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

Summary of Ph.D. thesis

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INTRODUCTION

In the development and application of evidence-based medicine the analytical epidemiology gained an important role.

Epidemiological methods allowed evaluating the effectiveness of treatments and the role of certain factors in different diseases. Epidemiological methods are also used in drug utilisation studies (pharmacoepidemiology), and - as a result - may provide useful information on drug treatments. Pharmacoepidemiology permits the comparison of everyday therapeutic practice, the reality with existing guidelines/recommendations/regulations.

In my PhD work I intended to show the possibilities and interpretations of pharmaeidemiological evaluations trough the study of systemic antibiotic consumption.

The discovery of antimicrobial agents was a milestone in the treatment of bacterial infections. However, the current accelerated trend in the evolution of antimicrobial resistance has greatly overshadowed their initial success. Further problem is that only a limited number of new antibacterial drugs will be introduced into the market in the forthcoming years.

The recognition that inappropriate antibacterial use can induce/worsen antibacterial resistance has led the surveillance of both antibiotic utilisation and antibacterial resistance rates became a priority. At international level, the European Surveillance of Antimicrobial Consumption (ESAC) project is tasked with collecting reliable antibiotic use and the European Antimicrobial Resistance Surveillance System (EARSS) project was founded to collect antimicrobial resistance data. Hungary is participating in both projects.

MAIN RESEARCH OBJECTIVES

A) National and regional ambulatory antibiotic consumption

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

B) Non-prescription antibiotic use in Hungary

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

C) Antibiotic use in the Southern Great Plain region

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

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

7. 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
8. To estimate the necessity of antibacterial therapy in adults and children with respiratory tract infections.
9. To evaluate the rate of adherence to antibacterial guidelines in cases of acute streptococcal tonsillopharyngitis (adults, children)
10. 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)

METHODS

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. 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.

A) National and regional ambulatory antibiotic consumption

The source of antibiotic sales data was the IMS (Intercontinental Medical Statistics) PharmMIS Consulting Company. During the analysis we applied the indicators established by the ESAC project. Trend analysis was set up to investigate the trends of ambulatory antibiotic use through the study period (1996-2007).

A set of possible determinants was tested to have impact on regional antibiotic use (the list of possible determinants of antibiotic use was developed previously by an expert panel group). A non-parametric correlation method (two-tailed Spearman coefficient (R)) was applied to investigate these associations. Because multiple hypotheses were tested, the Bonferroni correction was used.

B) Non-prescription antibiotic use in Hungary

Dispensing data on the regional (20 counties) antibiotic use were obtained from the Hungarian National Health Fund Administration (HNHFA) for a 5-year period (2000–2004).

After testing normality (Kolmogorov-Smirnov test), a paired T-test was used to demonstrate the differences in the rate of the non-prescription antibiotic use at the two endpoints (2000 vs. 2004). Associations between non-prescription antibiotic use versus prescription use and price were tested by the Pearson correlation. Data on the number of inhabitants and number of pharmacies were obtained from the Hungarian Central Statistical Office.

C) Antibiotic use in the Southern Great Plain region

The aggregated reimbursement data (for the 2007 January- June period) on antibiotic prescriptions were purchased from the HNHFA. The indications of antibiotic therapies were determined as the registered ICD (International Classification of Diseases) codes.

According to international and national guidelines and with the help of an infectologist consultant we identified respiratory indications where antibiotic treatment is probably needless; and determined the rate of adherence to the guideline in the therapy of acute streptococcal tonsillopharyngitis (AST).

Note: Narrow spectrum penicillins (J01CE) are the recommended first-line treatment in AST)

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

Twenty community pharmacies from the Southern Great Plain region were included in the study. Approval of the regional ethical committee was obtained. 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 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 necessity of antibiotic therapies in respiratory infections and the choice of antibacterial treatment in AST were determined as detailed in section C (with the exception that here patients were stratified to age-groups: children and adults separately).

Thereafter, based on the patient-level regional data collected in the 20 pharmacies (section D) , 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 (PAR_x, 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) in order to estimate the rate of antibiotic prescriptions indicated for children (PAR_x).

RESULTS

A) National and regional ambulatory antibiotic consumption

National ambulatory standardised antibiotic consumption between 1996 and 2007 remained relatively stable (mean \pm standard deviation: 18.6 \pm 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. Parenteral antibiotic use in the ambulatory care sector was marginal and showed further decrease during the study period (from 1.4% to 0.4 %).

Table 1. 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
J01FF Lincosamides	0.26	0.67	159.53	0.968	<0.001
J01M Quinolones	0.64	1.51	137.20	0.937	<0.001
Parenteral antibiotics	0.25	0.06	-77.19	-0.974	<0.001
Broad spectrum penicillins, cephalosporins and macrolides ^a	6.17	8.60	39.38	0.567	0.054
Narrow spectrum penicillins, cephalosporins and macrolides ^b	2.80	0.92	-8.00	-0.964	<0.001

nc: not calculated because of extreme low value (min \leq 0.01).

a: Narrow spectrum penicillins, cephalosporins and macrolides: *benzylpenicillin*, *phenoxymethylpenicillin*, *penamecillin*, *benzathine benzylpenicillin*, *procaine benzylpenicillin*, *benzathine phenoxymethylpenicillin*, *cefalexin*, *cefazolin*, *cefadroxil*, *erythromycin* (Coenen S. *Qual.Saf.Health.Care*. 2007)

each Hungarian pharmacy, it means that pharmacies dispensed antibiotics without prescriptions to 1.8 (~2%) of their inhabitants.

Expression in other measurement units has led to similar results: the population prevalence of non-prescription antibiotic sales from pharmacies was about 2 %.

The most frequently sold OTC antibacterials belonged to the tetracycline (doxycycline), the sulfonamide (sulfamethoxazol-trimethoprim) and the penicillin (penamecillin and amoxicillin) antibacterial groups.

Regional analysis revealed large variations both in the level and the share of non-prescription antibiotics sales. (2004: minimum vs. maximum: 22.8 vs. 94.0 DOT/pharmacy/month) 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.

C) Antibiotic use in the Southern Great Plain region

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

Antibiotic therapy was prescribed most commonly for respiratory tract infections (ICD:J00-J99; 66.4% of all antibiotic use). For the second most common diagnoses, genitourinary infections (ICD: N00-N99; mainly for acute cystitis) 12.3 % of the total ambulatory antibiotic use was prescribed. The third most frequent diagnoses were infections of the gastro-intestinal system (mainly diseases of the oral cavity). Within respiratory diseases the share of upper respiratory tract infections from the antibiotic use was 69.6%. Respiratory diseases were treated primarily with beta-lactam antibacterials (70.3%): namely extended-spectrum penicillins (20.4%) and penicillin combinations (30.3%). Genitourinary infections were mainly treated with fluoroquinolones (49.8% of all antibiotic use).

Based on the indicated ICD code, the infectious disease consultant judged antibiotic therapy as probably required and useful in 33.3%, probably needless in 60.3% and undeterminable in 6.4% of cases. Acute pharyngitis and acute bronchitis were the two most common indications for which antibiotic were prescribed unnecessarily. Extended spectrum penicillins and

penicillin combinations were the two antibacterial groups with the highest possible overuse (51.8%), and co-amoxiclav itself were responsible for almost 30% of the overall antibiotic overuse.

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). The guideline recommended as first-line agents the narrow spectrum penicillins (J01CE), which were ordered only in a minority (9.2 %) of streptococcal infections of the tonsillopharynx.

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

During the 120 study days around 50,000 prescriptions were dispensed in the 20 pharmacies, of which 2852 referred to antibacterials. In the followings the results pertain to the 2831 Hungarian patients with antibacterial monotherapies.

Most patients were adults (65%), where we detected a female dominance (female: 1127 patient, 61.8%). In contrast, in children boys received antibiotics in higher number (boys: 544 patients, 53.9%).

In both age groups disease of the respiratory tract (ICD: J00–J99, children: 84.3%; adults:57.6%) was the leading indication, while the second most frequent indication was genitourinary disease in adults (ICD: N00-N99; 19.2%) and ear/mastoid related disease (ICD: H60-H95; 5.6%) in children.

For both adults and children the co-amoxiclav (J01CR02) was the most frequently prescribed agent. In children amoxicillin and cefuroxime were the second and third on the consumption toplist, while in adults ciprofloxacin and clindamycin.

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. PDD differed considerably from DDD in the case of only three antibacterial agents (co-amoxiclav: WHO DDD=1 gram vs. PDD mean \pm SD=1.4 \pm 0.4. gram; amoxicillin: 1 gram vs.1.9 \pm 0.6 gram; cefuroxime: 0.5 gram vs. 0.8 \pm 0.3 gram). In these three cases, Hungarian doctors tended to prescribe higher doses than usual.

Antibiotic therapy of respiratory tract infections was considered to be probably needless in more than half of cases in both age groups, in children 52.2% and in adults 56.7%, respectively. According to the ICD-10 code based judgement, antibiotics were prescribed probably unnecessarily in mainly acute pharyngitis and acute bronchitis.

Antibiotics were prescribed for 77 children and 131 adults with AST. 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%).

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). Applying the result of the linear regression to the aggregated regional data (section C), 34.6% of the antibiotic prescriptions was ordered 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 it means that on average children were prescribed antibiotics three times more often than adults ($(34.6/14.9)/(65.4/84.1)=3.0$).

SUMMARY

Total ambulatory antibiotic consumption in Hungary expressed as DDD per 1000 inhabitant-days remained relatively stable (18.6 ± 1.5) between 1996 and 2007. 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.

In view of the diagnoses and recommendations we can say that the narrow-spectrum penicillins (JOICE) are highly underused. In contrast penicillin combinations are frequently used for indications, where antibiotic therapy is not needed.

There were constantly large (1.6 ± 0.1) interregional differences in the Hungarian ambulatory antibacterial use through the 12 years of assessment. These differences in total ambulatory antibacterial use were partly associated with socio-economic determinants.

Despite that antibacterials are prescription only medicines in Hungary, over the counter dispensing (i.e. non-prescription antibiotic use) exists. The rate of non-prescription antibiotic use were similar to other European countries, but showed an increasing trend. Decision makers should take into account that the rate of OTC antibiotic sale was influenced by product price.

It is worth to mention that the database of the Hungarian Health Insurance (HNHFA) contains diagnoses (ICD codes) since October, 2006. This fact enabled us not only to identify the most frequent diagnoses (respiratory diseases) for which antibiotics were prescribed, but to estimate the quality of antibiotic use. We observed high rate (over 50 %) of potential antibiotic overuse in upper respiratory tract diseases and registered low rate (~10%) of adherence to the AST treatment guideline.

Unfortunately, the demography (age and gender) linked database of the HNHFA is recently unavailable due to confidentiality issues. Also, data on the prescribed doses are not registered electronically, which means information could be gained only by the visual inspection of prescriptions. All these facts forced us to perform a manual data registration from individual prescriptions. With this kind of data processing we were able to show age linked peculiarities (e.g. distribution of indications) and confirm

that Hungarian doctors prescribed usual doses in almost every case. We also proved that possible antibiotic overuse affected both age groups.

The strong association between the share of liquid oral dosage forms and the rate of paediatric antibiotic prescriptions enabled us to estimate the share of paediatric antibiotic use from dosage form data. Taking into account the demographic composition, we can say that children were prescribed antibiotics three times more often than adults.

The pharmacoepidemiological data analysis based on different data sources enabled the characterization and interpretation of the Hungarian ambulatory antibiotic use data and could serve as the basis for evidence-based health care decisions.

PUBLICATIONS RELATED TO THE THESIS

Papers

- I. **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
- II. **Matuz M**, Benkő R, Doró P, Hajdú E, Soós Gy: Non-prescription antibiotic use in Hungary. *Pharmacy World & Science* 2007;29:695-698. IF(2007)= 0.764
- III. **Matuz M**, Benkő R, Doró P, Hajdú E, Soós Gy: [Analysis and interpretation of non-reimbursed antibiotic use data in Hungary] Támogatás nélküli antibiotikum fogyasztási adatok elemzése és értelmezése *Acta Pharmaceutica Hungarica* 2009;79(2):70-4

Abstracts

- I. **Matuz M**, Benkő R, Horváth E, Soós Gy: A magyarországi antibiotikum felhasználás néhány jellemzője *Hungaromed* 2007. Gyógyszerészeti tudományos konferencia; Budapest, 2007. november 9.
- II. **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
- III. **Matuz M**, Benkő R, Doró P, Mártha G, Hajdú E, Soós Gy: Estimation the necessity of antibacterial therapy in adults with respiratory tract infections ESCP (European Symposium on Clinical Pharmacy) 37th, Dubrovnik, Horvátország; 2008. október 22-24 Abstr.: *Pharmacy World & Science* 31(2): 256

- IV. **Matuz M:** Antibakteriális terápiát rendelő gyógyszerértári vények elemzésének néhány eredménye; populációra vonatkozó becslési lehetőség bemutatása; Magyar Tudomány Ünnepe; Szegedi Tudományegyetem Gyógyszertudományok Doktori Iskola PhD hallgatóinak eredményei; tudományos ülés, Szeged, 2008. november 27.
- V. **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.
- VI. **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)
- VII. **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)
- VIII. **Matuz M,** Benkő R, Hajdú E, Soós Gy: The rate of potentially inappropriate antibiotic use in respiratory tract infections. 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) P 1502; Vienna, April 10 – 13, 2010
- IX. **Matuz M,** Benkő R, Horváth E, Hajdú E, Soós Gy: Characteristics of outpatient antibacterial use in Hungary (1996-2007) 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) R 2199; Vienna, April 10 – 13, 2010

