Improving antimicrobial prescription in primary care: a multi-dimensional approach to antimicrobial resistance

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Chapter 1

Introduction

Antimicrobial resistance

Antimicrobial resistance (AMR) has become a major global health threat over the past few decades, and its prevalence continues to increase worldwide (1). AMR is defined as any adaptation by a pathogen that renders an antimicrobial ineffective. Morbidity, mortality and healthcare costs attributable to AMR are increasing worldwide, as affected patients generally require longer and more frequent hospital admissions and more complex treatment (2). Studies have demonstrated that AMR-related mortality in Europe is higher than mortality due to human immunodeficiency virus, tuberculosis and influenza combined (3, 4). While it is a natural phenomenon for bacteria to become non-susceptible to antimicrobials, the (over)use of antimicrobials has accelerated this process and is now the major driver of AMR (5). Use of antimicrobials worldwide has increased to such an extent that we can now speak in terms of an *AMR pandemic* or *silent* or *slow pandemic*.

The AMR pandemic exhibits similarities with the *tragedy of the commons* concept (6-9), a phenomenon whereby common resources that are unprotected by formal regulation tend to be depleted through unrestricted individual use. If users of such resources act to maximize their self-interest and do not coordinate with others to maximize the overall common good, the result may be exhaustion or even permanent destruction of the resource if the number of and demand from users exceeds availability (10). This concept is to a certain extent applicable to the development of AMR, as antimicrobials are widely available, easily accessible and available in some pharmacies without a physician prescription, factors that together result in often uncontrolled overuse.

From a broader perspective, AMR is the basis of a classic example of a conflict between personal versus common interest, and between current versus future generations. For the individual patient, use of antimicrobials can be easy and helpful and is unlikely to cause side effects. However, in the long term other patients will suffer from infections caused by resistant bacteria (11).

The high prevalence of AMR has resulted in many antimicrobials becoming less and less effective, which in turn leads to increased prescribing of broad-spectrum antibiotics by physicians. In countries with a high prevalence of AMR, physicians often assume drug-resistant micro organisms are at play when treating bacterial infections. This further encourages the prescribing of broad-spectrum antimicrobials, often supported by guidelines advising this course. This relatively uncontrolled spiral of increasing prescription of more and broader spectrum antimicrobials will eventually reach a tipping point beyond which few antimicrobials remain suitable for empirical use. This

process may ultimately lead to a *post-antimicrobial era*, in which few or no currently available antimicrobials remain effective and infections once again become a major cause of morbidity and mortality.

Antimicrobial prescribing

The discovery of antimicrobials was a major medical breakthrough and heralded a new era of effective treatment of bacterial infections (12). Before the discovery and use of antibiotics in clinical care, infections that are now considered minor were a leading cause of death. Use of antimicrobial treatment and prophylaxis is nowadays an indispensable routine medical treatment in primary and hospital care.

Antimicrobial prescribing is part of routine medical care in primary care. General practitioners prescribe antimicrobial drugs daily to patients with an acute presumed or confirmed infection. Pneumonia and cellulitis, which could potentially evolve into life-threatening infections, can be managed effectively and relatively simply in a primary care setting with antimicrobial treatment. Antimicrobial prescribing in primary care is, in general, empiric for the whole duration of the treatment. Cultures are not routinely obtained, except in case of treatment failure or a complicated or recurrent urinary tract infection (UTI). The initially prescribed antimicrobial is not altered during an infection, except in case of treatment failure or when culture results show that bacteria are susceptible for a narrower spectrum antimicrobial than initially prescribed. This empirical approach makes the selection of an appropriate antimicrobial even more important. Choosing an antimicrobial with a spectrum too broad can lead to preventable AMR, while a too narrow-spectrum antimicrobial may not be effective against a particular bacterial infection.

In hospital care antimicrobial medication is currently essential in many treatments, even if no actual infection is present, such as in the protocollary prevention of infection during an operation. In general, antimicrobial prescribing starts empirically with the treatment of an infection and a specific antimicrobial drug is chosen based on expected causative bacteria and the type and location of the presumed infection (13). Infections in patients admitted to the hospital are usually severe and these patients are at additional risk of complications. Hence, in hospital care initial treatment has to be effective to prevent further deterioration, usually resulting in the choice of a broad-spectrum antimicrobial effective against nearly all causative bacteria, often including less susceptible strains or species. As part of hospital treatment, cultures are routinely obtained, so when *antimicrobial stewardship* is practiced, antimicrobials

can be de-escalated during treatment based on the clinical course and the outcome of cultures, aiming for an antimicrobial with the narrowest spectrum possible.

One health approach

The *One health* approach is often used in the context of AMR. The *One health* approach recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent, sharing not only the same environment but also many infectious diseases (14, 15). Although the interdependence of humans, animals and nature has been acknowledged for centuries, the relatively new *One health* approach goes further by encompassing the health of the environment, humans and animals. It promotes the idea that, with ever-increasing human population growth, accompanied by climate change, pollution and depletion of the earth's resources, health disciplines and other fields must collaborate to ensure the future health and well-being of humans, animals and the environment (15, 16).

Antimicrobial selection pressure is an essential factor in the development of AMR and is defined as the extent to which the use of antimicrobials enhances the selective process, increasing the prevalence of resistant microorganisms (17). When applying the *One health* approach to antimicrobial selection pressure, antimicrobial use in all domains (hospital care, veterinary care, primary care or industrial use) contributes to overall antimicrobial selection pressure, regardless of the specific domain where the antimicrobial was used. It is still unclear to what extent each domain contributes to overall antimicrobial selection pressure.

Although various aspects of antimicrobial prescribing differ between primary and hospital care, both domains contribute to the risk of AMR through antimicrobial prescription. It could be argued that the impact of primary care on AMR is lower compared to hospital care, one element of which is the general view that antimicrobial prescriptions in primary care are mainly short-term, narrow-spectrum penicillins. Another is that even if a patient is a carrier of resistant bacteria, the risk of contaminating other patients is low outside of hospital. By contrast, in hospital care antimicrobial prescriptions are more often broad-spectrum antimicrobials, sometimes used for long periods. Resistant bacteria from admitted patients are more easily transferred to other patients. Nonetheless, around 80-90% of antimicrobial prescriptions for human use are estimated to originate from primary care in European countries (18). While this likely has a substantial effect on antimicrobial selection

pressure, the relative impact of each domain on antimicrobial selection pressure or the size of their role under a "*One health*" approach has been insufficiently studied.

Decisions regarding antimicrobial prescribing in primary care

The decision to prescribe an antimicrobial is or should be primarily based on the expected effectiveness of an antimicrobial drug in curing the patient with a particular infection, caused by a particular micro organism or group of micro organisms. In other words, use of an antimicrobial drug will prevent morbidity and mortality by changing the course of the infection. However, during our daily work in primary care many general practitioners (GPs), including myself, experience situations that are often not so clear and straightforward. Uncertainty about the diagnosis or severity of the disease, the expected course of disease and the risk of complications are daily challenges in primary care. In this context, reliance on antimicrobial medication might not be effective in reducing symptoms and preventing morbidity and/or mortality.

Determinants from several interacting domains (e.g., society, primary care practice, physician, patient) influence the decision to prescribe antimicrobial medication, an example of which is the presence of a comorbidity. Physicians tend to prescribe an antimicrobial more often if comorbidity is present, even though this is not a guideline recommendation for many infections. Physicians assume that a comorbidity will increase the risk of complications and that antimicrobial treatment will lower this risk. Indeed, many of the determinants that influence prescription behaviour have already been identified (19). However, information regarding associations between social-economic and primary care practice determinants is still lacking. A better understanding of social-economic determinants (such as those associated with immigrant groups),primary care practice determinants and as well as how these factors interact, is needed to understand and improve antimicrobial prescribing in primary care.

Once the decision has been taken to prescribe an antibiotic, the next step is to choose the specific antimicrobial drug. This choice is based primarily on the site and severity of the infection, expected causative bacteria, presence of comorbidities and contra-indications such as antibiotic allergies. Based on these criteria, recommendations in international guidelines advise a first choice antimicrobial, which generally has a narrow spectrum and few side effects (20-22). A second choice antimicrobial is recommended if the first choice antimicrobial conflicts with a registered antibiotic allergy or in case of treatment failure. To effectively treat unexpected causative or resistant bacteria the second choice antimicrobial has a broader spectrum, which can

potentially induce development of AMR. In addition, second choice antimicrobials - in general - tend to cause more side effects (23-26).

Although adequate registration of antimicrobial allergies is essential to prevent rare but potentially life-threatening reactions upon re-exposure, up to 90% of antibiotic allergy registrations are incorrect (27-29) and lead to many avoidable broad-spectrum antimicrobial prescriptions. Understanding the reasons for incorrect antibiotic allergy registrations would assist general practitioners (GP) in improving these registrations. This in turn would help reduce prescribing of second choice antimicrobials, lowering or avoiding consequent adverse effects and development of AMR.

Novel viral respiratory tract infections

Novel viral respiratory tract infections (RTI), such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have emerged in recent years and others are expected to emerge over the coming decades (30). Novel viral RTIs tend to change the antimicrobial prescription behaviour of physicians. Initially, little is known about effective treatment, morbidity and mortality. Due to this uncertainty, physicians sometimes prescribe antimicrobials hoping to change the course of the infection and prevent complications such as a bacterial superinfection, pneumonia or hospital admission (31, 32). Therefore, close surveillance of antimicrobial use and prescription behaviour is needed during a pandemic.

Antimicrobial stewardship

To prevent further increase of AMR, antimicrobial stewardship (AMS) initiatives have been designed and implemented. In brief, AMS is a coherent set of actions which promote the responsible use of antimicrobials. This definition can be applied to actions at the individual level as well as the national and global level, and spans human health, animal health and the environment (1). These actions are coordinated through an antimicrobial stewardship (AMS) programme, which is an organizational or system-wide health care strategy to promote appropriate use of antimicrobials through the implementation of evidence-based interventions. The *One health* approach is incorporated in AMS programs. the World Health Organisation has made decreasing AMR a priority and has promoted the development and implementation of AMS programmes on a national level (14). Worldwide implementation of AMS programs has started, but not all countries are making progress at the same speed (18).

Antimicrobial resistance in The Netherlands

In The Netherlands, the prevalence of AMR has increased only modestly over the past decade. Current prevalence is considered problematic but is not yet seen as a threat (33), as attributable mortality due to resistant infections is still limited in The Netherlands (34). However, vigilance is needed as many neighbouring European countries are already experiencing increasing and even problematic levels of AMR (35). Resistant pathogens can be easily transported to The Netherlands due to extensive travel by Dutch inhabitants and visitors. To prepare for this pandemic the Dutch government has set up a structure consisting of ten regional care networks, tasked with organizing and implementing AMS programs, which are coordinated and supported by the National Institute for Public Health and the Environment (RIVM). The Dutch Working Party on Antibiotic Policy (SWAB) has formulated several guidelines on AMS. The aim is to stop further spread of highly resistant micro organisms and to decrease AMR (36). The two main focus areas are hygiene measurements and prudent use of antimicrobials, while in primary care the focus is on improving the quality of antimicrobial prescribing. All major stakeholders (municipal health services, elderly care, primary care and hospital care) are involved in this network.

Role of Dutch primary care

The number of antimicrobial prescriptions originating from primary care in The Netherlands is much lower compared to other European countries (18). For example in 2022, GPs in Dutch primary care prescribed 9.1 defined daily doses (DDD) of antimicrobials per 1000 patients, compared with 21.9 prescribed by primary care physicians in Italy (18). Dutch GPs are, in general, cautious when prescribing antimicrobials and Dutch primary care guidelines have restraining recommendations for prescribing antimicrobials (21). Therefore, one could postulate that there is limited room for improvement in antimicrobial prescribing in the Netherlands. However, Dutch studies have found antimicrobial overprescribing rates of 40 to 50% for RTIs (37, 38), although information about potential improvements for other types of infections is limited at present.

Aim

This thesis focuses on the quality and quantity of antimicrobial drug prescription in primary care, exploring the background and determinants that influence it. The aim of this thesis was therefore to examine the impact and quality of antimicrobial prescribing

and to which extent the quality of antimicrobial prescribing can be improved. With this approach we hope to find starting points from which to restrain currently increasing AMR. Quality of antimicrobial prescribing is defined by two elements in this thesis:

1. an antimicrobial is only prescribed when effective in treating symptoms and preventing complications, morbidity or mortality
2. an appropriate antimicrobial is prescribed for the type, location and severity of the infection, with the narrowest spectrum possible.

Outline of the thesis

Five different studies, described in chapters 2-6, address the aims of this thesis, with each study examining a distinct dimension of AMR in primary care.

The impact of antimicrobial prescriptions originating in primary care on antimicrobial selection pressure and consequent AMR was examined in **chapter 2**. This open-source data study used publicly available data from the European Centre of Disease Prevention and Control (ECDC) and inventoried types and volumes of antimicrobials prescribed by primary care physicians in European countries. Antimicrobial pressure was calculated using a proxy indicator, the Antibiotic Spectrum Index (ASI), which we correlated with a country's AMR.

Different elements of antimicrobial prescribing in primary care were examined in **chapter 3.** The goal of this systematic literature review was to provide a framework of determinants of inappropriate antimicrobial prescribing in primary care in developed countries where GPs acts as a gatekeeper.

Our observational cohort study in **chapter 4** explored the influence of SARS-CoV-2 infections on the numbers of antimicrobial prescriptions in primary care. The proportion of antimicrobial prescriptions for patients during a COVID-19 infection was compared with the proportion of antimicrobial prescriptions for patients during an influenza or influenza-like infection in other years. The association between antimicrobial prescriptions and risk factors for an adverse course of a SARS-CoV-2 infections was examined.

In a mixed method study that included semi-structured interviews and a file analysis (**chapter 5**), we explored the details of incorrect antibiotic allergy registrations and what might be improved in the registration of antimicrobial allergies. The results show

how and to what extent the quality of antibiotic allergy registrations can be improved. In a retrospective observational cohort study, described in **chapter 6,** we used and combined large health care registries for the purpose of evaluation of antimicrobial use in primary care. The aim was to determine the number of appropriate and inappropriate antimicrobial prescriptions in primary care over a period of 10 years, which patient groups and determinants are associated with appropriate antimicrobial prescribing, and the degree to which antimicrobial prescribing in primary care might be improved.

Finally, the main results of all studies are summarized and critically appraised in **chapter 7**, and recommendations on how to incorporate the results of this thesis in AMS interventions are provided.

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