Antibiotic use in Dutch primary care: relation between diagnosis, consultation and treatment

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Objectives: Countries generally present their overall use of antibiotics as an indicator of antibiotic prescribing quality. Additional insight is urgently needed for targeted improvement recommendations: first, data on specific clinical indications for which antibiotics are used, and second, on distinguishing whether changes in patient consultation or changes in physician prescribing drive changing antibiotic use for particular indications. The aim of this study was to describe the antibiotic management of infectious diseases in the clinical context, by analysing prescribing by physicians and patient consultation incidences per indication over time.

Methods: A database with all contact data for infectious diseases from 45 primary care practices in the Netherlands (2007–10) was used. Consultation incidences, prescribing rates and choice of antibiotic were analysed per International Classification of Primary Care (ICPC) chapter and relevant ICPC codes.

Results: Antibiotics were prescribed in ~25% of infectious disease episodes, mainly respiratory infections, urinary infections and ear and skin infections. Overall, this resulted in 300 prescribed courses of antibiotics per 1000 patient-years. Given a stable prescription rate, a 19% increase in the number of consultations explained the increased antibiotic prescribing for urinary tract infections. Given a stable consultation incidence, an 8% reduction in prescribing rate explained the decreased antibiotic prescribing for respiratory tract infections. Macrolides were predominantly prescribed for respiratory disease (~66%), amoxicillin/clavulanate for respiratory disease (~42%) and urinary illness (~25%), and fluoroquinolones for urinary and genital indications.

Conclusions: Insight into the reasons for the decreased prescribing for respiratory tract infections and the increased prescribing for urinary tract infections was provided by a detailed analysis of incidences and prescribing rates. For respiratory disease, the second- and third-choice antibiotics were overused. Complete data on infectious disease management, with respect to patient and physician behaviour, are crucial for understanding changes in antibiotic use, and in defining strategies to reduce inappropriate antibiotic use.

Keywords: infections, disease management, prescriptions, ICPC, quality

Introduction

The excessive use of antibiotics is an urgent and worldwide public health problem. Compilation of evidence shows that antibiotics are heavily overused for many indications, with respiratory tract infections (RTIs) in the lead.1–3 This overuse drives the development of antimicrobial resistance, the medicalization of patients, and increasing healthcare costs.4 An awareness of antibiotic overuse has triggered action directed towards physicians, policy-makers and the public.5,6

In this respect, a proper recording of antibiotic use is essential to detect changes and to initiate appropriate action. Great progress has been made by the European Surveillance of Antimicrobial Consumption (ESAC) project, monitoring outpatient antibiotic use from 33 countries.7 These data have revealed that the quality of antibiotic prescribing is decreasing, as the total volumes, proportional use of second-choice antibiotics and seasonal variation have increased.8

Notwithstanding the relevance of these data, physicians, as well as policy-makers, would benefit from data providing more clinical context. In this respect, particularly relevant aspects are: (i) how many and which specific antibiotics are being prescribed for which indications; and (ii) the need to distinguish the changes in the consultation rates of patients from the prescribing rates of physicians as drivers for changing antibiotic use for specific indications.
ESAC, as well as the Happy Audit group, has proposed indication-specific quality indicators for outpatient antibiotic prescribing.\textsuperscript{9,10} For some indications, prescribing percentages were calculated using routine Belgian primary care data; data on patient consultations were not included.\textsuperscript{11} European data had already shown that differences in consultation, caused by differences in the threshold for consulting, e.g. due to the triage system or the need for a sickness certificate, obscure comparisons of prescribing rates.\textsuperscript{12} This emphasizes the need to analyse prescribing, as well as consultation rates; together they determine antibiotic use per indication in the population.

The Netherlands has a comparatively low and stable antibiotic use in primary care.\textsuperscript{13} Antibiotics can only be purchased with a physician’s prescription. Patients do not pay for their medication, although there is a yearly own-risk for medical costs. Primary care physicians function as a general first line of patient management and as gatekeepers for hospital care; they are paid per registered patient, as well as per consultation. Combined with a far-reaching digitization of patient data and physician prescribing, the Netherlands provides good opportunities to investigate trends in antibiotic management in light of the clinical context.

We aim to describe trends in antibiotic use by analysing physician prescribing rates and patient consultation incidences for the complete range of infectious disease indications in Dutch primary care. These data will provide insight for identifying focus areas, targeting improvement strategies and awareness campaigns, and optimizing surveillance systems.

**Patients and methods**

**Database: prescription and consultation for infectious diseases**

Contact data were obtained from the Julius General Practitioners Network database, containing anonymous routine healthcare data from the digital patient records of 45 general practices (160 GPs, full time and part time) in Utrecht and its vicinity. Participating practices were located in a typical Western European (sub)urban region, in the city of Utrecht and in the surrounding villages; single-, two-, and three-handed practices, as well as primary care centres, participated. We regard this group of physicians with their patient population as a representative Dutch sample. The database contains information on all office-hours contacts during week days. The vast majority of contacts are International Classification of Primary Care (ICPC)-coded,\textsuperscript{14} and all antibiotic prescriptions are registered according to the WHO guidelines for Anatomical Therapeutic Chemical classification (assignment 2013).\textsuperscript{15} Practitioners have been trained in correct ICPC coding, and have had experience in electronic medical records use and coding for over 10 years.\textsuperscript{16} All contacts with an ICPC code that might result in prescribing of a systemic antibiotic (Table S1, available as Supplementary data at JAC Online) were extracted from 2007 to 2010. Contacts with the same ICPC codes within a pre-set time frame, based on professional knowledge, were combined into a disease episode. This dataset was supplemented with non- or other ICPC-coded contacts in which a systemic antibiotic was prescribed.

**Outcome variables and analysis**

For a complete picture of infectious disease management, the following parameters were determined for each year:

1. The number of antibiotic prescriptions and subclasses [tetracyclines (J01A), amoxicillin (J01CA), β-lactamase-sensitive/resistant penicillins (J01CE/CF), amoxicillin/clavulanate (J01CR), sulphonamides and trimethoprim (J01E), macrolides (J01F), quinolones (J01M), nitrofurantoin (J01XE) per 1000 patient–years (PY)]. PYs refer to the number of patients in the participating practices per year, adjusted for when patients joined or left the practice.
2. The distribution of prescriptions over the ICPC chapters, and within this the percentages of the most frequently used ICPC codes and the most often prescribed antibiotics.
3. Second-choice antibiotics: the ICPC codes for which amoxicillin/clavulanate, macrolides and quinolones were prescribed.
4. Prescribing rate: per ICPC chapter and of the most relevant ICPC codes, the percentages of episodes in which at least one antibiotic course was prescribed.
5. The numbers of specific disease episodes per 1000 PY. To also incorporate episodes belonging to non-ICPC-coded antibiotic prescriptions, these non-coded prescriptions were distributed over the individual ICPC codes according to the same proportions as determined from all ICPC-coded prescriptions. For this purpose, the distribution of ICPC codes per specific antibiotic was determined. Using the ICPC-specific prescribing rates, the non-coded prescriptions were converted to episodes that were added to the number of coded episodes.

**Results**

The characteristics of the infectious disease dataset are shown in Table 1, with an increasing number of PY, due to a growing population in the area. The number of contacts per episode ranged from 1 to 17, with an average of 1.4; 74% of episodes had one contact, 17% two contacts, 5.8% three contacts and 2.3% four contacts. After small increases in the number of infectious disease episodes and in the number of antibiotic prescriptions per 1000 PY, antibiotic use seemed to level off in 2010. The overall prescribing rate was about constant; at least one antibiotic course was prescribed in 24.8% to 26.3% of infectious disease episodes. A slightly increasing percentage of antibiotics was prescribed as a subsequent course within one disease episode.

With respect to the type of antibiotic prescribed, the use of nitrofurantoin per 1000 PY increased by 34% from 2007 to 2010. Furthermore, the prescription of narrow-spectrum penicillins and amoxicillin/clavulanate per 1000 PY increased by 11% and 7%, respectively; the relative contributions of the other subgroups decreased (Figure 1).

**ICPC chapters: indications and classes of prescribed antibiotics**

To gain a picture of trends in the indications for which antibiotics were prescribed, the distribution of prescriptions over the ICPC chapters was determined (Figure S1, available as Supplementary data at JAC Online). This figure also shows which specific indications and which antibiotic classes were most often used within the various ICPC chapters. The proportion of prescriptions for RTIs decreased from 49% to 43.8%, whereas the proportion of antibiotics for urinary tract and skin infections increased from 22% to
The proportion of prescriptions for ear and digestive system indications remained stable. For respiratory infections, most antibiotics were prescribed for 'acute upper RTI', followed by 'sinusitis', 'bronchitis', 'tonsillitis', 'asthma', 'acute cough' and 'pneumonia'. These most frequently used indications were not subject to a significant change from 2007 to 2010, nor were the specific antibiotic classes prescribed for respiratory indications (Figure S1, available as Supplementary data at JAC Online), with tetracyclines and amoxicillin accounting for about 65% of prescriptions. The prescribing of macrolides and amoxicillin/clavulanate was stable at 14% and 9%–10%, respectively.

For urinary tract indications, 'cystitis' was the most frequent indication (83%), followed by 'urgency' and 'dysuria'. Nitrofurantoin was increasingly prescribed, rising from 54% to 59%, whereas the prescription of trimethoprim, with and without sulfamethoxazole, decreased. The prescribing of amoxicillin/clavulanate and quinolones remained stable, both at ~12%.

Within the ear chapter, most antibiotics were prescribed for 'acute otitis media' (71%), followed by 'otitis externa' (11%) and 'serous otitis media' (6%). A small shift was observed from amoxicillin prescribing towards macrolides.

'Other skin infection', 'impetigo' and 'boil/carbuncle' dominated prescribing within the skin chapter, with little variation over the years. The relative use of fluoroquinolones increased.

**Prescription of macrolides, amoxicillin/clavulanate and fluoroquinolones**

Prescriptions for macrolides and amoxicillin/clavulanate each represented more than 10% of total antibiotic prescribing and prescriptions for quinolones about 6% (Figure 1). In most Dutch
primary care guidelines macrolides, amoxicillin/clavulanate and quinolones are second- or third-choice antibiotics. Figure 2 shows the specific indications for which these antibiotics were prescribed. Amoxicillin/clavulanate was prescribed for a large range of indications, predominantly respiratory and urological, at $\approx 42\%$ and $\approx 25\%$, respectively; 'cystitis' was the most frequent indication for amoxicillin/clavulanate prescribing. The prescription of this antibiotic for a large range of respiratory indications and otitis media declined somewhat between 2007 and 2010.

Macrolides were predominantly prescribed for respiratory tract indications ($\approx 66\%$; headed by 'upper RTIs', 'sinusitis' and 'bronchitis'), ear ($\approx 10\%$) and skin ($\approx 8\%$) infections, with ample variation over time. Fluoroquinolones were mainly ($\approx 50\%$) prescribed for urinary tract indications (increasingly for cystitis), and for respiratory ($\approx 17\%$), male genital ($\approx 10\%$) and gastrointestinal ($\approx 8\%$) indications.

**Prescribing rates and consultation incidences per ICPC chapter and individual codes**

The numbers of disease episodes per 1000 PY and prescribing rates were determined per ICPC chapter and for relevant ICPC codes within these chapters (Table 2). For respiratory tract indications, the number of disease episodes per 1000 PY was relatively stable, with a peak in the pandemic influenza year of 2009. The prescribing rate however, decreased from 24.5% to 22.5% of episodes in which at least one antibiotic was prescribed. The highest disease incidence was found for acute upper RTI, asthma and acute cough. The highest prescribing rates were for bronchitis, sinusitis and tonsillitis; the prescribing rates for bronchitis and sinusitis decreased from 2007 to 2010.

The incidence of urological indications increased by 19% from 124 to 148/1000 PY, whereas the prescribing rate did not change. The increase in incidence was mainly due to increases in cystitis and urgency episodes; the prescribing rates for these indications were stable.

Within the ear chapter, the incidence of otitis media showed a small increase, whereas the prescribing rate seemed to decrease. For skin infections, both disease incidence as well as prescribing increased somewhat.

**Discussion**

Monitoring infectious disease management with antibiotics is important to assess concordance with guidelines, to detect
changes and to be able to initiate appropriate action. National pharmacy or insurance company data have limited use, as these do not capture the diagnoses the antibiotics were used for. We therefore analysed primary care-based data on consultation and antibiotic prescribing for the complete range of infectious diseases (ICPC). This revealed that, although total antibiotic prescribing was relatively constant, there was less prescribing for respiratory tract disease and increased prescribing for urinary tract disease between 2007 and 2010. A detailed analysis of prescribing rates and consultation incidences suggested that decreased antibiotic use for respiratory illness is at the physician’s discretion, by a decreasing prescribing rate, whereas the increased use for urinary disease depends on the patient’s influence, by an increasing consultation incidence. A remarkable finding for a low-prescribing country was that most antibiotics prescribed for respiratory disease were for upper RTIs and sinusitis, which is not in accordance with guideline recommendations. Furthermore, amoxicillin/clavulanate and macrolides, the second- and third-choice antibiotics in respiratory disease management, were frequently prescribed for these indications.

Comparison with the existing literature
Total antibiotic prescribing can best be compared with national pharmacy delivery data, showing prescriptions of 416, 420, 431, 429/1000 inhabitants, between 2007 and 2010.13 These data also incorporate prescriptions by professionals other than primary care physicians, e.g. hospital specialists and dentists, estimated to be 15% of prescriptions.17 Furthermore, our data did not include out-of-office hours prescriptions, explaining the remaining difference. Given the same trend as national data and the similar distribution of subclasses of antibiotics,13 we regard our data as reliable and complete. No information with respect to consultation incidences related to individual ICPC codes is available from other Dutch cohorts, so reliability in this aspect can therefore not be determined.

Various studies have been conducted on antibiotic prescribing in the Netherlands. Recently, using other primary care-based data, it was shown that overall prescribing for adults increased from 2000 up to 2009;18 the unit of analysis was the percentage of patients receiving at least one antibiotic per year, and no information on indications was available. A study analysing consultation and prescribing rates for a subset of respiratory disease found increased consultation rates between 1995 and 2005, as well as a prescribing rate increasing to a value of 36% in 2005.19 For the complete set of respiratory indications, we found a prescribing rate of 24.5% in 2007. The analysis of Van Deursen et al.19 was limited to a subset of 10 ICPC codes and linked prescriptions to these ICPC codes within a time frame of 7 days, without taking different disease durations into account. Compared with a study of 2001, we found significantly lower prescribing rates for sinusitis (70% in 2001 and 53% for 2007–10) and for tonsillitis (72% in 2001 and 55% for 2007–10),20 which is consistent with reduced prescribing for RTIs over the years in the Netherlands. Specifically with respect to otitis media, our prescribing rate of 47% was lower than Dutch prescribing for otitis media in 2001 (56%).21 Prior to our time frame, a decreasing incidence of otitis media was observed in the Netherlands, which could be due to

| Table 2. Prescribing percentages and consultation incidences within ICPC chapters R, U, H and S |
|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 |
| **episodes/1000 PY** | **prescribing %** | **episodes/1000 PY** | **prescribing %** | **episodes/1000 PY** | **prescribing %** | **episodes/1000 PY** | **prescribing %** |
| **Respiratory** | 543 | 24.5 | 537 | 23.9 | 595 | 22.1 | 550 | 22.5 |
| R74: acute upper RTI | 93.1 | 21.6 | 95.9 | 21.6 | 113 | 18.8 | 98.9 | 19 |
| R75: sinusitis | 34.1 | 57.2 | 32 | 53.7 | 32.9 | 52.1 | 32.6 | 49.7 |
| R76: tonsillitis | 19.3 | 55.2 | 17.8 | 53.2 | 17.8 | 52.1 | 17.4 | 58.2 |
| R78: bronchitis | 30.1 | 57.7 | 30 | 56.9 | 28.7 | 54.3 | 25.7 | 52.1 |
| R95: COPD | 44.8 | 18.5 | 46.6 | 18.6 | 48.8 | 17.8 | 50.6 | 18.1 |
| R96: asthma | 69.1 | 12.8 | 68.7 | 12.2 | 68.6 | 12.5 | 67.1 | 11.6 |
| R97: allergic rhinitis | 55.7 | 5 | 55.9 | 5 | 59.5 | 5.2 | 56.6 | 4.5 |
| R05: cough | 63.8 | 16.3 | 65 | 16.4 | 72.3 | 15.4 | 67.6 | 15.6 |
| **Urological** | 124 | 49 | 133 | 49.4 | 142 | 48.5 | 148 | 49.1 |
| U71: cystitis | 78.1 | 59.5 | 83.5 | 59.6 | 90.1 | 59.6 | 93.4 | 60.4 |
| U02: urgency | 15 | 20.8 | 17.2 | 20.4 | 18.8 | 19.5 | 20.2 | 20 |
| **Ear** | 88 | 27.1 | 88 | 28.4 | 91 | 27.6 | 91 | 27.2 |
| H71: acute otitis media | 34.9 | 47.3 | 36.4 | 49.7 | 38.1 | 47.3 | 38.2 | 45.8 |
| H70: otitis externa | 23.2 | 10.1 | 23.1 | 11.1 | 23.5 | 10.9 | 22.8 | 11.1 |
| **Skin** | 59 | 27.1 | 59 | 29.3 | 63 | 29.2 | 65 | 30.9 |
| S76: other skin infection | 8.1 | 54.1 | 8.9 | 54.9 | 9.3 | 52.7 | 9.4 | 56.5 |
| S84: impetigo | 13.3 | 25.6 | 13.4 | 24.6 | 14.3 | 27.2 | 14.7 | 27 |

COPD, chronic obstructive pulmonary disease.
Hib vaccination and changes in the Dutch otitis media treatment guidelines. The pneumococcal vaccine was gradually introduced to the Netherlands in 2006; our data did not show significant reductions in consultation and antibiotic use yet.

Specifically for respiratory infections, a UK study showed decreasing consultation, as well as falling prescribing rates from 1997 to 2006, whereas a Swedish study found decreasing consultation with a constant prescribing rate from 2000 to 2005. Although neither study analysed the complete set of diagnostic and symptomatic respiratory indications, these European data also suggest decreased prescribing for respiratory tract illness. One UK study has also analysed the complete spectrum of infectious diseases, resulting in 10 leading indications for antibiotic use: upper RTI, lower RTI and sore throat headed the list (40%), followed by urinary tract infections (8%), acute otitis media (8%) and conjunctivitis (6%); the authors did not describe how these groups were defined. When individual diagnoses were analysed, higher prescribing rates were found than in our study: 63% for acute otitis media, 85% for sinusitis, 91% for impetigo and 83% for cystitis. The same holds for Belgian prescribing rates for the leading ear, respiratory and urinary infections, which are consistently higher than the Dutch rates, e.g. 80% for bronchitis in Belgium versus 55% in the Netherlands. These data indicate the need for and relevance of using databases with prescribing as well as consultation information for relevant ICPC codes. To our knowledge, not many countries are able to provide these data based on a substantial cohort, only the UK, the Netherlands and Scandinavian countries. A complete picture of infectious disease management allows inter-country comparison and analyses of drivers of change.

Strengths and limitations

The main strength of our study is the complete description of patient consultation behaviour and physician prescribing behaviour over the whole range of infectious diseases. The internationally accepted and widely used ICPC coding system was used for this purpose. In antibiotic use, many steps interfere at various levels. First, symptomatic patients have to decide whether or not to contact a physician. Second, the physician’s triage system determines whether these complaints warrant a consultation. Third, upon consultation, the physician diagnoses the patient and has to decide whether or not to prescribe an antibiotic. Changes in antibiotic use can be due to changes in decisions and procedures in these steps. Simply comparing prescribing rates at the level of the physician can be tricky and provide non-comparable data. For example, when 50 patients out of a population of 1000 consult for sinusitis, with a prescribing rate of 60%, 30 sinusitis courses are used per 1000 patients. This differs from a situation where 100 patients consult with the same prescribing rate, resulting in 60 courses for sinusitis per 1000 patients. For insight into ongoing processes in disease management, and for quality comparison, both measures are of relevance. In the literature, a large focus has been on prescribing for respiratory, ear and urinary tract infections, whereas our data also allow for detailed analyses of other areas. Our database appears to be a valuable tool to describe patient consultation behaviour and physician prescribing behaviour, providing a more complete insight into infectious disease management.

Some limitations need to be acknowledged. First, not all antibiotic prescriptions have yet been ICPC coded. As the percentage of non-ICPC-coded prescriptions decreased between 2007 and 2010 from 14% to 8%, a coding-related increase in episodes would have been found when only ICPC-coded prescriptions were analysed without a correction or matching procedure. We described how non-ICPC-coded prescriptions and their associated consultations were incorporated into our analyses. Although we acknowledge that this is not ideal, we feel it was the best way to deal with non-coded prescriptions. Second, we analysed per ICPC code; the transition in ICPC coding within one disease episode, e.g. from R05 to R78, counts as two episodes in our analysis. Third, in analysing physician antibiotic prescribing, the dosage and duration of the course were not considered, and furthermore it was not clear whether the patients indeed took their prescribed medication. Francis et al. have shown that a proportion of prescribed antibiotics for acute cough is not (completely) used by patients. Fourth, in our analyses we did not take patient age and gender into account; increasing age, for example, might partly explain increasing consultation and antibiotic use for urinary infections. Age-related issues are under investigation. Fifth, routine retrospective data cannot demonstrate causality. Increasing or decreasing incidences of particular ICPC codes might not directly represent changes in patient consultations. Switches in labelling by the physician, or alterations in triage or diagnostic criteria, might be possible explanations as well. However, by analysing not only specific diagnostic ICPC codes, but also the corresponding symptomatic codes, we controlled for this coding bias. Furthermore, between 2007 and 2010, none of the Dutch primary care guidelines for infectious urinary, respiratory or ear illness were subject to revision, and therefore the triage and diagnostic criteria were likely to be similar in our time frame.

Implications

The reduction in antibiotic prescribing for RTIs is a favourable development. However, there is still considerable prescribing for self-limiting RTI conditions (upper RTIs, sinusitis, cough, sore throat), as well as the prescribing of second- and third-choice antibiotics. Improvement strategies for antibiotic conservancy should focus on these aspects, and on the rapidly increasing antibiotic use for urinary tract infections. In addition to generating accumulated data, primary care physicians would also personally gain by data linked to diagnoses, providing them with an insight into their own practice. Danish primary care practices started performing routine extractions from their digital patient records, to support quality management (A. Muńck, University of Southern Denmark, Odense, personal communication)

Our description of the antibiotic management of infectious diseases was meant as a reference for future analyses in the Netherlands. As these data show important problems in antibiotic use in a low-prescribing country such as the Netherlands, similar analyses from other countries are urgently needed. Inappropriate antibiotic use and resistance problems have received much attention worldwide. Data such as we have presented here are of pivotal importance to revert this by targeted action and for surveillance purposes.
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Transparency declarations
None to declare.

Supplementary data
Table S1 and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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