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

Sijbom, M.

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IMPROVING ANTIMICROBIAL PRESCRIPTION IN PRIMARY CARE

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ISBN: 978-94-6506-190-0
Cover design: Suze van der Velde
Lay-out and printing: Ridderprint | www.ridderprint.nl

The study in chapter 5 was part of a project on improving antibiotic allergy registrations, which was funded by the Dutch Ministry of Health, Welfare and Sport (Reference number 327952). The other studies were internally funded by the LUMC.

Improving antimicrobial prescription in primary care

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Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden

op gezag van rector magnificus prof. dr. ir. H. Bijl

volgens besluit van het college voor promoties

te verdedigen op donderdag 24 oktober 2024

klokke 16:00 uur

door

Martijn Sijbom

Geboren te Emmen

in 1977

Promotoren

Prof. dr. M.E. Numans
Prof. dr. M.G.J. de Boer

Copromotor

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Promotiecommissie

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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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Chapter 2

Trends in antibiotic selection pressure generated in primary care and their association with sentinel antibiotic resistance patterns in Europe

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J Antimicrob Chemother 2023; **78**: 1245–1252

Abstract

Objectives

We studied trends in antibiotic prescribing by primary care and assessed the associations between generated antibiotic selection pressure (ASP) and the prevalence of sentinel drug-resistant micro organisms (SDRMs).

Methods

The volume of antibiotic prescribing in primary and hospital care expressed in DDD/1000 inhabitants per day and the prevalences of SDRMs in European countries where GPs act as gatekeepers were obtained from the European Centre for Disease Control ESAC-NET. Associations were tested between (i) DDD and (ii) the Antibiotic Spectrum Index (ASI) as a proxy indicator for ASP, and the prevalences of three SDRMs: MRSA, MDR *Escherichia coli* and *Streptococcus pneumoniae* resistant to macrolides.

Results

Fourteen European countries were included. Italy, Poland and Spain had the highest prevalence of SDRMs and prescribed the highest volume of antibiotics in primary care (average 17 DDD per 1000 inhabitants per day), approximately twice that of countries with the lowest volumes. Moreover, the ASIs of these high antibiotic volume countries were approximately three times higher than those of the low-volume countries. Cumulative ASI showed the strongest association with a country's prevalence of SDRMs. The cumulative ASI generated from primary care was about four to five times higher than the cumulative ASI generated by hospital care.

Conclusions

Prevalences of SDRMs are associated with the volume of antimicrobial prescribing and in particular broad-spectrum antibiotics in European countries where GPs act as gatekeepers. The impact of ASP generated from primary care on increasing antimicrobial resistance may be much larger than currently assumed.

Introduction

Antimicrobial resistance (AMR) is increasing worldwide and represents a major threat to global healthcare (1). The major driver of the rise in AMR is the use of antibiotics (2). Worldwide, efforts are now being undertaken to decrease antibiotic prescribing and consequently reduce the rate of AMR development (1). Given that GPs are responsible for the majority of antibiotic prescriptions in a country, they potentially have an important role to play in reducing AMR (3). However, the extent to which antibiotic prescribing in primary care contributes to increasing AMR is still unclear (4). For varied reasons, not all GPs consider their antibiotic prescribing practices to be part of the process eventually leading to increasing AMR (5,6).

Part of the process leading to AMR is referred to as 'antibiotic selection pressure' (ASP), defined as the extent to which the use of antibiotics enhances the selective process increasing the growth of resistant microorganisms (7). According to the One Health concept, all antibiotic prescriptions contribute to ASP (8). The relative contribution to the ASP of an antibiotic most likely depends on the dosage, duration of use, and type and spectrum of an antibiotic.

The aim of this study was to inventory types and volumes of antibiotics prescribed by primary care practitioners in European countries where they act as gatekeepers. Importantly, this study investigates the correlation between a country's AMR and the overall level of antibiotic prescribing, and resultant antibiotic pressure, in that country. Testing associations between prescription data and the AMR levels in a country provides insight into the role primary care has compared with hospital care in increasing AMR.

Methods

In this study, we collected and analysed open source data on the volume of antibiotic prescriptions and on the prevalence of three drug-resistant micro organisms. The volume of antibiotic prescriptions was used to calculate ASP. The volume of antibiotic prescriptions and ASP were then correlated to the prevalence of a sentinel drug-resistant micro organism (SDRM).

The study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidance for reporting observational studies (9), and the STROBE-AMS recommendations for reporting epidemiological studies of AMR and informing improvement in antimicrobial stewardship (S1) (10)

Country selection

We analysed data on antibiotic prescriptions from European countries because they collect and report their data in a standardized format through the European Centre for Disease Prevention and Control (ECDC) (11). For a country to be included in the study, GPs had to act as a 'gatekeeper' in the healthcare system, defined as a compulsory GP referral to access most types of specialist care except in case of emergency (S2) (12). These countries generally have lower levels of antibiotic prescriptions (13).

Data extraction

Antibiotic prescriptions

The volume of antibiotic prescriptions per country was extracted from the ECDC open source antimicrobial consumption database (ESAC-NET) on 15 March 2022 (11). The volumes were represented in DDD per 1000 inhabitants per day for the years 2011 through 2020. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (14). To translate absolute volumes of prescribed antibiotics to a value representing the ASP in a country, we calculate and present the Antibiotic Spectrum Index (ASI) as a proxy indicator for ASP (15). The ASI incorporates the volume of used antibiotics and their activity against micro organisms, expressing these through an index number representing the spectrum of micro organisms that are susceptible to that drug (S3a). The ASI assigns numerical values for an antibiotic that has activity against 1 or more of 13 categories of pathogens, with lower values indicating narrow-spectrum agents and higher values broader-spectrum agents.

The ECDC website does not provide data on individual antibiotics, instead providing information per Anatomical Therapeutic Chemical Classification System (ATC) fourth-level chemical subgroup. Antibiotics in a subgroup are effective against the same micro organisms and have an equal index number (15). Only antibiotics in ATC subgroups macrolides and quinolones have different index numbers. Hence, a mean ASI had to be calculated for these subgroups. For antibiotics lacking a reported ASI, one was calculated using the method proposed by Gerber et al. on the basis of their activity against microorganisms (15). In total, 13 antibiotics were not indexed in the ASI (S3b) and were indexed instead by our research group. The ATC subgroup J01RA, combinations of antibacterials, was excluded from the ASI analysis because it was not possible to calculate an average.

The cumulative ASI per ATC subgroup was calculated by multiplying the volume of antibiotic prescriptions in DDD per 1000 inhabitants by the ASI number for that

subgroup. The cumulative ASI (i.e. cumulative antibiotic spectrum index per 1000 inhabitants) in a country was calculated by adding up the ASIs of each subgroup. For each country, this was calculated for (i) primary care, (ii) hospital care and (iii) primary and hospital care combined (i.e. the combined cumulative ASI).

AMR of sentinel micro organisms

AMR surveillance systems can use a set of drug-resistant micro organisms rather than a complete overview of micro organisms to monitor trends in AMR (16). This approach was taken and three so-called SDRMs relevant for primary care were selected: *Staphylococcus aureus, Escherichia coli* and *Streptococcus pneumoniae* are often used to monitor AMR (16). MRSA was used because *S. aureus* is the leading cause of skin and soft tissue infections. From the order Enterobacterales, *E. coli* resistant to third-generation cephalosporins and fluoroquinolones and aminoglycosides was selected, because *E. coli* is the leading pathogen causing urinary tract infections. *S. pneumoniae* is the most common cause of community-acquired bacterial pneumonia and was considered resistant if non-susceptible to macrolides. We chose to select non-susceptibility to macrolides instead of resistance to penicillin. Macrolides are regularly second-choice antibiotics for the treatment of community-acquired pneumonia in primary care guidelines, making it a reserved antibiotic only used where other antibiotics are not effective or administrable (17).

Country-level prevalences of the three SDRMs were obtained from the ECDC open source database, Surveillance Atlas Antimicrobial resistance, on 2 March 2022 for the years 2011–2020 (11). The ECDC uses the EUCAST guidelines for detecting and reporting specific resistant micro organisms. Treatment of infections in primary care is most often empirical, and obtaining cultures is therefore not part of standard care and not always feasible due to practical reasons. Anticipating a lack of SDRM cultures available from primary care, we combined primary and hospital care data to characterize AMR in each country because, according to the One Health concept, all antibiotic prescriptions contribute to ASP and eventually to AMR (8).

Descriptive statistics were used to describe and compare antibiotic volumes between countries and periods, as well as the trends in the volume of antibiotic prescriptions, and the prevalences of SDRMs. The combined cumulative ASI and combined DDD were plotted against the prevalence of each SDRM per country for the year 2020, because it is the most recent year with available data. Univariate linear regression was used to calculate associations between (i) ASI and (ii) DDD and each SDRM prevalence.

Results

Statistical analysis

Fourteen European countries (Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Slovenia, Spain, Sweden and the UK) were identified in which the GPs act as gatekeepers and from which data on antibiotic prescriptions and SDRMs could be obtained.

Volumes of antibiotic use in primary care and hospital care

The volume of antibiotic prescriptions in primary care decreased over the course of our observation period (2011–2020) in seven countries (Denmark, Finland, Italy, The Netherlands, Norway, Sweden and the UK—see Figure 1). Ireland, Italy, Poland and Spain had the highest volumes of antibiotic prescriptions in primary care in 2020, with DDDs between 16 and 17 per 1000 inhabitants per day. The volume of antibiotic prescriptions was in all countries at its lowest in the year 2020. The proportion of antibiotic prescriptions in hospital care compared with the total volume of antibiotic prescriptions ranged from a low of 7.4% in Poland to a high of 16.6% in Latvia.

Prevalence of resistant micro organisms

MDR *E. coli* was the SDRM with the lowest prevalence in most countries (Figure 2). The prevalence ranged from 1.2% (Norway) to 14.6% (Italy). The prevalence of MRSA was stable over the period 2011–2020 in most countries. Four countries (Ireland, Italy, Poland and Spain) had a prevalence above 10% for MRSA. The prevalence decreased over the observation period only in Ireland and the UK. Macrolide-resistant *S. pneumoniae* had the highest prevalence of the three SDRMs, with seven countries reporting a mean prevalence above 10% during the period 2011–2020.

Patterns of antimicrobial selection pressure

The cumulative primary care ASI in Italy and Spain was about three times higher than in the Netherlands and Sweden, whereas the volume of antibiotic prescribing in primary care in DDD was twice as high in Italy and Spain as The Netherlands and Sweden (Figure 3). Tetracyclines and penicillin were the largest contributors to the cumulative primary care ASI in all countries, respectively ranging from 3.6% (Italy) to 39.8% (Sweden) and from 22.9% (Norway) to 50.7% (Spain). Within the penicillin antibiotic group, penicillin combinations (ATC code J01CR) (e.g. amoxicillin/clavulanate) were the largest contributor to the cumulative primary care ASI in eight countries.

The contribution of primary care to the cumulative combined ASI (primary and hospital care) ranged from 80.4% (Finland) to 91.1% (Spain) (Figure 4).

Association of ASP and AMR in a country

The combined volumes of antibiotic prescribing in primary and hospital care, expressed both as DDD and the combined cumulative ASI, are shown plotted against the prevalence of the three SDRMs in Figure 5, and the standardized coefficients of association (beta) are presented in S4. The betas representing associations between SDRMs and combined cumulative ASI were all higher than those representing associations between SDRMs and combined total DDD.

Discussion

We studied the trends in volume of antibiotic prescribing in primary care, the prevalences of SDRMs, and the ASP using proxy indicators ASI and DDD in European countries where GPs act as gatekeepers. The volumes of antibiotic prescriptions in primary care and the prevalences of SDRMs varied significantly between countries. DDD and ASI were associated with SDRM prevalence. Primary care was a larger contributor to ASP than hospital care.

Total number of antibiotic prescriptions

We found a large variation in volume of antibiotic prescriptions between countries in primary care. This may be due to cultural effects on the prescription of antibiotics. Borg and Camilleri showed a high association between a high degree of uncertainty avoidance and the prescribing of more broad-spectrum antibiotics (18), and Fletcher-Lartey et al. showed uncertainty avoidance to be associated with inappropriate antibiotic prescribing (5). Italy, Poland and Spain had high uncertainty avoidance scores (19). In 2020, the volume of antibiotic prescriptions in primary care was lower in all countries than in preceding years. This is likely due to the trend of decreasing antibiotic prescriptions and the severe acute respiratory syndrome coronavirus-2 pandemic. During the pandemic, there were fewer non-coronaviral disease respiratory tract infections (20), leading subsequently to fewer antibiotic prescriptions.

SDRMs

The percentage of invasive isolates with MRSA declined in both Ireland and the UK between 2011 and 2020. The decline in Ireland and the UK is likely a result of the introduction of guidelines on the prevention and control of MRSA in 2007 and of multiple interventions including hygiene protocols and mandatory reporting of MRSA, respectively (21,22).

For all three SDRMs, Italy, Poland and Spain have the highest prevalences among the countries in our study. These three countries also have a higher volume of antibiotic prescribing as expressed in DDD, and a higher ASP as represented by ASI. The higher prevalence of an SDRM is a likely consequence of the high volume of antibiotic prescribing and will lead to prescribing of more broad-spectrum antibiotics. Physicians often assume drug-resistant micro organisms are at play when treating bacterial infections in locations where drug-resistant micro organisms are known to be an issue. This encourages prescribing broad-spectrum antibiotics, often supported by guidelines advising this course. The resulting evolutionary pressure on the microbiome leads to increased selection of antimicrobial resistance. This vicious circle of prescribing more and broader spectrum antibiotics can lead to a point of no return when few antibiotics suitable for empirical use remain.

Proxy indicators of ASP

The levels of DDD and ASI varied between countries. Primary care practitioners in Italy and Spain prescribed twice the volume of antibiotics compared with their colleagues in Denmark, The Netherlands and Sweden, but the cumulative ASI was three times higher in Italy and Spain. Furthermore, the DDD in Spain and Italy was comparable to those of Ireland and Poland for the year 2020, whereas the ASI in 2020 was 1.5 times higher in Spain and Italy. These differences may be largely explained by the very high number of prescriptions for penicillin combinations and quinolones in Italy and Spain in primary care. Both groups are broad-spectrum antibiotics and have high ASIs of 6 and 8, respectively.

The cumulative ASI seems to correlate better with the prevalence of a SDRM than does total antibiotic consumption expressed in DDD, as illustrated by data from Ireland and Italy. The DDD of Italy was only slightly higher than that of Ireland, but the prevalence of the selected SDRMs in Italy was significantly higher (Figure 2). Further, the ASI in Italy was much higher than that of Ireland and more strongly correlated with the prevalence of an SDRM (Figure 5 and S4). MRSA and *S. pneumoniae* showed the strongest associations with ASI, with standardized coefficients of 0.94 and 0.91,

respectively. Particularly relevant for primary care is the strong association with *S. pneumoniae* because this is a very common cause of respiratory tract infections in primary care, even more so than skin infections caused by *S. aureus* (23).

Comparison with existing literature

Although ASI has been examined in institutes such as hospitals and nursing homes (24–30), we found no studies exploring this at a national level. The studies who examined ASI in hospitals and nursing homes showed that ASI gives additional insight into antibiotic prescribing patterns compared with other proxy indicators such as DDD or days of therapy, and may be useful for internal and external comparisons of institutions (24,28,29). Monitoring antibiotic consumption combined with surveillance of resistant micro organisms is advised as part of the One Health strategy (31). Most healthcare systems still use DDD as the only measure to represent the volume of antibiotic use.

Strengths and limitations

A strength of our study is using absolute volumes of antibiotic prescriptions in primary and hospital care when calculating the proxy indicator cumulative ASI. The proxy indicator is in this way a better representation of the ASP in a country than, for example, weighted mean volumes. The applied method of calculating the ASP is relatively simple, which makes it easily implemented in almost every country or region as a proxy indicator.

A limitation of this study is that some of the prescribed antibiotics may not be directly related to increasing resistance found in a specific SDRM. However, exposure to antibiotics in general is sufficient to generate community-acquired resistant infections in members of the same community. Further, the cumulative ASI is a proxy indicator representing the level of implementation of antimicrobial stewardship and the prevalence of already existing AMR in a country. The ratio between antimicrobial stewardship and already existing AMR contributing to ASI is not deducible from our study.

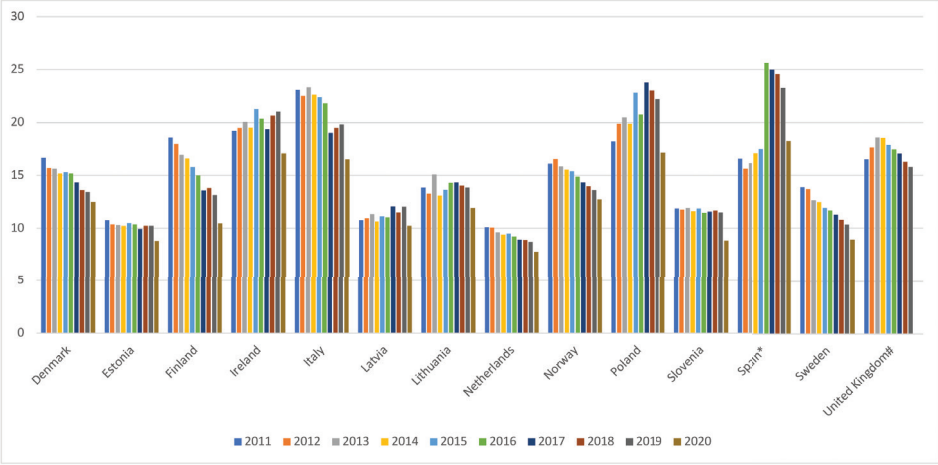
We used only three specific SDRMs in our study. Although using other SDRMs may lead to slightly different results, the expected trend would be similar. Because only European countries in which GPs act as gatekeepers were included in this study, the results may be less generalizable to countries with differently organized healthcare systems.

Conclusions

We found substantial variation in both the volume of antibiotic prescriptions in primary care and the prevalence of SDRMs between countries. There is, however, a clear association between the volume of antibiotic prescribing and the prevalence of SDRMs. Approximately 90% of the ASP expressed in the ASI originated from primary care, which is even more associated with the prevalence of SDRMs, compared with the volume of antibiotic prescribing. This emphasizes that the role of primary care in the development of AMR may be much larger than previously assumed by some GPs. This is an important insight, because some GPs may believe that antibiotic prescribing in their practice does not contribute to the development of AMR, but that instead AMR is driven by antibiotic prescriptions in hospitals or those used in veterinary care. The societal and medical impacts of this phenomenon warrant further investigation into mechanisms for improvement and implementation of antibiotic stewardship in primary care.

Figures

Figure 1. Volume of antibiotic prescription in Defined Daily Doses per 1000 inhabitans per day from primary care



*Spain saw a strong ostensible increase in prescription from 2016 onwards. However, this was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data (11)

#Data from primary care in the United Kingdom for the year 2020 was missing in the open source database of the ECDC.

Figure 2

Figure 2a. Meticillin-resistant *Staphyloccocus aureus*: percentage resistant isloates

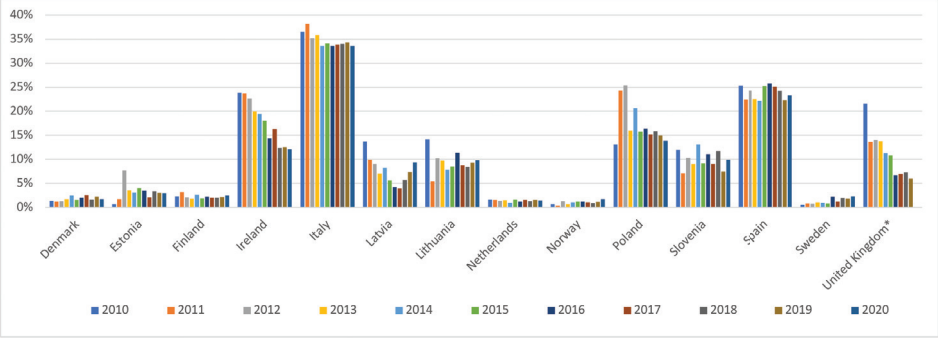


Figure 2b. *E.coli*, multidrugresistant*, percentage resistant isloates

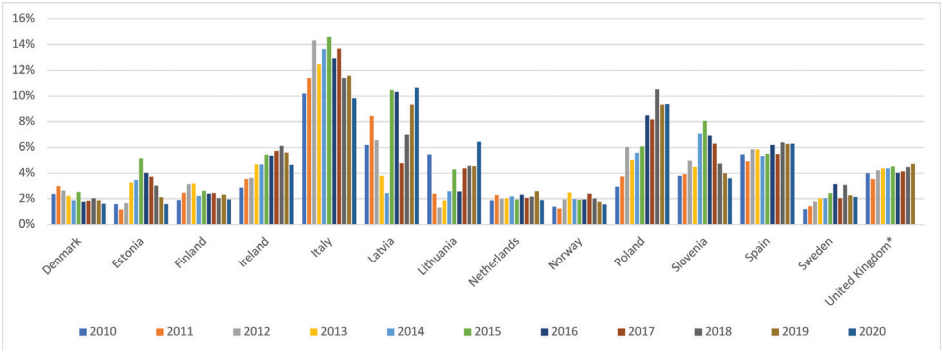
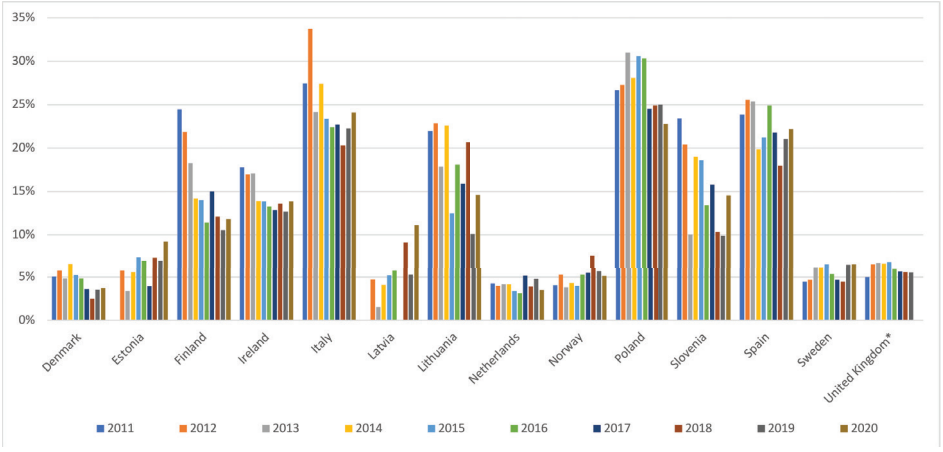
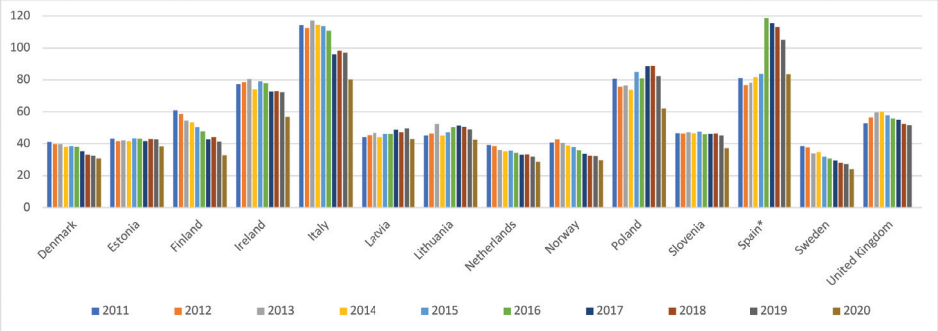


Figure 2c. *S.pneumoniae* non-susceptible to macrolides, percentage resistant isolates



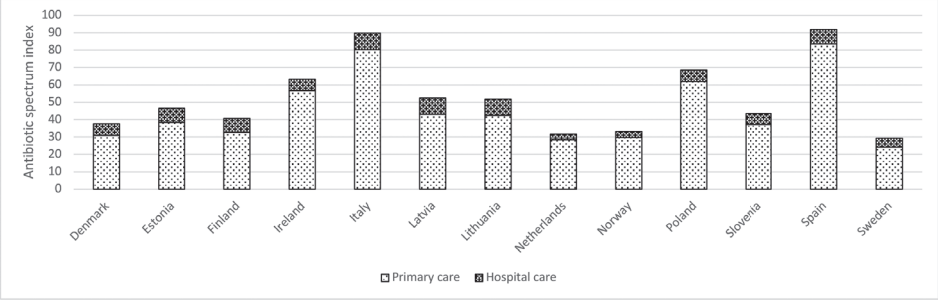
*Data from primary care in the United Kingdom for the year 2020 was missing in the open source database of the ECDC.

Figure 3. Antibiotic spectrum index for primary care



*Spain saw a strong ostensible increase in prescription from 2016 onwards. However, this was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data (11).

Figure 4. Antibiotic Spectrum Index for primary care and hospital care for the year 2020



*United Kingdom is not included due to missing data on the year 2020.

Figure 5. Antibiotic Spectrum Index and Daily Defined Doses plotted against prevalence Sentinel Multidrug Resistant Microorganisms

Figure 5a. Combined cumulative Antibiotic Spectrum Index plotted against prevalence Methicillin Resistant *S. Aureus* in 2020

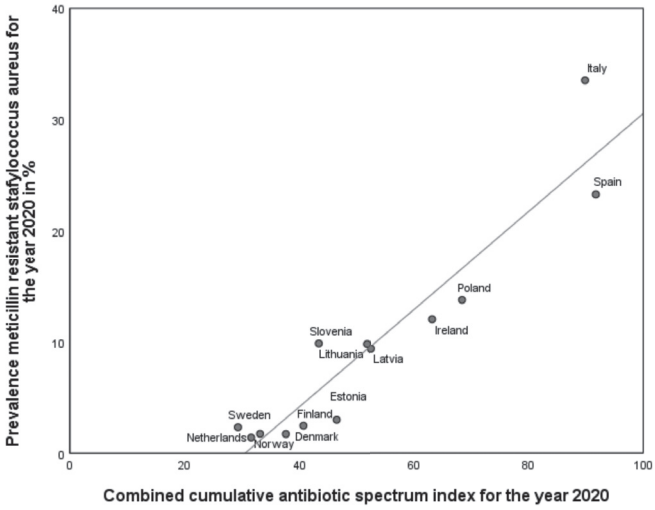


Figure 5b. Combined cumulative Antibiotic Spectrum Index plotted against prevalence *E. coli* in 2020

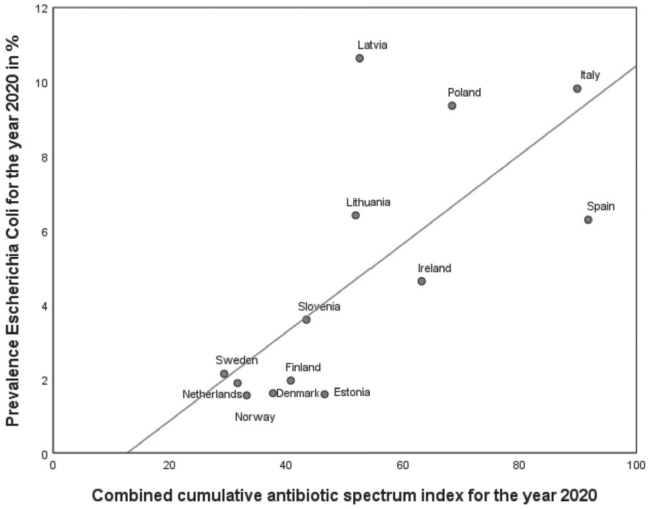


Figure 5c. Combined cumulative Antibiotic Spectrum Index plotted against prevalence *S. pneumoniae* in 2020

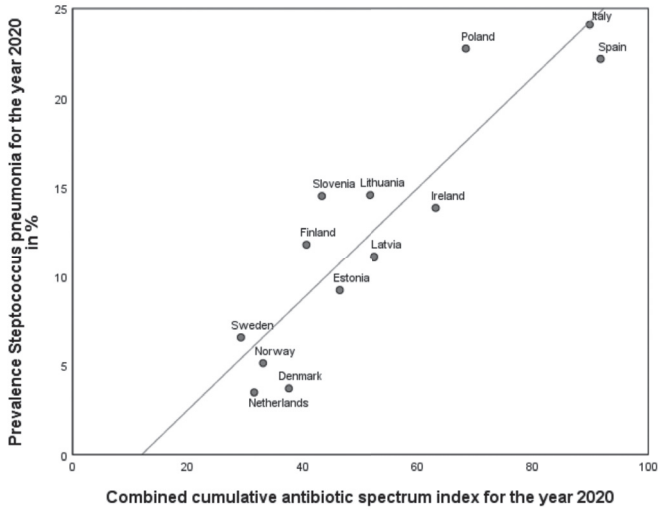


Figure 5d. Combined cumulative Daily Defined Doses plotted against prevalence MRSA in 2020

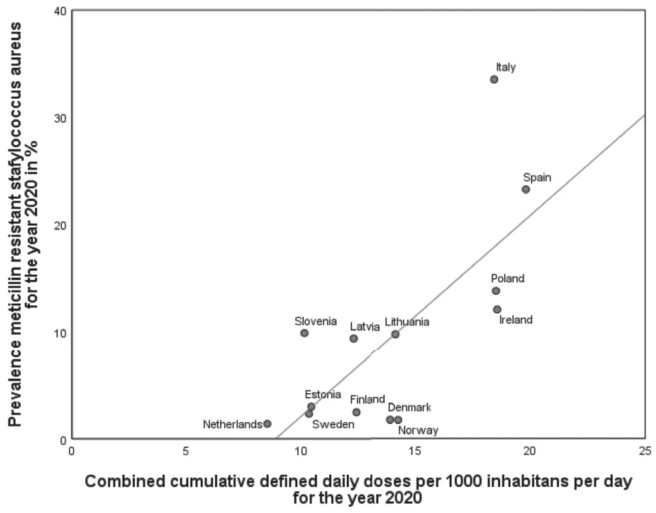


Figure 5e. Combined cumulative Daily Defined Doses plotted against prevalence *E. coli* in 2020

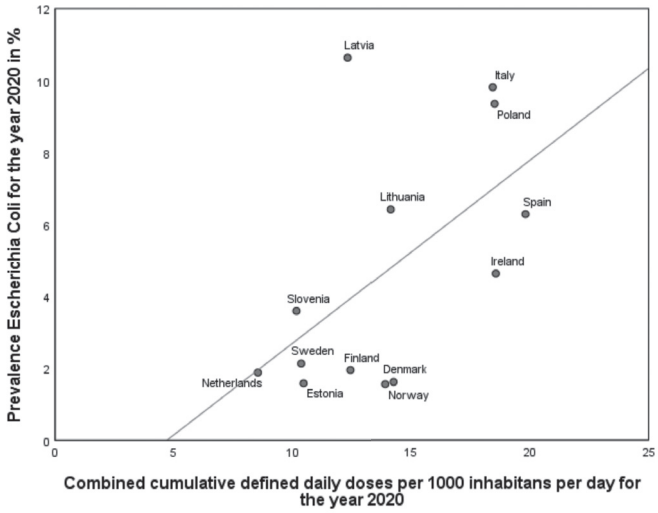
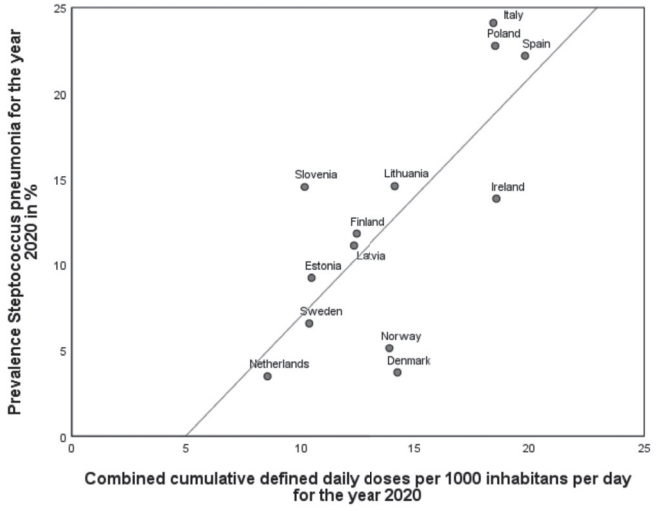


Figure 5f. Combined cumulative Daily Defined Doses plotted against prevalence *S. pneumoniae* in 2020.



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Supplements

Supplement 1. STROBE-AMS checklist

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	2.1 Report previous clinical in vivo and in vitro studies	4
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes		4
Methods					
Setting	5	Describe the setting, locations, relevant dates, including periods of recruitment, exposure, follow-up and data collection		5.1 Describe if setting is epidemic or endemic (high, low, medium) for the study outcome 5.2 Specify type of hospital or unit and characteristics of population served by the healthcare setting 5.3 Describe antimicrobial formulary in use at the study location related to the analysed antibiotics 5.4 Describe infection control measures dedicated to the target resistant bacteria applied at the study location	5
Participants	6	(a) *Cohort study*—Give the eligibility criteria, the sources and methods of selection of participants. Describe methods of follow-up *Case–control study*—Give the eligibility criteria, the sources, methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria, the number of exposed and unexposed *Case–control study*—For matched studies, give matching criteria and the number of controls per case		6.1 Define unit analysed (person, department or other) 6.2 Provide reasons (epidemiological and clinical) for choosing matching criteria	NA NA

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable		7.1 Specify antimicrobial usage according to: type, dosage, duration and route of administration 7.2 Provide information using defined daily dosages (DDDs) and, in addition, other definitions closer to local reality (packages, prescriptions). Provide justification for the measurement presented 7.3 Address antimicrobial combinations 7.4 Explain rationale for grouping of antimicrobials 7.5 Define time at risk for antimicrobial exposure and for resistance development 7.6 Include description of potential confounders (other than epidemiological variables) 7.7 Provide definition of resistance, multidrug resistance, including pattern of co-resistance; whether studies performed to identify location or resistance eg, plasmid, chromosome, integrin, transposon 7.8 Definition of infection and/or colonisation. If not a validated reference, provide evidence of robustness of the new definition	5-7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		8.1 Describe how antimicrobial consumption data were obtained (pharmacy, patients' charts, etc) and if it was actually used or purchased/dispensed	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		11.1 Provide subgroup analyses for immunocompromised, surgical/ medical patients and patients in intensive care units, if applicable	5-7
Results					
Descriptive data	14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders		14.1 Specify among the exposure: previous stay in long-term care facilities, nursing home and other healthcare settings	8-9

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
		(b) Indicate number of participants with missing data for each variable of interest			NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)			NA
Other analyses	17	Report other analyses performed—eg, analyses of subgroups and interactions, and sensitivity analyses		17.1 Report subgroup analysis by type of patients and type of microorganism, if applicable	9
Discussion					
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		19.1 Provide description of sources of selection bias, including infection control measures, audit and confounding	11
Generalis-ability	21	Discuss the generalisability (external validity) of the study results		21.1 Discuss study setting, type of hospital, local epidemiology for the generalisability	11-12
Other information					
Funding	22	Give the source of funding, the role of the funders for the present study and, if applicable, for the original study on which the present article is based			13

Bold typeface indicates main variables included in the STROBE tool.
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; STROBE-AMS, STROBE for antimicrobial stewardship.
NA: Not applicable

Supplement 2: List of countries with a health care system where the general practitioner act as s gatekeeper

Gatekeeper is defined as a compulsory GP referral to access most types of specialist care except in case of emergency (1).

- Australia
- Canada
- Chile
- Costa Rica
- Denmark
- Estonia
- Finland
- Ireland
- Italy
- Latvia
- Lithuania
- Netherlands
- New Zealand
- Norway
- Poland
- Slovenia
- Spain
- Sweden
- United Kingdom

1. Organisation for Economic Co-operation and Development (OECD): OECD Health System characteristics Survey [Available from: http://www.oecd.org/.

Supplement 3a. List of antibiotics in Antibiotic Spectrum Index

Antibiotic	Antibiotic Spectrum Index	ATC code
Amikacin sulfate	6	J01GB
Amoxicillin	2	J01CA
Amoxicillin-clavulanate	6	J01CR
Ampicillin	2	J01CA
Ampicillin-sulbactam	6	J01CR
Azithromycin	4	J01FA
Aztreonam	3	J01DF
Cefazolin	3	J01DB
Cefdinir	3	J01DD
Cefepime	6	J01DE
Cefixime	3	J01DD
Cefotaxime	5	J01DD
Cefoxitin	5	J01DC
Cefpodoxime	3	J01DD
Cefprozil	4	J01DC
Ceftaroline	8	J01DI
Ceftazidime	4	J01DD
Ceftriaxone	5	J01DD
Cefuroxime	4	J01DC
Cephalexin	2	J01DB
Chloramphenicol	4	J01BA
Ciprofloxacin	8	J01MA
Clarithromycin	4	J01FA
Clindamycin	4	J01FF
Colistimethate	5	J01XB
Daptomycin	5	J01XX
Dicloxacillin	1	J01CF
Doxycycline	5	J01AA
Ertapenem	9	J01DH
Erythromycin	2	J01FA
Gentamicin	5	J01GB
Imipenem-cilastatin	11	J01DH
Levofloxacin	9	J01MA
Linezolid	6	J01XX
Meropenem	10	J01DH
Metronidazole	2	J01XD
Minocycline	5	J01AA
Moxifloxacin	10	J01MA
Oxacillin	1	J01CF

Antibiotic	Antibiotic Spectrum Index	ATC code
Piperacillin	4	J01CA
Piperacillin-tazobactam	8	J01CR
Rifampin	3	J04AB
Telavancin	5	J01XA
Ticarcillin-clavulanate	6	J01CR
Tigecycline	13	J01AA
Tobramycin	5	J01GB
Trimethoprimsulfamethoxazole	4	J01EE
Vancomycin	5	J01XA

Supplement 3b. Missing antibiotic in antibiotic spectrum index.

Antibiotic	Antibiotic Spectrum Index	ATC code
Amphenicols*	4	J01BA
Beta-lactamase inhibitors*	6	J01CG
Flucloxacillin*	1	J01CF
Fosfomycin*	1	J01XX
Macrolides**	3.5	J01FA
Nitrofurantoin*	1	J01XE
Norfloxacin*	8	J01MA
Other quinolones	8	J01MB
Quinolones**	8.5	J01MA
Streptogramins*	5	J01FG
Streptomycins*	5	J01GA
Tetracyclines*	5	J01AA
Trimethoprim*	1	J01EA

* In incidental cases that was no index number in the ASI for an antibiotic, an index number was calculated based on activity against micro organisms. If this was not possible, the antibiotic(group) was excluded from the analysis.
** Average ASI had to be calculated for the ATC subgroups macrolides and quinolones, as the different antibiotics within these ATC subgroups showed different ASIs. For each subgroup, the ASI was calculated based on a weighted average level of antibiotic prescriptions.

Supplement 4. Slope coefficients of plotting antibiotic spectrum index and volume of antibiotic prescriptions against sentinel multidrug resistant microorganisms

	Combined cumulative ASI in 2020		Combined total DDD / 1000 inhabitants per day in 2020	
	Slope coefficient (Beta)	p-value*	Slope coefficient (Beta)	p-value*
MRSA	0.94	<0.001	0.73	0.004
E. Coli	0.72	0.006	0.56	0.047
S. Pneumoniae	0.91	<0.001	0.74	0.004

* A p-value less than 0.05 was considered clinically significant.

MRSA: Methicillin resistant *S. Aureus*

Chapter 3

Determinants of inappropriate antibiotic prescription in primary care in developed countries with general practitioners as gatekeepers: a systematic review and construction of a framework

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BMJ Open 2023;13:e065006

Abstract

Objectives

This study aimed to identify determinants of inappropriate antibiotic prescription in primary care in developed countries and to construct a framework with the determinants to help understand which actions can best be targeted to counteract development of antimicrobial resistance (AMR).

Design

A systematic review of peer-reviewed studies reporting determinants of inappropriate antibiotic prescription published through 9 September 2021 in PubMed, Embase, Web of Science and the Cochrane Library was performed.

Setting

All studies focusing on primary care in developed countries where general practitioners (GPs) act as gatekeepers for referral to medical specialists and hospital care were included.

Results

Seventeen studies fulfilled the inclusion criteria and were used for the analysis which identified 45 determinants of inappropriate antibiotic prescription. Important determinants for inappropriate antibiotic prescription were comorbidity, primary care not considered to be responsible for development of AMR and GP perception of patient desire for antibiotics. A framework was constructed with the determinants and provides a broad overview of several domains. The framework can be used to identify several reasons for inappropriate antibiotic prescription in a specific primary care setting and from there, choose the most suitable intervention(s) and assist in implementing them for combatting AMR.

Conclusions

The type of infection, comorbidity and the GPs perception of a patient's desire for antibiotics are consistently identified as factors driving inappropriate antibiotic prescription in primary care. A framework with determinants of inappropriate antibiotic prescription may be useful after validation for effective implementation of interventions for decreasing these inappropriate prescriptions.

Introduction

Antimicrobial resistance (AMR) is increasing worldwide and represents a major threat to global healthcare (1). The major driver of the rise in AMR is the use, frequently inappropriate, of antibiotics (2). Worldwide efforts are now underway to decrease unnecessary antibiotic prescribing and consequently reduce the development of AMR (1). The most common prescribers of antibiotics in developed countries are general practitioners (GPs), accounting for between 80% and 90% of all antibiotic prescriptions (3,4). As such, GPs play an important role in reducing AMR. However, there is currently insufficient insight into which potentially changeable determinants are associated with inappropriate antibiotic prescription in this setting.

GPs prescribe antibiotics for a variety of infectious diseases, ranging from respiratory tract infections (RTI) to cellulitis (5–10). However between 44% and 98% of the antibiotic prescriptions for RTIs are classified as inappropriate (11–14). The proportion of inappropriate antibiotic prescriptions for urinary tract infections is estimated at between 3% and 36.5% (15,16). Antibiotic prescriptions are generally considered inappropriate when, according to the guidelines, no or other antimicrobials should be used. The high proportion of inappropriate antibiotic prescriptions combined with the large quantity of antibiotics prescribed by GPs suggest that efforts to improve antibiotic prescribing in primary care may have a substantial effect on the development of AMR.

Determinants across several domains affect the proportion of inappropriate antibiotic prescribing in primary care. These domains include patient–doctor interactions, the organisation of primary care, the national role of primary care and the nationwide healthcare system (17,18). Reducing inappropriate antibiotic prescribing is therefore complex. To increase effectiveness, each domain should be taken into account in any intervention. However, it is still unclear which determinants play a role in each specific domain and how the different determinants may interact.

The aim of this review is to identify the determinants influencing inappropriate antibiotic prescribing by GPs, sort the determinants into a framework according to their domain and identify which determinants may be subject to antimicrobial stewardship interventions for reducing inappropriate antibiotic prescribing.

Methods

Systematic review search strategy and study selection

A systematic review was conducted. Briefly, the search included studies describing determinants in primary care in developed countries through 9 September 2021. The protocol developed to conduct this study was registered in PROSPERO (online supplemental file 1). PubMed, Embase, Web of Science and the Cochrane Library databases were searched. The full electronic search strategy can be found in online supplemental file 2. We additionally searched grey literature (i.e., abstracts of conferences, symposia and meetings) and relevant references found in initially identified studies found in Embase, Web of Science and the Cochrane Library. There were no language restrictions in the search. The reporting of our systematic review was based on the protocol specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplemental file 3) (19).

Studies were, regardless of their design, selected for reviewing if they provided a definition of inappropriate antibiotic prescription according to the guidelines used in that study. Only studies performed in developed countries, as defined by the United Nations (UN), in which the GP plays a 'gatekeeper' role in the healthcare system, were included (Supplemental files 4, 5) (20,21). This gatekeeper role is defined by the UN as a compulsory GP referral to access most types of specialist care, except in case of emergency (21). Studies had to report determinants that influence the inappropriate prescribing of antibiotics as an outcome. Studies on specific subgroups of patients (e.g., those with specific comorbidities) or specific diseases (such as asthma or chronic obstructive pulmonary disease) were excluded as reasons for appropriate or inappropriate antibiotic prescriptions for these groups differ, while our aim was to develop a framework for the whole population. Two reviewers (MS and FLB) independently reviewed the titles, index terms and abstracts of the identified references and rated each abstract according to the inclusion and exclusion criteria. Full texts of potentially relevant abstracts were assessed for eligibility by two reviewers (MS and FLB). Discrepancies were resolved by consensus. If consensus could not be reached, a third reviewer (MGJdB or MEN) was consulted.

Data extraction and quality assessment

The determinants of inappropriate prescription of antibiotics were extracted from the included studies, along with the study design, geographical location, disease group, definition of inappropriate prescribing, study population and research period. ORs describing associations between determinants and inadequate prescription were

extracted where provided. Study quality was assessed using the National Heart and Lung Institute (NHLI) study quality assessment tool for quantitative studies and the Critical Appraisal Skills Programme (CASP) for qualitative studies (22, 23).

Framework

Determinants were placed in a framework by a reviewer (MS) which was thereafter reviewed by the research group and adapted based on consensus in the groups' discussion. We used a practical framework set-up as described by Morgan et al. (17). This framework is specifically designed for understanding and reducing medical overuse in primary care and takes all relevant domains of influence into account, including the culture of healthcare consumption, patient factors and experiences, the culture of professional medicine, clinician attitudes and beliefs, practice environments and patient–clinician interactions. The domain 'government' was left out of the framework as it was found to be redundant owing to our selection of studies from developed countries in which GPs play a gatekeeper role.

If the definition of determinants showed large similarity, we choose to combine the determinants to prevent overlap in our framework. Determinants were eligible to be added to the framework if they had a positive or negative impact on inappropriate antibiotic prescribing. The determinants were classified as having either a positive or negative influence on inappropriate antibiotic prescription according to the findings and description in their study. Subsequently, each determinant was noted in the framework with a plus or minus sign. The identified determinants were categorised and attributed to the framework domains specified by a method described by Morgan et al. (17). Determinants specific to one country, as well as those on which studies reported conflicting results, were included to create a complete framework appropriate to various settings. Determinants on which studies returned conflicting results were noted in the framework with a plus or minus sign (±).

Patient and public involvement

Patients were not involved in designing the review, data collection, interpretation or write-up of this review.

Results

The literature search identified 2257 studies. Following screening of titles and abstracts, 285 studies were retained for full-text review, of which 17 were ultimately included in the review as they specified determinants of inappropriate antibiotic prescription (Figure 1) (24–40). Characteristics of the selected studies are presented in the supplemental materials S6a and S6b. The studies were conducted in six countries: Australia, Canada, Ireland, The Netherlands, Spain and the UK. Four studies (25,32,33,38) had a qualitative design (one explorative qualitative design, one cross-sectional survey, one focus group and one questionnaire), while 13 studies had a quantitative design (all observational in nature). The methodologies of the included studies as assessed by the NHLI or CASP tool all had a low risk of bias. Quality assessment tables are presented in the supplemental materials S7; S8.

Framework determinants of inappropriate prescriptions

In total, 54 determinants were identified from 17 studies. Seven determinants were directly not included in the framework as they showed no association with inappropriate antibiotic prescribing, either positive or negative (online supplemental materials S6b). Forty-five determinants were included and are presented in a framework (Figure 2). There were five determinants with conflicting results from the included studies and three determinants with a positive impact on inappropriate antibiotic prescribing. Three determinants showed similarity and were combined with each other to one determinant (34). Silverman et al. compared careers of between 11 and 24 years with careers shorter than 11 years and careers longer than 25 years with careers less than 11 years (34). These outcomes were combined to form one determinant, a career longer than 10 years.

Discussion

We systematically reviewed the determinants of inappropriate antibiotic prescription in developed countries in which GPs act as the gatekeepers. Comorbidity and GPs' perceptions of a patient's expectation for antibiotics were consistently identified as main factors that drive inappropriate prescription of antibiotics in primary care. There were no restrictions on the design of the study for the inclusion as our aim was to include as many determinants as possible.

Determinants of inappropriate antibiotic prescription in primary care

Comorbidity was the most frequently found determinant of inappropriate antibiotic prescription (25–27,29,35,37,40). However, it is not clear to what extent prescribing an antibiotic for a patient with one or more comorbidities is inappropriate. The guidelines for appropriate antibiotic use are largely based on studies of patients without comorbidities. Consideration of antibiotic prescription is also advised by guidelines in cases of comorbidity (5,9). GPs may quickly choose to prescribe an antibiotic to be on the safe side with regard to complications, leading to more antibiotic prescriptions for patients presumably at risk for complications.

Another important determinant was the GPs perception of a patient's expectation of getting antibiotics (24–26,30). GPs may assume the reason for a patient's visit is an antibiotic prescription, but may not verify this with the patient. Thus, more effort focused towards verifying the specific reason for the encounter may represent a typical primary care approach to further reducing inappropriate antibiotic prescriptions. Inability to effectively negotiate or explain antibiotic use also leads to more inappropriate prescriptions (32). Both determinants illustrate the benefits of the availability of time to communicate with patients and efficient communication skills. This was confirmed by a recent review of communication training aimed at reduction of antibiotic prescriptions for RTIs (41).

Remarkably, some GPs did not consider themselves responsible for antibiotic resistance (32). In their opinion, their prescribing at an individual level did not contribute to AMR. Rather, they believe AMR is mainly driven by antibiotic prescriptions in hospitals or those in veterinary use. This notion was confirmed by a study performed by the European Centre for Disease Control (42). In reality, up to 90% of antibiotic prescriptions find their origin in primary care (3,4). Furthermore, according to the one health concept, antibiotic prescriptions from all sectors contribute to antibiotic selection pressure (43). Additionally, more (inappropriate) antibiotic prescription is the cause of a vicious cycle of increasing AMR which leads to prescribing of second choice, mostly broad-spectrum antibiotics leading to increasing AMR. This points to the need for continuous education which emphasises that inappropriate antibiotic prescriptions give unnecessary antibiotic selection pressure and thus lead to more AMR.

There were conflicting results on some determinants. A study by Eggermont et al. specifically designed to investigate gender differences in inappropriate antibiotic prescriptions failed to detect any such association with gender (27). However, there were three studies reporting a gender association. Therefore, we included female

gender as a determinant associated with more inappropriate antibiotic prescribing in our framework (26,29,30).

Two studies found an association between larger practice size and inappropriate antibiotic prescription while a third study found no association with practice size (29,31,35). A higher daily patient load was associated with more inappropriate prescription of antibiotics in one study (34). As practice size and patient load are generally related, a larger practice was included in the framework.

The determinant age of the patient was investigated by seven studies (24–27,29,30,37). Two studies found that an age between 18 and 65 years was associated with increased inappropriate antibiotic prescription (26,29), one study concluded increasing age to be associated with greater inappropriate antibiotic prescription (37) and two studies failed to find any such association (24,27). Two studies focusing on otitis media found inappropriate antibiotic prescription more commonly occurred with children younger than 2 years of age as compared with children 2 years and older (25,30).This was therefore included in the framework as a determinant with conflicting results.

The healthcare payment model was researched in several studies exploring various determinants, with some finding an association with inappropriate antibiotic prescription (32–35). An explorative study in Ireland from O'Doherty et al. reported a higher rate of inappropriate antibiotic prescriptions in self-paying or fee-for-service insured patients versus patients with free access to healthcare (33). Likewise, a study in Canada found fee-for-service providers more commonly inappropriately prescribed antibiotics than salaried providers (35). Another study from Canada failed to detect this association (34) and likewise found no association between inappropriate antibiotic prescription and a healthcare capitation payment system. Protecting business was singled out as a reason for inappropriate antibiotic prescription in a cross-sectional survey study in Australia (32).

Framework determinants of inappropriate antibiotic prescribing

As our aim was to construct a comprehensive framework as possible. The determinants practice location (rural vs urban), hospital affiliation and medical education outside the USA and Canada were put in the framework despite being specific to a country or setting (29,31,34,35). Rural locations in Canada have a different context than rural locations in Europe and this determinant should be used in that context (29). One study found that physicians trained outside Canada or USA prescribed more inappropriate antibiotics while working in Canada (31). The constructed framework provides a

broad overview of all determinants by domain and can be used, after validation, to design interventions intended to reduce inappropriate prescriptions in primary care. For example, the framework shows that clinical judgement differs between GPs due to different interpretations of the severity of the symptoms (24,26,30). A career longer than 10 years was associated with more inappropriate antibiotic prescription with a possible cause being that they are less familiar with guidelines and rely more on their clinical experience (29,31,34). This illustrates that a more objective tool for judgement of severity is needed. A possible solution could be using C-reactive protein (CRP) and other point of care tests for patients with RTIs. CRP-guided treatment has been proven effective in reducing inappropriate antibiotic prescription for patients with RTIs (44). More examples of effective interventions per determinant are presented in Table 1. Only determinants associated with inappropriate antibiotic prescriptions that can be influenced by effective interventions were included (Table 1). Studies on effective interventions for reducing antibiotic prescriptions in primary care show that multifaceted interventions thus covering more determinants seem to be more effective in reducing antibiotic prescribing (44–48).

The focus and interpretation of the framework, and hence the needed interventions, differ by country. For example, patient expectations of an antibiotic may stem from local beliefs and attitudes and be more common in cultures placing an emphasis on masculinity as antibiotic prescription tends to be higher in such societies (49). A priority in a masculine society is an early return to work and antibiotics are seen as an important facilitator therefore (50). In societies in which this effect is smaller, illness is considered a legitimate reason for absence from work. Ireland, Spain and the UK have much higher masculinity scores than The Netherlands (51), and antibiotic prescription rates are indeed higher in those three countries as compared with The Netherlands (3). Interventions should focus on informing patients about the mild natural course of most infectious diseases and the low value of antibiotic use.

Strength and limitations

The strengths of our study include that our review summarises determinants covering many domains, thus providing a broad overview. Additionally, the Morgan et al. framework was specifically designed to reduce overuse in primary care (17), making it particularly useful when designing and/or implementing interventions to reduce inappropriate antibiotic prescription. Only studies from developed countries where GPs act as gatekeepers were included as both influence the level of appropriate antibiotic prescriptions in a country (52). This choice reduced the number of eligible studies and may have concurrently reduced the number of detected determinants.

Our framework has not been validated in this study, which is needed before it can be implemented. Another limitation was the lack of objective measure of the effect size due to the inclusion of qualitative studies. This makes it not possible to determine which determinants are more relevant.

Conclusions

The most important determinants of inappropriate antibiotic prescribing are comorbidity, diagnostic uncertainty, the GPs perception of a patient's wish for antibiotics, an inability to effectively negotiate or explain appropriate use of antibiotics and a direct request for an antibiotic by a patient. Although our framework needs validation before it can be used. It may provide a viable starting point for designing, implementing and conducting interventions aimed at evidence-based reduction of antibiotic prescriptions in primary care.

Tables

Table 1. Overview determinants with examples of potential effective interventions

DETERMINANTS ASSOCIATED WITH INAPPROPRIATE ANTIBIOTIC PRESCRIBING	EXAMPLES OF POTENTIAL EFFECTIVE INTERVENTIONS
Culture of professional medicine	
Diagnostic uncertainty	CRP POCT* (44-46, 53-57)
No access to guidelines due to high cost	Free access to guidelines (58)
Access to guidelines during consult is time-consuming	CDSS† (47, 58)
Culture of healthcare consumption	
Request by patient	Patient education‡ (45, 59-61) Mass media campaign§ (62) Delayed antibiotic prescription‖ (44, 63-65)
Clinician attitudes and beliefs	
Career > 10 years	Feedback on antibiotic prescribing (45, 65-68)
Primary care considered not responsible for development of antibiotic resistance	
Habit	
Inability to effectively negotiate or explain antibiotic use	CST# (53, 66, 69, 70)
GPs' judgement of more severe illness	CRP POCT* (44-46, 53-57)
Medical liability	Physician education** (45, 67, 70, 71)
Delayed antibiotic prescription‖ (44, 63-65)	Delayed antibiotic prescription‖ (44, 63-65)
The patient-clinician interaction	
Preserving GP–patient relationships	Delayed antibiotic prescription‖ (44, 63-65)
Empathy for patients and risk perception about the seriousness of the illness.	Physician education** (45, 67, 70, 71)
GPs' perception of high patient expectation for antibiotic	CST# (53, 66, 69, 70)
Disease behaviour of the patient	Patient education‡ (45, 59-61)
Patient factors and experiences patient	
Patients expect an antibiotic prescription due to past experiences and have high expectations of antibiotics Received antibiotics in previous year	Patient education‡ (45, 59-61)
Presence of comorbidity / belongs to risk group Ongoing use of corticosteroids Presence of fever Duration of symptoms ≥ 7 days More signs of inflammation (fever, etc.) Severity of illness at first contact	Physician education** (45, 67, 70, 71)

Legend:

*CRP POCT: C-reactive protein Point of Care testing for patients with a respiratory tract infection divers between uncomplicated and complicated respiratory tract infections and reduces antibiotic prescriptions.

†CDSS: clinical decision support system is integrated in an electronic medical system. It gives direct access to guidelines and supports clinical decision making

‡Patient education: Patient can be educated through handout/leaflets and waiting room posters on the limited effect of antibiotics for a viral infection

§Mass media campaign: Mass media campaign providing information on the appropriate use of antibiotic and reduces antibiotic prescriptions

|Delayed antibiotic prescription is prescribed directly at a consult but the patient is advised to use the antibiotic only when the symptoms persist or become more severe. It reduces antibiotic use by patients while maintaining patient satisfaction

¶Feedback: Feedback on antibiotic prescribing provides insight in the number of antibiotic prescriptions by a physician and the impact on antibiotic resistance which stimulates a physician to reflect on his own antibiotic prescription habits

#CST: Communication Skills training helps a physician to explain the limited effect of antibiotics to a patient and is effective in reducing antibiotic prescriptions

**Physician education: education of physicians about guidelines for infectious diseases, the limited effect of antibiotics for viral infections and which diagnostic tools can help to differ between a self-limiting infection and a more severe infectious diseases, such as a CRP POCT

Figure 1. Study Selection

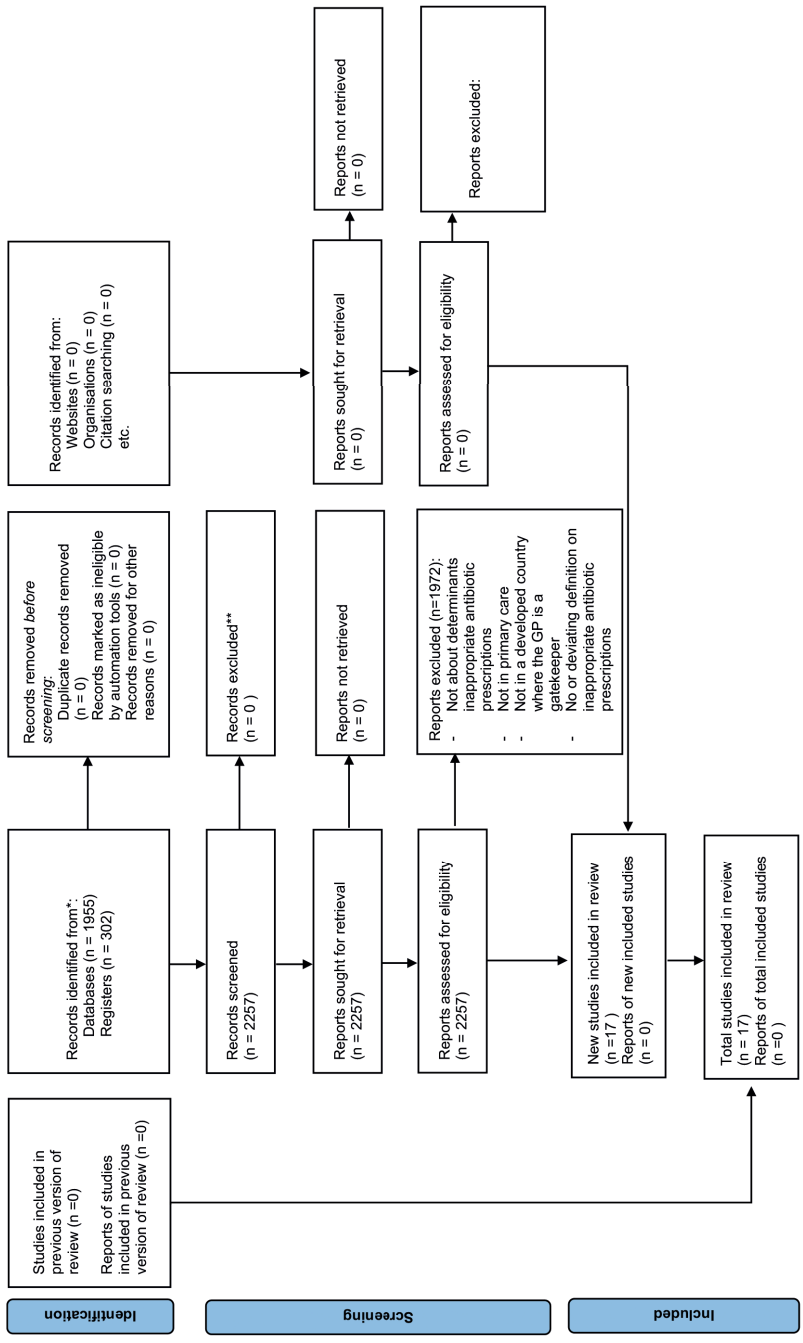
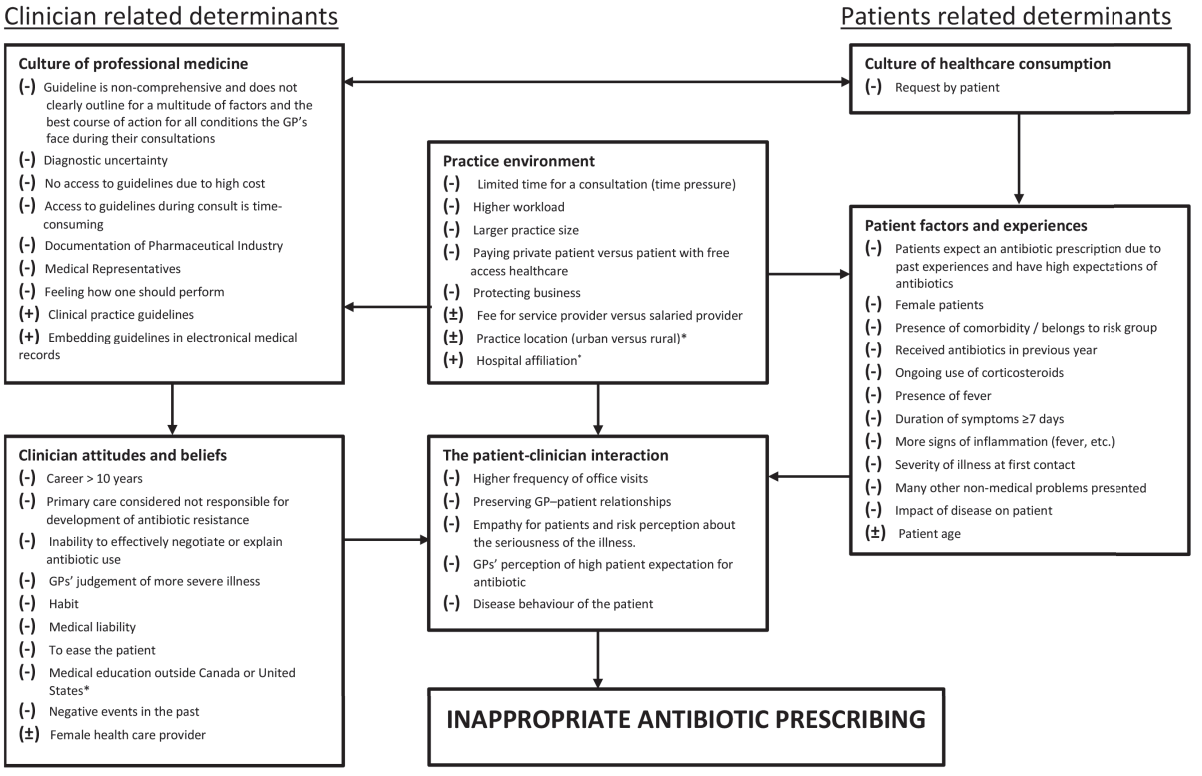


Figure 2. Framework for determinants of inappropriate antibiotic prescribing in primary care in developed countries



Legend:

Determinants associated with more inappropriate antibiotic prescribing

± Determinants with conflicting results on inappropriate antibiotic prescribing

+ Determinants associated with less inappropriate antibiotic prescribing

* Determinants found for only one country

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Supplements

Supplement 1. Original study protocol

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Constructing a framework for the eterminants of inappropriate antibiotic prescription in primary care: a systematic review

Martijn Sijbom, Frederike Büchner, Nicholas Saadah, Mark de Boer, Mattijs Numans

Citation

Martijn Sijbom, Frederike Büchner, Nicholas Saadah, Mark de Boer, Mattijs Numans. Constructing a framework for the eterminants of inappropriate antibiotic prescription in primary care: a systematic review. PROSPERO 2023 CRD42023396225 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396225

Review question

The aim of this review is to identify the determinants influencing inappropriate antibiotic prescribing by GPs, sort the determinants into a framework according to their domain, and identify which determinants may be subject to antimicrobial stewardship interventions for reducing inappropriate antibiotic prescribing.

Searches

PubMed, Embase, Web of Science and the Cochrane Library

Types of study to be included

There are no restriction on the types of studies.

Condition or domain being studied

Primary care and inappropriate prescription of antibiotics

Participants/population

General population, 18 years and older

Intervention(s), exposure(s)

Inappropriate prescription of antibiotics

Comparator(s)/control

Not relevant

Main outcome(s)

Determinants which influence inappropriate antibiotic prescription presented in a framework

Additional outcome(s)

Framework for primary care on inappropriate prescription of antibiotics

Data extraction (selection and coding)

2 reviewers (MS and FB) independently review the titles, index terms and abstracts of the identified references and rated each abstract as potentially relevant or not. Discrepancies are resolved by consensus and if necessary discussed with a third researcher (MdB). Potentially relevant abstracts are assessed full-text for eligibility by 2 reviewers and selected for inclusion in the review if they fulfill the inclusion criteria.

The data will be extracted from the included studies by using a standardized form. This form will be used for the assessment of the quality and evidence synthesis. The data will include: study setting, study population, participant demographics, definition of inappropriate antibiotic use, determinants which influence inappropriate use, study methodology, information for assessment of the risk of bias.

Risk of bias (quality) assessment

The study quality assessment tool of the National Heart and Lung institute will be used to asses the bias. If the risk of bias is (very) high, articles can be excluded.

Strategy for data synthesis

Determinants are placed in a framework by a reviewer (MS) to be able to provide a comprehensive overview of all determinants and their interactions. Discrepancies on the determinants on the framework are resolved by discussion with all authors . We use a practical framework setup as described by Morgan et al. This framework is specifically designed for understanding and reducing medical overuse in primary care and takes all relevant domains of influence into account, including the culture of healthcare consumption, patient factors and experiences, the culture of professional medicine, clinician attitudes and beliefs, practice environments, and patient-clinician interactions. The domain 'government' is left out of the framework as it was found to be redundant owing to our selection of studies from developed countries in which GPs play a gatekeeper role.

Determinants are eligible to be added to the framework if they were found in at least one quantitative study or repeatedly in two or more qualitative studies. The determinants are classified as having either a positive or negative influence on inappropriate antibiotic prescription according to the findings and description in their study. Subsequently, each determinant is noted in the framework with a plus or minus sign. The identified determinants are categorized and attributed to the framework domains specified (17). Determinants specific to one country, as well as those on which studies reported conflicting results, are included to create a complete framework appropriate to various settings. Determinants on which studies returned conflicting results are noted in the framework with a plus or minus sign (+/-).

Analysis of subgroups or subsets

None

Contact details for further information

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Organisational affiliation of the review

LUMC

Review team members and their organisational affiliations

Dr Martijn Sijbom. LUMC
Dr Frederike Büchner. LUMC
Dr Nicholas Saadah. LUMC
Professor Mark de Boer. LUMC
Professor Mattijs Numans. LUMC

Type and method of review

Narrative synthesis, Synthesis of qualitative studies, Systematic review

Anticipated or actual start date

01 February 2019

Anticipated completion date

30 December 2023

Funding sources/sponsors

LUMC

Conflicts of interest

Language

English

Country

Netherlands

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Anti-Bacterial Agents; Antimicrobial Stewardship; Humans; Inappropriate Prescribing; Prescriptions

Date of registration in PROSPERO

12 February 2023

Date of first submission

01 February 2023

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Submitting for publication

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

12 February 2023
12 February 2023
22 February 2023

Supplement 2. Search strategies

PubMed

((("prescribing"[ti] OR "prescription"[ti] OR "prescriptions"[ti] OR prescri*[ti]) AND ("Anti-Bacterial Agents"[majr] OR "anti-bacterial agents"[ti] OR "anti-bacterial agent"[ti] OR "antibacterial agents"[ti] OR "antibacterial agent"[ti] OR "antibacterials"[ti] OR "antibiotic"[ti] OR "antibiotics"[ti] OR antibiotic*[ti] OR "anti-biotic"[ti] OR "anti-biotics"[ti] OR anti biotic*[ti]) AND ("Primary Health Care"[majr] OR "General Practice"[majr] OR "General Practitioners"[majr] OR "Family Practice"[majr] OR "Physicians, Family"[majr] OR "Primary Health Care"[ti] OR "General Practice"[ti] OR "General Practitioners"[ti] OR "Family Practice"[ti] OR "Family Physicians"[ti] OR "Primary HealthCare"[ti] OR "Primary Care"[ti] OR "General Practitioner"[ti] OR "Family Physician"[ti]) AND ("prescription behavior"[tw] OR "prescribing behavior"[tw] OR "prescription behaviors"[tw] OR "prescribing behaviors"[tw] OR "prescription behaviour"[tw] OR "prescribing behaviour"[tw] OR "prescription behaviours"[tw] OR "prescribing behaviours"[tw] OR "reduced prescription"[tw] OR "reduced prescribing"[tw] OR "prescription rates"[tw] OR "prescription rate"[tw])) **OR** (("inappropriate antibiotic"[tw] OR "inappropriate antibiotics"[tw] OR (("Inappropriate Prescribing"[Mesh] OR "inappropriate prescribing"[tw] OR "inappropriate prescription"[tw] OR "inappropriate prescriptions"[tw] OR inappropriate prescri*[tw] OR "over prescribing"[tw] OR over prescri*[tw] OR "overprescribing"[tw] OR overprescri*[tw] OR "unnecessary prescribing"[tw] OR "unnecessary prescription"[tw] OR "unnecessary prescriptions"[tw] OR "inappropriate"[tw] OR inappropriat*[tw] OR "misprescription"[tw] OR "misprescriptions"[tw] OR misprescri*[tw] OR "mis prescription"[tw] OR mis prescription*[tw] OR "determinant"[tw] OR "determinants"[tw]) AND ("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action] OR "anti-bacterial agents"[tw] OR "anti-bacterial agent"[tw] OR "antibacterial agents"[tw] OR "antibacterial agent"[tw] OR "antibacterials"[tw] OR "antibiotic"[tw] OR "antibiotics"[tw] OR antibiotic*[tw] OR "anti-biotic"[tw] OR "anti-biotics"[tw] OR anti biotic*[tw]))) AND ("Primary Health Care"[Mesh] OR "General Practice"[Mesh] OR "General Practitioners"[Mesh] OR "Family Practice"[Mesh] OR "Physicians, Family"[Mesh] OR "Primary Health Care"[tw] OR "General Practice"[tw] OR "General Practitioners"[tw] OR "Family Practice"[tw] OR "Family Physicians"[tw] OR "Primary HealthCare"[tw] OR "Primary Care"[tw] OR "General Practitioner"[tw] OR "Family Physician"[tw]))**)**

Embase (OVID-version)

((("prescribing".ti OR "prescription".ti OR "prescriptions".ti OR prescri*.ti) AND (exp *"Antibiotic Agent"/ OR "anti-bacterial agents".ti OR "anti-bacterial agent".ti OR "antibacterial agents".ti OR "antibacterial agent".ti OR "antibacterials".ti OR "antibiotic".ti OR "antibiotics".ti OR antibiotic*.ti OR "anti-biotic".ti OR "anti-biotics".ti OR anti biotic*.ti) AND (exp *"Primary Health Care"/ OR *"General Practitioner"/ OR *"General Practice"/ OR "Primary Health Care".ti OR "General Practice".ti OR "General Practitioners".ti OR "Family Practice".ti OR "Family Physicians".ti OR "Primary HealthCare".ti OR "Primary Care".ti OR "General Practitioner".ti OR "Family Physician".ti) AND ("prescription behavior".mp OR "prescribing behavior".mp OR "prescription behaviors".mp OR "prescribing behaviors".mp OR "prescription behaviour".mp OR "prescribing behaviour".mp OR "prescription behaviours".mp OR "prescribing behaviours".mp OR "reduced prescription".mp OR "reduced prescribing".mp OR "prescription rates".mp OR "prescription rate".mp)) **OR** (("inappropriate antibiotic".mp OR "inappropriate antibiotics".mp OR ((exp "inappropriate prescribing"/ OR "inappropriate prescribing".mp OR "inappropriate prescription".mp OR "inappropriate prescriptions".mp OR inappropriate prescri*.mp OR "over prescribing".mp OR over prescri*.mp OR "overprescribing".mp OR overprescri*.mp OR "unnecessary prescribing".mp OR "unnecessary prescription".mp OR "unnecessary prescriptions".mp OR "inappropriate".mp OR inappropriat*.mp OR "misprescription".mp OR "misprescriptions".mp OR misprescri*.mp OR "mis prescription".mp OR mis prescription*.mp OR "determinant".mp OR "determinants".mp) AND (exp "Antibiotic Agent"/ OR "anti-bacterial agents".mp OR "anti-bacterial agent".mp OR "antibacterial agents".mp OR "antibacterial agent".mp OR "antibacterials".mp OR "antibiotic".mp OR "antibiotics".mp OR antibiotic*.mp OR "anti-biotic".mp OR "anti-biotics".mp

OR anti biotic*.mp))) AND (exp "Primary Health Care"/ OR "General Practitioner"/ OR "General Practice"/ OR "Primary Health Care".mp OR "General Practice".mp OR "General Practitioners".mp OR "Family Practice".mp OR "Family Physicians".mp OR "Primary HealthCare".mp OR "Primary Care".mp OR "General Practitioner".mp OR "Family Physician".mp))**)**

Web of Science

((ti=("prescribing" OR "prescription" OR "prescriptions" OR prescri*) AND ti=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*") AND ti=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician") AND ts=("prescription behavior" OR "prescribing behavior" OR "prescription behaviors" OR "prescribing behaviors" OR "prescription behaviour" OR "prescribing behaviour" OR "prescription behaviours" OR "prescribing behaviours" OR "reduced prescription" OR "reduced prescribing" OR "prescription rates" OR "prescription rate")) **OR** ((ts=("inappropriate antibiotic" OR "inappropriate antibiotics") OR (ts=("inappropriate prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ts=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ti=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician")) **OR** ((ts=("inappropriate antibiotic" OR "inappropriate antibiotics") OR (ti=("inappropriate prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ts=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ts=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician"))**)**

Cochrane

((("prescribing" OR "prescription" OR "prescriptions" OR prescri*):ti AND ("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"):ti AND ("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician"):ti AND ("prescription behavior" OR "prescribing behavior" OR "prescription behaviors" OR "prescribing behaviors" OR "prescription behaviour" OR "prescribing behaviour" OR "prescription behaviours" OR "prescribing behaviours" OR "reduced prescription" OR "reduced prescribing" OR "prescription rates" OR "prescription rate"):ti,ab,kw) **OR** ((("inappropriate antibiotic" OR "inappropriate antibiotics") OR (("inappropriate

prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician")):ti,ab,kw**)**

Supplement 3. Prisma Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1,7
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5,6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7, 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7, 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8, 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8, 9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 10, figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Supplement 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement 7 and 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement 6

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11
	23b	Discuss any limitations of the evidence included in the review.	Page 14
	23c	Discuss any limitations of the review processes used.	Page 14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3, 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3, 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18
Competing interests	26	Declare any competing interests of review authors.	Page 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement 6

Supplement 4. List of developed countries according to the United Nations (20)

- Australia
- Austria
- Belgium
- Britain
- Bulgaria
- Canada
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Italy
- Japan
- Latvia
- Lithuania
- Luxembourg
- Malta
- New Zealand
- Norway
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- The Netherlands
- United States

20. United Nations: Country classification 2014 [Available from: https://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf accessed May 2019.

Supplement 5. Countries with a health care system where the general practitioner act as a gatekeeper (21)

- Australia
- Canada
- Chile
- Costa Rica
- Denmark
- Estonia
- Finland
- Ireland
- Italy
- Latvia
- Lithuania
- Netherlands
- New Zealand
- Norway
- Poland
- Slovenia
- Spain
- Sweden
- United Kingdom

21. OECD Health System characteristics Survey 2019 [Organisation for Economic Co-operation and Development report]. Available from: http://www.oecd.org/ accessed May 2019.

Supplement 6a: Characteristics included studies

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Akkerman 2005	Prospective cohort study	Netherlands	2003	RTI	Not according to the guidelines	146 GP's/1469 consultations
Akkerman 2005	Prospective cohort study	Netherlands	2003	Acute otitis media	Not according to the guidelines	146 GP's/458 consultations
Biezen 2019	Focus-groups	Australia	2018	GPs	Not according to the guidelines	26 GPs
Cadieux 2007	Retrospective cohort study	Canada	1990-1998	Viral RTI, bacterial RTI and UTI	Antibiotic prescription for a viral infection	104,230 episodes viral infection/ 852 physicians
Damoiseaux 1999	Observational study with semi-structured interviews	Netherlands	1994-1995	Acute otitis media	Not according to the guidelines	22 GP's/362 patients
Dekker 2015	Observational study	Netherlands	2008-2010	RTI	Antibiotic prescription not according to the guidelines	2739 consultations/48 practices
Eggermont 2018	Retrospective cross-sectional	Netherlands	2013	Sore throat symptoms (ICPC R21, R22, R72, R74, R76, R77)	Not indicated by the international guidelines	11,285 consultations/ 25 GP's
Fernandez-Alvarez 2019	Questionnaire	Spain	2010	GPS	Not according to indicators	2100 GPs
Fletcher-Lartey 2016	Cross-sectional survey and semi-structured survey	Australia	2014	GP's	Not indicated	584 GP's filled in survey (response rate 23.7%), 32 GP's interviewed
Malo 2016	Retrospective cross-sectional	Spain	2011	acute bronchitis (ICPC code R78)	Not according to the guidelines	36955 episodes of acute bronchitis

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Nowakowska 2019	Observational study	United Kingdom	2010-2014	sinusitis	Not according to the guidelines	1,151,105 antibiotic prescriptions
				otitis externa		
				otitis media		
				upper respiratory tract infection (URTI) (including unspecified URTI, tracheitis, laryngitis, sore throat and tonsillitis)		
				lower respiratory tract infection (LRTI) (including bronchitis, unspecified chest infection and unspecified LRTI)		
				urinary tract infection (UTI)		
O'Doherty 2019	Explorative qualitive design	Ireland		Acute RTI	Antibiotic prescription for acute RTI	13 GP's
Pouwels 2018	Retrospective cohort	United Kingdom	2013-2015	Acute cough	Not indicated by the guidelines and above the range of a quality indicator	3.7 mil patients, 2,046,095 consultations
				Acute bronchitis		
				Asthma exacerbations		
				COPD exacerbations		
				Acute sore throat		
				Acute rhinosinusitis		
				AOM		
				Upper RTI		
				Lower RTI		
				Influenza-like illness		
				UTI		
				Impetigo		
				Acne		
				Gastroenteritis.		

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Silverman 2017	Retrospective database cohort	Canada	2012	Patients > 65 years with nonbacterial acute upper RTI.	Antibiotic prescription for a non-bacterial acute upper RTI	185,014 patients and visits/ 8990 primary care physicians
				Acute nasopharyngitis (common cold)		
				Acute bronchitis		
				Acute sinusitis		
				Acute laryngitis/tracheitis		
Singer 2018	Retrospective cohort	Canada		Acute mild-to-moderate sinusitis (ICD-9 461)	Antibiotic prescription for a viral infection as indicated in the disease group	16,742 patients (15,6%)/ 239 GP's
				Upper respiratory tract infection (ICD-9 465)		
				Bronchitis (ICD-9 466)		
				Acute rhinitis (ICD-9 460)		
				Acute laryngitis and tracheitis (ICD-9 464)		
				Nasopharyngitis (ICD-9 477)		
				Influenza (ICD-9 487/488)		
Singer 2018	Retrospective cohort	Canada	1999-2016	All antibiotic prescriptions	Not according to the guidelines	32 clinics/196,923 patients

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
van Esch 2018	Retrospective cohort	Netherlands	2016	Acute cough ICPC codes, 31% of the patients; Acute cough (R05) Whooping cough (R71) Laryngitis/tracheitis (R77) Acute bronchitis/bronchiolitis (R78) Acute rhinosinusitis ICPC codes, 34% of the patients Sinus symptom/complaint (R09) Upper respiratory infection acute (R74) Acute/ chronic sinusitis (R75) Urinary tract infection ICPC codes, 36% of the patients. Dysuria/painful urination (U01) Urinary frequency/urgency, (U02) Cystitis/urinary tract infection (U71)	Antibiotic prescription not indicated by the guideline.	8192 adults (15 practices)

GPs: General Practitioner
ICPC: International Classification Primary Care
ICPC R21: Throat symptoms
ICPC R22: Tonsils symptoms
ICPC R72: Strep throat
ICPC R74: Acute Upper Respiratory Infection
ICPC R76: Acute tonsillitis
ICPC R77: Laryngitis/tracheitis
RTI: Respiratory Tract Infection
UTI: Urinary Tract Infection

Supplement 6b: Determinants and their domains from included studies

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Akkerman 2005	More signs of inflammation (fever etc)	Patient age	
	GP's judgement of more severe illness		
	GP's perception of high patient expectation for antibiotic		
Akkerman 2005	Age of patient younger than 24 months		
	GP's judgement of more severe illness		
	GP's perception of high patient expectation for antibiotic		
Biezen 2019	Patients expect an antibiotic due to past experience and have high expectations of antibiotics		Imbedding guidelines in an EMR
	No access to guidelines due to high cost		
	Access to guidelines during consult is time-consuming		
Cadieux 2007	Medical education outside Canada or United States		
	More years in practice		
	Higher practice volume		
Damoiseaux 1999	Severity of illness at first contact		
	Co-morbidity		
	Young age (less than 2 years)		
	Belongs to risk group		
	Disease behaviour of the patient		
	Request by patient		
	GP's perception of high patient expectation for antibiotic		
	Many other non-medical problems presented		
	Impact of disease on patient		
	Habit		
	To ease the patient		
	Negative events in the past		
	Feeling how one should perform		

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	More signs of inflammation (fever etc)		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
	Age of patient younger than 24 months		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
		No access to guidelines due to high cost			Patients expect an antibiotic due to past experience and have high expectations of antibiotics
		Access to guidelines during consult is time-consuming			
		Medical education outside Canada or United States		More years in practice	
				Higher practice volume	
	Severity of illness at first contact	Feeling how one should perform	Habit		Disease behaviour of the patient
			To ease the patient		Request by patient
	Co-morbidity		Negative events in the past		GP's perception of high patient expectation for antibiotic
	Young age (less than 2 years)				
	Belongs to risk group				
	Many other non-medical problems presented				
	Impact of disease on patient				

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Dekker 2015	GP's perception of high patient expectation for antibiotic	Reduced general health	
	Presence of fever		
	GP's judgement of more severe illness		
	Age > 18 years		
	Duration of symptoms ≥ 7 days		
	Presence of comorbidity		
	Female gender		
Eggermont 2018	Comorbidity OR 1.21 (95% CI:1.01-1.32)	Concordance OR 0.92 (95% CI: 0.82-1.02)	
		Gender GP OR 0.83 (95% CI: 0.58-1.08)	
		Gender patient OR 0.96 (95% CI: 0.85-1.06)	
		Age patient OR 1.00 (95% CI: 0.99-1.00)	
Fernandez-Alvarez 2019	Documentation of Pharmaceutical Industry OR 2.09 (95% CI: 1.70–2.87)	Pharmaceutical Industry Training 1.45 OR (95% CI: 0.93–1.15)	Clinical Practice Guidelines OR 1.25 (95% CI: 1.02–1.54)
	Medical Representatives OR 2.50 (95% CI: 1.63–3.66)	Previous clinical experience OR 1.27 (95% CI: 0.77–2.12)	
		Other specialists OR 1.03 (95% CI: 0.93–1.23)	

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	Presence of fever		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
	Age >18 years				
	Duration of symptoms ≥7 days				
	Presence of comorbidity				
	Comorbidity				
		Documentation of Pharmaceutical Industry			
		Medical Representatives			

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Fletcher-Lartey 2016	Patients expect an antibiotic prescription	Age of GP	
	Time pressure	Years worked as a GP	
	Diagnostic uncertainty	Gender	
	Medical liability	Location of practice and socioeconomic profile of practice population	
	Primary care considered not responsible for development of antibiotic resistance		
	Preserving GP–patient relationships		
	Protecting business		
	Inability to effectively negotiate or explain antibiotic use		
	Empathy for patients and risk perception about the seriousness of the illness		
Malo 2016	Increasing age		Female patient
	Co-morbidity		
	Ongoing use of corticosteroids		
Nowakowska 2019	Comorbidity	Socioeconomic deprivation	
	Received antibiotics in previous year		
O'Doherty 2019	Guideline is non-comprehensive and does not clearly outline for a multitude of factors and the best course of action for all conditions the GP's face during their consultations		
	Paying private patient versus patient with free access healthcare		
	Patients expect an antibiotic due to past experience and have high expectations of antibiotics		
	Limited time for an consultation		
Pouwels 2018	Comorbidity	Weekday of consultation	

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
Patients expect an antibiotic prescription		Medical liability	Diagnostic uncertainty	Time pressure	Preserving GP–patient relationships
			Primary care considered not responsible for development of antibiotic resistance		Protecting business,
			Inability to effectively negotiate or explain antibiotic use		Empathy for patients and risk perception about the seriousness of the illness
	Co-morbidity				
	increasing age				
	ongoing use of corticosteroids				
	Comorbidity				
	Received antibiotics in previous year				
A paying private patient versus patient with free access healthcare		Guideline is non-comprehensive and does not clearly outline for a multitude of factors such as cough, sinus pain and the best course of action for all conditions the GP's face during their consultations		Limited time for an consultation	Patients expect an antibiotic due to past experience and have high expectations of antibiotics
	Comorbidity				

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Silverman 2017	Received antibiotics in previous year	Payment model (fee for service, capitation)	Female physician
	11-24 year career versus < 11 year career		Hospital affiliation (Canada)
	>25 year career versus < 11 year career		
	Medical education outside Canada or United States		
	Workload > 150 days/year		
	25-44 patients/day versus < 25 patients/day		
	> 45 patients/day versus < 25 patients/day		
Singer 2018	Female versus male patient OR 1.22 (95% CI: 1.15-1.30)	Practice location (urban versus Rural)	
	Age patient < 60 year versus > 60 year OR 1.19 (95% CI: 1.02–1.38)	Practice size (< 1055 patients versus > 1055 patients)	
	Comorbidity 3 or more versus 0 OR 2.02 (95% CI:1.90–2.14)	Provider age (= 43 year versus > 43 year)	
	Comorbidity 1 or 2 versus 0 OR 1.34 (95% CI: 1.28–1.39)	Provider sex (male versus Female)	
	Fee for service provider versus salaried provider OR 4.35 95% CI: (3.31–5.72)	No. Of encounters per week (< 53 versus ≥ 53)	
	Frequency of office visits (per 2 visit increase to the same primary care provider) OR 1.48 (95% CI: 1.30-1.69)		
Singer 2018	Patient age (per 10 year increase) OR 1.13 (95% CI: 1.03-1.24)	Female patients	
	Number of comorbid conditions OR 1.11 (95% CI: 1.07-1.17)	Country of graduation (other than Canada)	
	Office visit frequency 1.12 (95% CI: 1.08-1.22)	Higher prescriber age (per 10 years increase)	
	Rural practice location OR 1.47 (95% CI: 1.17-1.84)		
	Larger practice size OR 2.26 (95% CI: 1.76-3.16)		
Van Esch 2018		Shared decision making	

CI: Confidence interval
EMR: Electronic Medical Record
OR: Odds ratio

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	Received antibiotics in previous year		11-24 year career versus < 11 year career	Workload > 150 days/year	
			>25 year career versus < 11 year career	25-44 patients/ day versus < 25 patients/day	
			Medical education outside Canada or United States	> 45 patients/ day versus < 25 patients/day	
Fee for service provider versus salaried provider	Female				Frequency of office visits (per 2 visit increase to the same primary care provider)
	Age patient < 60				
	Comorbidity 3 or more versus 0				
	Female patients			Rural practice location	
	Number of comorbid conditions			Larger practice size	
	Office visit frequency				

Supplement 7. Quality assessment of cross-sectional studies

Study	Akkerman 2005a	Akkerman 2005b	Cadieux 2007	Dekker 2015	Eggermont 2018	van Esch 2018	Malo 2016	Nowakowska 2019	Pouwels 2018	Silverman 2017	Singer 2018	Singer 2018
1.Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Ye	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Study	Akkerman 2005a	Akkerman 2005b	Cadieux 2007	Dekker 2015	Eggermont 2018	van Esch 2018	Malo 2016	Nowakowska 2019	Pouwels 2018	Silverman 2017	Singer 2018	Singer 2018
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB

LB: Low risk of bias
NA: Not applicable
NS: Not stated

Supplement 8. Quality assessment of qualitative studies

Study	Biezen 2019	Damoiseaux 1999	Fletcher-Laherty 2016	O'Doherty 2018
Was there a clear statement of the aims of the research?	Yes	Yes	Yes	Yes
Is a qualitative methodology appropriate?	Yes	Yes	Yes	Yes
Was the research design appropriate to address the aims of the research?	Yes	Yes	Yes	Yes
Was the recruitment strategy appropriate to the aims of the research?	Yes	Yes	Yes	Yes
Was the data collected in a way that addressed the research issue?	Yes	Yes	Yes	Yes
Has the relationship between researcher and participants been adequately considered?	Yes	Yes	Yes	Yes
Have ethical issues been taken into consideration?	Not applicable	Not applicable	Not applicable	Not applicable
Was the data analysis sufficiently rigorous?	Yes	Yes	Yes	Yes
Is there a clear statement of findings?	Yes	Yes	Yes	Yes

Chapter 4

Comparing antibiotic prescriptions in primary care between SARS-CoV-2 and influenza: a retrospective observational study

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BJGP Open 2022; 6 (4)

Abstract

Background

Antibiotics are frequently prescribed during viral respiratory infection episodes in primary care. There is limited information about antibiotic prescription during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in primary care and its association with risk factors for an adverse course.

Aim

To compare the proportion of antibiotic prescriptions between patients with COVID-19 and influenza or influenza-like symptoms, and to assess the association between antibiotic prescriptions and risk factors for an adverse course of COVID-19.

Design & setting

An observational cohort study using pseudonymised and coded routine healthcare data extracted from 85 primary care practices in The Netherlands.

Method

Adult patients with influenza and influenza-like symptoms were included from the 2017 influenza season to the 2020 season. Adult patients with suspected or confirmed COVID-19 were included from the first (15 February 2020–1 August 2020) and second (1 August 2020–1 January 2021) SARS-CoV-2 waves. Proportions of antibiotic prescriptions were calculated for influenza and COVID-19 patients. Odds ratios (ORs) were used to compare the associations of antibiotic prescriptions in COVID-19 patients with risk factors, hospital admission, intensive care unit (ICU) admission, and mortality.

Results

The proportion of antibiotic prescriptions during the first SARS-CoV-2 wave was lower than during the 2020 influenza season (9.6% versus 20.7%), difference 11.1% (95% confidence interval [CI]= 8.7 to 13.5). During the second SARS-CoV-2 wave, antibiotic prescriptions were associated with being aged ≥70 years (OR 2.05; 95% CI = 1.43 to 2.93), the number of comorbidities (OR 1.46; 95% CI= 1.18 to 1.82), and admission to hospital (OR 3.19; 95% CI = 2.02 to 5.03) or ICU (OR 4.64; 95% CI= 2.02 to 10.62).

Conclusion

Antibiotic prescription was less common during the SARS-CoV-2 pandemic than during influenza seasons, and was associated with an adverse course and its risk factors. The findings suggest a relatively targeted prescription policy of antibiotics in primary care during COVID-19.

Introduction

The new SARS-CoV-2, like all viral respiratory tract infections (RTIs), carries a risk of bacterial superinfection (1–3). Antibiotics are often prescribed by GPs to reduce morbidity and mortality owing to these bacterial superinfections, particularly in the presence of certain risk factors (1,4–7). Influenza is a recognised major seasonal cause of viral RTIs and a trigger comparable with SARS-CoV-2 with regard to the risk of bacterial superinfections (4).

There is limited information on the extent of antibiotic prescriptions in COVID-19 patients in primary care and the associations of these prescriptions with outcomes of interest. The main disadvantage of the use of antibiotics is the development of antimicrobial resistance (AMR) (8). Another downside is the occurrence of potential side effects of antibiotics. Prudent antibiotic prescription is therefore still indicated and should be sustained in the current pandemic circumstances to reduce the risk of inappropriate antibiotic prescriptions to avoid unnecessary harm.

Antibiotic prescriptions were compared during recent influenza seasons with those of the first and second SARS-CoV-2 waves in The Netherlands. In addition, associations between antibiotic prescriptions and hospital admissions, ICU admissions, mortality, and various known risk factors were calculated.

Method

Study design and setting

Data collection

For this observational study, pseudonymised, coded routine healthcare data were used from patients enlisted between 2016 and 2020 with one of the 85 general practices participating in the Extramural LUMC Academic Network (ELAN) medical registry, operating out of the Leiden and The Hague area. GPs involved in this network provide complete and actively updated longitudinal data on their patients via their electronic medical records (EMRs). An informed opt-out procedure for the use of these pseudonymised data is in place.

Inclusion

Influenza

Patients aged ≥18 years with influenza, upper RTIs, or flu-like symptoms were identified in the ELAN registry by searching the dossiers for the International Classification of Primary Care first edition (ICPC-1) codes (Table 1). Patients were included if they had any of these codes registered during influenza seasons 2017, 2018, 2019, or 2020 (Box 1) (9,10).

Box 1. Definition and dates influenza season (9,10)

An influenza season is defined as more than 51 patients per 100,000 inhabitants with influenza like illness or symptoms visiting their GP. For season 2019-2020, the threshold was 58 patients per 100,000 inhabitants per week.
2017: November 28, 2016 up to including March 6, 2017.
2018: December 11, 2017 up to including April 9, 2018.
2019: December 10, 2018 up to including March 11, 2019.
2020: January 27, 2020 up to including, March 15, 2020

SARS-CoV-2

The following two definitions for diagnosis of a COVID-19 infection were accepted: (1) COVID-19 confirmed with a positive polymerase chain reaction (PCR) test and an appropriate ICPC code in the EMR (Table 1); and (2) COVID-19 highly suspected, based on symptoms (Box 2) and an appropriate ICPC code in the EMR (Table 1). The second definition was used owing to a lack of test capacity in The Netherlands from the start of the SARS-CoV-2 pandemic (February 2020) until 1 June 2020. Patients were included in the study if their PCR test or symptoms (Box 2) matched the definition of COVID-19, categorised as confirmed or suspected COVID-19, and divided in two groups according to their date of diagnosis (11). The first wave lasted from 15 February 2020–1 August 2020. The second wave lasted from 1 August 2020–1 January 2021. The SARS-CoV-2 index lineage was dominant in The Netherlands during both waves (12).

Box 2. Symptoms of SARS-CoV-2 (11)

- Coughing
- Cold
- Sore throat
- Shortness of breath while resting or during light exertion
- Loss of taste or smell
- Fever
- Sudden fatigue
- Diarrhoea
- Headache
- Conjunctivitis
- Muscle- and joint pains

Antibiotic prescriptions

The Anatomical Therapeutic Chemical Classification System code J01 was used to identify and extract data on oral antibiotic prescriptions from the ELAN registry. Prescriptions were linked with patients with influenza and patients with COVID-19 through the pseudonymised patient numbers following a check that the date of the antibiotic prescription corresponded with the registration date of the ICPC-1 code. If the date of the antibiotic prescription and the registration date did not correspond, the antibiotic prescription was not included.

Hospital and intensive care admissions and mortality

An adverse course of COVID-19 was defined in the study as a hospital admission, ICU admission, or mortality. Data on this adverse course were extracted from the EMR in the ELAN registry through examination of the free text in the EMR of each patient with COVID-19.

Risk factors for an adverse course of COVID-19

Risk factors tested for association with a severe course of COVID-19 were based on the definition by the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu; RIVM) and outcomes of recent literature reviews on risk factors for an adverse course of COVID-19 (13–15). Included risk factors

were as follows: age, sex, obesity, smoking, heart disease, diabetes mellitus, severe chronic respiratory disease, HIV infection, severe renal disease, severe liver disease and Down's syndrome. The definitions are listed in Table 2.

Outcome

The outcome measures were as follows: (a) number of antibiotic prescriptions and (b) proportion of patient contacts resulting in antibiotic prescriptions during influenza seasons 2017–2020 and during the two waves of the SARS-CoV-2 pandemic (2020); (c) the number of hospital admissions; (d) ICU admissions; and (e) deaths among patients with COVID-19.

Statistical analysis

For comparison of extent of antibiotic prescription between SARS-CoV-2 waves and influenza seasons, the number of antibiotic prescriptions and proportion of patient contacts resulting in antibiotic prescriptions were compared via unpaired t-tests. Association testing between risk factors and outcome measures was performed using multivariate logistic regression with age, sex, obesity, and smoking added to the model as covariates with the additional risk factors, heart disease, diabetes mellitus, severe chronic respiratory disease, HIV infection, severe renal disease, severe liver disease and Down's syndrome, merged into a composite comorbidity variable. For calculation of this composite variable, the presence of each risk factor or disease was counted as one and added together as a count variable. The multivariate logistic regression model tested the associations between these risk factors and outcome measures (a and b) antibiotic prescriptions, (c) hospital admissions, (d) ICU admissions, and (e) mortality.

Multiple imputation was used to address missing data for risk factors smoking and obesity. The imputation model included all covariates and outcomes (details of multiple imputation model in supplement 1). SPSS statistics (version 25) was used for statistical analysis.

Results

In total, 1702 patients were diagnosed by their GP with suspected or confirmed COVID-19 in the first wave of 2020 with 6904 patients diagnosed in the second wave (Table 3). The total number of antibiotic prescriptions was similar during the first wave compared with the second wave (209 versus 238 prescriptions, respectively). The proportion of

antibiotic prescriptions per patient contact was higher during the first wave, 9.6% (95% CI = 7.9 to 11.4), than during the second wave 2.7% (95% CI = 1.4 to 4.0). Influenza season 2020 had the lowest number of antibiotic prescriptions per contact (20.7%) of any influenza season analysed in the study. This was higher than during the first and second SARS-CoV-2 waves 9.6% (95% CI = 7.9 to 11.4) and 2.7% (95% CI = 1.4 to 4.0), respectively (Table 4). All influenza seasons had a higher proportion of antibiotic prescriptions per patient contact compared with both SARS-CoV-2 waves (Table 4). During the second wave, a higher proportion of the patients with suspected COVID-19 were prescribed antibiotics, 5.0% (95% CI = 3.8 to 6.2), compared with patients with confirmed COVID-19, 2.5% (95% CI = 1.3 to 3.7). During, the first wave, the proportion of prescribed antibiotics per contact was for patients with suspected, or confirmed COVID-19, 10.7% (95% CI = 7.8 to 13.6) and 6.1% (95% CI = 3.9 to 9.0), respectively.

Similar effect estimates were found with multivariate logistic regression using original or pooled imputed data. Therefore, results from multivariate logistic regression with pooled imputed data are presented. During the second wave, an antibiotic prescription was positively associated with an age of ≥70 years (OR 2.05; 95% CI = 1.43 to 2.93), the number of comorbidities (OR 1.46; 95% CI = 1.18 to 1.82) (Figure 1), a hospital admission (OR 3.19; 95% CI = 2.02 to 5.03) or ICU admission (OR; 4.64 95% CI = 2.02 to 10.62) (Figure 2).

Discussion

Summary

In this study, the frequencies of antibiotic prescription during SARS-CoV-2 episodes were compared with those of preceding influenza episodes. Antibiotic prescriptions were found to be less frequently used in primary care during SARS-CoV-2 waves than during influenza seasons 2017 up to and including 2020. Antibiotic prescriptions during the second SARS-CoV-2 wave were associated with older age, the number of comorbidities and also with hospital or ICU admission later. This association was not observed during the first wave.

Comparison with existing literature

In the study population, antibiotics were prescribed for 20–30% of patients with influenza-like illness or influenza. This may, according to the guidelines, be interpreted as inappropriate prescription. Other Dutch studies likewise show excessive antibiotic prescription during viral RTI episodes by GPs (6,16,17). However, these studies include

different symptoms and diseases, which makes them difficult to compare directly. The prescription of antibiotics was less common during the SARS-CoV-2 pandemic in The Netherlands compared with the rates recorded for RTIs pre-SARS-CoV-2.

The proportion of antibiotic prescriptions per contact for COVID-19 during the first wave (9.6%) was comparable with antibiotic prescribing in the management of RTI symptoms in Dutch primary care reported in a study of van der Velden et al. during the SARS-CoV-2 pandemic (7.1%) (18).

In the present study, the total sum of antibiotic prescriptions during SARS-CoV-2 did not differ much between the first and second waves. This, in spite of the burden of the SARS-CoV-2 pandemic being higher during the second compared with the first wave, reflected by the higher number of hospital admissions for COVID-19 patients in The Netherlands (19). The relatively higher frequency of antibiotic prescriptions during the first wave may partly be owing to registration bias, as not all COVID-19 patients during the first wave were registered. Another reason for the less frequent prescription of antibiotics during the second wave may be the increasing knowledge on disease course and risk factors for severe deterioration of COVID-19. Further, there were fewer non-COVID RTIs during the SARS-CoV-2 pandemic (20). The high probability of a SARS-CoV-2 infection combined with accessible PCR testing aids the GP with diagnostic accuracy and likely decreases antibiotic prescription.

Strengths and limitations

A strength of the study is the comparison of antibiotic prescriptions during influenza seasons with those during the SARS-Cov-2 pandemic. Influenza was already a major seasonal cause of viral RTIs and antibiotic prescriptions, and now SARS-CoV-2, at least initially, may have the same effect on GPs' prescribing behaviour in primary health care. Influenza patients and patients with COVID-19 present with similar symptoms. Therefore, the initial assessment does not differ between the two diseases. However, the study revealed increasing differences in antibiotic prescriptions, which may reflect increasing experience among physicians in judging disease severity, or better estimates of potential adverse disease course development.

The results of the study may be hindered by registration bias as not all COVID-19 patients were registered (correctly) before 1 June 2020. The gold standard for diagnosing COVID-19 patients is a positive PCR test from a nasal and throat swab (10). Until 1 June 2020, there was a lack of PCR-testing capacity in The Netherlands. As a consequence, only patients with COVID-19 symptoms assessed at an emergency

department were tested. Until June 1 2020, GPs mainly based a COVID-19 diagnosis on the medical history, patient characteristic, reported and observed symptoms. Patients were advised to contact their GP if they experienced severe symptoms. This led to under-registration of COVID-19 patients in the first wave, leading to a higher proportion of patients with a severe course of COVID-19 being registered. From June 2020 onwards, all patients with symptoms could be tested for SARS-CoV-2 by the municipal health services and test results were quickly passed on to GPs. But patients could have to wait up to 3 days before a PCR test was performed and the results were passed on. Meanwhile, they may have contacted their GPs, leading to a registration of suspected COVID-19. At the start of the SARS-CoV-2 pandemic in The Netherlands, patients with (suspicion of) COVID-19 were not uniformly registered in the EMR with the same ICPC code. A separate ICPC code, R83.03 SARS-CoV-2, was introduced in November 2020, and slowly implemented. Most patients were registered according to their 'influenza-like' symptoms. For this reason, patients aged ≥18 years with the ICPC codes listed in Table 1 were selected broadly from the study population. As only respiratory ICPC codes were selected, asymptomatic patients with COVID-19 or patients with only non-respiratory symptoms associated with SARS-CoV-2 were potentially missed. Use of routinely collected healthcare data always carries a risk of missing data, as was the case in the present study. The authors feel confident missing data in the study is missing at random. The percentage of hospital admissions and mortality during the second wave were comparable with national percentages, suggesting any selection and registration bias in the second wave was low (12,21). As such, the analysis of the second wave was addressed in the primary discussion.

Implications for research and practice

It was found antibiotic prescriptions were given less often during SARS-CoV-2 waves compared with influenza seasons. This may be owing to proper testing of patients for COVID-19, along with a coinciding lower prevalence of influenza and other respiratory viruses, leading to less diagnostic uncertainty about potentially missing a bacterial infection. This may have led to more confidence in the diagnostic accuracy among physicians and hence to communicating a diagnosis to a patient with more certainty.

As a result, antibiotics to prevent or treat a possible bacterial superinfection were largely restricted to those assessed to be at risk of developing or having a more adverse course of COVID-19. Since COVID-19 testing might be the most probable explanation of increased appropriateness in antibiotic prescriptions over time, rapid point-of-care tests for influenza and other viral RTIs may further reduce diagnostic uncertainty and result in fewer antibiotic prescriptions during viral RTI episodes. A Dutch study in

primary care has already suggested that point-of-care testing for patients with RTIs may decrease antibiotic prescriptions (22).

In conclusion, this study confirmed that a high proportion of patients with influenza in the past four seasons were treated with antibiotics by their GP. In contrast, the rate of antibiotic prescription in primary care during the first two waves of the SARS-CoV-2 pandemic in The Netherlands was lower than the influenza seasons studied. Patients with COVID-19 who were prescribed an antibiotic were more likely to have risk factors and more often experienced an adverse course of COVID-19, as is shown by an increased number of hospital or ICU admissions among those prescribed antibiotics. These observations suggest a relatively targeted antibiotic prescription policy during COVID-19, but also clearly suggest that inappropriate antibiotic prescription would potentially decrease further with diagnostic testing for other specific viral infections.

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Tables

Table 1. Overview of included ICPC-1 codes per disease group

ICPC-1 Code	Influenza group	SARS-CoV-2 group
R74 Acute upper respiratory infection	Yes	Yes
R75 Acute / chronic sinusitis	Yes	Yes
R77 Acute laryngitis/tracheitis	Yes	Yes
R78 Acute bronchitis / bronchiolitis	Yes	Yes
R80 Influenza	Yes	Yes
R81 Pneumonia		Yes, excluding R81.01 Legionella pneumonia
R83 Other respiratory infection		Yes, excluding R83.01 Diphtheria and R83.02 Sarcoidosis

ICPC-1: International Classification of Primary Care 1st edition. SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus-2

Table 2. Definition of risk factors on adverse course of SARS-CoV-2

Risk factor	Definition
Age ≥ 70 year	Patients 70 years and older per 1-01-2020
Sex	Male gender
Obesity, BMI > 29	Body mass index is higher than 29 per 1-01-2020
Smoking	Patents with an active or previous smoking status per 1-01-2020
Heart disease*	ICPC K74 Angina pectoris ICPC K75 and K76 Myocardial infarct ICPC K77 Heart failure ICPC K78 Atrial fibrillation
Diabetes mellitus*	ICPC T90 Diabetes mellitus
Severe chronic respiratory disease*	ICPC R91 Chronic bronchitis ICPC R89 Congenital anomaly respiratory ICPC R91 Bronchiëctasieën ICPC R95 COPD
Hiv-infection*	ICPC B90 Use of anti-viral medication for a Hiv-infection
Severe renal disease*	ICPC U99(.01) Renal impairment and eGFR is below 25 ml/min/1.73 m^2
Severe liver disease*	ICPC D97 Cirrhosis Liver failure of liver decompensation Contra-indication label liver impairment
Down syndrome*	ICPC A90.(01) Down syndrome

BMI: Body mass index. ICPC: International Classification of Primary Care codes 1st edition. Hiv: Human immunodeficient virus. COPD: Chronic Obstructive Pulmonary Disease. eGFR: estimated Glomerular Filtration Rate.
*These risk factors were merged into one co-morbidity variable. The presence of each single risk factor/disease was counted as 1 and added together as count variable.

Table 3. Patient characteristics

Diagnosis	Influenza				SARS-CoV-2	
Year/Season	2017	2018	2019	2020	1st wave	2nd wave
Population size*	254,586	276,275	288,703	288,305	288,305	288,305
Number of patients	4579	8016	4354	1422	1702	6904
Age range in years (mean)	18-100 (51)	18-102 (51)	18-101 (51)	18-99 (48)	18-100 (50)	18-100 (48)
Confirmed SARS-CoV-2 (n)	-	-	-	-	247	5682
Suspected SARS-CoV-2 (n)	-	-	-	-	1455	1222
Number of contacts with GP practices	4858	9298	4922	1542	2165	8867
Riskfactors for adverse course SARS-CoV-2 infection						
Age ≥ 70 year % (n)	18.8 (860)	18.2 (1457)	18.5 (804)	13.3 (189)	14.9 (253)	11.7 (806)
Male % (n)	35.4 (1622)	36.5 (2929)	34.6 (1507)	37.7 (536)	38.4 (653)	42.3 (2923)
Obesity, BMI > 29 % (n)†	17.6 (807)	18.2 (1456)	18.9 (823)	17.2 (245)	6.6 (113)	16.6 (1147)
Smoking: current and previous % (n)‡	25.9 (1185)	25.9 (2077)	25.2 (1099)	23.1 (329)	9.8 (166)	19.3 (1330)
Heart disease % (n) §	12.3 (565)	10.5 (844)	10.4 (452)	7.2 (102)	3.5 (59)	8.0 (550)
Diabetes mellitus % (n)|	10.4 (477)	10.5 (839)	9.8 (427)	8.2 (116)	10.6 (181)	9.9 (682)
Severe chronic respiratory disease (n)¶	3.4 (154)	3.5 (277)	3.4 (150)	2.8 (40)	6.2 (105)	2.9 (198)
Hiv-infection % (n)#	0.3 (13)	0.3 (21)	0.3 (15)	0.1 (1)	0.4 (6)	0.3 (20)
Severe kidney disease (eGFR<26) % (n)**	0.4 (19)	0.4 (35)	0.2 (9)	0.2 (3)	0.6 (11)	0.3 (21)
Liver failure % (n)††	0.1 (1)	0	0.1 (1)	0	0	0
Down syndrome % (n)	0.1 (1)	0.1 (1)	0.1 (3)	0	0	0.1 (1)

SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus-2. GP: General practitioner. ICPC: ICPC: International Classification of Primary Care codes 1st edition. BMI: Body mass index.

* In total, 348,553 individual patients were registered during the study period 2016-2020 in the ELAN Datawarehouse. The population size per year is the number of patients registered during that study year.

† Missing BMI (year/season, n): 2017, 2507; 2018, 4338; 2019, 2378; 2020, 847; 1st wave, 1434; 2nd wave, 4274.

‡ Missing smoke status (year/season, n): 2017, 2403; 2018, 4201; 2019, 2312; 2020, 805; 1st wave, 1404; 2nd wave, 4182.

§ Heart disease: ICPC K74 Angina pectoris, ICPC K75 and K76 Myocardial infarct, ICPC K77 Heart failure, ICPC K78 Atrial fibrillation.

| Diabetes mellitus: ICPC T90 Diabetes mellitus.

¶ Severe chronic respiratory disease: ICPC R91 Chronic bronchitis, ICPC R89 Congenital anomaly respirator, ICPC R91 Bronchiëctasieën, ICPC R95 COPD.

Hiv-infection : ICPC B90, Use of anti-viral medication for a Hiv-infection.

** Severe renal disease: ICPC U99(.01) Renal impairment and eGFR is below 25 ml/min/1.73 m^2.

†† Liver failure: ICPC D97 Cirrhosis, Liver failure of liver decompensation, Contra-indication label liver impairment.

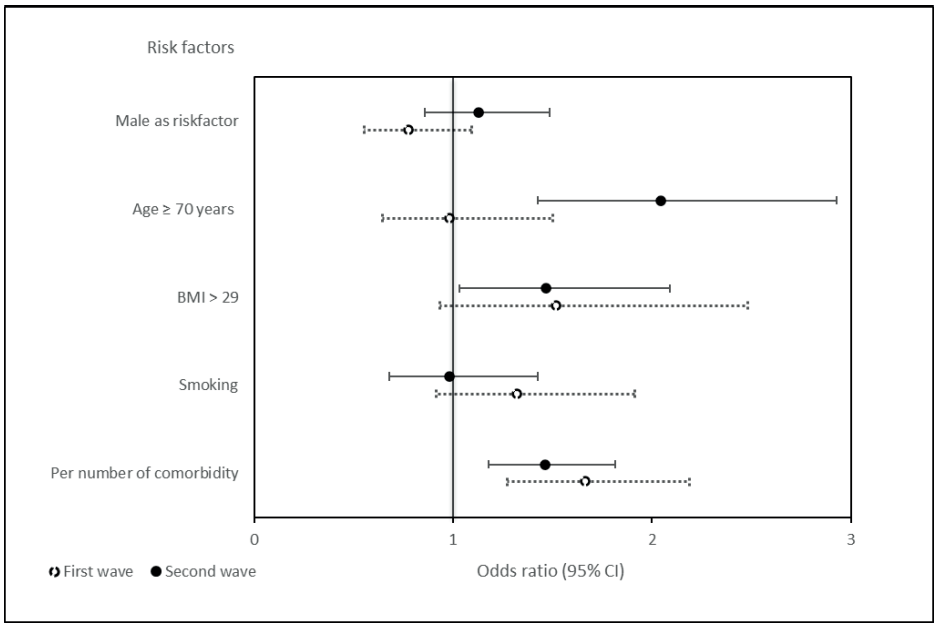
Table 4. Number of antibiotic prescriptions per season per group and observed outcome

Diagnosis	**Influenza**				**SARS-CoV-2**	
Year/season	**2017**	**2018**	**2019**	**2020**	**1st wave**	**2nd wave**
Number of patients	4579	8016	4354	1422	1702	6904
Number of contacts with GP practices	4858	9298	4922	1542	2165	8867
Antibiotic prescriptions per total contacts % (n)	25.1 (1221)	27.9 (2595)	29.6 (1458)	20.7 (319)	9.6 (209)	2.7 (238)
Penicillins % (n)	13.9 (676)	15.7 (1458)	17.7 (869)	12.6 (194)	6.7 (145)	2.2 (177)
Macrolides % (n)	3.0 (147)	3.9 (364)	3.7 (184)	2.5 (38)	1.0 (21)	0.3 (27)
Tetracyclines % (n)	8.1 (393)	8.1 (755)	8.1 (397)	5.5 (85)	1.7 (37)	0.3 (30)
Other % (n)	0.1 (5)	0.2 (18)	0.1 (8)	0.1 (2)	0.3 (6)	0.1 (4)
Observed outcome						
Hospital admissions % (n)	-	-	-	-	7.5 (128)	3.3 (227)
Intensive-care admissions % (n)	-	-	-	-	1.5 (25)	0.6 (41)
Mortality % (n)	-	-	-	-	2.1 (36)	1.0 (71)
Difference in proportion of antibiotic prescriptions between influenza seasons and SARS-CoV-2 waves						
1st wave % (95% CI)	15.5 (13.8-17.2)	18.3 (16.8-19.8)	20.0 (18.2-21.8)	11.1 (8.7-13.5)	-	-
2nd wave % (95% CI)	22.4 (21.1-23.7)	25.2 (24.2-26.2)	26.9 (25.6-28.2)	18.0 (15.9-20.1)	-	-

SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus-2. CI: Confidence Interval. GP: General practitioner

Figures

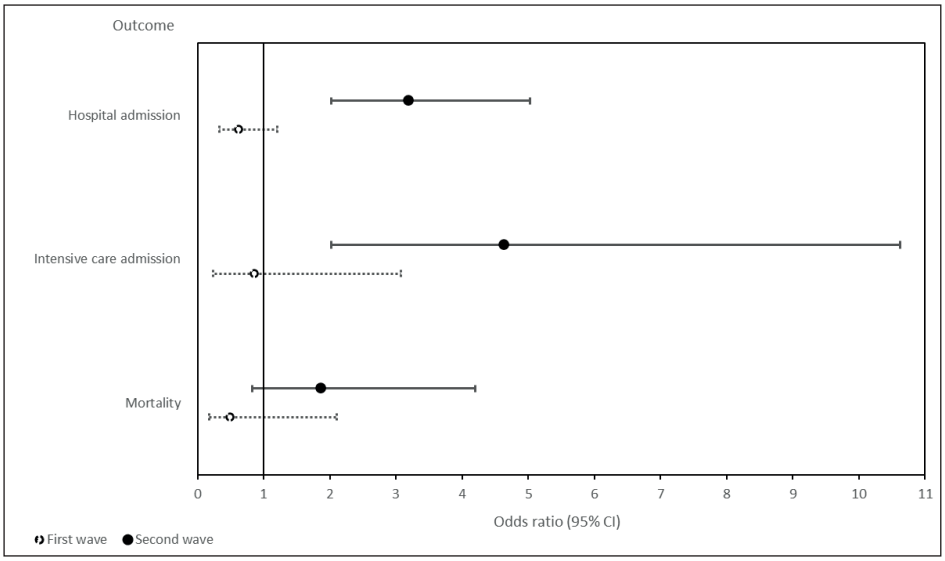
Figure 1. Risk factors associated with receiving an antibiotic prescription*



BMI: Body Mass Index. CI: Confidence Interval.

* Multivariate logistic regression was performed with pooled imputed data and outcomes were adjusted for all risk factors.

Figure 2. Observed outcome after antibiotic prescription for SARS-CoV-2*



BMI: Body Mass Index. CI: Confidence Interval.

* Multivariate logistic regression was performed with pooled imputed data and outcomes were adjusted for all risk factors.

Chapter 5

Cues to improve antibiotic-allergy registration: A mixed-method study

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PLoS ONE 17(4): e0266473

Abstract

Background

Approximately 2% of patients in primary care practice and up to 25% of hospital patients are registered as being allergic to an antibiotic. However, up to 90% of these registrations are incorrect, leading to unnecessary prescription of second choice antibiotics with the attendant loss of efficacy, increased toxicity and antibiotic resistance. To improve registration, a better understanding is needed of how incorrect labels are attributed.

Objective

To investigate the quality of antibiotic allergy registration in primary care and identify determinants to improve registration of antibiotic allergies.

Design

Registration of antibiotic allergies in primary care practices were analysed for 1) completeness and 2) correctness. To identify determinants for improvement, semi-structured interviews with healthcare providers from four healthcare domains were conducted.

Participants

A total of 300 antibiotic allergy registrations were analysed for completeness and correctness. Thirty-four healthcare providers were interviewed.

Main measures

A registration was defined as complete when it included a description of all symptoms, time to onset of symptoms and the duration of symptoms. It was defined as correct when the conclusion was concordant with the Salden criteria. Determinants of correct antibiotic allergy registrations were divided into facilitators or obstructers.

Key results

Rates of completeness and correctness of registrations were 0% and 29.3%, respectively. The main perceived barriers for correct antibiotic allergy registration were insufficient knowledge, lack of priority, limitations of registration features in electronic medical records (EMR), fear of medical liability and patients interpreting side effects as allergies.

Conclusions

The quality of antibiotic allergy registrations can be improved. Potential interventions include raising awareness of the consequences of incomplete and the importance of correct registrations, by continued education, and above all simplifying registration in an EMR by adequate ICT support.

Introduction

Allergies to antibiotics are among the most commonly reported adverse reactions to medication. Adequate registration of these allergies is essential to prevent rare but potentially life-threatening reactions upon re-exposure. In Dutch primary care, 0.6% to 2.1% of patients have an antibiotic allergy registration in their electronic medical record (EMR) [1, 2). Worldwide higher rates of antibiotic allergy registrations have been reported, ranging up to 25% (3). However, between 80 to 90% of antibiotic allergy registrations in primary care are incorrect (1, 4, 5).

Antibiotic allergy registrations are associated with more frequent visits to the doctor, higher healthcare costs and more frequent prescription of second-choice antibiotics (2, 6–8). Importantly, the efficacy and/or toxicity profiles of second-choice antibiotics are generally less favourable compared to the narrow spectrum antibiotics that most often constitute first choice of treatment. The use of broad-spectrum antibiotics also increases risk of Clostridiodes difficile-associated diarrhoea and promotes the emergence of antimicrobial resistance (9).

In The Netherlands antibiotic allergies are registered in all healthcare domains, including primary care, hospitals, pharmacies and long-term elderly care facilities. Primary care physicians play a pivotal role in the registration of antibiotic allergies, since in The Netherlands they function as gatekeeper for entry to most other healthcare fields. Ninety percent of antibiotic prescriptions, and the majority of antibiotic allergy registrations, originate in primary care (10). EMRs kept in primary care contain all essential medical data and function as a central medical record for most other healthcare domains. Antibiotic allergies registered in other healthcare domains are subsequently recorded in the patient's primary care EMR and vice versa, thus facilitating further dissemination of antibiotic allergy registrations from one healthcare setting to the other. The registration of antibiotic allergies transcends primary care practice. Therefore, any effort to tackle this issue should be collaborative and involve all relevant healthcare domains.

Although the quality of current antibiotic allergy registration is known to be insufficient (1, 7, 8, 11), detailed insight into the specific aspects of registration that could be improved is lacking. In addition, a better understanding of the determinants of incorrect antibiotic allergy registration and -in particular- the similarities and differences between healthcare domains is needed. This information will be essential to the effective design and implementation of interventions aimed at improving antibiotic allergy registration.

The primary goals of this study were to analyze the quality of antibiotic allergy registrations in primary care and to identify determinants related to the quality of registration in all involved healthcare domains.

Methods

Study design

The study consisted of a point prevalence analysis of the quality of antibiotic allergy registrations in primary care, together with a qualitative study based on semi-structured interviews to assess the determinants of incorrect registration. Before the start of this study, the study was approved by the institutional Ethics Review Board of the Leiden University Medical Center (file number G19.007).

Analysis of the quality of antibiotic allergy registrations in primary care

Data collection

Patient data were obtained through the Extramural LUMC Academic Network (ELAN), which includes 31 primary care practices in the Leiden-The Hague area and holds primary care data of approximately 200,000 patients. Primary care physicians involved in this network provide access to their anonymized EMRs medical data, that are accessible through the ELAN data warehouse.

Antibiotic allergy registrations were identified based on the following registrations in the EMR: International Classification of Primary Care version 1 (ICPC) code A12 (allergy/allergic reaction) or A85 (adverse event medical agent) or a registration for a contraindication (CIA) label antibiotic allergy for Anatomical Therapeutic Chemical (ATC) code J01 (antibacterials for systemic use). The EMR in primary care supports registration of all relevant details within the allergy label, including symptoms and time course of the reaction. All registrations dated up until the year 2018 were used.

EMRs from primary care and pharmacies are linked and exchange information on antibiotic allergies automatically. The primary care antibiotic allergy label is not electronically linked to the EMR in hospitals nor long term care facilities. Information on allergy labels between primary care and hospitals/long term care facilities is exchanged through referral letters.

Quality analysis of the allergy registration

Quality analysis consisted of an assessment on completeness and correctness of the antibiotic allergy registration in the primary care EMR based on a previously published checklist by Salden et al. (S1 Table) (1). The checklist was modified for one item: the maximal time between start of symptoms and first intake of antibiotic was extended to up to 6 hours for immediate type allergies (See Box 1, Immediate type versus delayed type antibiotic allergy). Assessment was conducted with information available in the registration. A complete registration was defined as a registration that contained a description of symptoms and time to onset of symptoms and duration of symptoms. Antibiotic allergy registrations were then classified as an 'immediate type reaction' (possible/probable), 'delayed type reaction' (possible/probable), 'non-allergic side effect' or 'insufficient data available for diagnosis'. A correct antibiotic allergy registration was defined as a registration in which the conclusion was concordant with the diagnosis according to the modified checklist.

Box 1. Immediate type versus delayed type antibiotic allergy

> Immediate type allergies are IgE mediated reactions. The symptoms are the result of immediate release of histamine and other cytokines upon exposure to an allergen. The most frequently reported symptoms are urticaria, angio-oedema, exanthema, dyspnoea and hypotension, and occur within a few hours. This is opposed to delayed type reactions, which generally develop a few days after exposure, as they are cell-mediated. A mild exanthema is the most frequent delayed type reaction.

To represent daily practice, analysis of antibiotic allergy registrations was limited to the five antibiotic groups most frequently prescribed in primary care in The Netherlands: penicillins, tetracyclines, nitrofuran derivatives (i.e. nitrofurantoin), macrolides and fluoroquinolones (10). A sample of 300 antibiotic allergy registrations was obtained for quality analysis. The size of the random sample was calculated using a random sample formula (12). We used a confidence level of 90% and a margin of error of 5%, including the entire ELAN data warehouse population for each type of registration. These 300 patients were selected through randomisation by SPSS (version 25, SPSS Inc., Chicago, IL). If a patient had multiple antibiotic allergy registrations, one registration was randomly selected and used for further analysis.

Statistical analysis

Analyses were conducted using SPSS, version 25. The prevalence of patients with an antibiotic allergy registration was calculated for all registrations and for the five most frequently prescribed antibiotics groups. Unpaired t-tests were applied to compare continuous variables with normal distributions and reported as a 95% confidence interval (95% CI). Age was reported as a median and with an interquartile range (IQR).

Determinants of correct antibiotic allergy registrations

Semi-structured interviews

To identify determinants of correct antibiotic allergy registration, five interviewers (KB, ML, YA, BH and MS) conducted semi-structured interviews with primary care, hospital care, elderly care and pharmacy healthcare workers in the Leiden and The Hague regions of The Netherlands. This region encompasses a large metropolitan area. This part of the study was conducted and reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (S2 Table) (13).

Participants were selected using a purposive sampling method to represent the healthcare workers in the region who encounter antibiotic allergy registrations, taking into account differences in experience and sex and asked to participate via e-mail or face-to-face (14).

The semi-structured interview (S3 Table) contained questions based on themes from a checklist by Flottorp et al. (15). This checklist describes themes that obstruct or facilitate improvements in healthcare: guideline factors, individual healthcare professional factors, patients factors, professional interaction, incentives and resources, capacity for organisational change, social, political and legal factors.

A pilot interview was performed and followed by semi-structured interviews that were conducted until saturation of answers occurred, with a minimum of 10 interviews (14). Saturation was defined as no new information in three consecutive interviews. At saturation, answers were considered to give a complete overview of all possible answers.

All interviews were digitally recorded after obtaining permission from interviewees and transcribed verbatim. Transcripts were uploaded in Atlas.Ti, version 8, and coded. A three-step plan was used for content analysis. The first step consisted of labelling individual quotes. In step two, labels were coded by theme. In the third and final step, labelled quotes were identified and coded per determinant, and then categorised as either facilitator and barrier. Two researchers (K.B, M.S.) independently performed

the coding. Any discrepancies in coding were resolved by discussion. If consensus could not be reached, a third reviewer was asked to resolve any outstanding issues (F.B.). The identified determinants were structured into a framework according to the themes in the checklist of Flottorp.

Results

Analysis of the quality of antibiotic allergy registrations in primary care

The ELAN data warehouse contained routine registry data on 196,038 enlisted patients (0–102 years) at the time of analysis. The prevalence of registered patients with an antibiotic allergy registration was 3.2% (6368/196,038), encompassing 11,841 antibiotic allergy registrations in total (Table 1). Of the 6368 patients with an antibiotic allergy registration, 2034 had multiple registrations, ranging from 2 to 22 per patient. Penicillin allergy was the most frequently registered antibiotic allergy, 45.0% (95% CI from 44.1% up to 45.9%).

Assessment of 300 antibiotic allergy registrations using the modified Salden checklist showed that none of these registrations were complete (Table 2). Information on the time course of symptoms were missing in 80% of cases. According to the Salden criteria, diagnosis of an antibiotic allergy was correct in 29.3% (n = 88/300) of registrations (Table 3). In 14.3% (n = 43/300) of cases, a non-allergic reaction was incorrectly registered as an antibiotic allergy.

Semi-structured interviews

In total, 31 primary care physicians (PCP), 4 medical specialists (MS), 11 Elderly Care physicians (ECP), 5 elderly care nurses (ECN) and 4 Pharmacists or pharmacy technicians (PH) were invited to participate. Data saturation was reached after interviews with 10 PCPs, 4 MSs, 11 ECPs, 5 ECNs and 4 PHs, of whom 56% was female and 53% had more than 10 years' experience. The MS consisted of a surgeon in training, a hospital physician and 2 gastroenterologists. Transcripts were analysed according to the three-step plan described in the methods (Fig 1 and Table 4).

Individual characteristics of care providers

All healthcare providers stated that side effects were sometimes registered as allergies, with the interviewees explaining that side effects were interpreted as allergies either due to lack of knowledge, medical uncertainty and/or fear of medical liability. In all

domains, healthcare providers admitted a lack of knowledge regarding distinguishing side effects from various types of antibiotic allergies. Interviewees who were aware of the issue of incorrect antibiotic allergy registrations, were more likely to verify existing registrations. They also indicated that these processes require education concerning antibiotic allergies and expressed a wish for more educational opportunities.

Patient factors

Patient factors, such as cognitive impairment or aphasia, hinder verification and classification of previously registered allergies. This problem was mentioned in particular by ECPs. According to interviewees, the patient's preferences and personal interpretation of symptoms lead to incorrect registrations. Patients sometimes prefer not to be prescribed a specific antibiotic based on previous experiences, i.e. side effects. This can lead to incorrect antibiotic allergy registration, but prevents patient exposure to the antibiotic.

Professional interactions

Interviewed PCPs reported hardly any problems regarding communication of antibiotic allergies with other healthcare providers both ways, stating that most communication was digital through their EMRs and was sufficient in their opinion. Interviewed PCPs also mentioned that more elaborate communication was mainly confined to pharmacists but was hindered by lack of time. Other healthcare providers occasionally experienced difficulties in communication, stating that EMR registrations were sometimes incomplete, referral letters were missing essential details. Reaching other healthcare providers to obtain missing information was time-consuming. Together, these issues made it difficult to verify an antibiotic allergy registration. According to PCPs, another barrier for correct registration of antibiotic allergies was limited availability or access to diagnostic tests, in addition to (presumed) long waiting lists for referral to an allergist.

Incentives and resources

Lack of time hindered complete and correct registration of new antibiotic allergies. Furthermore, lack of time often led to healthcare providers failing to verify whether an existing antibiotic allergy registration was correct.

Many different EMR systems are in use in The Netherlands. According to interviewees, all EMR systems presented greater or lesser difficulties when registering a reaction, and EMR systems did not support a clear distinction between a side effect/ intolerance and

allergy. Both registration of a new allergy and retrieval of information on previously reported allergies is time consuming. Interviewees mentioned that miscommunication between different EMRs resulted in missing information and hindered removal of incorrect antibiotic allergy registrations.

None of the interviewed healthcare providers used a protocol or specific procedure for registering antibiotic allergies, although some expressed a wish for a guideline. According to the interviewees, a guideline should be accompanied by a decision support system in an EMR and together these were seen as an effective solution.

Capacity for organizational change

Incorrect antibiotic allergy registrations were not deemed to be problematic by PCP's and hence they gave little priority to improving the verification of existing antibiotic allergies. They stated there is "no need as there is always an alternative antibiotic available". In contrast, ECPs more frequently perceived allergy registrations as a problem as they frequently encountered patients with multiple antibiotic allergy registrations, hindering the selection of an appropriate antibiotic. An ECP also commented that high staff turnover impeded the necessary changes in policy to ensure correct registration of antibiotic allergies.

Social, political and legal factors

One interviewee also stated that, based on previous personal experience, fear of medical liability can lead to incorrect registration of antibiotic allergies or omission to remove a previous registration.

Discussion

The main finding of our study is that in the majority of cases (56.3%) recorded information was insufficient to determine whether the reaction was of an allergic nature. Main causes of insufficient quality of registrations were lack of knowledge, lack of priority, limitations of registration features in EMRs and patients interpreting side effects as allergies.

Analysis of the quality of antibiotic allergy registrations in primary care

Our study provides detailed new insight into what is lacking in antibiotic allergy registrations. In our quality assessment, non-allergic reactions interpreted as antibiotic allergic reactions accounted for 14.3% of all registrations, a figure comparable to the 11.7% reported by Salden et al. (1). This is however an underestimate of the actual number of reactions that are incorrectly labelled as an allergy: 56.3% of antibiotic allergy registrations lacked essential information such as a description of symptoms, their time of onset and/or duration. Such detailed information is needed in order to determine the type and severity of the reaction and to be able to decide whether an antibiotic can be prescribed safely.

Although delayed type reactions cause discomfort, they are rarely life-threatening except in very rare cases such as Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). Risk of recurrence of a mild delayed type reaction is low and there is no additional risk of an immediate type reaction with the exception of severe cutaneous adverse reactions (16). Therefore, a mild delayed type reaction would not be an absolute contra-indication for the antibiotic in question. To be able to decide on re-exposure, a complete antibiotic allergy registration is needed. When the details of the reaction can't be retrieved, for example if the patient does not remember and there is no documentation, this should be indicated in the EMR.

Determinants of incorrect antibiotic allergy registration

Health care providers' lack of knowledge regarding the differentiation of allergic versus non-allergic reactions was perceived as a major determinant of incorrect registration. Similar findings were reported in one primary care study and two studies of hospital doctors (17–19). Improved education of healthcare providers registering antibiotic allergies is a possible solution to overcome incorrect interpretations.

Interviewees from all domains perceived patient related factors as important determinants of incorrect antibiotic allergy registrations. Firstly, patients may not remember the details of the reaction, especially if the reactions occurred in remote childhood. Secondly, patients may interpret side effects as an allergy and express a wish not to receive a particular antibiotic in the future, often resulting in the incorrect registration of an antibiotic allergy. A study by De Clercq et al. reported similar findings in primary care (17). Interviewees also stated that a clear explanation and effective communication with the patient can help to avoid an incorrect registration. Patient-orientated research in which patients are interviewed concerning their experiences

of side effects and antibiotic allergic reactions is needed to gain more insight into this particular determinant. These findings might then be used to design and implement patient-directed interventions.

In this study, unawareness of the problem of incorrect antibiotic allergy registration and its consequences was an issue in all healthcare domains, especially in primary care. While most PCPs were unaware of the problem of incorrect registration of allergies, ECPs by contrast regularly encountered patients with multiple antibiotic allergy registrations, severely hindering the prescription of the correct antibiotic. Multiple antibiotic allergy registrations are most likely the result of lifelong collection of registrations. The lack of awareness is concordant with earlier reports in primary and hospital care and suggests that greater awareness is needed to change the behaviour of healthcare providers (6, 7, 20). In a study by Schouten et al., improved awareness played a key role in removing barriers to optimal antibiotic therapy in a hospital setting (21). Interventions to improve antibiotic allergy registrations should therefore focus not only on improving knowledge but also on increasing awareness.

Another important perceived determinant was the failure of EMR software to support the quick and accurate registration of symptoms and their time-course. EMR software developers need to simplify registration and allow a distinction between allergy or side effect (17).

Some interviewees suggested development of a guideline accompanied by a clinical decision making system in the EMR. A study by Blumenthal et al. showed that this type of system can indeed improve the registration of antibiotic allergies in a hospital setting (22). Most incorrect antibiotic allergy registrations can be safely removed with a thorough history with or without a provocation test (23). In most cases skin testing is not needed. Guidelines on the clinical approach of a potential antibiotic allergy and removing of incorrect antibiotic allergies are highly needed.

To a greater or lesser extent, domains mostly shared the same determinants. This supports the development of interventions that transcend the individual healthcare domains. For example, educational programs may be developed targeting all domains, with the aim to improve knowledge, but also interdisciplinary communication and collaboration. Furthermore, ICT registration and decision tools could be developed to support both primary care and hospital care.

Validity and limitations

A strength of our quality analysis was the use of routinely registered medical data from primary care. This data reflects daily practice regarding the registration of antibiotic allergies. A strength of our interviews was the inclusion of healthcare workers from all domains that register antibiotic allergies, hence providing a complete overview. A comprehensive approach is important as antibiotic allergy registrations clearly transcend the individual domains. The relevance is illustrated by the determinants that were identified regarding the interactions between healthcare domains and individual healthcare professionals.

An advantage of semi-structured interviews is that it allows an interviewer the freedom to pursue more in-depth answers to specific questions, without compromising the comparison of interviews. One limitation of our semi-structured interviews was possible interviewer bias. Conscious or unconscious, an interviewer input may have influenced respondent answers. Participation bias may have also impacted our results, as participants with an affinity for or interest in antibiotic allergies may be more likely to participate in a study of this type. However, participating interviewees were diverse in terms of gender and experience and accurately represented healthcare providers.

Conclusion

Incorrect antibiotic allergy registration is a multifactorial and cross-domain problem. The causes are poor registration of symptoms and their duration, insufficient knowledge, lack of awareness and suboptimal communication between healthcare domains and ICT systems. Improving allergy registrations should be an antimicrobial stewardship priority and interventions should have a domain-transcending approach.

Tables

Table 1. Characteristics of patients with an antibiotic allergy registration.

	Cohort of patients with an allergy registration	Random selection of 300 allergy registrations
Patients (n)	6368	300
Patients with multiple registrations (n)	2034	0
Sex % female (n)	73.1% (4655)	73.3% (220)
Age at diagnosis of first antibiotic allergy registration (min-max years)	0-102 (median 51 years, IQR 31-68 years)	0-98 years (median 50 years, IQR 32-67 years)
Antibiotic allergy registrations (n)	11,841 (100%)	300 (100%)
Penicillins % (n)	45.0% (5323)	61.3% (184)
Tetracyclines % (n)	7.7 % (912)	10.0% (30)
Nitrofuran derivatives % (n)	10.3% (1224)	16.7% (50)
Macrolides % (n)	6.7% (793)	8.0% (24)
Fluoroquinolones % (n)	5.4% (641)	4.0% (12)
Other %	24.9% (2948)	0 (0)

95% CI, 95% confidence interval; IQR, Interquartile range.

Table 2. Analysis of a random selection of antibiotic allergy registrations for completeness and correctness.

Noted in registration	Total (n=300)
Registration of substance*	93.7% (281)
Time to start of symptoms†	20% (60)
Duration of symptoms‡	7.3% (22)
Description of symptoms§	46.3% (139)
Hospital admission|	0% (0)
Allergy test¶	0% (0)
Prescribed again#	20.3% (61)
Type of allergy**	0% (0)

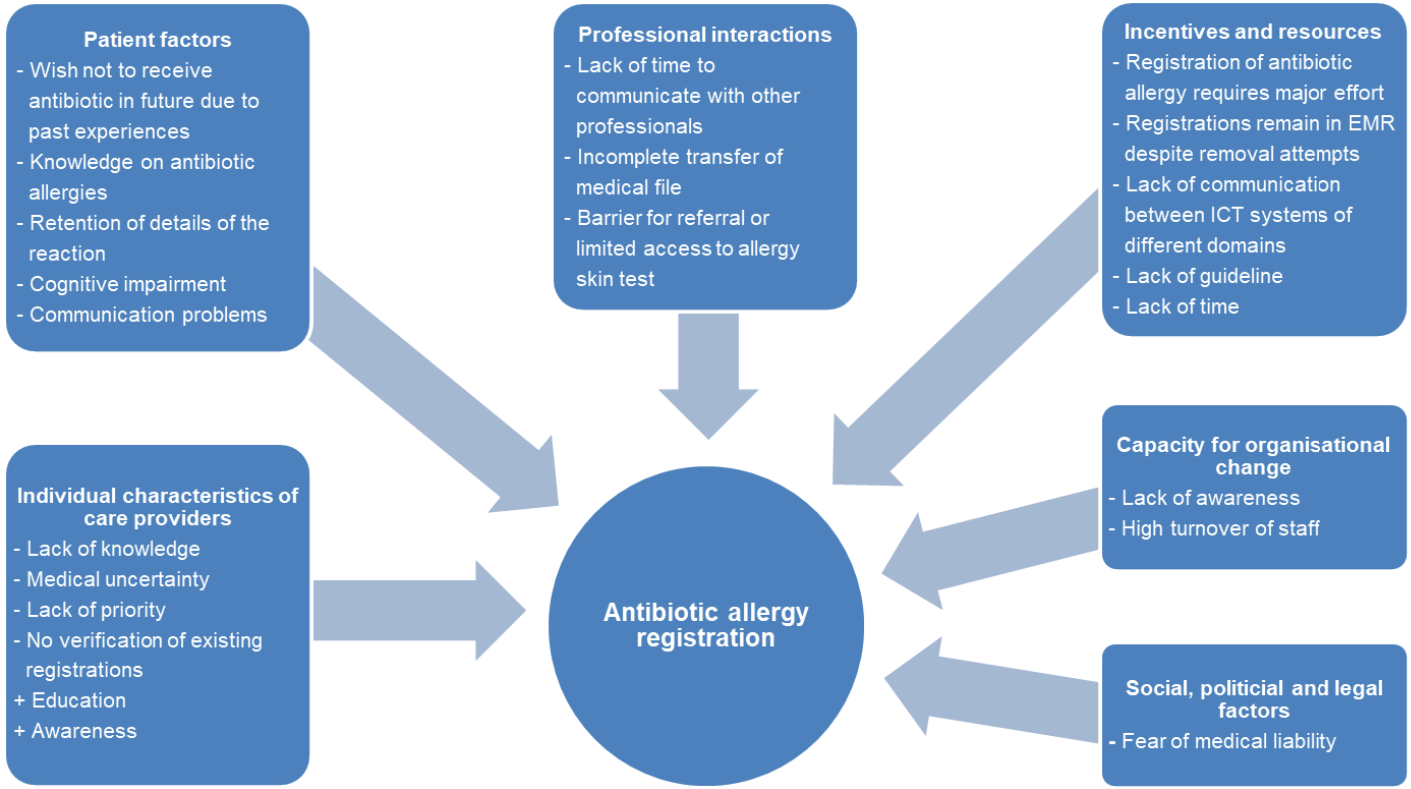
*Antibiotic was specified in registration.
†Time between first intake of antibiotic and start of symptoms.
‡Duration of symptoms after first intake of antibiotic.
§Description of symptoms present in registration.
|Registration of whether hospital admission was needed to treat antibiotic allergy reaction.
¶Registration of whether an allergy test was performed
#Antibiotic for which an allergy was registered was prescribed again after registration.
**Type of allergic reaction was specified in registration: immediate versus delayed type.

Table 3. Type of allergic reaction according to modified checklist of Salden*.

Type of reaction	Total (n=300)
Immediate type reaction probable	0% (0)
Immediate type reaction possible	2.0% (6)
Delayed type reaction probable	0% (0)
Delayed type reaction possible	18.3 % (55)
No distinction possible between immediate or delayed reaction	9% (27)
No allergic reaction	14.3% (43)
Type of reaction could not be determined	56.3% (169)

*Information in registrations was compared to modified checklist of Salden, see S 1 Table for details.

Figure 1 Determinants of antibiotic allergy registration:



Legend: + = facilitator; - = barrier; EMR: Electronic Medical Record; ICT: Information Communication Technology

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Supplements

S1 Table. Modified checklist of Salden*

Time to symptoms	Immediate type probable < 6 hours	Immediate type possible < 6 hours or unclear	Delayed type probable > 6 hours	Delayed type possible > 6 hours or unclear	Immediate/ delayed type Possible > 6 hours or unclear	Non-allergic reaction > 14 days OR any time
	AND	*AND*				*AND*
Symptoms						
Urticaria	Yes and/or	Yes and/or	No	No	Yes and/or	No
Angio-oedema	Yes and/or	Yes and/or	No	No	No	No
Rash or exanthema	Yes and/or	Yes and/or	Yes	Yes	Yes and/or	No
	AND TWO OF 1-5	*AND ONE OF 1-3 OR 5*				
1 Dyspnoea	Yes	Yes	No	No	No	No
2 Collapse	Yes	Yes	No	No	No	No
3 Nausea, vomiting or diarrhoea	Yes	Yes				
			AND ONE OF 4-5			*AND/ OR*
4 Repeated reaction when re-exposition to same antibiotic	Yes	No	Yes	No	No	No
5 Confirmed by dermatologist/ allergist	Yes	Yes	Yes	No	No	No

*Checklist is from Salden OA, Rockmann H, Verheij TJ, Broekhuizen BD. Diagnosis of allergy against beta-lactams in primary care: prevalence and diagnostic criteria. Family practice. 2015;32(3):257-62.

S2 Table. COnsolidated criteria for REporting Qualitative research* checklist

Topic	Item No.	Guide Questions/Description	Answers
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/ facilitator	1	Which author/s conducted the interview or focus group?	Five interviewers (KB, ML, YA, BH and MS) conducted semi-structured interviews
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	Karolina K. Braun, MD[1] Merel M.C. Lambregts, MD[2] Youssra Atmani, MSc[1] Bart J.C. Hendriks, MPharm[3] Martijn Sijbom, MD[4]
Occupation	3	What was their occupation at the time of the study?	Medical student Medical specialist Pharmacist Primary care physician
Gender	4	Was the researcher male or female?	Two were male (M.S. and B.H.).
Experience and training	5	What experience or training did the researcher have?	Interviewers had training in conducting semi-structured interviews.
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	Prior to the interviews, two interviewers (M.L and B.H.) had a working relationship with some participants, either in a hospital or in a pharmacy.
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research.	Participants were told that the interviews were conducted to collect data on improving antibiotic allergies registrations.
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic.	Goal of interviewers was to improve antibiotic allergy registration.
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis.	Content analysis was used.
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Purposive sampling was used.

Topic	Item No.	Guide Questions/Description	Answers
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	Participants were approached through mail and face-to-face.
Sample size	12	How many participants were in the study?	34
Non-participation	13	How many people refused to participate or dropped out? Reasons?	0
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace.	Interviews were conducted with participants at their workplace.
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	No other persons were present.
Description of sample	16	What are the important characteristics of the sample? e.g. demographic, data, date	10 PCP's, 4 MS, 11 ECP's, 5 elderly cares nurses and 4 PH's participated of whom 56% was female and 53% had more than 10 years' experience.
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	The semi-structed interview is included as supplement 3. A pilot interview was performed.
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	34
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	All interviews were digitally recorded.
Field notes	20	Were field notes made during and/or after the interview or focus group?	No notes were taken during interviews.
Duration	21	What was the duration of the inter views or focus group?	An interview took around 20 to 30 minutes
Data saturation	22	Was data saturation discussed?	Yes, no new information from answers in 3 consecutive interviews
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	Participants were not asked to comment on or correct the transcribed interview or to provide feedback on the outcome
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	Two, Karolina K. Braun and Martijn Sijbom.
Description of the coding tree	25	Did authors provide a description of the coding tree?	No
Derivation of themes	26	Were themes identified in advance or derived from the data?	In advance, through the checklist of Flottorp.[†]
Software	27	What software, if applicable, was used to manage the data?	AtlasTi, version 8

Topic	Item No.	Guide Questions/Description	Answers
Participant checking	28	Did participants provide feedback on the findings?	No
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	In table 4.
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Yes
Clarity of major themes	31	Were major themes clearly presented in the findings?	Yes
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Yes

*Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357

†Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Implementation science : IS. 2013;8:35.

S3 Table. Semi-structured interviews

Name of interviewee:
Position:
Institution / practice (solo / group / other):
Years of experience:
Trainer of medical specialist (MS)/ primary care physician (PCP):
Region:
Patient population (Education level / Social Economic Status / Ethnicity / language barrier):
Electronic Medical Record (EMR) System: (His / Hix / OmniHis / Medicom / MicroHis / HIX other?)

General

- Regarding the term antibiotic allergy registration, what do you think about it and what are your thoughts / associations? How do you feel about that?

Registration of antibiotic allergies in practice

- How do you inquire about antibiotic allergies?
  - Who inquires and records the allergy?
  - Do you inquire standard or only on indication? For example, when registering a new patient in your practice / institution?
  - Are there agreements about registration within your practice?
  - If yes, explain the method.
  - Do you use it?
  - If so, how does it work in practice?
  - Is the working method clear (defined) to you?
  - Who made the agreements?
  - Are the agreements accessible according to you?
  - Are the agreements practical?
  - What are the agreements based on?
  - Are the agreements comparable with other guidelines?
  - How reliable do you think the current working method is?
  - Is information requested from other institutions, if an allergy is reported?
  - How do you register antibiotic allergies (within your institution)?
  - What method do you use for registration?
  - What is registered (for example, means, type of reaction / evaluation, date, time between administration and occurrence, etc)?
  - How can antibiotic allergy information be found in the system (HIS) you use?
  - Warnings when prescribing? Banner? How can details be found?
  - Is a clear distinction possible between an allergy and a side effect?

- Are you satisfied with your current registration system / method?
- What are the advantages and disadvantages of the registration system / method with regard to allergy registration?
- How can you improve the system?
- Is the improvement feasible?

Dealing with suspected antibiotic allergy

- How do you deal with a suspected allergy?
  - With a patient who does not need antibiotics at that time?
  - With a patient who does need antibiotics?

Problems with registering antibiotic allergies in practice

- To what extent are incorrect allergy registrations a problem?
- Are you able to judge whether an allergy registration is correct or incorrect?
  - How do you do that?
  - When are you able/ are you not able?
- Do you run into incorrect or incomplete allergy registrations at your institution / practice?
  - Which one?
  - Incomplete / incorrect?
  - To what extent?
  - What will be done if there is doubt about whether or not an allergy registration is justified?
  - Do you ever leave allergy registration in doubt?
- What do you think are possible causes of incomplete / incorrect registrations?
- What would be the solutions?
- Have previous actions been taken to improve registrations? Which?
- How could you check whether a registration is correct?
  - Is it feasible?

Delabeling of incorrect allergies

- What do you do if there is doubt of an allergy registration is incorrect?
- When will an allergy be sorted out?
- Would you be willing to remove an allergy registration from an EMR? What problems do you encounter?

Communication about allergies with other institutions

- Is information about allergies shared with other healthcare institutions / providers?
  - And how?
  - Is there a need for that: how / who?
  - Is an allergy in a referral letter included as standard in the episode list?
- How could communication be improved?
- Is there ever feedback from another healthcare provider that the patient has an (alleged) antibiotic allergy?
  - How do you deal with this? (check EMR/ enter registration / ask the patient?)
  - Do you sometimes communicate an (alleged) incorrect antibiotic allergy registration to other heathcare providers?
- How is communication between healthcare providers going?
  - What is going well?
  - What is not going well?
  - What do you think is needed to improve communication about antibiotic allergy?

Patient perspective

- To what extent does the patient's presentation of symptoms affect the interpretation and registration of a suspected antibiotic allergy?
- Which factors (knowledge / education / experience of illness) determine the presentation of the symptoms?
- To what extent do you think previous experiences and preferences of patients determine the process of antibiotic allergy registration? (Explain this).
- Are there other patient-related factors that can influence registration?(language barrier, culture, media, guidelines from abroad)
- Could patient explanation about antibiotic allergy contribute to correct registrations?

Possible areas for improvement regarding the registration of allergies

- What suggestions do you have to improve registrations? (Training / ICT / Communication / documentation / protocols / website)
- How do you estimate the chance of improvement? (is it feasible? Realistic?)
- What could hinder or facilitate the improvement? (finance, knowledge, time, facilities, opinion / belief / habit and cognitions, management, effort)?
- Are you motivated to improve the allergy registration system in your practice?

Need for training / guidelines

- Is there a need for training in the field of allergies / communication / skills? (do you need it yourself?)
  - Focus on which aspects?
  - Which form? (e-learning, classroom, webinar)
- Is there a need for general guidelines with regard to allergy registration?

Chapter 6

Routine data registries as a basis to analyse and improve the quality of antimicrobial prescription in Primary Care

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Submitted

Abstract

Introduction

Antimicrobial resistance (AMR) is increasing worldwide, largely due to the overuse of antimicrobial medication. In most countries, 80-90% of antimicrobial prescription originate from primary care. With the goal of examining the quality of prescription, we explored its determinants in combined data from a primary healthcare registry and a national socioeconomic database.

Methods

Pseudonymized routine healthcare data from 269,547 patients (1,150,252 antimicrobial prescriptions) gathered between 2012 and 2020 from primary care practices in the region The Hague – Leiden were used. These data were linked with individual socioeconomic data to identify determinants of antimicrobial prescribing. The quality of prescription was analysed using predefined criteria based on primary care guidelines. Multivariable logistic regression analyses were performed to identify associations with appropriateness.

Results

Respiratory tract infections (RTI) were most commonly associated with overprescribing, with 14.5% of RTI prescriptions not following guidelines. For macrolide prescriptions, 77.1% did not correspond with first and second guideline choices. Certain migration backgrounds, female gender, comorbidities, age, and primary care practice size, a proxy for continuity of care and consultation time per patient, were associated with poorer guideline adherence.

Discussion

Combined analyses of socioeconomic and routinely collected healthcare data does reveal relevant additional information to answer medical questions in a broader context, such as AMR. Most room for improvement was found for RTIs and macrolides, especially in specific risk groups. Assuring continuity of care and/or providing extended consultation time per patient might be essential elements to establish, before disseminating and implementing improvement strategies.

Introduction

Antimicrobial resistance (AMR) is increasing worldwide and is a major threat to global health (2). The leading driver of AMR is the use of antimicrobials (3). The vast majority (between 80 and 90%) of antimicrobials for use in humans is prescribed in primary care (4). Although development of multi-resistant bacteria and other consequences of AMR occur mainly in hospitals, the role of primary care as the source of the increase in AMR is larger than previously assumed, presumably through antimicrobial selection pressure in the wider population (5). Improving the quality of antimicrobial prescription in primary care may play an important part in avoiding further increase of AMR.

Healthcare registries harbouring routinely collected healthcare data, such as electronic medical records (EMR) composed in primary care practices, are increasingly made available for research purposes. Combining those with several other large public dataset sources, do arise new opportunities for AMR research and data-driven healthcare. However, the responsible utilization of large registries that consist of routinely collected healthcare data presents challenges, such as non-ordered and unstructured crude data as well as the need to bring together data from different sources at the patient level. Currently, there is limited understanding of how large healthcare registries of routinely collected data can be combined and used in AMR research. In our current study we explore the feasibility and describe methods that can be used regardless of prescription rates, making our findings applicable for countries with either high or low antimicrobial prescription rates.

Although the number of antimicrobial prescriptions in The Netherlands is low compared to most other European countries (6), AMR has even increased in The Netherlands over the last 10 years (7). To illustrate our definition of a low prescription rate: the number of antimicrobial prescriptions in Dutch primary care was 8.7 defined daily doses (DDD) per 1000 patients per year. By contrast, the average number of prescriptions in European primary care was 16.7 DDD/1000 patients per year (6).

To improve prudent antimicrobial prescribing, we need to identify determinants of (in)appropriate antimicrobial prescribing on patient and practice level. These determinants may then allow us to define specific risk groups and to identify specific elements in a primary care practice that might be the target of antimicrobial stewardship interventions. Previously established determinants include female gender and presence of comorbidities (8-10). However, information on socioeconomic context and primary care practice characteristics as potential determinants is lacking.

The aim of our current study was to combine and use large registries to help identify patient - and practice associated determinants of antimicrobial prescribing and cues for further improvement. Our approach was to follow the number and trends of antimicrobial prescriptions for primary care patients with an acute infection over a period of ten years.

Methods

Study design and setting

In this observational study, we analysed antimicrobial prescriptions in primary care for appropriateness, based on a large set of routine healthcare data combined with socioeconomic data from Statistics Netherlands (SN) over a period of ten years. As the aim of the study was to examine trends in antimicrobial treatment of acute infections, prophylactic antimicrobial prescriptions with the intention to prevent infections (like recurrent urinary tract infections), were excluded. The potential determinants selected for analysis were derived from a previously conducted literature review (1). The study was approved by the Medical Ethical Review Committee of Leiden University Medical Centre (file number G20.020).

Data collection through combining two large registries

This study used pseudonymized routine healthcare data derived from a data registry covering EMR data from approximately 450,000 patients. Patient EMR data registered from 2012-2021 were extracted from 115 primary care practices affiliated with the Extramural LUMC Academic Network (ELAN), located in the Leiden-The Hague area of The Netherlands (the northern part of the province of South Holland). This network covers 2.6% of the general Dutch population, and previous studies have established that patient data from the network are well generalizable to the average Dutch population (11, 12). Primary care practices involved in the network provide continuous access to the pseudonymized EMR data of their practice population. An informed patient opt-out procedure concerning use of pseudonymized data for research and population health management is in place. Patients have been informed in writing about use of their pseudonymized data. The Medical Ethical Review Committee of the LUMC regards the opt-out procedure as written consent from patients. Using data from the ELAN data warehouse, the comorbidities (Supplement 1) and antimicrobial allergies of each patient were linked to each antimicrobial prescription. Statistics Netherlands (SN) hosts the other database, we were able to link data from both databases on a pseudonymized individual level. SN collects data on individual Dutch inhabitants both databases are

available to researchers in a secure environment (www.cbs.nl). Data from SN concern household income, migration background and number of parents in each household.

Oral antimicrobial prescriptions in the ELAN data warehouse were identified through Anatomical Therapeutic Chemical (ATC) code J01. All oral antimicrobials with ATC code J01 primarily prescribed by a primary care practice between 2012 and 2021 were included. International Classification of Primary Care (ICPC) codes included with the prescription were used to define the reason for prescribing the antimicrobial. In Dutch primary care in our network, ICPC codes version 1 is used to systematically classify symptoms and diseases.

Data analysis

Antimicrobial prescriptions were analysed using a syntax for appropriateness, which was defined as a prescription in accordance with prevailing Dutch primary care guidelines at the time of prescription (Supplement 3)(13). Antimicrobial prescriptions with an ICPC code corresponding with an infection were included in the analysis on appropriateness. An antimicrobial prescription was considered appropriate if the ICPC code accompanying the prescription matched an indication for an antimicrobial prescription in the Dutch primary care guidelines. If the ICPC code was missing or obviously registered incorrectly, for example for hypertension, the antimicrobial prescription was excluded from the examination on appropriateness and further analysis. In a separate analysis, the choice of an antimicrobial corresponding to the first or second choice antimicrobial in the prevailing guideline was viewed as corresponding to the guideline (Supplement 4). In case of a presumed antimicrobial allergy, Dutch primary care guidelines recommend a third choice. If a patient had an antimicrobial allergy registration for the first and/or second choice antimicrobial, the prescription of this third choice was classified as corresponding to the guideline. The variable 'appropriateness' was categorized as dichotomous, using appropriate as the reference category.

Primary outcomes were the number of appropriate and inappropriate antimicrobial prescriptions per year over the period 2012-2021. In the ELAN Datawarehouse we identified 1,496,461 unique oral antimicrobial prescriptions by all primary care practices (Supplement 2), of which 122,659 (8.2%) were identified as prophylaxis and subsequently excluded from further analysis. Prescriptions in the year 2021 (n=79,418) were not included because annual data for 2021 were not complete. As SN had no data available for 35,321 patients (with 144,312 antimicrobial prescriptions), these prescriptions were also excluded. In total, 1,150,252 antimicrobial prescriptions for 269,574 unique patients were included in the analysis, as shown in a flowchart (Supplement 2).

Determinants

An earlier systematic literature review was conducted to identify determinants associated with appropriate antimicrobial prescribing (1). Following that review, other potential determinants not yet investigated were defined, including migration background, household income, number of parents per household and day of antimicrobial prescription.

Patient level

Included determinants on patient level were age, gender, comorbidity, migration background, household income and number of parents in household. Comorbidities that implied an immunosuppressed state, as listed in supplement 1, were merged into a composite comorbidity variable. For the calculation of this composite variable the presence of each comorbidity was counted as 1, added together as a count variable and referenced against the absence of comorbidities. We defined 4 comorbidity categories: 0, 1, 2 and 3 or more, and defined patients with 3 or more comorbidities as 1 group.

Household income was divided into 3 groups based on the definition of the Dutch Standardized Income (14). In The Netherlands 33,500 euro per year was the modal household income between 2012 and 2022 (14). Our low income group had a household income of < 33,500 euro and was used as a reference group. Our middle income group had a household income between 33,500 and 67,000 euros and our high income group had a household income of > 67,000 euro. Migration background was defined by SN as the country with which a person is connected based on the country of birth of one's parents or oneself (15). Migration background was categorized into seven groups according to SN definitions: Dutch, Dutch-Caribbean, Moroccan, Surinamese, Turkish and Global South and Global North. A Dutch background was used as the reference group. Number of parents in household was classified as a dichotomous variable of either one or two parents, with a two-parent household as the reference group.

Practice level

Included determinants on the General Practice level were practice population size and day of prescription. During the study period, a primary care practice size of 2,168 patients was defined as the norm for The Netherlands by the Dutch Healthcare Authority (16). For the analyses, primary care practices were categorized into three groups according to the average size of their practice. A small practice was defined as <2,168 registered patients (and used as a reference), a medium size practice had

between 2,186 and 4,336 registered patients, and a large practice had >4,336 registered patients. Primary care practices were defined as outliers if the number of antimicrobial prescriptions was lower than 120 or higher than 750 antimicrobial prescriptions per 1000 patients per year. These outliers were attributed to incomplete EMRs. Data from these practices were not used in the final multivariable regression analyses. Day of prescription was divided into Monday-Thursday or Friday. The variable was categorized as dichotomous and Friday was used as the reference day of prescription.

Statistical analyses

Descriptive statistics were used to describe variables and trends of antimicrobial prescribing. Paired sample t-tests were performed to test for statistically significant differences ($p<0,05$) between number of antimicrobial prescriptions per year and the day of antimicrobial prescribing. Multivariable logistic regression analyses were performed to examine potential associations of the determinants with appropriate antimicrobial prescribing using four different models. Model 1 included gender (ref=female) and age (ref=0-4 years). Model 2 additionally included migration background (ref=Dutch). Model 3 added number of parents in household (ref=2 parents), household income (ref=low income) and number of comorbidities (ref=0 comorbidities). Model 4 additionally included size of primary care practice (ref=small size) and day of prescription (ref=Friday). Furthermore, a multivariable logistic regression analysis using model four was conducted. This analysis examined possible associations of determinants of appropriate antimicrobial prescribing for RTIs only. To check for possible bias due to missing patient data in SN database, a multivariable regression analysis was conducted that included patients with no determinants in the SN data.

Results

Trend of antimicrobial prescriptions

In our analyses, we included 1,150,252 antimicrobial prescriptions for 269,574 patients (56.7% female gender) (Table 1), with Dutch as the most prevalent migration background (69.3%). Approximately 50% of patients had a low income or were registered in a medium sized primary care practice. Fourteen primary care practices were excluded from the multivariable regression analysis, as data were missing on the total number of registered patients. The average number of antimicrobial prescriptions between the years 2012-2019 was 131,311 per year (range 124,154 – 138,255). In 2020 there were 99,762 antimicrobial prescriptions, which is a statistically significant decline

in the number of prescriptions compared to all previous years ($p<0.05$) (Figure 1). A statistically significant difference was found for day of the week, with antimicrobial prescriptions on Monday (242,487) and Friday (240,469) dominating compared to other weekdays, which varied between 194,704 and 211,276 prescriptions. Penicillins were the most prescribed antimicrobial group for every year of the study period (Figure 2).

Antimicrobial prescriptions according to guideline recommendations

Antimicrobial prescriptions with an ICPC code totalled 673,909, of which 585,117 had an ICPC code corresponding to an infection. Table 2 and table 3 show the distribution of determinants for appropriate and inappropriate antimicrobial prescriptions. Prescriptions classified as appropriate amounted to 480,792, compared with 104,325 inappropriate prescriptions. Urinary tract infections (UTI) (37.2%) and RTIs (36.2%) were the most common reason for an antimicrobial prescription. A substantial number of antimicrobial prescriptions were for RTIs and categorized as inappropriate (14.5%). Amongst prescriptions for RTIs alone, 39.6% were therefore classified as inappropriate (Figure 3). For the 480,792 appropriate antimicrobial prescriptions, 72.3% (347,846) corresponded with guidelines for the first or second choice antimicrobial for the diagnosis. With regard to macrolides, 41,363 appropriate prescriptions were for these compounds, of which over three-quarters (77.1%) were not the first or second choice according to Dutch primary care guidelines (Figure 4).

Determinants

Female gender, age of five years or older, a Turkish-, Surinamese- or Dutch- Caribbean background, a household with one parent, presence of comorbidities, a medium or large primary care practice size and Friday as day of prescription, were positively associated with antimicrobial prescription, meaning over prescription (Table 4). A Moroccan migration background was associated with relatively more appropriate antimicrobial prescriptions compared to a Dutch background. There was no association of household income with appropriateness (Table 4). Determinants associated with antimicrobial overprescribing for RTIs included male gender, age 5 years or older (except age group 15-44 years), Turkish, Surinamese or Dutch Caribbean background, a low household income, presence of a comorbidity, larger primary care practice and weekdays other than Friday as day of prescription (Table 5). A check for bias through a multivariable regression analysis that included patients without data in the SN data did not show different outcomes (Supplement 5).

Discussion

A primary goal of this study was to combine and to use two large registries to identify and determine the number of antimicrobial prescriptions in primary care and the determinants of appropriateness in prescription. Antimicrobial prescriptions were subsequently defined as appropriate or inappropriate following guidelines, and linked with potential determinants of appropriateness. By combining data from two large registries (ELAN and SN) at an individual patient level, we were able to explore associations of several determinants with appropriateness that are not registered in an EMR. Our principal findings were: 1) the highest rate of antimicrobial overprescribing, in both number and proportion, was for RTIs, 2) most prescriptions of macrolides did not correspond with the 1st and 2nd choice in guidelines, and 3) determinants including female gender, age 5 years and older, migration background (Turkish, Surinamese, Dutch-Caribbean), and a large primary care practice size were all associated with antimicrobial overprescribing.

Large registries

A major strength of our study was that we were able to identify potential determinants of antimicrobial prescription in the context of the patient by combining routine healthcare data with individual socioeconomic - and context data from SN. The use of routine healthcare data for medical research has many advantages, as it provides relatively easy access to rich, ecologically valid, longitudinal data from large populations (67). In other words, it potentially more accurately reflects daily practice in accordance with our aim of understanding patterns of daily antimicrobial prescribing in primary care (17). Combining primary care EMR data with data from SN allowed us to explore novel associations such as migration background, household income and number of parents per household, data that are not routinely recorded in an EMR.

A potential downside of routinely collected healthcare data is the risk of missing data. The data were not systemically recorded for research but for healthcare purposes, for which data are recorded only when relevant for the treatment of patients in the eyes of the provider or practice staff. ICPC codes for antimicrobial prescriptions were sometimes missing or a registered ICPC code was not related to the infection. We were also unable to verify registered diagnoses in this large dataset, which may have led to registration bias, with either under- and over-registration. To better gauge this risk, we compared our study with two prospective Dutch studies on appropriateness of antimicrobial prescribing for RTIs, as prospective data collection is less prone to incorrectly registered or missing data. Both studies had a comparable proportion,

at around 40%, of antimicrobial overprescribing for RTIs (18, 19). This confirmed our assumption that the large number of antimicrobial prescriptions included in our combined dataset had diluted any potential registration bias and allows us to interpret our findings accordingly. Moreover, an additional multivariable regression analysis (Supplement 5) including patients without determinants in the SN data showed similar outcomes, from which we concluded that there is a low risk of bias due to missing SN data.

These two specific registries (ELAN/SN) have been successfully combined in earlier studies, focussing on cardiovascular risk (11, 20), but this is the first time that the approach has been used for research into AMR. Those earlier studies had methodological issues similar to our study, but nevertheless produced reliable and valid data. Studies of patterns of antimicrobial prescription have been previously conducted using large healthcare registries, but without including socioeconomic data (21, 22).

Antimicrobial prescribing

The number of antimicrobial prescriptions per year was relatively stable except for the year 2020. This significant drop in antimicrobial prescriptions was largely due to the COVID-19 pandemic, which resulted in relatively fewer bacterial and viral infections and allowed physicians to test their patients before treating them with antimicrobial medication for any presumed bacterial infection (23). With fewer other RTIs registered, there was a corresponding decrease in GP visits and consequently less prescribing of antimicrobials (24). A report on the total prescription of antimicrobials in The Netherlands showed a comparable decline in antimicrobial prescribing in 2020 (4).

RTIs and UTIs were the most common reasons with similar prescription rates for an antimicrobial prescription in our study. Cross-sectional/longitudinal observational studies performed in the United Kingdom (UK) also reported RTI and UTI as the most common reason (21, 25), only with relatively fewer prescriptions for UTIs compared to RTIs. Our study showed relatively more antimicrobial prescription for an UTI. Other studies in this domain differ in details that might explain for differences in the results reported. The study by Pouwels et al. only included patients with an UTI who were older than 14 years (21), while UTI's at a young age are quite common. The study by Dolk et al. also included ear nose throat infections as a RTI (25).

In both absolute and relative numbers, RTIs in our study accounted for the vast majority of all antimicrobial overprescribing (81.5%) and within prescriptions for RTIs (39.6%).

This number would have been even higher if we had not used a broad definition of appropriate antimicrobial prescribing for an RTI. Prescribing an antimicrobial was considered inappropriate only if the recommendations advised against prescription. It is important to note that Dutch primary care guidelines on RTIs generally advise against prescribing an antimicrobial because RTIs are most commonly caused by viruses (26-28). In two other Dutch studies, one a prospective observational study with detailed registration of RTI episodes and the other a pragmatic, cluster-randomized intervention that examined appropriateness of antimicrobial prescriptions for RTI episodes, 46% and 44% of RTI prescriptions, respectively, did not follow guidelines (18, 19). Furthermore, an observational study by Dekker et al. focused on antimicrobial prescriptions for RTIs and reported justifications for antimicrobial prescriptions that did not follow recommendations in guidelines; these included a GPs' perception of high patient expectations for antimicrobial prescription, presence of fever, GPs' judgement of a more severe illness, age > 18 years, duration of symptoms ≥ 7 days, comorbidity, reduced general health state and female gender of the patient.

In our study, only a small proportion of antimicrobial prescriptions for UTIs failed to follow guideline recommendations. This is comparable to a study from the United Kingdom which showed that that 94% of consultations for a UTI led to an antimicrobial prescription within 30 days (21). Dutch primary care guidelines generally advise treatment of UTI's with antimicrobials (26).

The prescription of macrolides, that were neither first or second guideline choices recommended, was higher than for any other group of antimicrobial compounds. Another Dutch study found similar overprescribing of 2nd choice broad-spectrum antimicrobials (29). In The Netherlands, macrolides are usually only advised in case of antimicrobial allergy or proven antimicrobial resistance, and they are first or second choice antimicrobials for only a handful of infections. Overprescribing is probably due to the presumed lower burden of use associated with macrolides (fewer daily dosages, shorter courses, less side effects), as most prescriptions in our data were for children below 5 years of age. Macrolides are taken once a day for three days, whereas penicillin must be taken 3 to 4 times a day for five or more days (27, 28). Prescription of macrolides in a context where they might not be needed however, should nevertheless be reduced, as macrolides generally have a broader antibacterial spectrum compared to penicillin and consequently increase the risk of AMR.

Determinants

Regarding socioeconomic determinants with a significant impact on appropriateness of antimicrobial prescribing, migration background emerged as an important factor. While patients with a Moroccan migration background received more appropriate antimicrobial prescriptions compared to Dutch patients without a migration background, GPs were found to relatively more often inappropriately prescribe antimicrobials for patients with Turkish, Surinamese and Dutch Caribbean backgrounds. A prospective cross-sectional Dutch study including 1,939 patients reported that first generation migrants were more likely to be prescribed antimicrobial medication compared to second generation immigrants or patients with a non-immigrant Dutch background (30). By contrast, another Dutch study based on health insurance data from 21,617 patients did not find any differences in antimicrobial prescription across 6 migration backgrounds (including Turkish, Moroccan, Surinamese) (31)), although appropriateness was not examined as an outcome in that study.

A possible explanation for most of these results is that GPs presume that patients with an infectious disease want antimicrobial therapy, but fail to actually verify this tacit assumption during shared decision making with the patient (19, 32-34). In fact, when asked, patients are usually more worried about the seriousness of their symptoms than eager to be treated (35). Nevertheless, results from a focus group study suggested that the expectation of being prescribed an antibiotic by the GP may be higher among patients with a non-Dutch migration background (36). Furthermore, as these groups tend to visit their GP more often than people with a non-immigrant Dutch background (37), a higher frequency of GP visits may increase the risk of being prescribed more antimicrobial prescriptions and consequently more inappropriate antimicrobial prescriptions.

It is not completely clear to what extent knowledge and attitudes to antimicrobials amongst the various migration groups influence antimicrobial prescribing. A qualitative study from The Netherlands on this topic found no difference in attitudes towards antimicrobials amongst groups with different migration backgrounds compared to the overall Dutch population (38). However, several different migration backgrounds (Turkish, Moroccan, Surinamese, Syrian and Cape Verdean) were included in this study as one group. Another Dutch study reported that people from a non-Dutch migration background were less knowledgeable about antimicrobials compared to people with a Dutch background (31). When and how antimicrobials are used in the country of migration background may affect attitudes. For example, in Turkey antimicrobials are used not only for infections but for a broad variety of other diseases and symptoms (39), a pattern that might continue in The Netherlands for patients familiar with both cultures. The higher level of appropriate antimicrobial prescription amongst people

with a Moroccan background is likely attributable to lower rates of smoking, which is a known risk factor for RTIs (40). GPs also tend to prescribe antimicrobial medication more easily if there is a risk of a complicated RTI, and smoking is also a prominent risk factor for complicated RTIs. These findings highlight important disparities between groups with different migration backgrounds.

Comorbidity and female gender were also identified as determinants of antimicrobial overprescribing, associations previously reported in several studies (8-10, 19, 34). Comorbidity is considered a risk factor for severe course of an infection, so a GP may prescribe antimicrobials more readily to prevent more serious complications that might result in hospital admission (28). Female gender is associated with a higher incidence of infectious disease, leading to more frequent visits to the GP compared to men and consequently a higher number of antimicrobial prescriptions and a higher risk of overprescribing (41).

In our study, an age of 5 years or older was also associated with antimicrobial overprescribing. Other studies have reported different age associations, but as these studies varied in design or population direct comparison is difficult. Two studies that covered all ages, including a retrospective cohort study in Canada of antimicrobial prescriptions for viral infections and a prospective observational study in The Netherlands with detailed registration of RTIs episodes, both found an association between antimicrobial overprescribing and an age between 18 and 65 years (8, 42). A retrospective cross-sectional study of bronchitis in Spain, including patients 15 years and older, also concluded that increasing age is associated with antimicrobial overprescribing (43). By contrast, a Dutch prospective observational study with detailed registration of 1,469 RTI episodes, which included patients of all ages, found no association with age (32). A possible explanation for our findings is that children below the age of 5 years more commonly experience infections such as otitis media acuta (28, 44), which is appropriately treated with antimicrobials.

A further interesting finding of our study was the association of appropriate antimicrobial prescribing with a primary care practice size of less than 2,168 patients. Two Canadian studies found a comparable association for practice sizes less than 1,235 or 1,054 patients, respectively (8, 9). Conversely, a study from the UK reported no association between practice size and appropriate antimicrobial prescribing, although a medium size practice in that study was described as between 7,928 and 10,941 patients (10). Differences in practice location and definitions of practice size likely hamper proper comparison between studies. A possible explanation for antimicrobial overprescribing in larger primary care practices is that relatively less

time per consultation is available, which is independently associated with more antimicrobial overprescribing (45, 46). In our study, we interpret practice size also as a proxy for continuity of care in daily practice by the same provider. Larger primary care practices generally make use of locums, more GPs staffing the practice, and we know that a higher number of GPs involved with the same population is related to weaker continuity of care in practice. In transition there is a risk of loss of information essential to adequate follow-up and thus overprescribing due to medical uncertainty (47). The second GP confronted with the same problem may also view prescription of an antimicrobial as an appropriate decision simply on the basis of knowing that it is the second encounter with the same patient (33).

Our results also identified the Friday as the weekday prone for (over-)prescribing, in contrast to a UK study that found no differences per weekday (21). In our case, annex to workload effects, a possible additional explanation might be that GPs use a delayed antimicrobial prescription strategy. In this strategy patients are prescribed antimicrobials before they are actually needed and instructed to collect it, or use it only when specific symptoms worsen. However, this additional supposition would need verification in pharmacy records which we were unable to arrange.

In an analysis comparing associations of determinants of appropriate antimicrobial prescribing for all infections to those for RTIs only, some differences were noted. It now emerged that a higher household income was associated with more appropriate antimicrobial prescribing for RTIs, whereas an association of single-parent-households with appropriateness of antimicrobial prescribing was no longer present. Comorbidity showed a stronger association with antimicrobial overprescribing for RTIs compared to antimicrobial overprescribing for all disease groups. A possible explanation for these differences is that antimicrobial prescriptions for RTIs are more likely not needed, simply because most RTIs are caused by viruses that do not respond to antimicrobials. By contrast, UTIs, sexually transmitted diseases and skin infections can usually be appropriately treated with an antimicrobial.

Evaluating various findings, the overarching theme, as well as an entry for further improvement of primary care antimicrobial prescription, seems to be the availability of time for consultation and shared decision making. Some specific misunderstandings due to cultural differences when encountering patients with a migrant background, practice size as a measure for providing continuity of care and the availability of extended consultation time, Friday as a day of over prescription, the choice for macrolides thus prevailing convenience over rational arguments, all point in the direction of physicians presumably trying to cope with workload.

Implications for practice

Our findings may open up important implications entries for antimicrobial stewardship especially related to RTIs and macrolide use. Our first recommendation is to increase and improve feedback on antimicrobial prescribing, as this is a proven AMS intervention that reduces antimicrobial prescribing (48-52), making use of the determinants we found and focusing on RTIs and macrolides. The second recommendation is to provide room for extended consultation time by reducing practice workload. We hypothesize this can lead to less antimicrobial overprescribing, as it supports the clinical quality of primary care practice. A third recommendation might be the provision of information targeted to groups with a specific migration background, for example through public information campaigns. Further research into effective interventions tailored to specific migration backgrounds might still be needed.

Conclusion

Our study shows that data from two large registries can be used to examine the broader context of medical issues, in this case patterns of antimicrobial prescription. This approach is applicable to any health registry where corresponding individual or household socioeconomic data is relevant to explore. In our study, we gained new insights and uncovered previously unknown associations with antimicrobial prescription behaviour on patient and practice level. We advise action to improve antimicrobial prescribing especially for RTIs in primary care and explore entries to lower the number of macrolide prescriptions when they are not explicitly needed. Regarding overall antimicrobial overprescribing, we propose that any intervention would benefit from targeted endeavours to reduce practice workload and increase the room for extended consultation time per patient encounter. Antimicrobial prescription quality is another issue that would benefit from improved personal continuity of care in primary care practice and greater availability of culturally-tailored information would help to bridge expectations when organizing shared decision making in antimicrobial prescription.

Tables

Table 1 Characteristics of study sample

	Antimicrobial prescriptions n= 1,150,252	Patients n= 269,574
Female gender % (n)	64.6% (743,034)	56.7% (152,714)
Mean age at prescription range in years	47.9 years	41.9 years
Age groups in years, % (n)		
0 – 4	7.0% (80,238)	8.6% (23,268)
5 – 14	5.7% (65,015)	8.9% (23,904)
15 – 44	29.9% (344,447)	35.5% (95,827)
45 – 64	26.6% (306,331)	25.0% (67,481)
65 -107	30.8% (354,221)	21.9% (59,094)
With an ICPC code	58.6% (673,909)	NA
Without an ICPC code	41.4% (476,343)	
With an ICPC code related to an infection	50.9% (585,117)	NA
Number of antimicrobial allergies % (n)		
0	98.6% (1,134,169)	99.4% (267,966)
1	1.2% (13,406)	0.5% (1371)
2	0.2% (2247)	0.1% (194)
3 or more	0 (430)	0 (43)
Number of co-morbidities		
0	64.8% (745,910)	76.5% (206,352)
1	26.4% (304,198)	19.6% (52,874)
2	6.9% (79,470)	3.2% (8703)
3 or more	1.8% (20,674)	0.6% (1645)
Migration background % (n)*		
Dutch	72.7% (83,5944)	69.3% (186,884)
Morocco	3% (34,846)	3.4% (9098)
Turkey	2.6% (30,084)	2.8% (7503)
Suriname	4.4% (51,037)	4.7% (12,635)
Dutch Caribbean	1.4% (15,805)	1.7% (4466)
Other non-western countries	6.1% (69,687)	7.2% (19,437)
Western countries	9.8% (112,836)	11% (29,541)
Missing	0 (6)	0 (5)
Households with 1 parent	7.8 % (89,565)	7.6% (20,589)
Family income		
Low	53.0% (609,228)	49.4% (133,093)
Middle	32.3% (371,795)	39.0% (105,154
High	3.2% (36,755)	2.4% (6536)
Missing	11.5% (132,474)	9.2% (24,791)
Primary care practices size (101 offices)		
Small (n=25)	14.4% (165,921)	13.8% (37,271)
Medium (n=65)	53.3% (612,775)	52.2% (140,730)
Large (n=11)	32.2% (370,254)	33.8% (91,141)
Missing	0.1% (1302)	0.2% (432)

NA: Not applicable

Table 2. Distribution and characteristics of appropriate and inappropriate antimicrobial prescriptions

	Appropriate antimicrobial prescriptions	Inappropriate antimicrobial prescriptions
Number of antimicrobial prescriptions	480,792	104,325
Female sex % (n)	70.1% (336,910)	61.1% (63,722)
Age groups in years, % (n)		
0 – 4	8.4% (40,322)	8.6% (9022)
5 – 14	6.5% (31,279)	6.6% (6895)
15 – 44	30.0% (144,005)	34.7% (36,208)
45 – 64	24.7% (118,636)	29.6% (30,904)
65 and older	30.5% (146,550)	20.4% (21,296)
Antimicrobial allergy % (n)		
0	98.6% (474,062)	99.0% (103,240)
1	1.2% (5915)	0.9% (975)
2	0.1% (712)	0.1% (91)
3 or more	0.0% (103)	0.0% (19)
Patients with co-morbidities		
0	66.5% (319,639)	70.3% (73,313)
1	25.4% (122,168)	24.2% (25,213)
2	6.5% (31,268)	4772
3 or more	1.6% (7717)	1027
Ethnic background % (n)*		
Dutch	75.5% (363,027)	69.4% (72,414)
Moroccan	2.5% (12,087)	3.4% (3538)
Turkish	2.2% (10,458)	3.2% (3336)
Surinamese	3.7% (17,970)	5.2% (5459)
Dutch Caribbean	1.2% (5904)	1.4% (1456)
Global South	5.5% (26,353)	7.5% (7805)
Global North	9.4% (44,988)	9.9% (10,315)
Unknown	0% (1)	0% (2)
Households with 1 parent	12.9% (37,173)	11.9% (8319)
Family income		
Below average income	59.3% (257,008)	57.4% (56,161)
From 1 up to 2 times average income	38.6% (167,506)	40.3% (39,428)
More than 2 times average income	2.1% (9222)	2.3% (2275)
Per disease group % (n)		
UTI	45.3% (217,710)	0.0% (30)
STD	2.1% (10,048)	0.2% (238)
Ear	9.6% (46,154)	1.7% (1765)
GE tract	0.1% (667)	3.1% (3221)
Viral	0.0% (0)	1.6% (1694)
Skin	15.8% (76,069)	10.3% (10,711)
Gyn	0.1% (474)	1.5% (1605)
RTI	27.0% (129,670)	81.5% (85,061)

UTI: Urinary Tract infection
STD: Sexual transmitted disease
GE: Gastro - intestinal
Gyn: Gynaecologic
RTI: Respiratory tract infection

Table 3 Number of antimicrobials prescriptions per 1000 patients per size group primary care practice

	Appropriate antimicrobial prescriptions			**Inappropriate antimicrobial prescriptions**		
Size primary care practice	Mean (95% CI)	SD	Range	Mean (95% CI)	Range	SD
Small	162 (150-173)	27.9	111-205	38 (33-43)	19-64	12.1
Medium	169 (159-180)	41.6	17-270	36 (33-40)	3-87	15.1
Large	154 (128-180)	38.9	86-208	35 (26-44)	15-54	13.2

CI; Confidence interval. SD; Standard deviation.

Table 4. Association of determinants with inappropriate antimicrobial prescribing

	Model 1 OR 95% C.I.	Model 2 OR 95% C.I.	Model 3 OR 95% C.I.	Model 4 OR 95% C.I.
Sex (Female reference)	**0.66 (0.65-0.67)**	**0.67 (0.65-0.68)**	**0.67 (0.65-0.68)**	**0.67 (0.65-0.68)**
Age groups				
0 – 4 years (reference)	1	1	1	1
5-14 years	**1.40 (1.36-1.43)**	**1.11 (1.06-1.16)**	**1.08 (1.03-1.14)**	**1.08 (1.03-1.14)**
15-44 tears	**1.42 (1.38-1.47)**	**1.12 (1.07-1.17)**	**1.10 (1.05-1.15)**	**1.10 (1.05-1.15)**
45-64 years	**1.76 (1.72-1.79)**	**1.39 (1.33-1.45)**	**1.37 (1.31-1.43)**	**1.37 (1.31-1.43)**
65-and older	**1.81 (1.77-1.84)**	**1.48 (1.41-1.54)**	**1.46 (1.39-1.56)**	**1.46 (1.40-1.52)**
Migration background*				
Dutch (reference)		1	1	1
Moroccan		**0.90 (0.87-0.92)**	**0.90 (0.87-0.92)**	**0.89 (0.87-0.92**)
Turkish		**1.15 (1.10-1.21)**	**1.15 (1.10-1.21)**	**1.16 (1.10-1.22)**
Surinamese		**1.25 (1.18-1.31)**	**1.25 (1.19-1.31)**	**1.27 (1.21-1.34)**
Dutch Caribbean		**1.24 (1.19-1.30)**	**1.24 (1.19-1.30)**	**1.24 (1.18-1.29)**
Global South		0.99 (0.93-1.07)	0.99 (0.92-1.07)	0.99 (0.92-1.06)
Global North		**1.16 (1.11-1.21)**	**1.16 (1.11-1.21)**	**1.16 (1.11-1.20)**
Households with 1 parent (2 parents reference)		**1.07 (1.05-1.10)**	**1.07 (1.05-1.10)**	**1.08 (1.05-1.11)**
Household income				
Low (reference)		1	1	1
Middle		0.99 (0.96-1.04)	1.01 (0.96-1.05)	1.00 (0.95-1.04)
High		0.98 (0.94-1.02)	0.98 (0.94-1.02)	0.98 (0.93-1.02)
Number of comorbidities				
0 (reference)			1	1
1			**1.27 (1.11-1.453)**	**1.278 (1.12-1.46)**
2			**1.26 (1.10-1.438)**	**1.265 (1.11-1.45)**
3 or more			1.15 (1.00-1.328)	**1.157 (1.01-1.36)**
Primary Care practice size				
Small (reference)				1
Medium				**1.11 (1.08-1.14)**
Large				**1.03 (1.01-1.05)**
Day of prescription (Friday reference)				**0.96 (0.94-0.98)**

A multivariable logistic regression analysis was conducted in a chronologic order for 4 models to test for an association of determinants with inappropriate antimicrobial prescribing. Model 1 was the first and in an each new model determinants were added. **Bold** indicates a statistical significant association with inappropriate antimicrobial prescribing ($p<0.05$). OR: Odds ratio. CI; Confidence Interval.

Table 5 Association of determinants with inappropriate antimicrobial prescribing for respiratory tract infections

	Model 4 OR (95% C.I.)
Gender (Female as reference)	**1.09 (1.06- 1.11)**
Age groups	
0 – 4 years (reference)	1
5-14 years	**1.27 (1.18-1.33)**
15-44 tears	0.93 (0.88-0.99)
45-64 years	**1.23 (1.16-1.30)**
65-and older	**1.35 (1.80-1.43)**
Migration background	
Dutch (reference)	1
Moroccan	1.00 (0.96-1.04)
Turkish	**1.08 (1.01-1.15)**
Surinamese	**1.25 (1.17-1.33)**
Dutch Caribbean	**1.29 (1.21-1.37)**
Global South	1.07 (0.97-1.18)
Global North	**1.13 (1.07- 1.20)**
Households with 1 parent (2 parents reference)	1.01 (0.98-1.05)
Household income	
Low (reference)	1
Middle	**0.87 (0.82- 0.93)**
High	**0.92 (0.86-0.97)**
Number of comorbidities	
0 (reference)	1
1	**2.99 (2.56- 3.48)**
2	**1.82 (1.56- 2.12)**
3 or more	**1.30 (1.10- 1.53)**
Primary Care office size	
Small (reference)	
Medium	**1.17 (1.13-1.21)**
Large	**1.05 (1.02-1.08)**
Day of prescription (Friday reference)	**1.05 (1.02-1.08)**

A multivariable logistic regression analysis was conducted to test the association of determinants with antimicrobial prescribing for respiratory tract infections. **Bold** indicates a statistical significant association with inappropriate antimicrobial prescribing ($p<0.05$).
OR: Odds ratio.
CI; Confidence Interval.

Figures

Figure 1. Number of antimicrobial prescriptions per year.

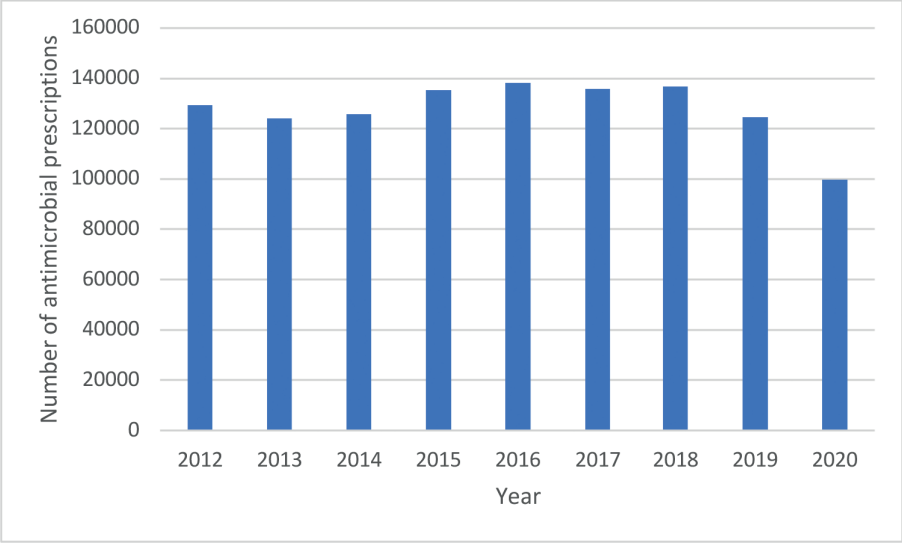


Figure 2 Antimicrobial prescriptions per antimicrobial group each year.

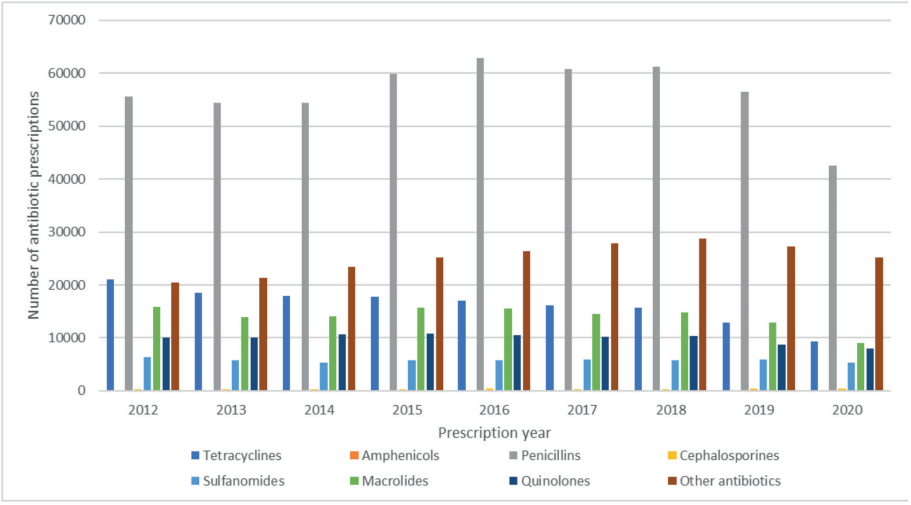
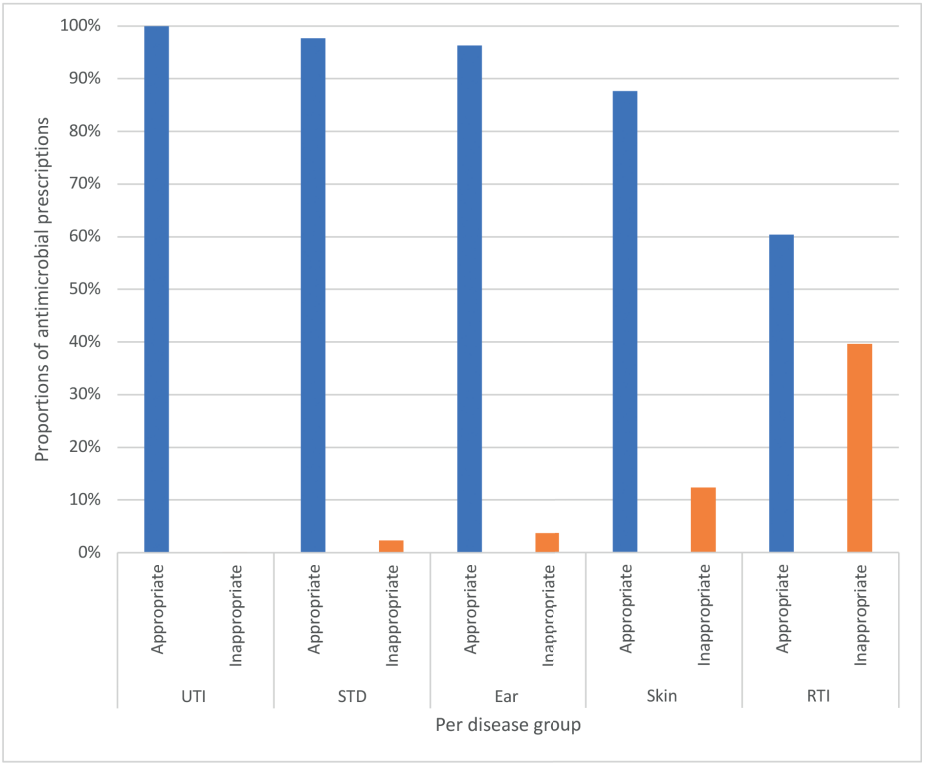
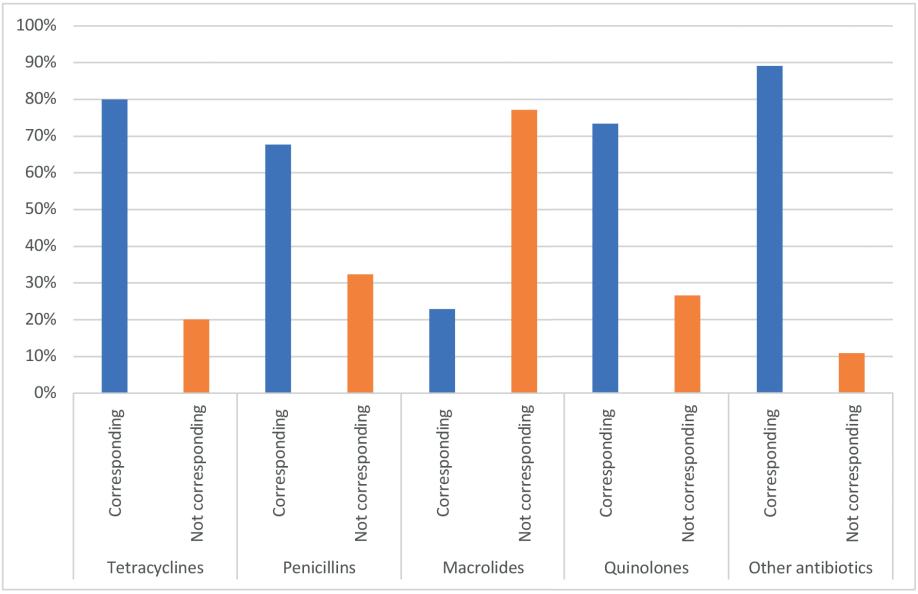


Figure 3 Proportions of appropriate and inappropriate antimicrobial prescriptions per disease group.



UTI: Urinary tract infection
STD: Sexual transmitted diseases
Ear: Ear infections
Skin: Skin infections
RTI: Respiratory tract infections

Figure 4 Appropriate antimicrobial prescriptions corresponding with 1st and 2nd choice in guideline.



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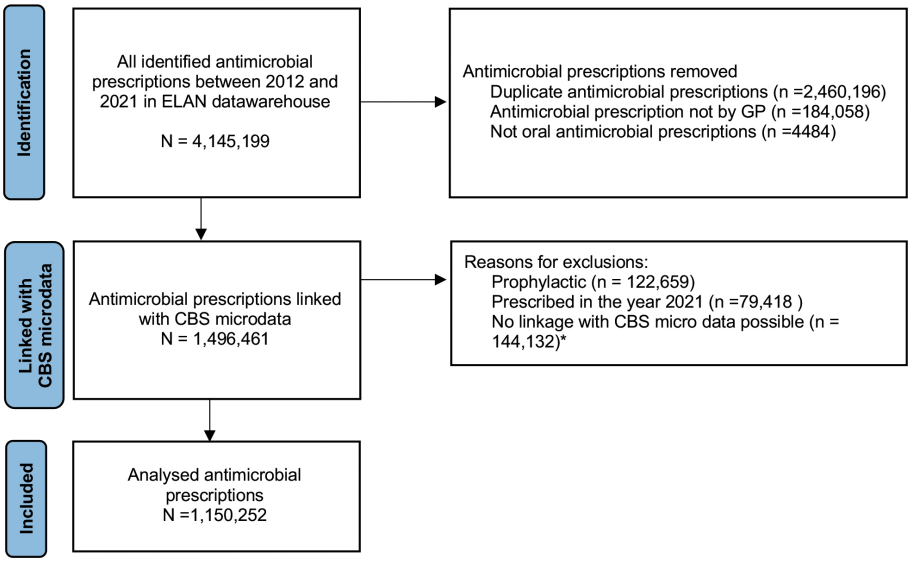
Supplements

Supplement 1

List of comorbidities

- A90 Congenital anomaly nos/multiple (Down syndrome)
- Immunosuppressed, blood forming organs
  - B72 Hodgking diseases
  - B73 Leukaemia
  - B74 Malignant neoplasma blood other
  - B90 HIV-infection/AIDS
- Immunosuppressed, digestive diseases
  - D72 Viral hepatitis
  - D73 Gastroenteritis presumed infection
  - D74 Malignant neoplasm stomach
  - D75 Malignant neoplasm colon/rectum
  - D76 Malignant neoplasm pancreas
  - D77 Malignant digestive neoplasm, other/NOS
  - D94 Chronic enteritis/ulcerative colitis
- Immunosuppressed, cardiovascular diseases
  - K77 Heart failure
- Immunosuppressed, musculoskeletal
  - L71 Malignant neoplasm musculoskeletal
  - L88 Rheumatoid/seropositive arthritis
- Immunosuppressed, neurological
  - N74 Malignant neoplasm nervous system
- Immunosuppressed, lung diseases
  - R83 Other infections airway
  - R89 Congenital anomaly respiratory
  - R91 Bronchiëctasieën
  - R95 COPD
  - R96 Asthma
- Immunosuppressed, urinary tract
  - U75 Malignant neoplasm of kidney
  - U76 Malignant neoplasm of bladder
  - U77 Malignant neoplasm urinary other
  - U85 Congenital anomaly urinary tract

Supplement 2 Flowchart inclusion process antimicrobial prescriptions



*Linkage was not possible for 35,321 patients. Statistics Netherlands does not collect data for people who stay for a short period in The Netherlands and have a social security number.

Supplement 3 List of inappropriate and appropriate indications for an antimicrobial prescriptions with International Classification of Primary Care (ICPC) codes

Inappropriate indication for antimicrobial prescription

Viral disease

- A71
- A72
- A74
- A76
- A76.01
- A76.02
- A76.03
- A77
- A78

Gastro-intestinal tract infections

- D11
- D13
- D22
- D22.01
- D22.02
- D22.03
- D70
- D70.02
- D70.01
- D70.03
- D70.04
- D72
- D72.01
- D73
- D83.02
- D87.01
- D92

Ear infections

- H72
- H74
- H74.01

Respiratory tract infections

- A75
- D71
- R05
- R07
- R08
- R09
- R21
- R21.01
- R22
- R71
- R72

- R72.01
- R72.02
- R74
- R74.01
- R74.02
- R75.01
- R77
- R77.01
- R80
- R90
- R96.01

Skin

- A78.05
- S10.02
- S11
- S11.01
- S70
- S70.01
- S71.01
- S74
- S74.01
- S74.02
- S74.03
- S75
- S75.01
- S75.02
- S75.03
- S76.02
- S90

Urinary Tract infections

- Y75
- Y75.01
- U95

Gynecology

- X72
- X84
- X84.02
- W12
- X90

Sexually Transmitted diseases

- S72
- S72.01
- S73
- S73.02
- S95
- X91
- Y72
- Y76

Appropriate indication for antimicrobial prescription

Gastro-intestinal tract infections

- D85
- D86
- D86.01

Ear infection

- H04
- H05
- H70
- H71
- H73
- H74.02

Respiratory tract infections

- R75
- R75.02
- R76
- R76.01
- R76.02
- R78
- R81
- R81.01
- R91
- R91.01
- R91.02
- R95
- R96
- R96.02
- R99.05

Skin

- A78.05
- R73
- S09
- S09.01
- S10
- S10.01
- S10.03
- S12.01
- S13
- S14
- S76
- S76.01
- S84
- S92.02
- S96
- S96.01
- S96.02
- W94
- X99.04

Urinary Tract infections

- U01
- U02
- U04
- U04.01
- U04.02
- U04.03
- U06
- U70
- U71
- U71.01
- U72
- Y74
- Y74.01
- Y74.02
- Y75
- Y03
- Y73
- W84.01

Gynecology

- W70.01
- X74

Sexually Transmitted diseases

- X13
- X23
- X70
- X71
- X73
- X74.01
- X84.01
- X85.01
- Y25
- Y70
- Y71
- Y99
- Y99.03

Supplement 4 ICPC codes with the recommended antimicrobial according to Dutch primary care guidelines

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
Gastrointestinal tract			
D85	J01CA04 Amoxicillin J01FA09 Clarithromycin		
D86	J01CA04 Amoxicillin J01FA09 Clarithromycin		
D86.01	J01CA04 Amoxicillin J01FA09 Clarithromycin		
Ear infections			
H04	J01CF05 Flucloxacillin		J01FA10 Azithromycin J01FA09 Clarithromycin J01FA01 Erythromycin
H05	J01CF05 Flucloxacillin		J01FA10 Azithromycin J01FA09 Clarithromycin J01FA01 Erythromycin
H70	J01CF05 Flucloxacillin		J01FA10 Azithromycin J01FA09 Clarithromycin J01FA01 Erythromycin
H71	J01CA04 Amoxicillin		J01EE01 Sulfamethoxazole and Trimethoprim Before 2016 J01EE01 Sulfamethoxazole and Trimethoprim J01FA10 Azithromycin
H73	J01CA04 Amoxicillin		J01EE01 Sulfamethoxazole and Trimethoprim Before 2016 J01EE01 Sulfamethoxazole and Trimethoprim J01FA10 Azithromycin
H74.02	J01CA04 Amoxicillin		J01EE01 Sulfamethoxazole and Trimethoprim 2016 J01EE01 Sulfamethoxazole and Trimethoprim J01FA10 Azithromycin
R73	J01CF05 Flucloxacillin		J01FA09 Clarithromycin J01FF01 Clindamycin
Respiratory tract infections			
R75	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA09 Clarithromycin J01FA10 Azithromycin

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
R75.02	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA09 Clarithromycin J01FA10 Azithromycin
R76	J01CE05 Pheneticillin J01CE02 Phenoxymethylpenicillin J01CR02 Amoxicillin-Clavulanicacid		J01FA01 Erythromycin J01FA10 Azithromycin
R76.01	J01CE05 Pheneticillin J01CE02 Phenoxymethylpenicillin J01CR02 Amoxicillin-Clavulanicacid		J01FA01 Erythromycin J01FA10 Azithromycin
R76.02	J01CR02 Amoxicillin-Clavulanicacid		J01FA01 Erythromycin J01FA10 Azithromycin
R78	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R81	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R81.01	J01AA02 Doxycycline		
R91	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R91.01	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R91.02	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R95	J01AA02 Doxycycline		J01FA01 Erythromycin J01FA10 Azithromycin
R96	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R96.02	J01AA02 Doxycycline J01CA04 Amoxicillin		J01FA01 Erythromycin J01FA10 Azithromycin
R99.05	J01CR02 Amoxicillin-Clavulanicacid		
Skin			
A78.05	J01AA02 Doxycycline J01FA10 Azithromycin	Before 2018 J01AA02 Doxycycline J01CA04 Amoxicillin	Before 2018 J01FA10 Azithromycin
S09	J01CR02 Amoxicillin-Clavulanicacid J01AA02 Doxycycline		
S09.01	J01CR02 Amoxicillin-Clavulanicacid J01AA02 Doxycycline		
S10	J01CF05 Flucloxacillin J01FA09 Clarithromycin J01FF01 Clindamycin J01FA09 Clarithromycin J01FA01 Erythromycin J01FA10 Azithromycin		

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
S10.01	J01CF05 Flucloxacillin J01FA09 Clarithromycin J01FF01 Clindamycin J01FA09 Clarithromycin J01FA01 Erythromycin J01FA10 Azithromycin		
S10.03	J01CF05 Flucloxacillin J01FA09 Clarithromycin J01FF01 Clindamycin J01FA09 Clarithromycin J01FA01 Erythromycin J01FA10 Azithromycin		
S12.01	J01AA02 Doxycycline J01FA10 Azithromycin	Before 2018 J01AA02 Doxycycline J01CA04 Amoxicillin	Before 2018 J01FA10 Azithromycin
S13	J01CR02 Amoxicillin-Clavulanicacid		J01AA02 Doxycycline J01FF01 Clindamycin
S14	J01CF05 Flucloxacillin		J01FA09 Clarithromycin J01FF01 Clindamycin
S76	J01CF05 Flucloxacillin		J01FA09 Clarithromycin J01FF01 Clindamycin
S76.01	J01CF05 Flucloxacillin		J01FA09 Clarithromycin J01FF01 Clindamycin
S84	J01CF05 Flucloxacillin		J01FA09 Clarithromycin J01FF01 Clindamycin Before 2018 J01FA09 Clarithromycin J01FF01 Clindamycin J01FA01 Erythromycin J01FA10 Azithromycin
S92.02	J01AA07 Tetracyline		
S96	J01AA02 Doxycycline J01FA01 Erythromycin J01AA07 Tetracyline		
S96.01	J01AA02 Doxycycline J01FA01 Erythromycin J01AA07 Tetracyline		
S96.02	J01AA02 Doxycycline J01FA01 Erythromycin J01AA07 Tetracyline		

Urinary tract infections

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
U01	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U02	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U04	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U04.01	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U04.02	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U04.03	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
U06	J01XE01 NITROFURANTOIN J01XX01 FOSFOMYCIN J01EA01 TRIMETHOPRIM J01MA02 CIPROFLOXACIN J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U70	J01MA02 CIPROFLOXACIN J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U71	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U71.01	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
U72	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim	Before 2014 J01MA06 Norfloxacin	
W84.01	J01XE01 Nitrofurantoin J01XX01 Fosfomycin J01EA01 Trimethoprim J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim		
Y03	J01DD04 Cefrtriaxone J01MA02 Ciprofloxacin J01CA04 Amoxicillin J01FA10 Azithromycin		
Y73	J01MA02 Ciprofloxacin J01CR02 Amoxicillin-Clavulanicacid J01EE01 Sulfamethoxazole and Trimethoprim		

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
Y74	J01XMA12 Levofloxacin J01XMA01 Ofloxacin J01EE01 Sulfamethoxazole and Trimethoprim J01AA02 Doxycycline		
Y74.01	J01XMA12 Levofloxacin J01XMA01 Ofloxacin J01EE01 Sulfamethoxazole and Trimethoprim J01AA02 Doxycycline		
Y74.02	J01XMA12 Levofloxacin J01XMA01 Ofloxacin J01EE01 Sulfamethoxazole and Trimethoprim J01AA02 Doxycycline		
Y75	J01FA09 Clarithromycin J01CR02 Amoxicillin-Clavulanicacid		
Gynecology			
W70.01	J01CA04 Amoxicillin		
W94	J01CF05 Flucloxacillin		J01FA01 Erythromycin
Sexual transmitted diseases			
X13	J01AA02 Doxycycline J01FA10 Azithromycin J01CA04 Amoxicillin		
X23	J01AA02 Doxycycline J01FA10 Azithromycin J01CA04 Amoxicillin		
X70	J01CE08 Benzylpenicillin		J01AA02 Doxycycline
X71	J01DD04 Ceftriaxone J01MA02 Ciprofloxacin J01CA04 Amoxicillin J01FA10 Azithromycin		
X73	J01XD01 Metronidazole J01FF01 Clindamycin		
X74	J01XMA01 Ofloxacin J01XMA12 Levofloxacin J01AA02 Doxycycline J01XD01 Metronidazole J01DD04 Ceftriaxone		

ICPC	Current 1e and 2nd choice according to guidelines ATC code Antimicrobial	Previous guidelines ATC code Antimicrobial	In case of antibiotic allergy ATC code Antimicrobial
X74.01	J01XMA01 Ofloxacin J01XMA12 Levofloxacin J01AA02 Doxycycline J01XD01 Metronidazole J01DD04 Cefrtriaxone		
X84.01	J01AA02 Doxycycline J01FA10 Azithromycin J01CA04 Amoxicillin		
X85.01	J01AA02 Doxycycline J01FA10 Azithromycin J01CA04 Amoxicillin		
X99.04	J01CF05 Flucloxacillin		J01FA01 Erythromycin
Y25	J01FA10 Azithromycin J01AA02 Doxycycline		
Y70	J01CE08 Benzylpenicillin J01AA02 Doxycycline		
Y71	J01DD04 Cefrtriaxone J01MA02 Ciprofloxacin J01CA04 Amoxicillin J01FA10 Azithromycin		
Y99	J01FA10 Azithromycin J01AA02 Doxycycline		
Y99.03	J01FA10 Azithromycin J01AA02 Doxycycline		

NHG: Dutch General Practitioner society

Supplement 5 Multivariable regression analysis including patients without data in Statistics Netherlands database

	Model 4 OR (95% CI)
Sex (Female as reference)	**0.67 (0.65-0.68)**
Age groups	
0 – 4 years (reference)	1
5-14 years	**1.08 (1.03-1.14)**
15-44 tears	**1.10 (1.05 -1.15)**
45-64 years	**1.37 (1.31-1.43)**
65 years and older	**1.46 (1.40-1.52)**
Migration background	
Dutch (reference)	1
Moroccan	**0.89 (0.87-0.92)**
Turkish	**1.16 (1.10-1.22)**
Surinamese	**1.27 (1.21-1.34)**
Dutch Caribbean	**1.24 (1.18-1.2**9)
Global South	0.99 (0.92-1.06)
Global North	**1.16 (1.11-1.20)**
Households with 1 parents (2 parents reference)	**1.08 (1.05-1.11)**
Household income	
Low (reference)	1
Middle	1.00 (0.951-1.06)
High	0.99 (0.93 -1.04)
Number of comorbidities	
0 (reference)	1
1	**1.28 (1.12-1.46)**
2	**1.27 (1.11-1.45)**
3 or more	**1.16 (1.01-1.36)**
Primary Care practice size	
Small (reference)	1
Medium	**1.11 (1.08-1.14)**
Large	**1.03 (1.01-1.05)**
Weekday of prescription (Friday reference)	**0.96 (0.94-0.98)**

OR; Odds Ratio. C.I.; Confidence Interval. GP; General practitioner.

Chapter 7

Discussion

Aim

The aim of this thesis was to examine the impact and quality of antimicrobial prescribing in primary care, and to determine the extent to which the quality of antimicrobial prescribing can be improved. This chapter discusses the main findings of this thesis per aim. A discussion of methodological considerations, recommendations concerning how to incorporate the main findings into AMS interventions, as well as future perspectives, is included in this chapter.

Main findings of the research in this thesis

An important finding, described in **chapter 2,** was that the impact of antimicrobial prescriptions originating in primary care may be much greater than previously assumed. The main determinants associated with inappropriateness of antimicrobial prescription, using the framework in **chapter 3,** were found to be 1) presence of comorbidity, 2) the view of many primary care physicians that their approach to antimicrobial prescribing is not responsible for AMR, 3) diagnostic uncertainty, and 4) the supposed expectations of patients regarding antimicrobial prescription. The studies in **chapters 2** and **3** were conducted with international data and the studies in **chapters 4** to **6** with data from The Netherlands .

In **chapter 4** we found that fewer antimicrobials were prescribed to patients during a SARS-CoV-2 episode compared to patients during influenza or influenza-like infection in four other influenza seasons**.** In **chapter 5**, rates for completeness and correctness of antibiotic allergy registrations were 0% and 29.3%, respectively. Perceived barriers to improved antibiotic allergy registration included insufficient knowledge, lack of priority, limitations of registration features in electronic medical records (EMR), fear of medical liability and patients interpreting side effects as allergies. In **chapter 6** we describe the overprescribing of antimicrobials for RTIs and of macrolides. Factors associated with more appropriate antimicrobial prescribing were a Moroccan migration background of the patient and a smaller primary care practice size, which we consider a proxy for sufficient consultation time and continuity of care by the same GP.

Impact of antimicrobial prescribing in primary care

The impact of antimicrobial prescribing in primary care on the development of AMR has not been previously established at country level. As already discussed in detail in the introduction, one could reasonably argue that the impact of primary care on AMR is likely to be low, as narrow-spectrum penicillins are presumably chosen for early disease stages. Results in **chapter 4** underline the necessity of actually assessing impact, as our study showed that some GPs believe that antimicrobial prescribing in primary care does not contribute to the development of AMR (1, 2) and that only hospital and veterinary care are responsible for AMR development. Analysis of antimicrobial prescriptions in **chapter 2** showed that these prescriptions are not primarily confined to narrow-spectrum penicillins, with proportions of penicillin prescriptions ranging from as low as 29% up to 65% in the 12 European countries included in the study. These findings were confirmed in **chapter 6,** where we found that penicillins represent only 44% of antimicrobial prescriptions in Dutch primary care. Furthermore, 11% of all antimicrobial prescriptions were for macrolides, a broad-spectrum antimicrobial, and 77.2% of these prescriptions were not first or second choice antimicrobials as defined in guidelines.

In **chapter 2** we used the antibiotic spectrum index (ASI), a proxy indicator for antimicrobial selection pressure, to assess the impact of antimicrobial prescribing in primary care. The ASI incorporates the volume of antimicrobials used as well as their activity against microorganisms, expressed as an index number representing the spectrum of microorganisms susceptible to that drug (3). This is a novel method to assess the impact of antimicrobial prescribing. The common method is to assess volumes using defined daily doses (DDD). A major advantage of the ASI compared to DDD is the incorporation of an antimicrobial activity spectrum. In our analysis we found a better correlation between ASI and the prevalence of AMR compared to DDD. Between 80-90% of the cumulative ASI in a country originates from antimicrobial prescriptions in primary care, demonstrating that the impact of primary care on antimicrobial selection pressure is much larger than previously assumed.

Our findings are supported by previous studies. A review of 243 studies showed a positive association between the volume of antimicrobial consumption in a country and the prevalence of AMR (4). Another review (n=24 studies) showed that antimicrobial prescriptions for individuals with a UTI in primary care lead to development of AMR to that antimicrobial, which may persist for up to 12 months (5). Compared to previous studies, ours was the first to use ASI to measure impact on antimicrobial selection pressure at the country level.

The high proportion of ASI generated in primary care highlights the central role of primary care in increasing AMR. The unexpectedly low proportion of penicillins and relatively high proportion of inappropriately prescribed macrolides show that antimicrobial prescribing in primary care is not confined to relatively harmless antimicrobials. These results underline the need to include primary care in nationwide AMS programs, and a better appreciation of the impact on AMR will raise awareness among GPs, whose knowledge and awareness will be crucial to the successful implementation of AMS interventions in primary care.

Quality of antimicrobial prescribing in primary care

Role of the patient

Patients play a crucial role in the decision to prescribe antimicrobials, as outlined in **chapters 3 to 6.** The systematic literature review in **chapter 3** identified several patient-related factors, including past experiences leading to expectations of antimicrobial prescription, high expectations of antimicrobial effectiveness, and requests for antimicrobial drugs without justification. Previous literature found an important interaction between patient and GP: the often unverified GP assumption that a patient's wish for an antimicrobial prescription was the reason for their visit (6-9). In fact, patients may visit their GP for a variety of other reasons, such as reassurance (10-12). In **chapter 6** we describe how patients with a Turkish, Surinamese and Dutch-Caribbean migration background were more often prescribed antimicrobial medications considered inappropriate compared to patients with a Dutch or Moroccan background. We assume these patterns are due to cultural differences and/or GP expectations regarding a patient's wish for an antimicrobial prescription. For these groups, it is therefore important to establish whether GPs have unverified expectations regarding a patient's wish for an antimicrobial prescription.

Several studies have explored the reasons underlying antimicrobial overprescribing for RTIs, which we found in **chapter 6**. The studies examined the beliefs, needs and perspectives of patients receiving antimicrobials for RTIs. A Dutch study by Duijn et al. compared patient and GP perspectives on RTIs through questionnaires. Patients placed more emphasis on the seriousness of symptoms, the need to consult a GP, the need to prescribe antimicrobials and the assumption that antimicrobials hasten recovery. By contrast, GPs place more emphasis on the self-limiting character of respiratory tract symptoms and on the side effects of antimicrobials (13). Another Dutch study based on an online questionnaire among 1,248 patients showed that 48% believed antimicrobials are effective in treating a viral infection (14). Encouragingly, around 92%

of patients felt that decisions regarding antimicrobial prescription are the physician's responsibility and that AMR can develop with use of antimicrobials. A German study with a similar design found that, among the 1,076 responders, circa 30% thought that antimicrobials help in case of a cold or flu and 25% thought that antimicrobials are effective against a virus (15). Although most patients with RTI symptoms visit their GP for reassurance and/or physical examination and not for an antimicrobial prescription (10-12), this belief may nonetheless lead to more antibiotic prescription. The results of our studies as described in this thesis, as well as studies by van Duijn et al., Cals et al. and Faber et al., emphasize the importance of effective communication directed to the needs and beliefs of patients (13-15).

Role of general practitioners

A GP's decision to prescribe an antimicrobial should be primarily based on clinical aspects such as severity, type and location of infection as well as expected course and risk of complications. However, the decision is as well influenced by non-clinical determinants such as diagnostic uncertainty, larger practice size, GPs' unverified assumptions regarding patient wishes for an antimicrobial prescription, or an inability to effectively negotiate or explain antimicrobial use. These factors were all observed in the studies described in **chapters 3 to 6**.

Diagnostic uncertainty was identified as an important determinant in **chapters 4 and 6**. Up to 40% of antimicrobial prescriptions for an RTI were not in accordance with primary care guidelines (**chapter 6**). This overprescribing may be partly due to diagnostic uncertainty, as the diagnosis, severity and individual patient risk for a severe RTI course are often uncertain in daily practice. This means that it is not always clear beforehand which patients with an RTI will benefit from an antimicrobial prescription. As shown in **chapter 4**, reducing diagnostic uncertainty may lead to fewer antimicrobial prescriptions. This was illustrated by the reduction in antimicrobial prescriptions for COVID-19 infections compared with influenza-like infections, which was most likely attributable to active testing for SARS-CoV-2 during the COVID-19 pandemic, while testing for influenza virus during influenza seasons is generally lacking. In cases of SARS-CoV-2 infection it was usually obvious to both the patient and the GP that a virus caused the symptoms and an antimicrobial prescription was unnecessary.

Our results showed that the context in which GPs work influences antimicrobial prescribing. A larger practice size was related to relatively more inappropriate antimicrobial prescribing in **chapters 3 and 6**. A scoping review published by Al-Azzawi et al. has examined antimicrobial prescribing in primary care, with a focus on context

(practice location, size and GP decision making) and how these factors influence decisions such as antimicrobial treatment (16). The authors of this review concluded that context has a profound impact on the decision to prescribe an antimicrobial and that this is not a "simple" decision.

Another important behavioural aspect is the ability of a GP to communicate, explain and negotiate effectively concerning antimicrobials and disease course (**chapter 3).** This was illustrated in a Danish study which explored the effect of empathy on the rate of antimicrobial prescription (17). GPs showing high empathy prescribed less penicillins compared to GPs showing less empathy. According to the authors, high empathy GPs may prescribe less penicillin because they take more time to explain and meet the patient's fears and expectations, as well as evaluating antimicrobial choices in their community with reference to local resistance patterns. High empathy GPs may be better at identifying patient's concerns and expectations and may be better able to contextualize the patient's infection in the community (17).

This thesis and previous studies have shown that antimicrobial prescribing in primary care is not always based on clinical aspects alone, but also involves nonclinical determinants such as practice size and an ability to communicate effectively. Patients, as well as a GP's practice context, influence GP behaviour up to a point, but the GP ultimately decides whether to prescribe an antibiotic. This is suggested in a Dutch report, which showed large variation in the number of antimicrobial prescriptions per primary care practice (18). This variation was partly due to differences in encountered infections per practice, patient populations, and factors such as comorbidity, patient age and practice size (19-21), but these differences did not fully explain variance between practices. Practice variation is therefore likely due to differences in style of work, which in turn influences a GP's decision to prescribe an antimicrobial.

Room for improvement in antimicrobial prescribing

We found significantly higher antimicrobial prescription rates during influenza infections compared to during SARS-CoV-2 infections (**chapter 4**), which was remarkable considering the very similar RTI caused by the two viruses. Both virus types cause a generally self-limiting disease, although both carry a risk of bacterial superinfection and a severe course, potentially leading to hospital admission or even death (22, 23). As previously described, an explanation for differences in prescription rates may have been the influence of SARS-CoV-2 diagnostic testing on decision making. One could therefore reasonably argue that testing for influenza will reduce antimicrobial prescriptions.

A study in the United Kingdom has shown that an influenza point-of-care (POC) test is feasible in primary care (24). A Dutch study concluded that an influenza POC test might contribute to a more precise diagnosis of RTIs (25). Two primary care cohort studies showed that the number of antimicrobial prescriptions is lower if patients with influenza-like symptoms are tested for influenza (26, 27). A randomized clinical trial has been suggested as a way to determine whether influenza POC tests are effective in lowering antimicrobial prescriptions for RTIs which is currently underway (28).

An important finding of this thesis, described in **chapter 6**, was that approximately 40% of antimicrobial prescriptions for an RTI can be considered inappropriate, a proportion similar to other Dutch studies (29, 30). While at first glance there appears to be room for a 40% improvement, there are valid reasons to prescribe an antimicrobial despite guideline recommendations. For example, GP familiarity with their patients and their medical history, as previous similar infections may have had an unexpectedly severe course that required antimicrobial treatment. Another factor when deciding to prescribe an antimicrobial is diagnostic uncertainty regarding RTIs, a problem that will persist as long as reliable tests are unavailable. One strategy to lower diagnostic uncertainty could be the use of prediction models, although these are still based on signs and symptoms, themselves subject to diagnostic uncertainty. Adding CRP testing may make a modest contribution to reducing uncertainty (31). However, we can conclude that reducing presumed inappropriate antimicrobial prescribing for RTIs will be a significant challenge.

In addition to the decision concerning whether to prescribe antimicrobials, we applied two approaches to examine factors influencing the choice between various antimicrobials: antibiotic allergy registrations, as discussed in **chapter 5,** and a simpler dosing scheme, as discussed in **chapter 6**.

Registration of antibiotic allergies may lead to avoidable prescribing of broad-spectrum antimicrobials, as discussed in detail in the introduction (32-38). GPs play a pivotal role in registering allergies and assessing antibiotic allergy registrations as part of their role as gatekeeper in the healthcare system. As described in **chapter 5**, many aspects of antibiotic allergy registration could be improved. All registrations lacked additional contextual information essential to determining the accuracy of registrations, such as the symptoms of an allergic reaction. Adding this information could theoretically lead to a reduction of up to 90% in antimicrobial antibiotic allergy registrations. For instance, one reported intervention in a hospital removed 50% of antibiotic allergy registrations simply by taking a medical history (39). A similar reduction of redundant allergy registrations in primary care is likely to be possible.

However, retrieving additional contextual information that should accompany any allergy registration will be a challenge and will often be impractical due to lack of GP time. Removal of incorrect interpretations of allergy registrations would help considerably in improving the quality of antimicrobial prescriptions, as 1st choice and/or narrow-spectrum antibiotics will be prescribed relatively more often.

Another finding from **chapter 5** was that GPs need a better understanding of antimicrobial allergies in order to be able to accurately assess possible allergic reactions and verify existing antibiotic allergy registrations. This could be initially promoted through education of primary care teams involved in registration, thus increasing knowledge and awareness. Verifying existing antibiotic allergy registrations can be effective in lowering the number of antibiotic allergy registrations.

Another observed problem was difficulty in entering or removing an antibiotic allergy registration in an EMR. Removing registrations is particularly difficult, as due to technical communication issues between different EMRs deleted registrations tend to reappear if not completely removed. When an allergic reaction is entered into any EMR in any domain, registrations in The Netherlands are centralized in a national hub ["landelijk schakelpunt" (LSP)] and subsequently communicated to other EMRs. Removal of the original allergy registration is required to achieve removal of the LSP registration and subsequent removal from other EMRs.

A substantial proportion of macrolides are prescribed to patients despite being neither the first nor second choice in guidelines, as described in **chapter 6**. This finding is corroborated by another Dutch study (40) and should be considered serious overprescription of macrolides to patients. A hypothesized explanation is the simpler dosing scheme of macrolides compared with many first or second choice antimicrobials. Some macrolides need only be taken once a day for only three days, whereas penicillin, for example, must be taken 3 to 4 times a day for 5 or more days. GPs assume that a lower burden for the patient may improve compliance. Indeed, as discussed in **chapter 6,** most macrolides were prescribed for children under the age of 5 years, for whom compliance can be a problem. However, there are no studies confirming our hypothesis. In addition, children in that age group have virtually no contraindications for the use of penicillins. Other explanations might be availability or deliverability, or may relate to the presumed causative microorganisms that justify macrolide treatment. This relative overprescription of macrolides should nevertheless be discouraged, as macrolides generally have a broader antibacterial spectrum compared to penicillin and consequently increase the risk of AMR. One can reasonably argue that a substantial proportion of these prescriptions could be avoided.

Antimicrobial stewardship interventions in primary care

Earlier sections described determinants that affect the quality of antimicrobial prescribing and what might be improved in primary care. This section is dedicated to how these results might be integrated into existing AMS interventions to improve the quality of antimicrobial prescribing. When implementing (more) effective AMS interventions, several aspects have to be considered: combined AMS interventions are more effective than a single intervention (41), active rather than passive implementation is most effective (42), and multilevel barriers and facilitators of AMS uptake should be identified before implementation of an AMS intervention (43).

Improving the patient experience

As described earlier, patients often have more diverse needs and beliefs about RTIs than GPs assume. Effective interventions should incorporate these needs and beliefs. Patients sometimes express the wish for an antimicrobial prescription without a medical reason. This wish or need can nevertheless be fulfilled through delayed antimicrobial prescribing, a scenario in which a GP prescribes an antimicrobial but persuades the patient to postpone its use until symptoms worsen or become too prolonged. Studies have found that patients with an RTI or UTI may be willing to postpone antimicrobial use (44, 45).

For a variety of RTIs this delayed antimicrobial prescribing strategy was found to be safe compared to direct antimicrobial prescribing (46), and no difference in patient satisfaction was found between the two strategies. A meta-analysis has shown that delayed antimicrobial prescribing is safe for most patients, even in a higher risk group (47), and no difference was seen in RTI complication rates or patient satisfaction. Delayed prescribing may reduce consultation rates compared to no antimicrobial prescribing, and postponing an antimicrobial prescription for UTIs reduced antimicrobial prescriptions by 63% (48). However, postponing an antimicrobial prescription for a UTI was associated with higher risk of incomplete recovery (OR 3.0 95% CI: 1.65 - 5.47) or a complicated UTI (OR 5.63 95% CI: 2.29-13.87) (48). Both can still be treated effectively and no urosepsis cases were reported in the review.

Patients often consult a GP for a physical examination or seek reassurance when nothing is seriously wrong (10-12). The actual need of the patient at that moment is reassurance, which can be fulfilled via other communication channels such as eHealth (e-mail and online consults). During the COVID-19 pandemic, the telehealth approach used for RTI consults satisfied patients (49, 50). Patients need easy access to reliable

information, and Thuisarts.nl has been shown to be a safe and effective online platform that can inform and reassure patients (51).

Assisting General Practitioners

Diagnostic uncertainty is a major determinant of inappropriate antimicrobial prescribing. In the case of an RTI this can be addressed through use of the C-reactive protein point-of-care (CRP-POC) test. When a GP is in doubt, a CRP-POC test can be used to discriminate between an uncomplicated versus complicated RTI. Use of this test has proven effective in lowering the number of antimicrobial prescriptions (52-56).

Antimicrobial overprescribing for RTIs and overprescribing of macrolides can be tackled using several interventions. For example, GP communication training on RTIs (57), GP education and a feedback session on antimicrobial prescribing were all effective in reducing prescriptions (41, 58-63). Feedback sessions may provide insight concerning the number of antimicrobial prescriptions a GP writes and their impact on antimicrobial resistance, which may in turn encourage a physician to reflect on his or her antimicrobial prescription habits.

Large practice size and GPs failing to verify assumptions about a patient wanting an antimicrobial prescription were the main determinants associated with more inappropriate antimicrobial prescribing in **chapters 3 and 6**. The latter factor is the most likely explanation of higher inappropriate antibiotic prescribing for patients with a Turkish, Surinamese and Dutch-Caribbean background (**chapter 6**). This illustrates the benefits of efficient communication skills and having sufficient time to communicate with patients.

Methodological considerations

The outcomes and interpretation of the studies described here should be viewed in the context of the strengths and limitations of each study. The studies described in **chapters 3, 4, 5 and 6** used routinely collected healthcare data. In **chapter 6,** a large healthcare registry was combined with a large registry containing data on social-economic determinants. A limitation of this approach is that health records are not primarily designed for research purposes, which can result in missing data as not all required information is systematically recorded. Missing data can lead to registration bias, causing either under - and over-registration. However, as the healthcare registries used in **chapter 4, 5 and 6** contained very large amounts of data, any registration

bias was probably diluted and unlikely to affect the results of our studies. Regarding strengths, the use of routinely collected healthcare data for medical research has many advantages, providing relatively easy access to rich, ecologically valid, longitudinal data from large populations (64). It reflects daily practice and combining two different registries at the patient level makes it possible to examine new causal associations.

A second methodological consideration is the use of proxy indicators as in **chapters 2 and 6**. Proxy indicators, such as ASI or size of a primary care practice can be used where it is not possible to extract the desired endpoint variable, in these cases antimicrobial selection pressure and time per patient visit, respectively, from available healthcare registries. Advantages of these proxy indicators are their availability, reproducibility and measurability compared to the desired endpoints. A disadvantage, however, is the somewhat simplified representation of reality.

A third methodological consideration is the context in which the studies took place. The main country of research in this thesis was The Netherlands, which differs from other European countries in a variety of ways. For example, the number of antimicrobial prescriptions in The Netherlands is lower compared to most European countries (65), which could be due to the fact that GPs in The Netherlands are both well informed and constrained by restrictive guidelines, leading to prudent antimicrobial prescribing. Consequently, AMR prevalence is lower compared to most other European countries (65). If AMR prevalence in a country is low, GPs already tend to prescribe narrow-spectrum antimicrobials, helping maintain the low prevalence of AMR. GPs in The Netherlands function as gatekeepers in the healthcare system and all inhabitants are registered with only one primary care centre. Both of these contextual factors help lower the number of antimicrobial prescriptions (66).

Despite the relatively lower number of antimicrobial prescriptions and low prevalence of AMR in The Netherlands, it is reasonable to generalize the results from **chapters 2, 3, 4 and 6** to other countries, as for example the high number of seemingly inappropriate antimicrobial prescriptions for RTIs described in **chapter 6** reflects results of many previous studies in other countries (67-70). Our study underlines the fact that inappropriate antimicrobial prescriptions for RTIs may be high, even in a country with a low overall antimicrobial prescription rate. Despite the low overall rate of antimicrobial prescription there is still room for improvement in The Netherlands, which could act as a reference point for other countries. Furthermore, our findings on specific migrant backgrounds may be reproducible in other European countries, although these findings may need to be reconfirmed in their specific context.

Future perspectives

The overarching goal of this thesis was to find starting points to improve the prescribing of antimicrobials to slow down the unavoidable increasing prevalence of AMR. The results from this thesis showed that antimicrobial prescribing in Dutch primary care can generally be considered as prudent. Dutch GPs tend to follow the recommendations provided by the guidelines (**chapter 6**), resulting in a lower prescription rate in primary care when compared to many other European countries (65). However, there is still room for improvement as can be deducted from the results of the studies described in **chapter 5** and **6**. Here we found that there is an overprescribing of antimicrobial therapy for RTIs and that there is an overuse of macrolides. In addition, the incorrect registrations of antibiotic allergies lead to avoidable prescription of broad-spectrum instead of low-spectrum antimicrobials. It is clear that these elements need to be improved.

An extra challenge in primary care regarding AMR is formed by epidemiological changes in the Dutch population, such as aging and the therewith increasing number of co-morbidities. Both are associated with antimicrobial overprescribing (**chapter 3** and **6**) and will probably lead to more antimicrobial use in the long-term with the risk of an increasing AMR prevalence. This makes the previously described need for improvement and continuation of already prudent antimicrobial prescribing practices even more important.

The aging population and increasing number of comorbidities will increase patients need to consult a GP for RTI symptoms as they seek reassurance (10-12). This need can not only be addressed through consultation in a primary care practice, as GPS are already experiencing to be overloaded with work. To address this need, other ways of communicating with and informing of patients has to be researched and implemented. For example, mass media campaigns informing patients on the self-limiting character of RTIs and interactive websites or smartphone apps informing patients when they have contact the primary care.

Another aspect regarding interventions, they have to focus on patient groups who visit a primary care practice more often and use more antimicrobials, as current interventions are mostly ‘one size fits all’. There is a need for tailored made interventions as shown in this thesis. For example, compared with other migrants groups, patients with a Turkish, Surinamese and Dutch-Caribbean background were more often prescribed inappropriate antimicrobials (**chapter 6**). This finding highlights our current lack of knowledge concerning the influence of migrant and cultural

background on antimicrobial prescribing in primary care. Qualitative research, such as focus groups or interviews, is needed to further explore and explain these findings.

Another future challenge is the expected increasing AMR prevalence. More treatment failure with small spectrum antimicrobials will probably occur, leading to more broad spectrum antimicrobials prescriptions. This cascade requires up-to-date and more proactive surveillance of antimicrobial use and resistance in primary care. In addition, this surveillance can be part of the pandemic preparedness as shown in **chapter 4**. If there is an increase in antimicrobial use, specifically broad-spectrum, or an increase in resistant bacteria groups, intervention aimed at these developments can be implemented immediately. For example, through adjustments in national guidelines, messages in newsletters of national organisations or by pharmacotherapy education. Artificial Intelligence (AI) or Big Data can contribute to this surveillance. **Chapter 6** showed that Big Data is applicable for analysis of antibiotic use. By use of these resources new relevant associations between antibiotic prescriptions and migrant groups were discovered. The use of AI in surveillance not only in the analysis of antimicrobial prescribing behaviour, but also in the support of prescribing process itself, is the next step to be investigated in this regard.

Conclusion

The aim of this thesis was to examine the impact and different elements of antimicrobial prescribing in primary care, and to define the extent to which the quality of antimicrobial prescribing can be improved. These goals were selected in light of our ultimate aim, which is to prevent a further increase in the prevalence of AMR. This can be achieved by, among others, improving the quality of antimicrobial prescribing in primary care. As antimicrobial prescribing in primary care is influenced by numerous varied factors this thesis took a multi-dimensional approach, with each study addressing a different dimension of AMR in primary care.

A important finding was that primary care may have a much larger impact on the development of AMR than previously assumed. Important determinants of this impact were diagnostic uncertainty, inability to effectively negotiate or explain antimicrobial use, as well as the assumption that patients expect an antimicrobial. Considerable improvements in antimicrobial prescribing in primary care can be achieved for RTIs, macrolide prescription and for patients with a specific migrant or cultural background (Turkish, Dutch-Caribbean, Surinamese). The registration of antimicrobial allergies could be improved through better education of GPs to increase

awareness and knowledge, by verifying existing antibiotic allergy registrations and through easier registration in the EMR. These improvements would help lower the number of antibiotic allergy registrations and therefore increase prescribing of first choice antimicrobials instead of second choice (broad-spectrum) antimicrobials.

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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.

Nederlandse samenvatting

De toename van antibioticaresistentie (ABR) vormt één van de grootste bedreigingen voor de mondiale gezondheidszorg. Er is sprake van antibioticaresistentie wanneer bacteriën zich aanpassen en ongevoelig worden voor één of meerdere antibiotica. Daardoor zijn deze antibiotica niet langer effectief. Het gebruik van antibiotica op velerlei manieren (in de humane en veterinaire geneeskunde en als “xenobiotica” in andere organismen) is de voornaamste oorzaak van deze toenemende resistentie. Antibioticaresistentie maakt de behandeling van patiënten met bacteriële infecties met antibiotica steeds moeilijker en dit kan uiteindelijk zelfs onmogelijk worden.

De ontdekking van antibiotica was een belangrijke medische doorbraak die de behandeling van bacteriële infecties mogelijk heeft gemaakt. Vóór die ontdekking was sterfte door bacteriële infecties hoog. In de huisartspraktijk en het ziekenhuis is het voorschrijven van antibiotica tegenwoordig een onmisbare dagelijkse medische routine. Huisartsen behandelen dagelijks relatief gemakkelijk patiënten met potentieel levensbedreigende bacteriële infecties, zoals longontstekingen of gecompliceerde urineweginfecties. In het ziekenhuis zijn antibiotica onderdeel van veel behandelingen en protocollen, zelfs als er nog geen sprake is van een infectie is, bijvoorbeeld ter preventie van een infectie na een operatie.

De *One-health*-benadering wordt vaak gebruikt in de context van antibioticaresistentie. In deze benadering is het uitgangspunt dat de gezondheid van mensen, huisdieren en wilde dieren, planten en de ruimere omgeving (met inbegrip van ecosystemen) nauw met elkaar verbonden en onderling afhankelijk zijn. Antibioticaselectiedruk maakt deel uit van het proces dat leidt tot antibioticaresistentie en wordt gedefinieerd als de mate waarin het gebruik van antibiotica het selectieproces van resistente bacteriestammen versterkt, waardoor de groei van resistente micro-organismen relatief toeneemt. In de *One-Health*-benadering draagt het gebruik van antibiotica uit alle domeinen (ziekenhuiszorg, diergeneeskunde, huisartspraktijk en industrieel gebruik) bij aan deze antibioticaselectiedruk, ongeacht het specifieke domein waar het antibioticum wordt gebruikt.

Momenteel kunnen de meeste bacteriële infecties in Nederland nog goed worden behandeld met een goed gericht toegediend smalspectrum antibioticum. Deze smalspectrum antibiotica zijn werkzaam tegen een beperkt aantal soorten veel voorkomende bacteriën en mits goed geïndiceerd, is hierbij een laag risico op resistentie-inductie. Desalniettemin is het gebruik van smalspectrum antibiotica alleen al dusdanig hoog, dat dit leidt tot een substantiële antibiotica selectiedruk met

als gevolg een toename van de antibioticaresistentie. Dit heeft als gevolg dat vaker 'breedspectrum' antibiotica moeten worden ingezet. Dit zijn antibiotica die werkzaam zijn tegen meerdere soorten bacteriën en vaak ook tegen meer resistente bacteriën. Het nadeel van het gebruik van breedspectrum antibiotica is dat ze een groter risico geven op de ontwikkeling van antibioticaresistentie dan smalspectrum antibiotica. Deze negatieve spiraal kan er uiteindelijk toe leiden dat artsen vaker dan nodig is breedspectrumantibiotica voorschrijven. Omdat ze er bij de behandeling van bacteriële infecties eerder van zullen uitgaan dat er sprake is van resistente bacteriën. Deze relatief ongecontroleerde spiraal van steeds meer en breder spectrum antimicrobiële stoffen voorschrijven, zal uiteindelijk een omslagpunt bereiken waarboven nog maar weinig antimicrobiële stoffen geschikt zijn voor empirisch gebruik. Dit proces kan uiteindelijk leiden tot een post-antimicrobieel tijdperk, waarin weinig of geen van de momenteel beschikbare antimicrobiële stoffen nog effectief zijn en infecties opnieuw een belangrijke oorzaak van morbiditeit en mortaliteit worden.

De antibioticaresistentie in Nederland is relatief laag vergeleken met de rest van de wereld. Dit kan toegeschreven kan worden aan het relatief geringe totale gebruik van antibiotica in vergelijking met de meeste Europese landen. Desondanks kent ook Nederland een toename van antibioticaresistentie. De enige mogelijkheid om deze toename te vertragen, is het optimaliseren van antibioticagebruik in Nederland. Huisartsen schrijven ongeveer 80 tot 90% voor van alle antibiotica in de Nederlandse gezondheidszorg. Dit grote aandeel maakt huisartspraktijken een essentiële ingang om te komen tot interventies die het antibioticagebruik optimaliseren.

Het doel van het in dit proefschrift beschreven onderzoek was om de bijdrage aan antibioticaselectiedruk door huisartspraktijken te kwantificeren, de kwaliteit van het voorschrijven van antibiotica in huisartspraktijken te onderzoeken en het verkennen van de mogelijkheden tot verbetering ervan. Voor dit doel zijn 5 onderzoeken uitgevoerd die staan beschreven in de **hoofdstukken 2 tot en met 6**. De resultaten van de onderzoeken zijn samengevat en bediscussieerd in **hoofdstuk 7**.

De impact van antibioticaprescriptie in huisartspraktijken

Het was uit de literatuur onvoldoende duidelijk in welke mate het voorschrijven van antibiotica in de huisartspraktijk bijdraagt aan de antibioticaselectiedruk. Men zou redelijkerwijs kunnen veronderstellen dat de bijdrage door huisartspraktijken lager is in vergelijking met ziekenhuizen, vooral omdat de behandeling van infecties in de huisartsprakijken voornamelijk met smalspectrum antibiotica en voor een korte periode plaatsvindt. In de ziekenhuiszorg worden relatief vaker breedspectrum

antibiotica voorgeschreven en regelmatig voor een langere periode en ook als er nog geen sprake is van een infectie. Als een patiënt drager wordt van een resistente bacteriestam dan is het risico op besmetting van andere patiënten zeer laag, zolang de drager niet wordt opgenomen in een ziekenhuis. Bij in het ziekenhuis opgenomen patiënten die drager zijn van resistente bacteriën bestaat wel het risico op overdracht van de resistente bacteriestam naar andere vaak kwetsbare patiënten.

De bijdrage van antibioticavoorschriften door huisartspraktijken op de antibiotica-selectiedruk hebben we gekwantificeerd in **hoofdstuk 2**. In deze studie, gebaseerd op openbrongegevens uit het Europees Centrum voor ziektepreventie en -bestrijding (ECDC), inventariseerden en vergeleken we de types en hoeveelheden antibiotica voorgeschreven in huisartspraktijken en in ziekenhuizen in 12 Europese landen waar de huisarts in meer of mindere mate als poortwachter fungeert. De antibioticaselectiedruk werd gekwantificeerd met een proxy-indicator, de antibiotica spectrumindex (ASI). De ASI omvat zowel de hoeveelheid gebruikte antibiotica als de activiteit tegen micro-organismen. De ASI drukt dit uit in een indexcijfer dat het spectrum van micro-organismen vertegenwoordigt dat gevoelig is voor dat geneesmiddel. Het kent numerieke waarden toe aan een antibioticum dat werkzaam is tegen 1 of meer van 13 categorieën bacteriën, waarbij lagere waarden duiden op middelen met een nauw spectrum en hogere waarden op middelen met een breder spectrum.

Onze analyse van antibioticavoorschriften levert op dat het aandeel penicilline-voorschriften uit de huisartspraktijk varieert tussen 29% en 65% in de 12 Europese landen. Tussen 80-90% van de cumulatieve ASI is afkomstig van die antibioticavoorschriften uit de huisartspraktijk. Dit aandeel is veel groter dan eerder werd aangenomen en een belangrijke bevinding, omdat eerdere studies lieten zien dat huisartsen nogal eens in de veronderstelling zijn dat het voorschrijven van antibiotica in de huisartspraktijk niet substantieel bijdraagt aan de ontwikkeling van antibioticaresistentie. De grote bijdrage aan de antibioticaselectiedruk door huisartspraktijken lijkt te maken te hebben met een verschuiving naar het voorschrijven van relatief meer breedspectrum antibiotica.

Determinanten van antibiotica voorschrijven

Uit een groot aantal eerdere studies blijkt dat een aanzienlijk aantal determinanten de beslissing beïnvloedt om een antibioticum voor te schrijven in de huisartspraktijk. Er ontbrak echter nog een overzicht van al deze determinanten en hoe die elkaar onderling beïnvloeden. Om het voorschrijven van antibiotica in de huisartspraktijk te

begrijpen en te verbeteren is een goed overzicht nodig. Hiervoor is het systematisch literatuuronderzoek verricht dat in **hoofdstuk 3** wordt beschreven.

Belangrijke patiëntgerelateerde determinanten waren dat patiënten soms een antibiotica voorschrift verwachten vanwege eerdere ervaringen, omdat ze hoge verwachtingen hebben van het effect van antibiotica of omdat ze er expliciet om vragen. Een belangrijke interactie tussen patiënt en huisarts die werd gevonden, was dat huisartsen aannamen dat patiënten een antibioticavoorschrift wilden als reden voor hun bezoek, maar deze veronderstelling in het consult met de patiënt niet verifieerden.

De beslissing om een antibioticum voor te schrijven moet, ook in de huisartspraktijk, in de eerste plaats gebaseerd zijn op een klinische werkdiagnose en op aspecten zoals patiëntkenmerken en de ernst, het type en de locatie van de infectie en het verwachte beloop en risico op complicaties. De beslissing bleek echter ook gebaseerd op niet-klinische determinanten. Hieronder vallen onder meer een grotere praktijkomvang en het ontbreken van de mogelijkheid om doeltreffend te onderhandelen over of uitleg te geven over het gebruik van antibiotica. Uit onze studieresultaten bleek dat determinanten uit meerdere domeinen (patiënten, praktijk, maatschappij en huisartsen) het voorschrijfgedrag beïnvloeden en elkaar met name versterken in het “overmatig” voorschrijven van antibiotica.

Kwaliteit en kwantiteit van antibioticavoorschriften gedurende de COVID-19 pandemie

Een nieuwe virale luchtweginfectie, het ernstige acute respiratoire syndroom coronavirus 2 (SARS-CoV-2), was de afgelopen jaren pandemisch aanwezig en zorgde voor veel ziektelast. Hoogstwaarschijnlijk zullen andere nieuwe luchtweginfecties de komende decennia volgen. Dergelijke nieuwe virale luchtweginfecties hebben de neiging om het antibiotica voorschrijfgedrag van artsen te veranderen. In de beginfase is er weinig bekend over een effectieve behandeling, morbiditeit en mortaliteit. Vanwege deze onzekerheid schrijven artsen soms antibiotica voor in de hoop het beloop van de infectie te veranderen en complicaties te voorkomen, zoals een bacteriële superinfectie, longontsteking of ziekenhuisopname. Inzicht in het voorschrijfgedrag is essentieel voor doelgerichte feedback aan huisartsen.

In een observationele cohortstudie (**hoofdstuk 4)** onderzochten we het effect van de COVID-19 pandemie op het aantal antibioticavoorschriften in de huisartspraktijk. De frequentie van antibioticavoorschriften voor patiënten tijdens een COVID-19-

infectie werd vergeleken met de frequentie van antibioticavoorschriften voor patiënten tijdens een influenza- of influenza-achtige infectie in andere jaren. Verder is de associatie van antibioticavoorschriften met risicofactoren op een ongunstig beloop van COVID-19 infectie onderzocht.

In onze studie bleken minder antibiotica te zijn voorgeschreven aan patiënten tijdens een COVID-19 infectie dan tijdens een vergelijkbare influenza of een influenza-achtige infectie in vier andere griepseizoenen. Dit komt overeen met de resultaten uit andere studies waaruit blijkt dat er tijdens de COVID-19 pandemie in totaal minder antibiotica werden voorgeschreven in vergelijking met voorgaande jaren. Het verminderde voorschrijven van antibiotica aan patiënten gedurende een SARS-CoV-2 infectie was mogelijk het gevolg van het intensief testen op SARS-CoV-2 tijdens de COVID-19 pandemie, terwijl er tijdens de voorafgaande griepseizoenen niet op het influenzavirus werd getest. Voor patiënten en huisartsen was het tijdens de pandemie na een test duidelijk dat SARS-CoV-2 de symptomen veroorzaakte en dat een antibioticum niet nodig was. Patiënten met risicofactoren op een ernstiger beloop kregen vaker wel een antibioticum voorgeschreven dan patiënten zonder risicofactoren. Het verminderen van diagnostische onzekerheid over de verwekker van een luchtweginfectie kan mogelijk leiden tot minder en gerichter antibioticavoorschriften.

Verbeteren registratie van antibiotica-allergieën

Allergieën voor antibiotica behoren tot de meest gerapporteerde bijwerkingen van medicatie. Adequate registratie van deze allergieën is essentieel om zeldzame maar mogelijk levensbedreigende reacties bij herhaalde blootstelling te voorkomen. In de Nederlandse huisartspraktijken heeft 0,6% tot 2,1% van de patiënten een antibiotica-allergieregistratie in het elektronisch patiëntdossier. Echter, 80 tot 90% van de registraties van antibiotica-allergieën in de huisartspraktijk blijkt onterecht. Onterechte antibiotica-allergieregistraties leiden tot meer doktersbezoeken, hogere zorgkosten en het vaker voorschrijven van tweede keuze antibiotica. De tweede keuze antibiotica hebben vaker een breder werkingsspectrum en dat bevordert de selectie van resistente bacteriën. Het verwijderen van een als “onterecht” ontmaskerde allergie-registratie blijkt bijzonder moeilijk: De elektronisch patiëntendossiers (EPD) in ziekenhuizen, apotheken en huisartspraktijken met antibiotica allergie registraties corrigeren elkaar niet adequaat.

In onze studie in **hoofdstuk 5** maakten we gebruik van dossieranalyse en van semigestructureerde interviews onder zorgverleners uit meerdere domeinen (apotheek, verpleeghuis, ziekenhuis en huisartspraktijk). Daarmee onderzochten we

welke informatie bij een antibiotica-allergie registratie staat in een EPD, de oorzaken van onjuiste registraties van antibiotica-allergieën zijn en hoe registraties verbeterd kunnen worden.

Een belangrijke bevinding van deze studie was dat in de meeste gevallen (56,3%) de geregistreerde informatie onvoldoende was om te bepalen of de reactie inderdaad van allergische aard was. Dit benadrukt dat het registreren van reacties na inname van antibiotica in grote mate verbeterd kan worden. De belangrijkste oorzaken van onvoldoende kwaliteit van de registraties waren een gebrek aan kennis, gebrek aan gevoel voor prioriteit, beperkingen van registratiefuncties in het EPD en patiënten en artsen die bijwerkingen interpreteren als allergieën. Het unieke van onze bevindingen was dat de determinanten in alle onderzochte domeinen overeenkwamen. Dit ondersteunt de noodzaak van het ontwikkelen van domein overstijgende interventies.

Verbeteren van kwaliteit van antibioticavoorschriften in de huisartspraktijk

Hoewel in **hoofdstuk 3** al veel determinanten waren geïdentificeerd, ontbraken in dat en eerder onderzoek elders, de sociaaleconomische determinanten en contextinformatie over de huisartspraktijken. Het was onvoldoende duidelijk langs welke route en in welke mate dan, de kwaliteit van het voorschrijven van antibiotica in de huisartspraktijk verbeterd kan worden. Middels een retrospectieve observationele cohortstudie (**hoofdstuk 6)** hebben wij vervolgens bruikbaarheid van grote gekoppelde gezondheidszorgregisters voor onderzoek naar antibioticavoorschriften in de huisartspraktijk onderzocht. Een tweede vraag was hoe groot het verbeterpotentieel in het voorschrijven van antibiotica zou kunnen zijn en in welke mate de bovengenoemde nieuwe patiënt – en praktijkdeterminanten van invloed zijn op het passend voorschrijven van antibiotica.

Het was mogelijk twee grote registers, huisartsendata uit het extramuraal Leiden Academische (ELAN) netwerk en data van het Centraal Bureau voor de statistiek (CBS), op individueel patiëntniveau te combineren. Hierdoor konden we toch de associaties onderzoeken van verschillende determinanten die niet routinematig in een EPD zijn geregistreerd, met de verschillende eindpunten, zoals passend antibiotica voorschrijven.

In ons onderzoek waren 17,8% van alle antibioticavoorschriften niet in overeenstemming met de aanbevelingen in de richtlijnen. Van de antibioticavoorschriften voor een luchtweginfectie waren 39,6% niet noodzakelijk volgens de richtlijnen. Het gevonden percentage overprescriptie van antibiotica voor luchtweginfecties komt overeen met dat in eerdere Nederlandse studies. Ook buitenlandse studies hadden vergelijkbare

en met regelmaat hogere percentages. Daarnaast kwam 77,1% van de macroliden voorschriften niet overeen met de eerste en tweede keuze in richtlijnen. Een eerdere Nederlandse studie vond een vergelijkbaar percentage overprescriptie van macroliden.

Wij vonden verschillende patiëntdeterminanten die geassocieerd zijn met het overmatig voorschrijven van antibiotica: vrouwelijk geslacht, leeftijd van 5 jaar en ouder en migratieachtergrond (Turks, Surinaams, Nederlands-Caribisch). Vrouwelijk geslacht en leeftijd waren al bevestigd in meerdere studies als belangrijke patiëntdeterminanten. Dat migratieachtergrond een determinant is, was nog niet eerder vastgesteld.

Een niet eerder in Nederland vastgestelde praktijkdeterminant die bleek te zijn geassocieerd met overmatig antibiotica voorschrijven was een grotere praktijkomvang. Eerdere onderzoeken uit het Verenigd Koninkrijk en Canada presenteerden hierover tegenstrijdige resultaten. Het Engels onderzoek vond wel een associatie en het Canadese onderzoek niet. De context en locatie (stad of platteland) van de praktijk was in deze onderzoeken een mogelijke verklaring van het verschil. Wij hebben het onmiskenbare verschil dat wij vonden, voorzichtig geïnterpreteerd als een argument “meer tijd en continuïteit voor de patiënt” te creëren.

Conclusie en aanbevelingen

Een belangrijke overkoepelende bevinding in onze studies is dat antibioticavoorschriften vanuit huisartspraktijken een veel grotere bijdrage leveren aan de ontwikkeling van antibioticaresistentie dan eerder werd aangenomen en dat uit de Europese data (inclusief Nederland) blijkt dat de mate van voorschriften uit de eerste lijn correleert met resistentieontwikkeling.

De belangrijkste determinanten voor het overmatig voorschrijven van antibiotica zijn diagnostische onzekerheid, de omvang van de huisartspraktijk (wellicht als maat voor beschikbare tijd in consulten en continuïteit in de “arts-patiënt-relatie”), de onmogelijkheid om doeltreffend te onderhandelen - of uitleg te geven over antibioticagebruik en de veronderstelling van huisartsen dat patiënten ‘een antibiotica voorschrift verwachten’.

Er zijn drie in het oog springende aspecten waarop het voorschrijven van antibiotica in huisartspraktijken kan worden verbeterd. Er zijn te veel antibioticavoorschriften voor patiënten met een luchtweginfectie. In plaats van de breedspectrum antibioticagroep macroliden kan veelvuldig voor een smalspectrum antibioticum worden gekozen. En er

wordt relatief overmatig antibiotica voorgeschreven aan patiënten met een specifieke migratie achtergrond (Turks, Nederlands-Caribisch, Surinaams).

Verder kan de registratie van antibiotica-allergieën worden verbeterd door onderwijs aan huisartsen om meer bewustzijn en kennis over antibiotica-allergieën te creëren, door het verifiëren van bestaande registraties van antibiotica-allergieën en het vergemakkelijken van registratie in een EPD zodat de verschillende EPD's beter op elkaar aansluiten en elkaar niet tegenwerken. Dit kan leiden tot vermindering van het aantal onbevestigde antibiotica-allergieregistraties en daarmee bijdragen aan het voorschrijven van eerste keuze antibiotica in plaats van tweede keuze (breedspectrum) antibiotica.

De toename van ABR vergt een actuele en meer proactieve surveillance van antibioticagebruik en resistentie in de huisartsenzorg. Bij een toename van antibioticagebruik en specifiek van breedspectrum antibiotica of van resistente bacterie groepen kan direct een interventie gericht op deze ontwikkelingen plaats vinden, bijvoorbeeld door aanpassingen in nationale richtlijnen, berichten in nieuwsbrieven van nationale organisaties of aandacht voor deze ontwikkelingen in het farmacotherapeutisch onderwijs. *Artificial Intelligence* (AI) of *Big Data* analyses kunnen bijdragen aan deze surveillance. In dit proefschrift hebben we laten zien dat Big Data toepasbaar is voor analyse van antibioticagebruik. Hierdoor zijn ook relevante associaties ontdekt zoals die tussen overmatig antibiotica voorschrijven en praktijkgrootte. Het gebruik van AI bij surveillance en analyse van antibioticavoorschrijfgedrag is wellicht de volgende, nog te onderzoeken, stap.

Curriculum vitae

Martijn Sijbom was born in 1977 and raised in Emmen. He attended the Gemeentelijk Scholen Gemeenschap in Emmen, where he passed his VWO exams in 1995. Initially, he was unable to study medicine and instead studied bio-pharmaceutical sciences at Leiden University. In 1996, he was accepted into the study of medicine at Leiden University. During his studies, he conducted research at the department of paediatric cardiology at Massachusetts General Hospital in Boston, USA. This experience sparked his interest in research. He completed an internship in paediatrics at Kanti Children's Hospital in Kathmandu, Nepal, where he witnessed the possibility of achieving a lot with limited resources. This experience inspired him and fellow Dutch students to establish the Medicine for ALL foundation, which raises funds for the treatment of childhood leukaemia in Nepal. After graduating as a physician in 2004, he began working in the paediatrics department of the Albert Schweitzer hospital in Dordrecht, and later at the Wilhelmina children's hospital. In 2006, he began the GP training, which he successfully completed in 2009. Since then, he has worked in various primary care practices in the Hague area. From 2011 to 2018, he worked as a scientific collaborator at the Dutch General Practitioner Society (NHG), where he was involved in making and updating (NHG) guidelines. In 2018, he joined the LUMC campus The Hague as a GP researcher and began work on this dissertation. The author combined thesis writing with work for the antimicrobial resistance network Holland West. During the winter of 2020, the author and their family resided in Cape Town, South Africa for three months. The author worked with Professor Marc Mendelsson at the Infectious Diseases Department of Groote Schuur Hospital in Cape Town. He currently holds a permanent position as a researcher in infectious disease and antibiotic use in primary care and a lecturer in the Master Population Health Management at the Hague Campus of the Department of Public Health and Primary Care of LUMC. He is a member of the SWAB working group on Antibiotic Surveillance and the working group Antibiotic Stewardship in Primary Care. He lives in The Hague with his spouse, Ymre, and their two children, Niven and Wende. In his leisure time, he enjoys windsurfing when the wind is blowing from the southwest at speeds of 6 Beaufort or even more and mountain biking in the Ardennes with his friends.

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Nawoord

De afgelopen jaren als promovendus heb ik als een voorrecht beschouwd. Het LUMC bood me de mogelijkheid om me volledig te gaan verdiepen in antimicrobiële resistentie en antibioticagebruik. Het was niet altijd even gemakkelijk door de periodes van migraine aanvallen, deze zijn nu gelukkig over, maar desondanks heb ik enorm van mijn promotietijd genoten. Uiteraard kon ik dit promotie traject niet alleen volbrengen en had ik hiervoor een geweldig team om me heen. Zonder hen was ik niet met zoveel plezier, uitdaging en reflectie door het onderzoek gelopen en ik wil ze graag bedanken.

Allereest professor M.E. Numans, Mattijs, zonder jou was dit proefschrift niet tot stand gekomen. Je haalde me over om te gaan werken bij het LUMC als onderzoeker en als lid van het AMR netwerk Holland West. Tijdens het promotietraject wist je bij onze onderzoeken de rode draad vast te houden, te benadrukken wat belangrijk voor de huisartsgeneeskunde is en heel snel de vinger op de zere plek te leggen. Professor M.G.J. de Boer, Mark, ondanks je drukke schema maakte je altijd ruim tijd vrij voor ons onderzoek. En elke keer als ik dacht dat een onderzoek af was, kwam je altijd met een zeer scherpe extra analyse, nieuwe invalshoek of verdieping. Steeds zijn onze onderzoeken hierdoor verscherpt en verdiept.

Frederike Buchner, dank voor je hulp met het leren schrijven van een wetenschappelijk artikel. Je bleef altijd hameren op structuur en details (niet mijn sterkste punt). Zoals je veelvuldig schreef in reactie op mijn manuscripten, ’ik heb een paar gemene opmerkingen in het manuscript gezet’. Nicholaas Saadah, of te wel Nic, je was onmisbaar als native speaker Engels en met je kennis van epidemiologie. Je wordt nog altijd gemist bij de lunch op de campus en om je grote kennis van feiten ‘waar je niks aan hebt’. Mirte Boelens, dank voor je hulp bij het afronden van het laatste manuscript en het proefschrift. Achter je bescheiden verschijning gaat een heel grote bron van epidemiologische kennis verscholen, ondanks dit je eerste stappen als co-promotor waren wist je al heel veel.

Meerdere onderzoeken in dit proefschriften gebruikten data uit het datawarehouse van het Extramurale Leiden Academisch Netwerk (ELAN). Het datawarehouse is gevuld met medische informatie uit medische dossiers uit huisartspraktijken. Ik ben veel dank verschuldigd aan de huisartsen die deze data beschikbaar hebben gesteld. Ook ben ik zeer erkentelijk voor de hulp van de ELAN werkgroep. In het bijzonder van de datamanagers Henk de Jong en Frank Ardesch. Jullie hebben met veel geduld en snelheid al mijn (onmogelijke) verzoeken en aanvragen om data behandeld en jullie

dachten actief mee hoe ik bepaalde informatie uit de data kan halen. Zonder jullie hulp was dit proefschrift niet tot stand gekomen.

Hedwig Vos en Jessica Kiefte-de Jong, dank voor jullie hulp als promotiebegeleidingscommissie.

Dear Josh Turknett, we never met and you did not actually help to write this thesis. But without your book “the Migraine Miracle”, this thesis never would have been finished. I would still being suffering from weekly migraines and not have been able to work.

Dear professor Marc Mendelson, thank you for accommodating me at your department of infectious diseases at the Groote Schuur Hospital in Cape Town, South Arica. Our stay in South Africa was wonderful, we enjoyed it very much.

Lieve Niven en Wende, dank voor wie jullie zijn. Jullie laten me zien wat echt belangrijk is. Lieve Ymre, we zijn al meer dan 15 jaar samen. Elkaar blijven steunen in goede én slechte tijden heb je zeker gedaan in die 15 jaar, jouw steun is onontbeerlijk geweest. Van de zuidwest 6 clausule hoop ik nog wel even gebruik te maken.