How to Impact antibiotic prescribing?

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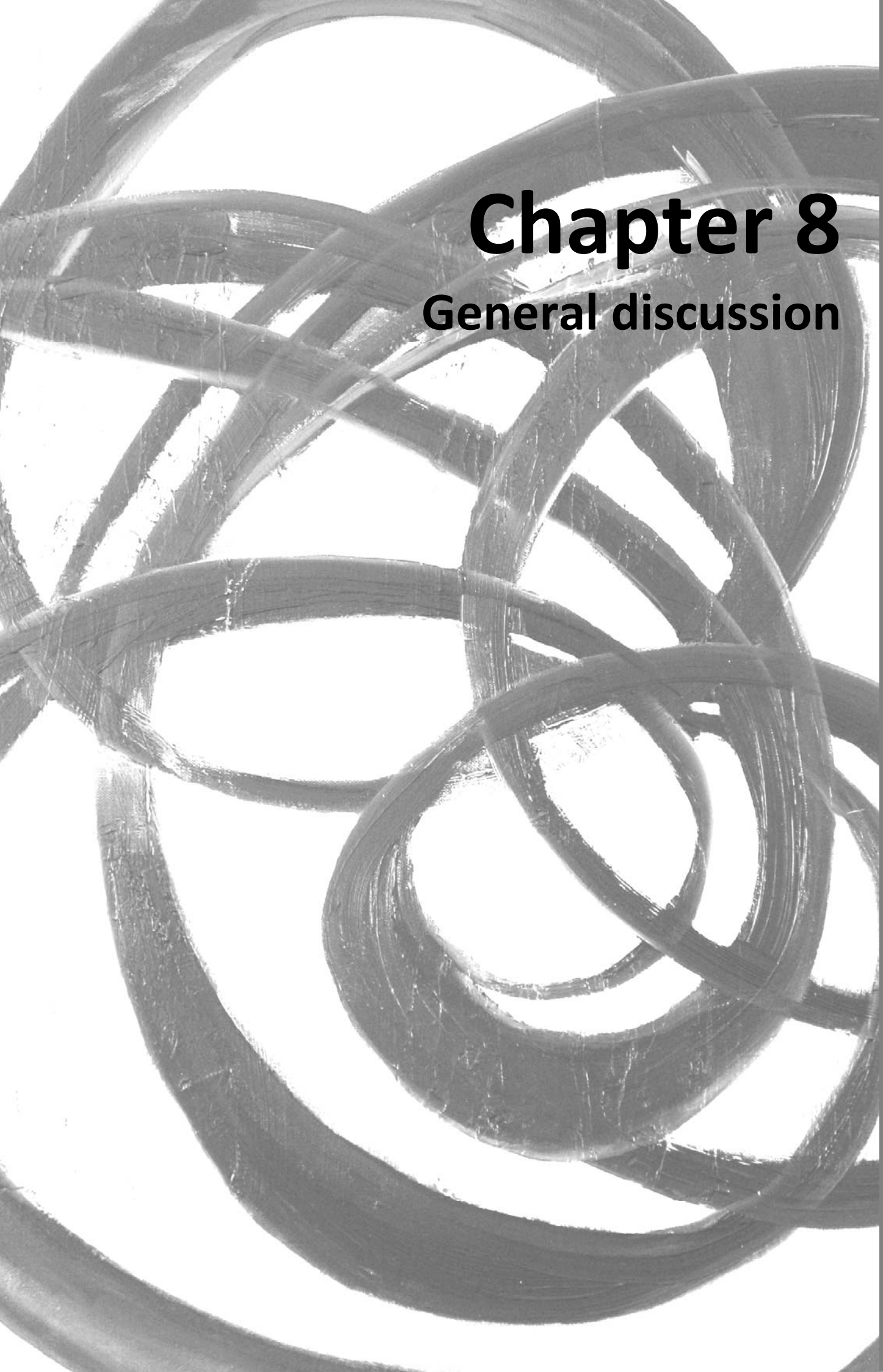

Chapter 8
General discussion

The previous chapters of this thesis reported on the Improving Rational Prescribing of Antibiotics in Long-term Care Facilities (IMPACT) study. This study started with an investigation of the appropriateness of decisions to prescribe or withhold antibiotics (referred to as 'prescribing decisions'), antibiotic use, and guideline-adherent antibiotic selection in two types of long-term care facilities (LTCFs) in the Netherlands: nursing homes (NHs) and residential care facilities (RCFs). These study results served as input for the development of tailored interventions directed at improving appropriate antibiotic prescribing. A participatory action research (PAR) approach was used for the development, implementation, and evaluation of these tailored interventions. This approach is characterized by the involvement of local stakeholders, who are considered 'co-researchers', in: 1) the identification of opportunities for improved practice, 2) the development and implementation of interventions directed at these opportunities, and 3) the evaluation of the implemented interventions. The IMPACT study evaluated the effect of tailored interventions developed and implemented with the PAR approach on the appropriateness of prescribing decisions, antibiotic use, and guideline-adherent antibiotic selection in NHs and RCFs.

Key findings

Insight into antibiotic prescribing in LTCFs

- Our systematic review of the literature showed that antibiotic use in LTCFs is substantial (i.e. between 47% and 79% of the residents receive at least one course of antibiotics per year), and that up to 51% of these antibiotics are potentially prescribed inappropriately. Only a few Dutch studies were included in this review, which confirmed that little research on these topics has been conducted in LTCFs in the Netherlands.
- Qualitative interviews with physicians and nursing staff (i.e. nurses and nurse assistants) in five NHs and two RCFs in the Netherlands resulted in the development of a conceptual model that integrates six categories of factors that influence antibiotic prescribing decisions. These categories include: the clinical situation, advance care plans, utilization of diagnostic resources, physicians' perceived risks, influence of others (i.e. colleagues, nursing staff, patients and family members), and influence of the environment (e.g. availability of guidelines). Some of these categories hold factors that may result in inappropriate antibiotic prescribing, such as prescribing to avoid perceived risks of withholding antibiotics ('better safe than sorry'), adaptation to peer practice, and prescribing to meet expectations of patients, family members or nursing staff.
- Our prospective study in ten NHs in the Netherlands showed that, overall, 76% of the prescribing decisions were appropriate. They were less often appropriate in case of urinary tract infections (UTIs) compared to respiratory tract infections (RTIs) and skin infections (SIs). Further, overprescribing (i.e.

inappropriately prescribing antibiotics) occurred more often than underprescribing (i.e. inappropriately withholding antibiotics). Most inappropriate decisions to prescribe antibiotics were in clinical situations indicative of asymptomatic bacteriuria and viral RTI.

- At baseline, the number of antibiotic prescriptions per 1,000 resident-care days was 5.1 in NHs and 4.6 in RCFs. The number of total defined daily doses (DDDs) per 1,000 resident-care days was 54.3 in NHs and 41.7 in RCFs.
- At baseline, the percentage of first-choice antibiotic prescriptions for UTIs in residents without a catheter[1] was 47% in both NHs and RCFs. The percentage of first-choice antibiotic prescriptions for RTIs[2] was 8% in NHs and 17% in RCFs.

The development and implementation of tailored interventions directed at improving appropriate antibiotic prescribing, and the effect of these tailored interventions on antibiotic prescribing in LTCFs

- The PAR approach resulted in the implementation of a variety of interventions by local stakeholders in the intervention LTCFs. These interventions were directed at a combination of the following, thereby focusing on UTIs, RTIs, or both types of infection: improving physician knowledge (e.g. by guideline discussion, knowledge tests), improving communication between physicians and nursing staff (e.g. by nursing staff education, multidisciplinary meetings, protocol development), optimizing medication formularies (e.g. in pharmacotherapy counselling meetings), understanding local UTI resistance patterns by evaluating urine culture results, increasing the use of urine cultures, and aligning prescribing preferences with the cross coverage group.
- In NHs, there was no effect of the tailored interventions on the appropriateness of prescribing decisions, antibiotic use, or guideline-adherent antibiotic selection. An increase in appropriate prescribing decisions in control NHs was attributable to physician turnover. Higher levels of appropriate prescribing decisions were observed at the start of the data collection (after a kick-off meeting was held to introduce the study goals and data collection procedures) and at the end of data collection (after it was announced that feedback on antibiotic prescribing behaviour would soon be provided).
- In RCFs, no change in trends related to antibiotic use was observed in intervention RCFs compared to control RCFs. However, guideline-adherent antibiotic selection for RTIs increased more strongly in intervention RCFs compared to control RCFs (55% versus 9%). Guideline-adherent antibiotic

[1] NHs: nitrofurantoin, trimethoprim, or trimethoprim/sulfamethoxazole; RCFs: nitrofurantoin

[2] NHs and RCFs: amoxicillin

selection for UTIs in residents without a catheter also increased in intervention RCFs (14%), whereas this decreased in control RCFs (-20%).

Methodological considerations

This section addresses some methodological aspects of the IMPACT study that should be considered when interpreting the study findings.

Study design

The design of the IMPACT study is displayed in Figure 1. The participating LTCFs were matched pairwise based on facility type (i.e. NH or RCF), the number of residents, and the quantity of antibiotic use at baseline (derived from pharmacy data). Two and three LTCFs were affiliated with the same healthcare organization, and these were allocated to the same study arm to avoid contamination. We chose to assign the three LTCFs affiliated with the same healthcare organization to the control group. This was based on the assumption that loss-to-follow up of three LTCFs, in the event the healthcare organization would decide to withdraw from the study, would be less desirable in the intervention group compared to the control group. This decision automatically resulted in the assignment of the two other LTCFs affiliated with the same healthcare organization to the intervention group, as one of these was matched to one of the three LTCFs affiliated with the other healthcare organization. Hence, LTCFs were not randomly assigned to a study arm, and therefore the IMPACT study was a quasi-experimental study.[1]

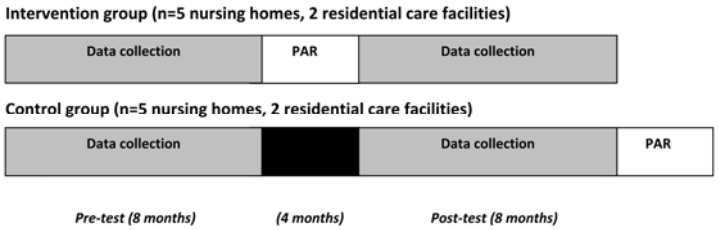

Figure 1. Design of the IMPACT study.

The matching criterion 'quantity of antibiotic use' is not necessarily related to the appropriateness of antibiotic prescribing decisions, the primary study outcome. Indeed, a large difference in appropriateness of antibiotic prescribing decisions was found between the intervention and control group at baseline. Ideally, we should have matched facilities based on the primary study outcome, to avoid a baseline difference for this outcome. This was not performed in the current study for practical reasons, i.e. the assessment of the outcome measure was a time-consuming process which did not allow for the evaluation of a substantial number of prescribing decisions before the onset of the intervention phase of the study (i.e. the PAR phase in Figure 1). The baseline difference in the primary study outcome may not only be explained by the matching procedure, but also by the fact that the study was unblinded, i.e. both the researchers and the participants were aware of the group to which a LTCF was allocated. Awareness regarding the group to which a facility was assigned may have altered prescribing behaviour (i.e. performance bias). In retrospect, to avoid

such an undesirable effect, we should have informed facilities about their group allocation only shortly before the onset of the intervention phase of the study, rather than at the initiation of the pre-test phase.

Inclusion of study facilities

We intended to include 6 NHs and 6 RCFs in the study, with half of the facilities of each type assigned to the intervention and the control group. However, due to recruitment issues in RCFs (i.e. most RCFs are affiliated with a substantial number of general practices, and we encountered difficulties in involving all these in the study), only 4 RCFs were included. These 4 RCFs were all affiliated with a limited number of general practices, resulting in limited numbers of local stakeholders that we needed to involve in the study. This, and the small number of RCFs included in the study calls for the study results in RCFs to be interpreted with caution. To compensate the inclusion of fewer-than-intended RCFs, we included more NHs (i.e. 10), since no recruitment difficulties were encountered in this setting.

Measurements

A variety of quantitative and qualitative data sources were used for the collection of data in the IMPACT study. The qualitative interviews and the collaboration with local stakeholders during the PAR phase of the study enabled us to place the quantitative data on antibiotic prescribing into a broader context, as these provided understanding of the reasoning behind antibiotic prescribing decisions. The quantitative data sources (i.e. infection recording forms completed by physicians, chart review, and pharmacy data) allowed for investigating the study outcomes: the appropriateness of prescribing decisions, antibiotic use, and guideline-adherent antibiotic selection. The primary study outcome, the appropriateness of prescribing decisions, could only be assessed for the participating NHs. This assessment was based on the infection recording forms that were completed by the physicians in this setting. In RCFs, physicians did not complete such infection recording forms due to time constraints, and data collected by chart review appeared of insufficient quality to evaluate the appropriateness of prescribing decisions with the algorithms that we had developed for this purpose. Pharmacy data were used to create an overview of total antibiotic use in the participating LTCFs. A limitation of these data was that they do not include the indications for prescribed antibiotics. Therefore, these data could not be used for the evaluation of guideline-adherent antibiotic selection. We instead resorted to data from the infections recorded by physicians (NHs) and chart review (RCFs) to determine, per type of infection, the proportion of guideline-adherent antibiotic prescriptions.

Reflection on the findings

Appropriateness of antibiotic prescribing in LTCFs: the role of guidelines

There is a lack of evidence on signs and symptoms indicative of common infections in LTCF residents,[2,3] which translates into a lack of universal recommendations regarding diagnostic evaluation and antibiotic prescribing decision-making in this setting.[3] In the IMPACT study, we therefore newly developed algorithms for the evaluation of the appropriateness of prescribing decisions, which were based on national and international guidelines.[2,4-7] We encountered several issues with regard to these guidelines, and therefore adjusted some of the guideline-derived criteria for antibiotic prescribing in collaboration with an expert panel. The first issue is that, for RTIs and SIs, no long-term care-specific national guidelines exist. We therefore relied on guidelines developed for the primary care population,[4,5] and refined some criteria based on specific characteristics of the long-term care population. For example, approximately one-third of the LTCF residents with pneumonia does not present with cough.[8,9] We additionally used international criteria for the initiation of antibiotics for RTIs in LTCF.[2] However, these criteria do not consider findings on lung auscultation whereas abnormalities on lung auscultation have been reported to be predictive for pneumonia.[10,11] For UTIs, a national guideline specifically for NHs is available.[6] However, it does not describe in detail which clinical situations justify antibiotic prescribing and which do not, which is likely caused by the abovementioned lack of evidence on signs and symptoms indicative of infections.[2,3] For example, the guideline does not distinguish between different types of nonspecific symptoms in recommending treatment decisions. To illustrate this: the guideline recommends antibiotics for a patient who is not ill, has nonspecific symptoms, and a positive dipstick test (i.e. the presence of nitrite and leukocyte esterase). However, it does matter what type of nonspecific symptoms are involved in deciding whether antibiotics should be prescribed or not. Antibiotics may be justified if in the abovementioned case the patient presents with fever, whereas appropriateness of antibiotic prescribing is questionable if this patient presents with a decrease of appetite.

The lack of available evidence and the resulting lack of recommendations regarding antibiotic prescribing decision-making in LTCFs has implications for both practice and research. For practice, the lack of recommendations results in a lack of guidance on antibiotic prescribing decision-making. This implies that physicians have much freedom in their decisions to prescribe antibiotics. For research, the lack of evidence translates into difficulties in evaluating antibiotic prescribing decisions. For the assessment of the appropriateness of prescribing decisions in the IMPACT study, for instance, we had to rely on guidelines that were based on limited evidence (as described in the previous paragraph). Even though we adjusted some of the guideline-derived criteria, the algorithms that we developed mostly reflect the guidelines on which they are based. One may argue that the liberal nature of the guidelines

reflected in these algorithms may explain the relatively high percentage of appropriate prescribing decisions at baseline. However, other studies that similarly used guideline-derived criteria to evaluate appropriateness of prescribing decisions found lower percentages of appropriateness.[12-18] Although the criteria used in these studies were based on different guidelines than in the IMPACT study, it is likely that these guidelines are similarly based on the limited evidence available on antibiotic prescribing decision-making in LTCFs. It is therefore unlikely that the relatively high baseline percentage of appropriate prescribing decisions in the IMPACT study is explained by the characteristics of the algorithms used. Instead, it may be explained by the physicians in the IMPACT study being conservative in antibiotic prescribing, or by physicians' recording of presumed infections leading to increased awareness of appropriate antibiotic prescribing.

Appropriateness of antibiotic prescribing in LTCFs: the role of nursing staff

In LTCFs, nursing staff is responsible for 24-hour nursing care, including the recognition of signs and symptoms in residents.[9,19-21] In NHs, and to a larger extent in RCFs due to the absence of on-site physicians, physicians therefore rely on nursing staff in the provision of medical care to residents. This section reflects upon three issues regarding physician-nursing staff communication that are important to consider in infection-related medical decision-making. The first issue includes the lack of structured recording and reporting of signs and symptoms by nursing staff, which can translate into diagnostic uncertainty in physicians, and consequently complicate antibiotic prescribing decision-making.[22,23] For example, the majority of recording forms completed by physicians in the IMPACT study did not include information on temperature, blood pressure, and pulse. This suggests that this information is often not available at the time of antibiotic prescribing decision-making, which was confirmed by physicians in our interview study. The second issue involves dipstick testing by nursing staff in case of suspected UTI. Nursing staff may take the initiative to perform a dipstick test based on signs and symptoms that do not necessarily indicate a UTI, such as behavioural change (in Dutch often referred to as 'anders dan anders') or a change of urine odour or appearance.[24-27] Considering the high prevalence of both asymptomatic bacteriuria and pyuria among LTCF residents, and consequently the high likelihood that positive dipstick test results will be found, a dipstick test should only be performed if signs and symptoms indicative of a UTI are present.[22,24,28-30] This implies that nursing staff should be taught which symptoms are indicative of UTIs, which in turn emphasizes the need for more evidence on signs and symptoms indicative of infections in LTCF residents (as described in the previous section). A final issue in the physician-nursing staff communication are situations in which nursing staff expects a physician to prescribe antibiotics. If nursing staff expresses such expectations, physicians may be inclined to fulfil them even in situations where they believe antibiotics should not be prescribed, possibly because this is less time-consuming compared to convincing nursing staff that no antibiotics are required, or because physicians lack awareness of issues regarding antibiotic

resistance. Alternatively, they may decide to not comply with such expectations, and if no rationale for this decision is provided, the nursing staff may not understand the background of the decision. These issues underline the importance of communication between physicians and nursing staff in antibiotic prescribing decision-making. To this end, clear agreements and good conditions for collaboration between these disciplines are important.[21,31] In particular, nursing staff should be informed about the argumentations of physicians in antibiotic prescribing decision-making, to foster their understanding of the diagnosis of an infection and of decisions to (not) prescribe antibiotics.

The use of PAR in the development of tailored interventions directed at improving appropriate antibiotic prescribing in LTCFs

The IMPACT study is, to our knowledge, the first to use PAR for the development and implementation of tailored interventions directed at improving appropriate antibiotic prescribing in LTCFs. An advantage of this approach that we encountered, is that the involvement of local stakeholders throughout the study provided valuable insights into the facilitators and barriers to appropriate antibiotic use. The opportunities for improved antibiotic use identified by the stakeholders varied between facilities, which is reflected by the different types and focus of interventions that were selected and implemented. This supports the notion that there is no one-size-fits-all approach to improving antibiotic prescribing.[32,33]

Nevertheless, the appropriateness of antibiotic prescribing decisions in NHs did not improve following the implementation of these tailored interventions. Our study findings do not support the idea that the high percentage of appropriate antibiotic prescribing at baseline explains this lack of an intervention effect. First, the finding that antibiotic prescribing for UTIs was less often appropriate compared to RTIs and SIs suggests that treatment decisions for this infection type could be improved. In addition, our interview study identified several influencing factors that may result in inappropriate antibiotic prescribing. Although no conclusions can be drawn regarding quantitative measures based on such qualitative research, it may be assumed that these findings indicate room for improvement with regard to appropriate antibiotic prescribing. Finally, the percentage of appropriate prescribing decisions varied over time, which suggests that the lower percentages of appropriate prescribing decisions could be increased. Considering these findings, further improvement of the percentage of appropriate prescribing was likely possible.

The lack of an intervention effect may be due to characteristics inherent to the PAR approach. A possible disadvantage of the approach is the dependence on local stakeholders for the selection of interventions. Figure 2 visualizes the factors that influence antibiotic prescribing that were addressed by the interventions implemented in the IMPACT study. The figure shows that the local stakeholders did not select interventions that focused on dealing with perceived risks or with influence

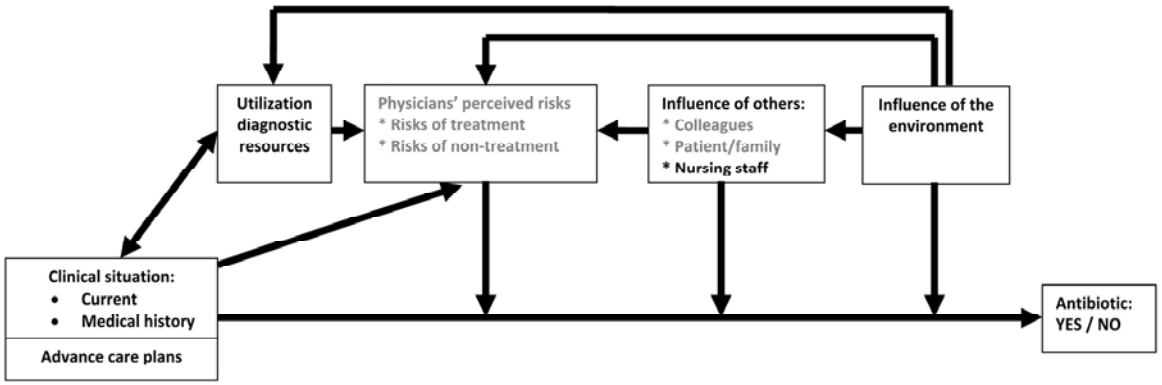

Figure 2. Factors that influence antibiotic prescribing in LTCFs that were addressed by the local stakeholders with their choice of interventions in the IMPACT study, pointed out in our conceptual model (Chapter 3): **black**; factor addressed by interventions, **grey**; factor not addressed by interventions.

of patients, family members, and colleagues. This may explain the lack of an intervention effect, as such behavioural factors are considered important to address in efforts to improve antibiotic prescribing.[32,34] The reason for the failure to address these behavioural factors may be that local stakeholders opted for interventions that require limited efforts (e.g. education, pharmacotherapy counselling meetings), rather than for the more complex interventions that are required for changing prescribing behaviour.[33,35,36] In addition, the collaborative deciding on intervention selection in multidisciplinary meetings may not represent an environment that is considered 'safe' for addressing more sensitive issues such as the participants' behaviour.[37,38] Another possible explanation for not addressing behavioural factors may be that antibiotic resistance is not perceived an important problem in LTCFs.[39] Indeed, our interview study and some other qualitative studies suggested that antibiotic resistance development is not commonly considered in prescribing decisions.[40-42] One of these studies found parallels between physician perceptions and the stages of Prochaska's transtheoretical model that assesses an individual's readiness to health behaviour change; physicians who did not consider antibiotic resistance in their prescribing decisions were less willing to change their prescribing behaviour.[42] A final explanation for not addressing behavioural factors may be that the relatively high baseline level of appropriate treatment decisions reduced motivation to undertake action to improve antibiotic prescribing behaviour, which is in line with reporting that professional practice is more likely to change if baseline performance is low.[43]

The potential of PAR as an effective approach for the development of interventions directed at improved antibiotic prescribing may also have been hampered by the way the approach was applied in the IMPACT study. For example, we allowed a limited period of time for the selection, development, and implementation of interventions. This may have reduced chances that selected interventions address complex issues, including the behavioural factors described above. In addition, the selection of interventions was probably affected by the limited project budget, resulting in the

inability to financially support, for example, the purchase of diagnostic resources. Finally, only one PAR cycle of planning action, taking action, and reflecting on action was conducted in the study, whereas this cycle should ideally be repeated until the desired outcomes are achieved.[44]

Since it cannot be determined whether the PAR approach itself or the way it was embedded in our study design resulted in the absence of an intervention effect, we cannot draw conclusions on whether PAR is a suitable approach for the development of tailored interventions directed at improved antibiotic prescribing. Therefore, PAR should not be disqualified as a research method for the implementation of interventions directed at improved antibiotic use, based on the IMPACT study, especially as the approach was well-appreciated by the study participants, and brought important insights into the facilitators and barriers to appropriate antibiotic prescribing.

Antibiotic stewardship in LTCFs

Antibiotic stewardship programs include interventions aimed at optimizing the appropriate use of antibiotics.[45] To date, little is known about which antibiotic stewardship interventions can improve antibiotic prescribing in LTCFs.[3,9,45] Previous studies on antibiotic stewardship efforts in LTCFs are scarce, and they are inconclusive regarding the effects of antibiotic stewardship activities on antibiotic prescribing.[3,31,46] Based on the IMPACT study, no final conclusions can be drawn either on how to develop effective antibiotic stewardship interventions, due to the lack of an intervention effect in NHs and the preliminary nature of the study findings in RCFs. Nevertheless, the study did provide some clues as to what is important to consider in the development of antibiotic stewardship programs in LTCFs.

A central theme that evolved in the IMPACT study is the complexity of antibiotic prescribing decision-making in LTCFs. In this decision-making process, physicians balance the risks of unjustified *withholding* of antibiotics (e.g. deterioration of the clinical situation) against the risks of antibiotic *prescribing* (e.g. development of resistance, adverse events). The complexity of the patient population (e.g. atypical presentation of symptoms, multiple comorbidities, communication impairments) combined with a variety of external factors (e.g. influence of nursing staff, opinions or requests of family members, the degree of familiarity with the patient) makes physicians refrain from the risk of unjustified withholding of antibiotics, accepting that at times, an antibiotic prescription is unjustified. After all, one treatment decision that resulted in adverse outcomes in the past and is retrospectively perceived as a wrong decision has a greater impact than many decisions with positive outcomes. This defensive attitude towards antibiotic prescribing decision-making can be captured as 'better safe than sorry'.

In the IMPACT study, we experienced that physicians do want to use antibiotic more conservatively, but that this desire is often overruled by the above mentioned risk perceptions. Therefore, it is important that physicians are provided with grips to confidently refrain from antibiotic use in situations that otherwise would result in 'better safe than sorry' antibiotic prescribing. This thesis revealed several possible grips to achieve this, which can be regarded as a first step toward antibiotic stewardship initiatives in LTCFs in the Netherlands. They are described in the section 'recommendations for practice'. In addition, the IMPACT study suggests some promising interventions to improve antibiotic prescribing which need further research before they can be recommended for inclusion in antibiotic stewardship programs. These are included in the section 'recommendations for research'.

Recommendations for practice

- *Guidelines*
  The lack of detail in the recommendations regarding antibiotic prescribing decision-making in the national UTI guideline of the Dutch Association of Elderly Care Physicians and Social Geriatricians ('Verenso' in Dutch)[6] results in much freedom for physicians in the decision-making process. This guideline should therefore be revised by further specifying the recommendations. In addition, the development of LTCF-specific guidelines on RTIs and SIs may be helpful, as the recommendations in the currently used guidelines for other patient populations do not always apply to the long-term care population. The algorithms that we developed for the IMPACT study may be useful in the development and revision of the abovementioned guidelines. Further, LTCF specific guidelines should be disseminated to general practitioners providing care in RCFs, as these guidelines apply better to this patient population than the general practice guidelines do.
- *Physician-nursing staff communication*
  With regard to physician-nursing staff communication, it should be encouraged that agreements are made on the systematic recording and communication of signs and symptoms in residents (including temperature, blood pressure, and pulse), and on when nursing staff should perform a dipstick test (i.e. either on physicians' orders or only if predefined signs and symptoms are present). Efforts should be made to ensure that such agreements are indeed acted upon in daily practice. Furthermore, to facilitate understanding in nursing staff, it is important that physicians communicate the reasons underlying treatment decisions in individual situations. In case of decisions to not prescribe antibiotics, this may raise awareness among nursing staff of the importance of the conservative use of antibiotics.
- *Awareness*
  This thesis and previous research found that antibiotic resistance is not commonly considered in antibiotic prescribing decision-making in LTCF. Considering the increasing threat that antibiotic resistance poses to human health, awareness of

this issue should be encouraged. In each individual case, physicians should balance the interests of the patient (i.e. provision of the best possible care) against the interests of public health (i.e. prevention of the development of antibiotic resistance). Guidelines, such as the ones developed by the Dutch Association of Elderly Care Physicians and Social Geriatricians ('Verenso' in Dutch), may play a role in raising this awareness by emphasizing the importance of considering antibiotic resistance in antibiotic prescribing decision-making. Awareness may also be encouraged by the recurrent inclusion of the topic on the agenda of pharmacotherapy counselling meetings ('FTOs' in Dutch). In addition to ensuring awareness among physicians, awareness of antibiotic resistance should also be ensured among nursing staff and LTCF management, to encourage support for antibiotic stewardship initiatives and activities related to infection prevention. Infection (prevention) committees or antibiotic committees established in LTCFs may play an active role in facilitating this.

In addition to awareness of antibiotic resistance, it should be encouraged that physicians are also aware of other clinical and nonclinical considerations that influence their prescribing decisions. The conceptual model that we developed in the IMPACT study (Chapter 3) may be a helpful tool to explore and discuss these factors and their potential to result in inappropriate antibiotic use, for example during pharmacotherapy counselling meetings. It may also be beneficial to discuss prescribing practices in case of changes in the physician team, as physician turnover was shown to affect appropriateness of antibiotic prescribing in NHs. Creating a dialogue on the topic of appropriate antibiotic prescribing may lead to optimization of the local antibiotic prescribing policy, and facilitates that all physicians of the team act according to this policy.

- *Monitoring prescribing behaviour*

  Higher percentages of appropriate antibiotic prescribing decisions in NHs were found at times attention was drawn to the monitoring of prescribing behaviour, possibly due to increased awareness of appropriate antibiotic use. Positive effects of audit and feedback have been reported in other studies as well, although these studies emphasized that audit and feedback is likely to be more effective if combined with other interventions, such as interventions addressing behavioural factors.[33,43,47] Therefore, audit and feedback may be recommended as an activity that guides further antibiotic stewardship efforts, rather than as a single intervention. The method used in the IMPACT study to monitor appropriateness of prescribing decisions was time-consuming, since physicians recorded data on presumed infections, and researchers evaluated each infection for the appropriateness of antibiotic prescribing decisions. As an alternative, physicians may regularly discuss the appropriateness of treatment decisions of a number of random cases of infection, for example during a pharmacotherapy counselling meeting. On a less detailed level, pharmacy data may be used to evaluate antibiotic use, similar as was conducted in the IMPACT study. Pharmacists may play a role in the extraction and analysis of this data. They may also take initiatives

to improve the data, for example by ensuring that each prescribed antibiotic in their information system is linked to the type of infection, which would facilitate the analysis of data per infection type.

Recommendations for research

- Considering the limited number of studies conducted on antibiotic stewardship in LTCFs, and their inconclusive outcomes, further research is needed to identify interventions that are effective in improving antibiotic prescribing in this setting.[3,46] Based on the IMPACT study, three types of possible interventions are recommended for further investigation:
    - The use of diagnostic resources reduces diagnostic uncertainty, which can in turn reduce the occurrence of situations in which physicians prescribe antibiotics to be 'better safe than sorry'. One of the NHs that participated in the IMPACT study performed urine cultures on-site, with bacterial growth confirmed after one day and antibiotic susceptibility after two days (as opposed to laboratory results that are usually available after one week). Quickly available culture results can assist in antibiotic prescribing decision-making, however, to our knowledge no studies have evaluated the effect of on-site urine culturing on antibiotic prescribing in LTCF. In the general practice setting, the implementation of a C-reactive protein (CRP) point-of-care test led to a reduction in antibiotic use for RTIs.[48,49] No research is currently available on the application of this diagnostic tool in LTCF. Future studies should evaluate the effect of using diagnostic tools such as on-site urine culturing and CRP point-of-care testing on antibiotic prescribing in LTCFs, thereby taking into account relevant ethical considerations such as the burden of diagnostic tools for residents, and financial considerations.
    - The IMPACT study suggests a positive effect of monitoring activities on the appropriateness of antibiotic prescribing decisions. This effect, however, did not sustain over time. The decrease in the percentage of appropriate prescribing decisions over time may represent the fading out of a Hawthorne effect, a phenomenon that refers to behaviour change caused by the study participants' awareness of being observed.[50] Further research is needed to test this hypothesis, and to investigate how the effect of monitoring activities can be sustained over time.
    - The feedback on antibiotic prescribing patterns and guideline-based evaluation of medication formularies may have resulted in the increase in guideline-adherent antibiotic selection in RCFs. Further research is needed to elucidate if these interventions can indeed improve prescribing patterns in RCFs, also if they are affiliated with larger numbers of general practices.
- The current evidence base for antibiotic prescribing guidelines for LTCFs is modest,[2] which translates into a lack of recommendations on antibiotic prescribing decision-making. Therefore, a stronger evidence base is needed with regard to

diagnostic criteria for the initiation of antibiotics in LTCF residents. In addition, it would be helpful to develop universally applicable criteria for the evaluation of prescribing decisions in LTCF, to facilitate (international) comparison of the appropriateness of antibiotic prescribing.

- This thesis raises the question of whether PAR can be a suitable approach to develop antibiotic stewardship programs if the approach is optimally applied, by allowing sufficient time and budget for the development and implementation of interventions, and by facilitating the conduction of multiple PAR cycles. Further research may elucidate this.
- Finally, this thesis confirms that addressing facilitators and barriers to antibiotic prescribing is important for any antibiotic stewardship effort.[3,31-33,46,51,52] Future research in this area should therefore be encouraged to include an analysis of these determinants in their approach.

Overall conclusion

This thesis demonstrates the complexity of antibiotic prescribing decision-making in LTCFs. A consequence of this complexity is that, in practice, the risks of unjustified *withholding* of antibiotics (e.g. deterioration of the clinical situation) often outweigh the risks of antibiotic *prescribing* (e.g. development of resistance, adverse events). This contributes to inappropriate use of antibiotics. Therefore, physicians need grips to confidently refrain from antibiotic prescribing when in doubt about whether antibiotics are needed. For practice, these grips should be sought in improving existing guidelines and developing new guidelines, in optimizing communication between physicians and nursing staff, and in facilitating awareness of rational and non-rational considerations in antibiotic prescribing decision-making. The monitoring of prescribing behaviour may guide antibiotic stewardship efforts, and may encourage awareness of appropriate antibiotic use. In future research, grips should be sought in possibilities to support the diagnosing of infectious diseases in LTCF residents, such as by investigating the added value of diagnostic tools, and by improving the evidence base regarding criteria for the initiation of antibiotics.

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