortality. The recent focus on 24/7 equal health care quality warrants the question to what extent the moment that the culture is flagged positive influences the speed of blood culture-processing and the optimisation of antimicrobial therapy.

Methods: We performed a retrospective study assessing the time delay of a positive blood culture result during versus after office hours and its impact on adequate antimicrobial therapy. Process duration from moment of culture positivity to gram stain completion was compared at different moments of the day in a medium-sized hospital with an offsite microbiological laboratory.

Results: Ninety-four patients with positive, non-contaminated blood cultures were included. Sixty-six patients (70%) received adequate empirical therapy, increasing to 76 cases (82%) and to 88 cases (95%) after gram results and complete determination respectively ($p<0.05$ for all comparisons). Median duration from culture positivity to gram stain completion (including offsite culture transport) increased from (a median of) 4 to 12 hours if time of culture positivity was after office hours ($p<0.05$), irrespective of adequacy of empiric coverage. This also resulted in a median 12-hour delay for the complete process from time of culture positivity to administration of the antimicrobial drug ($p<0.05$).

Conclusion: After office hours blood culture processing is delayed. This can lead to a delay in adequate antimicrobial therapy in bloodstream infections.

Introduction

A timely adequate treatment of bloodstream infections is important to reduce mortality and morbidity,[1-5] so in most suspected cases patients immediately receive empiric broad-spectrum antibiotics. Nevertheless, due to a later adequate coverage, delayed reporting of blood culture results is associated with increased infection-related mortality.[6,7] Delayed culture reporting may also hold back important antimicrobial stewardship goals such as streamlining and deescalating of antimicrobial therapy.[8,9] It is therefore important to search for unnecessary delays in the process from blood culture collection to administration of a culture-based antimicrobial agent.

Previous studies have shown patient care delivered during hospital office hours is associated with lower mortality and shorter length of stay in comparison to care delivered after hospital office hours.[10-13] In the UK, this has even led to a call for equal standards of performing care all seven days a week.[14] With regard to blood culture processing, one study showed that culture yield can be lower at the weekend,[15] possibly due to lower staff presence or delayed incubation or processing.[16] Immediately incubating collected blood samples has been shown to reduce these delays.[17] However, most microbiological laboratories do not process blood cultures after daytime, leaving room for potential delays. Furthermore, there is an increasing number of onsite hospital microbiological laboratories currently being moved offsite to save costs and to increase performance.[18,19] As culture specimen transport is generally only performed during the day/office hours; culture-processing for cultures signalled positive after the last transport of the day is delayed until the next morning. Having the laboratory and clinical ward at a different site has been shown to increase time to start of culture incubation.[16,20] However, influence on the actual time of administration of the (changed) antibiotic in these circumstances and depending time of culture positivity is thus far unknown. We performed a retrospective study determining the duration of each step from culture positivity to antimicrobial administration in a hospital with an offsite microbiological laboratory. We compared the duration of each step during and outside of laboratory office hours.

Materials and Methods

Setting: the hospital

The study was performed in a 550-bed general teaching hospital in Amsterdam, the Netherlands. It had no on-site microbiological laboratory, except for a small facility where blood culture bottles can be immediately incubated, using the BacT/ALERT incubation system (BioMérieux, Marcyl'Etoile, France). Thrice-daily clinical samples, including blood culture bottles that were flagged positive were transported to the offsite microbiological laboratory by transport van, taking 15-25 minutes, depending on traffic. Van departure times were 9.30h, 12.00h and 16.00h on weekdays and 10.00h at the weekend with, in the case of positive blood cultures, an additional transport in the afternoon, which was then always processed in the offsite laboratory the same day. There were no transports

at other times. At least one of the two regular microbiologists were present in the hospital for consultation and communication of results during 8-17.30h on weekdays, but not during the weekend. Outside of these hours, microbiological consultation was performed by telephone by one of nine microbiologists that were affiliated with the hospital and the offsite laboratory. When present on weekdays, the microbiologist telephoned results of all positive blood cultures to the treating physician. At weekends, only relevant positive cultures (as judged by the microbiologist) were reported to the physician. Microbiologic results and therapeutic advice were also communicated to clinicians via the electronic health record system Epic (Epic systems corporation, USA). The hospital had local antibiotic guidelines on which the microbiologists based their advice.

Setting: the offsite laboratory

Gram stains were performed on every positive blood culture. Blood culture pathogen determination and susceptibility testing was performed using MALDI-TOF (VITEK®MS; bioMérieux, Marcyl'Etoile, France) and disk diffusion testing according to EUCAST-methodology. Laboratory opening hours were from 8-19.30 on weekdays and varied depending on work demands during the weekend. Gram stains and pathogen determination were not performed outside these hours. At least one microbiologist was present at this site during these hours. Both the laboratory and the hospital used the Glims microbiology laboratory system (Clinisys group, UK) to document all logistic steps and therapeutic recommendations. Microbiologists were immediately notified of any culture positivity via this system.

Data collection

We performed retrospective case reviews of hospital inpatients with positive blood cultures during two pre-selected non-consecutive weeks per month between December 1st 2011 and October 31st 2012. Cultures with multiple pathogens (of which there was one) were treated as one culture. Subsequently drawn cultures were only included as a new case if separated by eight days or more. The microbiologist on duty excluded cultures with pathogens judged as contaminants after complete determination of and consultation with the treating physician. We retrieved all information on blood cultures, starting time of each logistic step, and given antimicrobial advice from the Glims laboratory system. Time of culture collection could not be retrieved from this system. We had no data to separate culture transportation from the gram staining process so this was analysed as a single step. For each case we assembled information on the empiric antimicrobial regimen, and all changes in this regimen until 48 hours after the final determination report became available. Time of prescribing and nurse-reported time of administration were retrieved from the electronic pharmacy system Pharma (VCD Healthcare, the Netherlands)). The responsible medical ethical board approved the study.

Office hours variables

We created a dichotomous variable named 'regular office hours' based on the moment the culture was flagged positive by the incubator, denoting 8-17h as during and 17-8h as outside of office hours.

Because the variable depended on the moment of culture positivity in the hospital and not time of arrival in the offsite laboratory, we used the 17h time point rather than 19.30h (actual laboratory closing time) to demarcate the end of regular office hours. To zoom in on the effect of laboratory closing times in our data, we constructed a second variable named 'alternative office hours' that divided the 24h day in a most optimal (which was between 2 and 14h) and least optimal (14-2h) period with regard to timely culture processing.

Primary and secondary outcomes

Primary outcome for the study was the duration of each culture-processing step between incubation completion and the administration of the first dose of the changed antimicrobial regimen. We assessed the influence of the time of day of culture positivity on culture transport and gram stain duration and all subsequent culture processing steps using the two office hours variables introduced above. To check whether severity of the infection impacted culture-processing time, we also had a specific focus on the processing of *Staphylococcus aureus* bacteraemia cases and patient admitted on the ICU.[21]

Additionally, an infectious disease specialist from a neighbouring hospital judged if each administered antimicrobial regimen provided adequate coverage for the microorganisms in the blood culture. Adequate coverage after gram staining was defined as therapy with high expectation of clinical activity against the pathogen. Adequate coverage after full determination was defined as therapy for which the pathogen was susceptible in vitro. Naturally, treatments with antimicrobial drugs with insufficient pharmacokinetic characteristics were always judged inadequate, e.g. nitrofurantoin for *Escherichia coli* bacteraemia. In our definition of adequate therapy, whether or not a treatment is adequate is independent of for instance guideline adherence, e.g. treating amoxicillin-susceptible *Escherichia coli* with ceftriaxone constitutes adequate coverage, despite the fact that the lack of streamlining may be seen as inappropriate from the viewpoint of antimicrobial stewardship.[22] Judgments by this specific infectious disease specialist on the related concept of appropriateness of antimicrobial therapy have been shown valid and reliable when compared to colleagues.[23] Finally, we also report data on treatment advice adherence.

Statistical analysis

Linear regression was used to compare durations between office hours. All time variables were logistically transformed prior to the analysis. Additionally, a variable denoting antimicrobial coverage of the cultured microorganism(s) was added to each crude model to assess potential confounding. Confounding was considered relevant if the regression coefficient from the univariable analysis differed from the coefficient in the multivariable model (containing the potential confounder) by more than 10%. We compared antimicrobial coverage percentages of the cultured microorganism(s) between the empiric phase, after gram stain completion, and after final determination/susceptibility using logistic generalized estimating equations to adjust for clustering within patient cases. All analyses were performed using Stata 13 (StataCorp, USA). $P<0.05$ was considered significant for all analyses.

Results

Patients and cultures

We included positive blood cultures drawn from 136 patients. Culture results from 37 patients were judged to be a result of contamination and were excluded. Five patients were excluded because they were discharged or died before complete microorganism determination. See Table 1 for baseline characteristics.

Impact of time of day of incubation completion

Median durations of each post-incubation culture-processing step during or outside of office hours are shown in Figure 1. The difference in processing times between culture positivity during versus outside of office hours was largest for the transport and gram stain step, also resulting in significant differences when all post-incubation steps were added together. Figure 2 shows how the duration of the transportation and gram stain step varied per hour of the moment of incubation completion. Cultures positive for *Staphylococcus aureus* were highlighted to illustrate that processing times for this finding, which indicates a serious infection with high mortality,[21] were similar to those of cultures with other microorganisms. The same applied to patients admitted to the ICU. Based on the pattern of Figure 2, we constructed an alternative office hours variable denoting 02:00h-14:00h as the optimal period for speedy culture processing, results of which are also shown in Figure 1. Adding a variable denoting adequacy of empiric treatment to the model did not change the above findings substantially.

Table 1
Baseline characteristics

Patient characteristics				
Age in years, median (range)	69 (0-96)			
Admitted ward	n (%)	Adequate empiric coverage, %	Adequate coverage after Gram stain, %	Adequate coverage after determination, %
- Internal medicine	42 (45)	79	90	98
- ICU	13 (14)	54	62	100
- Cardiology	12 (13)	75	75	100
- Other (including surgery)	27 (29)	67	81	85
Site of suspected infection at time of culture collection, n (%)				
- Urinary tract	25 (27)	80	92	96
- Abdominal	18 (19)	67	67	88
- Sepsis without known site	17 (18)	65	88	100
- Lung	13 (14)	85	85	100
- Other	14 (15)	93	93	93
- No suspected infection	7 (7)	0	43	86
Total cultures/patients	94 (100)	70	82*	95**
Other characteristics			After Gram stain	After determination
Incubation in hours, median (IQR)	21 (17-34)			
Therapeutic advice given, %			88	72
Advice comprised antimicrobial change, %			33	54
Advice compliance, %			95	93
Drugs & microorganisms				
Most cultured microorganisms (%)	*Escherichia coli* (21, ESBL 4)	*Staphylococcus aureus* (18, all methicillin-susceptible)	*Enterococcus faecium (11)*	
Most prescribed antibiotics empirically (%)	Ceftriaxone (47)	Amoxicillin-clavulanate (17)	Meropenem (11)	
Most prescribed antibiotics after Gram stain	Ceftriaxone (35)	Amoxicillin-clavulanate (16)	Flucloxacillin (11)	
Most prescribed antibiotics after determination	Ceftriaxone (22)	Flucloxacillin (17)	Amoxicillin-clavulanate (12)	

ESBL, Extended spectrum betalactamase; IQR, interquartile range;
*p=0.03 compared to empiric treatment, ** p<0.05 compared to either previous phase

Discussion

Our findings suggest that blood culture-processing time is influenced by time of day a culture is flagged positive, in a medium-sized teaching hospital with offsite microbiological laboratory. We showed that median time from incubation completion to gram stain completion increased from 4 to 12 hours or even 16 hours depending on the definition of office hours, irrespective of the adequacy of the empirical antimicrobial regimen. This translated to a similar increase in the cumulative time from culture positivity to administration of the (changed) antibiotic. Previous studies showed that the offsite location of the laboratory is associated with increased time to start of culture incubation,[16,20] but delaying influence on the whole process from culture positivity including antibiotic administration has not been reported before. Interestingly, our data showed that the delay already showed for cultures completing incubation at 14h. In the context of the literature supporting early adequate treatment of bacteraemia and sepsis to reduce mortality,[1-7] this delay potentially undermines optimal clinical outcomes.

It could be argued that microbiologists might speed up culture processing if they knew that a certain patient was suspected of having a serious infection (i.e. sepsis, endocarditis etc.) To check whether our results also applied for patients with severe infections like those admitted to the ICU or with *Staphylococcus aureus* bacteraemia, we showed culture processing for these patients separately. We assumed ICU patients' culture transport and processing may have been fast-tracked. Similarly, although clinicians and microbiology would not yet have known the responsible pathogen for the *Staphylococcus aureus* patients at this stage, we hypothesized that these patients may have presented with more severe or typical symptoms leading to quicker processing as well.[21] However as Figure 2 shows, cultures for these two groups of patients followed the same delay pattern, suggesting that this was not the case.

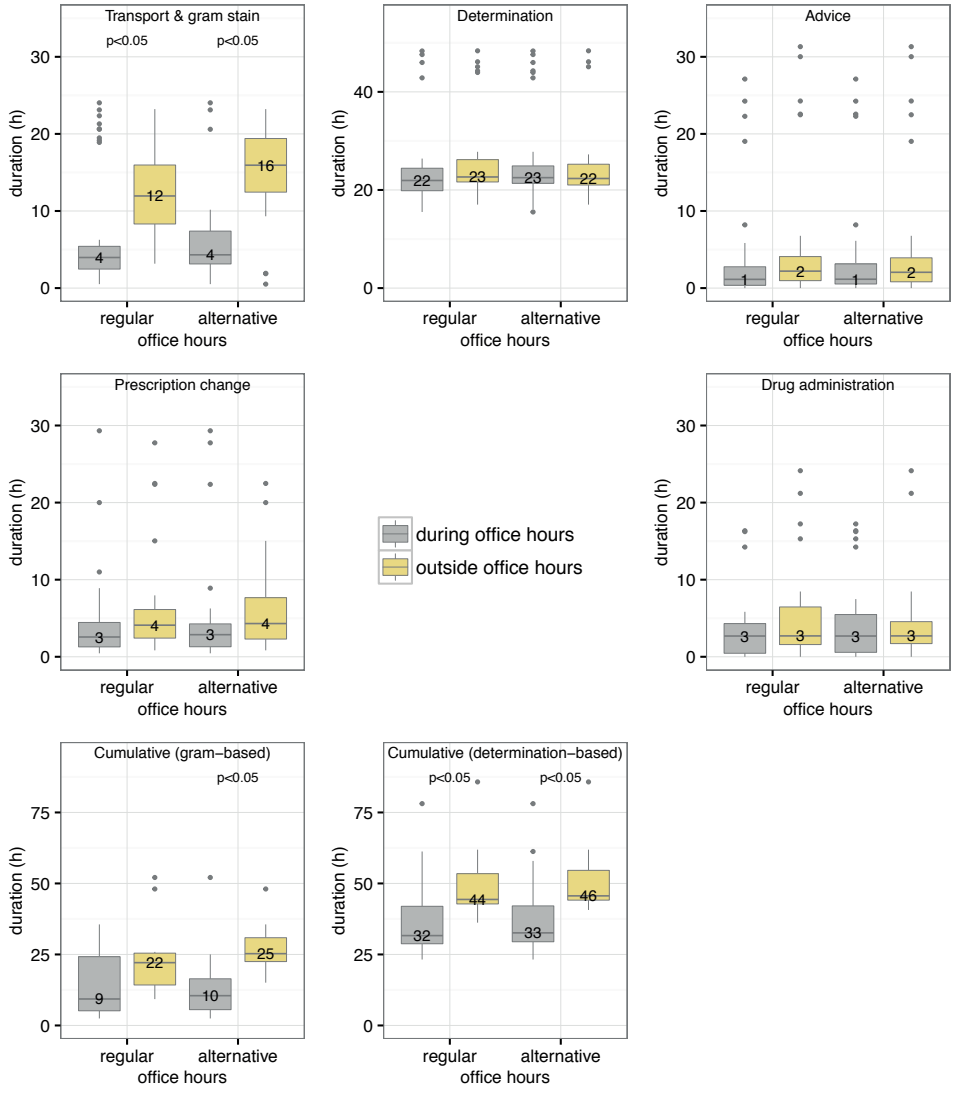

Figure 1

Box-plots of the duration of each culture-processing step stratified by two office hours variables denoting the moment culture positivity. Regular office hours were defined as the 8-17h period while alternative office hours were defined as the 2-14h period. Numbers in the boxes represent medians. In each of three culture-processing steps (transport & gram stain, determination, and cumulative (determination-based)), one outlier exceeded the y-axis limits and is thus not shown.

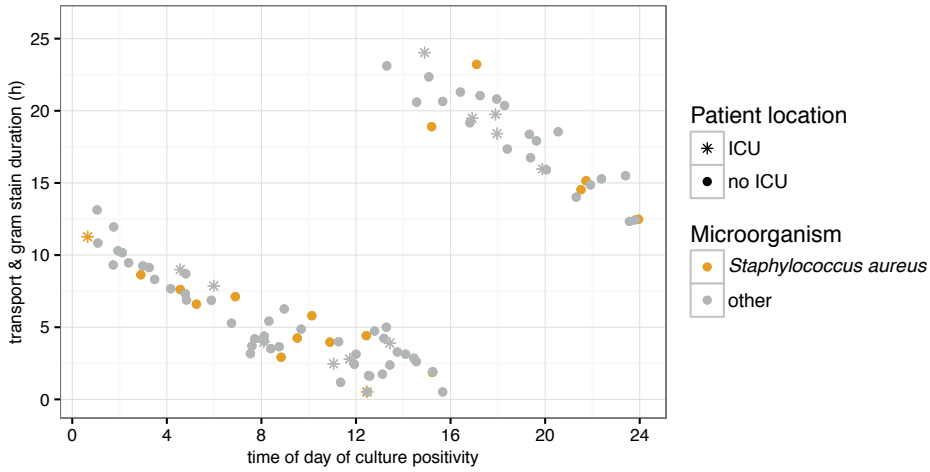

Figure 2

Scatterplot of the duration of culture transport & gram stain by hour of day of incubation completion. Cultures with *Staphylococcus aureus* and from patients admitted to the ICU are distinctly marked for illustrative purposes. One outlier exceeded the y-axis limits and is thus not shown.

An obvious solution would be to extend transportation and laboratory activity into the evening and night, or to use a transport and stain on demand solution. We would expect that in hospitals with similar characteristics to the hospital in our study, per four weeks, on average 6.3 positive, new, non-contaminated blood cultures would complete incubation between 14:00h and 02:00h. Of these cultures, 1.9 (30%) would belong to patients who thus would not receive adequate antimicrobial coverage for the cultured microorganism. Complete culture determination in our study decreased this non-coverage to 9% so the number of patients that would potentially benefit would be 1.3 every four weeks. Assuming that this solution would completely solve the problem of the after hours delay, it would allow on average 1.3 patients every four weeks to receive adequate antimicrobial coverage a median of 13 hours earlier than in the current situation. In other words, the delay is substantial in duration but is actually relatively infrequent. This naturally depends on hospital size and local epidemiology.

Another potential solution can be deduced by the finding that the delay already showed for cultures completing incubation as early as 14h. This suggests that increased efforts and coordination to get cultures flagged positive between 14 and 16h on the final transport to the laboratory and perform a Gram stain before closing time may prevent delays for these cultures.
Our results suggest there was no influence of time of day of incubation completion on culture processing speed after gram staining. This is not unexpected because the delays in the transport and gram stain step meant that this step often finished during office hours, which allowed the subsequent steps to take place during office hours as well. It must be noted that the timing of the treatment advice from the microbiologist is not the only determinant of the duration of prescription

change and drug administration. Other factors may have played a role, like physician-specific advice adherence rate or sufficient appreciation of the urgency of timely adequate treatment.

Our study has limitations. It contains a relatively small number of cultures, so a comparison of clinical patient outcomes was not feasible. Due to time-constraints, we could not collect every culture available in the inclusion period, so selection bias cannot be ruled out. However, the included cultures were from all parts of the calendar year to prevent influence of specific seasons. Moreover, the specific inclusion periods were chosen before data collection took place to prevent outcome bias. The single centre design and availability of data made it impossible to perform an isolated estimation of the effect of the offsite location of the laboratory. Still, our findings suggest that work done inside or outside of office hours results in a unequal standard of care for patients with bacteraemia. This inequality is infrequent, can be substantial and may be preventable. As outcomes and costs-effectiveness considerations are subject to local circumstances and epidemiology, we advise hospitals with similar offsite laboratories to investigate the extent of the problem in their centre to be able to act accordingly.

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and increased their self-rated confidence in presc study is unique
in that it estimates intervention impact by asse nts' behaviour in
a situation that simulates prescribing in clinic using an approach
recommended in literature.18 It is one of v ies to evaluate the
long-term impact (>12weeks) of a tempor nal intervention on
antimicrobial prescribing.11 The design of nd the availability of
prior student grades allowed us to create c comparisons between
intervention and control groups. The the short-term effect
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analyses show that intervention impa cant when averaged for the
whole group, although a considerab e of students either did not
access the e-learning at all or only s reflects intervention impact
in practice, as participation in nor y education is seldom expected
to be perfect. The as-treated r t the 'true effect' is higher, as
would be expected. The e-lear mprised certain factors that may
have enhanced its effectivene important to mention for future
replication attempts.5 They roblem-based architecture;2,15 the
inclusion of interactive el cises and feedback;16 and the use
of the WHO six step pla escribing, which is a method known
to improve therapeutic f medical students.17,20 Moreover,
the e-learning was im urriculum with pharmacotherapy

Improving antibiotic prescribing skills in medical students: the effect of e-learning after 6 months

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long-term effects of a short interactive e-learning course among fourth year medical students in a Dutch university. The e-learning was temporarily implemented as a non-compulsory course during a 6 week period. Six months later, all students underwent an infectious disease-based objective structured clinical examination (OSCE) aimed at simulating postgraduate prescribing. If they passed, each student did the OSCE only once. We created a control group of students from a period when the e-learning was not implemented. Main outcomes were the OSCE pass percentage and knowledge, drug choice and overall scores. We used propensity scores to create equal comparisons. Results: We included 71 students in the intervention group and 285 students in the control group. E-learning participation in the intervention group was 81%. The OSCE pass percentage was 86% in the control group versus 97%

Abstract

Background: Antimicrobial prescribing behaviour is first established during medical study, but teachers often cite lack of time as an important problem in the implementation of antimicrobial stewardship in the medical curriculum. The use of electronic learning (e-learning) is a potentially time-efficient solution, but its effectiveness in changing long-term prescribing behaviour in medical students is as yet unknown.

Methods: We performed a prospective controlled intervention study of the long-term effects of a short interactive e-learning course among fourth year medical students in a Dutch university. The e-learning was temporarily implemented as a non-compulsory course during a 6 week period. Six months later, all students underwent an infectious disease-based objective structured clinical examination (OSCE) aimed at simulating postgraduate prescribing. If they passed, each student did the OSCE only once. We created a control group of students from a period when the e-learning was not implemented. Main outcomes were the OSCE pass percentage and knowledge, drug choice and overall scores. We used propensity scores to create equal comparisons.

Results: We included 71 students in the intervention group and 285 students in the control group. E-learning participation in the intervention group was 81%. The OSCE pass percentage was 86% in the control group versus 97% in the intervention group (+11%, OR 5.9, 95% CI 1.7–20.0). OSCE overall, knowledge and drug choice grades (1–10) were also significantly higher in the intervention group (differences +0.31, +0.31 and +0.51, respectively).

Conclusions: E-learning during a limited period can significantly improve medical students' performance of an antimicrobial therapeutic consultation in a situation simulating clinical practice 6 months later.

Introduction

Education is an essential pillar of antimicrobial stewardship.[1] The basis for professional behaviour is laid during the first years of medical study. Interventions to promote prudent antimicrobial prescribing should therefore increasingly focus on undergraduates, rather than on postgraduates only.[2] A recent survey revealed that European medical teachers feel the subject of prudent antimicrobial prescribing should be prioritized. However, teachers cited time restriction as the most important obstacle.[3] Electronic/internet-based learning (e-learning) offers an interesting potential solution to this problem because, after creation, large groups of students can participate with a relatively small investment of time and cost.[4,5]

E-learning can be equally effective as an alternative education method in improving patient-related outcomes and influencing healthcare professionals.[6] E-learning has shown positive effects on drug prescribing, but more evidence regarding behaviour change in practice and long-term retention (>12weeks) is needed.[4,7–9] Educational interventions on antimicrobial prescribing have shown effectiveness,[10–14] but effects could not always be isolated from other intervention effects. The question remains whether a short period of e-learning can improve antimicrobial prescribing skills and behaviour in undergraduates in the long term.

We developed a problem-based, interactive e-learning module on antimicrobial prescribing for fourth year medical students, con- forming to scientific recommendations.[2,15,16] We tested the e-learning's long-term (after 6 months) effectiveness in improving student competence in performing a therapeutic infectious dis- ease consultation in a simulated patient situation.

Methods

Design

Prospective controlled intervention study of long-term effects, combined with randomized controlled intervention study of short-term effects (knowledge only).

Population

Medical students at the VU University Medical Centre Amsterdam, The Netherlands.

Participant selection and study groups

The e-learning module was introduced in the fourth year (out of six) of the medical curriculum between September 2011 and August 2012. Students were informed about the e-learning programme during an education lecture and asked to complete an antimicrobial knowledge pre-test. Afterwards, students were randomized to either direct e-learning access for 6 weeks or no e-learning (control group 1). E-learning group students received an e-mail link to the e-learning and up to three reminder e-mails in the case of >80% e-learning completion. E-learning access ended shortly before the antimicrobial knowledge post-test. To allow each student equal access to education, students in control group 1 were given access to the

e-learning after the post-test. Owing to the potential risk of exposure to the e-learning (i.e. contamination), control group 1 was excluded from the long-term analysis.

We created another control group (control group 2) for the long-term effect analysis of all students not included in the intervention group or control group 1 who had started their fourth year of the curriculum between September 2009 and September 2012. Figure S1 (see supplement) shows the full inclusion process for each study group. The study was approved by the national educational ethical review board (NVMO-ERB).

E-learning module

The e-learning module was built into the Dutch e-learning portal MedischOnderwijs.nl (in Dutch, to access: click https://www.medischonderwijs.nl?LESSONID=1693, register for free and click link again), comprised eight clinical cases and was based on the WHO's guide to good prescribing,[17] similar to the paradigm of the pharmacotherapy education in the curriculum. The e-learning included an evaluation survey (created in SurveyMonkey, http://www.surveymonkey.com).

Measurements

The antimicrobial knowledge tests comprised 57 multiple-choice questions each, validated by several experts.

The objective structured clinical examination (OSCE) aimed to simulate prescribing behaviour in clinical practice and was set up concordant with recommendations from literature including use of a patient actor;[18] also see the Supplementary methods and previous literature.[19] The final product of the exam was a written prescription for an infectious disease case. Students were scored on overall performance based on a standardized score system including subscores for drug choice and knowledge. Examiners were blinded to group allocation.

Outcomes

Primary outcomes were based on evaluation of long-term e-learning effects and comprised overall drug choice and knowledge OSCE scores (all grades 1–10, higher scores indicating a better performance) and OSCE pass percentage (overall score >5.5). Secondary outcomes were the short-term effect of e-learning on knowledge by comparing scores on the second antimicrobial knowledge test while controlling for scores on the first test; and students' evaluation of the e-learning.

Statistical analysis

We used the intention-to-treat principle to define intervention status. We determined the effect of the intervention by comparing outcomes between the intervention group and control group 1 for short-term effects and control group 2 for long-term effects. Univariate linear or logistic regression was used for all comparisons. We used propensity scores to control for confounding effects of students' prior level, case differences and use of different examiners to allow valid comparisons. We also performed an as-treated analysis. We considered $p>0.05$ significant.

See the Supplementary methods for more details on the medical curriculum, outcome measures and statistics.

Results

Inclusion

We included 56 students in control group 1, 68 students in the e- learning group for the short-term comparison, 285 students in control group 2 and 71 students in the e-learning group for the long-term comparison. Details of inclusion are shown in Figure S1 (see supplement). Baseline characteristics of study groups are shown in Table 1.

Table 1
Baseline characteristics of study groups.

Short-term effects analysis			
	E-learning group	Control group 1	Total
N	68	56	124
Female (%)	49 (72)	43 (77)	92 (74)
Age in years (range)	23.5 (20-38)	23.4 (21-48)	23.5 (20-48)
Average score on antimicrobial test 1 (range)	4.0 (1.7-7.4)	4.0 (1.7-6.0)	4.0 (1.7-7.4)
Average score on pharmacotherapy exam in prior year	6.7 (3.9-9.1)	6.4 (2.5-8.8)	6.6 (2.5-9.1)
E-learning			
- ever opened (%)	56 (82)	-	-
- up to 25% completed (%)	11 (16)	-	-
- 25 to 75% completed (%)	17 (25)	-	-
- 75 to 100% completed (%)	28 (41)	-	-
Long-term effects analysis			
	E-learning group	Control group 2	Total
N	71	285	356
Female (%)	52 (73)	200 (70)	252 (71)
Age in years (range)	23.5 (20-38)	23.1 (20-41)	23.2 (20-41)
Average score on pharmacotherapy exam in prior year	6.7 (2.8-9.1)	6.8 (2.5-9.6)	6.8 (2.5-9.6)
E-learning			
- ever opened (%)	58 (82)	-	-
- up to 25% completed (%)	11 (15)	-	-
- 25 to 75% completed (%)	18 (25)	-	-
- 75 to 100% completed (%)	29 (41)	-	-

E-learning effects

Students in the e-learning group scored significantly higher on all continuous outcomes compared with control group students (Figure 1). OSCE pass percentage was also significantly higher for e-learning group students compared with control group students (97% versus 86%, n=346, OR 5.90, 95% CI 1.74–20.01, p=0.004). Effect sizes increased when using an as-treated approach (Figure S2, see supplement).

Evaluation survey

Students rated the e learning as instructive (average score from 1 to 10 was 7.4), 77% rated it as entirely relevant, but 55% rated it as too extensive. When questioned on their confidence in prescribing antimicrobial therapy in clinical practice prior to and subsequent to the e-learning, the percentage of students indicating insecurity or severe insecurity decreased from 74% to 37% (p=0.002).

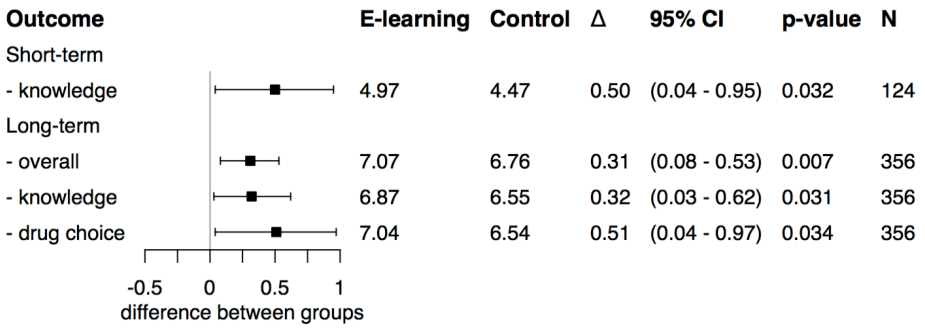

Figure 1
Continuous outcomes from students in the e-learning group compared with control group students. The possible grade range was 1–10, with higher scores indicating a better performance.

Discussion

This prospective controlled intervention study showed that access to e-learning for a limited time period significantly improved medical students' long-term antimicrobial drug choice, antimicrobial knowledge and overall performance during an antimicrobial therapeutic consultation with a patient actor. In order to shape future antimicrobial prescriber behaviour, it is very important to identify resource-effective tools that can improve undergraduates' prescribing competence, rather than at a later stage when physicians have already begun clinical practice.[2] Our results suggest that e-learning may be just that. Although the main results on the continuous outcomes were relatively small

(0.31–0.51 difference on a 1–10 scale; Figure 1), results on the pass percentage (11% difference) suggest that the intervention made a difference where it matters: among students whose prescribing competence balanced around the fail/pass level. The e-learning was rated positively by students and increased their self-rated confidence in prescribing.

Our study is unique in that it estimates intervention impact by assessing students' behaviour in a situation that simulates prescribing in clinical practice, using an approach recommended in literature.[18] It is one of very few studies to evaluate the long-term impact (>12weeks) of a temporary educational intervention on antimicrobial prescribing.[11] The design of the study and the availability of prior student grades allowed us to create optimal equal comparisons between intervention and control groups. The inclusion of the short-term effect analysis made it possible to assess direct impact on knowledge and a potential fade of knowledge retention over time.
The results of the intention-to-treat analyses show that intervention impact was significant when averaged for the whole group, although a considerable percentage of students either did not access the e-learning at all or only partially. This reflects intervention impact in practice, as participation in non-compulsory education is seldom expected to be perfect. The as-treated results suggest the 'true effect' is higher, as would be expected.

The e-learning used comprised certain factors that may have enhanced its effectiveness, which are important to mention for future replication attempts.[5] They include its problem-based architecture;[2,15] the inclusion of interactive elements, exercises and feedback;[16] and the use of the WHO six step plan to good prescribing, which is a method known to improve therapeutic competence of medical students.[17,20] Moreover, the e-learning was implemented in the curriculum with pharmacotherapy education using the same paradigm.[20] Although the curriculum was identical for the control group students, the interaction between e-learning and the curriculum may have supported long-term retention of learning effects.

We need to address some limitations. Assessment of students' skills is subjective and can lead to inconsistent results, which we aimed to diminish by using a structured assessment approach and adjustment for examiner effects. The results of the antimicrobial knowledge post-test were low across groups, suggesting the test may have been too difficult. This may have caused an imperfect measurement of student knowledge level. Finally, because our study included students who had to study for an additional 2 years after the OSCE, it is unclear how much of the e-learning effect will be present when they start prescribing in practice. Repeating the e-learning, for instance in postgraduate training, may be important.

We have shown that e-learning access during a limited time period can significantly improve medical students' long-term antimicrobial drug choice, antimicrobial knowledge and overall performance of an antimicrobial therapeutic consultation in a situation simulating clinical practice.

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Supplement

Methods

Medical curriculum

The medical curriculum in which the study was performed had a bachelor (three years) and masters (three years) structure, in which the bachelor comprised mostly theoretical education in the faculty, combined with a few short internships. The bachelor included a course on infectious diseases and microbiology, including antimicrobial chemotherapy. The master comprised a series of internships inside and outside the hospital, combined with a two-month science internship, and three months of free choice education. Every three weeks, a group of around 20 students started with the fourth year of the Master. Because we wanted to include each student at the exact same time point in their study, we followed this group structure in our inclusion. E-learning participation was voluntary and unlinked to study credits or grades. All interventions and measurements were part of the regular curriculum at the time of the study. Students did not have experience of prescribing antibiotics under supervision at time of inclusion.

Randomisation

Randomisation was performed using the random number function in the SPSS version 20 software package, using a 55:45 ratio in favour of the intervention group, in order to account for student dropout in the long term analysis.

Antimicrobial knowledge tests

Both antimicrobial knowledge tests comprised 57 unique multiple choice questions. Difficulty was targeted at medical study end terms. The quality and difficulty of the tests were validated by two infectious disease specialists, a clinical microbiologist, a clinical pharmacologist, a general practitioner and a medical examination specialist.

OSCE

The OSCE took 15 minutes, and was observed and assessed by an examiner from the pharmacotherapy department. The OSCE comprised three parts: 1. case preparation, 2. consultation, in which the student performed a therapeutic consultation with a patient-actor, discussing the therapeutic options, therapy choice, side effects and follow-up instructions; and 3. structured discussion with the examiner on pre-defined topics. During the OSCE (discussion part excluded), use of any information resource (e.g. internet) was allowed. Prior to the OSCE, students were informed that the case would deal with one of 19 diagnoses. Only a minority of these diagnoses were infectious diseases but for the current study only infectious disease cases were used. Examiners used a standardised scoring form to score overall performance on the OSCE based on the WHO 6-step, and contained several sub-scores including prescription quality (20% of total score) and knowledge (20% of total score). In the curriculum, exam failure resulted in postponement of continuance of the course until the exam was successfully retried.

Statistical analysis

To determine students' prior level in the long-term analysis we used scores on the pharmacotherapy exam in their third year, a similar exam to the OSCE but without patient-actor consultation. Students' scores on the antimicrobial knowledge pre-test were used for the short-term analysis. All analyses were performed using Stata version 12 (Stata Corp, College Station, TX, USA). Sample size calculations showed that a minimum sample size of 63 students per group was needed to detect a difference of 0.75 on continuous scores, assuming a baseline of 6.5, and a standard deviation of 1.5. To detect a 10% OSCE pass difference and assuming a 90% baseline, the minimum sample size was 71 students per group. We used a power of 80% and considered $p<0.05$ as significant. We also performed analyses according to an as-treated model in which intervention group status was determined by actual E-learning participation rather than study group allocation.

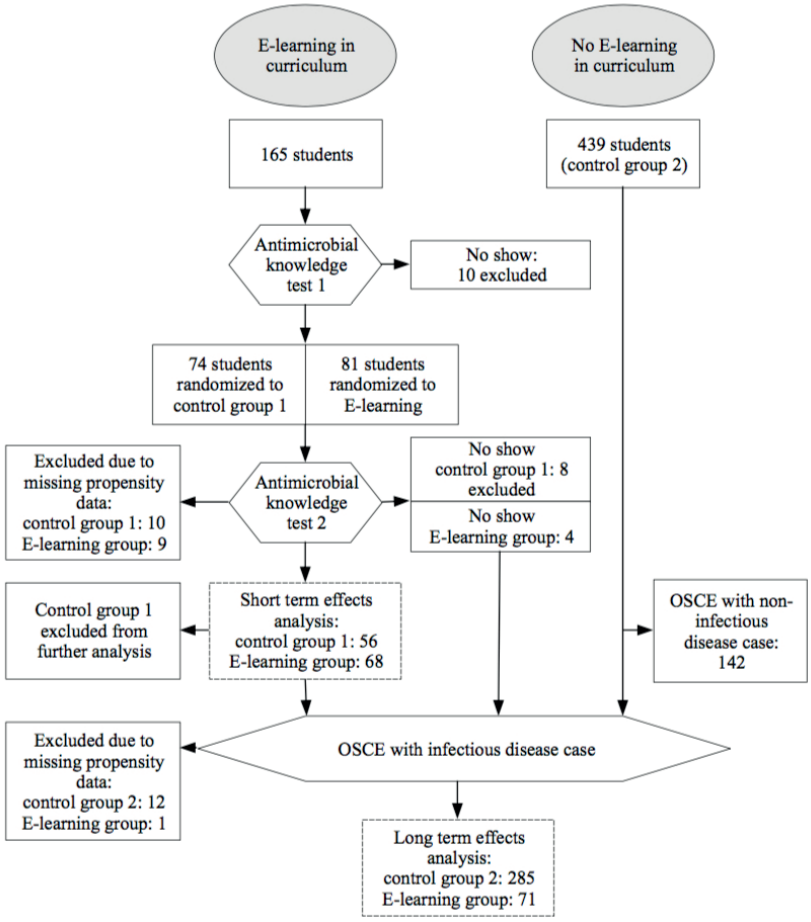

Figure S1
Inclusion and exclusion of participants at specific time points.

Results

Inclusion

Due to a miscalculation, some students had to be excluded from the analysis as propensity variable information was missing, see Figure S1 (above) for all inclusion details.

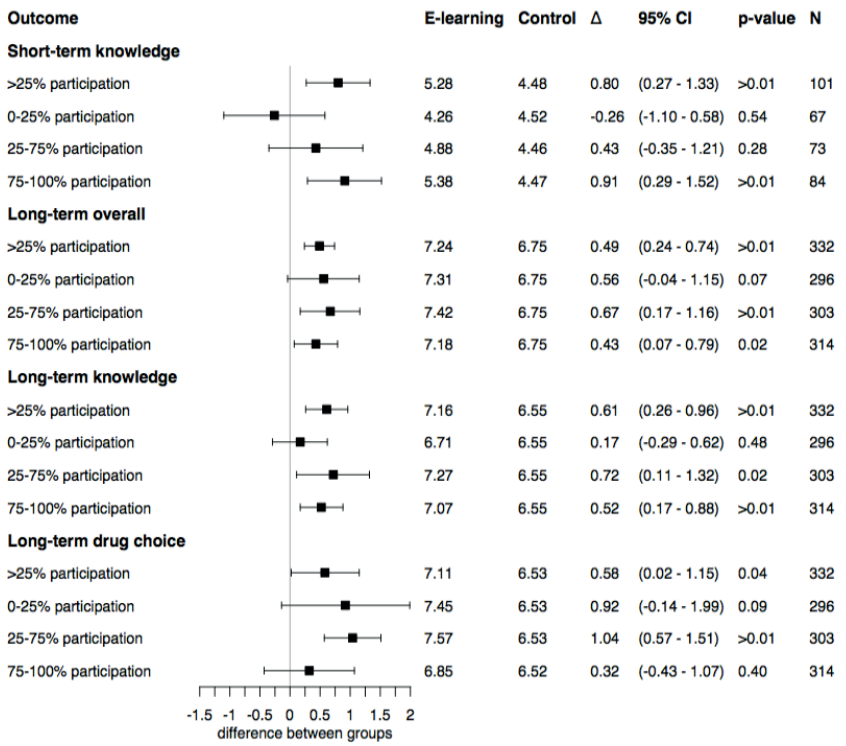

Figure S2

As-treated results on OSCE continuous outcomes. Outcomes from students in the E-learning group compared to control group students for continuous outcomes, using an as-treated approach based on the extent of E-learning completion by the student.

As-treated results on OSCE pass-percentages

OSCE pass percentage results according to the same as-treated approach were (E-learning versus control):

>25% completed: 98% versus 86%, OR 10.01, 95% CI 1.34-75.02, p=0.03;

0-25% completed: 87% versus 86%, OR 1.11, 95%, CI 1.34-75.02, p=0.89;

25-75% completed: 100% versus 85%, OR could not be calculated due to 100% pass mark;

75-100% completed: 100% versus 88%, OR could not be calculated due to 100% pass mark.

Due to unequal distribution between groups, the as-treated analyses could not be controlled for the effect of the OSCE examiner or case differences.

Participants provided bac[illegible] filled out a questionnaire consisting of a kno[illegible] on the perceived importance of [illegible] the Dutch [illegible] Self-Regulation Questionnair[illegible]e (SRQ-a). The Engl[illegible] the SRQ-a is downlo[illegible] the SDT website, after[illegible] and after providing [illegible]n that it will be used for [illegible]oses only (http://s[illegible]iontheory.org/self-regulation-q[illegible]). All respond[illegible]pleted the questionnaire receiv[illegible]ntials for the e-le[illegible]which were valid for two weeks[illegible]eks, non-respon[illegible]minder, extending the creden[illegible]ner week. The kn[illegible]rised 37 questions. This t[illegible]ed slightly from a p[illegible]which had been asses[illegible]nt validity by infectious [illegible]dical microbiol[illegible]al practitioner and an asse[illegible]on was [illegible] content validity once more, b[illegible]us diseases physicians. The Dutch ve[illegible]otivation for a specific educational activity [illegible] assessed for internal consistency.15 It is used[illegible]tivation (RAM), an index that provides [illegible]timating the amount of auton[illegible]ontrolled motivation. R[illegible]ed by assig[illegible]s of the four subsc[illegible]regulation (+2), ide[illegible]jected regulatio[illegible]regulation. This generate[illegible]48, in which [illegible]uggests a predominantly autono[illegible]ofile, and a [illegible]ndicates a predominantly contro[illegible]ofile. We [illegible]e-learning module through P-[illegible]ased progr[illegible]n the WHO Guide to Good Presc[illegible]acks partic[illegible]module comprised a case of endo[illegible]ersed with i[illegible]antibiotics. The subject was cho[illegible]more compli[illegible]such as endocarditis, allowed[illegible]om for backgro[illegible]Participants were not aware[illegible]ct before participati[illegible]e module included quest[illegible]ct feedback to increase [illegible]and national [illegible] provided to assist in decisio[illegible]prescribing in the clinical setting. Com[illegible]participants were allowed

to stop and resume. One physician-researcher and three infectious diseases physicians independently assessed the module for content validity. After completion of the module, we administered the Instructional Materials Motivation Survey (IMMS). The IMMS is a frequently used questionnaire that measures motivation for educational materials, and has been tested extensively for validity in medical education.17,18 The IMMS consists of 36 statements on four domains (ARCS)19: The Attention domain assesses whether the material can hold the student‘s attention; Relevance assesses whether the content relates

E-learning on antibiotic prescribing–the role of autonomous motivation in participation: a prospective cohort study

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SPSS 22.0 for Windows (IBM SPSS Inc., Chicago, IL, USA). Results RAM and participation Eighty-six residents participated in the study (characteristics in table 1). Overall participation in the e-learning was 58% (n=50). Participation was 41% in residents with negative RAM (i.e. more controlled motivation) and 62% in residents with positive RAM (i.e. more autonomous motivation). Figure 1 shows the mean participation in the RAM percentile groups. education using the same paradigm.20 Although the curriculum was identical for the control group students, the interaction between e-learning and the curriculum may have supported long-term retention of learning effects. We need to address some limitations. Assessment of students' skills is subjective and can lead to inconsistent results, which we aimed to diminish by using a structured assessment approach and adjustment for examiner effects.

Abstract

Objectives: E-learning is increasingly used in education on antimicrobial stewardship, but participation rates are often low. Insight into factors that affect participation is therefore needed. Autonomous motivation is associated with higher achievements in medical education and could also play a role in e-learning participation. We therefore aimed to investigate the role of residents' autonomous motivation in their participation in e-learning on antibiotic prescribing.

Methods: We performed a multicentre cohort study in two academic and two teaching hospitals. Residents who filled out questionnaires on antibiotic knowledge, the perceived importance of antibiotics and motivation [Self-Regulation Questionnaire – Academic (SRQ-a)] received e-learning access. We used the SRQ-a to calculate relative autonomous motivation (RAM), an index that estimates the amount of autonomous motivation compared with the amount of controlled motivation. We then analysed associations between RAM and participation in e-learning with logistic regression.

Results: Eighty-six residents participated (74% female, mean age 30 years). Overall e-learning participation was 58% (n=50). Participation was 41% in residents with negative RAM (i.e. more controlled motivation) and 62% in residents with positive RAM (i.e. more autonomous motivation). RAM was positively associated with participation, adjusted for residency in an academic hospital (adjusted OR 2.6, 95% CI 1.5–4.6).

Conclusions: Participation in non-obligatory e-learning on antibiotic prescribing is higher in residents with more autonomous motivation. Interventions to increase autonomous motivation could improve participation. Preceding e-learning on antibiotic prescribing with face-to-face education, to explain the importance of the subject, could enhance autonomous motivation and thus optimize e-learning efficiency.

Introduction

A common scenario in the clinical setting is that residents report a lack of knowledge on antibiotics and ask for more education on antibiotic prescribing. Yet when we offer them e-learning on the subject, participation rates are low. Why do they not participate, when they say they want to learn?

This question is important, as e-learning is increasingly used in antimicrobial stewardship programs.[1,2] The advantages of e-learning are legion: it provides flexibility and allows interactivity and progress tracking, and, after initial development, modules are easily distributed among large groups and across the globe, against relatively small investments of time and costs.[3,4] At the same time, e-learning requires a lot of motivation, as it is usually non-obligatory and followed individually.

In contrast to earlier beliefs, as stated by the Self-determination Theory, motivation should not be viewed as a trait that is either present or absent, but rather as a continuum with different states. More extrinsically motivated states, in which motivation comes from rewards (such as credits) are collectively called controlled motivation. Autonomous motivation comprises the more intrinsically motivated states, meaning that motivation originates from an interest in the subject or an understanding of its importance.[5] Studies have shown that autonomous motivation is associated with higher study effort in medical students,[6] higher achievements in residents[7] and more participation in continuing education among pharmacists.[8] Autonomous motivation could therefore also play a role in e-learning participation.

We investigated this for the important subject of antibiotic prescribing. Inappropriate use of antibiotics can be found in up to a staggering 50% of prescriptions,[9,10] which can lead to unnecessary side effects, costs and development of antimicrobial resistance. Education is viewed as an essential element of any hospital program that aims to influence antibiotic prescribing behavior.[11] This is recognized by residents, who have expressed the need for more education on the subject.[12,13] We therefore developed an e-learning module on antibiotic prescribing and performed a multicentre cohort study among residents to investigate the association between autonomous motivation and participation in e-learning.

Materials & methods

Design

We conducted a multicentre cohort study and asked residents from two university medical centres (providing tertiary care) and two teaching hospitals to participate during a scheduled teaching session. The study was conducted in the departments of internal medicine, cardiology and clinical geriatrics, because of their high number of in-hospital antibiotic prescriptions. At the time of study, none of the departments had mandatory education on antibiotic prescribing.

Data-collection

Participants provided background information and filled out a questionnaire consisting of a knowledge test on antibiotics, questions on the perceived importance of antibiotics, and the Dutch version of the Self-Regulation Questionnaire – Academic (SRQ-a). The English version of the SRQ-a is downloadable from the SDT website, after registration and after providing a declaration that it will be used for research purposes only (http://selfdeterminationtheory.org/self-regulation-questionnaires/). All respondents who completed the questionnaire received login credentials for the e-learning module, which were valid for two weeks. After two weeks, non-responders received a reminder, extending the credentials for another week.

The knowledge test comprised 37 questions. This test was adapted slightly from a previously designed test, which had been assessed for content validity by infectious diseases physicians, a medical microbiologist, a general practitioner and an assessment expert. The new version was assessed for content validity once more, by one physician researcher and three infectious diseases physicians.

The Dutch version of the SRQ-a[14] assesses motivation for a specific educational activity using four subscales and was previously assessed for internal consistency.[15] It is used to measure Relative Autonomous Motivation (RAM), an index that provides a general self-determination score by estimating the amount of autonomous motivation compared with the amount of controlled motivation. RAM is calculated by assigning weights, and adding scores of the four subscales of intrinsic regulation (+2), identified regulation (+1), introjected regulation (−1) and external regulation (−2). This generates a score from -48 to +48, in which a positive RAM suggests a predominantly autonomous motivation profile, and a negative RAM indicates a predominantly controlled motivation profile.

We developed an e-learning module through P-scribe, a web-based programme based on the WHO Guide to Good Prescribing, which tracks participation.[16] The module comprised a case of endocarditis, interspersed with information on antibiotics. The subject was chosen because a more complicated infection, such as endocarditis, allowed us more room for background information. Participants were not aware of the subject before participation. The e-learning module included questions with direct feedback to increase interactivity. Local and national guidelines were provided to assist in decision-making and to mimic the process of prescribing in the clinical setting. Completion took 60-90 minutes; participants were allowed to stop and resume. One physician-researcher and three infectious diseases physicians independently assessed the module for content validity.

After completion of the module, we administered the Instructional Materials Motivation Survey (IMMS). The IMMS is a frequently used questionnaire that measures motivation for educational materials, and has been tested extensively for validity in medical education.[17,18] The IMMS consists of 36 statements on four domains (ARCS)[19]: The Attention domain assesses whether the material can hold the student‘s attention; Relevance assesses whether the content relates to future application; Confidence assesses the connection with prior knowledge; and Satisfaction assesses appreciation of

the material. We used the IMMS scores to assess the value of our e-learning as an educational tool.

Analysis

Descriptive analyses were used to summarize study population characteristics and IMMS scores. We calculated means with standard deviations for normally distributed data, and medians with IQRs for data with non-normal distribution.

To our knowledge, there is no literature on the psychometric properties of the SRQ-a regarding responsiveness (i.e. whether the questionnaire is capable of measuring changes in score). As the scale of RAM spans from -48 to +48, we considered a 10-point difference relevant, indicating a change in RAM of around 10%. We therefore divided RAM by 10 and then assessed the association between RAM and e-learning participation with logistic regression analysis, adjusting for residency in an academic hospital, gender, clinical experience and prior knowledge on antibiotic prescribing (measured as test score). All analyses were performed in SPSS 22.0 for Windows (IBM SPSS Inc., Chicago, IL, USA).

Results

RAM and participation

Eighty-six residents participated in the study (characteristics in table 1). Overall participation in the e-learning was 58% (n=50). Participation was 41% in residents with negative RAM (i.e. more controlled motivation) and 62% in residents with positive RAM (i.e. more autonomous motivation). Figure 1 shows the mean participation in the RAM percentile groups.

Table 1
Study population characteristics

Age (years), mean (SD)	30 (5)
Female, n (%)	64 (74)
Clinical experience (years), n (%)	
≤ 1	24 (28)
1-4	40 (47)
> 4	22 (26)
Academic hospital, n (%)	58 (67)
Residency, n (%)	
cardiology	14 (16)
clinical geriatrics	5 (6)
internal medicine	63 (73)
other	4 (5)
RAM	
median (IQR)	7.3 (2-18)
min–max	-22 to +37

Logistic regression analysis showed a significant association between RAM and participation in e-learning, with a crude OR of 2.1 (95% CI 1.3-3.4). This means that for every 10-point increase in RAM, the odds of participation increase by 2.1. Residency in an academic hospital was a significant confounder, providing an adjusted OR of 2.6 (95% CI 1.5-4.6), but was not an effect modifier. More clinical experience and prior knowledge were not significant confounders in either model, and there were no differences between female or male participants, nor was there an association between receiving a reminder and participation.

Almost all residents (97%) agreed or strongly agreed that strong knowledge of antibiotics is important in their career and that they would like more education on the appropriate use of antibiotics and on antibiotic resistance.

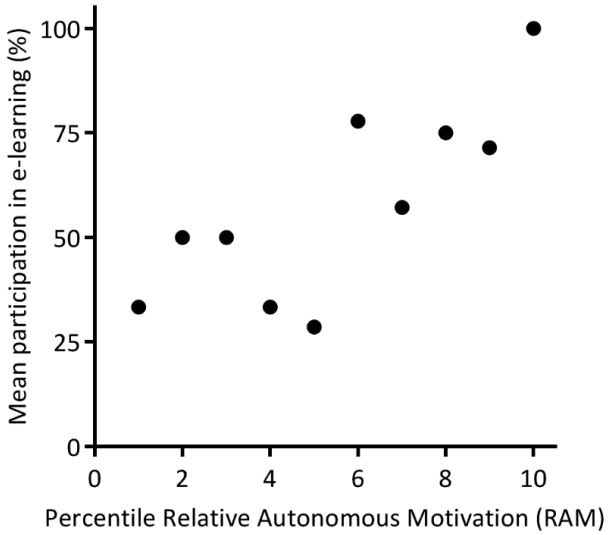

Figure 1
Mean participation in e-learning in RAM percentile groups.

IMMS

More than half of the participants completed the e-learning module (n=28, 56%), of which 23 completed the IMMS. The median overall IMMS score was 71% (IQR 66%-78%). Median scores on the separate domains of Attention, Relevance, Confidence and Satisfaction were 70% (IQR 65%-82%), 76% (IQR 69%-82%), 76% (IQR 62%-78%), and 63% (IQR 57%-73%), respectively.

Discussion

Our study shows that residents who report more autonomous motivation for education on antibiotics are more likely to engage in an e-learning module on the subject. These findings are in line with earlier studies on type of motivation and performance in medical education: autonomous motivation was associated with higher study effort in medical students[6] and more participation in continuing education among pharmacists.[8] However, the role of autonomous motivation in e-learning participation on antibiotic prescribing has not been previously described.

In our study, 97% of residents indicated that strong knowledge of antibiotics is important in their career, and that they would like more education on its appropriate use. Still, participation in the e-learning was only 58%. This discrepancy, i.e. the wish for more education but lack of participation when this is provided, is in line with the small amount of data available on the subject,[20] and is often attributed to a lack of motivation. However, in contrast to earlier beliefs, motivation should not be viewed as a trait that is either present or absent, but rather as dynamic along a continuum with different states. More importantly, a person's state of motivation is not set in stone, but can vary across different subjects,[21] and can change over time.

The self-determination theory (SDT) describes motivation as controlled (originating from sanctions or rewards) or autonomous (coming from a genuine interest in the subject, or identifying with the subject's value or importance).[5,22] In contrast to controlled motivation, autonomous motivation facilitates deep learning and integration of what is taught[23] and is therefore the sought after state of motivation. Making e-learning obligatory, although perhaps effective, would thus not be a desirable solution. The SDT points to several prerequisites for autonomous motivation: autonomy (the perception of having a choice in learning efforts), competence (feeling capable of mastering the material) and relatedness (a sense of belonging to a professional learning community).[24] This means that we can enhance autonomous motivation by incorporating these prerequisites in our educational activities.[21,25]

So how can this help us to improve participation in e-learning? E-learning already appeals to autonomy and competence, as it provides learners with a flexible, adaptive form of learning. However, as a remote learning method, it can lack a sense of relatedness. Relatedness can be enhanced by providing learners with a meaningful rationale, so that they can identify with reasons to learn more on the subject and thus engage in learning activities.[26] This approach is supported by several behaviour change models such as the theory of planned behaviour (TPB)[27] and the Knowledge, Attitude, Behaviour change (KAB) model, which focus on the importance of attitude when aiming to change behaviour. The KAB model, for instance, states that better understanding leads to a change in attitude, which in turn leads to a change in behaviour, thereby suggesting that education can influence behaviour.[28] This has also been shown in relation to autonomous motivation: if students identify with the value or importance of the subject, their autonomous motivation for

education increases, indicating that attitude towards a subject influences motivation to learn.[5,22] For e-learning in antimicrobial stewardship, this means that face-to-face education prior to the module, explaining the importance and thereby influencing attitude, could enhance autonomous motivation and thus increase participation.[29,30] This is already applied in "blended" learning, which is increasingly used as an innovative and effective method to integrate e-learning with face-to-face instruction.[31]

Our study has strengths and limitations. To our knowledge, this is the first study to address the role of autonomous motivation in participation in e-learning on antibiotic prescribing. Although our sample was limited, we included residents from multiple centres and specialties, and found a consistent association between autonomous motivation and participation across subgroups. We adjusted for factors that could have influenced participation such as workload (which is usually considered lower in University Medical Centres compared with teaching hospitals), clinical experience, and previous knowledge on the subject of antibiotics. Our findings are supported by the SDT, which is a rigorously investigated and validated theory on motivation, and fit into the larger frameworks of behaviour change. However, supervisors of the participating residents were aware of the study and availability of the e-learning. This may have triggered participation in residents with more controlled motivation, which could have reduced differences in participation with their autonomously motivated colleagues. The module was available for three weeks; participation rates could have been higher had availability been extended. We did not collect data on reasons for non-participation; factors unrelated to autonomous motivation, such as distractions at work or at home, could have influenced the effect.

E-learning is increasingly used in antimicrobial stewardship interventions, but simply making a module available may not be sufficient, as many people may not participate.[26] Participation could be improved by increasing autonomous motivation, for instance by combining e-learning with face-to-face education that explains the importance and relevance of prudent use of antibiotics. Future studies should focus on ways to provide these learning environments, and investigate the effect of enhanced autonomous motivation on participation.

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study is 3.1, which m H1 bei ue to
the study findings. For context, the optimal RCT of 5.7
and the Bayes factor of the observational studies f is 1.7.
With regard to the 'morning dip' study (Chapte ulations
may be seen as unfavourable, since the proba y being a
morning dip is only 30% after the study, an only a 10%
rise in probability. Of course, this reflects t udy finding is
unexpected, which makes it harder to reach el this is a good
thing, because it is based on a rational s probably in line
with the overall scientific reaction to So what is the value
of this finding? In my opinion it m pen the eyes of hospital
management and those work stewardship (AMS) to the
possibility that hospital s when quality of antimicrobial
prescribing is lo ts further investigation. Even if this
effect is spe here the study was performed, it highlights

that prescribing doctors may be influenced by the context of prescribing (like time of day or consultation of an expert), which had been shown before.17 Both studies about E-learning (Chapters 7 & 8) had a similar and modest effect on the probability of H1, reflecting their observational nature. As the resulting PPVs were above 50%, the probability that these findings are true is higher than that they are false, but this is far from the 95% certainty that the p-value falsely suggests. Finally, it is important to mention that Ioannidis' formula differs from regular Bayesian inference methods in that it does not require specification of a prior

General discussion

The specifics of measuring appropriateness of antimicrobial prescriptions AMS aims and outcomes. One of antimicrobial stewardship's (AMS) important dilemmas is which outcomes are best used to measure impact of interventions. Of course, the best way would be to literally measure whether AMS' ultimate aims were achieved, but this is not always feasible. As a reminder from Chapter 1, these aims are to curb development of antimicrobial resistance, to reduce costs and to improve patient outcomes. The last of these aims is certainly the most important, but is not often measured in AMS studies.18 Therefore, many AMS studies measure antimicrobial use as a process measure instead which is less optimal but has some good supporting arguments: 1. the total amount of antimicrobial use in a specific institution/ward is a strong determinant of resistance development,19 and 2. the achievement

This chapter comprises a general discussion of the implications of my research findings, starting with a critical reflection on the epidemiological value and merits of my research. It is then followed up by a more content-focused discussion, focusing on how appropriateness should be measured, how to judge the merits of PAR (participatory action research), and how to utilize E-learning in the future. Finally, I will discuss future directions for research.

Mr. Ioannidis, are my research findings false?

At the end of any research project it is important to critically reflect on its merits. And who better to help me reflect than one of medical science most prominent critics, John Ioannidis. Let me start by introducing his most important article, titled 'Why Most Published Research Findings Are False'.[1]

Introducing Ioannidis & p-values

In this article published in 2005, Ioannidis expresses his concerns that most findings from studies claiming statistical significance are untrue.[1] His main argument comprises the widespread use of the p-value (and whether it is below 0.05) as the sole judge of whether a study result is true, while among others ignoring the impact of pre-study probability (prior), power and bias. It has been known for some time that a p-value below 0.05 strongly improves the likelihood and speed of publication of a study.[2] This phenomenon is undesirable because it devalues so-called negative findings (e.g. finding no effect) and may lead to p-value hunting (e.g. repeated analysing until a significant result is reached). It also causes a skewed view of the overall evidence due to overrepresentation of positive findings (i.e. publication bias). Moreover, this attributes way too much importance to the p-value, which is probably based on the wide misconception that the p-value stands for the chance that the research finding under study is untrue. However, a p-value has a far more limited meaning, which is the chance of finding a study result (or more extreme) *given* that the null-hypothesis (often formulated as: there is no effect) is true, and *assuming* a specific statistical model.[3,4] In fact, a p-value cannot be equal to the probability of a study finding being untrue, because it is calculated without using any information about bias, power, prior probability and the specifics of a research field. Despite the fact that this has been known since its invention by Fisher,[4,5] and he did not mean for the p-value to be used this way, p-values are still being used widely. Moreover most published articles mention at least one p-value <0.05.[1,6,7] *Many alternatives have been proposed, such as reporting effect sizes and confidence intervals instead of p-values, or even using prior probabilities to estimate the probability of research results, which is in other words: the use of Bayesian statistics (see next paragraph).*[1,7]

How is the pre-study probability (prior) of a hypothesis related to its post-study probability?

Statistical methods using p-values are based on the so-called frequentist school of thought. The main alternative to frequentist statistics is Bayesian statistics. First developed by the reverend Thomas Bayes in the 18th century, Bayes' Theorem explains how prior probabilities translate to posterior

probabilities via multiplication with a likelihood ratio.[2,8,9] A likelihood ratio has two forms: positive or negative. A positive likelihood ratio is the ratio of the probability of a true positive (e.g. a study/test showing a positive finding which is also true in reality) and the probability of a false positive (e.g. a study/test showing a positive finding which is in fact untrue), while the negative likelihood ratio is similar but for negative study (or test) outcomes. Instead of expressing the results of a fictional study as 'the difference between groups was 10%, the p-value was <0.05', using Bayesian inference this study result can be expressed as follows: 'assuming a pessimistic prior (e.g. there is no difference between groups in reality), there is a 78% chance that the difference between groups was 10% or more', which is much more informative.[3,4,10,11]

The fact that Bayesian statistics are able to quantitatively use information about prior probabilities is its major selling point, but also the focus of its heaviest criticism. As the estimation of prior probabilities is subjective, critics feel that this taints the objectivity of this method, and that it therefore should not be used. However, since the subjective component of the Bayesian analysis is transparent and can be easily varied to suit anyone's preferences, this may not be such an important flaw after all. Moreover, it seems highly preferable over using a measure (the p-value) that is widely misunderstood and misused, and comprises critical flaws like the ignorance of prior probability, which is the reason the American Statistical Association advised against using p-values like they are now.[3-5]

As a side note, Bayes' theorem is known for its value in diagnostic testing, for instance to calculate predictive values of diseases after testing. For an interestingly different perspective on this, see another article from my hand (not included in this thesis).[12]

How to estimate post-study probability of a hypothesis incorporating information on prior, bias and research field?

Although Bayes is not mentioned in his article, Ioannidis used a form of Bayesian reasoning to use prior probabilities in his calculations.[13] He developed formulas to calculate post-study probabilities (or positive predictive value, PPV) that incorporated power, p-values, pre-study probabilities, bias and other research field characteristics like the number of researchers on the same subject.[1] Using these calculations, he showed that it is difficult to exceed a PPV of 50% in many situations even though statistical significance was reached; this applied for instance to meta-analyses of small inconclusive studies and underpowered phase I-II RCTs. In other words, the chance that a study finding is true is often below 50% despite having a p-value below 0.05. It is interesting to note the fact that a study's power also influences the PPV, since this is not always recognized.

Applying Ioannidis' formula to my research

Despite the publication of Ioannidis' well-written article, studies using (solely) Bayesian inferential methods remain scarce. Reporting effect sizes and confidence intervals without reporting p-values is only a little more common.[7] In this thesis and for this reason, **Chapters 4,5** and 8 report results

of research studies using confidence intervals without p-values. In order to critically reflect on the merits of my research, it may be interesting to apply Ioannidis' method of calculating PPVs to the studies in this thesis. I used the formula that includes U, which is an assessment of bias defined as the proportion of studies that should not have been research findings but were reported as such due to bias. It also includes power (1-β), significance (as p-value or α), and prior (expressed as chance rather than odds like in the original study) of the study hypothesis, which is a subjective estimation usually based on previous studies, expert opinion and biological plausibility. I will express all probabilities based on the likelihood of the alternative hypothesis (H1).

First, I will show the calculation for three fictional studies to act as context for the calculations below (adapted from Ioannidis et al.):[1]

a well executed and powered RCT: prior 50%, power 80%, α =0.05, U=0.1.
Results: PPV of 85%, meaning a 35% increase in H1 probability.
a well powered exploratory study: prior 9%, power 80%, α =0.05, U=0.3.
Results: PPV of 20%, meaning an 11% increase in H1 probability.
an underpowered poorly executed early-phase RCT: prior 16.7%, power 20%, α =0.05, U=0.8.
Results: PPV of 17.2%, meaning a 0.5% increase in H1 probability.

Second, I will discuss how the research studies in this thesis relate to the above examples. For the sake of conciseness I will skip the studies from **Chapters 2 & 6** here, since these studies had a more descriptive nature.

the DUMAS study, **Chapter 4.** This was an experimental two-centre intervention study, combining interrupted time series and a non-randomized stepped-wedge design. Outcomes were evaluated using a validated and blinded but subjective method. The risk of bias (U) should be higher than the 0.1 of the optimal RCT above, but its design offers many advantages over a standard observational study (see also **Chapter 1**), which had been assigned a U of 0.3 by Ioannidis. So, although perhaps a U of 0.2 would be suitable, I ended up choosing 0.3 because this is the moment and place to be critical rather than forgiving. Many credible estimations can be made for the prior of a 13% rise in appropriateness (which is what we found); for instance 50% (if you think behaviourally-founded interventions often succeed), 70% (if you feel stewardship interventions are generally effective), or 25% (if you feel that there is a risk that non-restrictive bottom-up interventions may not have sustainable effects). Because of the previous literature that supports behavioural interventions and for better comparability with the RCT above, I chose the first option of 50% (see **Chapters 1 & 4**). Although not reported in the chapter, the exact p-value and power for the main analysis were 0.02 and 95% respectively. Assuming these parameters, this results in a PPV of 75%, meaning a 25% increase in H1 probability.

the studies described in **Chapters 5, 7 & 8** share a few characteristics: these were all observational studies with α =0.05, they were adequately powered (power was 80%) and all adjusted their analysis for potential confounding. Ioannidis assigned a U of 0.3-0.4 to examples of similar studies, so similar to above, to be on the safe side I assigned these a U of 0.5. However, these studies differed in credible estimations for the prior probability of H1. The study that found the morning dip in appropriateness (**Chapter 5**) should have a low prior of H1, since the result was unexpected, both by the research team and the work floor, as was shown in the survey results. Therefore, a probability of 20% seems appropriate, leading to a PPV of 30%, which means a 10% increase in H1 probability. For the study on effectiveness of E-learning on prescribing competence (**Chapter 7**), due to the length of the interval between intervention and outcome measurement (6 months), a not-too-high prior of 40% would seem appropriate. This results in a PPV of 53%, meaning a 13% increase in H1 probability. Finally for the study from **Chapter 8**, based on previous literature supporting the role of autonomous motivation in achieving better education outcomes, a prior of 50% seems appropriate. This results in a PPV of 63%, meaning a 13% increase in H1 probability again.

In the above sections I assigned values to the prior and level of bias, which is of course subjective. As mentioned, one of Bayesian statistics' strongpoints is that it allows anyone to vary the assumptions to see what effect it has on the outcome. This also applies to the formula of Ioannidis. To enable the reader to use their own assumptions I created two figures illustrating the effects of changing these parameters. Figure 1 shows how the PPV varies for the above selection of research studies and for different estimations of the prior. I added the outcomes for the example of the optimal RCT for better comparison. Figure 2 is similar but for varying estimations of the level of bias (U). Of course, it is possible to make figures using each of the formula's other parameters on the x-axis so these figures (and the R code) are available on request.

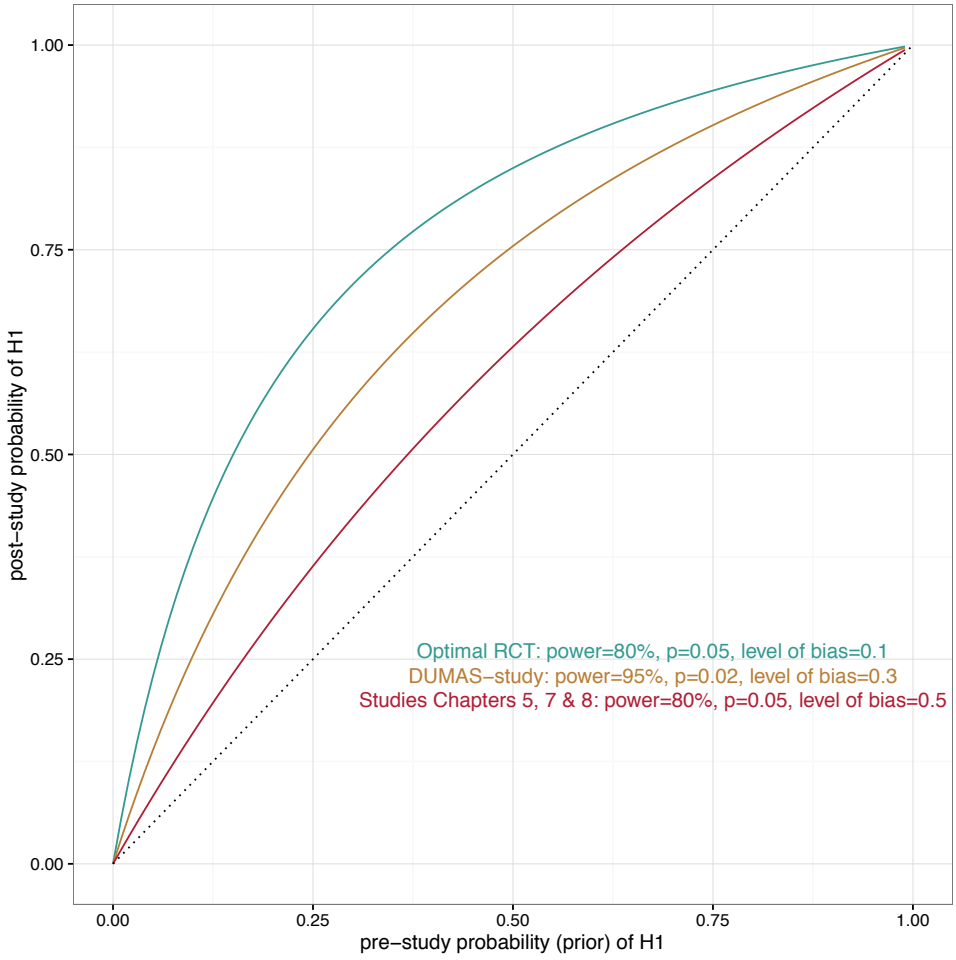

Figure 1
The relationship between prior and post-study probability (PPV)

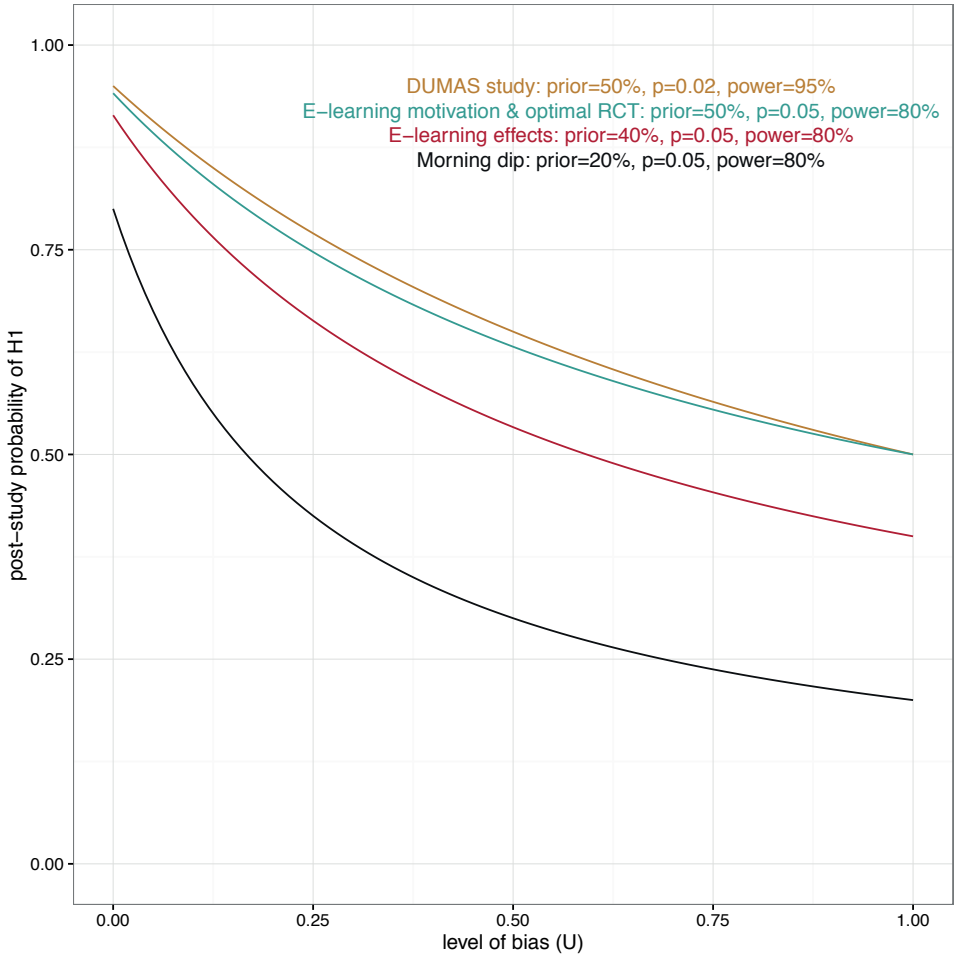

Figure 2
The relationship between level of bias and post-study probability (PPV)

Are my research findings false?

The above calculations have suggested that each study had its own unique impact on how the prior of the tested hypothesis changed. This is insightful because their p-values were more or less the same, once again illustrating the limited value of expressing results that way. It also reminded us that power also determines the PPV, although Figure 2 shows that the influence of power is relatively small in case of powers exceeding 80%.

The DUMAS study research findings are probably true, since the PPV will be above 50% as long as the prior is assigned a value >25%, which seems a reasonable assumption because of the good theoretical foundation of the approach and previous successes of behavioural interventions (see **Chapters 1, 3 & 4**). For instance, a recent very well designed study by Meeker et al. showed that

2 out of 3 tested behavioural interventions were successful in reducing inappropriate antibiotic prescribing.[14]

However, I feel the dichotomy of the question whether a research finding is false does not do justice to all research efforts. Is a study finding really true because it exceeds a certain threshold of probability, for instance the 50% as used by Ioannidis? Any study finding with a prior for H1 of at least 50% (or another arbitrary threshold) should then be labelled a true study (provided that power exceeds α) irrespective of how biased it is.[1] Conversely, in that case even the optimal RCT (see above) cannot yield a true result when the prior is below 16% (see Figure 2), but there is agreement that trials in these situations are still useful (for instance early phase drug trials). A more reasonable suggestion for a good appreciation of a study finding is to look at both the absolute value of the PPV and the relative impact of a study. In the calculations above, I mentioned an example parameter of this relative impact: the increase in probability of H1, which showed that the DUMAS study increased the H1 probability by 25%. This is substantial considering the impact of the aforementioned observational studies, but not as much as the optimal RCT. A disadvantage of this parameter is that it is strongly influenced by the prior. An example of a measure that is independent of the prior would be the relative increase in probability, which is in fact (provided that probability is expressed as odds instead of chances) a kind of likelihood ratio or as it is called in this context, a Bayes factor.[15,16] The Bayes factor of the DUMAS study is 3.1, which means that the odds of H1 being true are tripled due to the study findings. For context, the optimal RCT has a Bayes factor of 5.7 and the Bayes factor of the observational studies from **Chapter 5, 7 & 8** is 1.7.

With regard to the 'morning dip' study (**Chapter 5**), the above calculations may be seen as unfavourable, since the probability of there really being a morning dip is only 30% after the study, and this represents only a 10% rise in probability. Of course, this reflects the fact that this study finding is unexpected, which makes it harder to reach a high PPV. But I feel this is a good thing, because it is based on a rational calculation, and it is probably in line with the overall scientific reaction to surprising findings. So what is the value of this finding? In my opinion it means that it should open the eyes of hospital management and those working in antimicrobial stewardship (AMS) to the possibility that hospital mornings are moments when quality of antimicrobial prescribing is lower, and that this warrants further investigation. Even if this effect is specific to the hospital where the study was performed, it highlights that prescribing doctors may be influenced by the context of prescribing (like time of day or consultation of an expert), which had been shown before.[17]

Both studies about E-learning (**Chapters 7 & 8**) had a similar and modest effect on the probability of H1, reflecting their observational nature. As the resulting PPVs were above 50%, the probability that these findings are true is higher than that they are false, but this is far from the 95% certainty that the p-value falsely suggests.

Finally, it is important to mention that Ioannidis' formula differs from regular Bayesian inference methods in that it does not require specification of a prior distribution, but only of a prior. This makes the formula easier to use[13] but probably less accurate. It is also important to note that these calculations do not address the question whether the effect size of a study finding is indeed big enough to be relevant, but that subject is addressed in the studies' respective chapters.

Conclusion

It follows that using a form of Bayesian analysis like the Ioannidis' formula can be really helpful to critically reflect on the merits of research. Although experienced readers of research papers may have already reached the same conclusions made above using only their intuition and experience, this approach can help both less experienced readers and the researchers themselves to improve science as a whole.

In conclusion, on condition of accepting the earlier assumptions, it shows that all discussed research studies had at least a modest influence on the prior beliefs about H1. The DUMAS study even increased the prior by a sizeable 25%. Except for the 'morning dip' finding, all post-study probabilities exceeded 50% (Ioannidis' threshold for truth) indicating that H1 is more probable than H0.

The specifics of measuring appropriateness of antimicrobial prescriptions

AMS aims and outcomes

One of antimicrobial stewardship's (AMS) important dilemmas is which outcomes are best used to measure impact of interventions. Of course, the best way would be to literally measure whether AMS' ultimate aims were achieved, but this is not always feasible. As a reminder from Chapter 1, these aims are to curb development of antimicrobial resistance, to reduce costs and to improve patient outcomes. The last of these aims is certainly the most important, but is not often measured in AMS studies.[18] Therefore, many AMS studies measure antimicrobial use as a process measure instead which is less optimal but has some good supporting arguments: 1. the total amount of antimicrobial use in a specific institution/ward is a strong determinant of resistance development,[19] and 2. the achievement of several components of appropriate antimicrobial prescribing (i.e. prescribing according to guidelines) have been associated with improved clinical outcomes.[20] Appropriateness of antimicrobial prescribing is therefore commonly used as AMS outcome, although measuring AMS aims directly should be a priority for future research. So how to measure appropriateness of prescribing?

Quick and narrow: the case for billing records

There are several ways to define and measure appropriateness of antimicrobial prescribing, with corresponding up- and downsides. For instance, recent studies about prescribing for respiratory

infections in primary care linked billing data that contained diagnoses to prescribed antibiotics. They defined prescriptions as inappropriate when an antibiotic was prescribed during a primary care visit where also a specific diagnoses like influenza or acute bronchitis was billed.[14,17,21] This outcome has the advantage of being quite easy to measure in large numbers but depends on the possibility to find diagnoses whereby the prescription of an antibiotic can be assumed to be inappropriate nearly all the time. If this is the case like it probably was for these cited articles (although they did not check this as far as I can tell), then it can be a valid and useful outcome. There are several downsides to this method: it could be that in some cases the diagnosis and the prescription were not related, and the antibiotic was prescribed for another reason. Also, for many diagnoses it is not that clear-cut that every antibiotic prescription for this diagnosis is indeed inappropriate, for instance in case of acute pharyngitis or catheter-related bacteraemia. The explicit and often narrow focus of such an outcome precludes getting a broader, more overall view of antimicrobial prescribing in a certain setting. For instance, prescribing in hospitals often comprises a wide array of diagnoses so only measuring prescribing for one specific diagnosis may limit generalizability, and perhaps statistical power as well. Finally, and especially when prescribers are aware of the measurement, there is the possibility of a diagnostic-shift distorting the results, for instance when prescribers bill bronchitis increasingly as pneumonia (for which an antibiotic can be appropriate) instead of acute bronchitis (for which it is generally not).

Broad but slow: case-by-case appropriateness

On the other side of the spectrum are appropriateness definitions using a more broad view, for instance concerning guideline-adherence for empiric treatment of infections, or even appropriateness of all prescriptions regardless of their indication. I used this latter definition to evaluate appropriateness in the studies described in **Chapters 4 & 5** and studied its reliability and validity in **Chapter 2**.[22-24] The upside of using the method used in these chapters is that it measures the overall quality of prescribing in a certain setting and that appropriateness is judged for each case individually and using all case-specific information available. Perhaps the biggest advantage of the method is that it opens up the richness of qualitative information in the cases, which can make one better understand why prescribers act like they do. A downside is that its inaccuracies are less systematic compared to the respiratory-infections based method described above, due to the case-by-case judgment, which is subjective. It is also a time-consuming method. Finally, this outcome method is not immune either to diagnostic shift or changes in case mix.

Case-by-case appropriateness: do experts agree?

Fortunately, the study described in **Chapter 2** shows that the problem of subjectivity may only have a limited influence on validity and reliability of this measure of appropriateness: experts do agree in around 80% of cases with the reference standard. Moreover, it seems less experienced judging experts like fellows in infectious diseases or medical microbiology can perform these judgments without a drop in accuracy, which may also partially alleviate the problem of sufficient resources for the measurements. Luckily, to preserve the good

relations between the experts working in the field of AMS, accuracy was also similar between infectious disease specialists and medical microbiologists. However, that may have been expected since the 'gold standard' comprised the aggregate judgments of a balanced mix of the two specialties. On a more serious note, for future AMS initiatives it would be preferable if validity and reliability could be improved even further. In order to achieve this, it would be paramount to increase discussion about what constitutes appropriate prescribing, and for opinion leaders and guideline writers to take a clear stance about certain topics, like for instance on the judicious use of quinolones. Most importantly, these discussions could lead us to better identify further areas for research, for instance on the comparative clinical effectiveness of specific antibiotics or treatment durations for a certain indication (e.g. fever of unknown origin and neutropenia), and on the relative impact of each antibiotic on development of resistance in patients.[25] In other words, it may be that we know increasingly well how to steer prescriber behaviour, but do we know enough about which direction to steer to?

Ideas for measuring quality of prescribing in the future

Since measuring appropriateness on a case-by-case basis is time consuming, it is necessary to explore more efficient ways to measure this. Nearly all solutions that come to mind comprise a way to reduce the number of cases that need to be assessed case-by-case, by automatically categorizing some cases as appropriate or inappropriate. So how can we preselect those cases that can be judged automatically? One way would be use rules based on clinical logic to categorize cases. One could use available data on diagnoses (for instance from the electronic health record (EHR) or billing data) to identify cases with a high probability of a certain judgment. To illustrate, the prescription of oral amoxicillin in an adequate dose for a patient admitted with pneumonia less than 5 days ago (which is information that could probably be extracted from most EHR systems) may perhaps safely be assumed to be appropriate (in the Netherlands). Or in other words, there is not a lot to gain for the AMS team in this case, because the therapy is reasonably narrow, adheres to national (and probably local) guidelines in case of mild to moderately severe pneumonia, and the treatment is already oral rather than intravenous. Of course, the patient could have been allergic but the AMS team would then be too late to prevent administration anyway. Also the patient could have a severe pneumonia instead (for which the current guideline advices a more broadspectrum antibiotic) or could be unresponsive to treatment, but in these circumstances the treating physician nearly always takes some form of action (change therapy, ask for help etc.), at least according to my experience of collecting and assessing more than 2000 patient cases in two hospitals. Another option to judge appropriateness without assessing all details is to measure performance on specific quality indicators for antibiotic use, which have been developed before and, as mentioned several times before, have shown patient-related benefits.[20] It remains to be seen however whether the isolated measurement of performance on (some of) these indicators is really more time-efficient compared to the method used in this thesis.

An idea to take this one step further is to use predictive regression analysis to identify those factors that best predict a specific judgment (inappropriate or appropriate), and use all information available in the EHR in the model. Examples of potential predictors include admitted ward, prescriber, supervisor, time of prescribing (see **Chapter 5**), prescription details (drug, dose, administration route), EHR diagnosis, laboratory results etc. The idea is that this would result in an algorithm that would outperform the decision rules designed through logical thinking like the example above. Another benefit would be that it could yield a better understanding of appropriateness determinants, although external validity would have to be ascertained first, because predicting variables may lack case-mix stability.[26] However, this kind of analysis requires the availability of one or rather more large datasets of case-by-case judgments. Moreover, once the algorithm is used to guide AMS interventions like for instance audit & feedback on cases selected by the algorithm, the prediction model may become invalid and would need further calibration using a new dataset of case-by-case judgments. Although this method may not turn out to be that time-efficient in the end, this exercise may yield some valuable lessons for AMS in general.

Should all future AMS programs use PAR?

Comparisons with traditional methods

The results from the DUMAS-study (**Chapter 4**) show that an approach grounded in behavioural theory, and specifically using the participatory action research method (PAR), in combination with a root cause analysis for local prescribing determinants can be effective to improve appropriateness until at least 12 months after intervention start. Considering that contact of the intervention team with each department was most intensive at the start and reduced gradually to zero depending on the wishes and initiatives of the department, the lack of a clear drop-off in intervention effect until 12 months suggests good sustainability. The study's respect for prescriber autonomy and focus on causes rather than symptoms of inappropriate prescribing may have helped to prevent the regression to previous behaviour ('boomerang effect') that has been shown when restrictive or enabling interventions like audit and feedback have been discontinued.[18,27] On the other hand, although only a single study, the effect of a behavioural approach in primary care was still discernable 12 months after intervention removal.[28]

It is difficult to really compare the effect size and sustainability between the DUMAS method (or a similar method) and the traditional AMS methods (e.g. restriction, audit & feedback, education) because DUMAS nor other studies contained a 'traditional method' comparator arm. Moreover, most past AMS studies compared their intervention to 'no intervention' so any debate about interventions strengths and weaknesses is based on inter-study comparisons and therefore subject to confounding due to differences in population (patients, doctors and health care system) and study design.[18,29]

It's all about context

These differences are what makes AMS research different (and interesting) compared to regular medical research, because the latter usually targets a homogenous group of patients with a specific disease, which are often reasonably comparable across institutions and countries, while the former targets physicians working in a socio-cultural (e.g. their colleagues) and professional environment (e.g. their hospital) prescribing for various patients. Research suggests that even within these doctors there can be inconsistencies in prescribing depending on the context, see for instance my study in **Chapter 5**,[24] or the study about decision fatigue in primary care.[17] The case for the importance of context is reflected by the fact that preferences for AMS interventions also varied between environments in the DUMAS study (variations between departments) and a PAR AMS approach performed in nursing homes (variations between nursing homes).[23,30] Although of course it is possible (but unlikely) that doctors do not know what is best for them with regard to AMS interventions, it does suggest that a one-size-suits-all approach is suboptimal. Health care environments also differ in the availability and the logistics of infectious disease diagnostics that affect antimicrobial prescribing (see **Chapter 6**). AMS programs should therefore be preceded by an inventory of barriers and facilitators (as was DUMAS), which was also the conclusion of previous AMS overview articles.[18,29,31-35]

Things I've learned from speaking with prescribers

As mentioned in the section about measuring appropriateness, one of the most important advantages of measuring appropriateness case-by-case is the opportunity to learn about the qualitative aspects of prescribing. This is especially true if the method incorporates talking to prescribers at the wards during their work (like it did for DUMAS). On top of this, I interviewed nurses, doctors and quality improvement personnel in the context of the root-cause analyses. These experiences have given me a unique insight into AMS, and these activities are highly recommendable for any person working in AMS. The nature of the general discussion chapter gives me the opportunity to share three (out of many) anecdotal observations from these meetings on the work floor.

1. 'There is a big gap between policy makers and the work floor'. When I started with DUMAS, I took seat in the hospital's antibiotic committee where a recurring discussion concerned the problems with the pre-authorization procedure of restricted antibiotics. Doctors' lack of understanding of the procedure led to frustration and many calls to the microbiologists, and the doctors complained they were not made aware of the system. The committee members thought this was strange because it was included in the introductory course for new personnel, which they checked with the person teaching the course, who then replied the subject was indeed taught in the course. Due to some earlier experiences where theory and practice did not match, and due to contrasting information from the work floor doctors, I inspected the Power Point presentation for the course personally and found that the work floor was right; the subject was not in the presentation and was not spoken of at all. In the end, it turned out that this was just one of many

things that were assumed by the committee about the prescribing doctors and that were untrue, as found out by speaking with these doctors. Many of these concerned the way the hospital antibiotic guidelines were used, or rather not used. An illustrative example that gave me insight about why some doctors are not susceptible to warnings about increasing resistance stemmed from an interview with a surgeon who only performed soft-tissue surgery. He said: ' I don't understand all the fuss about resistance. I have been prescribing amoxicillin-clavulanate for years and I never encountered any resistance to it.' He was right as he prescribed antibiotics mainly for patients with superficial surgical site infections and these pathogens are nearly always susceptible to this antibiotic in the Netherlands. Moreover, he did not come in contact with patients with urinary tract infections and sepsis caused by amoxicillin-clavulanate resistant Gram-negatives. After realizing this, we could adapt our AMS interventions accordingly by for instance addressing this point in our AMS educations sessions for his department. These experiences have led me to believe any AMS program should have members that make contact with the work floor and discuss the daily work flow in a non-threatening way.

2. ' IT and guideline makers often undervalue the importance of ergonomics'. Antibiotic committee members often openly wondered why doctors did not use the antibiotic guidelines and why they said they could not find them. On one occasion, one of the committee members said while standing by the computer: 'It's really not hard to find it, just click here, and then there, and then (…many clicks…) and then there it is!' (Note: this was pre-EPIC). Similarly, when I was trying to get the hospital IT department to make a desktop hyperlink to the antibiotic guidelines, the first answer I got from every new IT person I was re-directed to was (and there were many): 'why do you need this, the guideline can be easily found if they want by just clicking there and then there (many clicks etc.). Just explain that to the doctors'. The main problem here is this: guidelines are only used if people know they exist and the information in it can be found quick and easily, unless it concerns a highly motivated doctor with considerable stamina. And the problem of AMS is: everyone prescribes antibiotics, not only the highly motivated ones. Guideline makers should therefore take the subject of ergonomics and publicity serious, and it should be an item for any significant guideline update. Optimally, any antibiotic guideline should be present in an appealing and attractive form in the daily workflow of doctors, without annoying them when they do not need it. In the end, it took me more than one year of lobbying with IT to get the simple hyperlink done.
3. 'Infectious disease experts are role models'. A frequent theme in my contacts with prescribers was their apparent frustration with the example set by infectious disease specialists and clinical microbiologists. According to them, these experts did not always follow or even know the antibiotic guidelines, gave inconsistent advice and did not always comment on inappropriate antibiotic prescribing by others when discussed during meetings. Moreover, these prescribers said this was a reason why they felt they did not need to adhere to the guidelines themselves. This is a practical example of the

fact that antimicrobial prescribing is influenced by social and cultural factors. Any expert in infectious diseases should be aware of this phenomenon and should be stimulated to know, promote and adhere to the relevant antibiotic guidelines and only deviate from the guidelines in public while also stating clear reasons for this.

When not to use PAR?

First and foremost, the only evidence about the effectiveness of PAR in AMS practice so far is from the DUMAS study, because another study, using a slightly different PAR approach (less freedom of choice for doctors) and in another population, was not successful in improving quality of prescribing in nursing homes (see also **Chapter 3**).[30] As this is not enough to prove overall effectiveness or how this relates to other intervention types, PAR cannot yet be recommended as a proven-effective approach. The effect on ultimate aims of AMS like resistance and clinical outcomes is also yet unknown. However, the approach is supported by behavioural theory, promotes contact and collaboration between AMS personnel and prescribers, preserves the autonomy of prescribers which reduces chances of conflicts/obstruction, is adaptable and suited to many health care environments, and entails an inventory of barriers and facilitators which has been recommended for AMS overall,[18,29,31-35] so perhaps the better question is: why not try PAR, or at least some form of participation? One of the most important downsides of PAR is that it can be time-consuming to engage with all stakeholders during the process. An AMS setting with time-constraints, or where there are a lot of isolated prescribers, like for instance a large network of general practitioners might be less suitable for participation, unless there is a well-functioning and trusted spokesperson available. Another situation where PAR might not be less ideal is when AMS personnel or the main spokesperson for the prescribers are less socially inclined. As an example, one department head who was contacted to participate in DUMAS, reacted in a very hostile way during the introductory meeting, and participation in the study was ultimately not possible. Knowing this person, this was not unexpected but these kind of personalities can thwart the success of PAR, although it is not easy to say which other AMS approach would be more successful in such a case. Finally, not enough is known about potential unintended outcomes of PAR so it is unclear whether it is contraindicated in some situations. However the DUMAS study showed no evidence of adverse consequences (unchanged length of stay). Given the preserved autonomy of doctors in PAR, adverse consequences would also be unexpected.

Conclusion, should PAR be used in all AMS programs?

In short, the evidence for its effectiveness is not yet sufficient to recommend it as a must-use. However the approach comes with several theoretical and practical benefits, the promise of a sustained effect on appropriateness and no real expectation of relevant unintended effects, so further use of PAR or at least some element of participation in AMS seems logical.

How to fit voluntary education like E-learning into AMS?

Education in AMS

Education is an essential part of AMS.[36] As doctors from a wide variety of backgrounds all prescribe antibiotics, it is paramount that every doctor receives education on the subject of appropriate prescribing early in their career or during medical study. This can come in many forms, e.g. lectures, workshops, spread of educational material, assignments, electronic learning (E-learning) etc. E-learning offers a unique set of features that can be suited to circumstances where there is limited time in the education roster, or a lack of teachers.

Can education change prescribing behaviour?

It is not hard to accept that the medical study as a whole does influence how junior doctors prescribe in practice. However, as the prescribing environment of each doctor is shaped by social, cultural and organisational factors that form a 'prescribing etiquette',[37] it is unclear to how big the influence of the medical study is on prescribing behaviour. Moreover, when zooming in on the medical study itself, it was thus far unclear to what extent an isolated temporary educational intervention could influence prescribing behaviour and competence beyond 12 weeks post-intervention. The results from the study described in **Chapter 7** suggest that E-learning cannot only improve knowledge but also prescribing behaviour and competence six months after stopping the intervention.

How to increase E-learning participation?

Students randomized to E-learning in the study described in **Chapter 7** were free to do the E-learning, since there were neither study credits nor other benefits attached to E-learning participation. Still 82% of them at least opened the course once but only 41% completed at least 75%, which was after three e-mail reminders. Similarly, 58% of junior doctors participated (after one reminder) in the equally voluntary E-learning module from the study described in **Chapter 8**. This shows that it is a challenge to get students and doctors to participate in voluntary E-learning. The study from **Chapter 8** showed that doctors with relatively more autonomous motivation participated more, although participation was only perfect for doctors with a very high autonomous to controlled motivation ratio (see figure 1 in **Chapter 8**). This suggests that it is necessary to increase autonomous motivation before offering such educational interventions. Although doctors whose motivation is relatively more controlled would probably be sensitive to external participation incentives like study credits, this may not be the best solution in the long-term. This because autonomous motivation is also associated with higher efforts and better achievements,[38,39] so the effect of E-learning on these externally incentivized doctors may be smaller.

So how to improve autonomous motivation? An attractive idea is to offer learners a meaningful reason to participate in the E-learning, or in other words convince them that this is something they want to learn. Although this is much easier said than done, a possible way to achieve this is to use face-to-face education about the importance of the subject prior to introducing the E-learning: blended-learning.[40]

Do we really need education in AMS?

Of course, doctors who prescribe antibiotics a lot like internists or general practitioners should know what they are prescribing and why. However, is it really realistic to expect every surgeon to know the difference in pharmacodynamics between ciprofloxacin and amoxicillin-clavulanate, and do they really need to know? Could it be that it is more important to create a health care environment where in easy situations the right choice is the easy default (e.g. cefazolin included in surgical order set), and where in more difficult situations doctors are stimulated and facilitated to use an easy-to-use guideline or ask for help? Perhaps we need to redesign our choice architecture (i.e. the way choices are presented to a decision maker)[41] to ensure that the best choice in any situation is also the easiest choice, and teach our doctors how and when to ask for help, instead of teaching them about ciprofloxacin's spectrum of activity? Interestingly, this suggestion for practical rather than theoretical education was echoed by the survey respondents from the study in **Chapter 5**. For instance, they said they wanted to be taught about where to find guidelines and the ins and outs of IV lines for patients with antibiotics.

Conclusion

Education and specifically E-learning can be a useful tool to improve antimicrobial prescribing, but we need to know more about how to improve participation without compromising its effectiveness, for instance by focusing on increasing autonomous motivation. We also need to ask the question whether it is realistic to teach every prescriber enough about antimicrobials to be able to prescribe appropriately or that (post-graduate) education should be used more as a tool to support decision making within the prescribing choice architecture designed to favour appropriate therapy.

Future studies and AMS directions

Head-to-head comparisons

As mentioned before, the current AMS literature is lacking in head-to-head comparisons of different intervention types.[18,29] Future studies on AMS effectiveness should incorporate active comparator arms to create knowledge about the relative strengths of intervention approaches in different situations, preferably including outcomes like resistance and clinical outcomes wherever possible. We also need to acknowledge that, at least in the Netherlands and many other Western countries, AMS activities have become omnipresent which means there is no tabula rasa for studying AMS. Rather, any new study should be robust to the carryover effects of previously started AMS efforts. Let's take the example of a cluster randomized trial comparing the effects of a behavioural intervention to an audit & feedback intervention. In the Netherlands, it would be hard to find enough departments/hospitals that do not already employ audit & feedback to participate. Of course, the audit & feedback arm of the trial could be executed as a 'no change'-arm. However, in that case the behavioural arm of the trial is not only different from the comparator by its intervention approach, but also because it is new and involves a change of practice, which may increase the

placebo effect. A possible solution is to 'tweak' the audit & feedback arm so that prescribers really notice a difference, for instance by delivering feedback differently (by person or via the electronic health record if this was not yet the case).

Study designs

In the general introduction (**Chapter 1**), I discussed the relative merits of several methodological designs for AMS. It followed that the cluster-randomized design, the stepped-wedge design and interrupted time-series were the most suited for evaluation of AMS effectiveness. In my experience, due to the unpredictably changing prescribing environment, which can induce time-dependent confounding, incorporating a time-series component in every design is preferable. The use of these longitudinal measures can elucidate if and when changes occur, and allows for statistical adjustment of outside influences and pre-existing trends. Even though cluster-randomized controlled trials are less vulnerable, information about trends can be highly informative, especially since the number of clusters can be quite low due to practical constraints. Additionally, varying the moment of the start of the intervention will reduce the chance that any confounding event takes place at the exact same moment so this should be done whenever possible.

Promising behavioural mechanisms

As discussed before, the DUMAS intervention approach that coupled PAR with unlimited intervention choice with a root-cause analysis deserves further testing in a trial, for instance comparing it to more traditional methods. However, there are more behavioural principles that should be tested in the context of AMS, separately or combined with the DUMAS approach. Because trials as those proposed above cost considerable time and money, a logical approach would be to test the effects of several behavioural principles on antimicrobial prescribing in smaller studies, for instance starting with hypothetical vignettes to better understand the determinants of inappropriate prescribing. If it turns out the mechanism is potentially interesting to use as an AMS intervention, then it can be tested in practice. For example, an interesting behavioural focus would be the extent to which some doctors use more reflective thinking (as opposed to a snap judgment) to make decisions and how this affects appropriate prescribing. This cognitive characteristic can be tested with a cognitive reflection test (CRT),[42] and higher scores on the CRT have been associated with better diagnostic reasoning.[43] A previous study showed that increased reflection (but not too much) was associated with better antibiotic prescribing for respiratory infections.[44] Other potentially interesting behavioural mechanisms to test in AMS are base rate neglect (the tendency to ignore the real prevalence of a disease), availability bias (judging things more likely if they are easier remembered, for instance due to recent exposure) and representativeness bias (confusing plausibility for probability).[45,46]

Optimizing choice architecture in AMS: can we afford not to?

The optimal design of the choice architecture of prescribing is a topic that deserves its own paragraph. Choice architecture is a term coined by Richard Thaler and Cass Sunstein in their book

'Nudge: Improving Decisions about Health, Wealth and Happiness'.[41] It entails the way choices are presented to consumers or professionals. Thaler and Sunstein argued that due to the naturally lazy character of the human mind which includes the use of heuristics and the presence of cognitive biases, people's choices are influenced by the way choices are presented to them. One of the main consequences is the default rule: people will be inclined to choose the path of least resistance, which means they often choose the default option, whether or not it is good for them.[41] Thaler and Sunstein argue that not influencing people is not an option, because every choice environment promotes some options over others, so choice architecture must be optimized to 'nudge' people in the direction that does them the most good and the less harm.

With the rise of electronic prescribing and the electronic health record (EHR), choice architecture is omnipresent in the medical world, and so is its influence.[47] For example, I encountered a simple form of problematic architecture in the EHR of my own hospital: when trying to prescribe amoxicillin the EHR showed amoxicillin-clavulanate as suggested favourite option. On the positive side, changing the EHR architecture to improve drug prescribing has been shown effective in previous studies. [48-51] Because of the importance of AMS (and optimal prescribing in general) it would be strange and counterproductive to invest so much in AMS interventions while letting suboptimal prescription systems suggest and stimulate inappropriate prescribing. For future research it would be really interesting to compare the effect sizes of choice architecture tweaks to those of other AMS interventions. Simultaneously, a broad inventory of the extent and severity of the problem of suboptimal architecture in our health care system seems warranted.

Effect of E-learning on outcomes relative to motivation

The results of the two studies on E-learning suggest further research into the effect of autonomous motivation on education effectiveness, especially on antimicrobial prescribing behaviour. Additionally, it would be important to see whether autonomous motivation could be increased, for instance by blended learning. An example of such a study would be a cluster-randomized trial in pre- or post-graduates on the effect of E-learning on antimicrobial prescribing while measuring motivation at several time points, and comparing several arms: no E-learning, no E-learning but a motivation lecture, E-learning without motivation lecture, E-learning with motivation lecture.

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Antimicrobial drugs like antibiotics can be very effective in treating patients with infections, but due to increased use of these drugs, their effectiveness is diminishing because of development of antimicrobial resistance. This leads to increased morbidity, mortality, side effects and costs. Due to a lack of development of new antibiotics [illegible] priate use of antibiotics (i.e. only use antibiotics when really needed, [illegible] ort as possible, use the most narrow-spectrum antibiotic possible) is [illegible] Therefore, antimicrobial stewardship (AMS) programs have been [illegible] nprove antimicrobial prescribing. To measure AMS effective[illegible] ant to measure appropriateness of antimicrobial prescrib[illegible] t this can be hard since it relies on a subjective e[illegible] factors, such as prescribing guidelines, patient ch[illegible] s [illegible] soning of the physician, microbiological results [illegible] ocal [illegible] erefore performed a study validating the judgm[illegible] bout a[illegible] ropriateness by an index infectious disease s[illegible] st, using [illegible] his peers (Chapter 2). We showed that i[illegible] us disease [illegible] linical microbiologists agreed with the [illegible] expert's jud[illegible] of cases, giving the method sufficie[illegible] dity to be use[illegible] of AMS programs. Improving ant[illegible] bial prescribing [illegible] changing human behaviour, as r[illegible] nto changing their current presc[illegible] practice. However, prev[illegible] have by and large failed to acc[illegible] r the intricacies and comp[illegible] ehaviour, which may have [illegible] suboptimal effectiveness. [illegible] d behavioural theory to [illegible] n and implement an interv[illegible] to improve appropri[illegible] s of hospital antimicrobial presc[illegible] cations: the Dutch [illegible] Method for Antimicrobial Stewar[illegible] study. The appro[illegible] inspired by the participatory action [illegible] h, which f[illegible] tion and empowerment [illegible] e in other compl[illegible]

In essence, we measured antimicrobial appropriateness on seven wards in two hospitals and presented our results to the prescribing physicians themselves and asked them to reflect on it. We also presented them the findings of a root cause analysis of their inappropriate prescriptions, and we subsequently asked us what they wanted and needed to improve (e.g. better guidelines, education). We then acted upon these wishes in close collaboration with them.

For instance, one department with prior low guideline adherence wished to rewrite the antibiotic guideline and so we did and appropriateness increased afterwards. Overall, the DUMAS approach was associated with a 13% increase in antimicrobial appropriateness sustained for 12 months post intervention-start. We found no reduction in antimicrobial consumption (Chapter 4). More evidence on the importance and complexity of behaviour in prescribing was presented by our study showing antimicrobial appropriateness to be worse during mornings and when prescribed by inexperienced residents (Chapter

Appendices

curricula; and questions remain about long-term retention of knowledge and skills in traditional learning. We showed that e-learning on antibiotics can significantly improve medical students' performance of an antimicrobial therapeutic consultation in a situation simulating clinical practice six months later (Chapter 7). With these promising results, it is even more important to achieve high e-learning participation rates, but these are often low, both in our studies and in literature. We therefore sought to get insight into the factors that determine E-learning participation. We found that participation in non-obligatory e-learning is higher in residents with more autonomous motivation (i.e. coming from within, as opposed to controlled motivation i.e. coming from external factors). Preceding e-learning on antibiotic prescribing with face-to-face education, to explain the importance of

Summary

Antimicrobial drugs like antibiotics can be very effective in treating patients with infections, but due to increased use of these drugs, their effectiveness is diminishing because of development of antimicrobial resistance. This leads to increased morbidity, mortality, side effects and costs. Due to a lack of development of new antibiotics, appropriate use of antibiotics (i.e. only use antibiotics when really needed, treat as short as possible, use the most narrow-spectrum antibiotic possible) is paramount. Therefore, antimicrobial stewardship (AMS) programs have been initiated to improve antimicrobial prescribing.

To measure AMS effectiveness it is important to measure appropriateness of antimicrobial prescribing adequately, but this can be hard since it relies on a subjective evaluation of several factors, such as prescribing guidelines, patient characteristics, clinical reasoning of the physician, microbiological results and local practice. We therefore performed a study validating the judgments about antimicrobial appropriateness by an index infectious disease specialist, using judgments of his peers (**Chapter 2**). We showed that infectious disease specialists and clinical microbiologists agreed with the index expert's judgment in 80% of cases, giving the method sufficient validity to be used in evaluation of AMS programs.

Improving antimicrobial prescribing actually means changing human behaviour, as prescribing physicians need to be persuaded into changing their current prescribing practice. However, previous AMS efforts have by and large failed to account for the intricacies and complexity of human behaviour, which may have lead to suboptimal effectiveness. We therefore used behavioural theory to design and implement an intervention approach to improve appropriateness of hospital antimicrobial prescribing for all indications: the Dutch Unique Method for Antimicrobial Stewardship (DUMAS) study. The approach was inspired by the participatory action research approach, which focuses on collaboration and empowerment of the stakeholders in the change process and is effective in other complex health care situations (**Chapter 3**). In essence, we measured antimicrobial appropriateness on seven wards in two hospitals and presented our results to the prescribing physicians themselves and asked them to reflect on it. We also presented them the findings of a root cause analysis of their inappropriate prescriptions, and we subsequently asked us what they wanted and needed to improve (e.g. better guidelines, education). We then acted upon these wishes in close collaboration with them. For instance, one department with prior low guideline adherence wished to rewrite the antibiotic guideline and so we did and appropriateness increased afterwards. Overall, the DUMAS approach was associated with a 13% increase in antimicrobial appropriateness sustained for 12 months post intervention-start. We found no reduction in antimicrobial consumption (**Chapter 4**).

More evidence on the importance and complexity of behaviour in prescribing was presented by our study showing antimicrobial appropriateness to be worse during mornings and when prescribed by inexperienced residents (**Chapter 5**). The follow-up qualitative survey showed that work-floor

physicians relate these findings to a suboptimal prescribing environment and they suggested improving this environment and improving supervisory support and education of physicians in antimicrobial prescribing and stewardship. Another variable to be influenced by time of day was blood culture-processing duration: in a retrospective study we found that median time from culture incubation-completion increased from a median of 4 to 16 hours depending on time of day of incubation completion. For clinicians, this means a sizable delay in the availability of potentially critical information about the responsible pathogen in bloodstream infections, with uncertain clinical consequences. The delay is caused by absence of laboratory night-time staffing and the offsite location of the laboratory, which is increasingly the case in the Netherlands (**Chapter 6**).

Education is an important intervention in AMS but it can be challenging to find the time and place for education on AMS in the crowded medicine curricula; and questions remain about long-term retention of knowledge and skills in traditional learning. We showed that e-learning on antibiotics can significantly improve medical students' performance of an antimicrobial therapeutic consultation in a situation simulating clinical practice six months later (**Chapter 7**). With these promising results, it is even more important to achieve high e-learning participation rates, but these are often low, both in our studies and in literature. We therefore sought to get insight into the factors that determine E-learning participation. We found that participation in non-obligatory e-learning is higher in residents with more autonomous motivation (i.e. coming from within, as opposed to controlled motivation i.e. coming from external factors). Preceding e-learning on antibiotic prescribing with face-to-face education, to explain the importance of the subject, could enhance autonomous motivation and thus optimize e-learning efficiency (**Chapter 8**).

Samenvatting

Antimicrobiële geneesmiddelen zoals antibiotica of antischimmelmiddelen (hierna voor het gemak antibiotica genoemd) zijn over het algemeen zeer effectief in het behandelen van patiënten met een infectie, zoals bijvoorbeeld een blaasontsteking. Echter, door veelvuldig gebruik van deze middelen neemt hun effectiviteit steeds meer af omdat bacteriën resistent worden. Dit leidt ertoe dat patiënten vaker dan voorheen overlijden, langer of ernstige ziek zijn, meer bijwerkingen ervaren en dat de zorgkosten toenemen. Omdat het ontwikkelen van antibiotica commercieel niet erg interessant is en de meeste voor de hand liggende methodes voor het vinden van antibiotica al gebruikt zijn, zijn er de laatste jaren slechts weinig nieuwe antibiotica bijgekomen, en de verwachting is dat dit in de nabije toekomst niet anders zal zijn. Het is daarom erg belangrijk om antibiotica gepast te gebruiken, door bijvoorbeeld alleen antibiotica voor te schrijven als het echt nodig is, de behandeling zo kort mogelijk te houden en zoveel mogelijk smalspectrum antibiotica (smalspectrum = werkzaam tegen weinig soorten bacteriën) voor te schrijven. Om dit te bewerkstelligen zijn zogenaamde antimicrobial stewardship (AMS) programma's opgericht, die focussen op het verbeteren van voorschrijven van antibiotica.

Om te kunnen meten hoe effectief AMS programma's zijn is het belangrijk om goed te kunnen meten of antibiotica gepast worden voorgeschreven. Dat is lastig omdat het beoordelen van antibioticagebruik gebaseerd is op een subjectieve beoordeling van verschillende factoren, zoals antibioticarichtlijnen, het klinisch redeneren van de arts, patiëntkenmerken, microbiologische resultaten (bijvoorbeeld bacteriekweken) en lokale gebruiken. Daarom hebben we een studie verricht naar de validiteit van de beoordeling van de gepastheid van antibioticagebruik door een internist-infectioloog door zijn beoordelingen te vergelijken met die van vakgenoten (internist-infectiologen en medisch microbiologen). Deze beoordelingen bleken in 80% van de gevallen met elkaar overeen te komen, waarmee de methode als voldoende valide wordt gezien om te worden gebruikt in de beoordeling van de effectiviteit van AMS programma's (**Hoofdstuk 2**).

Verbeteren van antibiotica voorschrijven betekent eigenlijk het veranderen van menselijk gedrag, omdat voorschrijvend artsen overtuigd moeten worden hun vaste voorschrijfpatroon te doorbreken. Echter, voorgaande AMS studies hielden over het algemeen onvoldoende rekening met de complexiteit van het menselijke gedrag, waardoor de effectiviteit suboptimaal zou kunnen zijn geweest. Daarom hebben we gebruik gemaakt van inzichten uit gedragstheorie om een interventieaanpak te ontwikkelen gericht op het verbeteren van antibioticagebruik in ziekenhuizen voor alle indicaties: the Dutch Unique Method for Antimicrobial Stewardship (DUMAS) studie. De aanpak is geïnspireerd op de participatieve actieonderzoeksmethode die focust op samenwerking met en bekrachtiging van de mensen op de werkvloer zelf gedurende het veranderproces. Deze aanpak is effectief gebleken in andere complexe zorgsituaties (**Hoofdstuk 3**). Concreet gezien was de aanpak als volgt: we beoordeelden de gepastheid van het antibioticagebruik op zeven klinische afdelingen in twee ziekenhuizen en presenteerden de resultaten hiervan aan de afdelingsartsen en

verpleegkundigen en vroegen ze hierop te reflecteren. Verder presenteerden we heb de resultaten van een bronoorzakenanalyse naar de niet-gepaste antibioticavoorschriften. Vervolgens vroegen we hen wat ze nodig dachten te hebben om dit te verbeteren (bijvoorbeeld betere richtlijnen, onderwijs). Samen met hen probeerden we deze wensen daarna in te willigen. Als een voorbeeld van deze aanpak: een afdeling met voorafgaand veel niet-gepast antibioticagebruik wilde graag dat de antibioticarichtlijn werd aangepast. Vervolgens werd de richtlijn mede door henzelf herschreven waarna het niet-gepast antibioticagebruik afnam. De complete resultaten van de DUMAS studie toonden dat de aanpak samenging met een verbetering van gepast antibioticagebruik van 13% (absolute toename) wat gedurende 12 maanden na start van de aanpak werd vastgehouden. De antibioticaconsumptie nam niet af (**Hoofdstuk 4**).

We vonden meer bewijs voor het belang en de complexiteit van menselijk gedrag bij antibioticavoorschrijven in ons onderzoek naar andere determinanten van gepast antibioticagebruik. Deze studie toonde dat antibioticavoorschrijven het minst gepast was als het was voorgeschreven in de ochtend of door onervaren artsen. Een follow-up enquête toonde dat artsen dachten dat er de ochtendvisite geen optimale situatie was om adequaat te kunnen voorschrijven, en ze suggereerden dat ondersteuning van supervisoren verbeterd kon worden, net als onderwijs over antibioticagebruik en AMS (**Hoofdstuk 5**). De tijd van de dag bleek in een andere studie ook van invloed op een ander belangrijke parameter in infectieziekten, namelijk de duur van bloedkweek logistiek. Een bloedkweek is een laboratoriumonderzoek naar de aanwezigheid van bacteriën in het bloed van een patiënt met een infectie. Als in het bloed een bacterie gevonden wordt is er sprake van een zogeheten bloedvergiftiging, een meestal zeer ernstige infectie. Hoe sneller dit bekend is, hoe eerder de antibiotica hierop kunnen worden aangepast, waardoor de behandelingsuitkomst van de patiënt vaak verbeterd kan worden. Onze studie liet zien dat de duur van de bloedkweekdiagnostiek toenam van 4 uur (mediaan) naar 16 uur, afhankelijk van het tijdstip op de dag waarop de diagnostiek zou kunnen starten (het startpunt wordt bepaald door het moment dat de incubatie klaar is, wat afhankelijk is van de snelheid van groeien van de bacterie in de kweek). De vertraging was geassocieerd met de afwezigheid van laboratoriumpersoneel in de nacht, en het feit dat het laboratorium buiten het ziekenhuis was gelokaliseerd, wat in Nederland steeds vaker het geval is (**Hoofdstuk 6**).

Onderwijs is een belangrijke interventie in AMS maar het is vaak lastig om voldoende tijd en geld te krijgen voor AMS onderwijs in de al overvolle geneeskunde onderwijscurricula. Daarnaast zijn er twijfels over de lange termijn opbrengsten van kennis en vaardigheden van traditioneel onderwijs. E-learning is een relatief nieuwe onderwijsmethode, die na initiële ontwikkeling weinig tijd vraagt van de docent, en op elke gewenste tijd en plaats kan worden doorlopen. In een studie bij medisch studenten lieten we zien dat een e-learningmodule over antibiotica de prestaties van studenten bij een gesimuleerd patiëntencontact waarbij antibiotica moest worden voorgeschreven significant kan verbeteren, 6 maanden nadat de e-learning was doorlopen (**Hoofdstuk 7**). Vanwege deze en andere veelbelovende resultaten, is het van groot belang om te zorgen dat e-learning participatie goed is, maar het blijkt dat vaak weinig mensen een aangeboden e-learning ook daadwerkelijk doen. Daarom

wilden we graag uitzoeken wat onderliggende gedragsfactoren zijn die e-learning participatie bepalen. In een studie bij arts-assistenten vonden we dat deelname aan een niet-verplichte e-learning beter is bij artsen met meer autonome motivatie (autonome motivatie = motivatie van binnenuit zoals interesse, in tegenstelling tot gecontroleerde motivatie = motivatie bepaald door externe factoren zoals geld of verwachtingen van anderen). We leerden hiervan dat om deelname en effectiviteit te optimaliseren, toekomstige e-learnings wellicht het beste voorafgegaan kunnen worden door een (korte) face-to-face bijeenkomst waarin het belang van het onderwerp wordt uitgelegd.

One question

Which of the following would be brighter, in terms of the amount of energy delivered to your retina:
- a supernova, seen from as far away as the Sun is from the Earth, or
- the detonation of a hydrogen bomb *pressed to your eyeball*?

The answer is…. the supernova, *by nine orders of magnitude!*

(adapted from: *What if? Serious scientific answers to absurd hypothetical questions*, by Randall Munroe, 2014)

Biography

Jonne Sikkens was born on the 22nd of September 1983 in Delft, as a son of Anke van Lon and Jan Roelf Sikkens. He spent his early childhood in Delft, together with his two younger brothers Rinde and Jip. After finishing primary school (Jac P. Thijsse, Freinet primary school, Delft), he went to the Grotius college (secondary school, Delft) for two years until moving with his family to Zaandam and shortly thereafter Krommenie at the age of thirteen. He switched schools to the Saenredam college in Zaandijk where he finished atheneum in 2001. He then studied psychology at the Vrije universiteit Amsterdam, graduating 'propedeuse' in 2002 followed by a 'doctoraal' exam in neuropsychology (which is equivalent to a master's degree) in 2006. He had moved to Amsterdam during this first study. This first study was followed up by a bachelor and master degree in medicine (graduated in 2011, *cum laude*) at the same university. He did his final internship in internal medicine (infectious diseases) performed at the Sint Lucas Andreas hospital (currently OLVG) under the guidance of dr. Jan Veenstra. Afterwards he started working as a PhD student (2011-2016) at the department of internal medicine at the VU university medical centre (currently Amsterdam UMC) under the guidance of prof.dr. Mark Kramer and prof.dr. Michiel van Agtmael, which resulted in the current thesis. During the PhD traject, he also acquired a master's degree in clinical epidemiology at the EpidM institute, Amsterdam. In 2016 he started his training to become an internist at the same VU university medical centre, supervised by prof.dr. Yvo Smulders.

Jonne currently lives in Weesp together with his wife Djoeke, and their three sons (Melin, born in 2014, Leo, born in 2016, and Sietse, born in 2018).

Biografie

Jonne Sikkens werd geboren op 22 september 1983 in Delft, als zoon van Anke van Lon en Jan Roelf Sikkens. Hij bracht zijn vroege jeugd door in Delft, samen met zijn jongere broers Rinde en Jip. Na het voltooien van de Jac. P. Thijssebasisschool (Freinet-onderwijs) vervolgde hij zijn scholing op het Grotius college gedurende twee jaar totdat hij op dertienjarige leeftijd met zijn ouders en broers verhuisde naar Zaandam en later Krommenie. Hij vervolgde de middelbare school op het Saenredam college te Zaandijk, waar hij in 2001 slaagde voor het atheneum. Hij ging vervolgens psychologie studeren op de Vrije Universiteit in Amsterdam, waar hij in 2002 slaagde voor zijn propedeuse, en in 2006 voor zijn doctoraal examen in klinische neuropsychologie (equivalent aan de tegenwoordige master titel). Hij was inmiddels in Amsterdam gaan wonen. In 2005 startte hij met een nieuwe studie, namelijk geneeskunde aan dezelfde universiteit, waarvan hij de bachelor en de master titel (2011, *cum laude*) behaalde. Hij deed zijn laatste, 'oudste' co-schap in het Sint Lucas Andreasziekenhuis te Amsterdam (tegenwoordig OLVG) bij de interne geneeskunde (infectieziekten) onder supervisie van dr. Jan Veenstra. Hierna begon hij aan een promotietraject (2011-2016) bij de interne geneeskunde van het VU medisch centrum (tegenwoordig Amsterdam UMC) onder

supervisie van prof.dr. Mark Kramer en prof.dr. Michiel van Agtmael, wat resulteerde in het huidige proefschrift. Tijdens deze periode behaalde hij een master in de klinische epidemiologie, bij het EpidM instituut te Amsterdam. In 2016 is hij gestart met de opleiding tot internist in het VU medisch centrum onder supervisie van prof.dr. Yvo Smulders.

Jonne woont tegenwoordig in Weesp, samen met zijn vrouw Djoeke, en hun drie zoons (Melin, geboren in 2014, Leo, geboren in 2016, en Sietse, geboren in 2018).

Dankwoord

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'If we knew what it was we were doing, it would not be called research' – Albert Einstein

Aan het eind van deze lange reis naar wetenschappelijke verlichting (…) wil ik nog een aantal mensen in het zonnetje zetten die mij op de een of andere manier geholpen hebben bij het volbrengen hiervan. Bij nader inzien altijd achteraf.

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bij het lezen van mijn stukken wist ik dat ik het weer eens te moeilijk had opgeschreven. Die frons (of eigenlijk de afwezigheid hiervan) was een lakmoesproef voor het publicatie-klaar zijn van artikelen. Ik hoop dat we de samenwerking kunnen blijven continueren de komende jaren want volgens mij zijn we een goed team.

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'I may not have gone where I intended to go, but I think I have ended up where I needed to be' – Douglas Adams

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1. Sikkens JJ, Peters EJG, van Agtmael MA. The 'morning dip' in antimicrobial appropriateness: circumstances determining appropriateness of antimicrobial prescribing-authors' response. J Antimicrob Chemother. 2018 Oct 23.

2. Sikkens JJ, Möhlmann MC, Peerbooms PG, Lettinga KD, Peters EJG, Kramer MHH, van Agtmael MA. The impact of laboratory closing times on delay of adequate therapy in blood stream infections. Neth J Med. 2018 Oct;76(8):351–7.

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