How to Impact antibiotic prescribing?

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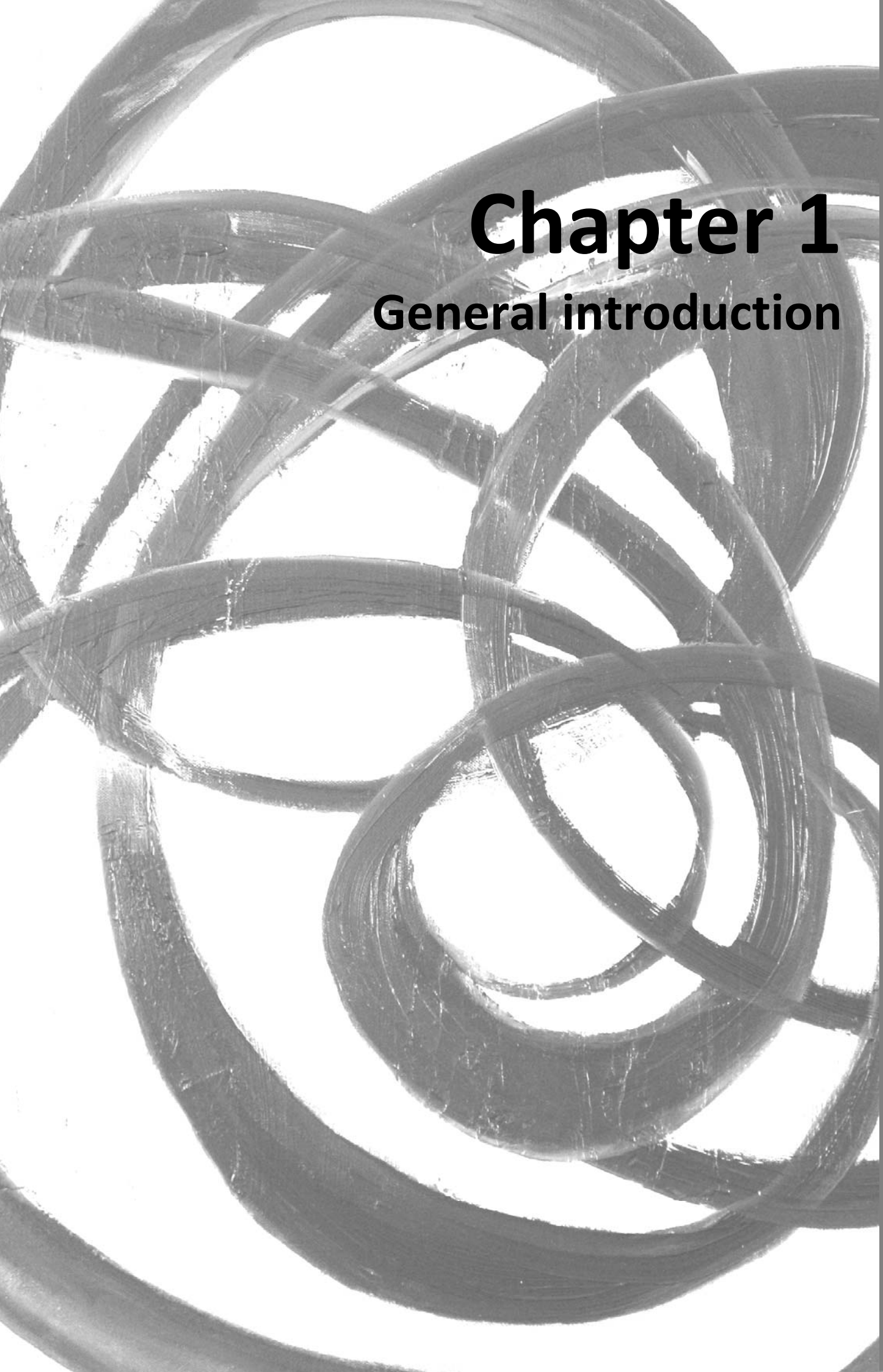

Chapter 1
General introduction

Antibiotics, the miracle drugs of the 20th century

Antibiotics are referred to as the miracle drugs of the 20th century.[1,2] With their introduction in the 1930s, many formerly fatal infectious diseases became treatable. Ever since, millions of lives have been saved, and outcomes for millions of patients have improved.[3] Nevertheless, only one year after the widespread use of the first antibiotic (i.e. penicillin), the bacterium targeted by this antibiotic (i.e. *Staphylococcus aureus*) developed resistance against it.[2] More (classes of) antibiotics were developed in the years that followed, and bacteria responded by developing a variety of mechanisms to resist them.[4-6] The ability of bacteria to adapt to their environment makes antibiotics a unique drug class as, unlike most other pharmaceuticals, their effectiveness diminishes over time.[4,7] This process is accelerated by the (over)use of antibiotics, both in human and in veterinary medicine, because antibiotic consumption is the main driver of antibiotic resistance.[4,5,8] To date, worrisome levels of antibiotic resistance have been reached worldwide.[1,6] At the same time, the development of new (classes of) antibiotics by pharmaceutical companies has stagnated.[5] An important reason for this is the limited profitability of antibiotics, as a consequence of: 1) the short treatment duration (compared to drugs for chronic conditions), 2) the fact that sooner or later resistance against the drug will evolve, and 3) the restricted use of new antibiotics as physicians are encouraged to prescribe them only when no other antibiotic options are available.[3,5] Another reason for the lack of investments in antibiotic development by pharmaceutical companies are the increasing difficulties in identifying new antibiotics.[5]

These developments – the increase in antibiotic resistance and decrease in the development of new antibiotics – triggered calls for action.[1,5,7] If no efforts are being made to bring these developments to a halt, we will enter a 'post-antibiotic era', where no effective antibiotic treatment will be available for common infections, as well as for a variety of other medical interventions that rely on antibiotics for the prevention or treatment of complications (e.g. cancer treatment, surgery, organ transplantation, and neonatal care).[1,3,5] This will lead to disastrous increases in mortality and morbidity.[3,5] For this reason, antibiotic resistance is regarded as one of the biggest threats to human health.[4]

There are three main strategies to preserve antibiotics, the miracle drugs of the 20th century, as resources for future generations.[4,5] The first is to stimulate and support the development of new (classes of) antibiotics. The second strategy includes infection prevention and control: the fewer infections there are, the fewer antibiotics are needed. This thesis focuses on the third strategy, antibiotic stewardship, which is described in the next paragraph.

Antibiotic stewardship

Antibiotic stewardship is defined as: *activities that aim to promote appropriate use of antibiotics, thereby maximizing clinical outcomes while at the same time limiting unintended consequences*.[9] 'Unintended consequences' mainly refers to antibiotic resistance development, but they also include adverse drug events and healthcare costs. 'Appropriate use of antibiotics' is defined as: *only prescribing antibiotics when there is a clinical indication to do so, and if antibiotics need to be prescribed, to optimize drug selection, dosing, administration, and duration of therapy*. Examples of antibiotic stewardship activities include audit and feedback on prescribing behaviour, education, the development of diagnostic and therapeutic guidelines, formulary restrictions, and preauthorization of prescribing specific drugs. Antibiotic stewardship programs that incorporate such activities have been shown to limit antibiotic resistance development in hospital settings.[9,10] However, limited research on antibiotic stewardship interventions is available for other healthcare settings including general practices and long-term care facilities (LTCFs).[9,11,12] This thesis focuses on antibiotic stewardship in LTCFs.

The need for antibiotic stewardship in LTCFs

LTCFs are institutions that provide living accommodation and health care to people who are unable to live independently in the community.[12] They include nursing homes (NHs), residential care facilities (RCFs), LTCFs for persons with intellectual disabilities, and psychiatric hospitals. The research presented in this thesis focuses on NHs and RCFs, which accommodate mainly older people.

In 2009, the Netherlands counted 1,131 RCFs, 479 NHs, and 290 combined facilities (i.e. RCFs with specialty NH units).[13] In the same year, these facilities altogether accommodated approximately 120,000 residents.[14] A difference between NHs and RCFs is that RCF residents require less intense care, although this difference is becoming less obvious due to increasing care needs in RCF residents.[15] Nevertheless, NH residents generally have more disabilities and need more help with their activities of daily living. They reside in three types of care units: 1) somatic units, for physically disabled residents, 2) psychogeriatric units, mostly for residents with dementia, and 3) rehabilitation units.[16] Another difference between NHs and RCFs involves the provision of medical care. Medical care in RCFs is provided by general practitioners, who operate from their own practice. On the contrary, medical care to NH residents is provided by elderly care physicians (formerly called nursing home physicians), who are employed by, and based in NHs. The Netherlands is the only country in the world where 'the elderly care physician' is a distinct medical specialty. In other countries, medical care in NHs is provided by general practitioners or by hospital specialists on a consultation basis. Having an on-site physician specialized in the complex care for NH residents has several advantages. For example, it facilitates the physician-patient relationship and promotes collaboration between the physician and other disciplines

in the NH (i.e. nursing staff, physiotherapists, psychologists, occupational therapists, speech therapists, dieticians, social workers, pastoral workers, and recreational therapists).[16,17]

Residents of NHs and RCFs in the Netherlands have several characteristics in common. Their mean age is comparable (i.e. RCFs: 84, NHs: 80), and most residents (77%) are female.[16,18] In addition, many residents in both types of facilities suffer from declined immune function, functional disabilities, and multiple comorbidities. These ageing-related characteristics make residents more susceptible to infectious diseases. The risk of acquiring infectious diseases is further increased by factors related to institutionalized living, such as shared dining and social activities, and close contact with healthcare workers and medical equipment.[19,20]

Indeed, infections are common among LTCF residents and, as a consequence, so is the use of antibiotics.[20-23] In a three-year annual point-prevalence study in the Netherlands, it was found that 6.6% of the NH residents received antibiotics on the days of the survey.[21] A similar point-prevalence of 6.5% was reported for Dutch NHs in a European study.[24] There are no studies that report on antibiotic use in Dutch RCFs, but findings from other countries suggest that the prevalence of antibiotic prescribing in RCFs is similar to the prevalence in NHs.[25,26] Based on the aforementioned European study, the level of antibiotic use in NHs in the Netherlands is average compared with other European countries: 12 countries had lower point-prevalence rates and 7 countries had higher point-prevalence rates.[24] This contradicts the reporting of the Netherlands as the country with the lowest outpatient antibiotic use in Europe,[27] and suggests room for improving antibiotic use in the long-term care setting.

The substantial use of antibiotics has led to increased antibiotic resistance in LTCFs.[11,28] For example, two recent Dutch studies reported that antibiotic resistance has resulted in a decline in antibiotic treatment options for urinary tract infections caused by *Escherichia coli*.[29,30] Further, there is increasing evidence that LTCFs serve as a reservoir for transmission of resistant organisms to other healthcare settings (e.g. hospitals, the community), and vice versa.[11,30-32] Considering these developments regarding (transmission of) antibiotic resistance, antibiotic stewardship efforts are much needed in LTCFs.

Considerations regarding antibiotic stewardship in LTCFs

The long-term care setting is a particularly challenging setting for the development of antibiotic stewardship interventions.[11] Decision-making regarding antibiotic prescribing is often complicated by difficulties in diagnosing an infectious disease in residents. The latter can be due to atypical presentation of symptoms, the presence of multiple comorbidities, difficulties in obtaining specimens for diagnostic testing, and

communication difficulties caused by cognitive impairments or hearing and speech difficulties. The lack of on-site diagnostic resources, and the dependence of physicians on nursing staff for the assessment of signs and symptoms can further complicate the establishment of a proper diagnosis.[11,32-34] For the hospital setting, three categories of factors that influence antibiotic prescribing decisions were identified: cultural factors (e.g. different ideas about antibiotic use in different countries), contextual factors (e.g. pressure from peers or patients, availability of guidelines, organization of care), and behavioural factors (e.g. attitudes towards antibiotic use, dealing with diagnostic uncertainty).[35] Such factors are likely to also apply to other healthcare settings, including the long-term care setting. Given the complex patient population, and the variety of factors and disciplines involved in antibiotic prescribing decision-making in LTCFs, it is crucial to consider local facilitators and barriers prior to the development and implementation of antibiotic stewardship programs.[11,35,36]

Participatory action research (PAR)

Participatory action research (PAR) is an approach that accounts for local facilitators and barriers in its aim to improve practice. This is achieved by a close collaboration between researchers and local stakeholders, latter of which are referred to as 'co-researchers'. Local stakeholders are involved in a cyclical process including: 1) the identification of opportunities for improved practice (i.e. planning action), 2) the development and implementation of tailored interventions directed at these opportunities (i.e. taking action), and 3) the evaluation of the implemented interventions (i.e. reflecting on action).[37,38] Given these characteristics, PAR is considered a suitable approach to complex issues. The approach has been applied increasingly in healthcare research over the past decades,[39] however, to our knowledge there are no reports on its application to the development of antibiotic stewardship interventions.

Problem statement, hypothesis & objectives

The levels of antibiotic use and antibiotic resistance are substantial in NHs and RCFs, yet research on antibiotic stewardship interventions in these settings is lacking. The long-term care setting is a particularly challenging setting for the development of antibiotic stewardship interventions, due to the complex patient population, and the multiple factors and disciplines involved in antibiotic prescribing decision-making.

This thesis describes the Improving Rational Prescribing of Antibiotics in Long-Term Care Facilities (IMPACT) study, which was conducted in NHs and RCFs in the Netherlands. A PAR approach was incorporated in the design of the IMPACT study. We hypothesized that the bottom-up nature of this approach may result in effective development and implementation of interventions directed at appropriate antibiotic prescribing, as the involvement of local stakeholders ensures that facilitators and barriers specific to antibiotic prescribing in local settings are accounted for.

The main objectives of the IMPACT study are:

1. To **investigate (the appropriateness of) antibiotic use** for urinary tract infections (UTIs), respiratory tract infections (RTIs), and skin infections (SIs) in NHs and RCFs.
2. To **develop interventions directed at improving appropriate antibiotic prescribing**, tailored to the local needs in NHs and RCFs by using a **participatory action research (PAR)** approach.
3. To **evaluate the effect of the tailored interventions developed with a PAR approach** on the appropriateness of decisions to initiate or withhold antibiotic treatment, antibiotic use, and guideline-adherent antibiotic selection, for UTIs, RTIs, and SIs in NHs and RCFs.

Outline of this thesis

Chapters 2 to 4 focus on the *first study objective*. **Chapter 2** includes a systematic review of the literature on antibiotic use, antibiotic resistance, and strategies to control antibiotic resistance in the long-term care setting. **Chapter 3** describes a qualitative study that provides insight into the factors that influence antibiotic prescribing decisions. A conceptual model that integrates these factors is presented in this chapter. **Chapter 4** involves a baseline measurement of the appropriateness of decisions to prescribe or withhold antibiotics in NHs. This chapter also includes the algorithms that were used to evaluate the appropriateness of prescribing decisions.

The results described in Chapter 3 and Chapter 4 served as input for the development of tailored interventions directed at improving appropriate antibiotic prescribing (*second study objective*). **Chapter 5** describes how the PAR approach was incorporated in the study design to develop these interventions in LTCFs. **Chapter 6** and **Chapter 7** elaborate on the development and implementation of the interventions, and describe their effects on the study outcomes (i.e. the appropriateness of decisions to initiate or withhold antibiotic treatment, antibiotic use, and guideline-adherent antibiotic selection) in respectively NHs and RCFs (*third study objective*).

In **Chapter 8**, the general discussion, the main findings of the IMPACT study are reflected upon. Furthermore, methodological strengths and limitations are considered, as well as implications and recommendations for practice and future research.

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