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

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English summary

The increase of antimicrobial resistance (AMR) poses one of the greatest threats to global healthcare. AMR occurs when bacteria adapt and become insensitive to one or more antimicrobials, rendering them ineffective. The use of antimicrobials in many ways (human and veterinary medicine and xenobiotics) is the main cause of this increasing resistance. AMR makes treating patients with bacterial infections increasingly difficult and this may eventually even become impossible.

The discovery of antimicrobials was a major medical breakthrough that made the treatment of bacterial infections possible. Before that discovery, mortality from bacterial infections was high. In primary care practice and hospitals, antimicrobial prescription is now an indispensable daily medical routine. General practitioners (GP) can relatively easy, effectively and safely treat patients with potentially life-threatening bacterial infections, such as pneumonia or complicated urinary tract infections. In the hospital, antimicrobials are part of many treatments or prophylactic regimens, for example to prevent wound infection after surgery.

The "*One-health*" approach is often used in the context of AMR. In this approach, the basic premise is that the health of humans, domestic and wild animals, plants and the wider environment (including ecosystems) are closely connected and interdependent. Antimicrobial selection pressure is part of the process that leads to AMR and is defined as the extent to which antimicrobial use enhances the selection process that increases the growth of resistant micro-organisms. From the *One Health* perspective, antimicrobial use from all domains (hospital care, veterinary medicine, primary care practice and industrial use) contributes to antimicrobial selection pressure, regardless of the specific domain where the antimicrobial is used.

Currently, most bacterial infections in the Netherlands can still be treated well with a targeted, narrow-spectrum antimicrobial. These antimicrobials are effective against a limited number of types of common bacteria and, if properly indicated, carry a low risk to induct resistance. However, the use of narrow-spectrum antimicrobials alone is so high that it leads to substantial antimicrobial selection pressure and consequently to an increase in AMR. This results in more frequent use of broad-spectrum antimicrobials. These are antimicrobials effective against multiple types of bacteria and often against more resistant bacteria. Broad-spectrum antimicrobials have the general disadvantage that their use carries a greater risk of developing AMR than narrow-spectrum antimicrobials. This negative spiral can eventually lead to increased prescribing of broad-spectrum antibiotics by physicians. As they will

more easily assume drug-resistant microorganisms are at play when treating bacterial infections. This relatively uncontrolled spiral of ever 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.

In the Netherlands, AMR rates for relevant microorganisms is relatively low compared to other countries, which can be attributed to the limited use of antimicrobials compared to most European countries. However, the Netherlands is also experiencing an increase in AMR. The only way to slow down this increase is to optimise antimicrobial use. GPs in the Netherlands prescribe approximately 80-90% of all antimicrobials in the Dutch healthcare system. This significant proportion highlights the importance of the primary care practice as a crucial starting point for implementing interventions that enhance the appropriate use of antimicrobials.

The aim of the studies brought together in this thesis was to quantify the contribution to antimicrobial selection pressure by primary care practices, examine the quality of antimicrobial prescribing in primary care practices and explore opportunities for improvement. For this purpose, 5 studies were conducted, which are described in **chapters 2 to 6**. The results of the studies are summarised and discussed in **chapter 7**.

The impact of antimicrobial prescribing in primary care practices

It was unclear from the literature to what extent antimicrobial prescribing in primary care practice contributes to antimicrobial selection pressure. It could reasonably be argued that primary care practices contribute less, compared to hospitals, as they mainly prescribe narrow-spectrum antimicrobials for a short period of time. In hospital care, broad-spectrum antimicrobials are in general prescribed more frequently and for a longer period and even without confirmed infection. If a patient becomes a carrier of a resistant bacterial strain, the risk of infecting other patients is very low as long as carriers in general are not admitted to a hospital. Resistant bacteria who are carried by hospitalised patients can more easily be transmitted to other, often vulnerable, hospitalized patients.

We quantified the contribution of antimicrobial prescriptions by primary care practices on antimicrobial selection pressure in **chapter 2**. This study with open-source data from the European Centre for Disease Prevention and Control (ECDC) inventories and compares the types and quantities of antimicrobials prescribed in primary care

practices and in hospitals in 12 European countries where the GP can be considered a 'gatekeeper' in the healthcare system. Antimicrobial selection pressure was quantified with a proxy indicator, the antibiotic spectrum index (ASI). The ASI includes both the number of antimicrobials used and the activity against microorganisms. The ASI expresses this in an index number representing the spectrum of micro-organisms susceptible to that drug. It assigns numerical values to an antimicrobial effective against 1 or more of 13 categories of bacteria, with lower values indicating narrow-spectrum agents and higher values indicating broader-spectrum agents.

Our analysis of antimicrobial prescriptions reveals that the proportion of penicillin prescriptions finding its origin in primary care varies between 29% and 65% across the 12 European countries. Between 80-90% of cumulative ASI comes from these antimicrobial prescriptions in primary care practices. This proportion is much higher than previously assumed and an important finding, as previous studies showed that GPs tend to be under the assumption that antimicrobial prescribing in primary care practice does not substantially contribute to the development of AMR. This relatively large contribution to antimicrobial selection pressure from primary care seems to be related to a shift towards prescribing relatively more broad-spectrum antimicrobials.

Determinants of antimicrobial prescribing

Numerous studies have demonstrated that various factors impact the decision to prescribe antimicrobials in primary care practice. However, a comprehensive overview of these determinants and their interrelationships was previously unavailable. To enhance understanding and improve antimicrobial prescribing in primary care practice, a systematic literature review was conducted and is included in **Chapter 3.**

Important patient-related determinants were that patients sometimes expect an antimicrobial prescription because of previous experiences, have high expectations of the effect of antimicrobials, or explicitly ask for it. An important patient-general practitioner interaction found was that GPs assumed that patients wanted an antimicrobial prescription as the reason for their visit but did not verify this assumption.

The decision of a GP to prescribe an antimicrobial should be based primarily on a clinical working diagnosis and aspects such as patient characteristics and the severity, type and location of the infection and the expected course and risk of complications. However, the decision was also found to be based on non-clinical determinants. These include determinants such as a larger practice size or the lack of possibilities to effectively negotiate or explain the use of antimicrobials. Our study results showed that

determinants from multiple domains (patients, practice, society and GPs) influence prescribing behaviour and reinforce each other, especially in the "over-prescribing" of antimicrobials.

Quality and quantity of antimicrobial prescriptions during the COVID-19 pandemic

In recent years, a new viral respiratory infection known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a significant burden of disease and has become a pandemic. It is likely that other new respiratory infections will emerge in the coming decades. These infections tend to influence doctors' antimicrobial prescribing behaviour. In the early stages of an epidemic or pandemic, effective treatment, morbidity, and mortality are often unknown. Due to the uncertainty surrounding infections, doctors may prescribe antimicrobials in the hope of altering the infection's course and preventing complications such as bacterial superinfection, pneumonia, or hospitalization. It is crucial to comprehend prescribing behaviour to provide targeted feedback to GPs.

In an observational cohort study (**chapter 4**), we investigated the effect of the COVID-19 pandemic on the number of antimicrobial prescriptions in primary care practice. The frequency of antimicrobial prescriptions for patients during SARS-CoV-2 infection was compared with the frequency of antimicrobial prescriptions for patients during influenza or influenza-like infection in four influenza seasons. Furthermore, the association between antimicrobial prescriptions and risk factors on an unfavourable course of SARS-CoV-2 infection was assessed.

Our study showed that fewer antimicrobials were prescribed to patients during COVID-19 infections than during similar influenza or influenza-like infections in four influenza seasons. This is consistent with results from other studies that have shown a decrease in antimicrobial prescriptions during the COVID-19 pandemic compared to previous years. The reduced prescribing of antimicrobials to patients during SARS-CoV-2 infections may have been due to intensive testing for SARS-CoV-2 during the COVID-19 pandemic, while no such testing was conducted for influenza during flu seasons. It became evident to patients and GPs that SARS-CoV-2 was the cause of the symptoms and that antimicrobials were unnecessary. Patients with risk factors for a more severe course were prescribed antimicrobials more frequently than those without risk factors. Reducing diagnostic uncertainty regarding the causative agent of respiratory infections could potentially result in fewer antimicrobial prescriptions.

Improving antibiotic allergy registration

Allergies to antibiotics are among the most reported adverse reactions to medication. Accurate registration of these allergies is crucial to prevent rare but potentially life-threatening reactions upon repeated exposure. In Dutch primary care practices, between 0.6% and 2.1% of patients have records of antibiotic allergies in the electronic patient records. However, approximately 80-90% of antibiotic allergy registrations in primary care practice turn out to be unjustified. As a result, antibiotic allergy registrations lead to an increase of physician encounters, higher healthcare costs and the more frequent prescription of second-choice antimicrobials. Second-choice antimicrobials are often broad-spectrum antimicrobials which have a greater risk of inducing the development of AMR. Removing an allergy registration that has been deemed "unjustified" can be particularly difficult: electronic health records (EHR) in hospitals, pharmacies and primary care practices containing registrations do not correct each other adequately.

In **chapter 5**, we conducted a mixed-methods study using reviews of EHR and semi-structured interviews with healthcare providers from different domains (pharmacy, nursing home, hospital and primary care practice). We investigated what information on the reaction is registered as an antibiotic allergy in an EHR, what causes incorrect antibiotic allergy registrations and how registrations can be improved.

The study revealed that in 56.3% of cases, the recorded information was inadequate to confirm whether the reaction was allergic in nature. This emphasises the necessity for better recording of reactions following antimicrobial intake. The primary reasons for inadequate quality of registrations were lack of knowledge, lack of priority, limitations of registration functions in the electronic health record (EHR), and patients and doctors interpreting adverse reactions as allergies. The findings were unique in that the determinants were similar across all domains studied. This supports the need for developing cross-domain interventions.

Improving quality of antimicrobial prescriptions in primary care practice

Many determinants have already been identified in **chapter 3**, but this and previous research lacked socioeconomic determinants and information on primary care practices. It was unclear to what extent the quality of antimicrobial prescribing in primary care practice could be improved.

A retrospective observational cohort study (**chapter 6**) was conducted to explore the feasibility of using and combining large health care registers for research on antimicrobial

prescribing in primary care practice. A second question was to determine the extent to which antimicrobial prescribing could be improved and the extent to which the factors mentioned above were associated with appropriate antimicrobial prescribing.

It was possible to combine two large registries, GP data from the extramural Leiden Academic network (ELAN) and data from Statistics Netherlands (SN), at the individual patient level. This allowed us to examine the associations of various determinants that are not recorded in an HER with various endpoints such appropriate antibiotic prescribing,

Our study showed that 17.8% of all antimicrobial prescriptions were not in accordance with guidelines, and 39.6% of antimicrobial prescriptions for respiratory infections not following guidelines. The rate of overprescription of antimicrobials for respiratory infections was consistent with previous Dutch studies. Studies in other countries also showed similar rates and with regularly higher rates. In addition, 77.1% of macrolide prescriptions were not first and second choices according to guidelines. A previous Dutch study found a similar percentage of macrolide overprescribing.

We found several patient determinants associated with overprescription of antimicrobials: female gender, age 5 years and older and a migration background (Turkish, Surinamese, Dutch Caribbean). Female gender and age have been identified as important determinants in several earlier studies. Migration background is a newly identified determinant associated with overprescription of antimicrobials.

A previously unidentified practice determinant in the Netherlands was found to be associated with excessive antibiotic prescribing: larger practice size. Previous studies from the UK and Canada presented conflicting results on this. The UK study found an association, while the Canadian study did not. The context and location (urban or rural) of the practice may have been a contributing factor to the difference in these studies. We cautiously interpreted the undeniable difference we found as an argument for creating "more time and continuity for the patient"

Conclusion and recommendations

An important overarching finding of the studies in this thesis, is that antimicrobial prescriptions from primary care practices are a much larger contributor to the development of AMR than previously thought, and that the European data (including the Netherlands) show that the amount of antibiotic prescribing correlates with the development of resistance.

The main determinants of antimicrobial overprescribing were diagnostic uncertainty, GP practice size (perhaps as a measure of time available during consultations), inability to effectively negotiate or explain antimicrobial use and GPs' assumption that patients 'expect an antimicrobial prescription'.

There are three major aspects in which antibiotic prescribing in general practices can be improved. There is antibiotic overprescribing for patients with respiratory tract infections. Instead of the broad-spectrum antibiotic group macrolides, narrow-spectrum antibiotics can be chosen frequently. Finally, antibiotics are relatively over-prescribed to patients from specific migratory backgrounds (Turkish, Dutch-Caribbean, Surinamese).

In addition, registration of antibiotic allergies can be improved by educating GPs to increase awareness and knowledge of antibiotic allergies, by verifying existing registrations of antibiotic allergies and by facilitating registration in an EHR so that the different EHRs are more compatible and do not contradict each other. This may lead to a reduction in the number of antibiotic allergy registrations and thus contribute to the prescription of first-choice antimicrobials instead of second-choice (broad-spectrum) antimicrobials.

The increasing prevalence of AMR requires up-to-date and more proactive surveillance of antimicrobial use and resistance in primary care. If antimicrobial use and in particular the use of broad-spectrum antimicrobials or resistant bacterial groups increases, actions can be taken to address these developments. For example, through adjustments in national guidelines, messages in newsletters of national organisations or attention to these developments in pharmacotherapy education. Artificial Intelligence (AI) and/or big data can contribute to improved surveillance. The studies in this thesis show that big data can be used to analyse antimicrobial use. This has let to the discovery of relevant associations, such as antimicrobial prescriptions and practice size. The use of AI in surveillance and analysis of antimicrobial prescribing behaviour maybe the next step to be investigated in this regard.