QUANTITATIVE AND QUALITATIVE ANALYSIS OF THE HUNGARIAN AMBULATORY ANTIBIOTIC CONSUMPTION ON NATIONAL AND REGIONAL LEVEL BASED ON DIFFERENT DATA SOURCES 1996-2007

Ph.D. thesis

Mária Matuz

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University of Szeged
Department of Clinical Pharmacy

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Mária Matuz

Supervisor:
Prof. Dr. Gyöngyvér Soós

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PUBLICATIONS RELATED TO THE THESIS

Papers

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Abstracts

IV. **Matuz M**, Benkő R, Horváth E, Soós Gy: A magyarországi antibiotikum felhasználás néhány jellemzője Hungaromed 2007. Gyógyszerészeti tudományos konferencia; Budapest, 2007. november 9.

V. **Matuz M,** Benkő R, Doró P, Hajdú E, Soós Gy: In-depth analyses of systemic antibacterial monotherapy among adult outpatients 24th International Conference on Pharmacoepidemiology &Therapeutic Risk Management, Copenhagen, Dánia; 2008. augusztus 17-20 Abstr.: Pharmacoepidemiol. Drug Saf. 2008 17 S224 S224

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VIII. **Matuz M**; Benkő R; Doró P; Németh Á; Hajdú E; Soós Gy: Outpatient antibacterial use in children. Abstr.: Pharmacy World & Science 31(2): 324-324 ESCP 37th European Symposium on Clinical Pharmacy Dubrovnik, Horvátország 2008. október 22-24.

IX. **Matuz M**, Benkő R, Horváth E, Hajdú E, Soós Gy: [Trends of ambulatory antibiotic use in Hungary (1996-2007)] Járóbeteg antibiotikum felhasználás elemzése (1996-2007) Congressus Pharmaceuticus Hungaricus XIV. Budapest, 2009. nov 13-15. Abstr.: Gyógyszerészet Supplementum 2009(53):11 S123 (P-132)

X. **Matuz M**, Benkő R, Horváth E, Hajdú E, Soós Gy: [Do unnecessary antibiotic prescription exist in Hungary?] Előfordul-e vélhetően indokolatlan antibiotikum alkalmazás hazánkban? Congressus Pharmaceuticus Hungaricus XIV. Budapest, 2009. nov. 13-15. Abstr.: Gyógyszerészet Supplementum 2009(53):11 S123 (P-131)

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TABLE OF CONTENTS

1. INTRODUCTION

The discovery of penicillin is considered to be one of the ten greatest public health achievements [1]. Antimicrobials have played an important role in the management and control of infectious diseases [2,3] but nowadays the evolution of drug-resistant organisms has greatly impaired their therapeutic efficacy [4-6]. Although antimicrobial resistance has existed since the introduction of antibiotic therapy into clinical practice, the phenomenon has worsened in the last two decades. Antimicrobial resistance is now reaching alarming levels in certain pathogens and certain geographical regions [7-12] .

The causes of antimicrobial resistance are complex and multi-factorial in nature [12,13]. Driven by natural selection, it is an inevitable accompaniment of even appropriate antibiotic use [14,15]. However, evidence has proved that misuse of antibacterials further amplifies the emergence and spread of antibacterial resistance [13,15-19]. The problem of antimicrobial resistance is heightened by the current limited introduction of novel antibacterials onto the market [20-22]

Antibiotics are one of the most commonly used medicines in acute ambulatory care (e.g. in 2007, two out of the three most-prescribed active agents were antibiotics in Hungary [23]). Antibiotics have also substantial share of the drug budget [24,25]. As their inappropriate use has serious public health consequences substantial efforts are needed to rationalise their use.

Every rationalising step should be preceded by data collection and evaluation to identify problematic fields. At international level, the European Surveillance of Antimicrobial Consumption (ESAC) project is tasked with collecting reliable antibiotic use data [26,27].

As drug use can be evaluated at different levels (e.g. national, regional) and from different perspectives (quantitative, qualitative), it is intended to assess ambulatory care antibiotic use by applying all these approaches in this Ph.D. work.

2. BACKGROUND

2.1. Pharmacoepidemiology

Pharmacoepidemiology (PE) is "the study of the utilization and effects (beneficial and adverse) of drugs in large numbers of people" [28]. As a post-marketing study, PE describes, explains and forecasts the use and effects of pharmacological treatments in a defined time, space and population [29]. PE has two main fields: one includes studies of side effects, adverse drug effects and long-term effects of specific drugs in a population. The other - drug utilisation studies – was defined by the World Health Organization (WHO) as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences [30]. Practically, drug utilisation studies may provide insights into the pattern of drug use (e.g. the extent, the trends), assess the quality of use, identify predictors for use and generate explanatory hypotheses [28,31].

The principal aim of pharmacoepidemiological research is to enhance the rational and cost-effective use of medications in the population [28]. Collecting data on drug consumption is a prerequisite to rationalising drug use. Ideally, all drug policy decisions should be based – and regularly re-evaluated– on comprehensive drug utilisation data [32]. It is important to keep in mind that although drug utilisation studies can contribute to rational drug use by identifying the areas that require attention and action, they do not necessarily offer the solutions for the problems [28].

2.2. The history of drug utilisation studies

The first drug utilisation studies were performed in the 1960s [33]. At that time, the use of different measurement units and methods made international comparisons impossible. The need for a common classification system for drugs, as well as a technical unit of comparison in drug utilisation studies, was first framed in 1969, at a seminal symposium in Oslo (entitled the "Consumption of Drugs") [34]. Scientists, mainly from Northern European countries, solved the problem with the development of a new measurement unit, initially called the agreed daily dose [35], and later the defined daily dose (DDD) [36,37]. The uniform Anatomical Therapeutic Chemical (ATC) classification system was introduced in the mid-1970s [37].

The first publication applying the ATC/DDD principles appeared in 1975 [35], while from 1981, the ATC/DDD system was proposed for drug utilisation studies.

To maintain and develop the ATC/DDD system, the WHO Collaborating Centre for Drug Statistics Methodology was established in 1982 in Oslo [32,37]. In 1996, the WHO realised that

the ATC/DDD system should be implemented and used outside of Europe as well, and the expert panel of the WHO International Working Group for Drug Statistics Methodology was founded to facilitate the globalisation of the ATC/DDD system.

2.3. The Anatomical Therapeutic Chemical (ATC) system

In the ATC coding system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified into groups at five different levels, where a seven digit code identifies a unique active agent (e.g. clarithromycin: J01FA09). In Table 1, an example of ATC grouping is given through the beta-lactam antibacterials. Medicinal products are classified in the ATC system according to the main therapeutic indication of their main active ingredient. An active ingredient can be classified under more than one ATC code if it is marketed in different strengths and/or formulations with clearly different therapeutic uses (e.g. oral and rectal metronidazole: P01AB01; intravenous metronidazole: J01XD01 [28]).

Table 1. The ATC classification of the beta-lactam antibacterials available in Hungary

J01C Beta-lactam antibacterials, penicillins		
J01CA Penicillins with extended spectrum	J01CE Beta-lactamase sensitive penicillins (narrow-spectrum penicillins)	J01CR Combinations of penicillins, including. beta-lactamase inhibitors (penicillin combinations)
J01CA01 Ampicillin	J01CE01 Benzylpenicillin	J01CR01 Ampicillin and enzyme inhibitor
J01CA03 Carbenicillin	J01CE02 Phenoxymethylpenicillin	J01CR02 Amoxicillin and enzyme inhibitor
J01CA04 Amoxicillin	J01CE06 Penamecillin	J01CR04 Sultamicillin
J01CA06 Bacampicillin	J01CE08 Benzathine benzylpenicillin	J01CR05 Piperacillin and enzyme inhibitor
J01CA09 Azlocillin	J01CE09 Procaine benzylpenicillin	
J01CA10 Mezlocillin	J01CE10 Benzathine phenoxymethylpenicillin	
J01CA12 Piperacillin		

J01CF Beta-lactamase resistant penicillins: 1999-2005 J01CF04 oxacillin, with marginal use

J01D Other beta-lactam antibacterials		
J01DB First-generation cephalosporins	J01DC Second-generation cephalosporins	J01DD Third-generation cephalosporins
J01DB01 Cefalexin	J01DC01 Cefoxitin	J01DD01 Cefotaxime
J01DB04 Cefazolin	J01DC02 Cefuroxime	J01DD02 Ceftazidime
J01DB05 Cefadroxil	J01DC03 Cefamandole	J01DD04 Ceftriaxone
	J01DC04 Cefaclor	J01DD07 Ceftizoxime
	J01DC10 Cefprozil	J01DD08 Cefixime
		J01DD10 Cefetamet
		J01DD12 Cefoperazone
		J01DD14 Ceftibuten

J01DE Fourth-generation cephalosporins, J01DH Carbapenems - with marginal ambulatory use

2.4. Drug utilisation research: concept of the defined daily dose

The defined daily dose (DDD) is an internationally accepted technical unit in drug utilisation studies. It means the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasised that the DDD does not necessarily correspond to the actually prescribed daily dose (PDD) [28].

Drug utilisation figures should ideally be standardised as DDD per 1000 inhabitants and per day (DDD per 1000 inhabitant-days). This is the most widely used measurement unit, which enables international comparison [28].

Although the WHO intend to keep the number of alterations to a minimum, it is important to be aware that the ATC/DDD methodology is a dynamic system to which changes are made continually (e.g. DDD of oral and parenteral levofloxacin was changed from 0.25 gram to 0.5 gram in 2004) [28]. For enhancing meaningful comparisons of drug consumption data, the applied DDD should be indicated in the published data.

2.5. Drug utilisation research: relation to Evidence-Based Medicine

Healthcare schemes aspire for continuous quality development. The approach which aims to support clinical decision-making by finding and applying the best available therapy and finding and eliminating the unsound, excessively risky practices is called evidence-based medicine. Evidence-based guidelines are the practice of evidence-based medicine at the level of patient care. This includes the set up of guidelines, policy and regulations. Evidence-based methods ensure that guidelines provide valid recommendations based on a critical appraisal of the best available evidence rather than informal, opinion-based processes [38].

The best treatment/procedure/technology, i.e. the one which provides the best long-term health/quality of life for the patient and ensures the sustainability of the health care, is selected with the help of large prospective or retrospective studies. One cornerstone of improvement in clinical efficiency is the study of therapeutic technologies and treatments. Quality improvement in healthcare can be achieved by analysing the current clinical practice and identifying and correcting its weaknesses. In healthcare three types of mistake can occur:

1. the underuse,
2. the overuse, or
3. the misuse of available technologies/treatments.

For example, the lack of antibiotic prophylaxis belongs to the first type; the use of antibiotics for viral infections belongs to the second/third, while the incorrect dosage or length of treatment belongs to the third kind of error. These mistakes could delay or impede the recovery of the patient and puts extra expense on the healthcare system.

Descriptive and analytical epidemiology has gained an important role in the healthcare quality improvement process. Drug utilisation research – as a branch of pharmacoepidemiology – is an essential tool as it permits the comparison of everyday therapeutic practice with the guidelines/regulations and can reveal typical mistakes. This function of drug utilisation research has increased during the years, as the focus of studies has shifted from being merely descriptive to being outcome and quality orientated [39-43]. As concerns antibacterials, quality indicators of ambulatory antibiotic use have been recently developed by the ESAC [44].

2.6. Drug utilisation research: data sources

Drug utilisation studies may use different data sources. We can distinguish distribution, prescription, dispensing or reimbursement data. The characteristics of each type of data source and the connection to different parts of this thesis are summarised in Table 2.

Table 2. Available Hungarian data sources and their main characteristics

	Drug distribution chain			
	 **Wholesalers**	 **Pharmacies**		 **Patients**
Data source	IMS PharmMIS– distribution/sales data	HNHFA – reimbursement data (and dispensing data until 2006)		Manual analysis of prescriptions – dispensing data
Characteristics of data	Total coverage for a country or region	Total coverage for a country or region		Patient-level sampling
Prescription (Rx) and non prescription use (OTC-over the counter)	Rx and OTC (total)	Rx, OTC separately until 2006	Only Rx from 2006	Rx
Indications	No	No Until 2006 October	Yes from 2006 November	Yes
Prescribed dosage	No	No		Yes
Patient demographics (age, gender)	No	No		Yes
Part of my work	**A**	**B**	**C**	**D**

A: National and regional ambulatory antibiotic consumption (1996-2007)
B: Non prescription antibiotic use in Hungary (2000-2004)
C: Antibiotic use in the Southern Great Plain region (2007. I. part)
D: In depth analysis of ambulatory patient-level antibiotic use data from 20 pharmacies (2007. I. part)
HNHFA: Hungarian National Health Fund Administration

2.7. Drug utilisation research: Hungarian antibiotic studies

The Ministry of Health 12/1978 ordinance appointed the National Institute of Pharmacy (OGYI) to execute the adaptation of the ATC/DDD system, and to collect national drug utilisation data in Hungary. Besides the official drug utilisation duties of the OGYI, only a few researchers have taken the initiative within the country and have carried out drug utilisation studies [45].

Despite the low interest in performing drug utilisation studies, several works were published concerning antibiotic policies and antibiotic use [3,25,46-66]. Many of these studies reported aggregated national antibiotic use data for the 1980s and 1990s [3,51,57-59,67].

Separate ambulatory care data were published in six works [46,49,50,56,68,69], while regional level data were revealed in two studies [50,51]. The published studies applied different units of measurement: number of sold packages [49,56,57,68], costs [46,50,56-59,69] or number of DDDs [3,50,67,69] and only a few of them expressed antibacterial use in the comparable and standardised unit, the DDD per 1000 inhabitant-days [46,50,51,56,57].

Whilst these are very valuable pioneering pieces of research, some criticisms may be levelled at some of them, particularly concerning essential methodological information (e.g. lack of ATC classification, the used DDD version and/or the data source is not displayed). There has been only one study by Graber which applied the ATC/DDD methodology and provided national coverage of separate ambulatory antibacterial drug use in Hungary for 1990-1996 [50] .

Patient-level surveys [48,61,63-65] were done by Katona who focused on the frequency and expense of antibiotic use and misuse. The rate of antibiotic overuse and misuse was the main focus of his work[48,63,70]. Katona was also the only author who surveyed paediatric antibiotic use in Hungary [48,66].

Numerous papers about the optimal antibiotic use and/or the consequences of suboptimal antibacterial use were also published by several authors [15,68,71-75].

Therefore, the drug utilisation research performed in this thesis work was motivated by the following considerations:

- Systemic antibacterials have a key role among acute care ambulatory drugs [23]
- The number of studies that use standardised drug consumption units for ambulatory antibacterial use and thus enable international comparison is limited
- Recent published data on ambulatory antibacterial use in Hungary is scarce

- The regional distribution of ambulatory antibiotic use and its possible determinants have not been disclosed
- The rate of non-prescription antibiotic use in Hungary is unknown
- Data on the indications of ambulatory care antibiotic use is lacking
- The possible rate of antibiotic overuse in respiratory tract infections has been rarely studied
- Extensive patient-level data (e.g. demographics, data on prescribed doses, indications) which enables in-depth analysis of ambulatory antibiotic use has never been published
- No recent data on paediatric antibiotic use is available

In summary, there is a shortage of evidence about antibiotic use. This work aims to fill this gap.

3. MAIN RESEARCH OBJECTIVES

3.1. A) National and regional ambulatory antibiotic consumption

- To analyse the changes of Hungarian ambulatory antibiotic consumption between 1996 and 2007
- To identify possible regional variations and investigate determinants of antibiotic use in ambulatory care in Hungary

3.2. B) Non-prescription antibiotic use in Hungary

- To estimate the extent, prevalence and trends of non-prescription antibiotic use in Hungary between 2000 and 2004, at national and regional levels

3.3. C) Antibiotic use in the Southern Great Plain region

- To assess characteristics of antibiotic use at a regional level, data specifically focusing on the main diagnoses and their therapy
- To estimate the rate of antibiotic overuse in respiratory tract infections
- To evaluate the rate of adherence to antibacterial guidelines in cases of acute streptococcal tonsillopharyngitis (AST)

3.4. D) In-depth analysis of ambulatory patient-level antibiotic use data

- To study patient characteristics (age, gender, age-linked distribution of indications), the prescribed doses and dosage forms of antibiotic use in the Southern Great Plain region
- To estimate the necessity of antibacterial therapy in adults and children with respiratory tract infections.
- To evaluate the rate of adherence to antibacterial guidelines in cases of acute streptococcal tonsillopharyngitis (adults, children)
- To present a new methodology for estimating the rate of antibiotic therapy prescribed for children. (estimation is applied for aggregated regional level data - Southern Great Plain - mentioned above)

4. METHODS

4.1. General methods

All statistical analyses were performed with SPSS (version 15) and a *p* value less than 0.05 was considered as statistically significant. MS Excel, MS Access and the R programming language and environment (2.9.0) were also used during the data analysis.

4.2. Common methods applied

Similar to other drug utilisation publications, in the present thesis the term 'drug use', 'drug utilisation' and 'drug consumption' are synonyms and are used interchangeably. All retrieved data is pertaining to systemic antibacterials (Anatomical Therapeutic Chemical = ATC code J01) and calculations were always performed according to the *WHO ATC/DDD* index of the last year of data analysis. Antibiotic consumption was expressed in *DDD per 1000 inhabitant-days* unless stated otherwise.

The number of active agents accounting for *90% of the total antibacterial use* (i.e. *DU90%* segment) was determined as proposed by Bergman [76]. The DU90% method ranks drugs by volume of DDD and sets the cut-off where the cumulative percental share of the ranked drugs reaches 90% of total drug consumption.

Table 3. The classification of the narrow and broad spectrum antibacterials [44]

Narrow spectrum penicillins, cephalosporins and macrolides ("N")					
J01CE01	Benzylpenicillin	J01DB01	Cefalexin	J01FA01	Erythromycin
J01CE02	Phenoxymethylpenicillin	J01DB04	Cefazolin		
J01CE06	Penamecillin	J01DB05	Cefadroxil		
J01CE08	Benzathine benzylpenicillin				
J01CE09	Procaine benzylpenicillin				
J01CE10	Benzathine phenoxymethylpenicillin				
Broad spectrum penicillins, cephalosporins and macrolides ("B")					
J01CR01	Ampicillin and enzyme inhibitor	J01DC01	Cefoxitin	J01FA02	Spiramycin
J01CR02	Amoxicillin and enzyme inhibitor	J01DC02	Cefuroxime	J01FA06	Roxithromycin
J01CR04	Sultamicillin	J01DC03	Cefamandole	J01FA07	Josamycin
J01CR05	Piperacillin and enzyme inhibitor	J01DC04	Cefaclor	J01FA09	Clarithromycin
		J01DC10	Cefprozil	J01FA10	Azithromycin
		J01DD01	Cefotaxime	J01FA13	Dirithromycin
		J01DD02	Ceftazidime	J01FF01	Clindamycin
		J01DD04	Ceftriaxone	J01FG02	Quinupristin/dalfopristin
		J01DD07	Ceftizoxime		
		J01DD08	Cefixime		
		J01DD10	Cefetamet		
		J01DD12	Cefoperazone		
		J01DD14	Ceftibuten		

Most of the *22 quality indicators* proposed by the ESAC project [44] were also used (e.g.: *ratio of the consumption of broad to the consumption of narrow spectrum penicillins, cephalosporins and macrolides* (see grouping in Table 3).

4.3. A) National and regional ambulatory antibiotic consumption

Retrospective analysis of wholesaler distribution data was performed on a 12-year period (1996-2007). For the whole country and for each Hungarian region (county), yearly crude data were kindly provided by the IMS (Intercontinental Medical Statistics) PharmMIS Consulting Company. This dataset means 100 % ambulatory coverage. In Hungary ambulatory care consumption includes any use for outpatients (i.e. patients in the community and also hospital outpatient departments). Drug utilisation in nursing homes, social homes, foster homes, prisons and dentists are also allocated to ambulatory care.

Table 4. The classification of the macrolides [77] and quinolones [78]

J01FA Macrolides					
Short acting macrolides (half life <4 h)		Intermediate acting macrolides (half life from 4-24 h)		Long acting macrolides (half-life > 24h)	
J01FA01	Erythromycin	J01FA06	Roxithromycin	J01FA10	Azithromycin
J01FA02	Spiramycin	J01FA07	Josamycin	J01FA13	Dirithromycin
		J01FA09	Clarithromycin		

J01M Quinolones					
First generation quinolones		Second generation quinolones		Third generation quinolones	
J01MA06	Norfloxacin	J01MA01	Ofloxacin	J01MA13	Trovafloxacin*
J01MB02	Nalidixic acid	J01MA02	Ciprofloxacin	J01MA14	Moxifloxacin
		J01MA03	Pefloxacin		
		J01MA12	Levofloxacin		

** withdrawn from the market*

A *linear regression (trend analysis)* was set up to investigate the trends in the national ambulatory antibiotic utilisation through the study period. Additionally, the top list of antibacterials and the *DU90% segment* were determined.

Besides the WHO defined ATC classification, the chemical structure and antimicrobial activity based *grouping of quinolones* introduced by Ball [78] and the mean plasma elimination half-life based *classification of macrolides* (Table 4) [77] were adapted.

Regional variations of ambulatory antibiotic consumption and its determinants

To assess the interregional variation in antibiotic consumption on the above mentioned dataset, the *maximum/minimum (max/min) ratio* was calculated. The top list of antibacterials and the number of active agents in the *DU90% segment* were also compared between regions. To investigate the associations between the possible determinants for regional differences and total regional ambulatory antibiotic consumption, the *two-tailed Spearman coefficient (R)* for non-parametric correlations was applied. Because multiple hypotheses were tested, the *Bonferroni correction* was used. The list of possible determinants of antibiotic use was developed by an expert panel group (European Conference on Antibiotic Use in Europe, Brussels, 15–17 November 2001). The following (Table 5.) available detemining factors were retrieved and evaluated in this work:

Table 5. Predisposing and protective factors of ambulatory antibiotic use

Variables related to	**Available independent variables (2003)**
Extreme ages	Proportion of population aged 0-5 year
	Proportion of population aged 60 and over
Immunosuppressive states	Prevalence of type 1 and type 2 DM
	Prevalence of malignant neoplasms
Certain diseases	Incidence of emphysema and chronic obstructive pulmonary disease
	Incidence of microbiological foodborne diseases (Salmonellosis, Campylobacteriosis)
Breastfeeding	Proportion of infants breastfed at 6 months of age
Vaccinations	Vaccination against influenza
Economic and social issues	Monthly net income (after taxation)
	Number of public medicine services (recipients per 10,000 inhabitants)
	Regular social assistance (recipients per 10,000 inhabitants)
	Gross domestic product (GDP) per inhabitant
Peculiarity of households	Number of persons per 100 rooms
	% dwellings supplied with premises for bathing and washing
GPs and doctors	Number of active GPs and family paediatricians per 10,000 inhabitants
	Percental rate of active doctors over the age of 65

DM: Diabetes Mellitus; GP: General Practitioner; GDP: Gross domestic product

Demographic data and data on independent variables were extracted from the 2003 yearbooks of the Hungarian Central Statistics Office [79-81].

4.4. B) Non-prescription antibiotic use in Hungary

Data on the regional (20 counties) consumption of systemic antibiotics were obtained from the *Hungarian National Health Fund Administration* (HNHFA) for a *5-year period* (2000−2004). In Hungary all antibacterials are prescription only medicines and reimbursed to the same extent. In this work we distinguished prescription and non-prescription sales. (The HNHFA had a peculiarity before 2006 as it could track both the reimbursed (prescription) and the non-reimbursed (non-prescription=OTC) medication sales.

The number of inhabitants and number of pharmacies were obtained from the Hungarian Central Statistical Office [80,82]. The *DU90% segment* of non-prescription drug sales was determined. Consumption in each region was expressed as: DDD per 1000 inhabitant-days,packs per 100 inhabitants per year, Days of Treatment (DOT = sum of DDDs) per month per pharmacy, packs per month per pharmacy, and as percentage (%) of total antibiotic use.

Assuming that one pack of antibacterial corresponds with one treatment course, an estimation of average length of antibacterial treatment was made. To do so, the average DOT content of the solid oral packages (capsules, tablets, dragees) that were used in the study period was counted, and weighted them according to their national total consumption level in 2004. The average DOT content of the solid oral products was found to be 7, so 7 days was defined as the average length of antibacterial treatment. Although this consideration almost certainly means an estimate of the average length of antibiotic courses, it gives a more practical approach to the understanding of consumption values.

After testing normality (*Kolmogorov-Smirnov test),* a *paired T-test* was used to demonstrate the differences in the rate of the non-prescription antibiotic consumptions at the two endpoints (2000 vs. 2004). Associations between non-prescription antibiotic use versus prescription use and price were tested by *the Pearson correlation*.

4.5. C) Antibiotic use in the Southern Great Plain region

The aggregated, crude, regional (Southern Great Plain region: Bacs-Kiskun, Bekes, and Csongrad counties; with 19.7 % area and 13.3 % population coverage in Hungary) dispensing data on systemic antibiotic prescriptions were obtained from the HNHFA. The study period was between January and June 2007. All antibiotic claims in the pharmacies of the region (n= 445 pharmacies) during this half year were included in the analysis.

The indications of antibiotic therapies were determined according to the registered ICD (International Classification of Diseases version 10) codes [83]. The dosage form data of applied antibiotic therapies were also determined. For doing this systemic antibacterial products were grouped into three categories according to the dosage form: parenteral, solid oral (e.g. capsule, tablet, coated tablet) and liquid oral (e.g. powder for suspensions). The share of liquid oral antibacterial use within oral antibacterial use (as percent of DDDs) was calculated.

It was planned to estimate the necessity of antibiotic therapies prescribed for respiratory tract infections. According to international and national guidelnes and with the help of an infectious disease consultant we *classified indications* (based on registered ICD-10 codes) into three categories:

1) antibiotic therapy is probably required and useful
2) antibiotic treatment is probably needless
3) indeterminable due to the inadequate nomenclature of the ICD codes.

The quality of the antibacterial prescribing habits was also analysed by a so-called prescribing indicator. For this purpose, the antibacterial treatment of acute streptococcal tonsillopharyngitis (AST) was chosen. The rate of adherence to first-line antibacterial therapy (i.e. narrow spectrum penicillins: J01CE) of *AST recommended by national guidelines* [84-86] was determined. This prescribing indicator was selected due to the frequent diagnosis of AST, the well-defined treatment and the easy computability of the indicator.

4.6. D) In-depth analysis of ambulatory patient-level antibiotic use data.

Patient-level crude data originated from the individual prescriptions dispensed at community pharmacies. Twenty retail/community pharmacies from the Southern Great Plain region were included in the study. Data were collected from the prescriptions retrospectively. From every month during the first half of 2007, from each pharmacy, dispensed prescriptions of one workday were reviewed (i.e. in total 6 workdays per pharmacy). The official name, strength, quantity, indication (ICD-10 code), prescribed dosage and dosage form (e.g. capsule, suspension) of the dispensed product, and the gender and age of the patient were recorded for all systemic antibacterial prescriptions.

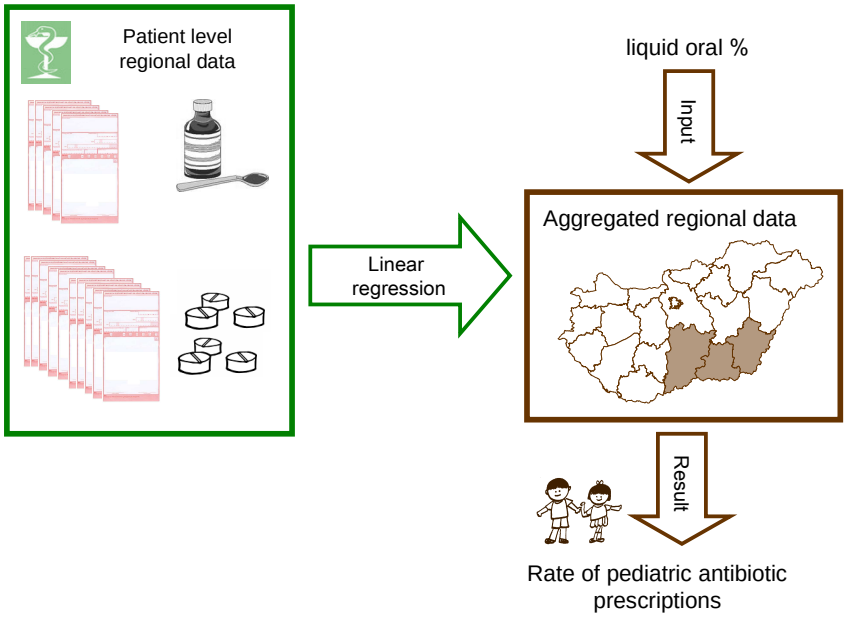
Patients were classified as children if under the age of 14 years and as adults if above 14 years of age. The daily prescription turnover of each pharmacy was retrieved from electronic databases. Combination therapy was defined as the dispensing of two or more

prescriptions for the same patient on the same day with the same ICD code.

The assessment of the necessity of antibiotic therapies prescribed for the respiratory tract infections and determination of the quality of antibacterial therapies in acute streptococcal tonsillopharyngitis were performed similarly as detailed in section C (with the exception that here patients were stratified to age-groups: children and adults separately).

The dosage form data of applied antibiotic therapies was also assessed as detailed in section C. Thereafter, based on the patient-level regional data collected in the 20 pharmacies, the association between the share of liquid oral antibacterial use in DDDs within oral antibacterial use and the rate of antibiotic prescriptions indicated for children (PARx, as % of all antibiotic prescriptions) was analysed by *linear regression*. The result of the linear regression was applied to the aggregated regional-level dosage form data (section C of the thesis) in order to estimate the rate of *antibiotic prescriptions indicated for children (PARx).* (see also Figure 1.)

Figure 1. The concept of the method used to estimate the rate of antibiotic prescriptions indicated for children

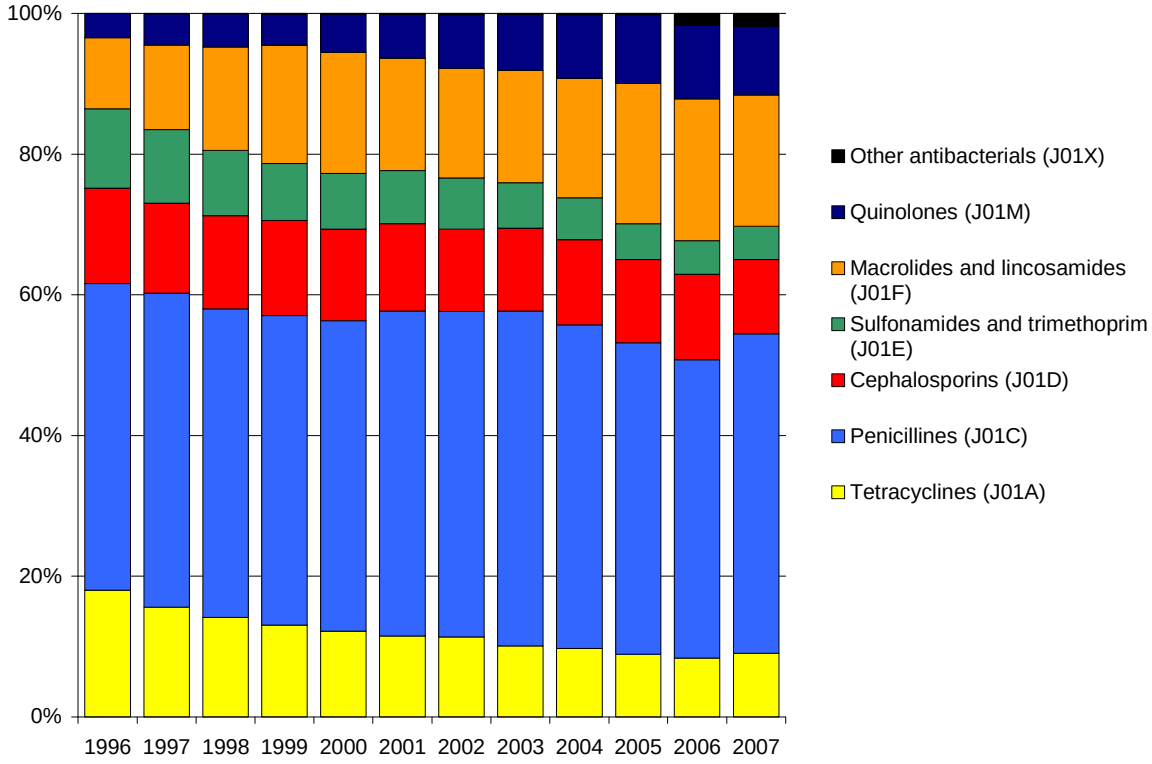


5. RESULTS

5.1. A) National trends in antibacterial utilisation

National ambulatory antibiotic consumption in total number of DDDs (often referred to as DOT) has decreased by 17 % (from 68.5 to 56.7 million DDDs) between 1996 and 2007 and the standardised consumption unit remained relatively stable (mean ± standard deviation: 18.5±1.5 DDD per 1000 inhabitant-days). In each year, ambulatory-based antibiotic use accounted for 91.8 ─ 94.0 % of the total national antibiotic consumption. The gradual change in the pattern of ambulatory antibiotic use can be followed in Figure 2.

Figure 2. Distribution of main antibiotic groups in the total ambulatory antibiotic consumption

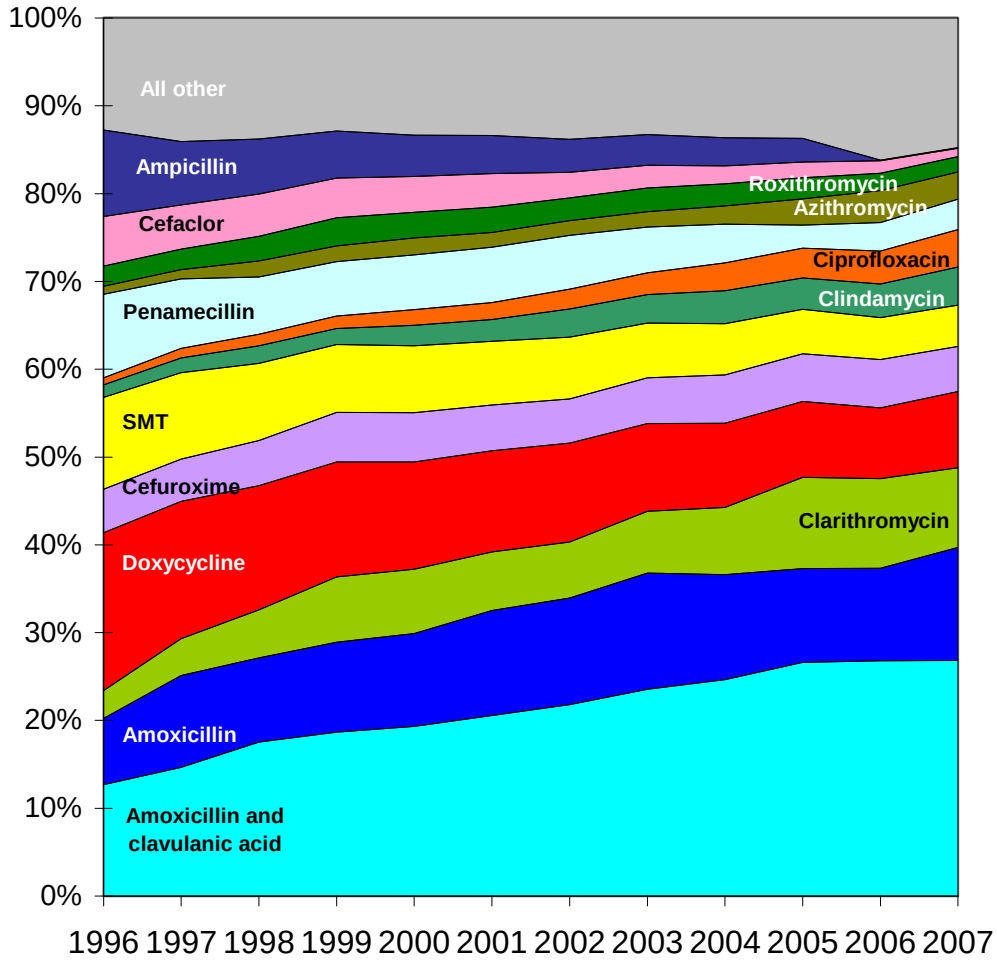


The results of the trend analysis and the top 10 list of antibacterials with their relative share from total ambulatory care use can be followed in Table 6 and Figure 3, respectively.

In this section all values in the text in parenthesis refer to the two endpoints of the study: 1996 and 2007. In 1996 doxycycline ranked the first in use (Figure 3), then the consumption of tetracyclines diminished to less than half of the previous value by 2007. In parallel, the share of tetracyclines also decreased considerably (Table 6 and Figure 2). In all years, penicillins represented the most frequently prescribed antibiotics in Hungary. The penicillin plus enzyme inhibitors (penicillin combinations) were the most dynamic

antibacterials: both their overall use (Table 6) and their share from total penicillin use (31.6 % vs. 59.4%) gradually rose year by year. The co-amoxiclav (i.e. amoxicillin and clavulanic acid) combination was the number one antibacterial (had the highest consumption) each year from 1998 onwards, with almost a two-fold increase in use (from 2.3 to 4.1 DDD per 1000 inhabitant-days) during the 12 years of assessment (Figure 3).

Figure 3. The relative share of the top 10 antibacterials from total ambulatory antibacterial use in Hungary, 1996-2007



SMT: sulfamethoxazole and trimethoprim

All other penicillin groups displayed a significant drop in relative and absolute use (Table 6, Figure 4), although the use of penicillins with extended spectrum (mainly amoxicillin) was still considerable in 2007. The beta-lactamase resistant penicillin group (ATC code: J01CF) had very marginal consumption (it had a peak in 2002 with 0.04 DDD per 1000 inhabitant-days) and all products were withdrawn from the Hungarian market in 2003.

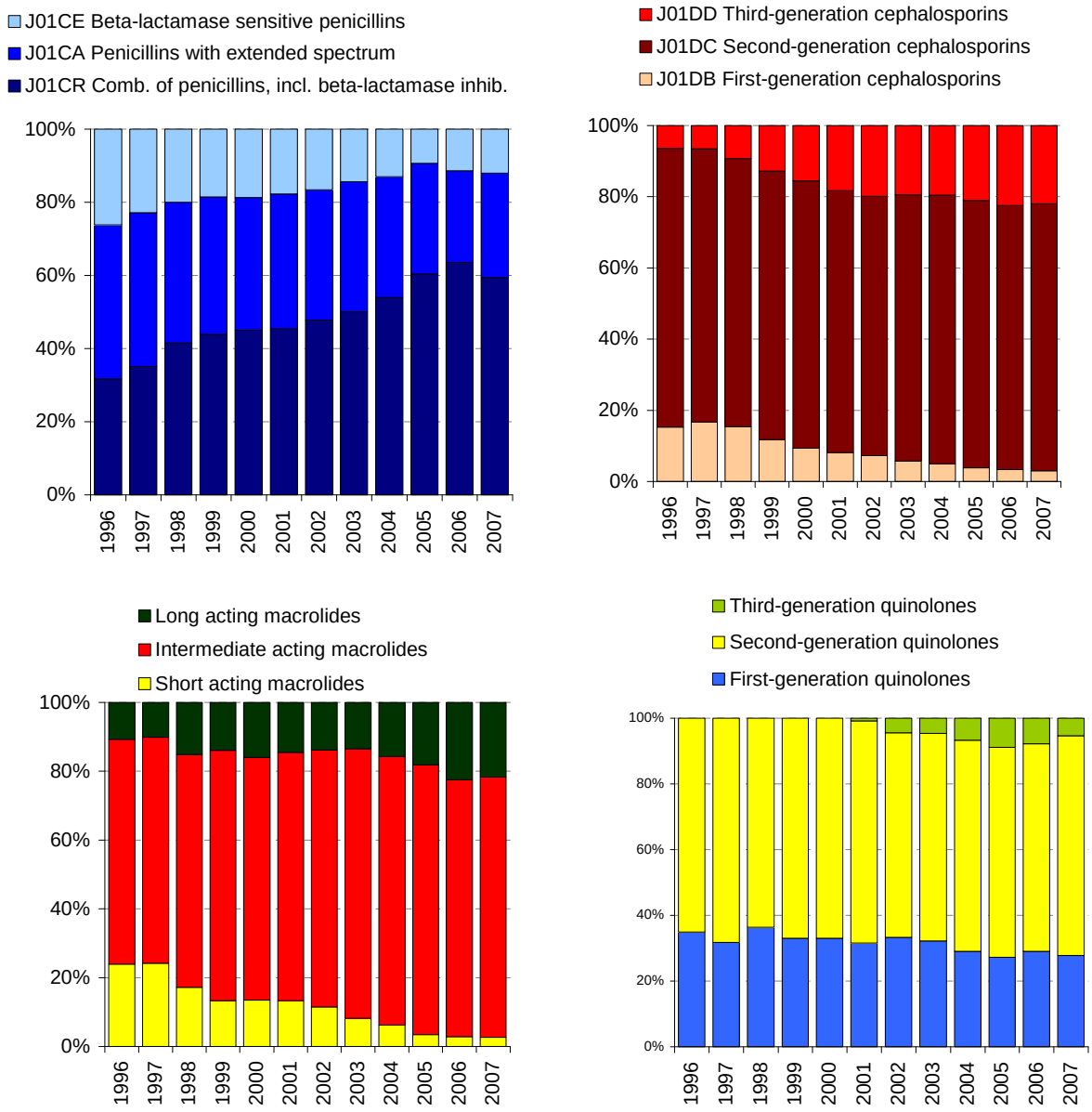
Table 6. National consumption of antibiotics in ambulatory care (DDD per 1000 inhabitant-days) in 1996 and 2007 and results of the trend analysis for the 12 years of assessment

	1996	2007	% Change	Correlation coefficient	P value
	(A)	(B)	(B-A)/A x 100	(R)	
J01	18.39	15.44	-16.03	-0.518	0.084
J01A Tetracyclines	3.31	1.4	-57.66	-0.977	<0.001
J01CA Penicillins with extended spectrum	3.38	2.00	-40.84	-0.858	<0.001
J01CE Beta-lactamase-sensitive penicillins (narrow-spectrum penicillins)	2.1	0.84	-60.09	-0.977	<0.001
J01CR Penicillin combinations including beta-lactamase inhibitors (penicillin combinations)	2.54	4.16	63.88	0.827	0.001
J01DB First-generation cephalosporins	0.38	0.05	-87.17	-0.967	<0.001
J01DC Second-generation cephalosporins	1.95	1.23	-37.06	-0.767	0.004
J01DD Third-generation cephalosporins	0.16	0.36	123.39	0.786	0.002
J01E Sulfonamides and trimethoprim	2.08	0.73	-65.02	-0.994	<0.001
J01FA Macrolides	1.59	2.21	38.87	0.358	0.253
Short acting macrolides[b]	0.38	0.06	-83.09	-0.949	<0.001
Intermediate acting macrolides[b]	1.04	1.67	60.54	0.523	0.081
Long acting macrolides[b]	0.17	0.48	177.10	0.728	0.007
J01FF Lincosamides	0.26	0.67	159.53	0.968	<0.001
J01M Quinolones	0.64	1.51	137.20	0.937	<0.001
First-generation quinolones[c]	0.22	0.42	88.77	0.899	<0.001
Second-generation quinolones[c]	0.41	1.01	143.41	0.947	<0.001
Third-generation quinolones[c]	0.00[a]	0.08	nc	0.803	0.016
Parenteral antibiotics	0.25	0.06	-77.19	-0.974	<0.001
Broad spectrum penicillins, cephalosporins and macrolides[d]	6.17	8.60	39.38	0.567	0.054
Narrow spectrum penicillins, cephalosporins and macrolides[e]	2.80	0.92	-8.00	-0.964	<0.001

a: data from 1999 (products are available from 1999)
nc: not calculated because of extreme low value (min≤0.01).
b, c: see definitions in the methods (Table 4.)
d, e: see definitions in the methods (Table 3.)

Among cephalosporins the second generation agents (mainly cefuroxime and cefaclor) were the most widely used in all years of assessment (Table 6 and Figure 3 and Figure 4). The use of second and third generation cephalosporins gradually increased at the expense of first generation agents. (Table 6 and Figure 4).

Figure 4. Relative use of different penicillins, cephalosporins, macrolides and quinolones between 1996-2007



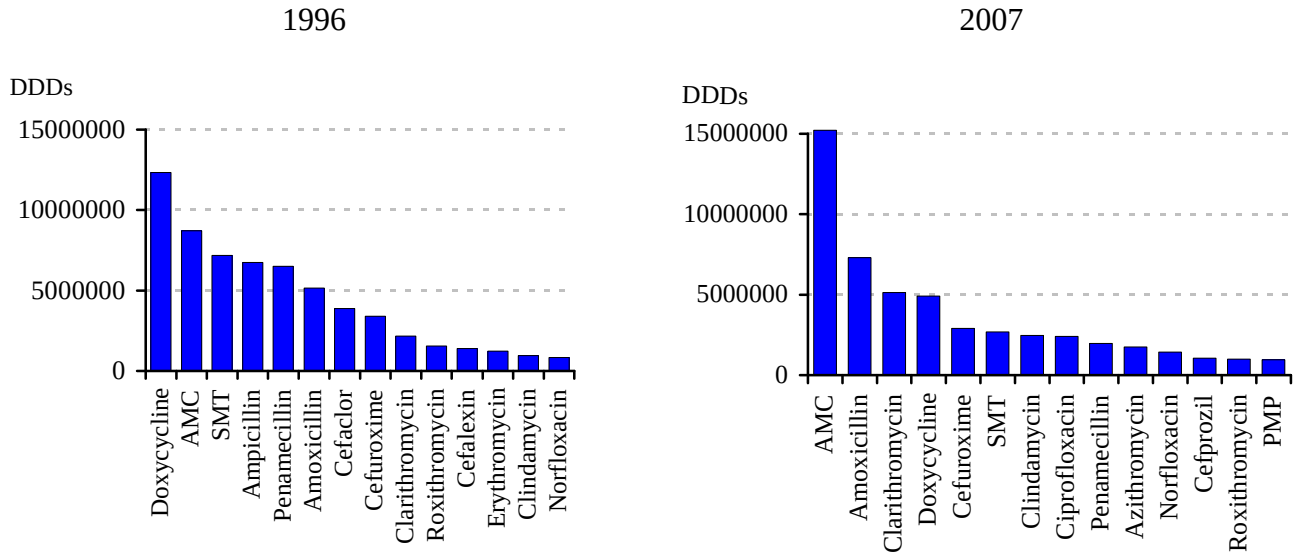
In this pharmacological subgroup (J01D) the consumption of carbapenems was marginal in the ambulatory care sector. The usage of the sulfonamides fell to one third (Table 6) by the last year of observation *(these values were displayed erroneously in the article published in the Orvosi Hetilap).*

The total use and the relative share of the macrolide group showed an increase (1996 vs. 2007: 10.1% vs. 18.7%). The intermediate acting macrolides had consistently the most use in this antibiotic subgroup. Short- and long- acting macrolides recorded a significant

decrease and increase in use, respectively (Table 6, Figure 4). Three macrolide agents were represented continuously in the top ten list (Figure 3). For lincosamides (represented by clindamycin in Hungary), a significant growth in use was observed (Figure 3). Overall, aminoglycoside use was virtually negligible in ambulatory care. As concerns the quinolones, all generations showed a positive trend in use. (Table 6, Figure 4). Second-generation quinolones (ciprofloxacin) were the most prominent quinolone group (Table 6, Figure 3 and 4). The use of the other antibiotic group (J01X) was minor and was dominated by nitrofurantoin and fosfomycin (these two agents were responsible for 99.97% of the J01X use in 2007).

The two quality indicator groups introduced by the ESAC showed opposite trends: broad spectrum penicillins, cephalosporins and macrolides ("B") gained extended use over the years while the narrow spectrum penicillins, cephalosporins and macrolides ("N") showed decreased consumption, hence the B/N ratio considerably increased (from 2.2 to 9.3).

Figure 5. Antibiotics and their consumption in DDDs in the DU90% segment
Ambulatory care



Antibacterials in rank order of DDDs

AMC: Amoxicillin and clavulanic acid (co-amoxiclav)
SMT: Sulfamethoxazole and trimethoprim
PMP: Phenoxymethylpenicillin

Parenteral antibiotic use in the ambulatory care sector was marginal and showed further decrease during the study period (from 1.4% to 0.4 %). At both endpoints the procaine benzylpenicillin products were responsible for more than two-thirds (1996: 84.63% and 2007: 71.83%) of the parenteral antibacterial use. The heterogenity of antibacterial use was evaluated by means of the DU90% segment method. The high dominance of co-amoxiclav

and amoxicillin use can be observed on Figure 5 (their summed share of total antibacterial use was 39.7% in 2007).

Regional differences in antibacterial utilisation

Despite the quantitatively stable national standardised ambulatory antibacterial use, there were large variations depending on the region (Figure 6). For each year during 1996-2007, the difference between the regions with the lowest and the highest total antibiotic consumption (maximum/minimum ratio) ranged between 1.5–1.72. The pattern of use also differed considerably between the Hungarian regions: both at the start and end point of the study, the use of all antibiotic classes varied around a factor of 2 (Table 7). These regional differences were also present when only the parenteral antibacterials, narrow or broad spectrum agents were considered (Table 7). The relative share of sulfonamides showed the highest deviation: in 2007 its relative use ranged between 3.1 % and 9.4 %. The most prominent group, the penicillins recorded a relative use between 40.1 % and 50.3 % in 2007. Analysis at the active agent level revealed that the top 3 agents in 2007: co-amoxiclav, amoxicillin and clarithromycin exhibited a relative use of 20.8 % to 32.1 %, 5.9 % to 18.0 % and 6.2 % to 11.3 %, respectively, depending on the region.

Determinants of regional ambulatory antibacterial use

Out of the studied factors (see Table 5.) only two determinants showed a significant association with total antibiotic consumption: the number of persons receiving free access to selected medicines from the public health system (“közgyógy”) ($r=0.84$, $P<0.00001$) and the number of persons regularly receiving social assistance per 10 000 inhabitants ($r=0.64$, $P<0.001$). No significant correlation was found for the other tested determinants, although there was a trend towards a positive association between antibiotic use and the prevalence of COPD ($r=0.54$, $P=0.013$), the number of yearly consultations and home visits per GP ($r=0.46$, $P=0.041$), and towards a negative association between antibiotic use and the percent of homes with premises for bathing and washing ($r=–0.59$, $P=0.006$) and the GDP per inhabitant ($r=–0.59$, $P=0.006$).

Figure 6. Regional ambulatory care antibiotic consumption (DDD per 1000 inhabitant-days) in Hungary

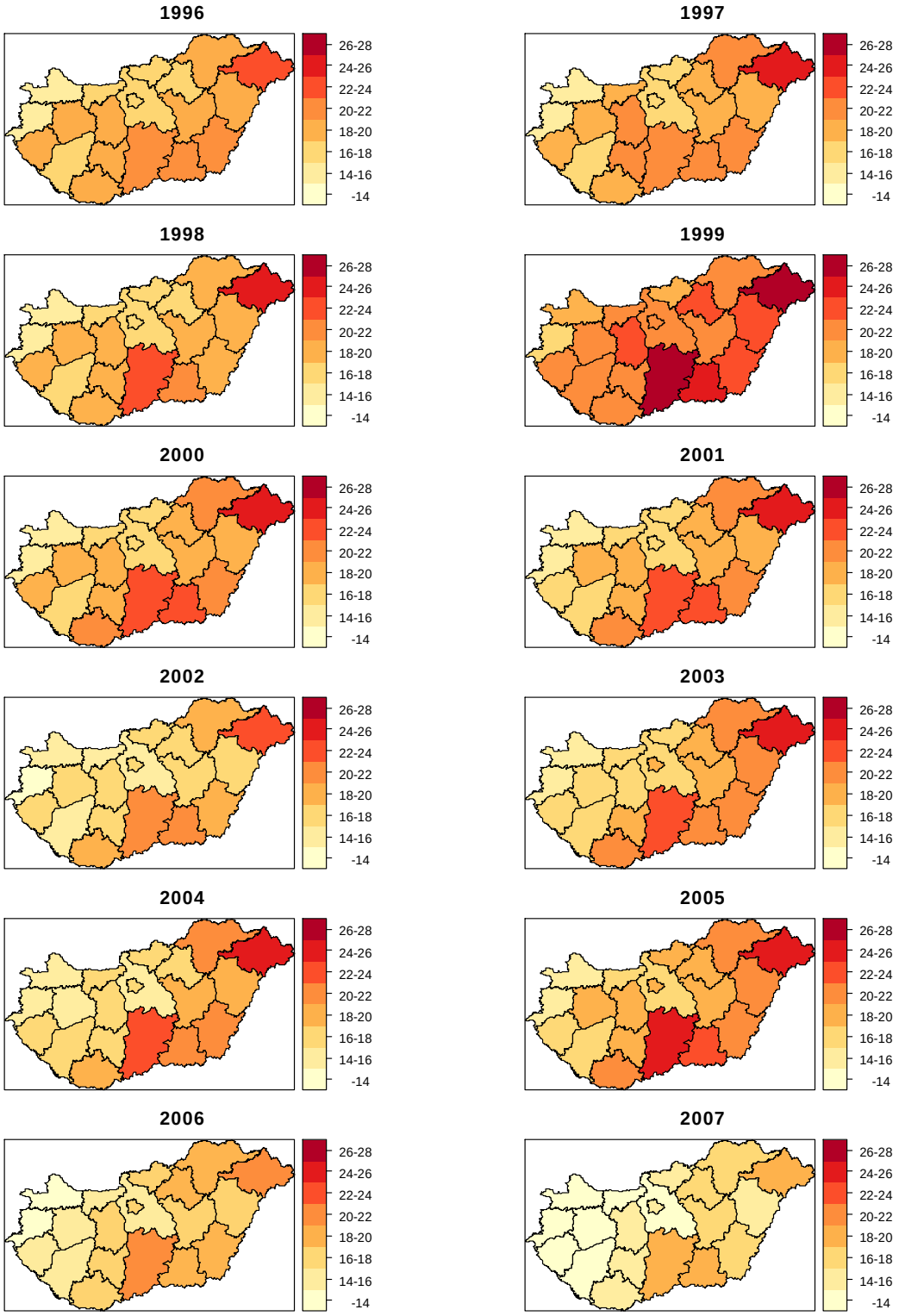


Table 7. Ambulatory care antibiotic consumption of Hungarian regions (in 1996 and 2007, expressed in DDD per 1000 inhabitant-days)

	1996				2007			
	Mean ± SD[a]	Min	Max	Ratio Max/Min	Mean ± SD[a]	Min	Max	Ratio Max/Min
J01 Systemic antibacterials	18.55±1.95	14.71	22.12	1.50	15.31±2.11	11.76	19.65	1.67
J01A Tetracyclines	3.3±0.58	2.36	4.35	1.84	1.39±0.23	1.07	1.98	1.85
J01C Penicillins	8.12±1.31	5.52	11.39	2.06	6.99±1.13	4.99	9.87	1.98
J01CA Penicillins with extended spectrum	3.46±0.92	1.38	5.20	3.76	2.03±0.64	0.69	3.55	5.14
J01CE Beta-lactamase-sensitive penicillins (narrow-spectrum penicillins)	2.11±0.32	1.62	2.70	1.67	0.84±0.29	0.41	1.48	3.56
J01CR Penicillin combinations including beta-lactamase inhibitors (penicillin combinations)	2.56±0.54	1.77	4.02	2.27	4.12±0.65	2.82	5.36	1.90
J01D Other beta-lactam antibacterials	2.61±0.43	1.84	3.31	1.80	1.73±0.39	1.18	2.37	2.00
J01DB First-generation cephalosporins	0.39±0.1	0.25	0.61	2.40	0.05±0.02	0.01	0.11	8.90
J01DC Second-generation cephalosporins	2.05±0.33	1.44	2.55	1.78	1.32±0.34	0.85	1.82	2.16
J01DD Third-generation cephalosporins	0.17±0.05	0.05	0.27	5.49	0.36±0.1	0.23	0.59	2.61
J01E Sufhonamides and trimethoprim	2.06±0.37	1.35	2.93	2.17	0.72±0.3	0.45	1.59	3.56
J01F Macrolides, lincosamides	1.86±0.25	1.33	2.14	1.61	2.76±0.36	2.18	3.64	1.67
Short acting macrolides[b]	0.38±0.08	0.28	0.63	2.29	0.06±0.02	0.03	0.10	2.98
Intermediate acting macrolides[b]	1.06±0.19	0.69	1.34	1.95	1.63±0.21	1.32	2.06	1.55
Long acting macrolides[b]	0.17±0.04	0.10	0.28	2.72	0.47±0.16	0.27	0.83	3.01
J01FF Lincosamides	0.26±0.08	0.16	0.45	2.81	0.59±0.17	0.36	1.21	3.37
J01M Quinolones	0.6±0.17	0.37	1.07	2.85	1.45±0.29	1.06	2.05	1.94
Second generation quinolones[b]	0.39±0.07	0.27	0.59	2.21	0.98±0.19	0.66	1.33	2.03
First generation quinolones[b]	0.22±0.16	0.08	0.78	9.90	0.4±0.14	0.21	0.65	3.09
Third generation quinolones[b]		d			0.08±0.03	0.04	0.15	3.78
Broad spectrum penicillins, cephalosporins and macrolides[c]	6.3±0.85	5.08	8.12	1.60	8.53±1.15	6.43	10.72	1.67
Narrow spectrum penicillins, cephalosporins and macrolides[c]	2.83±0.39	2.19	3.77	1.72	0.92±0.3	0.47	1.53	3.22
Parenteral antibiotics	0.27±0.13	0.07	0.60	8.23	0.06±0.04	0.01	0.19	15.70

a: standard deviation (SD); b, c: see definitions in the methods section (Table 3, Table 4); d: not marketed in 1996

5.2. B) Non-prescription (over the counter=OTC) antibiotic use in Hungary

National non-prescription antibiotic sales, expressed in different units of measurement, are summarised in Table 8. As consumption of parenteral antibiotic formulations was very limited in the Hungarian ambulatory care sector (0.5 % of total antibiotic use), only oral products were considered.

In 2004, the non-prescription antibiotic use in DDD per 1000 inhabitant-days was 0.38, which equates to 13.87 DDD per 100 patients per year. As 7 days was defined as the average length of antibiotic treatment, this corresponds to ~ 2 (precisely: 1.98) antibiotic courses per 100 patients per year. Expression in other measurement units has led to similar results: the population prevalence of non-prescription antibiotic sales from pharmacies was about 2 %. (Table 8, see detailed explanation in the annex)

Table 8. National non-prescription sales of systemic antibacterials expressed in different units, 2000–2004 (percentage of total use)

Measurement unit	2000	2001	2002	2003	2004
DDD per 1000 inhabitant-days	0.13 (0.67 %)	0.14 (0.72 %)	0.34 (1.95 %)	0.39 (2.04 %)	0.38 (2.08 %)
DDD/pharmacy/month	19.87	21.45	52.93	59.33	57.96
DDD/1000 inhabitants/year	9.43 (0.71 %)	9.55 (0.75 %)	23.82 (2.09 %)	25.70 (2.13 %)	24.40 (2.14 %)
Package /pharmacy/month	3.93	4.04	10.06	10.82	10.27

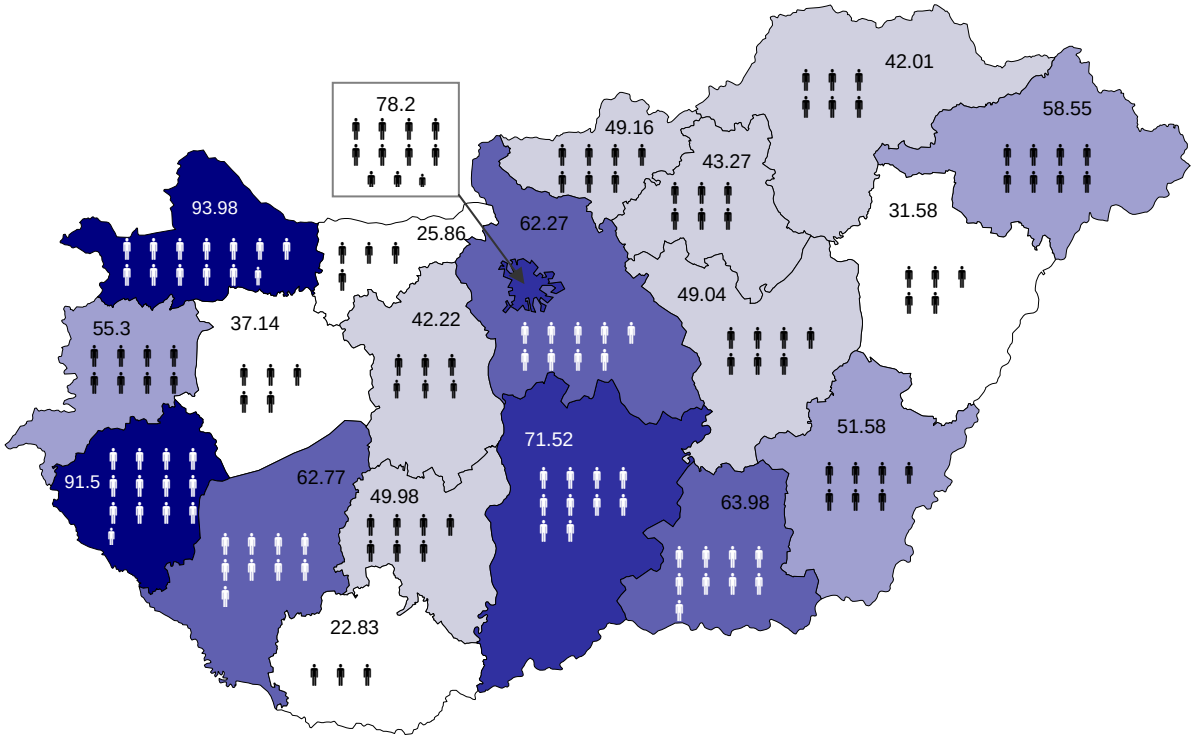
During the study period the nationwide non-prescription sales of antibiotics sharply increased from 2002 (Table 8). Analysing the non-prescription antibiotic sales in 2000 and 2004, a significant difference was found (0.16 ± 0.23 vs. 0.35 ± 0.14 DDD per 1000 inhabitant-days).

Regional analysis revealed large variations both in the level and the share (data not shown) of non-prescription antibiotics sales (Figure 9). An association between non-prescription and prescription sales could not be found ($R=0.122$, $p=0.226$). An inverse correlation ($R= -0.732$, $p=0.016$) was found between the price and non-prescription sales of antibacterials. The most frequently sold OTC antibacterials belonged to the tetracycline, the sulfonamide and the penicillin antibacterial groups.

In 2004, ten drugs were in the DU 90 segment of non-prescription antibiotic use (in descending order of DDD per 1000 inhabitant-days: doxycycline, co-amoxiclav, co-

trimoxazole, penamecillin, ampicillin, amoxicillin, clindamycin, clarithromycin, norfloxacin, cefuroxime).

Figure 9. Regional non-prescription antibiotic sales expressed as the average number of DDDs per month per pharmacy in 2004. The number of people shows the average number of patients supplied with a seven-day non-prescription antibiotic course per month per pharmacy in the particular county



5.3. C) Antibiotic use in the Southern Great Plain region

General characteristics of antibiotic use, main indications and their therapy

Aggregated regional data showed that during the study period (first half of 2007) 4 795 967 DDDs of antibiotics were dispensed and the standardised antibiotic use was: 21.1 DDD per 1000 inhabitant-days in the Southern Great Plain region. Almost only oral antibacterial products were consumed (99.5%) of which 11.5% were liquid oral dosage forms.

Table 9 shows the main indications and their proportional share from total ambulatory antibiotic use. The most common illnesses for which antibiotic therapy was prescribed were: respiratory tract infections, genitourinary infections (in 64.1% acute cystitis) and infections of the gastro-intestinal system (in 97 % diseases of oral cavity), respectively.

Table 9. Main indications and the proportional share of the related antibiotic use from total ambulatory antibiotic use.

IDC	IDC main class	DDD per 1000 inhabitant-days	%	cum %
J00-J99	Diseases of the respiratory system	14.0	66.4	66.4
N00-N99	Diseases of the genitourinary system	2.6	12.3	78.7
A00-B99	Certain infectious and parasitic diseases	1.0	4.7	83.4
K00-K93	Diseases of the digestive system	1.0	4.6	87.9
L00-L99	Diseases of the skin and subcutaneous tissue	0.6	2.8	90.7
	Other*	1.9	9.2	100

Other**:Diseases of the ear and mastoid process (H60-H95); Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99); Diseases of the circulatory system (I00-I99); Injury, poisoning and certain other consequences of external causes (S00-T98); Diseases of the musculoskeletal system and connective tissue (M00-M99); Neoplasms (C00-D48); Factors influencing health status and contact with health services (Z00-Z99); External causes of morbidity and mortality (V01-Y98); Diseases of the eye and adnexa (H00-H59); Pregnancy, childbirth and the puerperium (O00-O99); Endocrine, nutritional and metabolic diseases (E00-E90); Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99); Mental and behavioural disorders (F00-F99); Codes for special purposes (U00-U99); Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89); Diseases of the nervous system (G00-G99); Certain conditions originating in the perinatal period (P00-P96)*

As antibiotics prescribed for respiratory tract infections were responsible for two-thirds of the total ambulatory antibiotic use (Table 9), the more detailed ICD codes – presented in Table 10 - may be important. It can be concluded from Table 10 that upper respiratory tract infections were the indications of therapies in more than 70% of respiratory tract infections.

Table 10. Most frequent respiratory tract infections and the percentile share of the related antibiotic use.

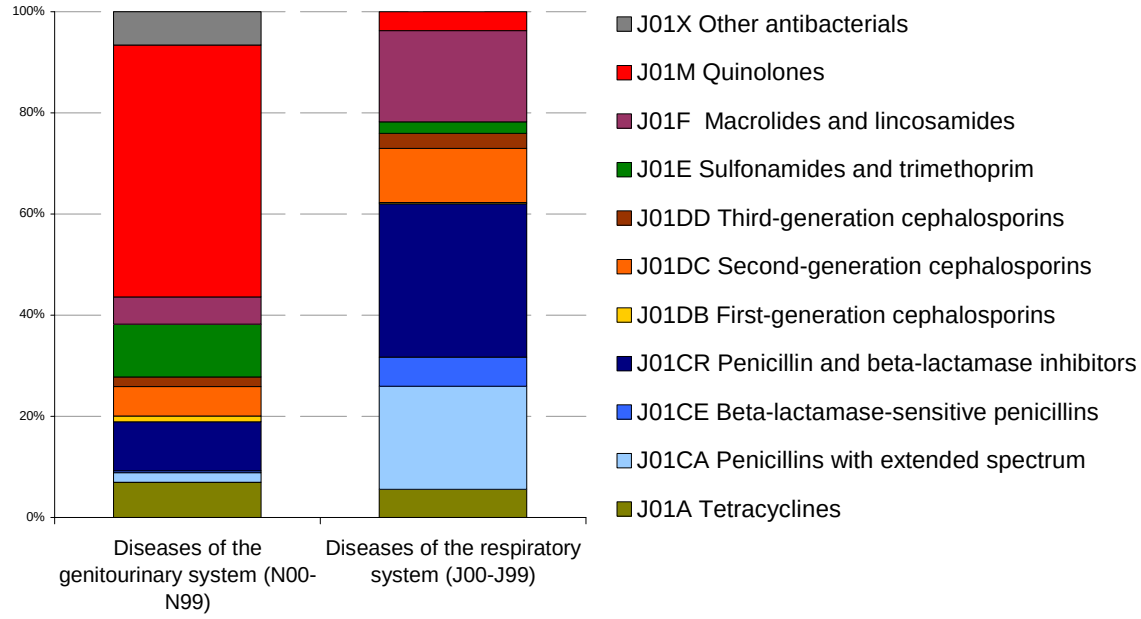
	subclass	DDD per 1000 inhabitant-days	%
J00-J06	Acute upper respiratory infections	9.8	69.6
J09-J18	Influenza and Pneumonia	0.6	4.0
J20-J22	Other acute lower respiratory infections	3.1	22.4
J30-J39	Other diseases of upper respiratory tract	0.2	1.5
J40-J47	Chronic lower respiratory diseases	0.3	2.3
J60-J70	Lung diseases due to external agents	< 0.05	0.0
J80-J84	Other respiratory diseases principally affecting the interstitium	< 0.05	0.0
J85-J86	Suppurative and necrotic conditions of lower respiratory tract	< 0.05	0.0
J90-J94	Other diseases of pleura	< 0.05	0.1
J95-J99	Other diseases of the respiratory system	< 0.05	0.0
J00-J99	**Diseases of the respiratory system**	**14.0**	**100**

Respiratory tract infections were mainly treated with beta-lactams (cumulative share: 70.3 %, see also Figure 10). Extended spectrum penicillins (J01CA) and penicillin combinations (J01CR) were used extensively: amoxicillin and co-amoxiclav consumption together were responsible for about half (30.2% + 16.8 %) of antibiotic use in respiratory tract diseases. Clarithromycin, cefuroxime and doxycycline made up 11.7 %, 6.9 % and 5.5 % of antibiotic use in respiratory diseases, respectively.

For genitourinary infections, mainly fluoroquinolones were prescribed (share: 49.8%, see also Figure 10); the share of norfloxacin was 22.2% and the share of ciprofloxacin was 17.6% of total antibiotic use in this indication. The other three most frequently used agents in genitourinary diseases were the sulfamethoxazole/trimethoprim combination (10.5%); co-amoxiclav (9.4%) and ofloxacin (8.4%).

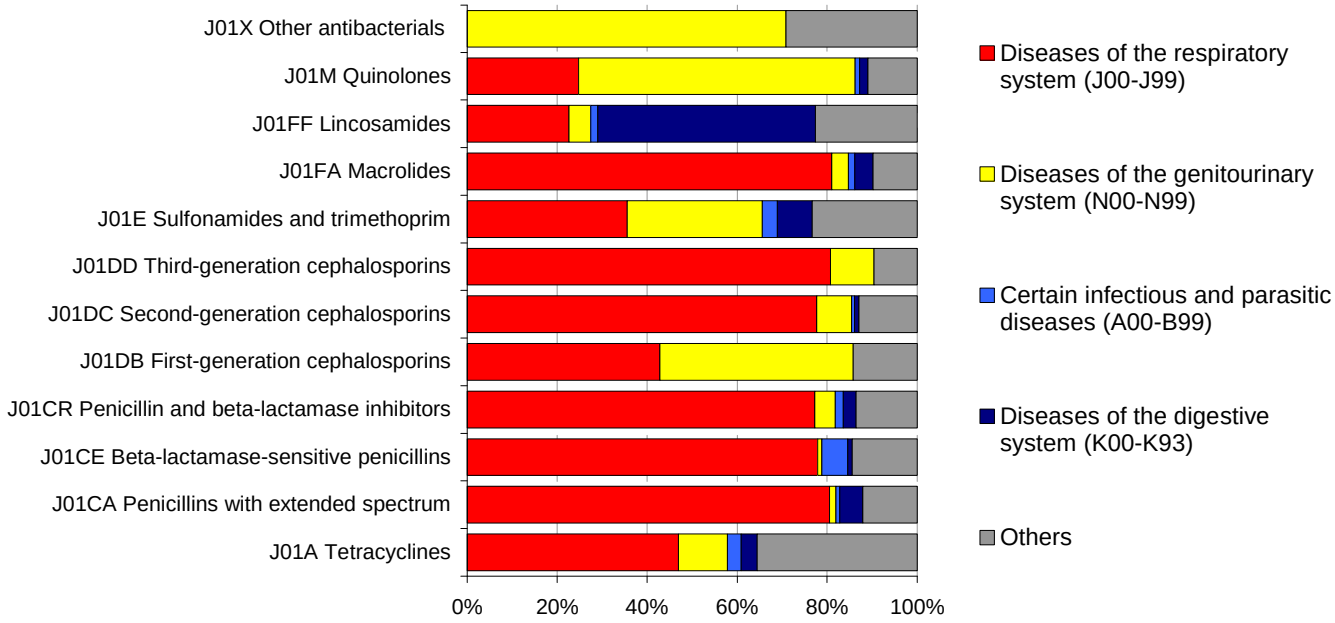
Diseases of the digestive system which were treated with antibiotics were mainly treated by clindamycin (47.5%). Considering all indications, the ESAC defined broad spectrum penicillins, cephalosporins and macrolides were used in 54.2% while narrow spectrum penicillins, cephalosporins and macrolides were used in 5.6 %, hence the B/N ratio was 9.6.

Figure 10. The relative use of different antibacterial groups in respiratory and genitourinary diseases. (according to dispensed DDDs)



From the perspective of the medicines, an overview of the distribution of prescribed indications in each antibacterial group is given in Figure 11. To a lesser or greater extent, almost all antibacterial groups were used to treat respiratory tract infections. All penicillin groups, macrolides and second and third generation cephalosporins were prescribed in high percent for respiratory diseases. The main indications of tetracyclines and sulfonamides were also respiratory tract infections. The other antibacterial group (J01X), quinolones, first generation cephalosporins and sulfonamides were indicated primarily for genitourinary infections (Figure 11), while lincosamides (clindamycin) were used principally for diseases of the digestive system, mainly for infections of the oral cavity.

Figure 11. The distribution of prescribed indications in different antibacterial groups (according to dispensed DDDs)



To estimate the rate of antibiotic overuse in respiratory tract infections

The infectious disease consultant judged antibiotic therapy as probably required and useful in 33.3% of cases, probably needless in 60.3% and undeterminable in 6.4% (Table 11). Acute pharyngitis and acute bronchitis were the two most common indications with possible antibiotic overuse. The top five agents with the highest potential overuse are depicted in Table 12. As can be seen from Table 12 more than half of the total antibiotic use was probably needless.

To evaluate the rate of adherence to antibacterial guidelines in case of acute streptococcal tonsillopharyngitis (AST)

Considering all respiratory tract infections, 7.85 % of the prescribed antibacterial quantity (1.10 DDD per 1000 inhabitant-days) was ordered for acute streptococcal tonsillopharyngitis (AST). Mainly different penicillin products were prescribed (68.8 % of all DDDs) for AST. Cephalosporins and macrolides were used in 12.7 % and 10.6 %, respectively. Most often co-amoxiclav (34.3% of all DDDs) and amoxicillin (18.7% of all DDDs) were prescribed for this condition. The guideline recommended as first-line agents the narrow spectrum penicillins, which were ordered only in a minority (9.2 %) of streptococcal infections of the tonsillopharynx.

Table 11. Necessity of antibacterial use in different respiratory diseases

			DDD per 1000 inhabitant-days	Cum %
Probably required and useful ∑=4.7 DDD per 1000 inhabitant-days (100%)	J0390	Acute tonsillitis	1.7	36.9
	J0200	Acute streptococcal pharyngitis	0.7	51.6
	J0100	Acute sinusitis	0.5	61.8
	J0300	Acute streptococcal tonsillitis	0.4	70.7
	J2000	Acute bronchitis (Mycoplasma pneumoniae)	0.3	76.3
	J1890	Pneumonia	0.2	81.4
	J1800	Bronchopneumonia	0.2	86.1
	J0190	Acute sinusitis	0.2	89.5
	J40H0	Bronchitis, unspecified	0.1	91.6
Probably needless ∑= 8.5 DDD per 1000 inhabitant-days (100%)	J0290	Acute pharyngitis	3.5	41.0
	J2090	Acute bronchitis	2.8	73.8
	J0690	Upper respiratory tract infection	1.0	85.4
	J00H0	Common flu	0.5	91.2
Undeterminable (grey zone) ∑= 0.9 DDD per 1000 inhabitant-days (100%)	J0410	Acute tracheitis	0.3	39.1
	J0400	Acute laryngitis	0.2	64.7
	J0420	Acute laryngotracheitis	0.2	86.1
	J0600	Acute laryngopharyngitis	0.1	96.4

Table 12. Antibacterial with the highest probably needless use in respiratory diseases (DDD per 1000 inhabitant-days and %).

Active agent	DDD per 1000 inhabitant-days			%
	Probably required and useful	**Probably needless use**	**Undeterminable**	**Probably needless (as % of all)**
Co-amoxiclav	1.54	2.47	0.22	58.4
Amoxicillin	0.64	1.59	0.13	67.4
Clarithromycin	0.49	0.99	0.15	60.6
Cefuroxime	0.34	0.55	0.08	56.5
Doxycycline	0.19	0.54	0.05	69.4

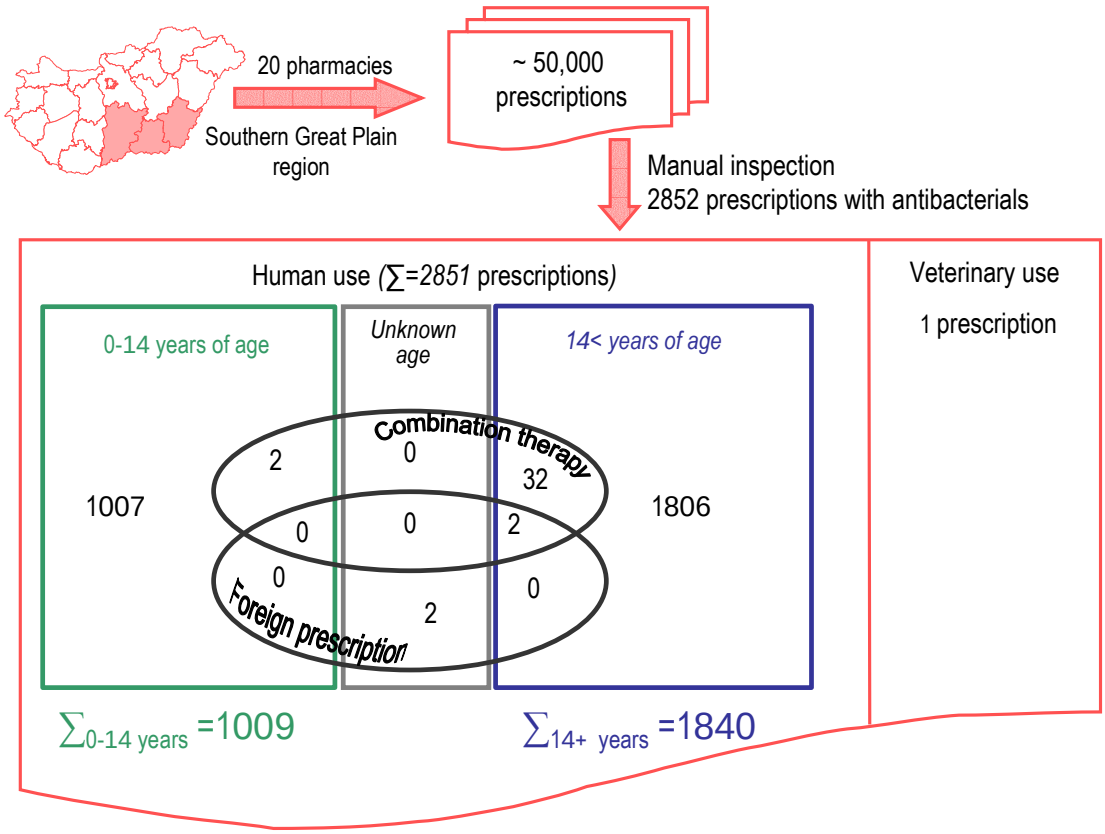
5.4. D) In-depth analysis of ambulatory patient-level antibiotic use data

Patient characteristics (age, gender, age-linked distribution of indications), the prescribed doses and dosage forms

During the 120 study days around 50,000 prescriptions were dispensed in the 20 pharmacies, of which 2852 referred to antibacterials (Figure 11). Doctors mainly prescribed antibacterial monotherapies. The average number of dispensed antibiotic prescriptions was 142.6 per pharmacy (minimum: 44 prescriptions; maximum 223 prescriptions). In total 1008 patients (35.7%) were children (As one child received combination therapy the

number of prescriptions ordered for children was 1009, see Figure 11). Doctors prescribed oral antibacterial products almost exclusively, parenteral products were ordered only in 20 cases. Within oral antibacterial products, the average share of liquid oral forms was ranged between 5.9 % and 25.0 %. Liquid oral antibacterial products were indicated in 651 cases, which were mainly prescribed for children (646 cases).

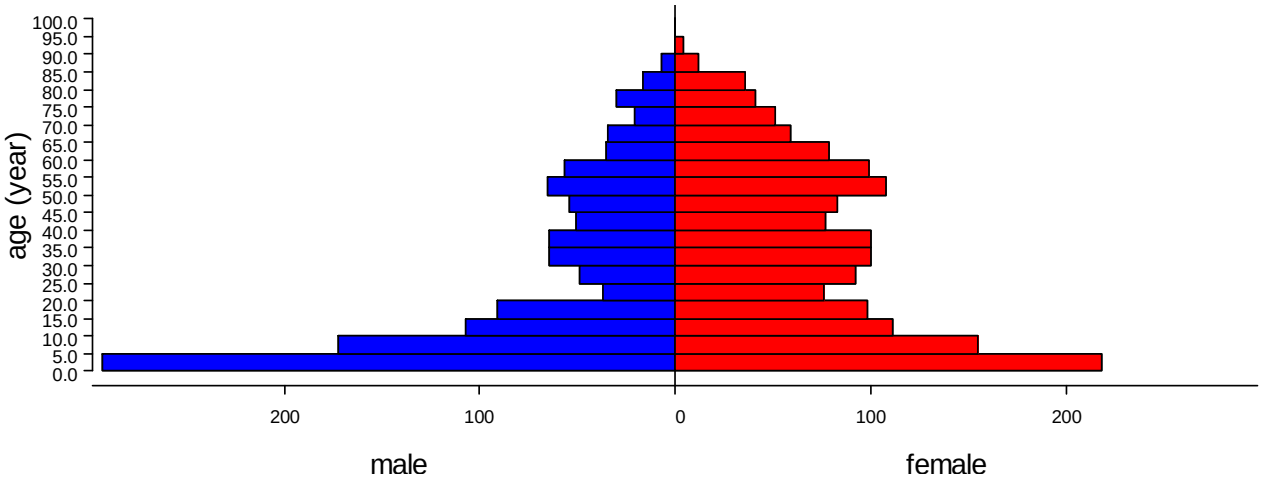
Figure 11. Details of the overviewed prescriptions



The age-distribution of patients is displayed in Figure 12. In the patient population we detected a female dominance in adults (female: 63.4%, male: 36.6%) while in children boys received antibiotics in higher number (girls: 46.5%, boys: 53.4%). The gender of one patient was undeterminable due to the illegible name on the prescription.

Overall, the main indications of antibacterial monotherapies were respiratory tract infections (1889 cases, 67.2%), urogenital infections (360 cases, 12.8%) and infections of the gastrointestinal system (146 cases, 5.2%).

Figure 12. Age distribution of antibiotic users



Stratification by age group is displayed in Table 13. In both age groups disease of the respiratory tract was the leading indication, while the second most frequent indication was genitourinary disease in adults and ear/mastoid related disease in children.

Table 13. Main indications of antibacterial monotherapies.

	IDC main classes	cases (%) <14 years of age	Adult cases
J00-J99	Diseases of the respiratory system	849 (84.3%)	1040 (57.6%)
H60-H95	Diseases of the ear and mastoid process	66 (6.6%)	19 (1.1%)
A00-B99	Certain infectious and parasitic diseases	38 (3.8%)	98 (5.4%)
N00-N99	Diseases of the genitourinary system	13 (1.3%)	347 (19.2%)
K00-K93	Diseases of the digestive system	12 (1.2%)	134 (7.4%)
L00-L99	Diseases of the skin and subcutaneous tissue	8 (0.8%)	54 (3.0%)
	Other	21 (2.0)	114 (6.3)

Other: Diseases of the circulatory system *(I00-I99);* Injury, poisoning and certain other consequences of external causes *(S00-T98);* Diseases of the eye and adnexa *(H00-H59);* Pregnancy, childbirth and the puerperium *(O00-O99);* Factors influencing health status and contact with health services *(Z00-Z99);* Endocrine, nutritional and metabolic diseases *(E00-E90)*

The next two figures (Figure 13 and 14) show the change in the relative rate of indications according to patient age. From Figure 13 it can be concluded that urogenital infections were rare in children but their frequency gradually grew in parallel with increasing patient age. In the elderly the frequency of urogenital and respiratory indications was similar.

In all age groups up to 80 years old the upper respiratory tract infections dominated, but the share of lower respiratory tract infections increased with patient age. Over the age of 80, the relative rate of lower respiratory tract infections outweighed the rate of upper respiratory tract diseases.

Figure 13. The relative frequency of urogenital and respiratory indications (% of all ICD codes) in different age groups.

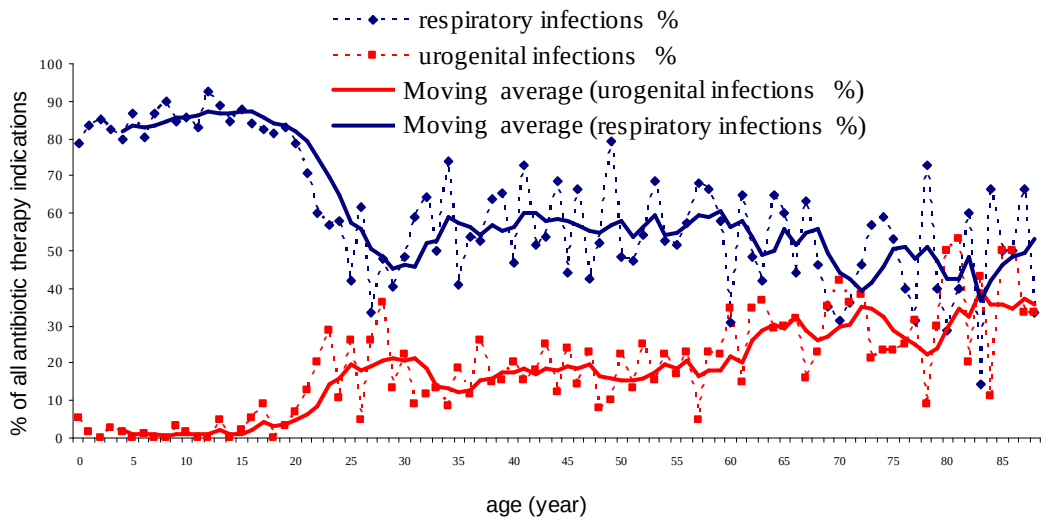
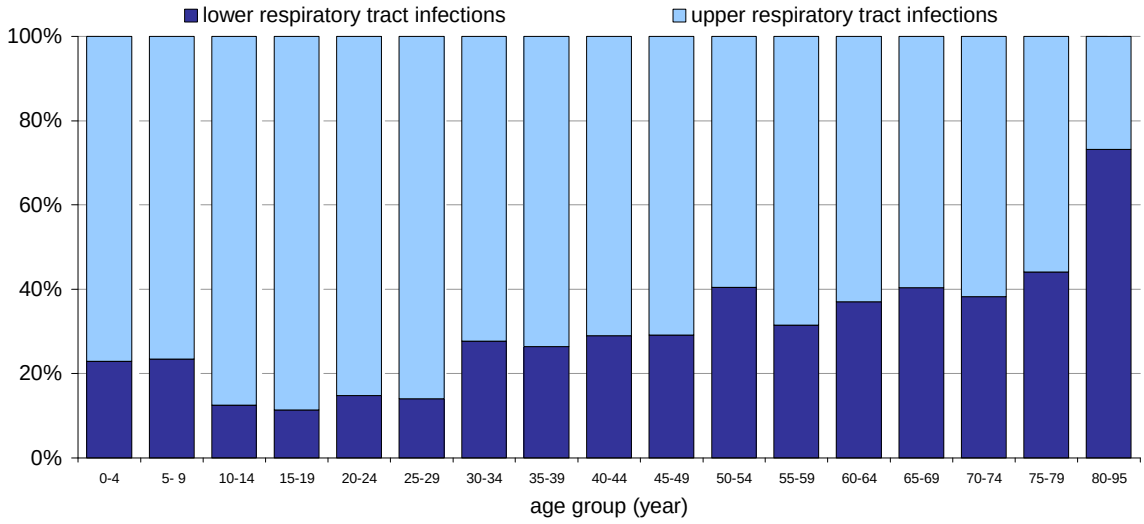


Figure 14: The relative share of lower and upper respiratory tract infections in different ages.



For respiratory tract infections, penicillins (37.1% of all cases) and macrolide antibacterials (10.2% of all cases) were prescribed most often. Second generation cephalosporins were also prescribed quite often (11.9% of all cases). For both adults and children the amoxicillin and clavulanic acid combination was the most frequently prescribed agent (Table 14.). In genitourinary indications the use of quinolones (mainly ciprofloxacin and norfloxacin) outweighed all other antibacterials, as they were prescribed in every second case (49.6 % of all cases; see also Table 14). In children the second most frequent indication (diseases of the ear and mastoid process) was mainly treated with beta-lactams (Table 14).

Table 14: The most frequently used antibacterial agents in the two most frequent main indications of adults and children

	Diseases of the respiratory system (J00-J99)				Diseases of the genitourinary system (N00-N99) adults		Diseases of the ear and mastoid process (H60-H95) children	
	adults		children					
	Active agent	patients	Active agent	patients	Active agent	patients	Active agent	patients
1	AMC	275	AMC	230	Ciprofloxacin	83	AMC	23
2	Clarithromycin	121	Amoxicillin	107	Norfloxacin	54	Cefuroxime	12
3	Amoxicillin	89	Cefuroxime	90	Ofloxacin	35	Azithromycin	9
4	Cefuroxime	84	Clarithromycin	71	AMC	27	Cefprozil	7
5	Doxycycline	68	Cefixime	51	SMT	25	Ceftibuten	7

AMC: Amoxicillin and clavulanic acid (co-amoxiclav)
SMT: Sulfamethoxazole and trimethoprim

The WHO defined DDD corresponds to the average maintenance daily dose in adults, while PDD (prescribed daily dose) is the actually prescribed dose for a particular patient. As Table 15 shows PDD differs considerably from DDD in the case of three antibacterial agents (highlighted in bold letters). Hungarian doctors tended to prescribe higher doses than usual.

Table 15: Comparison of the prescribed and defined antibacterial doses

		WHO DDD (gram)	Average±SD of prescribed adult dose	Cases *
Tetracyclines	Doxycycline	0.1	0.15±0.06	112
Penicillins with extended spectrum	**Amoxicillin**	**1**	**1.89±0.57**	**104**
	Ampicillin	2	1.99±0.70	38
Beta-lactamase sensitive penicillins	Penamecillin	1.05	1.23±0.29	35
Penicillins with beta-lactamase inhibitors	**AMC**	**1**	**1.44±0.39**	**301**
Second generation cephalosporins	Cefprozil	1	0.79±0.25	41
	Cefuroxime	**0.5**	**0.83±0.25**	**93**
	Cefixime	0.4	0.40±0.10	26
Third generation cephalosporins	Ceftibuten	0.4	0.40±0.00	20
Sulfonamides	SMT	1.92	1.59±0.48	67
Macrolides	Azithromycin	0.3	0.47±0.19	77
	Clarithromycin	0.5	0.57±0.18	121
	Roxithromycin	0.3	0.31±0.07	30
	Clindamycin	1.2	0.89±0.18	134
Quinolones	Ciprofloxacin	1	0.81±0.26	139
	Levofloxacin	0.5	0.46±0.14	36
	Norfloxacin	0.8	0.81±0.12	59
	Ofloxacin	0.4	0.40±0.00	47

Data refers only to adults (patients above 18 years of age). Maintenance monotherapies with solid oral agents case number of above 20 were included. AMC: Amoxicillin and clavulanic acid (co-amoxiclav); SMT: Sulfamethoxazole and trimethoprim

Necessity of antibacterial therapy in adults and children with respiratory tract infections

Antibiotic therapy of respiratory tract infections was considered to be probably needless in more than half of cases in both age groups (Table 16). According to the ICD-10 code based judgement, antibiotics were prescribed probably unnecessarily in mainly acute pharyngitis and acute bronchitis.

Table 16. Necessity of antibacterial use in respiratory diseases of children and adults

	Probably required and useful	Probably needless	Undeterminable
Children (0-14 years)	363 (42.9%)	442 (52.2%)	41 (4.8%)
Adults (> 14 years)	382 (36.8%)	588 (56.7%)	67 (6.5%)
Total	**745 (39.6%)**	**1030 (54.7%)**	**108 (5.7%)**

To evaluate the rate of adherence to antibacterial guidelines in cases of acute streptococcal tonsillopharyngitis (adults, children)

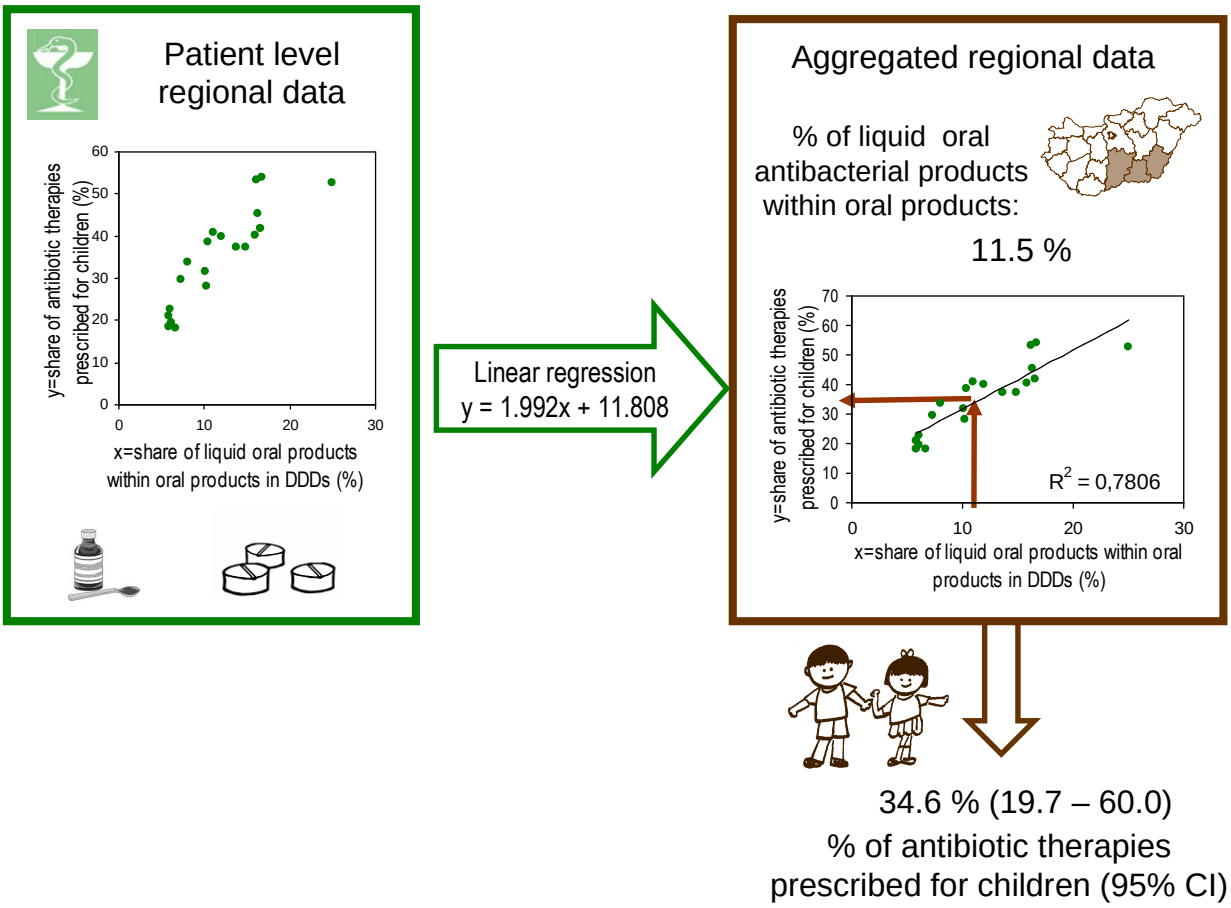
Antibiotics were prescribed for 77 children and 131 adults with acute streptococcal tonsillopharyngitis (AST). In children co-amoxiclav and amoxicillin, and in adults co-amoxiclav and cefuroxime, were the most frequently prescribed antibacterials. The guideline recommended as first-line agents the narrow spectrum penicillins (J01CE), which were ordered in 13 % of children and 7.6 % of adult AST cases (in total in 9.6%).

Estimating the rate of antibiotic therapy prescribed for children.

A strong association was found between the share of liquid oral antibacterial use and the rate of paediatric antibiotic prescriptions (R^2=0.781; p<0.001; unstandardised coefficient (B)= 0.392 with 95% confidence interval: 0.289–0.495; see also Figure 16).

Applying the result of the linear regression to the aggregated regional data (section C), 34.6% of the antibiotic prescriptions were for children while the rest (65.4%) were prescribed for adults. Considering the rate of child (14.9%) and adult (84.1%) inhabitants of the region [87] it means that on average children were prescribed antibiotics three times more often than adults ((34.6/14.9)/(65.4/84.1)=3.0).

Figure 16. Summary of the regression model (concept and substituted values)



6. DISCUSSION

6.1. A) National and regional ambulatory antibiotic consumption

The first (and only) comparable data on ambulatory antibiotic use in Hungary reports consumption data between 1990 and 1996 [50]. As the author, Graber showed, soon after the change of the political regime, antibiotic consumption in Hungarian ambulatory care started to decrease (from 23.9 in 1990 to 20.6 DDD per 1000 inhabitant-days in 1996) and slow change in the pattern of use was detected. Parallel to these changes the antibiotic assortment widened considerably.

From the results of this current work, ambulatory antibiotic consumption in Hungary between 1996 and 2007 remained relatively stable. Some of the changes in the pattern of use were continued from the earlier years of the 1990s: the decrease in the utilisation of the tetracyclines, the narrow-spectrum penicillins and the sulfonamide-trimethoprim group, which began in 1990 [50] continued until the end of the study period. The significant growth of fluoroquinolone consumption and of the penicillin and enzyme inhibitor combinations has also been unbroken since 1990.

Comparison of Hungarian antibacterial use with other European countries

Extensive data from the European Surveillance of Antimicrobial Consumption (ESAC) project provided the opportunity to compare Hungarian national antibiotic use data with other European countries.

Data from ESAC have shown striking inter-country variations in ambulatory antibiotic consumption [88] and that antibiotic consumption in Hungary was, with 21.1 DDD per 1000 inhabitant-days, in the middle-range of European countries in 1998 [89] and then was in the third tier of European antibiotic use according to the ESAC (European Surveillance of Antibiotic Consumption) survey from 2002 [88,90].

The proportion of parenteral antibiotic treatment in ambulatory antibiotic use was low in Hungary and showed a downward trend. Similarly low parenteral antibiotic use was reported from other European countries (e.g. Ireland, Belgium, Croatia and Austria) despite parenteral administration outside of hospital walls potentially being a convenient and cost-effective way of treating serious infectious diseases. In Hungary, procaine benzylpenicillin was the most used parenteral formulation (the proportional Hungarian procaine

benzylpenicillin use ranked 1st among European countries; [91] while on average the four most commonly used antibacterials for parenteral treatment were gentamicin, ceftriaxone, cefazolin and lincomycin in Europe [91].

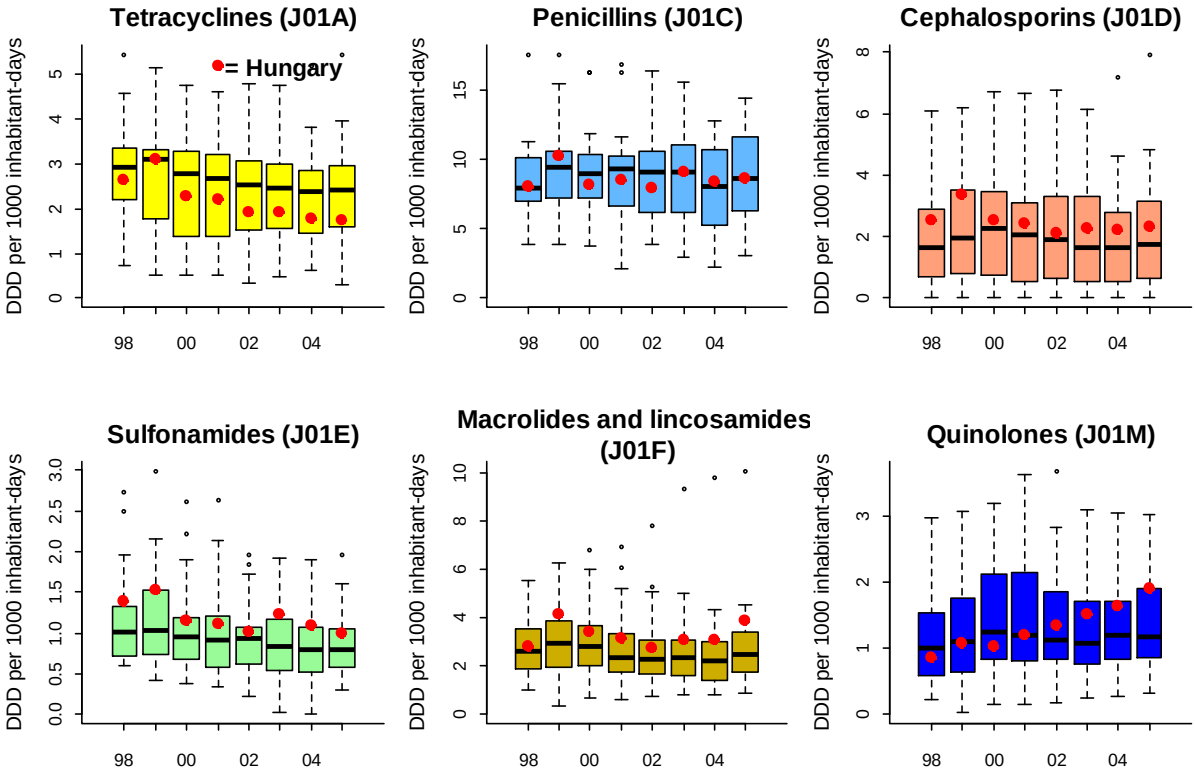
During the 12 years of assessment, substantial changes in the pattern of Hungarian ambulatory antibacterial use were detected. Penicillin combinations represented the most dynamic antibiotic class (their use increased by more than 1.5 DDD per 1000 inhabitant-days during the study period). The observed decline in the use of older antibacterials (e.g. sulfonamides, tetracyclines, short-acting macrolides, narrow spectrum penicillins, first generation cephalosporins) and increased use of newer and/or more broad spectrum chemotherapeutics (fluoroquinolones, co-amoxiclav, second and third generation cephalosporins and long-acting macrolides) were also detected (in various extent) in other European countries [77,88,92-94] and outside Europe as well [95,96].

Some of these changes are meaningful and follow clinical recommendations (e.g. short-acting macrolides (e.g. erythromycin) are inferior to the newer analogues (e.g. clarithromycin and azithromycin) in terms of pharmacokinetic profiles and side-effects), while other trends are alarming and should be avoided (e.g. increased use of penicillin combinations to the detriment of narrow spectrum penicillins).

Hungarian antibiotic use data were matched to other European countries. Data comparison (data from this current work versus the most recent data from other European countries available at the ESAC database [97]) is presented in Figure 17 and Figure 18.

As can be read from Figure 17, the use of sulfonamides, quinolones, macrolides and lincosamides in Hungary was above the European median, while the Hungarian tetracycline use was below it. It should be remarked that the highest lincosamide (clindamycin) use in Europe was observed in Hungary. The use of penicillins was average in Hungary (Figure 17) but the relative use of different penicillin subgroups showed peculiarities (Figure 18): the proportional use of penicillin combinations was almost the highest within Europe (~60%) in 2005; only Spain, Portugal and Luxemburg had higher proportional consumption. Conversely, the use of penicillins with narrow spectra (J01CE) had only a marginal share in Hungary, while these agents were the most prominent penicillin group in the Scandinavian countries (Figure 18).

Figure 17. Distribution of use of different antibiotic subclasses in European countries (1998-2005). Hungary is highlighted as a red dot.



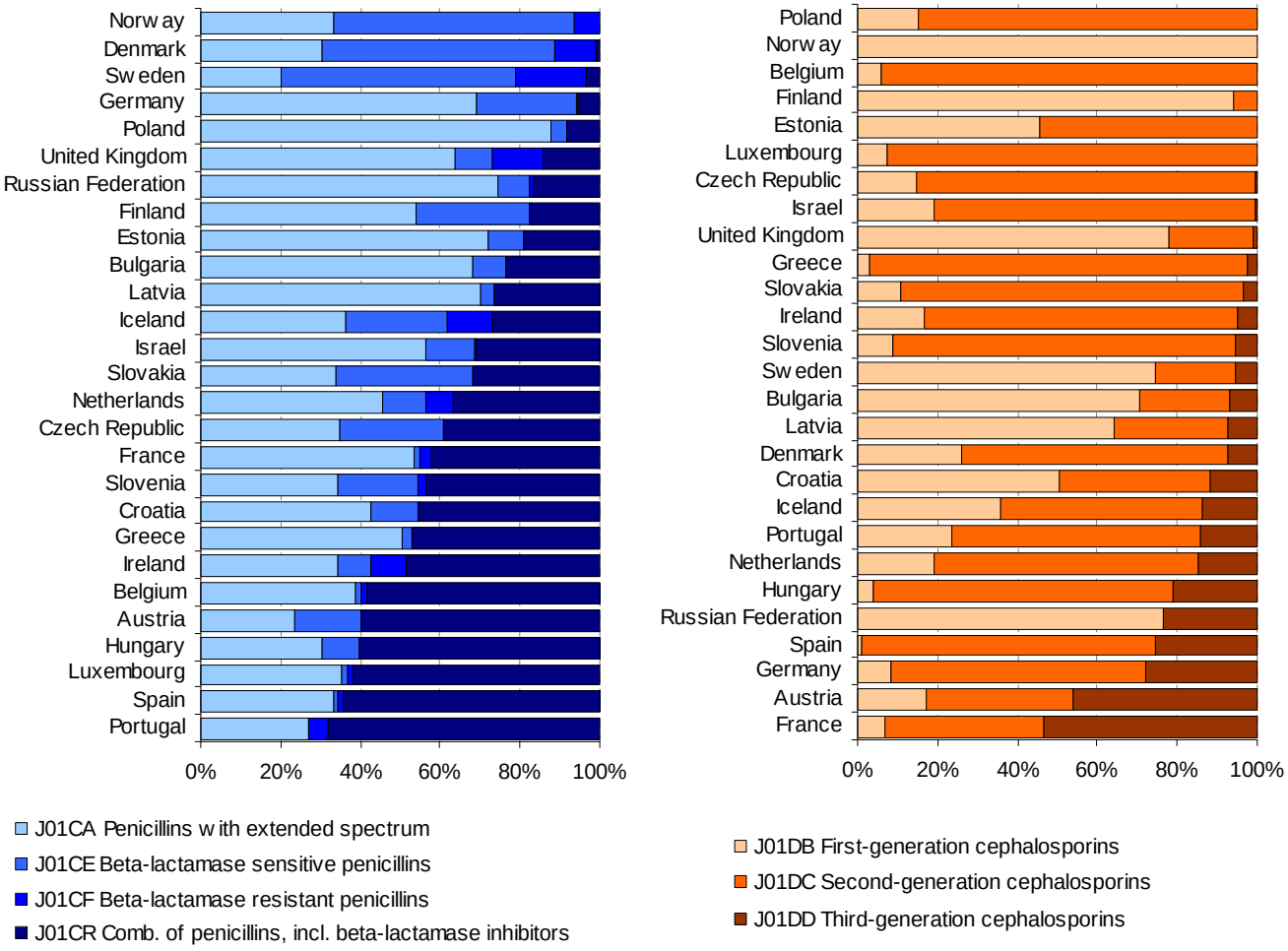
Hungarian cephalosporin use was amongst the highest in Europe. Mainly second generation agents were used, as in most European countries (Figure 18.) Within Europe first generation agents had the lowest proportional share in Hungary.

Heterogeneous use of antibacterials would be desirable to reduce the selection pressure for antibacterial resistance [71,73]. Unfortunately, as the number of active agents in the DU90 segment decreased, and the co-amoxiclav combination, in particular, dominated antibacterial use, the national ambulatory antibacterial use became less heterogeneous by 2007.

Regional differences in antibacterial utilisation and its determinants

The present work showed large and stable interregional variations in antibiotic consumption in Hungarian ambulatory care during 1996–2007. Therefore, Hungary should not be regarded as a homogeneous territory.

Figure 18. Relative use of beta-lactam antibacterials in European countries (2005). [97]



Such regional differences have been reported by other European countries, including Denmark, Germany, Italy, Spain, Sweden, The Netherlands and Switzerland [98-105], and have been mentioned in an older publication in Hungarian [50]. In Hungary, the interregional variations of antibiotic consumption showed a West–East gradient (with East being higher) in contrast to the notable pan-European North-South gradient [90]. When examining interregional variations, Germany is shown to have an opposite East–West gradient [103], whereas other countries have shown a North–South gradient (e.g. Italy, Spain and Sweden), or no clear pattern (e.g. Denmark). With a ratio of 1.7 between the highest and the lowest antibiotic consumption county in Hungary, the extent of the regional variation was above that found in Denmark (1.4), Sweden (1.5) and The Netherlands (1.6), but below that found in Germany (1.9), Spain (1.9) and Italy (2.2) [100,101].

Hungarian citizens that benefit from the 'public medicine service' ("közgyógy") could receive certain medicines free of charge without limitation in quantity. This includes some antibiotics from each ATC group. The proportion of persons having access to this service was positively associated with antibiotic consumption. This association, however, does not tell us the exact reason for the increase in antibiotic use, e.g. whether citizens that benefit from this service more frequently suffer from community-acquired infections, or if doctors simply tend to prescribe medicines more frequently, including antibiotics, to such citizens that have free access to medicines. The other significant and positive association was between antibiotic consumption and the proportion of regular recipients of social assistance – an indicator of poor social and economic conditions. It may be that recipients of social assistance more often suffer from community-acquired infections and therefore receive antibiotics more often (in a morbidity study from 2008, higher respiratory tract infection rates were observed in deprived counties [106]). There was no relationship between antibiotic consumption and the average monthly net income and only a trend towards a negative association with the GDP per inhabitant. This could be explained by the fact that many population groups with low income, such as the unemployed and the retired, are excluded from the net income statistics in Hungary. There was also a trend towards a negative association between regional antibiotic use and the percent of homes with premises for bathing and washing. Again, this suggests that poor socio-economic status is a determinant of antibiotic consumption in Hungary, at least at regional level. In Spain, regional variations in the proportion of population aged < 14 years were associated with antibiotic use while the proportion of elderly population was not [98]. In Hungary, no association was found between the proportions of various age groups and regional antibiotic use. Patients diagnosed with chronic diseases such as COPD, diabetes and malignant neoplasm are more susceptible to infections. There was no association between the prevalence of diabetes or malignant neoplasm and regional antibiotic use and only a trend towards association with the prevalence of COPD. These factors therefore cannot explain the large regional variation in antibiotic use in Hungarian community care. Additionally, there was little regional variation in the percentage of citizens vaccinated against influenza, which could not be an explanation for the large differences in antibiotic use. Unfortunately, other determinants of antibiotic consumption, such as the incidence of community-acquired respiratory tract infections, prescriber- and patient-related factors or promotional activity, could not be studied because of the lack of data on these determinants.

Data were available for some diseases such as AIDS or microbiological foodborne diseases; however, all AIDS cases are treated in the capital, Budapest, and the reported incidence of foodborne diseases was considered too low to be of relevance to this study. In Hungary, each patient (inhabitant) is enrolled with one GP. The average number of enrolled patients per GP does not vary much among regions and there was no relationship between antibiotic use and the number of enrolled patients per GP. Additionally, there was only a trend towards association between antibiotic use and GP activity measured by the yearly number of consultations and home visits per GP. There was no relationship between regional antibiotic use and the density of pharmacies. In Hungary, the number of pharmacies per number of inhabitants was controlled by law at 1 per 5000 and ends up being rather even over the country. Although antibiotics are only available from the pharmacy with a doctor's prescription, one cannot exclude regional differences in illegal, over-the-counter purchases without a prescription. This phenomenon, however, was showed to be rare in Hungary (see section B of the thesis). Finally, since our data are based on sales, regional differences could in principle be related to differences in sales to foreign visitors from the seven countries that have common borders with Hungary. Such sales are known to happen, but their extent, as well as possible regional differences, is unknown. It is unlikely, however, that sales to foreign visitors explain the large differences in consumption observed between regions.

6.2. B) Non-prescription antibiotic use in Hungary

The inappropriate use of antibacterials is associated with self-medication. To obtain comprehensive information about self-medication in Europe, the SAR project (Study on Self-Medication with Antibiotics and Resistance levels in Europe) was launched in 19 European countries (Hungary was not included in this study). Because no published information had been available about self-medication or non-prescription antibiotic use in Hungary, the objective was to fill this gap. In this study, different units of measurement used to quantify the extent of non-prescription antibiotic use all showed the prevalence of self-medication directly from the pharmacy was just below 2%. (This statement is based on the assumption that one person would buy *only* one course for self-medication each year). Since in former socialist countries the major source of self-medication is the pharmacy (without prescription), the non-prescription sales data in this study are considered a good estimate of the real extent of self-medication in Hungary [107]. The extent of self-medication was found to be close to the self-medication value found by the SAR project in

Israel (1.5%), Ireland (1.4%), and Slovenia (1.7%); that project used different research methods, however, which hinders meaningful comparison [107]. In addition to OTC acquisition of antibiotics, other sources of self-medication might exist [107,108] (e.g. leftover antibiotics from courses prescribed earlier; from friends; from abroad) which could result in underestimation of the level of self-medication. Overestimation is also possible, because data on non-prescription antibiotic dispensing in the HNHFA's database includes dispensing for foreign prescriptions and legal OTC sales for Hungarian doctors/pharmacists; such cases are believed to be rare, however. It was also shown that there was large interregional variation in non-prescription antibiotic sales. Although other studies had found that non-prescription antibiotic use is driven by the extent of prescription use [109], an association between prescribed and non-prescribed use at a regional level was not found in this work. A marked elevation in the sales of non-prescription antibiotics during the study period was revealed. As the sharp increase in 2002 coincided with the change of the reimbursement rate from 70 to 50%, the crucial role of price is postulated. Further evidence is that an inverse relationship was found between price and the extent of OTC sales of antibiotics. The finding that the most widely sold antibiotic without prescription was doxycycline, followed by co-amoxiclav and co-trimoxazole, is in contrast with results from Scandinavia where phenoxymethylpenicillin was the most widely OTC saled [110,111]. Because Eastern European countries used significantly more broad-spectrum penicillins for self-medication, Hungary fits into the Eastern group, with the high co-amoxiclav OTC sales. A further increase in non-prescription sales of antibiotics could be prevented by price elevation, intervention, focusing on the pharmacist and the general public, and stricter law enforcement.

6.3. C), D) Antibiotic use in the Southern Great Plain region (regional and patient-level data)

Due to the overlap in the objectives of section C and section D, the results are discussed together.

Indications and prescribed therapy

It is very rare that electronic databases contain information on the treatment indication [112]. Even in Sweden and Norway - two countries which lead in pharmacoepidemiological research - this is lacking in the prescription databases [113,114]. Therefore the Hungarian dispensing database could be looked on as a very valuable

resource that enables sophisticated analysis. A similar database can be found in Canada [115].

As expected, respiratory tract infections were the most frequent indications and were responsible for the majority of antibiotic use. This is not surprising, as according to the Hungarian GP register, respiratory tract infections are the third most frequently diagnosed ICD code [116]. This result is in line with the findings of other reports [112,117].

With the help of the indication-linked antibiotic use data, it was proved that beta-lactams, macrolides, sulfonamides and also tetracyclines were prescribed primarily for respiratory tract infections, while the quinolones, first-generation cephalosporins and the other antibacterials were indicated most often in genitourinary diseases. Clindamycin was the main active agent in the therapy of oral cavity infections.

The reason for internationally high (and increasing) quinolone use is certainly the high use of these agents in genitourinary diseases. The quality of antibacterial use in genitourinary diseases was not evaluated,but as the five most prescribed agents for these diseases are more or less identical with the five recommended agents (only cefalexin was used rarely) for acute cystitis by the national guideline [118,119] this might reflect rationale antibacterial choice in urinary infections.

On an international scale, sulfonamide use was also high in Hungary. This can be explained by the extensive use of sulfonamides in respiratory tract infections. In Hungary, sulfonamides have been used in the empirical treatment of respiratory diseases for decades, they have a low price, and contrary to the international Sanford guide [120] is (still) recommended in the national product information (Summary of Product Characteristics) as an empirical therapy of several respiratory tract infections [121]. For the high lincosamide and low tetracycline use in Hungary compared to other European countries, no obvious explanation can be given.

The detected primary use of beta-lactams and macrolides, and the avoidance of tetracyclines and quinolones, in the paediatric population is in accordance with clinical recommendations [121]. Although antibiotics are the most widely prescribed medicines in children, especially in the ambulatory care [122,123], paediatric comparable antibiotic consumption data are reported to be limited [124] and originate from few countries. Comparing the five most prescribed antibacterials with those of Italy, Canada and Netherlands, the pattern of Hungarian paediatric antibacterial use resembles that of Italy,

where co-amoxiclav and amoxicillin were also the most frequently prescribed antibacterials in the paediatric population [125]. In Denmark, the narrow spectrum phenoxymethylpenicillin was used most often in children – which indicates judicious antibacterial use.

As ambulatory dispensing databases do not contain information on the prescribed doses, and one-by-one manual inspection of prescriptions would be an enormous workload, it is hard to compare results. Dosage habits may differ by country; for example prescribed daily doses of all antibiotics tend to be lower in the United Kingdom than in other European countries [126].

For amoxicillin, its combination with clavulanic acid (co-amoxiclav) and for cefuroxime, it was found that Hungarian doctors tended to prescribe larger doses compared to the current defined daily dose by WHO. These larger doses seem to be appropriate as larger amoxicillin doses (1.5-3 gram/day) are generally recommended by the national product information and may suggest an increase of the current WHO DDD (1 gram/day) is warranted.

Possible rate of antibiotic overuse in respiratory tract infections and adherence to antibacterial guidelines for streptococcal tonsillopharyngitis

Viral respiratory tract infections are self limiting and often easily self managed [124,127-129]. From the doctor's perspective, the fear from sequelae is one of the main drivers of antibiotic overuse. A cohort study – performed in the United Kingdom - revealed that the number needed to treat (NNT) to prevent a single case of a serious complication like pneumonia, mastoiditis and quinsy after upper respiratory tract infections was generally over 4000 (95% confidence interval: 2393 to14586), irrespective of patient age [130]. This means that antibiotics are not justified to reduce the risk of serious complications for upper respiratory tract infections.

Over-prescribing antibiotics in these infections unnecessarily exposes patients to risk of side effects, encourages re-consulting for similar problems and enhances antimicrobial resistance. Despite the weight of evidence available, viral respiratory tract infections drive antibiotic overprescribing in the ambulatory care setting [131-137]. Many studies have examined the antibiotic prescription rate for different respiratory tract infections [92,96,112,117,138-140]. In these studies the proportion of patients receiving needless antibiotic treatment after visits for upper respiratory tract infections was up to 85 %.

As the Hungarian data presented in this present study is based on dispensed antibiotic prescriptions rather than doctor visits, the prescribing rates for these diseases are unknown. Nevertheless it is estimated that in more than 50% of the respiratory tract infections, antibiotics were prescribed unnecessarily in both adults and children. Considering the individual antibacterials, it was concluded that the most popular agents (e.g. co-amoxiclav) also had the highest needless use (see also Table 12). As previously discussed, Hungary is a high user of penicillin combinations, macrolides and sulfonamides - and at least in part - the high percentage of injudicious prescriptions may lead to this result. In the experience of the author, the availability of numerous low-price generics, the high number of approved therapeutic indications and the massive promotion of the products also contributes to the high use of penicillin combinations.

If antibiotic treatment is needed, the rate at which doctors follow guidelines (adherence rate) may give an insight into the quality of prescribing. In acute streptococcal tonsillopharyngitis (AST) the adherence of Hungarian doctors to the national guideline was very low as they prescribed the first-line treatment (narrow spectrum penicillins) in less than 10 % of cases. This value is worse than that found in Bosnia and Herzegovina, where phenoxymethylpenicillin, the recommended first –line treatment of AST, was prescribed by family doctors in 46.3% of cases[139]. Surveys from Russia, Spain and Czech Republic found that doctors neglected guideline recommendations and treated upper respiratory tract infections (including streptococcal tonsillopharyngitis) primarily with ampicillin, amoxicillin or penicillin combinations [141-143].

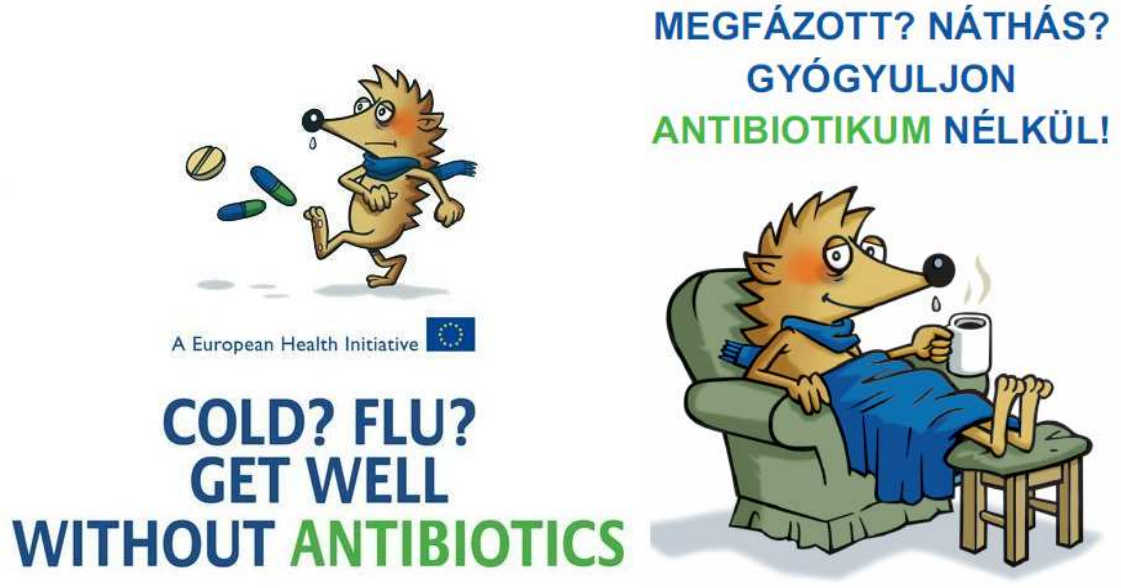
All these results are disappointing, as the Hungarian medical-scientific literature had been drawing attention to avoiding unnecessary antibiotic therapy in certain respiratory tract infections from the early 1980s [144]. Overuse of antibacterials, and prescribing of too broad spectra antibacterial agents in paediatric infections, was revealed by Katona [48]. In further publications he confirmed these findings, and extended to the adult population, and also pointed out the consequential financial burden [61,63-65,70]. Graber mentioned the international endeavour for judicious antibiotic prescribing and stated that the antibiotic use in Hungary is twice as much as needed (this statement was not underpinned by any data) [54]. From the 1990s several Hungarian opinion leaders –including Ludwig - highlighted the consequences of antibiotic overuse and promoted the rational use of this pharmacological group [15,68,71,73-75,145]. The whole issue of the “Gyógyszereink” journal in December 1993 was devoted to the prudent use of antibacterials. Matejka –from

the perspective of the Health Insurer - also expressed her worries about the extent of Hungarian antibacterial use [49]. The work of Magyar, who evaluated the financial burden of antibiotic overuse, must also be mentioned [55].

It is proved by several works that overprescribing is influenced by patient demand and expectations [146-148]. A recent study from the US [149] revealed that patient satisfaction is not correlated with antibiotic prescribing and stated that clinicians' perceptions that patients expect antibiotics were incorrect. In reality, patients seek effective symptom management and reassurance. As public misconceptions about the appropriate indications of antibiotic use exist [150-152], often originating from previous experience with prescribed antibiotics, the responsibility of professionals is the determining force.

Looking back over the last 30 years of massive publication of the problem in scientific journals, it may be concluded that this has been ineffective in alter prescribing habits. As stated by others, no single quality improvement strategy is superior. Active education both for professionals [153] and patients [149], and broad-base interventions targeting all respiratory tract infections, may yield a larger reduction in ambulatory antibiotic use [154] .

Figure 19. Information leaflet of the European Antibiotic Awareness Day launched by the European Centre of Disease Prevention and Control (ECDC 2008.)



French and Belgian examples showed that national campaigns (mass education campaigns) could improve national antibacterial use and found that television advertising is the most important tool to change patient attitudes and behaviour [155].

The success of the French and Belgian campaigns led to a Europe-wide initiative: the European Antibiotic Awareness Day (EAAD). On the first EAAD (18 November 2008), the public awareness campaign focused on not taking antibiotics for viral infections such as cold or flu. Under the aegis of the EAAD several national activities were undertaken and several information leaflets and posters were released in Hungary as well (Figure 19), but unfortunately the most powerful campaign material –TV spots – were not broadcast [156] .

Estimating the rate of antibiotic therapy prescribed for children.

In the present PhD thesis, a strong association between the utilisation of liquid oral antibacterials and the rate of paediatrics antibiotic prescriptions (PARx) was shown.

While the availability of comprehensive, age-specific, patient-level, drug use data is often limited [114,157,158], data on the use of different dosage forms – due to the inclusion of dosage form in the official brand name (e.g. tablet, powder for suspension) – are easily available for researchers in simple aggregated drug use data. Despite the relatively easy computability of dosage form data, not even descriptive ambulatory care data have been published in the literature on the use of different oral dosage forms of antibacterials. Bronzwaer – who extensively studied the relationship between antimicrobial use and antimicrobial resistance – was the first who expressed the need for age-stratified antibacterial use data and recommended that analysis of liquid formulation data might be helpful in accessing antibacterial use in children [159].

Liquid oral products are age-adapted drug formulations. They are developed primarily for children, but also for those patients (e.g. some of the very elderly) who have difficulties safely swallowing solid oral dosage forms (e.g. classic tablets, capsules) [160]. Since in the present study liquid oral products were prescribed almost exclusively for children (646 out of 651 cases), an association between the use of liquid oral antibiotic forms and proportion of prescriptions indicated for children (PARx) could be analysed and detected.

A previous study from Hungary showed that the number of people who were prescribed antibiotic therapy more than once during a year is considerable [161]. As in the present work the rate of multiple-time users is unknown (both in adults and in children), only the proportion of antibiotic medication (prescriptions) prescribed for children could be estimated, and not the rate of exposed children.

Similar associations between the use of certain dosage forms and certain age groups could be revealed by the analysis of patient-level data in other countries as well. After applying the determined coefficient of linear regression to the aggregated-level data, the rate of drug

therapies prescribed for children could be estimated. This methodological approach could presumably be applied in other countries where electronic patient-level databases do not contain age-linked data, or age-linkage is impossible due to confidentiality issues, or simply where rapid, crude estimation is needed for the rate of antibiotic therapies prescribed for children in simple aggregated databases like ESAC (European Surveillance of Antimicrobial Consumption database).

7. SUMMARY

In this thesis I set out to show characteristics of outpatient antibacterial use in Hungary: to describe the trends of national use, to reveal and find explanation for the regional differences and to survey non prescription antibiotic sales in Hungary. By using different data sources and data mining methods I also intended to provide data on indications, on patient characteristics, on dosage and dosage form data and estimate the rate of potential antibiotic overuse in respiratory tract infections. Finally I aimed to introduce a new methododology for enabling the estimation of the rate of antibiotic therapy prescribed for children.

My main findings are as follows:

- Total ambulatory antibiotic consumption in Hungary expressed as DDD per 1000 inhabitant-days remained relatively stable (18.6±1.5) between 1996 and 2007 and some of the observed changes in the pattern of consumption are consistent with the national and international recommendations (e.g. decreased used of tetracyclines and short-acting macrolides). However, the low first-generation cephalosporin and narrow spectrum penicillin (i.e. beta-lactamase sensitive penicillins) use as well as the high penicillin combination use require attention.
- There were constantly large (1.6±0.1) interregional differences in the Hungarian ambulatory antibacterial consumption. These differences in total ambulatory antibacterial use were associated with socio-economic determinants.
- Non prescription antibiotic use has been increased during the years of assessment, but it was still rare with a prevalence of 2% in 2004. The significant inverse correlation between price and non-prescription sales of antibacterials suggests that price elevation (including decreased reimbursement rate) may impede the further increase of non prescription antibiotic use.
- The antibiotic use was 21.1 DDD per 1000 inhabitant-days in the Southern Great Plain. Two-thirds of the antibacterials were prescribed for respiratory tract infections, while for genitourinary diseases 12 % of the antibacterials were used. We found that Hungarian doctors scarcely ordered parenteral antibiotics, mainly prescribed broad spectrum beta-lactams and macrolides to treat respiratory diseases and primarily fluoroquinolones to combat genitourinary diseases.

- According to our estimation more than 60% of the antibacterials prescribed for respiratory tract infections were probably unnecessary. We also recorded that the Hungarian doctors' adherence rate to the national AST guideline was very low indicated by the fact that they prescribed the first-line agents in less than 10%.
- By manual data processing of individual patient data we identified several characteristics of antibiotic use: we recorded adult and female dominance. Both the absolute and the relative frequency of indications showed age related characteristics. The prescribed doses were in good accordance with the WHO recommended defined daily doses in most cases. The significant deviation from the WHO DDD in the prescribed dosage of amoxicillin products was justified.
- Our age-stratified analyses confirmed that possible antibiotic overuse were present in more than 50% of cases in both children and adults. The use of narrow spectrum penicillins in acute streptococcal tonsillopharyngitis (rate of guideline adherence) was found to be low in both age groups (adults: 7.6 %, children: 13 %)
- The parallel information on patient age and the rate of liquid oral dosage forms in the patient-level data enabled us to set up an association (linear regression model) between these two variables. Applying the determined coefficient of the linear regression to the aggregated regional level data we estimated that the rate of antibiotic therapy prescribed for children was 34.6 % in the Southern Great Plain. Taking into account the demographic composition of the region we can state that children receive antibiotic treatment three times more often than adults. We presume the wide applicability of this new methodological approach in other countries where electronic patient-level databases do not contain age-linked data or age-linkage is impossible due to confidentiality issues.It could be also used where rapid, crude estimation is needed *for the rate of antibiotic therapies prescribed for children* in simple aggregated databases like ESAC.

From the aspect of evident based medicine we can conclude that considerable proportion of antibacterial therapies seems to be unjustified in Hungary. To overcome this problem broad based interventions and continuous monitoring of antibacterial use is needed.

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10. ANNEX

10.1. Publications related to the thesis

Matuz M, Benkő R, Doró P, Hajdú E, Nagy G, Nagy E, et al.: Regional variations in community consumption of antibiotics in Hungary, 1996-2003. Br.J.Clin.Pharmacol. 2006;61(1):96-100. IF(2006)= 2.718

Matuz M, Benkő R, Doró P, Hajdú E, Soós G: Non-prescription antibiotic use in Hungary. Pharmacy World & Science 2007;29:695-698. IF(2007)= 0.764

Matuz M, Benkő R, Doró P, Hajdú E, Soós Gy: [Analysis and interpretation of non-reimbursed antibiotic use data in Hungary] Támogatás nélküli antibiotikum fogyási adatok elemzése és értelmezése Acta Pharmaceutic Hungarica 2009;79(2):70-4