University of Szeged

Faculty of Pharmacy

Doctoral School of Pharmaceutical Sciences

Institute of Clinical Pharmacy

CHARACTERISTICS AND TRENDS OF SYSTEMIC ANTIBIOTIC UTILIZATION BEFORE, DURING, AND AFTER THE COVID-19 PANDEMIC IN THE HUNGARIAN OUTPATIENT SECTOR

Ph. D Thesis

Dr. Helga Hambalek

Supervisors:

Dr. Ria Benkő, PhD

Dr. Mária Matuz, PhD

Szeged

2026

University of Szeged

Doctoral School of Pharmaceutical Sciences

Pharmacology, Biopharmacy and Clinical Pharmacy Program

Program director: Prof. Dr. István Zupkó

Institute of Clinical Pharmacy

Supervisors: Dr. Ria Benkő, Dr. Mária Matuz

dr. Hambalek Helga

Characteristics and trends of systemic antibiotic utilization before, during, and after the COVID-19 pandemic in the Hungarian outpatient sector

Complex examination committee:

Head: Prof. Dr. Soós Gyöngyvér

Members: Dr. Réka Viola

Prof. Dr. Dezső Csupor

Dr. Róbert Vida

Reviewer committee:

Head: Prof. Dr. Rita Ambrus

Reviewers: Dr. Tamás Tábi, Ph.D

Dr. Gábor Oszlánczi Ph.D

Members: Dr. Anita Kovács, Ph.D

Dr. Gerda Szakonyi, Ph.D

1. INTRODUCTION

Antimicrobials – including antibiotics, antivirals, antifungals, and antiparasitistics – are essential medicines used to prevent and treat infections in humans, animals, and even plants. Antibiotics are among the most significant medical innovations of the 20th century and are used to prevent and treat bacterial infections. Antibiotics enabled significant decrease in infectious disease related mortality. . However, after the golden era of antibiotics, with the emergence and spread of antimicrobial resistance (AMR) scientist forecast scenarios which resembles the pre-antibiotic era.

AMR is defined as the ability of a microorganism to survive exposure to an antimicrobial agent, making standard therapies ineffective and increasing the risk of disease transmission, severe illness, and death. Although the term commonly refers to antibiotics, AMR can exist in a variety of pathogens, including bacteria, viruses, fungi, and parasites. AMR has evolved from a local clinical problem into a major global health and development threat. According to recent estimates there were 4,71 million deaths associated with AMR in 2021, with 1,14 million bacterial AMR deaths. Many human, animal, environmental, and social factors contribute to the antimicrobial resistance (AMR). There are many risk factors associated with AMR. For example, overuse or inappropriate use of antibiotics (including the use of antibiotics in the environment and agriculture), inadequate sanitation and hygiene. Developing successful preventive and stewardship initiatives within the One Health paradigm requires an understanding of these risk factors. The ECDC's European Antimicrobial Resistance Surveillance Network (EARS-Net) tracks the changes in the resistance profile of the most significant human pathogens.

As the development of new antibacterial agents is insufficient, we must focus on preserving the effectiveness of existing ones. The aim of Antimicrobial Stewardship (AMS) is to promote the appropriate use of antimicrobials by selecting the optimal antimicrobial drug, dose, duration, and route of administration. The aim of AMS is to maximize clinical results while reducing adverse effects of antimicrobial use, such as toxicity and resistance development.
To ensure the responsible use of antibiotics, Antimicrobial Stewardship (AMS) programs should be set up. These programs might involve numerous interventions, such as surveillance of antimicrobial use, audit and feedback, prescribing restrictions, prescriber education, and the application of clinical guidelines. Drug Utilization (DU) research is an important tool to support AMS, which could offer both quantitative and qualitative insights into antimicrobial use trends and patterns. DU research on aggregate data evaluates antibiotic consumption, using standardized metrics such as Defined Daily Dose (DDD). DU study results can identify suboptimal utilization patterns and help benchmarking between/within countries. The European Surveillance of Antimicrobial Consumption Network (ESAC-NET), coordinated by ECDC, collects antimicrobial use (AMU) surveillance data in the countries of the EU/EEA. The aim of this surveillance is to provide comprehensive, comparable data on the use of antimicrobial agents, including antibiotics, in both community and hospital care.

2. OBJECTIVES

The overall aim of the dissertation is to analyze the national ambulatory care antibiotic consumption (antibiotic use) in Hungary before, during, and after the COVID-19 pandemic.

The first part of our research was to assess the impact of the pandemic (2020-2022) on antibiotic use in ambulatory care, comparing it with the average values of the preceding period (from 2015 to 2019).

We focused our analysis to determine:

- the scale of systemic antibiotic (J01) use (DDD/1000 inhabitants/day),
- the patterns and trends of antibiotic use,
- the top 10 list of antibiotic use.
- antibiotic use in different COVID-19 pandemic sub-periods

The second part of our study was to determine the changes in the ambulatory care antibiotic use after the pandemic (2022-2023) correspond to preceding periods.

We focused our analyses to determine:

- the scale of systemic antibiotic (J01) use (DDD/1000 inhabitants/day),
- the patterns and trends of antibiotic use,
- the top 10 list of antibiotic use,
- antibiotic exposure of patients (for selected active agents),
- percental share of antibiotic subgroups according to the WHO AWaRe classification,
- seasonal fluctuation trends

3. METHODS

3.1 Shared methodology in both studies

3.1.1 Study design

For the purpose of examining systemic antibiotic consumption trends in Hungary before, during, and after the COVID-19 pandemic, both studies employed a longitudinal ecological design. We selected this study design to examine the temporal effects of the COVID-19 pandemic on antibiotic use.

3.1.2 Data sources

The data were obtained from the publicly available database of the National Health Insurance Fund of Hungary (abbreviated as NEAK in Hungarian). As the only health insurance company in Hungary, NEAK data guarantees coverage for almost the entire Hungarian population. Given that antibiotics in Hungary are prescription-only medicines and most products are reimbursed, the NEAK database has excellent drug coverage (captures approximately 95% of all antibiotics dispensed). Data on redeemed prescriptions were collected at the package level and monthly intervals.

The package-level data were converted and finally expressed as defined daily doses (DDD) per 1000 inhabitants per day (DID) following WHO guidelines.

Annual population data were obtained from the Hungarian Central Statistical Office.

3.1.3 Antibiotic classification

These studies focused on antibiotics for systemic use, i.e., J01 products, as classified by the WHO's Anatomical Therapeutic Chemical (ATC) Classification Index (version 2022-2023). The data were further categorized by ATC antibiotic subgroups.

3.1.4 Statistical tools

We primarily used Microsoft Excel and Microsoft Access softwares for data management, organization, and initial statistical computations during the data analysis process.

3.2 Specific Methods for Study 1

Before and during COVID-19 pandemic antibiotic use in ambulatory care.

3.2.1 Defining Study Periods and Pandemic Phases

We categorized the study timeframe into two primary periods: the pre-COVID period (January 2015 to December 2019) and the COVID-19 pandemic period (from January 2020 to February 2022).

Hungary introduced strict measures to reduce the spread of COVID-19. These restrictions were adjusted over time to reflect changes in the epidemiological situation. To analyze antibiotic usage, we further defined specific pandemic sub-periods:

- Sub-period 0: January and February 2020
- Sub-period 1: March to May 2020
- Sub-period 2: June to October 2020
- Sub-period 3: November 2020 to April 2021
- Sub-period 4: May to October 2021
- Sub-period 5: November 2021 to February 2022

In conclusion, we experienced severe lockdowns throughout period 1 and 3, which included closing schools, restricting gatherings, requiring masks to be used outside, and requiring social separation of 1.5 to 2 meters in all public areas. In other sub-periods, curfews were lifted, moderate restrictions were in effect, and we were allowed to participate in sport, cultural, and social events, although with certain restrictions. During the sub-period 3, the COVID-19 vaccine became accessible. After that, we had to provide proof of our current vaccination status in order to enter public indoor activities.

3.2.2 Analyzing Monthly Antibiotic Use Across Study Periods

We analyzed antibiotic utilization data by comparing the pre-COVID and pandemic periods overall, followed by a more detailed examination across the six defined COVID sub-periods. For the pre-COVID period, we calculated the five-year monthly average of systemic antibiotic use and compared it to the corresponding months during the COVID-19 pandemic years.

3.3 Specific Methods for Study 2

Before, during and AFTER COVID-19 pandemic antibiotic use in ambulatory care.

3.3.1 Defining Study Periods and Pandemic Phases

Hungary initially declared a state of COVID-19 pandemic emergency on 11 March 2020; hence, we defined the COVID-19 pandemic period from March 2020 to February 2022 (we used different time periods than in the first study). Then, we defined two more periods: the Before COVID period (from March 2018 to February 2020) and the After COVID period (from March 2022 to February 2024). Each period involved 24 months (Table 1).

Table 1. Visualization of the three study periods

		Months											
		1	2	3	4	5	6	7	8	9	10	11	12
Years	2018												
	2019												
	2020												
	2021												
	2022												
	2023												
	2024												

- Blue colour: Before the COVID-19 pandemic period (24 months),
- Red colour: COVID-19 pandemic period (24 months),
- Green colour: After the COVID-19 pandemic period (24 months).

3.3.2 Analyzing Monthly Antibiotic Use Across Study Periods

For each period, we calculated the average monthly systemic antibiotic use and compared it to the corresponding averages from the other two periods. Additionally, in this study we analyzed the number of patients exposed to the most used antibacterial agents. Although patient-level antibiotic utilization data are not publicly available in Hungary, NEAK provides information on the number of individuals who obtained at least one antibiotic product during a given month.

3.3.3 Seasonality Analysis for Ambulatory Care Antibiotic Utilization

Compared to the first study, in this study we also assessed the quality of ambulatory care antibiotic use, by using drug-specific quality indicators developed by the European Surveillance of Antimicrobial Consumption (ESAC) network. Among these indicators are the seasonal variation in systemic antibiotic use, "J01_SV". This quality indicator might reflect increased systemic antibiotic use in the "winter" quarters (October–December and January–March) compared to the "summer" quarters (July–September and April–June) within a year starting in July and ending the next calendar year in June, and expressed as a percentage: [DDD (winter quarters)/DDD (summer quarters) − 1] × 100.

3.3.4 AWaRe Classification of Antibiotic

In addition to using the ATC classification, the drug use data in this study were categorized using the WHO-defined AWaRe classification (version 2023). To promote the use of antibiotics, improve treatment outcomes, and address the worldwide problem of antimicrobial resistance, the WHO created the AWaRe framework, which groups antibiotics into three categories: Access, Watch, and Reserve.

- **Access antibiotics:** These are drugs with a narrower spectrum of activity, generally less expensive, with a good safety profile and a lower risk of resistance development. They are most often recommended as the empirical first- or second-line choice for treating common infections.
- **Watch antibiotics:** These are drugs with a broader spectrum of activity and are generally more expensive. They are primarily recommended as the first choice for patients with more severe clinical presentations or for infections where pathogens are more likely to be resistant to Access antibiotics (e.g. upper urinary tract infections).
- **Reserve antibiotics:** These are last-resort drugs reserved for the treatment of infections caused by multidrug-resistant pathogens.

3.3.5 Statistical Analysis

Descriptive statistics were presented as the mean ± standard deviation of the mean (SD), maximum, and minimum values for continuous variables, and as the count and percentage for categorical variables. Normality was tested by visual interpretations (histogram and density plot). Continuous variables were tested via the independent t-test. Statistical tests were performed using R statistical software version 4.2.3 (R Foundation, Vienna, Austria) and IBM SPSS software (IBM SPSS Statistics for Windows, Version 29.0, IBM Corp., Armonk, NY, USA).

4. RESULTS

4.1 Specific Results for Study 1

Before and during COVID-19 pandemic antibiotic use in ambulatory care.

4.1.1 Scale of Systemic Antibacterial (J01) Use

In the Hungarian ambulatory care 288 million DDDs of systemic antibiotics were prescribed during the study period (January 2015 – February 2022 – 7 years). Before the COVID-19 pandemic, the average daily consumption of antibiotics was 12.10 DDD per 1,000 inhabitants. However, this decreased by 23.22% during the pandemic to 9.29 DDD per 1,000 inhabitants per day.

The relative and absolute consumption of antibiotic classes is shown in Table 2. Except for tetracyclines, the majority of antibiotic classes had a notable decline in usage. At ATC 3 level, Quinolones (J01M) and Penicillins (J01C) showed the biggest decreases, from 2.22 to 1.41 DDD per 1,000 inhabitants per day (a 36.5% reduction) and from 4.15 to 3.06 DDD per 1,000 inhabitants per day (a 26.3% reduction), respectively. While, at the ATC 4 level we observed the biggest decrease in the group of Second-generation cephalosporins (J01DC) by 36% (from 1.70 to 1.08 DID), and an approximately 20% decrease (from 3.37 to 2.71 DID) in the use of Combinations of penicillins, incl. beta-lactamase inhibitor group (J01CR).

Table 2. Means of systemic antibiotic use in the two main periods.

	preCOVID period Jan. 2015-Dec. 2019		**COVID period** Jan. 2020- Feb. 2022	
	DID[1]	**%**	**DID**[1]	**%**
J01A Tetracyclines	0.77	6.34	0.78	8.35
J01CA Penicillins with extended spectrum	0.61	5.04	0.29	3.12
J01CE Beta-lactamase sensitive penicillins	0.17	1.41	0.06	0.65
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	3.37	27.85	2.71	29.17
J01C Beta-lactam antibacterials, penicillins	4.15	34.28	3.06	32.91
J01DC Second-generation cephalosporins	1.70	14.05	1.08	11.62
J01DD Third-generations cephalosporins	0.27	2.23	0.24	2.58
J01D Cephalosporins	1.97	16.25	1.32	14.24
J01E Sulfonamides and trimethoprim	0.43	3.57	0.36	3.88
J01FA Macrolides	2.00	16.53	1.89	20.34
J01FF Lincosamides	0.50	4.13	0.47	5.06
J01F Macrolides, lincosamides	2.49	20.59	2.35	25.34
J01M Quinolone antibacterials	2.22	18.35	1.41	15.15
J01X Other antibacterials	0.06	0.53	0.01	0.07
J01 Antibacterials	12.10	100.00	9.29	100.00

1 DID: DDD per 1000 inhabitants per day

4.1.2 Top 10 list of antibacterial use

The top ten list of antibacterials in the two main periods is shown in Table 3, demonstrating minimal changes in the ranking. The same active substances dominated in both periods, with co-amoxiclav consistently leading the top list. Notable shifts within the ranking include azithromycin rising to become the second most used antibacterial, capturing over 15% of the systemic antibacterial use in ambulatory care, and clindamycin advancing from ninth to sixth place. On the other hand, some substances declined in the rank; cefuroxime, for example, dropped from second to third or amoxicillin from 8th to 10th place. Levofloxacin and ciprofloxacin both remained in the top 10 ranking.

Table 3. The most used top 10 antibacterials (J01) in the two main periods

	Pre-COVID Period January 2015 – December 2019					**COVID-19 Period January 2020 – February 2022**				
No.	**ATC Code**	**Substance**	**DID [1]**	**%**	**Cum% [2]**	**ATC Code**	**Substance**	**DID [1]**	**%**	**Cum% [2]**
1.	J01CR02	AMC [3]	3.36	27.80	27.80	J01CR02	AMC [3]	2.70	29.10	29.10
2.	J01DC02	cefuroxime	1.34	11.12	38.92	J01FA10	azithromycin	1.41	15.14	44.24
3.	J01FA10	azithromycin	1.22	10.05	48.97	J01DC02	cefuroxime	0.84	9.07	53.31
4.	J01MA12	levofloxacin	1.10	9.07	58.04	J01AA02	doxycycline	0.78	8.35	61.66
5.	J01AA02	doxycycline	0.77	6.34	64.38	J01MA12	levofloxacin	0.64	6.93	68.58
6.	J01FA09	clarithromycin	0.73	6.05	70.44	J01FF01	clindamycin	0.47	5.04	73.63
7.	J01MA02	ciprofloxacin	0.66	5.46	75.89	J01MA02	ciprofloxacin	0.46	5.00	78.62
8.	J01CA04	amoxicillin	0.61	5.01	80.91	J01FA09	clarithromycin	0.46	4.97	83.59
9.	J01FF01	clindamycin	0.50	4.09	85.00	J01EE01	SMX-TMP [4]	0.36	3.88	87.47
10.	J01EE01	SMX-TMP [4]	0.43	3.57	88.57	J01CA04	amoxicillin	0.29	3.08	90.55

[1] DID: DDD per 1000 inhabitants per day; [2] cum%: cumulative percentage; [3] AMC: amoxicillin and clavulanic acid;
[4] SMX-TMP: sulfamethoxazole and trimethoprim.

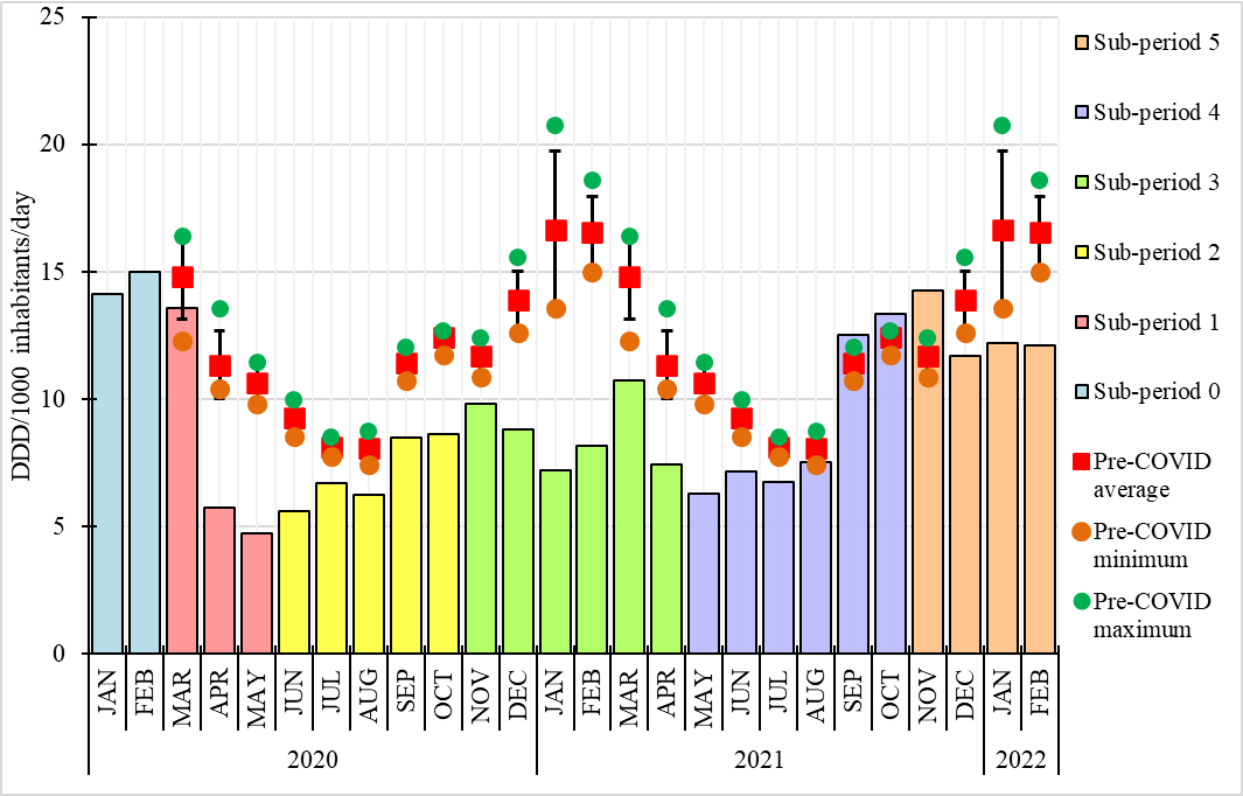
4.1.3 Antibiotic use in different COVID-19 pandemic sub-periods

Figure 1 illustrates the monthly usage of systemic antibiotics (J01) during the COVID-19 sub-periods (sub-periods 0 to 5), compared to the corresponding monthly statistics (minimum, maximum, and mean) from the pre-COVID period (2015–2019).

Overall, systemic antibiotic use (J01) during the pandemic months was generally lower than the pre-COVID averages, except for three months (September to November 2021, during sub-period 4). Sub-periods 1 and 3 showed the biggest differences in antibiotic use between the pre-COVID monthly means and the pandemic monthly means. For example, systemic antibiotic use decreased to 4.73 DDD per 1,000 inhabitants per day in May 2020 (sub-period 1), which was 55.46% lower than the pre-COVID May mean of 10.62 DDD per 1,000 inhabitants per day. This significant decrease followed the declaration of state of emergency, with antibiotic use reaching nadir in May 2020. Antibiotic use began to rise slightly from June 2020 (sub-period 2), but the usual seasonal winter peak did not appear. In sub-period 3, the highest antibiotic use occurred in March 2021, though it remained significantly below the pre-COVID

monthly mean for the same months. We examined the trends in the use of antibacterial subgroups and the results are detailed in the dissertation.

Figure 1 The time trends of the systemic antibiotic (J01) use



Coloured bars show the monthly usage during the different COVID-19 sub-periods, the red squares represent the average monthly usage of antibiotics in the pre-COVID years. Other indicators include whiskers that represent the standard deviation, a green circle that displays the maximum value before the COVID period, and orange circles that show the minimum values.

4.2 Specific Results for Study 2

Before, during and AFTER COVID-19 pandemic antibiotic use in ambulatory care.

4.2.1 Scale of Systemic Antibacterial (J01) Use

Over the 72-month study period (March 2018 – February 2024 – 6 years) a total of 244 million DDDs of systemic antibiotics were utilized in Hungary's outpatient sector. In the Before the COVID-19 pandemic period (March 2018 - February 2020), the national average usage was 11.61 DDD per 1,000 inhabitants perday (DID). During the pandemic (March 2020 - February 2022), this figure dropped to 8.99 DID, and then returned to 11.11 DID in the After COVID period (March 2022 – February 2024). A summary of the average monthly usage of antibiotics is shown in Table 4. We didn't observe statistically significant change in antibiotic use at the J01 level during the study periods, while analysis of J01 subgroups showed an important redistribution, with macrolides (J01FA) showing the most notable and statistically significant change (Table 4.).

Penicillins (J01C) showed the highest absolute usage among all antibiotic groups over all three periods. During the COVID-19 period, this antibiotic subgroup's use decreased significantly with nearly 30% (Table 4.). Following the pandemic, its use increased and even exceeded pre-COVID levels, with 4.12 DID. The J01CR (combinations of penicillins, incl. beta-lactamase inhibitors) ATC subgroup, the most widely used penicillin subgroup, showed a similar tendency. Other penicillin subgroups, on the other hand, demonstrated a consistent decreased use over the study period. Throughout all periods, beta-lactamase-sensitive penicillins (J01CE) continuously showed low consumption with a slight decrease during and after the pandemic.

Compared to the Before COVID period the usage of cephalosporins (J01D) decreased by 38.0% in the COVID period (see Table 4.). Through the study periods, second-generation cephalosporins (J01DC) were consistently the most commonly used cephalosporins. However, during the pandemic, their usage declined remarkably (~40%), and this lower level of use persisted in the post-pandemic period. In contrast, third-generation cephalosporin use (ATC code: J01DD) showed a notable increase after the pandemic compared with the other two periods (see Table 4).

Similarly, to cephalosporins, quinolone use decreased by one third during the pandemic. Following the pandemic, both groups (J01D: 1.50 DID; J01M: 1.52 DID) exhibited a modest recovery in use, though their usage levels remained lower than those recorded in the pre-COVID period (see Table 4.).

In the subgroup analysis we observed a notably increase in the macrolides subgroup (J01FA) with a 20% increase (from 1.912 DID in Before COVID period to 2.41 DID to the After COVID period, see (Table 4.).

Table 4. The mean monthly antibiotic use in the three study periods expressed as DDD per 1000 inhabitants per day - DID)

	Before COVID Period		COVID Period		After COVID Period		p*
	March 2018 – February 2020		March 2020 – February 2022		March 2022 – February 2024		
	DID (mean) ± SD	min - max	DID (mean) ± SD	min - max	DID (mean) ± SD	min - max	
J01A Tetracyclines	0.74 ± 0.15	0.45 – 1.05	0.77 ± 0.22	0.46 – 1.17	0.67 ± 0.11	0.49 – 0.92	0.157
J01CA Penicillins with extended spectrum	0.43 ± 0.10	0.27 – 0.68	0.27 ± 0.09	0.14 – 0.46	0.22 ± 0.17	0.01 – 0.43	*<0.001*
J01CE Beta-lactamase sensitive penicillins	0.16 ± 0.04	0.08 – 0.24	0.05 ± 0.02	0.03 – 0.12	0.04 ± 0.03	0.04 – 0.03	*<0.001*
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	3.44 ± 0.79	2.35 – 5.47	2.60 ± 0.79	1.44 – 4.21	3.87 ± 0.84	2.68 – 5.47	*0.024*
J01C Beta-lactam antibacterials, penicillins	4.03 ± 0.94	2.70 – 6.39	2.93 ± 0.90	1.60 – 4.78	4.12 ± 0.80	3.03 – 5.77	0.443
J01DC Second-generation cephalosporins	1.70 ± 0.48	0.93 – 2.88	1.01 ± 0.33	0.53 – 1.86	1.05 ± 0.20	0.70 – 1.51	*<0.001*
J01DD Third-generation cephalosporins	0.29 ± 0.10	0.16 – 0.50	0.23 ± 0.11	0.09 – 0.43	0.45 ± 0.12	0.25 – 0.66	*<0.001*
J01D Cephalosporins	2.00 ± 0.57	1.10 – 3.39	1.24 ± 0.41	0.63 – 2.20	1.50 ± 0.28	1.04 – 2.02	*0.008*
J01E Sulfonamides and trimethoprim	0.42 ± 0.06	0.33 – 0.56	0.36 ± 0.07	0.24 – 0.51	0.39 ± 0.06	0.32 – 0.51	0.364
J01FA Macrolides	1.91 ± 0.73	0.93 – 3.64	1.84 ± 1.13	0.45 – 4.22	2.41 ± 0.83	1.09 – 4.06	*0.007*
J01FF Lincosamides	0.49 ± 0.02	0.44 – 0.53	0.47 ± 0.03	0.41 – 0.55	0.47 ± 0.02	0.44 – 0.53	*0.004*
J01F Macrolides, lincosamides	2.40 ± 0.74	1.39 – 4.18	2.31 ± 1.15	0.87 – 4.71	2.89 ± 0.84	1.54 – 4.46	*0.009*
J01M Quinolone antibacterials	1.98 ± 0.52	1.28 – 3.30	1.36 ± 0.34	0.86 – 2.06	1.52 ± 0.33	1.01 – 2.12	*0.001*
J01X Other antibacterials	0.04 ± 0.04	0.00 – 0.11	0.01 ± 0.00	0.00 – 0.01	0.01 ± 0.00	0.01 – 0.02	*0.006*
J01 Systemic Antibacterials	11.61 ± 2.90	7.41 – 18.88	8.99 ± 2.87	4.73 – 14.28	11.11 ± 2.28	7.69 – 15.60	0.871
J01 Access antibacterials	5.68 ± 1.14	4.09 – 8.54	4.53 ± 1.13	2.77 – 6.72	5.78 ± 0.91	4.37 – 7.58	0.740
J01 Watch antibacterials	5.92 ± 1.78	3.32 – 10.33	4.45 ± 1.78	1.95 – 7.83	5.70 ± 1.40	3.31 – 8.01	0.628
J01 Access %	49.51 ± 2.79	43.58 – 55.20	51.63 ± 4.68	44.38 – 59.62	50.80 ± 2.93	46.11 – 57.13	0.124

* independent sample T test (between the Before COVID and the After COVID periods)

4.2.2 Top 10 list of antibacterial use

We examined the top 10 antibacterial agents during the study periods. Before, during, and after the pandemic, the same five active agents were ranked highest, with co-amoxiclav leading the lists. However, significant changes were seen, as azithromycin moved to the second-most-used antibiotic during the COVID period and continued to remain in this position after the pandemic. On the other hand, cefuroxime, which had been ranked second before COVID, dropped to fifth place following the pandemic. Cefixime (7th place) and cefprozil (10th place), two broad-spectrum cephalosporins, entered the top ten, while amoxicillin and sulfamethoxazole combined with trimethoprim dropped off from the top list in the after COVID period. We examined also the changes in the distribution of Access and Watch group agents. The after-pandemic top list had more agents from the Watch group (7 agents) compared to pre-pandemic and pandemic periods (5-5 agents).

4.2.3 The rate of antibiotic exposure

The changes in the top antibacterials list were also evident in the average monthly rate of exposed patients, as shown in Table 5. For amoxicillin and clavulanic acid (co-amoxiclav) and azithromycin, the minimum mean monthly rate of exposed patients doubled in the After COVID period compared to the COVID period. In contrast, for the other three antibacterials listed in the table, the rate of exposed patients declined in the After COVID period.

Table 5. The mean monthly rate of exposed patients for the five most used antibacterial agents across the three study periods.

Mean monthly rate of exposed patients					
			Before COVID Period Mar. 2018–Feb. 2020	**COVID Period Mar. 2020–Feb. 2022**	**After COVID Period Mar. 2022–Feb. 2024**
J01CR02	Co-amoxiclav	mean	140 494	99 246	156 208
		min - max	89 124 – 227 533	51 685 – 166 902	97 410 – 220 223
J01FA10	Azithromycin	mean	66 869	66 538	97 367
		min - max	30 329 – 129 604	13 831 – 160 368	37 441 – 160 572
J01DC02	Cefuroxime	mean	41 890	23 251	18 391
		min - max	22 458 – 69 290	12 828 – 44 588	10 824 – 29 549
J01MA12	Levofloxacin	mean	39 450	22 909	28 240
		min - max	17 716 – 82 602	9 642 – 44 438	13 159 – 46 138
J01AA02	Doxycyline	mean	8 292	8 185	6 987
		min - max	4 873 – 12 732	4 600 – 13 208	4 795 – 9 914

4.2.4 Seasonal Variation in Systemic Antibiotic Use

The seasonality indexes (J01_SV) for the three study periods are shown in Table 6. The seasonality index for systemic antibacterials (J01) increased in the COVID period, from 46.86% to 53.42%, and then dropped to 39.68% during the After COVID period. The ATC subgroup that showed the most profound change was the macrolides (J01F), whose seasonality index increased significantly from 60.63% to 104.74% during the pandemic. However, it returned to

before COVID levels in the After COVID period. As seen in Table 6, the seasonality index decreased after the pandemic for all other antibacterial subgroups.

Table 6. Seasonality index for the different antibiotic subgroups during the study periods.

	Seasonality index+		
	Before COVID Period Mar. 2018-Feb.2020	**COVID Period** Mar. 2020-Feb. 2022	**After COVID Period** Mar. 2022-Feb. 2024
J01A Tetracyclines	38.92	60.29	22.48
J01CA Penicillins with extended spectrum *			
J01CE Beta-lactamase sensitive penicillins *			
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	44.52	37.97	38.53
J01C Beta-lactam antibacterials, penicillins	43.63	35.68	34.07
J01DC Second-generation cephalosporins	50.92	27.96	27.76
J01DD Third-generation cephalosporins	69.82	82.12	62.26
J01D Cephalosporins	53.39	36.26	37.32
J01E Sulfonamides and trimethoprim	28.11	30.17	22.54
J01F Macrolides, lincosamides	60.63	104.74	59.74
J01M Quinolone antibacterials	42.22	42.73	35.01
J01X Other antibacterials*			
J01 Systemic Antibacterials	46.86	53.42	39.68

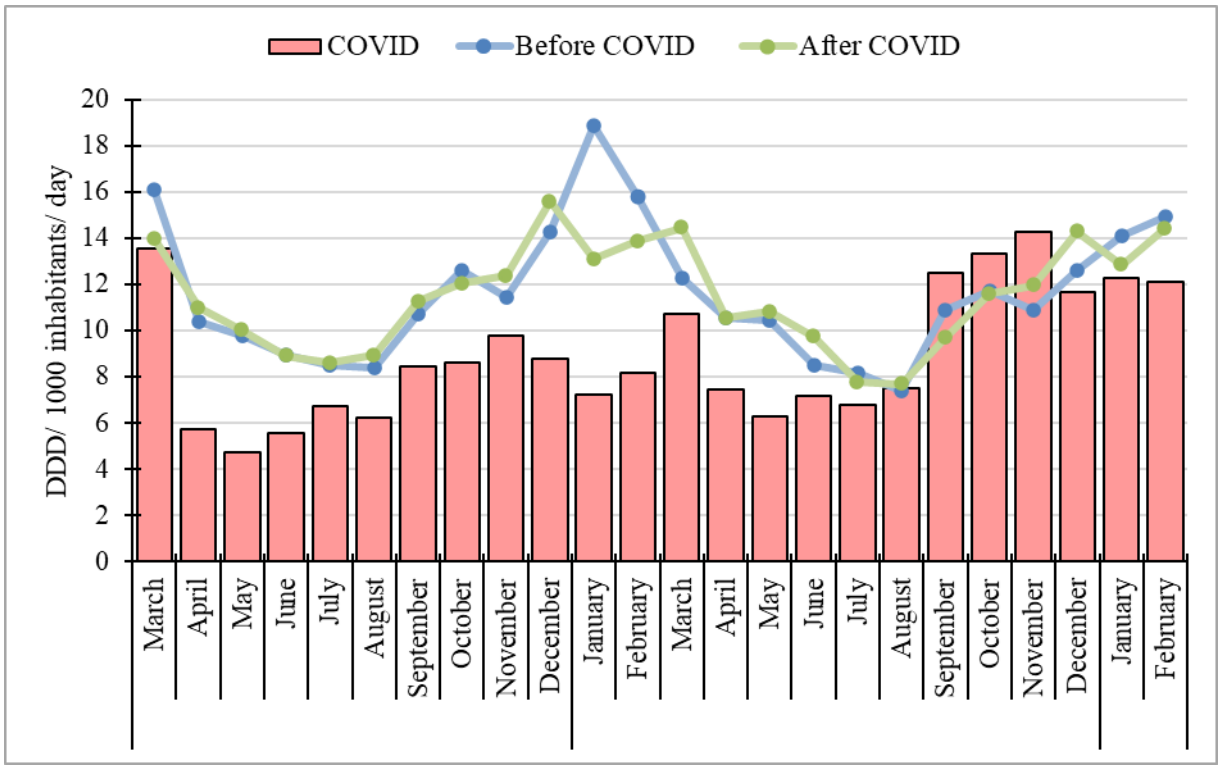
* low consumtion < 0.5; reduced consumption; and/or a prolonged period with product shortages

+ Antibacterial overuse in the winter months (October–December and January–March) compared with the summer months (July–September and April–June) for a 2-year period starting in March and ending in February, expressed as percentage: [DDD (winter quarters)/DDD (summer quarters) − 1] × 100

4.2.5 Time Trends of Systemic Antibacterial Use

Figure 2 illustrates the monthly usage of systemic antibiotics (J01) during the COVID-19 period, in addition to the corresponding monthly values from the Before and After COVID periods. A comprehensive overview of monthly utilization for the main antibiotic subgroups were examined in the dissertation. In the different subgroups, the After COVID period's monthly systemic antibiotic use was similar to the Before COVID period. Both periods showed a winter peak in consumption; however, the peak was slightly less noticeable in the After COVID period.

Figure 2. Time series of systemic antibacterials (J01) use during the three study periods.



The colored columns represent systemic antibiotic use during the COVID period, while the blue and green lines correspond to usage levels from the Before COVID and After COVID periods, respectively.

5. SUMMARY AND CONCLUSIONS

Our research highlights, for the first time in a Central European country, the significant impact of the COVID-19 pandemic on antibiotic use trends in ambulatory care. We analyzed the utilization of antibiotics before, during, and after the pandemic. The COVID-19 pandemic-related restrictions led to a notable decrease in overall antibiotic use in the Hungarian ambulatory care sector. Positive finding was the reduced reliance on fluoroquinolones. However, an increase was observed in the use of macrolides (e.g., azithromycin) during the pandemic, despite evidence of their ineffectiveness against COVID-19.

Monthly fluctuations in antibiotic use closely mirrored the implementation and suspension of pandemic-related social restrictions. Overall, antibiotic consumption in the After COVID period returned to levels similar to those observed before the pandemic. However, several concerning patterns in prescribing quality emerged during and after the pandemic. The use of broad-spectrum penicillin combinations (J01CR) increased, while the use of narrow-spectrum beta-lactamase-sensitive penicillins (J01CE) and second-generation cephalosporins decreased. At the same time, the use of third-generation cephalosporins (J01DD) and macrolides (J01F) significantly increased. These changes may partly reflect prescribing habits formed during the pandemic, the widespread empirical use of azithromycin in the early phases of COVID-19, and the limited availability of some narrow-spectrum agents, which together may have shifted prescribing toward broader-spectrum antibiotics.

In the future, healthcare practitioners will need to adopt evolving evidence-based recommendations more rapidly. Policymakers might consider maintaining certain pandemic measures, such as requiring mask use, to control the spread of other infectious diseases (e.g. influenza) and consequently reduce antibiotics prescribing. Since the pandemic caused significant modifications in healthcare services and prescribing procedures, additional research is necessary to confirm if these changes have contributed to changes in antibiotic use. The long-term impacts of the COVID-19 pandemic on antibiotic use require additional future research.

LIST OF PUBLICATIONS

1. Publications related to the Ph.D. thesis

I. **Hambalek H.;** Matuz M.; Ruzsa R.; Engi Zs.; Visnyovszki Á.; Papfalvi E.; Hajdú E.; Doró P.; Viola R.; Soós Gy., Csupor D., Benkő R.: Impact of the COVID-19 Pandemic on Ambulatory Care Antibiotic Use in Hungary: A Population-Based Observational Study *ANTIBIOTICS 12: 6 Paper: 970, 10 p. (2023)*
[IF: 4.8; Q1 in Pharmacology & Pharmacy / Infectious Diseases (2023)]

II. **Hambalek H.,** Matuz M., Ruzsa R., Papfalvi E., Nacsa R., Engi Zs., Csatordai M., Soós Gy., Hajdú E., Csupor D., Benkő R.: Returned Rate and Changed Patterns of Systemic Antibiotic Use in Ambulatory Care in Hungary after the Pandemic—A Longitudinal Ecological Study *ANTIBIOTICS 13: 9 Paper: 848, 13 p. (2024)*
[IF: 4.6; Q1 in Infectious Diseases / Q1 in Pharmacology & Pharmacy (2024)]

2. Presentations related to the Ph.D. thesis

I. **Hambalek H.,** Matuz M., Ruzsa R., Engi Zs., Csupor D., Doró P., Soós Gy., Visnyovszky Á., Hajdú E., Benkő R.: Ambuláns antibiotikum alkalmazás: volt – e a pandémiának hatása? [Ambulatory care antibiotic use in Hungary: was there a pandemic effect?] *ACTA PHARMACEUTICA HUNGARICA 93: Suppl 1 pp. S47-S48., 2 p. (2023)* (poster presentation)

II. **Hambalek H.,** Matuz M., Ruzsa R., Engi Zs., Csupor D., Doró P., Soós Gy., Visnyovszky Á., Hajdú E., Benkő R.: Impact on COVID-19 pandemic on national outpatient antibiotic use, *EuroDURG Conference 2023: Sustainability of drug use: equity and innovation (2023) 230 p. pp. 10-10., 1 p.* (poster presentation)

III. **Hambalek H.,** Matuz M., Papfalvi E., Ruzsa R., Csatordai M., Nacsa R., Csupor D., Benkő R.: COVID and Antibiotic Use: How They are Related? *In: Magyar Gyógyszerésztudományi Társaság; EUFEPS - Magyar Gyógyszerésztudományi Társaság; EUFEPS (szerk.) Congressus Pharmaceuticus Hungaricus XVII. and EUFEPS Annual Meeting 2024: Abstracts, Budapest, Magyarország: Magyar Gyógyszerésztudományi Társaság (MGYT) (2024) 451 p. pp. 283-283., 1 p.* (poster presentation)

IV. **Hambalek H.,** Ambrus R., Ruzsa R., Papfalvi E., Nacsa R., Matuz M., Benkő R.: Ciprofloxacinnal az élen: antibiotikumok az idősek UTI kezelésében [Ciprofloxacin leads the way: antibiotics in the treatment of UTIs in the elderly] *ACTA PHARMACEUTICA HUNGARICA 95: Suppl. 1 pp. S40-S40., 1 p. (2025)* (poster presentation)

V. **Hambalek H.**, Ambrus R., Ruzsa R., Papfalvi E., Nacsa R., Matuz M., Benkő R.: UTI-lizing Antibiotics in the Hungarian Elderly Population, *European Drug Utilization Conference 2025 Abstract book Bridging Data, Policy & Patients in Drug Utilization Research Uppsala, Svédország: Uppsala Universitet (2025) 360 p. pp. 152-152. Paper: 191, 1 p.* (poster presentation)

VI. **Hambalek H.,** Matuz M., Ambrus R., Ruzsa R., Papfalvi E., Nacsa R., Benkő R.: Aging and quality of antibiotic use? *Zorana, Kovačević (szerk.) 4th Antimicrobial Resistance - Current State and Perspectives 2025: Book of abstracts Novi Sad, Szerbia: University of Novi Sad, Faculty of Agriculture (2025) 90 p. pp. 83-83., 1 p.* (poster presentation)