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

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Chapter 6

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

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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.

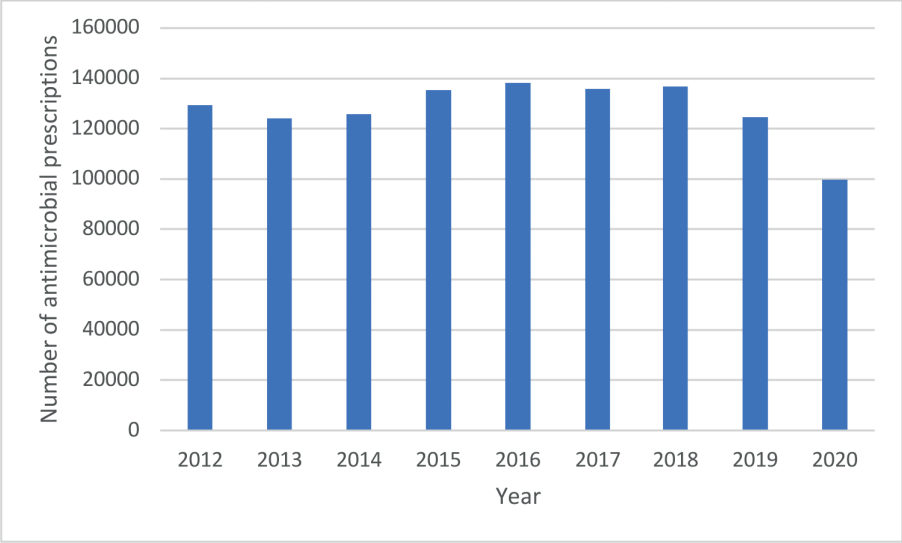


Figure 2 Antimicrobial prescriptions per antimicrobial group each year.

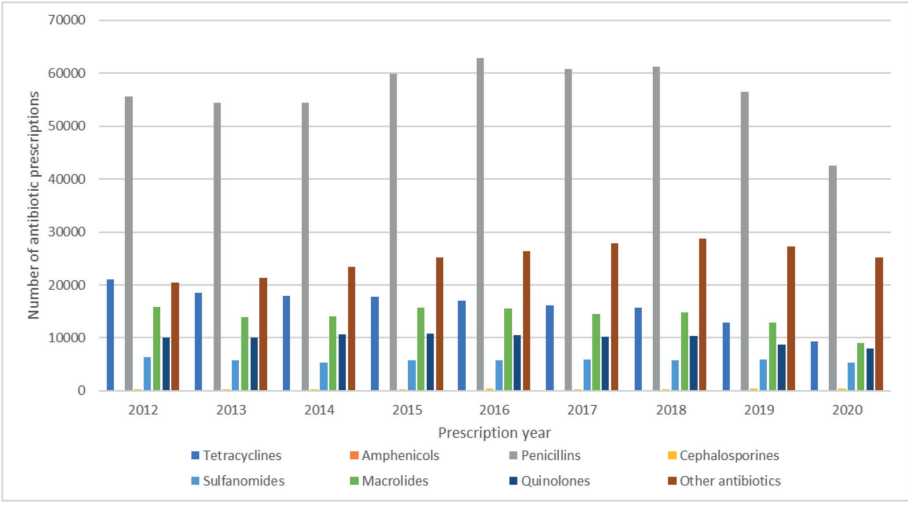
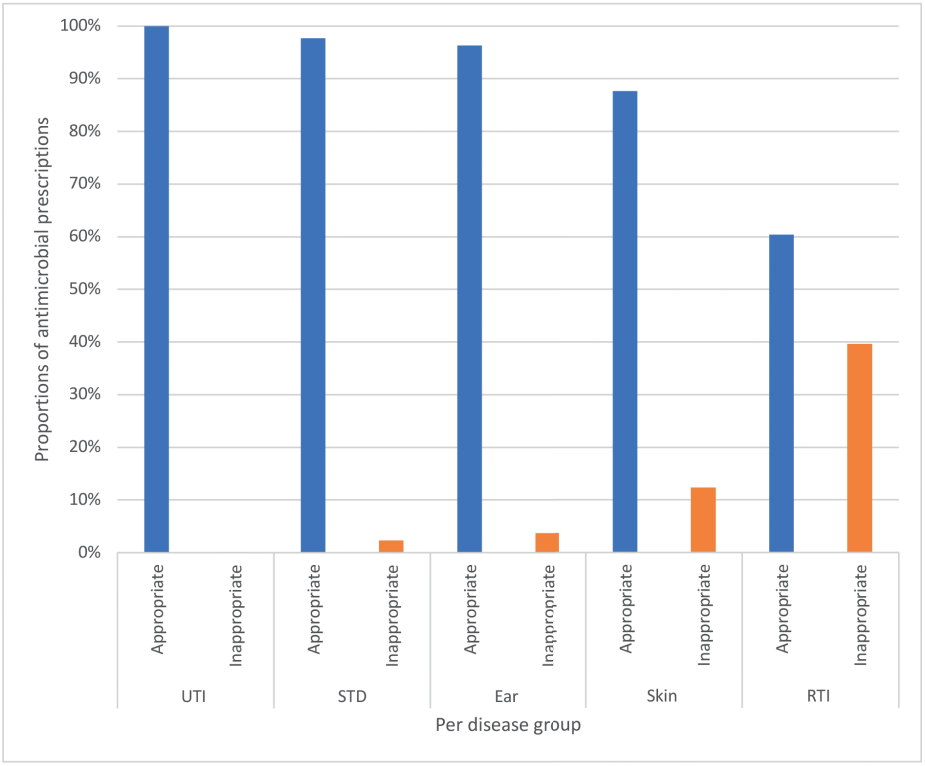
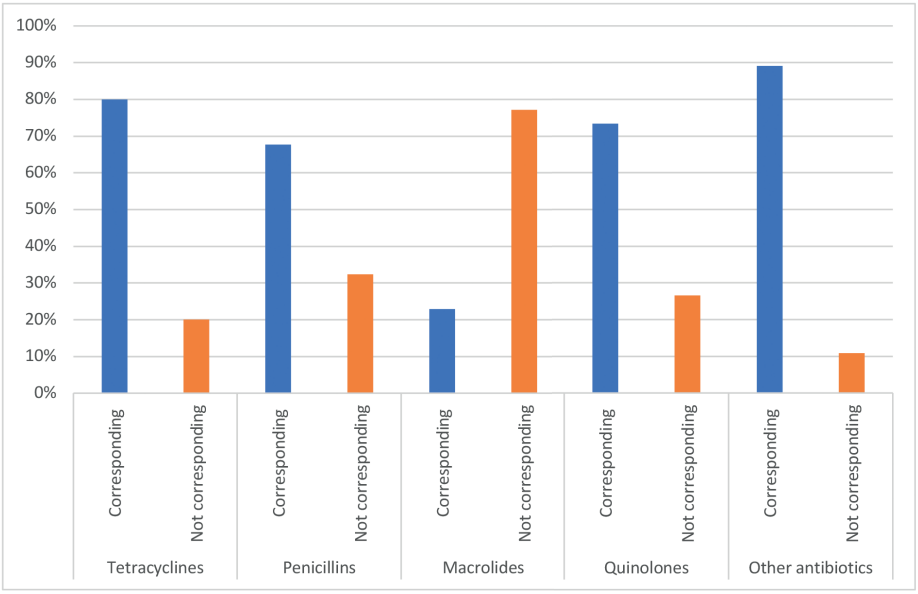


Figure 3 Proportions of appropriate and inappropriate antimicrobial prescriptions per disease group.



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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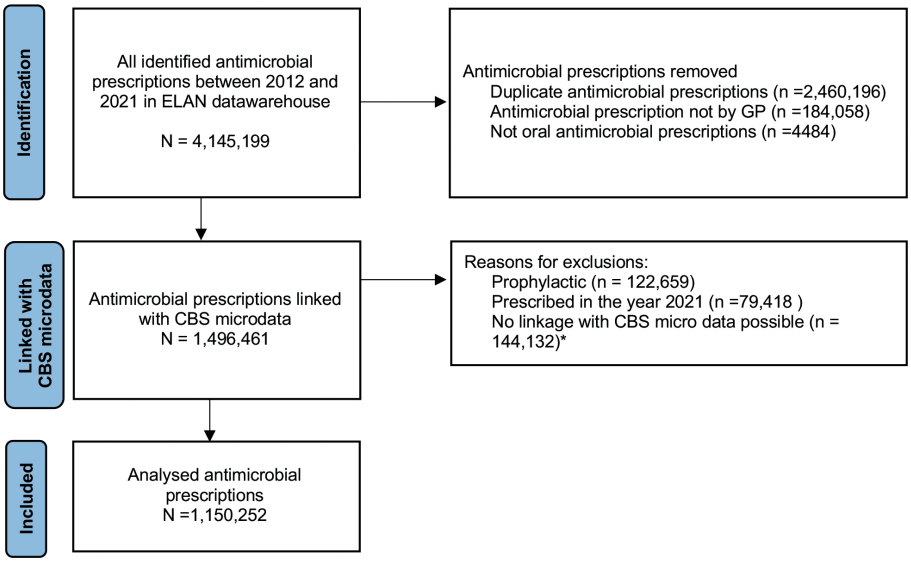
Supplements

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.