Mismatch between Prescription and Dispensing of antibiotics in Community Pharmacies.

Khadija Ibrahim (5842638)

Master Pharmacy, Utrecht University

Daily supervisor: Milad Sadreghaemy

Referee: Dr. E.S. (Ellen) Koster

Examinator: Prof. dr. A.C.G. (Toine) Egberts

Division Pharmacoepidemiology & Clinical Pharmacology, Utrecht University

Abstract

Background: Antimicrobial resistance has become a global threat to public health systems around the world. Various factors contribute to the development of antimicrobial resistance such as overuse and inappropriate prescribing of antibiotics.

Aim: This cross-sectional study aims to determine the frequency of a mismatch between prescribed and dispensed quantities of antibiotics in community pharmacies and the causes thereof.

Methods: Prescription and pharmacy dispensing data on antibiotics for systematic use were obtained from pharmacy information systems for this cross-sectional study (PIS). The data was collected from 63 different community pharmacies. Using descriptive statistics and binary logistic regression the collected data was analysed.

Results: A total of 1577 prescriptions were included in the study. There was a mismatch between prescription and dispensed antibiotics in 10,6% (n=167) of the prescriptions. The most frequent discrepancy was caused by a mismatch between the number of prescribed antibiotics and standard packing sizes, which accounted for 59.9% of the total. In 65.2% of the mismatches, patients received fewer antibiotics than prescribed and 30% of the patients received more antibiotics.

Conclusion: This study's findings revealed that most of the antibiotic prescriptions are in line with the prescription made by the prescriber. And discrepancies in antibiotic prescription and pharmacy dispensing are primarily caused by a mismatch between clinical guidelines followed by prescribers and antibiotic packaging sizes.

Introduction

Antimicrobial resistance has become a global threat to public health systems around the world [1]. The main consequence of antimicrobial resistance is that severe infections will become increasingly difficult to treat. Various factors contribute to the development of antimicrobial resistance such as overuse, and inappropriate prescribing of antibiotics [1]. A mismatch between prescription and medication dispensing in the pharmacy might contribute to unused antibiotics [2].

Different reasons may contribute to a mismatch between prescription and dispensing. One of the reasons is the poor accordance of antibiotic packaging size with the actual treatment duration. Prescribers follow clinical practice guidelines when prescribing antibiotics to ensure appropriate antibiotic use with clinical indication, suboptimal dosing, and duration. Factors such as the package size might have an impact on antibiotic use [2]. Most antibiotics are packaged by manufacturers in packs that are influenced by duration. The most common package size for doxycycline is an eight-tablet packet in the Dutch market. This means that the packing size matches the guideline recommendations for specific infections, however for other indications, there might be a discrepancy between the packing size and the prescription [3][4]. Any discrepancy might contribute to unused antibiotics and, if taken by patients on some other occasion without indication, might contribute to antimicrobial resistance [5][6]. Dispensing fewer antibiotics can cause inadequate antimicrobial treatment of infections. In studies, it is observed that the widespread use of less than recommended doses of antibiotics may affect the health of the population by facilitating the development of antimicrobial resistance [7].

Medication waste is another possible result of a mismatch between prescription and dispensing. Medication waste can occur during prescribing and dispensing of antibiotics and contribute to antibiotic resistance and raise healthcare costs [8]. During the prescribing phase, medication waste can occur when the prescriber prescribes excessive quantities. This may result in medication remaining unused. Most unwanted or expired medicines are disposed of by household waste, toilet, or sink and only a minority are returned to pharmacies [9]. This inappropriate disposal ends up in landfills, water supplies, and drains that lead to contamination of the environment, contribute to antibiotic resistance, and raise healthcare costs [10]. To find sustainable solutions for these challenges, it is important to identify how often there is a mismatch between the prescription and dispensing of antibiotics.

Aim of the study

This study aims to determine the extent of mismatch between prescription and dispensing of antibiotics in the pharmacy. Additionally, the study aims to evaluate the reasons for changing the prescriptions, as well as the impacts on patients.

Methods

Study design

For this cross-sectional study prescription data and pharmacy dispensing data on antibiotics for systematic use were retrieved from pharmacy information systems (PIS). The data collected, were used to review whether there was a frequent mismatch between antibiotic prescription and dispensing. The study population consisted of all patients with an oral-systemic antibiotic prescription. Prescriptions for suspensions, parenteral dosage forms, ear drops, and eye drops, topical dosage forms such as ointments were excluded from the data.

The study was conducted in 63 community pharmacies. Prescription data and pharmacy dispensing data from 60 pharmacies were collected by pharmacy master students at Utrecht University. These pharmacies belong to the Utrecht Pharmacy Practice Network for Education and Research (UPPER). The students collected the data for an assignment for their intern period at a community pharmacy. The three other pharmacies where data was also collected, was a pharmacy group with different subsidiaries.

This cross-sectional study was conducted between November 2021 and March 2022. Prescription and dispensing data for 18 different antibiotics were obtained from the PIS (Appendix A).

Data Collection

The Dutch pharmacies possess individual dispensing records for their patients. This record contains personal information about the patient (sex, date of birth, address) as well as information on drugs dispensed (name, dose, dose form, and drug brand). Prescriptions written by the prescriber can also be kept digitally in this medical record. It was possible to extract patients who had received an antibiotic from the pharmacy from the PIS. Depending on the type of PIS used by the pharmacy, the dispended drug could be retrieved utilizing their Anatomical Therapeutic Chemical groups (WHO). A dataset was created using the patient's medical record and the dispensing information about the antibiotic. The dataset contained anonymous patient information such as age and gender and medication characteristics such as the antibiotic prescribed, dose, frequency, duration in days, and differences between prescription and dispended antibiotics (appendix A). The dispensing and prescribing data that were collected, were from medications that were given out at the pharmacy during a two-month period.

Primary outcome

The primary outcome of this cross-sectional study was a mismatch between antibiotic prescription and dispensed antibiotics in the pharmacy. A mismatch was defined as the quantity of antibiotics stated on the prescription did not match the number of antibiotics dispensed.

Data Analysis

Data from the PIS were imported into Microsoft Excel (Appendix A). IBM SPSS Statistics version 28 was used to perform statistical analysis. Descriptive statistics were used to describe prescription and dispensing data. Frequencies and percentages were determined for patient characteristics (age and gender), classes of antibiotics, dosage forms, type of prescriber, and duration of the therapy. For the same determinants odds ratios and the corresponding 95% confidence intervals were calculated using binary logistic regression.

Results

Characteristics of antibiotic prescriptions and their users.

The study included a total of 1577 prescriptions from 63 different pharmacies (Appendix B). The majority of prescriptions, 50.4 %, were written by a general practitioner. The mean age of the patients who received an antibiotic prescription was 54.8 ± 22.04 years and 60.5% of the patients were women. The most often prescribed antibiotic class was penicillin (38%), and the most prescribed antibiotic was nitrofurantoin (21.9%) (Appendix B). Most therapies lasted up to a week (74.6%) (Table 1).

Table 1: Population characteristics of antibiotic prescriptions and pharmacy dispensing data

	Antibiotic prescriptions(N=1577)	
	Frequency (n)	Percent (%)
Gender		
Men	623	39.5
Women	954	60.5
Age		
<65 (men)	377	23.9
>65 (men)	246	15.6
<65 (women)	613	38.9
>65 (women)	341	21.6
Classes of antibiotics		
Penicillin	601	38
Macrolides (and clindamycin)	201	12.8
Fluoroquinolones	148	9.3
Sulphonamides/trimethoprim	132	8.4
Nitrofurantoin	346	21.9
Tetracyclines	149	9.5
Dosage form		
Capsules	774	49.1
Conventional tablets	500	31.7
dispersible tablets	122	7.7
Film-coated tablets	144	9.1
Unknown dosage form	37	2.3

Prescriber		
General practitioner	795	50.4
Dentist	112	7.1
Medical specialist	119	7.5
Unknown prescriber	551	34.9
Therapy duration (in days)		
0-7	1176	74.6
14-21	245	15.5
>21	156	9.9

Mismatch

There was a mismatch between prescription and dispensed antibiotics in 10.6% (n=167) of the prescriptions. In 65.2% of the mismatches(n=109), patients received fewer antibiotics than prescribed. While in 30% of the mismatches(n=50), patients received more antibiotics than prescribed (Appendix B). Penicillin prescriptions accounted for 52.1 % of the discrepancy, whereas macrolides accounted for 12% of the mismatch (including clindamycin). Tetracyclines contributed to 11.4% of the mismatches. Dispensing antibiotics from the classes sulphonamides/trimethoprim and nitrofurantoin resulted in 10.8% of mismatches. The fluoroquinolone classes had the least mismatches (3%) (Table 2). The most frequent discrepancy was caused by a mismatch between the number of prescribed antibiotics and standard packing sizes, which accounted for 59.9% of the total. Because pharmacies only filled a portion of the prescription and had the remaining amount filled as a refill prescription, 10,2% of the prescribed antibiotics were mismatched.

The percentage of mismatches that occurred as a result of the prescriber prescribing antibiotic therapy for an exceedingly longer duration than the recommended guidelines was 7.2%. In addition, 5.2% of the prescriptions had a therapy duration that was too short. The mismatches were caused by 'other' factors, such as the prescribed antibiotic being out of stock and the antibiotic being changed to avoid drug interactions in 20.4% of cases (Figure 1)

Table 2: Frequency of mismatch by classes of antibiotics

Classes of antibiotics (N=167)	
Penicillin	87 (52.1%)
Macrolides (and clindamycin)	20 (12.0%)
Tetracyclines	19 (11.4%)
Sulphonamides/trimethoprim	18 (10.8%)
Nitrofurantoin	18 (10.8%)
Fluoroquinolones	5 (3.0%)

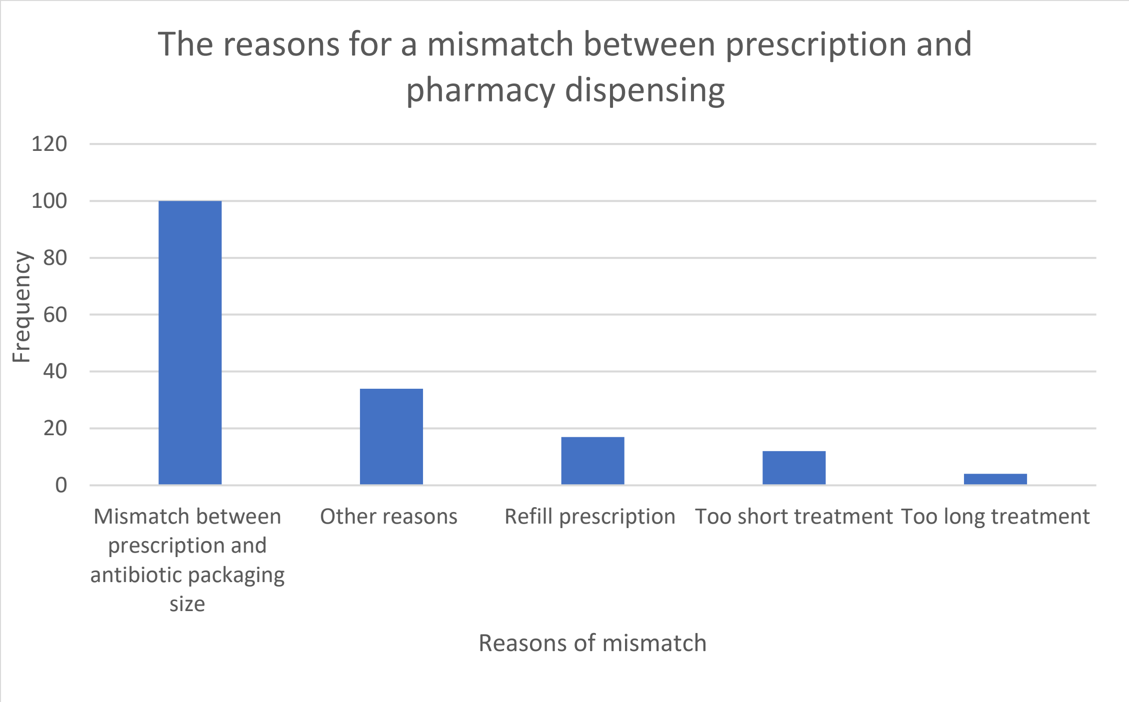

Figure 1: The reasons for a mismatch between prescription and pharmacy dispensing.

Associations between prescription characteristics and mismatch

Mismatches were significantly associated with antibiotic classes (macrolides OR 3.35 [1.857-6.028], fluoroquinolones OR 8.36 [3.051-22.925], sulphonamides/trimethoprim OR 2.08 [1.042- 4.161], nitrofurantoin OR 3.72 [2.044-6.765], and tetracyclines OR 2.43 [1.260 – 4.703] (in comparison with penicillin) and prescribers (dentist OR 0.37[0.154-0.906], medical specialist OR 0.27[0.112-0.664] (in comparison with general practitioner). Furthermore, there were significantly fewer mismatches in film-coated tablets in comparison with capsules OR 0.39 [0.155-0.982] and during therapies lasting more than 21 days OR 0.30[0.201-0.462] compared to therapies up to 7 days (Table 3).

Table 3: Factors associated with a mismatch between prescription and dispensed antibiotic

	Amended (n)	Not amended (n)	Adjusted OR (95% CI) *
Gender			
Men	65	558	Ref
Woman	102	852	0.77 (0.529-1.19)
Age			
<65 (men)	48	329	Ref
>65 (men)	17	229	**1.97 (1.102-3.504)**
<65 (women)	71	542	1.11 (0.753-1.647)
>65 (women)	31	310	1.45 (0.905- 2.352)
Classes of antibiotics			
Penicillin	87	514	Ref
Macrolides (and clindamycin)	20	181	**3.35 (1.857- 6.028)**
Fluoroquinolones	5	143	**8.36 (3.051-22.925)**

Sulphonamides/trimethoprim	18	114	**2.08 (1.042- 4.161)**
Nitrofurantoin	18	328	**3.72 (2.044-6.765)**
Tetracyclines	19	130	**2.43 (1.260 -4.703)**
Dosage form			
Capsules	84	690	Ref
Tablets	57	443	1.66 (0.997- 2.765)
Dispersible tablets	6	116	0.73 (0.270- 1.951)
Film-coated tablets	10	134	**0.39 (0.155- 0.982)**
Unknown dosage form	10	27	1.05 (0.448 - 2.476)
Prescriber			
General practitioner	16	779	Ref
Dentist	9	109	**0.37 (0.154-0.906)**
Medical specialist	10	103	**0.27 (0.112- 0.664)**
Unknown prescriber	132	419	**0.03 (0.018-0.063)**
Therapy duration (in days)			
0-7	105	1071	Ref
14-21	24	221	0.90 (0.566-1.439).
>21	38	118	**0.30 (0.201-0.462)**

**Adjusted odds ratios for the prevalence of mismatch*
Significant associations are shown in bold

Policies in the pharmacies

The different pharmacies (n= 63) had different policies and regulations regarding changing antibiotic prescriptions. The majority of pharmacies (n= 41) had a policy of altering the number of antibiotics so that new packaging was not opened. This frequently occurred when dispensing amoxicillin and amoxicillin-clavulanic acid; if the doctor prescribed 21 tablets, most pharmacies reduced this to 20 tablets to match the packaging size. In some pharmacies (n=6), the prescriber (usually a general practitioner) considers the packaging size when prescribing antibiotics. In nine pharmacies, the policy was that no changes were made to the prescription and that the prescriber will be consulted if the duration of therapy was too short or too long, or if a different strength was required. There were no policies in five pharmacies regarding changing antibiotic prescriptions to match the packaging size, and the exact amount specified was always dispensed. In two pharmacies, the opened packaging had to be used during dispensing before using an antibiotic from an unopened pack.

Discussion

This study was designed to determine the extent of mismatches between the prescription received in the community pharmacy and the actual dispensed number of antibiotics. In 10.6% (n=167) of antibiotic prescriptions, there was a mismatch between the prescription and the number of antibiotics dispensed. The main finding of this study was that most of the mismatches (59.9%) were caused by a mismatch between packaging size and therapy duration. In 65.2% of the mismatches, patients received fewer antibiotics than prescribed. While in 30% of the mismatches, patients received more antibiotics than prescribed.

The results indicate that in 89.4% of the cases (n=1410) the prescribed amount of antibiotics matched with the packaging size or was in line with the clinical guidelines, or the prescriber considers the packaging size when prescribing antibiotics. However, in 10.6% of the dispensed antibiotics, there was a mismatch with the prescription. This finding was in line with the results of studies on the mismatch between antibiotics in packaging sizes and recommended therapy guidelines. Füri et al. concluded in their study that there was a mismatch between the recommended oral antibiotic regimens for the treatment of infections and the size of the antibiotic packaging available in 36% of the clinical guidelines. This resulted in patients getting more antibiotics than needed, which potentially could lead to patients using antibiotics longer than needed or improper disposal of antibiotics [11]. McGuire et al. found in their study a mismatch in the duration of treatment described in guidelines and the actual duration dictated by the antibiotic packaging. Of the 32 common antibiotic prescribing guidelines that were reviewed in this study, 10 had surplus doses, 18 had a shortfall, and only four prescribing scenarios matched with the antibiotic packaging [5]. The risks of mismatches were that patients who get antibiotics prescribed for too short a period could cause treatment failure, delayed return to health, or development of complications. When mismatches leave patients with the leftover antibiotics after the therapy, that can increase the risk of resistance, non-adherence, inappropriate use of leftover antibiotics, and health cost. This can ultimately lead to antimicrobial resistance [2].

Pharmacists can play an active role in reducing the number of antibiotics that patients receive as leftovers. This was the case in most pharmacies (65%) that participated in this study. In these pharmacies, there were internal regulations to adjust the amount of the antibiotic on the prescription to prevent open antibiotic packaging in the pharmacy. This happened only when the amount changed without affecting the therapy. A prescription for amoxicillin or amoxicillin/clavulanic acid tablets is an example of this situation. When a prescriber follows the guidelines and writes a prescription, the pharmacy must dispense 21 tablets for a seven-day therapy period. Amoxicillin and amoxicillin/clavulanic acid are available in packaging sizes of 20 tablets. Most pharmacies considered that one missed dose of medication was clinically acceptable. This topic was investigated by Rafailidis et al. In their review of 13 meta-analysis they concluded that the duration of antibiotic treatment of infections commonly occurring in the community can be shortened without compromising patient outcomes [12].

Strengths and limitations

One of the strengths of this study is the use of pharmacy information systems to extract prescription and pharmacy dispensing data. This data reflects real-world evidence and was relatively simple and reliable method to collect data. One potential limitation of this study is that pharmacy master students collected some pharmacy prescription and dispensing data. Because various individuals had collected data, it could have an impact on the reliability of the data. To reduce differences in the data collected, the students were provided with written instructions. The data of 1026 prescriptions and pharmacy dispensing data were gathered from three subsidiaries of one pharmacy group, which may have resulted in selection bias. One potential limitation of this study was the exclusion of oral antibiotic prescriptions, which meant that prescriptions for most children under the age of six were excluded from the study. This may result in an underestimation of the mismatches. In general, pediatric antibiotic dosing is based on weight, and there is a greater chance of prescription and packaging size mismatch [13]. Amoxicillin is the most prescribed antibiotic for children under the age of ten years old. In 2018, Dutch pharmacies provided amoxicillin to 231000 children [14]. Therefore, if oral antibiotic prescriptions were included in the study, more mismatches would possibly be observed in the penicillin group. Future research should look into the effect of pediatric dose regimens on the mismatch between prescription and dispensing amounts of antibiotics.

Implications and future recommendations

In 14% of pharmacies, the prescriber (mainly a general practitioner) considered the number of antibiotics in the packaging size when prescribing antibiotics. If more pharmacies reach agreements with different prescribers, this could be a solution to reduce mismatches between dispensed antibiotics and prescriptions. Given how frequently these guidelines change, expecting antibiotic packaging sizes to be fully compliant with clinical guidelines is unrealistic. However, some antibiotics have default clinical guidelines. Manufacturers could package these antibiotics in accordance with commonly accepted guidelines. For example, manufacturers could provide packaging of 21 amoxicillin and amoxicillin/clavulanic acid doses instead of packaging sizes of 20 tablets/capsules.

Conclusion

The findings of this study revealed that the majority of antibiotic prescriptions are not adjusted to pack quantity for most of the patients. Mismatches in antibiotic prescription and pharmacy dispensing, on the other hand, are primarily a result of a mismatch between clinical guidelines followed by prescribers and antibiotic packaging sizes. This mainly resulted in fewer antibiotics being dispensed than were prescribed by the prescriber.

References:

1. Ferri, M., Ranucci, E., Romagnoli, P., & Giaccone, V. (2017). Antimicrobial resistance: A global emerging threat to public health systems. Critical reviews in food science and nutrition. 2015 Oct 13;57(13):2857–2876. https://doi.org/10.1080/10408398.2015.1077192
2. McGuire TM. Does size matter? Addressing pack size and antibiotic duration. Aust Prescr. 2019;42:2-3.
3. KNMP Kennisbank. Doxycycline. [Internet]. Available from://kennisbank-knmp-nl.proxy.library.uu.nl/article/Informatorium_Medicamentorum/S547.html 2020. [20 december 2021].
4. Farmaceutisch Kompas. Doxycycline. [Internet]. Available from: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/d/doxycycline#dosering. [17 december 2021].
5. McGuire TM, Smith J, Del Mar C. The match between common antibiotics packaging and guidelines for their use in Australia. Aust N Z J Public Health. 1 December 2015;39(6):569–72.
6. McNulty CAM, Boyle P, Nichols T, Clappison P, Davey P. The public's attitudes to and compliance with antibiotics. J Antimicrob Chemother. Augustus 2007;60(SUPPL. 1).
7. Ekins-Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? A retrospective observational study in primary care. Br J Clin Pharmacol. 1 Juli 2003;56(1):92–5.
8. Bekker CL, Melis EJ, Egberts ACG, Bouvy ML, Gardarsdottir H, van den Bemt BJF. Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy. Res Soc Adm Pharm. 1 januari 2019;15(1):100–5.
9. Alhomoud F. "Don't Let Medicines Go to Waste"—A Survey-Based Cross-Sectional Study of Pharmacists' Waste-Reducing Activities Across Gulf Cooperation Council Countries. Front Pharmacol. 28 Augustus 2020;11:1334.
10. Anwar M, Iqbal Q, Saleem F. Improper disposal of unused antibiotics: an often overlooked driver of antimicrobial resistance. Vol. 18, Expert Review of Anti-Infective Therapy. Taylor & Francis; 2020. p. 697–9.
11. Füri J, Widmer A, Bornand D, Berger C, Huttner B, Bielicki JA. The potential negative impact of the antibiotic pack on antibiotic stewardship in primary care in Switzerland: A modelling study. Antimicrob Resist Infect Control. 8 mei 2020;9(1).
12. Rafailidis PI, Pitsounis AI, Falagas ME. Meta-analyses on the Optimization of the Duration of Antimicrobial Treatment for Various Infections. Vol. 23, Infectious Disease Clinics of North America. Infect Dis Clin North Am; 2009. p. 269–76.
13. Bielicki JA, Barker CIS, Saxena S, Wong ICK, Long PF, Sharland M. Not too little, not too much: Problems of selecting oral antibiotic dose for children. BMJ. 3 november 2015;351.
14. SFK. Amoxicilline meest gebruikt onder kinderen tot 10 jaar. [Internet]. Available from: https://www.sfk.nl/publicaties/PW/2019/amoxicilline-meest-gebruikt-onder-kinderen-tot-10-jaar. [March 30,2022].

Appendices

APPENDIX A: data collection of antibiotic prescription and dispensing data

Table 1: classes of antibiotics and the associated drugs that were included in the study

Classes of antibiotics	***Studied drugs of the classes***
Penicillin	Amoxicillin, amoxicillin/clavulanic acid, flucloxacillin, pheneticillin
Macrolides (and clindamycin)	Clindamycin, azithromycin, clarithromycin, erythromycin
Fluoroquinolones	Ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin
Sulphonamides and trimethoprim	Cotrimoxazole, trimethoprim
Nitrofurantoin	Nitrofurantoin
Tetracyclines	Doxycycline, tetracycline, minocycline

Table 2: Collected information from the pharmacy information system.

Age	Gender	Classification	Dosage and use as the prescription	quantity decided by the prescriber	Dosage and use by dispensing	Quantity dispensed	Reason of mismatch	Prescriber	Dosage form

Tabel 3: Coding of the dataset

	Code
Gender	
Men	1
Woman	2
Age	
<65	1
>65	2
Classes of antibiotics	
Penicillin	1
Macrolides (and clindamycin)	2
Fluoroquinolones	3
Sulphonamides/trimethoprim	4
Nitrofurantoin	5
Tetracyclines	6
Dosage form	
Capsules	1
Tablets	2
dispersible tablets	3
Film-coated tablets	4
Unknown dosage form	5
Prescriber	

General practitioner	1
Dentist	2
Medical specialist	3
Unknown prescriber	4
Therapy duration (in days)	
0-7	1
14-21	2
>21	3
The causes for a mismatch between prescription and pharmacy dispensing.	
The packaging size didn't match the duration and amount prescribed by the prescriber.	1
Excess doses compared to the recommended antibiotic clinical guidelines.	2
The shortfall of doses compared to the clinical guidelines.	3
Refill prescription	4
other reason	5

Appendix B: results

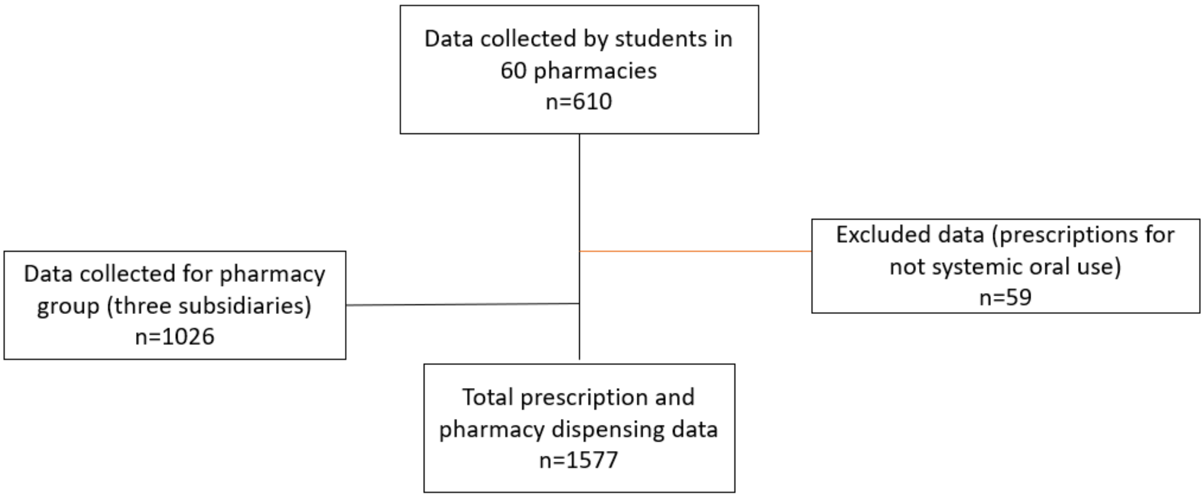

Figure 2: Flowchart of prescription and pharmacy dispensing data

Table 4: Antibiotics from prescription and pharmacy dispensing data (number of drugs included)

Penicillin (601)	Amoxicillin (311)	Amoxicillin/clavulanic acid (146)	Pheneticillin (32)	Flucloxacillin (112)	-
Macrolides +clindamycin (201)	Azithromycin (124)	Clarithromycin (29)	Erythromycin (1)	Clindamycin (47)	-
Fluoroquinolones (148)	Ciprofloxacin (131)	Norfloxacin (2)	Levofloxacin (8)	Moxifloxacin (5)	Ofloxacin (2)
Sulphonamides (132)	Cotrimoxazole (83)	Trimethoprim (49)	-	-	-
Nitrofurantoin (346)	-	-	-	-	-
Tetracyclines (149)	Doxycycline (136)	Tetracycline (7)	Minocycline (6)	-	-

Table 5: Difference between prescription and dispensing of antibiotics

Mismatched antibiotic prescriptions (N=167)	
Situation	Frequency (percentage)
Patient received more antibiotics than prescribed	50 (30%)
patient received fewer antibiotics than prescribed	109 (65.2%)
Unknown	8 (4.8%)