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

Ph. D Thesis

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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)*
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2. Presentations related to the Ph.D. thesis

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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)

LIST OF ABBREVATIONS

AMR = Antimicrobial Resistance

AMS = Antimicrobial Stewardship

AMC = amoxicillin and clavulanic acid

AMU = Antimicrobial Utilization

ATC = Anatomical Therapeutic Chemical Classification Index

AWaRe = Access, Watch, Reserve

BPPL = Bacterial Priority Pathogen List

COVID-19 = Coronavirus Disease 2019

Cum% = Cumulative Percentage

DDD = Defined Daily Dose

DID = Defined Daily Dose (DDD) per 1000 inhabitants per day

DU = Drug Utilization

EARS-Net = European Antimicrobial Resistance Surveillance Network

EEA = European Economic Area

ECDC = European Centre of Disease Prevention and Control

E. coli = *Escherichia coli*

ESAC-Net = European Surveillance of Antimicrobial Consumption-Network

ESBL = Extended-spectrum beta-lactamase

EU = European Union

GPs = General Practitioners

J01 = ATC code for antibacterials for systemic use

J01_SV = Seasonality index

MRSA = Methicillin-resistant *Staphylococcus aureus*

NEAK = National Health Insurance Fund of Hungary

p = Independent sample T-test

RTIs = Respiratory Tract Infections

S. aureus = *Staphylococcus aureus*

SD = Standard deviation

SMX-TMP= Sulfamethoxazole and trimethoprim

WHO = World Health Organization

1. INTRODUCTION

1.1 Burden of infectious diseases and role of antibiotics

Antimicrobials – including antibiotics, antivirals, antifungals, and antiparasitistics – are essential medicines used to prevent and treat infections in humans, animals, and even plants [1–4]. Antibiotics are among the most significant medical innovations of the 20th century and are used to prevent and treat bacterial infections. More than half of all deaths in the pre-antibiotic era were caused by infectious diseases, with septicaemia, pneumonia, and wound infections often being fatal [5]. Previous mortality statistics demonstrated the devastating effects of infectious diseases. In 1900, in United States the infectious disease mortality rate was around 800 deaths per 100,000 inhabitants per year, mostly from diphtheria, diarrheal illnesses, tuberculosis, and pneumonia (Figure 1). By the 1930s, public health initiatives such as immunization, hygiene, and infection control had begun to lower these rates, but a significant and long-lasting decrease did not occur until the discovery of antibiotics [5]. The introduction of antibiotics has drastically reduced the burden of infectious disease mortality and contributed to a global increase in life expectancy by one to two decades within less than a century [1,2,6,7]. Overall, the infectious disease mortality rate decreased to about 50 per 100,000 by 1952 [5]. Antibiotics are essential to modern medicine beyond curing infections directly. By ensuring the efficient prevention and management of bacterial complications, they support the success of many life-saving and life-extending interventions, including surgery, organ transplantation, cancer chemotherapy, and (neonatal) critical care. In this way, antibiotics have become essential to maintaining the safety and efficacy of modern medicine.

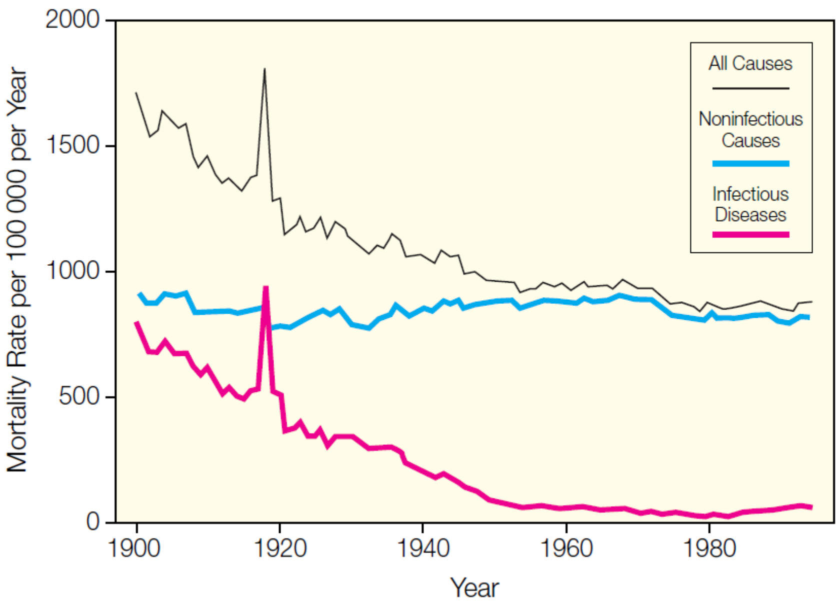


Figure 1. Mortality Rates from the United States in the 20th Century [5].

The broad application of antibiotics extends beyond human medicine to veterinary practice, agriculture, and food production, making antibiotics a key medicine in all sectors, contributing largely to the One Health Concept [8,9].

1.2 Discovery of antibiotics: golden age and current discovery gap

Paul Ehrlich led the first organized effort to develop antimicrobial agents in the early 20th century. His 1910 research on *Salvarsan (arsphenamine)* established the idea of selective toxicity. However, the effectiveness of these early chemotherapeutic agents were limited [7,10]. A significant turning point in medical history was reached in 1928 when Alexander Fleming discovered *penicillin* [11]. Although Fleming observed the antibacterial effect of *Penicillium notatum* by chance, it was not until more than a decade later that Howard Florey and Ernst Chain successfully purified and clinically applied *penicillin* during World War II (Figure 2) [11–13]. Their work demonstrated the enormous therapeutic potential of antibiotics and led to the large-scale industrial production, supported by wartime governments [7,14].

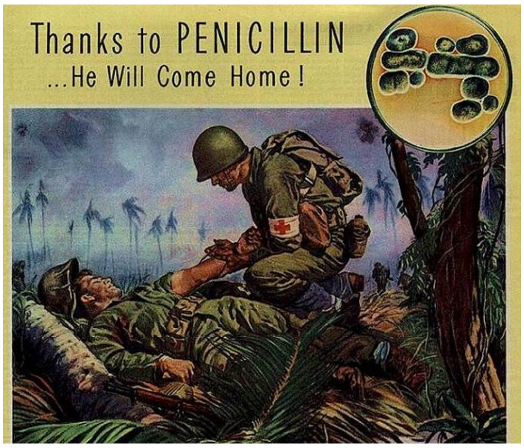


Figure 2. "Thanks to PENICILLIN… He Will Come Home!" from Life Magazine 1944 [15].

The history of medicine was radically changed by the clinical success of *penicillin* in treating bacterial infections that were previously impossible to treat. In addition to lowering mortality from illnesses like syphilis and streptococcal infections, it made improvements in maternal health and surgical safety. The "antibiotic era" or "golden era of antibiotics" began with the widespread use of *penicillin* between the early 1940s and the late 1960s [1,2,14]. The development of antibacterial agents increased at an unprecedented rate during this era, with the majority of these agents being isolated from natural sources, especially soil-dwelling *Actinomycetes* like *Streptomyces spp.* [16–19]. Selman Waksman discovered *streptomycin* in 1943. Waksman won the 1952 Nobel Prize in Physiology or Medicine for recognizing that *streptomycin* was the first antibiotic that worked against *Mycobacterium tuberculosis*, which was a milestone in the treatment of tuberculosis [1,7,18–20].

Many antibiotics from various structural classes, such as *erythromycin, tetracyclines, rifampicin,* and *chloramphenicol,* were discovered over the following decades [10,13]. Another milestone was the 1952 isolation of *erythromycin*, the first *macrolide* antibiotic with clinical significance from *Streptomyces erythraeus.* This drug provided a useful substitute for *penicillin*, especially for those patients with *β-lactam* allergies, and set the stage for the subsequent development of *macrolides* [17]. The majority of the currently used classes of antibiotics, such as *aminoglycosides, tetracyclines, macrolides,* and *glycopeptides,* had already been identified by the end of the 1960s, as shown on Figure 3. The rapid development of new antibiotics had considerably slowed down by the early 1970s. Most natural antibiotic structures had already been identified, and few novel classes emerged thereafter [16,21]. In parallel, pharmaceutical companies began prioritizing more profitable drugs for chronic diseases over short-course antibiotics [1,22]. Many new antibiotic candidates were ineffective and offered little therapeutic innovation [7,23]. The so-called "innovation gap" grew as a result, especially for agents that are active against *Gram-negative* pathogens [18,24].

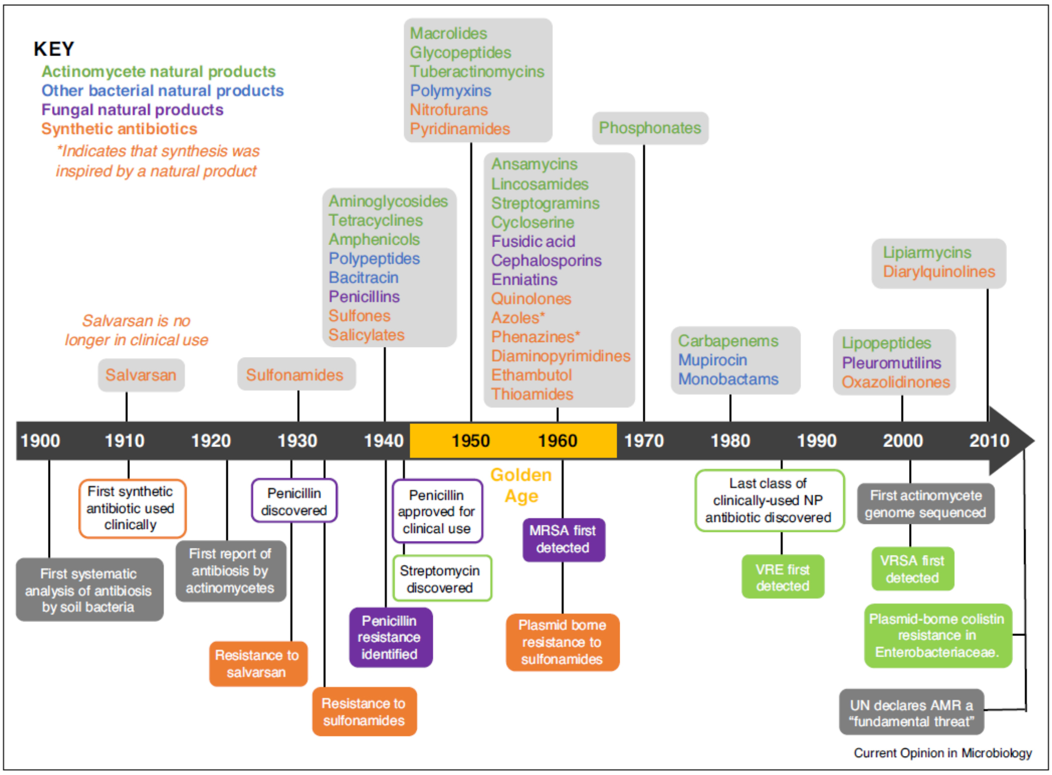


Figure 3. Timeline of Antibiotic Class Introduction and Resistance Milestones [14]. *Antibiotic classes are color-coded according to their origin: green for actinomycetes, blue for the other bacterial sources, purple for fungal-derived antibiotics, and orange for synthetics* [14].

1.3 Antimicrobial resistance (AMR): definition and WHO ranking

Antimicrobial resistance (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 [25–27]. Although the term commonly refers to antibiotics, AMR can exist in a variety of pathogens, including bacteria, viruses, fungi, and parasites [22,28]. AMR has evolved from a local clinical problem into a major global health and development threat [25]. According to recent estimates there were 4,71 million deaths associated with AMR in 2021, with 1,14 million bacterial AMR deaths [29].

The two main types of bacterial resistance are acquired resistance and the intrinsic (innate) resistance.

- **Intrinsic (innate) resistance:** Based on their physiological or structural characteristics, certain bacterial species are naturally resistant. *Pseudomonas aeruginosa*, for instance, possesses efflux pumps and low outer membrane permeability, which explain its resistance to many antibiotics [21,27,30].

- **Acquired resistance:** When bacteria develop the ability to resist previously effective antibiotics. This happens as a result of spontaneous mutations or horizontal gene transfer. Mobile genetic elements that help resistance determinants spread across species and ecosystems, like integrons, transposons, and plasmids, may be involved in this [28,31,32].

The World Health Organization (WHO) ranks the pathogens according to the severity of their resistance level, their clinical significance, and their importance to public health. Based on this, the Bacterial Priority Pathogen List (BPPL), which was last updated in 2024, has been published by the WHO. In this list, the pathogens are divided into three priority levels: critical, high, and medium (Figure 4) [33].

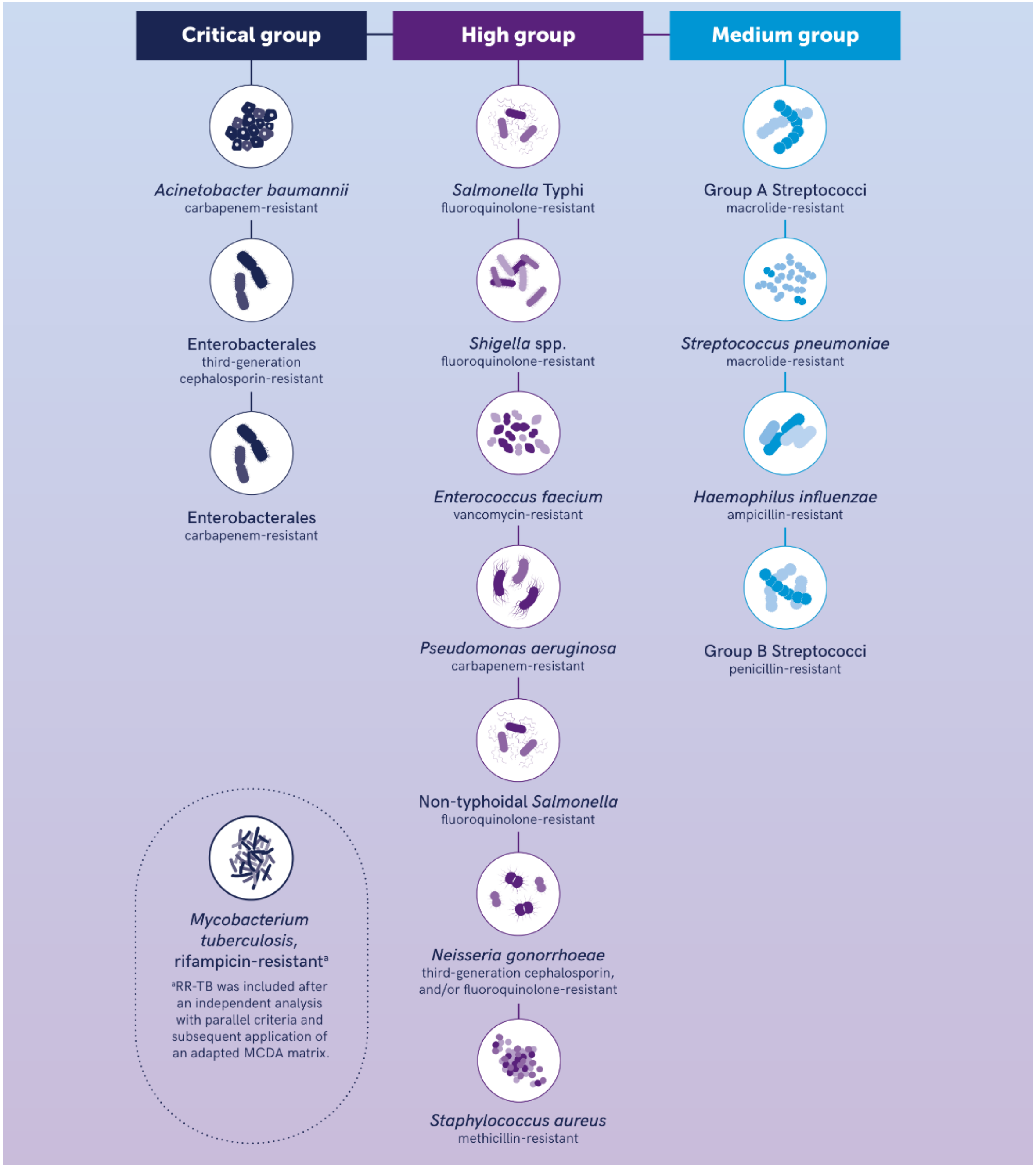


Figure 4. WHO Bacterial Priority Pathogen List (BPPL), 2024 update [33].

Many human, animal, environmental, and social factors contribute to the antimicrobial resistance (AMR) [25]. 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 [22,30,34]. Developing successful preventive and stewardship initiatives within the One Health paradigm requires an understanding of these risk factors [25,35].

1.4 The current trends and burden of AMR

The ECDC's European Antimicrobial Resistance Surveillance Network (EARS-Net) tracks the changes in the resistance profile of the most significant human pathogens (already mentioned in the WHO priority pathogen list) in EU/EEA countries. In Europe, *E. coli* is a leading pathogen of bloodstream infections. According to ECDC's analysis of the health impact of AMR in the EU/EEA for the years 2016–2020, infections with third-generation cephalosporin-resistant E. *coli* (Extended-spectrum beta-lactamase - ESBL producing *E. coli*) accounted for the greatest number of cases and fatalities [36,37]. In the EU/EEA, the population-weighted mean AMR percentage for third-generation cephalosporin resistant *E. coli* was 16.0% in 2024 compared to 12.0% in 2014, showing a significantly increasing trend. In 2024 the percentage was 20.7% in Hungary. (Figure 5) [38–40].

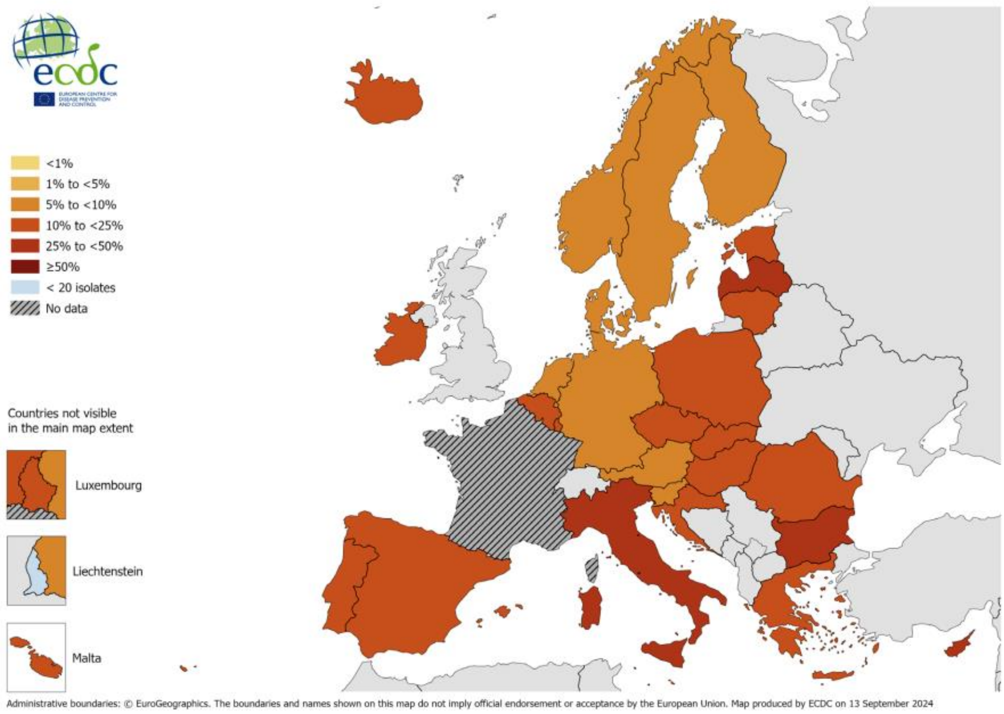


Figure 5. *Escherichia coli*. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime), by nation, EU/EEA, 2024 [36].

Furthermore, at the EU/EEA level, based on the EARS-Net 2024 report, at least half (53.5%) of the invasive *Escherichia coli* isolates were resistant to at least one of the antimicrobial groups under surveillance (aminopenicillins, fluoroquinolones, third-generation cephalosporins, aminoglycosides, and carbapenems) [36].

The second-largest burden of disease was caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in EU/EEA countries between 2016 and 2020 [37].

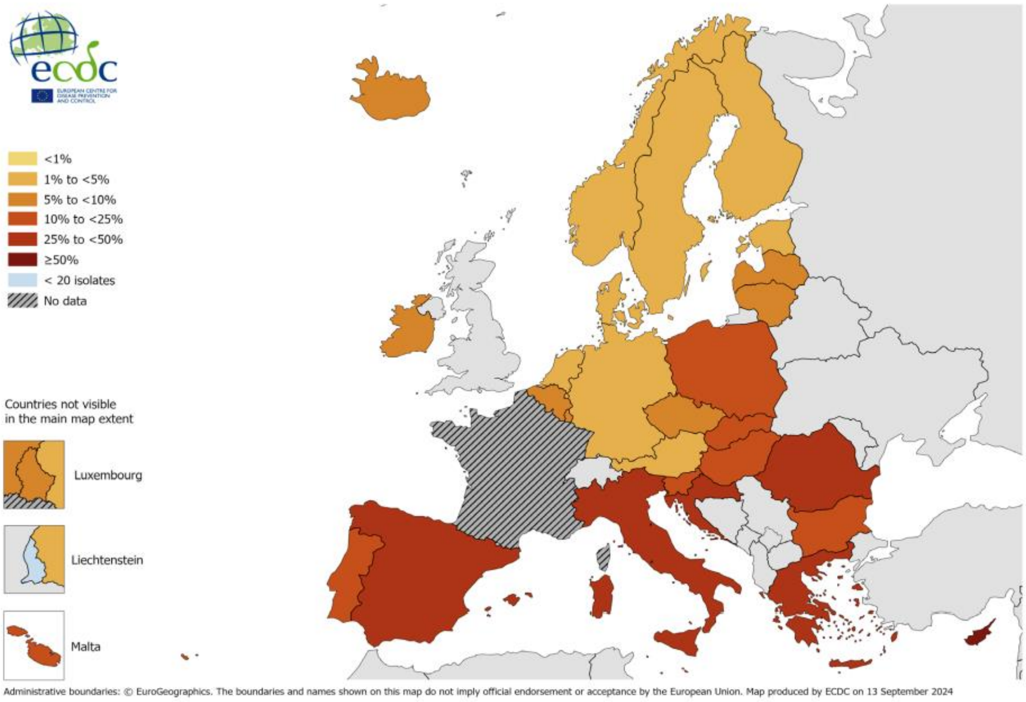


Figure 6. *Staphylococcus aureus.* Percentage of invasive isolates resistant to methicillin (MRSA) by nation, EU/EEA, 2024 [36].

Furthermore, resistance to at least one of the antibiotic categories under monitoring (methicillin/MRSA, fluoroquinolones, and rifampicin) was present in slightly less than one-fifth (18.5%) of the invasive *S. aureus* isolates reported by EU/EEA countries to EARS-Net for 2024 [36].

If these AMR trends continue, there is a risk of entering a post-antibiotic era, where routine infections and minor injuries could again be fatal [41]. The WHO states that antimicrobial resistance is one of the top ten global public health threats facing humanity [42]. Thus, it is our collective and pressing responsibility to maintain the effectiveness of currently available antibiotics through responsible use, international cooperation, and sustainable practices [29].

1.5 Antimicrobial Stewardship (AMS)

The aim of Antimicrobial Stewardship (AMS) is to promote the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug, dose, duration, and route of administration. Thus, the aim is to maximize clinical results while reducing adverse effects of antimicrobial use, such as toxicity, pathogen selection, and resistance development [43–46].

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 [43–45]. Table 1 summarizes the “8D points” that should be considered before prescribing antibiotics to patients [47–50].

Table 1. The 8 Pillars (8 Ds) of AMS [47–50]

Think 8D – before prescribing!	
Diagnosis	What is the clinical diagnosis? Is there evidence of a significant bacterial infection?
Decide	Are antibiotics really needed? Do I need to take any cultures or other tests?
Drug	Which antibiotic to prescribe? Is it an Access or Watch or Reserve antibiotic? Are there any allergies, interactions or other contraindications?
Dose	What dose, how many times a day? Are any dose adjustments needed, for example, because of renal impairment?
Delivery	What formulation to use? Is this a good quality product? If intravenous treatment is needed, when is step down to oral delivery possible?
Duration	For how long? What is the stop date?
Discuss	Inform the patient of the diagnosis, the likely duration of symptoms, any likely medicine toxicity and what to do if not recovering.
Document	Write down all decisions and the management plan.

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 [27,51].

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. The ESAC-Net publishes the Annual Epidemiological Report every year. The most recent report, which includes data from 2024, was released in November 2025 with 27 reported countries, including Hungary [52]. The Antibiotic Working Group of the Institute of Clinical Pharmacy, University of Szeged, Hungary, has been responsible for submitting AMU data to ESAC-Net since 2005.

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) [53]. 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 [54].

Annual population data were obtained from the Hungarian Central Statistical Office [55].

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 [56].

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 declared a state of emergency on March 11, 2020, and 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

Details of the restrictions implemented during these sub-periods are summarized in Box 1.

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 [57–63]. (Box 1 and Table 2.)

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.

3.2.3 Hungarian pandemic restrictions

Box 1. Summary of pandemic related restrictive measures in Hungary [57–63]

Sub-period 1 (March 2020–May 2020): First lockdown
The first COVID-19 patient in Hungary was reported on 4 March 2020. Measures included social distancing (1.5–2 m in public places) and the closing of kindergartens, while schools and universities switched to online education. Restaurants were open until 3 pm, providing only delivery services. Shopping centers were closed after 3 p.m., except for pharmacies, grocery stores, bakeries, and markets, with an isolated purchase period for elderly people. Sport and culture events were cancelled. Weddings and funerals were limited to close relatives. Hotels, cinemas, museums, libraries, and sports facilities were also closed. There was a curfew order that meant people could only leave their homes for a legitimate reason, for example, in case of emergency or work duties. People had to wear face masks in indoor spaces.
Sub-period 2 (June 2020–October 2020):
The intermediate phase during summer with fewer COVID-19 infections and fewer restrictions. Restaurants could open the terraces and, later, the inner spaces. Shops were open with longer opening hours. Sports and cultural events were organized with a 1.5 m protective distance, and weddings and funerals were held with a maximum of 200 participants. Outdoor events could be organized with up to 500 participants. Curfew was suspended. However, wearing a mask was obligatory in indoor places. Schools maintained online education until the end of the school year, followed by in-person education from September.
Sub-period 3 (November 2020–April 2021): Second lockdown
The second and third wave of infections came with stricter lockdown measures, including social distancing. At first, high schools and universities switched to online education; after one month, this was extended to all educational institutions. Restaurants, hotels, cinemas, theatres, and sports facilities were closed. A general ban on events was in place, so cultural and sports events were cancelled, while weddings and funerals could be organized with just 50 participants. Shops were first open until 7 pm, and later, all shops were closed, except for bakeries, grocery stores, and pharmacies. Curfew was in place between 8 p.m. and 5 a.m. Mask wearing was obligatory in outside places, too. Vaccination began in January 2021.
Sub-period 4 (May 2021–October 2021):
The second intermediate phase had lighter restrictions again, except for basic guidance regarding social distancing. Schools slowly returned to in-person education. Visiting hotels, cinemas, museums, and cultural and sports events was only permitted with a vaccination card. Weddings and funerals could be organized with a maximum of 200 participants. Outdoor events could be organized again with up to 500 participants.
Sub-period 5 (November 2021–March 2022): Third lockdown
The fourth and fifth wave of infections passed with lighter measures, e.g., hand hygiene fostering measures and mandatory face masks in indoor places. In-person education returned to schools. Shops were open with regular opening hours. Events were permitted for people with a vaccination card, with 200 participants in inner spaces and a maximum of 500 participants outdoors.

Table 2. COVID-19 pandemic-related restrictions in Hungary [57–63]

	1. sub-period	2. sub-period	3.sub-period	4. sub-period	5. sub-period
	Mar. 2020-May 2020	**June 2020-Oct. 2020**	**Nov. 2020-Apr. 2021**	**May 2021-Oct. 2021**	**Nov. 2021-Feb. 2022**
Nursery/Kindergarten	Close	Open	Open, but 08/Mar-07/Apr closed	Open	Open
Elementary School	Online education	Online education From September in person education	Under 14 years in-person education, over 14 years online education, but 08/Mar.-07/Apr for everyone online education	First, in-person education ≤10 years of age, then for everyone	In-person education
High School	Online education	Online education From September in person education	Online education	First, just online, then in-person education	In-person education
University	Online education	Online education	Online education	Hybrid education	Hybrid education
Hospitals	Visiting ban	Visiting allowed	Visiting ban	Visiting allowed	Visiting ban
Shops	Open until 3 p.m., except: pharmacy, bakery, grocery store, market	Normal opening hours	Open until 7 p.m., then 08/Mar-22/Apr closed except: pharmacy, bakery, grocery store, market	Normal opening hours	Normal opening hours
Purchase period for the elderly (over 65 years)	9 a.m.-12 a.m.	-	9 a.m.- 11 a.m. (weekends 8 a.m.-10 a.m)	-	-
Restaurants, Confectioneries	First open until 3 p.m. then just home delivery	Opening the terrace first, then the inner places	Just home delivery	Opening the terraces first , then the inner places with a proof of vaccination card	Open
Hotels	Close	Open	Closed, except: business, education	Receive guests only with proof of vaccination card	Receive guests only with proof of vaccination card
Cinema, Museum, Library, ZOO	Close	Permitted for all with a 1.5-meter protective distance	Close	Permitted only with proof of vaccination card	Permitted only with proof of vaccination card
Sport facilities (Gym, Swimming pools, etc.)	Close	Open with a 1.5-meter protective distance	Close	Permitted only with proof of vaccination card	Permitted only with proof of vaccination card

Events – Inner spaces	First maximum with 100 participants, then cancelled	Maximum of 200 participants	General ban on events	Parties permitted only with proof of vaccination card Family events, maximum 50 participants	Parties permitted only with proof of vaccination card maximum with 200 participants
Events - Outside	First maximum with 500 participants, then cancelled	Maximum of 500 participants	General ban on events	Maximum of 500 participants	Maximum of 500 participants
Cultural events	Cancelled	Permitted for all with a 1.5-meter protective distance	General ban on events	Permitted only with proof of vaccination card	Permitted only with proof of vaccination card
Weddings, funerals	Just with close family, weddings without a party	Limited maximum of 200 participants	General ban on events, just with close family, a maximum of 50 participants, weddings without party	Maximum of 200 participants	Maximum of 200 participants
Sport events	First, just without supporters/fans, then cancelled	Permitted for supporters with a 1.5-meter protective distance	-	Permitted only with proof of vaccination card	Permitted only with proof of vaccination card
Curfew	Abode, leaving just in case of emergency or work duties, or to the shops	Suspended	First between 0 a.m. and 5 a.m., then between 8 p.m. and 5 a.m.	First between 10 p.m. and 5 a.m., then suspended	Suspended
Mask wearing (Inner spaces)	Required in shops and on public transport	Required in shops, on public transport, in theatres, and in customer offices	Required everywhere	-	Required in shops, in shopping centers, post offices, in theatres, in cinemas, in museums, in sports events
Mask wearing (Outside)	-	-	Required first in outside events, then everywhere	-	-

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 3).

Table 3. 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 color: Before the COVID-19 pandemic period (24 months),
- Red color: COVID-19 pandemic period (24 months),
- Green color: 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 commonly 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 [53].

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 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 [64–67].

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 outcomes from treatment, and address the worldwide problem of antimicrobial resistance, the WHO created the AWaRe framework, which groups the antibiotics into three categories: Access, Watch, and Reserve [50,68,69].

- **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 [50].
- **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) [50].
- **Reserve antibiotics:** These are last-resort drugs reserved for the treatment of infections caused by multidrug-resistant pathogens [50].

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 4. 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 4. Means of systemic antibiotic use in the two main periods.

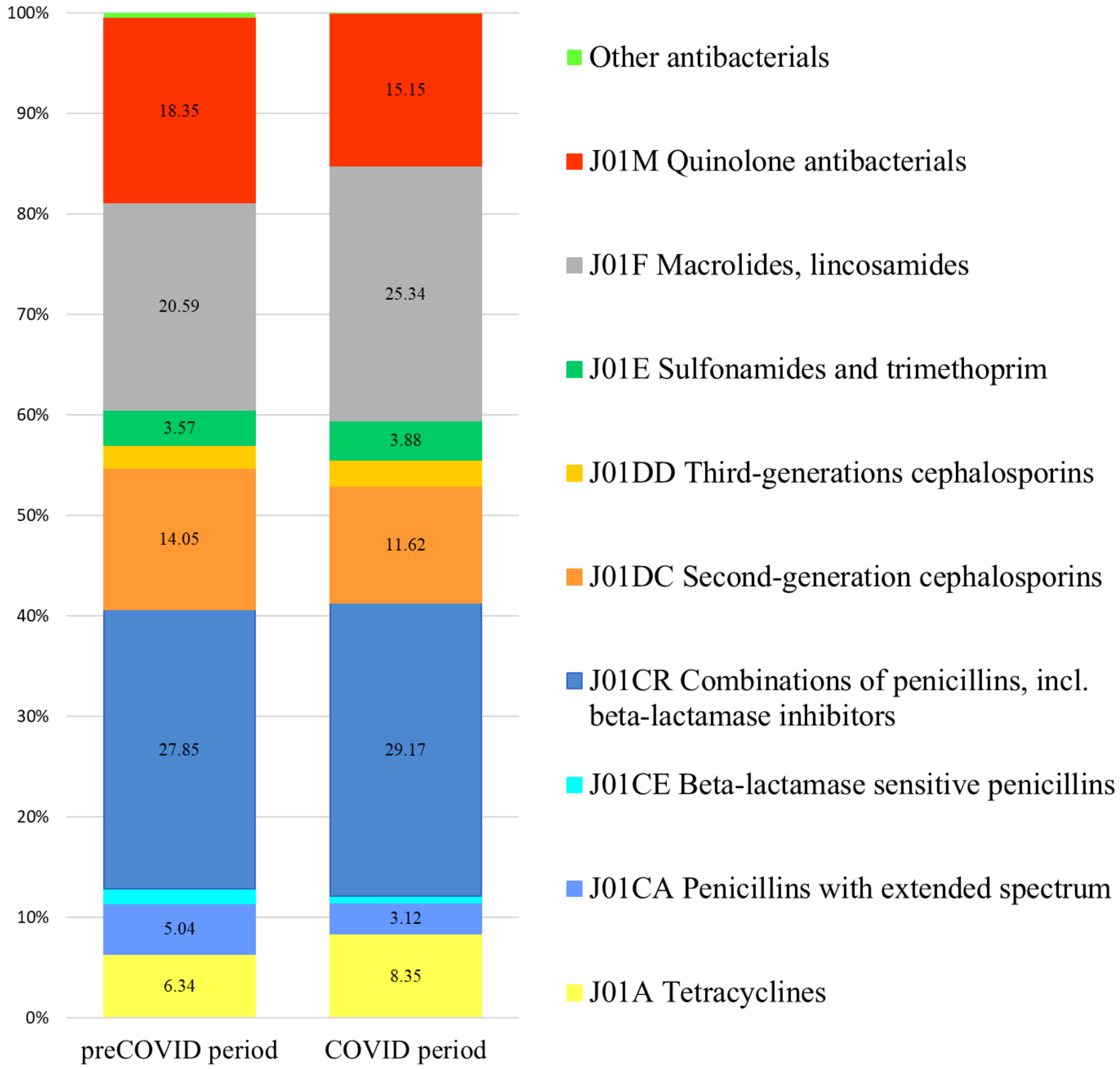
	preCOVID period Jan. 2015-Dec. 2019		**COVID period** Jan. 2020- Feb. 2022	
	DID[1]	**%**	**DID**[1]	**%**
J01A Tetracyclines	0.77	6.34	0.78	8.35
J01CA Penicillins with extended spectrum	0.61	5.04	0.29	3.12
J01CE Beta-lactamase sensitive penicillins	0.17	1.41	0.06	0.65
J01CR Combinations of penicillins, 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 Pattern of Systemic Antibiotic (J01) Use

There were some differences in the antibacterial use pattern between the pre-COVID and COVID period. The relative use different antibacterial classes are shown in Figure 2. During both periods, the most used antibiotic classes were broad-spectrum penicillins (Penicillin combinations-J01CR), second-generation cephalosporins (J01DC), quinolones (J01M) and macrolides (J01F). Notably, relative use of macrolides increased from 16.53% to 20.34%. Similarly, the proportional use of tetracyclines (J01A) increased from 6.36% to 8.35%. In contrast, a minor decline was observed in the relative use of quinolones (J01M), which decreased from 18.35% to 15.15%. (Table 4, Figure 8.)

Figure 8. Pattern of systemic antibiotic use (J01) in the two main periods.



4.1.3 Top 10 list of antibacterial use

The top ten list of antibacterial in the two main periods is shown in Table 5, 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 5. 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

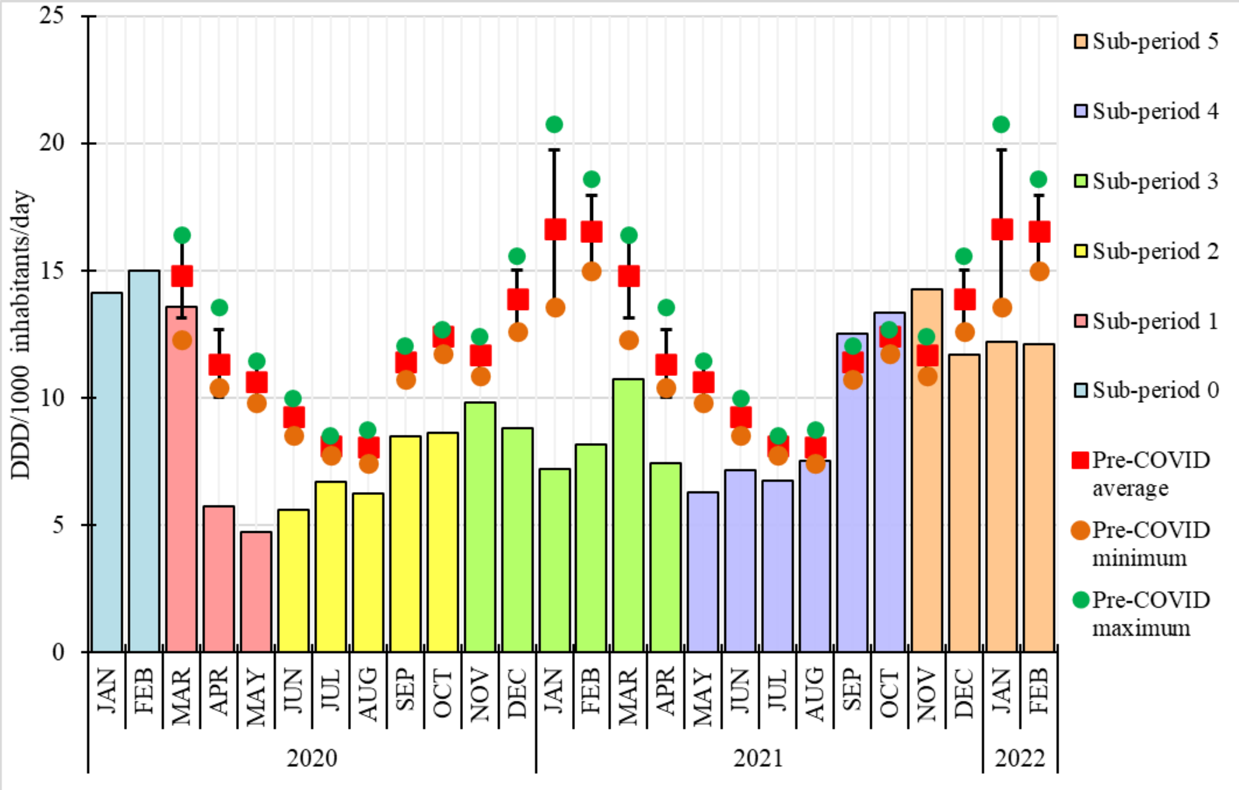
[1] DID: DDD per 1000 inhabitants per day; [2] cum%: cumulative percentage; [3] AMC: amoxicillin and clavulanic acid;
[4] SMX-TMP: sulfamethoxazole and trimethoprim.

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

Figure 9 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 its lowest point 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.

Figure 9 The time trends of the systemic antibiotic (J01) use



Colored 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.

4.1.5 Trends in Antibacterial Subgroup Use

Figures 10–13 display the monthly usage trends of various antibiotic subgroups (J01C, J01D, J01F, J01M) during the COVID-19 period, along with the corresponding monthly mean values from the pre-COVID period.

The usage patterns of antibiotic subgroups are compared in these figures, which also illustrate trends and differences resulting from the pandemic's impact on outpatient antibiotic use.

Regarding the two beta-lactam subgroups (see on Figure 10.-11.), both penicillin and cephalosporin use followed the trends of systemic antibiotic use. In April 2021, the utilization of co-amoxiclav (J01CR02) was reduced by half. This decreased use persisted until September 2021, when co-amoxiclav use resumed.

Figure 10 The time trends of Beta-lactam antibacterials: Penicillins (J01C)

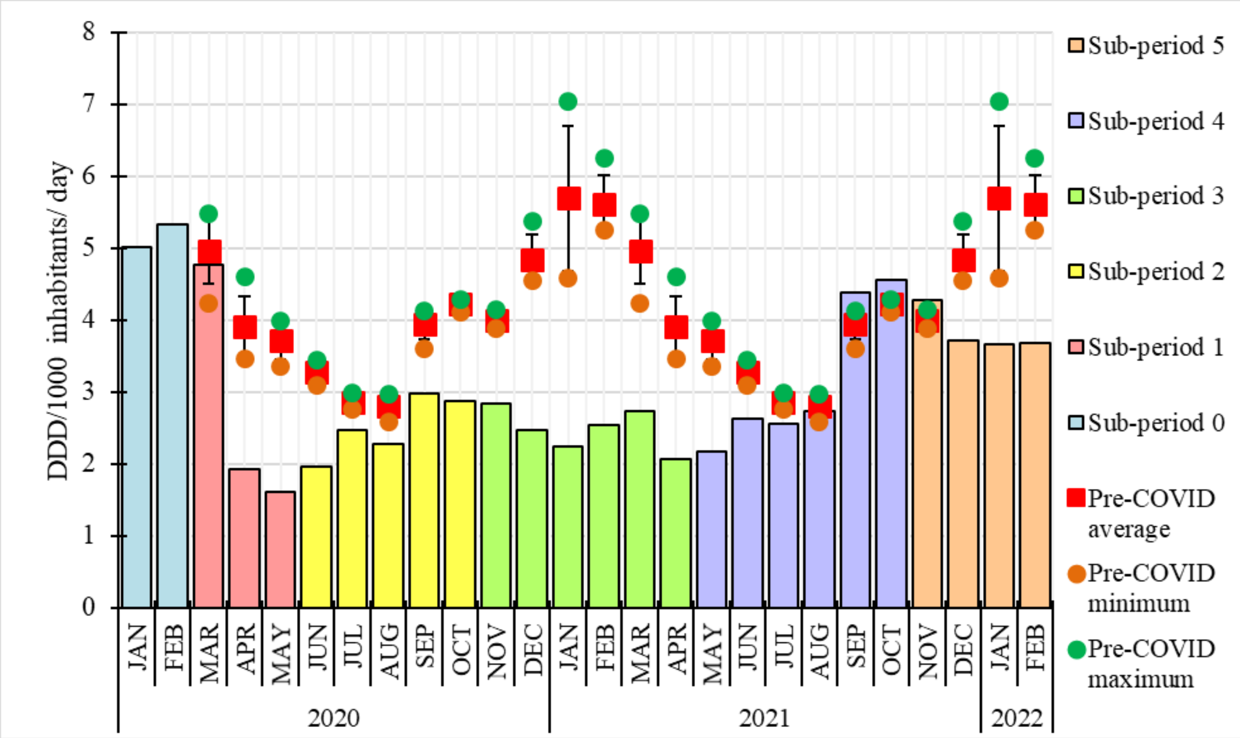


Figure 11. The time trends of Cephalosporins (J01D)

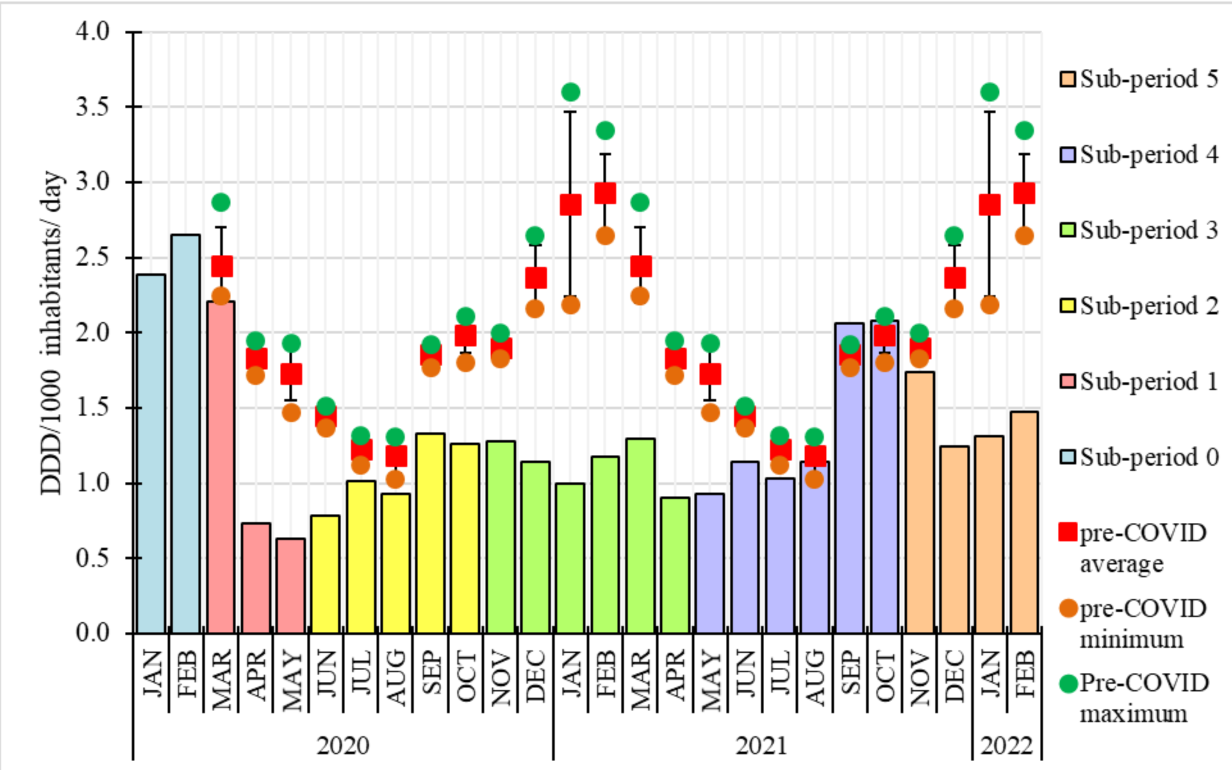
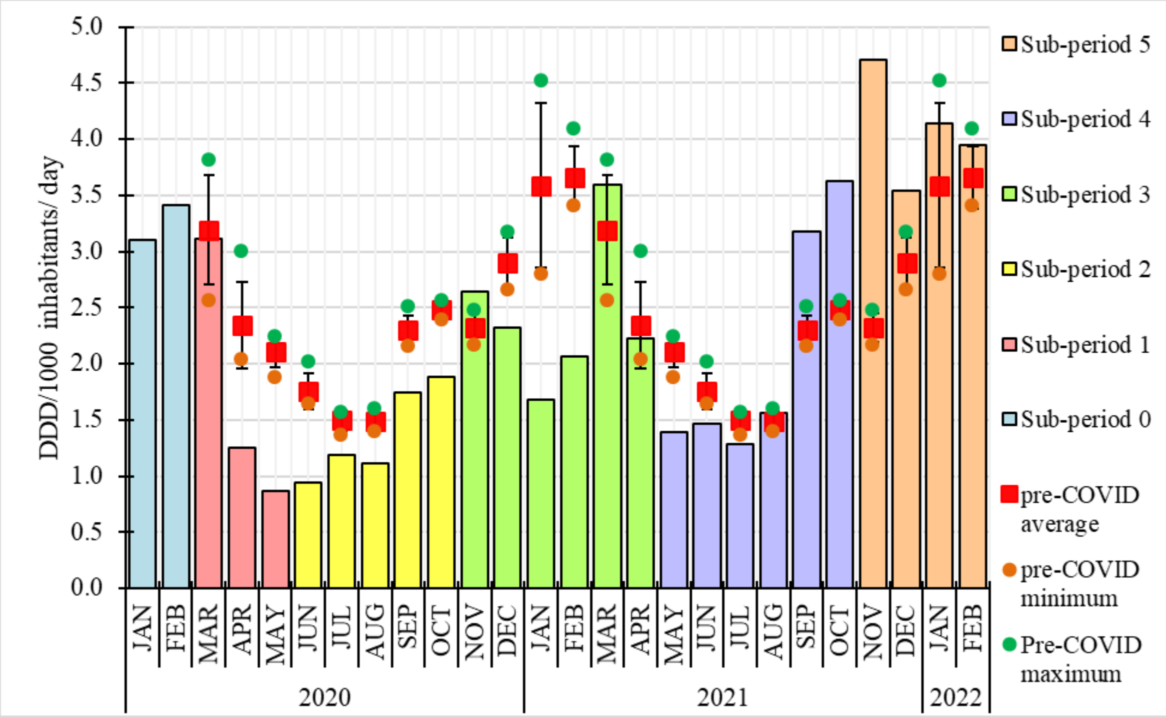


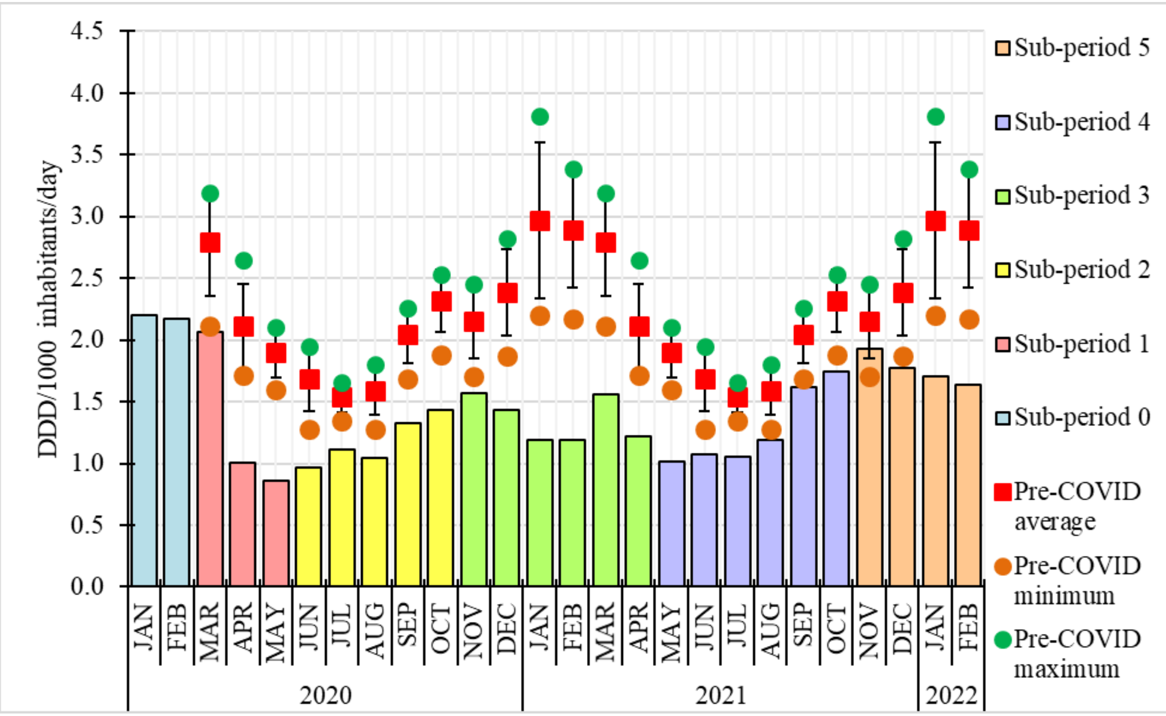
Figure 12. The time trends of Macrolides (J01F)



Macrolide use during the COVID-19 period had different trends (Figure 12). It first peaked in March 2021, and after a summer nadir a second increment started in September 2021. In comparison, from September 2021, it consequently and significantly exceeded the pre-COVID monthly means. The highest peak in the use of macrolides was in November 2021 (4.71 DDD per 1000 inhabitants per day).

The subgroup of quinolones was the only antibacterial subgroup where the monthly scale of antibiotic use during the pandemic never reached the pre-COVID period's monthly means.

Figure 13. The time trends of Quinolone antibacterials (J01M)



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/1,000 inhabitants/day (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 6. 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 6.).

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 6.). 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 6.). Through the study period, 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 6).

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 6.).

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 6.).

Table 6. The mean monthly antibiotic use in the three study periods expressed as DDD per 1000 inhabitants per day - DID)

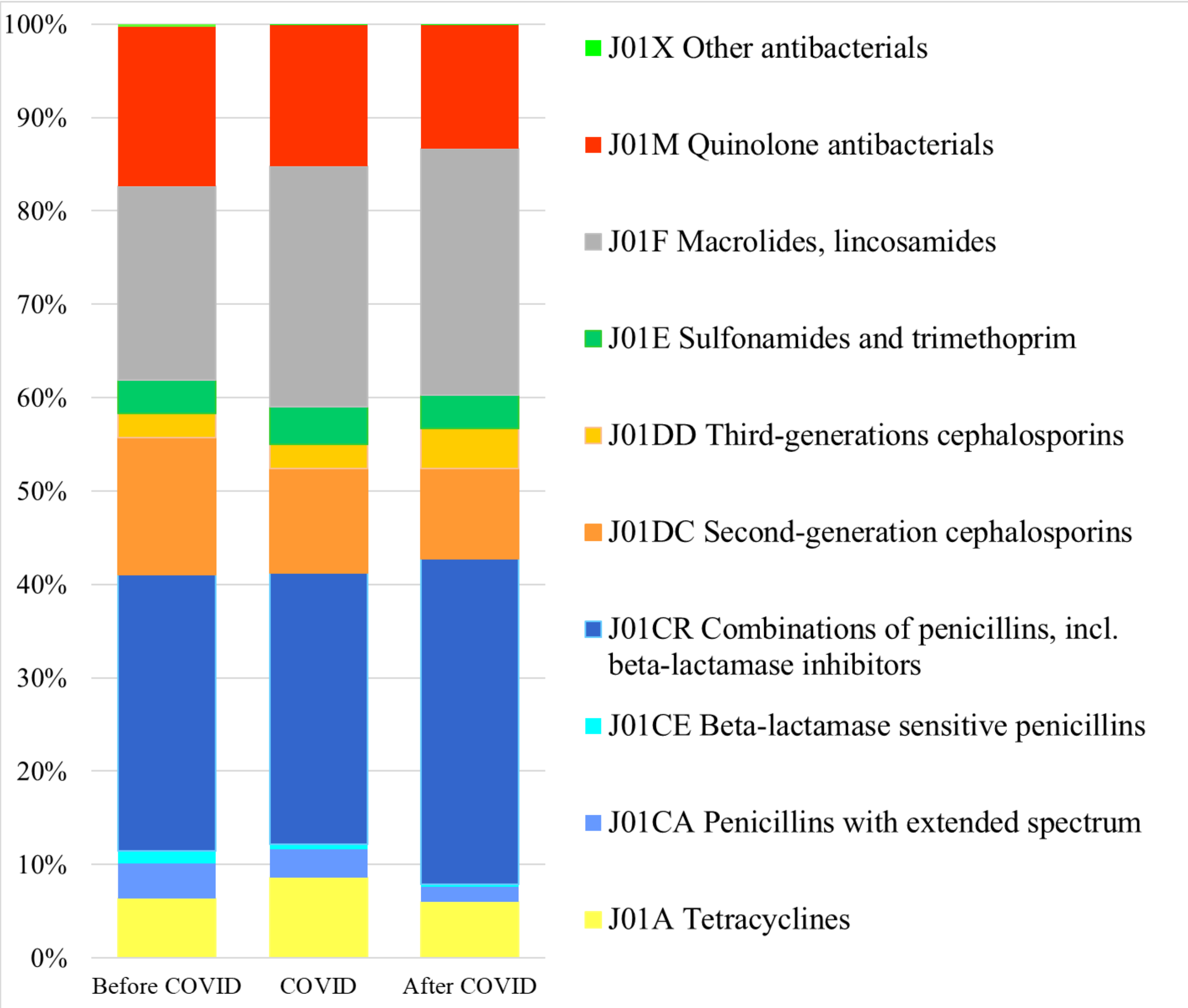
	Before COVID Period March 2018 – February 2020		**COVID Period March 2020 – February 2022**		**After COVID Period March 2022 – February 2024**		**p***
	DID (mean) ± SD	**min - max**	**DID (mean) ± SD**	**min - max**	**DID (mean) ± SD**	**min - max**	
J01A Tetracyclines	0.74 ± 0.15	0.45 – 1.05	0.77 ± 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 Pattern of Systemic Antibiotic (J01) Use

During all three study periods, there were differences in the patterns of antibacterial usage. Beta-lactam antibacterials (J01C and J01D), was continuously accounting for the highest relative use as seen in Figure 14. Through all time periods, penicillin and beta-lactamase inhibitor combinations (J01CR) retained the highest relative share within this group. Before the pandemic, there was a notable decrease in the use of narrow-spectrum beta-lactamase-sensitive penicillins (J01CE), and this trend remained during and after the pandemic. There was a decrease in the relative use of second-generation cephalosporins (J01DC) throughout the periods. On the other hand, the relative use of third-generation cephalosporins (J01DD) increased significantly in the post-COVID period. The relative use of macrolides (J01FA) increased significantly both during and after the pandemic, while the absolute use of this group initially slightly decreased during the pandemic and after that increased. In the meantime, the relative use of quinolones (J01M) decreased slightly in the pandemic period and continued to decrease in the After COVID period.

Figure 14. The proportional share of different antibacterial subgroups



4.2.3 *Top 10 list of antibacterial use*

The top 10 antibacterial agents during the study periods are shown in Table 7. 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. Changes in the distribution of Access and Watch group agents are also shown in Table 7. The after-pandemic top list had more agents from the Watch group compared to pre-pandemic and pandemic periods.

4.2.4 *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 8. 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. Figures 15–19 illustrate these trends.

Table 7. The most used top 10 antibacterials (J01) in the three study periods The green color represents the Access group antibacterials based on the WHO's AWARE classification, 2023.

	Before COVID Period					COVID-19 Period					After COVID Period				
	March 2018 - February 2020					March 2020 – February 2022					March 2022 – February 2024				
No.	**ATC Code**	**Substance**	**DID [1]**	**%**	**Cum% [2]**	**ATC Code**	**Substance**	**DID [1]**	**%**	**Cum% [2]**	**ATC Code**	**Substance**	**DID [1]**	**%**	**Cum% [2]**
1.	J01CR02	co-amoxiclav	3.43	29.55	29.55	J01CR02	co-amoxiclav	2.60	28.90	28.90	J01CR02	co-amoxiclav	4.00	34.78	34.78
2.	J01DC02	cefuroxime	1.34	11.52	41.06	J01FA10	azithromycin	1.40	15.55	44.45	J01FA10	azithromycin	1.98	17.20	51.98
3.	J01FA10	azithromycin	1.22	10.47	51.54	J01DC02	cefuroxime	0.70	8.84	53.29	J01MA12	levofloxacin	0.73	6.40	58.38
4.	J01MA12	levofloxacin	1.00	8.59	60.13	J01AA02	doxycycline	0.77	8.61	61.90	J01AA02	doxycycline	0.68	5.95	64.33
5.	J01AA02	doxycycline	0.74	6.36	66.49	J01MA12	levofloxacin	0.60	6.69	68.58	J01DC02	cefuroxime	0.64	5.58	69.61
6.	J01FA09	clarithromycin	0.66	5.65	72.13	J01FF01	clindamycin	0.47	5.27	73.85	J01FA09	clarithromycin	0.57	4.99	74.91
7.	J01MA02	ciprofloxacin	0.58	4.97	77.11	J01MA02	ciprofloxacin	0.46	5.15	79.01	J01DD08	cefixime	0.49	4.30	79.20
8.	J01FF01	clindamycin	0.49	4.25	81.36	J01FA09	clarithromycin	0.43	4.74	83.75	J01MA02	ciprofloxacin	0.48	4.20	83.40
9.	J01CA04	amoxicillin	0.43	3.70	85.06	J01EE01	SMX-TMP [3]	0.36	3.96	87.71	J01FF01	clindamycin	0.47	4.13	87.53
10.	J01EE01	SMX-TMP [3]	0.42	3.62	88.68	J01CA04	amoxicillin	0.27	2.99	90.70	J01DC10	cefprozil	0.45	3.90	91.93

[1]DID: DDD per 1000 inhabitants and per day; [2]cum%: cumulative precentage; [3]SMX-TMP: sulfamethoxazole and trimethoprim

Table 8. 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

Figure 15. Time series of co-amoxiclav (J01CR02) exposure

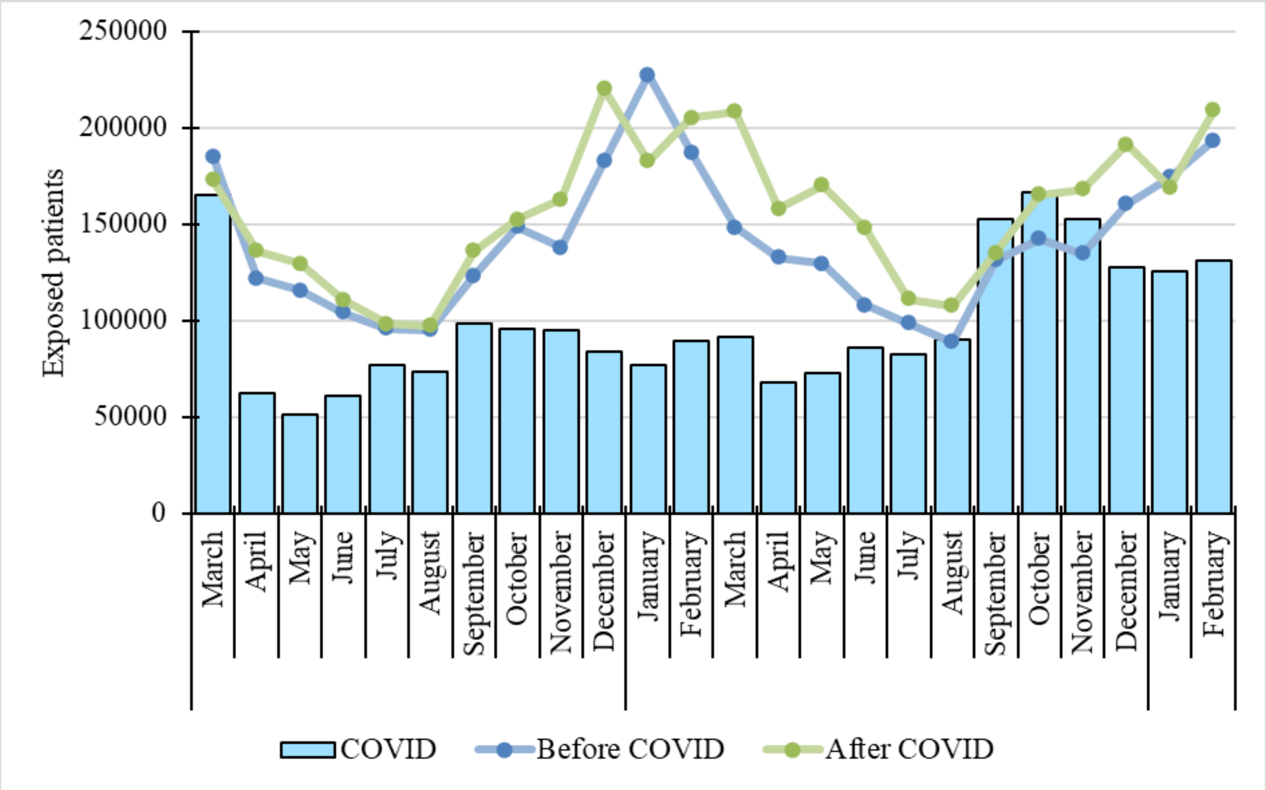


Figure 16. Time series of azithromycin (J01FA10) exposure

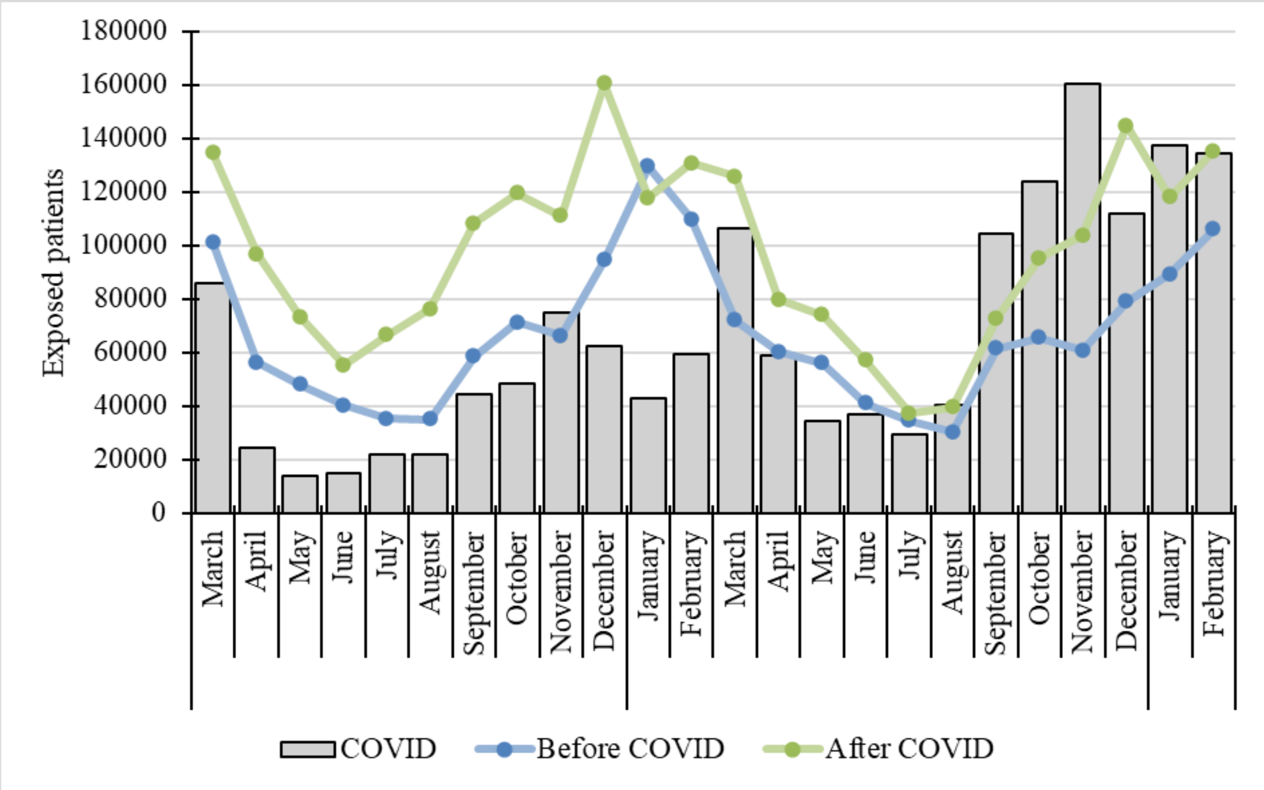


Figure 17. Time series of cefuroxime (J01DC02) exposure

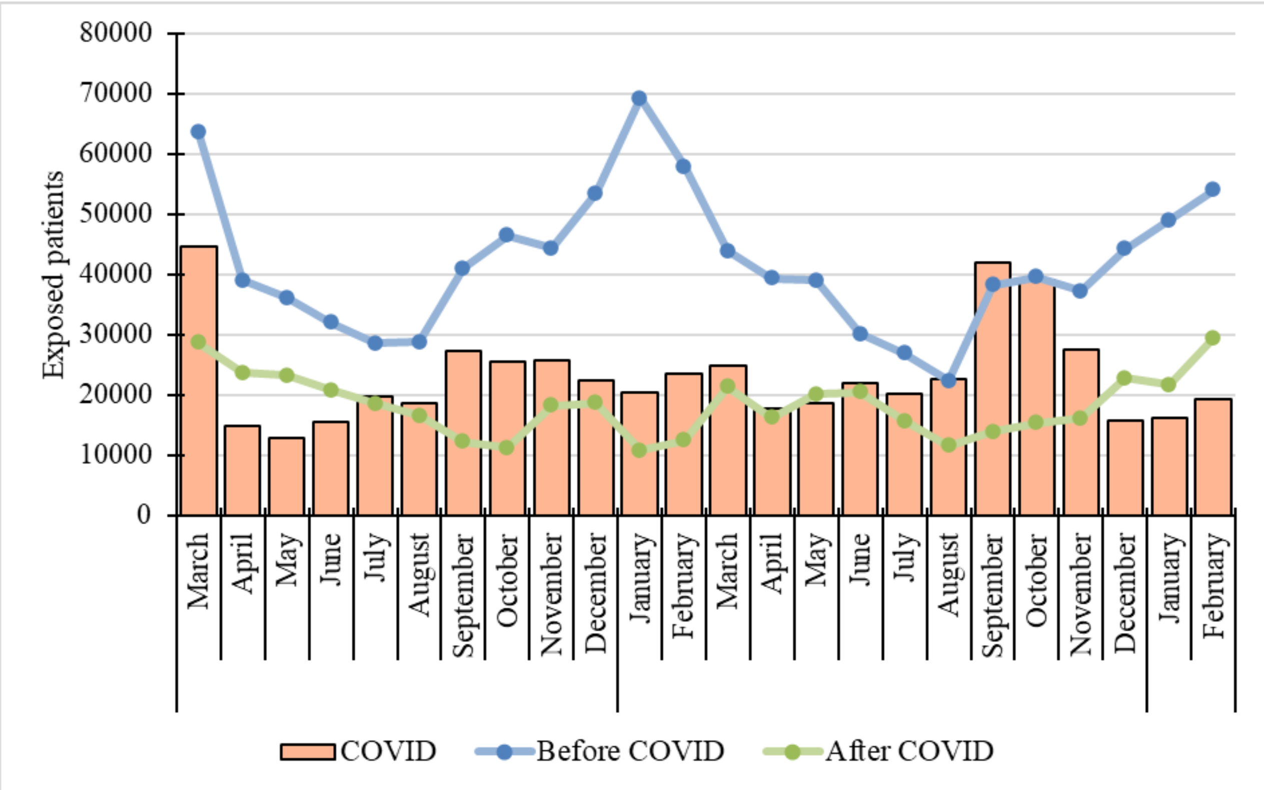


Figure 18. Time series of levofloxacin (J01MA12) exposure

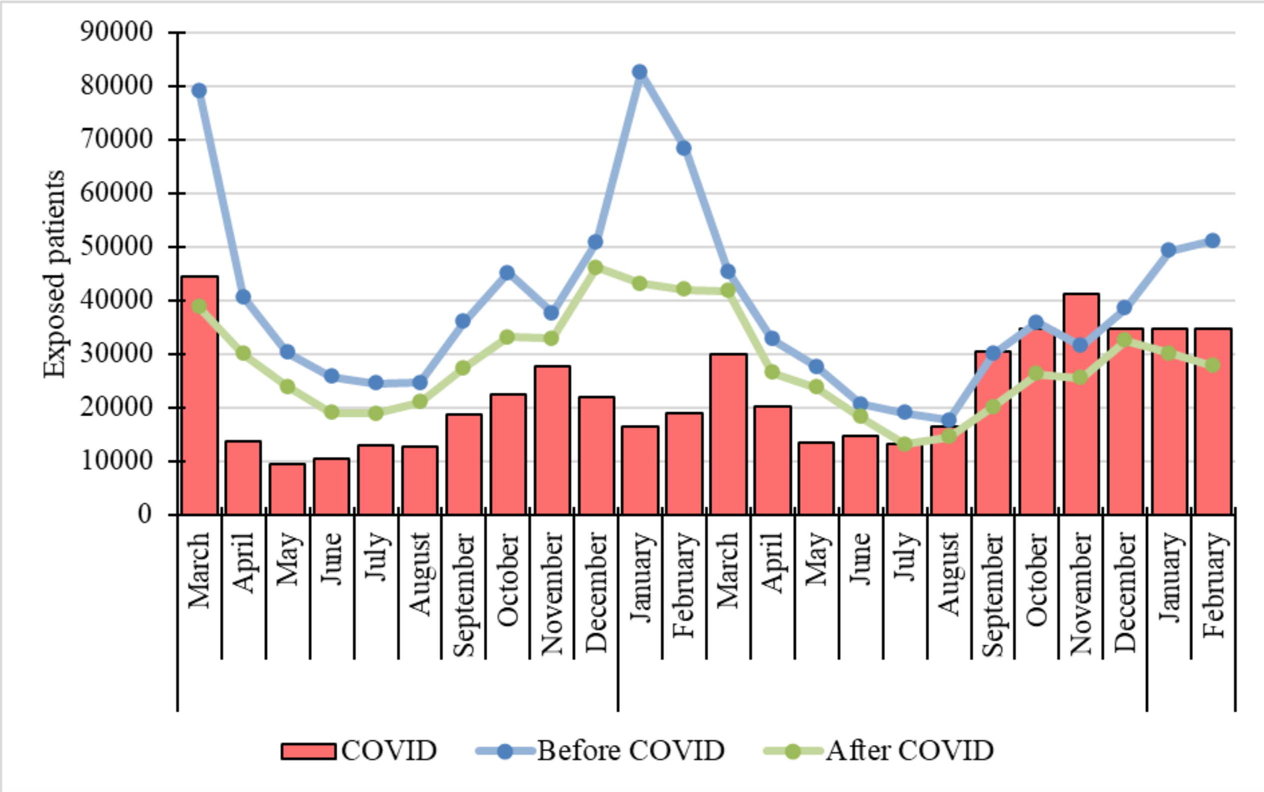
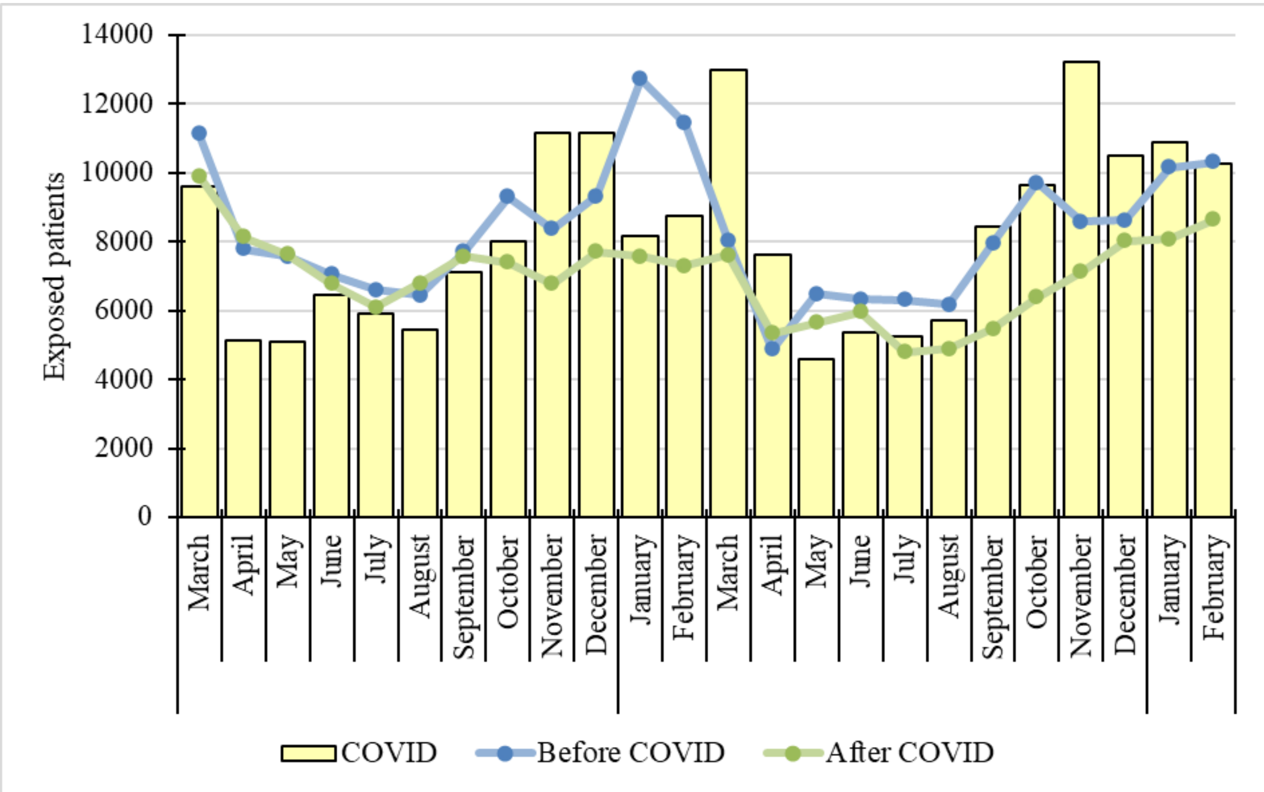


Figure 19. Time series of doxycycline (J01AA02) exposure



4.2.5 *Antibiotic use based on AWaRe Classification*

Figure 20 shows the distribution of antibiotics based on the WHO AWaRe classification (Access, Watch, and Reserve categories) across the three periods. The Access Category (green color remained stable across all three periods with ~ 50% relative share. Antibiotics in the Watch group (yellow color) also showed consistent usage across the periods. They represented around 50% of the total antibiotic use, indicating a persistent reliance on these antibiotics. Reserve antibiotic use (red color), remained negligible in all three periods in the Hungarian ambulatory care. In summary, there have been no significant changes in the distribution of AWaRe categories during the study periods.

Figure 20. Trends in AWaRe Antibiotic Use Before, During, and After COVID-19

4.2.6 *Seasonal Variation in Systemic Antibiotic Use*

The seasonality indexes (J01_SV) for the three study periods are shown in Table 9. 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 (J01FA), 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 9, the seasonality index decreased after the pandemic for all other antibacterial subgroups.

Table 9. Seasonality index for the different antibiotic subgroups during the study periods.

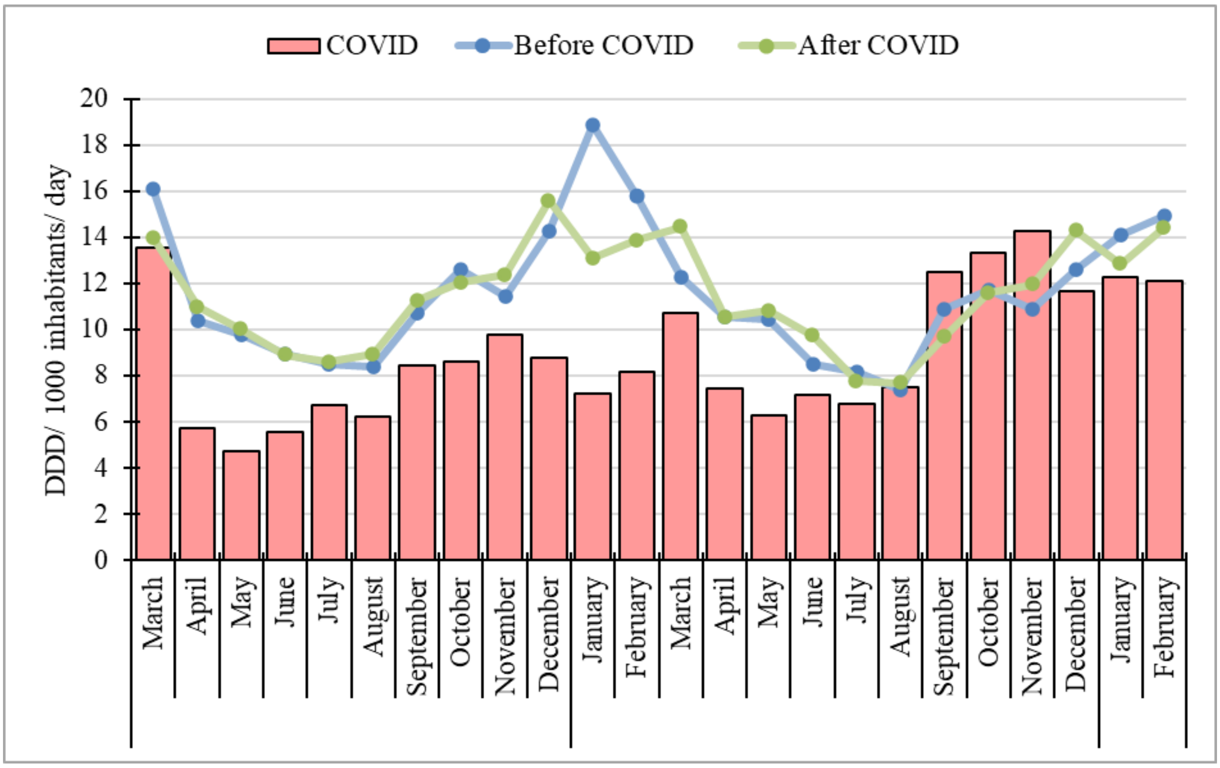
Seasonality index+			
	Before COVID Period Mar. 2018-Feb.2020	**COVID Period** Mar. 2020-Feb. 2022	**After COVID Period** Mar. 2022-Feb. 2024
J01A Tetracyclines	38.92	60.29	22.48
J01CA Penicillins with extended spectrum *			
J01CE Beta-lactamase sensitive penicillins *			
J01CR Combinations of penicillins, 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 [65]

4.2.7 Time Trends of Systemic Antibacterial Use

Figure 21 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 is shown in Figures 22–25. 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 21. 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.

Figure 22. Time series of beta-lactam antibacterials, penicillins (J01C) use

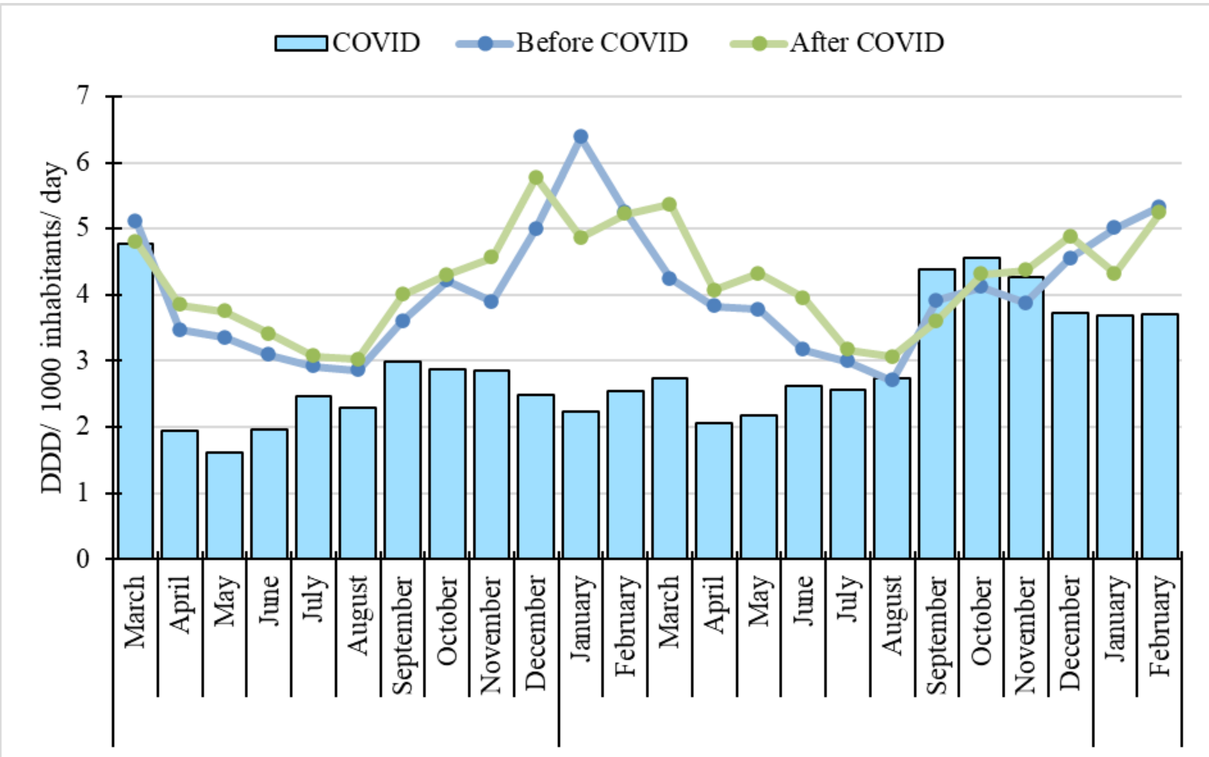


Figure 23. Time series of cephalosporins (J01D) use

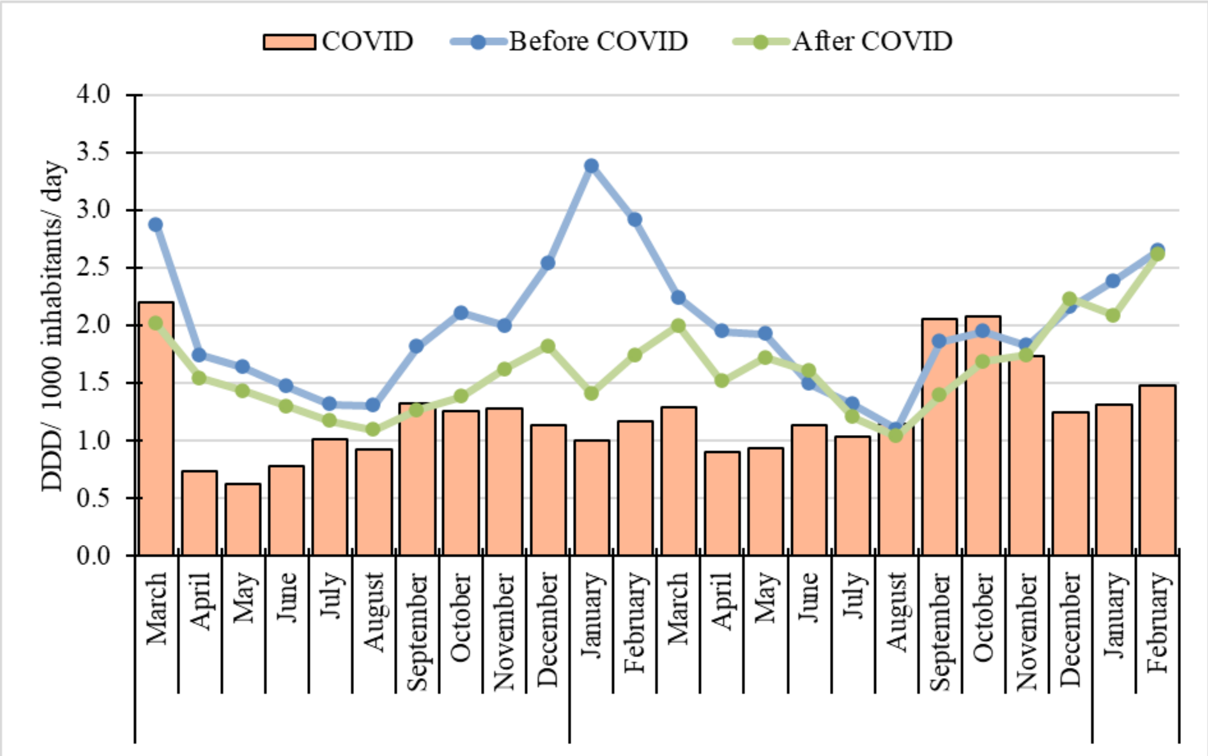


Figure 24. Time series of macrolides, lincosamides (J01F) use

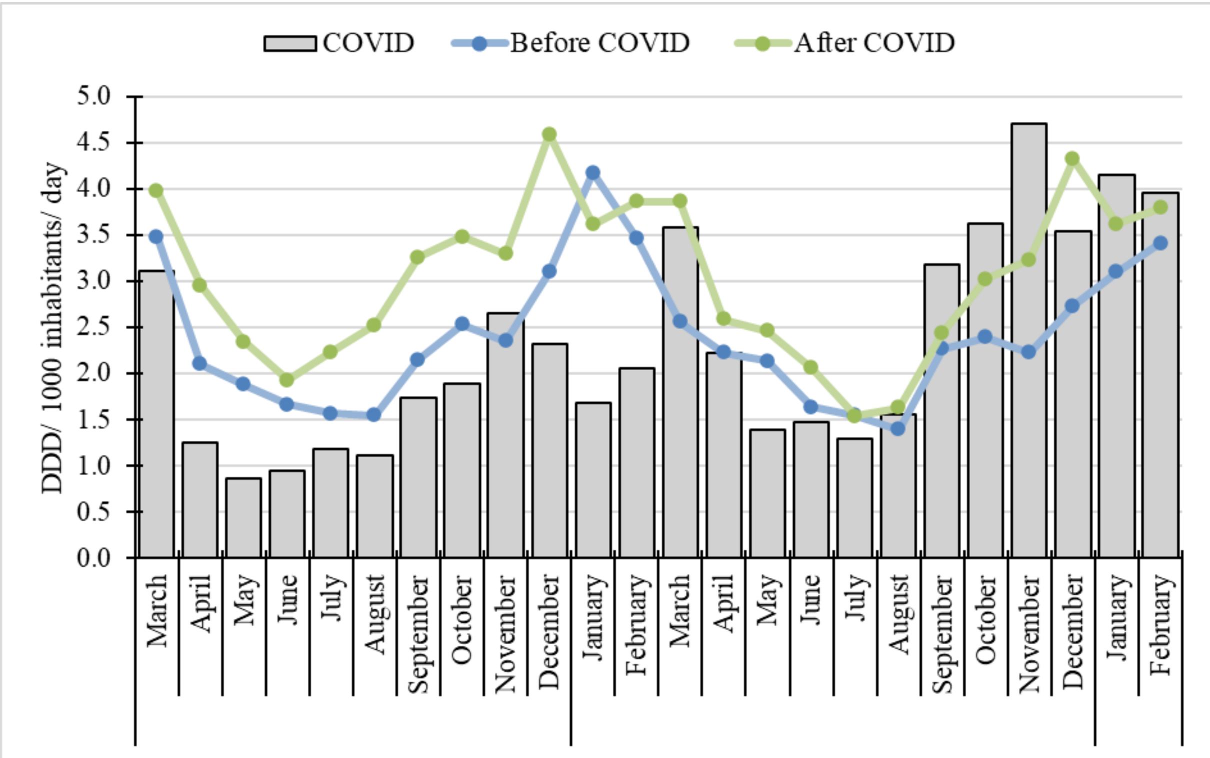
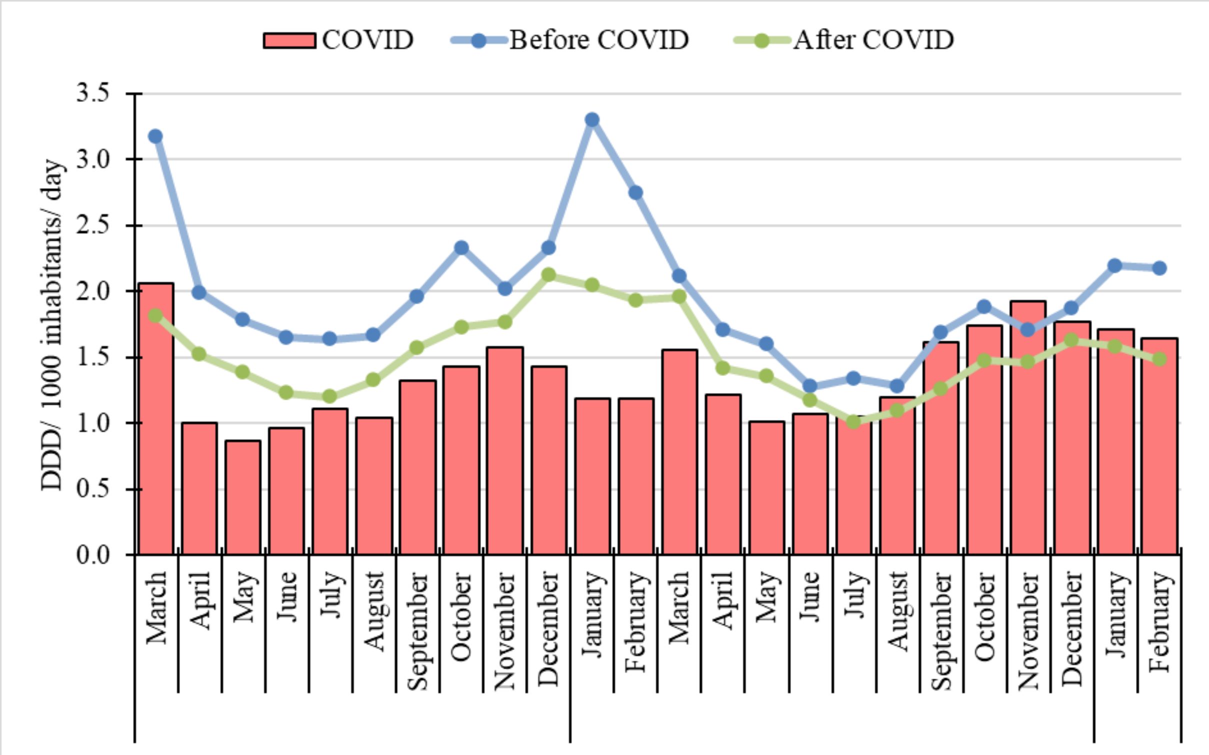


Figure 25. Time series of quinolone antibacterials (J01M) use



5. DISCUSSION

5.1 Discussion for Study 1

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

5.1.1 Summary of Key Findings

Our study revealed a remarkable 23.22% reduction in the total use of systemic antibiotics in ambulatory care during the COVID-19 period compared to the pre-COVID period. To the best of our knowledge, this was the first analysis of ambulatory care antibiotic use in a Central European country during the COVID-19 pandemic and one of the few drug utilization studies spanning two full years of the pandemic (January 2020–February 2022). However, it is essential to note that comparisons with other studies should be approached with caution due to variations in study periods and reported outcome measures. In addition, we defined somewhat differently the pre- and COVID period in our two studies, hence, concrete values in the comparisons slightly differ and requires alertness in reporting.

5.1.2 International benchmarking

5.1.2.1 <u>Systemic antibiotic (J01) level</u>

The decline in systemic antibiotic use in ambulatory care was also observed in other countries during the pandemic. *Portuguese* researchers examined how the pandemic affected antibiotic use in 2020 and detected that ambulatory care antibiotic prescriptions had significantly decreased. In 2018, 2019, and 2020, their statistics revealed that systemic antibiotic use (J01) was 9.65, 9.62, and 7.04 DDD per 1000 inhabitants per day, respectively. Also, according to monthly analysis of data, systemic antibiotic use in *Portugal* decreased by about 45% during the early pandemic months (April and May 2020) when compared to the same months in the preceding two years [70]. This finding is similar to the Hungarian data, which showed a 55.46% decrease in May 2020 when compared to the monthly averages of the same month (May) before the COVID-19 pandemic. In a *Spanish region (Navarre)*, the number of patients receiving systemic antibiotics decreased sharply between the first and second quarters of 2020 (18.48 DID in Q1 vs. 9.85 DID in Q2). This lower level remained steady throughout 2020 and 2021, ranging from 10.11 to 10.95 DID, before starting to rise in the fourth quarter of 2021 (14.12 DID) [71]. In *Canada*, the most significant decline in national antibiotic prescriptions dispensed per 1000 inhabitants per day was recorded in May 2020, representing a 39.56% decrease compared to May 2019 [72]. Similarly, a *Belgian* study focused on out-of-hours services revealed that the number of antibiotic prescriptions per weekend per 100,000 inhabitants dropped by 42.9% immediately after the lockdown was implemented [73]. Researchers examined patterns of general practice issued antibiotic prescriptions during the COVID-19 pandemic in the *Netherlands*. They analyzed weekly antibiotic prescription rates per 100,000 inhabitants and evaluated changes during different pandemic phases, which were defined identical to the Hungarian definition of phases (COVID Phase 0=Sub-period 0, Phase 1=Sub-period 1, Phase 2=Sub-period 2, Phase 3=Sub-period 3, Phase 4=Sub-period 4). The average number of antibiotic prescriptions in the *Netherlands* decreased by 17.3% in Phase 1 and

22.74% in Phase 3 compared to pre-pandemic levels. Different outcome measures make direct comparisons difficult, but the Dutch results are consistent with those in Hungary, where significant declines were found in sub-periods 1 and 3 [74]. In *Finland*, a sharp decrease in prescriptions per 1,000 inhabitants in the J01 group was observed during the first two years of the pandemic. Before the pandemic, the monthly number of antibiotic prescriptions was 248,590 in *Finland*, with a decreasing trend of 1,202 prescriptions per month. After the pandemic began, there was a decline of 48,470 prescriptions per month in *Finland (-19.5%)* [75]. Based on a cross-national comparison study published in 2023 - which summarized outpatient antibiotic use data from 28 countries in the *EU/EEA* - the average systemic antibiotic consumption (ATC: J01) decreased by 3.4 DID (from 18.36 DID to 14.95 DID, -18.6%) between 2019 and 2020. Afterwards, the *EU/EEA* average of systemic antibiotic use increased slightly (+0.03 DID, +0.20%). The largest decline in antibiotic use between 2019 and 2020 was observed in *Austria* (-27.23%), while the smallest decrease occurred in *Romania* (-1.21%). Between 2020 and 2021, the highest increase was observed in *Slovakia* (+10.49%), whereas the largest decrease was noted in *Greece* (-17.41%) [76]. Based on a follow-up article published in 2024, which processed data from these 28 *EU/EEA countries*, systemic antibiotic consumption continued to increase in 2022. It was 18.04 DID in 2022 from 18.89 DID in 2021, corresponding to a +3.06% absolute change in overall consumption of systemic antibiotics (J01) in the EU/EEA countries. Between 2021 and 2022 the largest absolute increase was in *Greece, Malta and Slovakia* in the overall antibiotic consumption (>+5.0 DID), while the smallest was in *Estonia* and in the *Netherlands* (<+1.0 DID) [77].

In contrast to the reported findings all other countries including our findings in Hungary, a study conducted in the *Republic of Srpska (region of Bosnia-Hercegovina)* observed a 53.80% increase in systemic antibiotic use (J01) in outpatient settings from 2019 to 2020 (from 20.24 DID to 31.13 DID) mostly due to increase in the utilization of some agents, for example amoxicillin, cefixime, azithromycin or levofloxacin. Although neither edition of the COVID-19 treatment protocol, issued by an expert groups of the *Republic of Srpska*, recommended the use of antibiotics for COVID-19 outpatients, at least one antibiotic prescription was prescribed for 91.04% of COVID-19 outpatients in Banja Luka County (*Republic of Srpska*) during 2020 [78].

5.1.2.2 Antibiotic subgroup and substance level analysis

Analysis of the Beta-lactam antibacterials, penicillins (J01C) subgroup

In our research a significant reduction was observed in the use of several antibacterial subgroups in the COVID period (January 2020 – February 2022). In the case of the most commonly utilized subgroup, the penicillins (J01C) the absolute use showed 26% decrease (see Table 4.), which corresponded with the drop in relative use of this group (from 34.28% to 32.91%). In addition, the Penicillin combinations (J01CR), experienced approximately 20% decline during the COVID-19 period compared to pre-pandemic period (January 2015 – December 2019) averages in Hungary (see Table 4.). Similarly, in a *Canadian region (Ontario)* the mean monthly prescriptions for penicillin combinations (J01CR) decreased by 21.85% during the pandemic (March – December 2020) [79]. The penicillins' use decreased by 42% in the *US*, which was the largest reduction among antibiotic classes [80]. In the *US*, the most notable decrease was seen in co-amoxiclav prescriptions in the fourth quarter of 2020 (October to December), as the average monthly use was 40% lower than expected [81]. The J01C group (Penicillins) showed a clear decline across all quarters during the pandemic year (2020) in a *Spanish region (Navarre)*. Compared to 2019, significant decreases were observed in Q2 of 2020 (from 9.16 DID in 2019 to 4.86 DID in 2020) and Q3 (from 7.52 DID in 2019 to 5.06 DID in 2020), with a slight recovery beginning in Q4 of 2021 (7.23 DID). Between 2019 and 2021 comparing the same quarters, the use of co-amoxiclav in *Spain (Navarre region)* showed a consistent decline, with reductions of 43% in Q1, 33% in Q2, 24% in Q3, and 16% in Q4 [71]. During the study period (2018–2020) in the *Republic of Srpska*, Penicillins (J01C) were the most frequently used antibacterial subgroup in the ambulatory care sector. In contrast to our findings, the use of this antibiotic subgroup increased by 61.31% in 2020 (17.12 DID) compared to 2019 (10.61 DID). At the substance level, amoxicillin was the most commonly used antibacterial agent in the *Republic of Srpska*, with its utilization doubling (a 100.08% increase) in 2020 compared to 2019. The use of co-amoxiclav also exhibited an increase of 8.32% during the same period [78]. In the *EU/EEA*, penicillin group (J01C) use initially decreased by 1.92 DID in average (-22.97%) between 2019 (8.36 DID) and 2020 (6.44 DID). The decrease in Penicillin use was significantly higher than the *EU/EEA* average in *France, Greece, Ireland*, and *Spain*, while it was lower in *Bulgaria*, *Estonia*, *the Netherlands*, and *Norway* [76]. However, in 2021 followed by a slight increase of 0.08 DID (+1.24%) from 2020 to 2021 (6.52 DID) in the J01C group, which continued in 2022 [77].

Analysis of Cephalosporins (J01D) subgroup

Our findings show that in the Hungarian outpatient sector the absolute use of cephalosporins (J01D) decreased by 32% (see Table 4), which corresponded to a drop from 16.25% to 14.24% in the relative use of cephalosporins in the pandemic period. Regarding subgroups, the use of second-generation cephalosporins (J01DC) decreased by 36% (see Table 4) in the outpatient care, while the relative use of J01DC group dropped from 14.05% to 11.62% (comparing pre-COVID period to the pandemic period). In a *Spanish region (Navarre),* there was a notable decrease in the use of cephalosporins (J01D) during the pandemic, in comparison to 2019. In Q2, its use dropped from 1.98 DID in 2019 to 1.45 DID in 2020, and further decreased in Q3 from 1.83 DID in 2019 to 1.69 DID in 2020. A slight increase was seen in Q4 of 2021, reaching 2.09 DID. Furthermore, comparing 2019 and 2021, a significant decrease in cefuroxime use was observed in the first two quarters of 2021 (Q1 2019: 1.56 DID to Q1 2021: 1.12; Q2 2019: 1.32 DID to Q2 2021: 1.16 DID), while a moderate decrease was observed in the latter two quarters [71]. Cephalosporin use decreased by 33% in the *US*, which was the third-largest reduction among antibiotic classes [80]. In the *Republic of Srpska* the utilization of cephalosporins (J01D) rose significantly by 121.40% between 2019 and 2020. Among the cephalosporins, first- and third-generation cephalosporins (J01DB, J01DD) showed increases of 200% and 39.96%, respectively, while second- and fourth-generation cephalosporins (J01DC, J01DE) experienced declines of 14.75% and 89.83%, respectively.[78]. Across the *EU/EEA*, the consumption of cephalosporins (J01D) decreased during both years (2019 vs.

2020: -0.58 DID, -25.78%; 2020 vs. 2021: -0.08 DID, -4.79%). In *Germany, Greece, Poland, and Slovakia*, the reduction of cephalosporin use (J01D) was higher than the average in the *EU/EEA*, while it was lower in *Denmark, the Netherlands, Slovenia, and Sweden* [76]. However, a slight increase was observed in the EU/EEA countries from 2021 to 2022 (population weighted average of +0.49 DID, + 30.82%) [77].

Analysis of Fluoroquinolones (J01M) subgroup

In our research the fluoroquinolone (J01M) consumption declined by 36.5% during the COVID-19 period, compared to pre-COVID level ambulatory sector use (see Table 4). They also witnessed a substantial decline in fluoroquinolone use in a *Spanish region (Navarre)* measured as DID, particularly in Q2, where J01M use decreased from 1.60 DID in 2019 to 0.89 DID in 2020. In Q3, there was comparable decrease (1.29 DID in 2019 to 0.92 DID in 2020). By Q4 of 2021, the fluoroquinolone uses partially rebounded to 1.20 DID *in Navarre (Spain)*. This Spanish study showed a decline in levofloxacin use between 2019 and 2021, as significant decreases were observed in all quarters in these years [71]. In the *US*, fluoroquinolone use decreased by 18% during the pandemic [80]. Meanwhile in *Canada*, the mean monthly number of second- and third-generation fluoroquinolone prescriptions fell by 25.4% and 58.4%, respectively between the pre-COVID period (January 2017-February 2020) and the COVID period (March – December 2020) [79]. In the *Republic of Sprska*, the utilization of quinolones (J01M) increased by 8.49% between 2019 and 2020 (from 2.23 DID to 2.05 DID), in contrast to our findings in Hungary. The usage of specific agents, such as ciprofloxacin and levofloxacin decreased, while moxifloxacin showed a significant increase of 124.60% in the *Republic of Sprska* [78]. Similar to our findings, the average use of quinolone antibacterials (J01M) decreased in the *EU/EEA* (2019 vs 2020 -0.21 DID, -14.89%; 2020 vs 2021 - 0.04 DID, -3.33%) [76]. However, a slight increase was observed in 2022 from 2021 at the EU/EEA level (+0.14 DID, 12.07%) [77].

Analysis of Macrolides and lincosamides (J01F) subgroup

The use of macrolides and lincosamides (J01F) in Hungary showed two distinct peaks: the first in March 2021 and the second in November 2021, when usage significantly exceeded the average pre-COVID monthly levels. In Hungary, azithromycin became the second most commonly used antibacterial during the pandemic, largely due to its proposed immunomodulatory and antiviral properties, which initially suggested its potential for COVID-19 treatment [82–84]. This assumption likely contributed to the increased use of macrolides during the COVID-19 period. However, concerns about its effectiveness emerged in August 2020, and by March 2021, studies confirmed that azithromycin was ineffective against COVID-19, limiting its recommendation treating bacterial superinfections [85,86]. Despite this evidence, the use of azithromycin in Hungary peaked in March 2021, started to increase again in September 2021, and peaked again in November 2021, exceeding the typical monthly levels before the COVID-19 pandemic. This means that the evidence of its ineffectiveness was not implemented by Hungarian prescribers. In contrast, a *Canadian region (Ontario)* reported a significant decrease in the average monthly number of the prescription of macrolides, with a

65.6% decrease between the pre-COVID period (January 2017–February 2020) and the COVID-19 period (March–December 2020) [79]. The consumption of macrolides and lincosamides in *Spain (Navarre region)* decreased significantly in the second, third and fourth quarters of 2019 compared to 2020. However, it remained below pre-pandemic levels in 2021 across all quarters. This Spanish study found decreased azithromycin use comparing quarters of 2021 to quarters of 2019 (Q1 -66%; Q2 -54%; Q3 -47%; Q4 -21%) [71]. During the study period (2018–2020) in *the Republic of Serbia*, macrolide antibiotics (J01F), similarly to our findings, showed an increase. At the substance level, azithromycin use increased by 117.43% in 2020 compared to 2019 [78]. The consumption of macrolides and lincosamides (J01F) in the *EU/EEA* initially decreased by -0.50 DID (-17.42%) from 2019 to 2020, followed by a slight increase of 0.01 DID (+0.42%) from 2020 to 2021 [76]. This increasing trend continued in 2022 (+0.83 DID, +34.87% from 2021 to 2022) [77]. At the *EU/EEA* level, changes in antibiotic consumption reflect country-specific variations in azithromycin use. For example, on one hand they reported a consistent decrease in the use of azithromycin in *Denmark, Finland, Germany, Portugal, Slovenia, Spain and the Netherlands* in the whole study period (2019-201). On the other hand, they observed increased usage of this agent in *Bulgaria* and in *France.* In some countries, including Hungary, a decreased was observed first, followed by an increase. [76].

5.1.3 Factors Behind the Decline in Antibacterial Use During the Pandemic

According to ECDC ESAC-Net annual reports, Hungary has continuously been among the EU/EEA countries with lower rates of ambulatory care antibiotic use before the COVID [87]. Therefore, it is essential to understand the primary causes of the additional decrease in antibiotic consumption during the pandemic. A lower incidence of other respiratory tract infections (RTIs) than COVID-19 resulting from pandemic-related preventive measures, such as closure of schools, some public places, social distancing, isolation, regular mask use, and required home confinement, may be partially responsible for this decline in Hungary. Limited access to healthcare and a subsequent decline in General Practitioners' (GP) consultation rates may have also contributed to the reduction in antibiotic use during the pandemic [57–62]. In Hungary, the average annual number of consultations during the pre-COVID period (2015–2019) was 66,625,096 (including face-to-face visits at doctors' offices or at patients' homes). In contrast the average annual number of consultations was 61,080,883 during the pandemic years (2020–2021), corresponding to an 8.3% decrease. However, in 2021, telemedicine consultations (primarily telephone calls) were introduced into the statistics. When these are included, the total number of average consultations rose to 68,147,204, marking a 2.3% increase compared to the pre-COVID period [55].

The causes of decreased antibiotic use during the COVID-19 pandemic have also been discussed in some other research. BARA et al., in *France* also explained the reduction of antibiotic prescriptions by the decreased use of health care due to pandemic restrictions. Analysis of antibiotic prescriptions in *France* between 2019 and 2020 revealed a decrease of 6,195,075 prescription (-18.2%) from 34,047,337 prescriptions in 2019 to 27,852,262 in 2020 [88]. According to the Spanish authors, possible reasons for the reduction in antibiotic use included the widespread lockdowns in *Spain*, which resulted in fewer consultations. Moreover, they mentioned the role of the non-pharmaceutical measures (hygienic prevention, hand washing, mask use and social distancing). The overall number of patients receiving systemic antibiotics decreased from 92,186 in the first quarter of 2018 to 79,952 in 2020 and then to 43,256 in 2021, according to data from a *Spanish region (Navarre)*. This decline was consistent across quarters, except in the fourth quarter of 2021, when a slight recovery was noted, with 62,580 patients [71]. Vermeulen et al., also explained the important impact of restrictions and non-pharmaceutical interventions in the reduction of the antibiotic use in the *EU/EEA* countries [76,77]. In contrast of these findings, increased antibiotic use was observed in the *Republic of Srpska*. The possible reason was that in the beginning of the pandemic more than 55% of COVID-19 outpatients were prescribed an antibiotics [78].

5.2 Discussion for Study 2

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

5.2.1 Summary of Key Findings

This part of the thesis mainly explored whether antibiotic use reverted after the pandemic. In Hungary, we found that systemic antibiotic use in the community sector decreased during the pandemic and then recovered to Before COVID levels after the pandemic. To the best of our knowledge, aside from the ESAC-Net annual epidemiological report and an ESAC-Net surveillance paper, this study was among the first to examine ambulatory care antibiotic use in a Central European country following the COVID-19 pandemic [89,90]. Furthermore, it was the first study to analyze antibiotic utilization over two years post-pandemic. These factors significantly hinder cross-national comparisons. Also it is important to note that, we used different time periods in our two studies, thus comparison requires caution.

5.2.2 International Benchmarking: Scale of Antibacterial Utilization

5.2.2.1 Systemic antibiotic (J01) use

In Hungary, systemic antibiotic use in ambulatory care decreased significantly during the COVID period, showing a 22.57% reduction compared to the Before COVID period (from 11.61 DID to 8.99 DID), but it reverted after the pandemic near to the before COVID level (11.11 DID). This is very similar to the result of the first study, (from 12.1 in pre-COVID to 9.29 DID in COVID period, 23.22% decrease). However, in the first study, the pre-COVID period was five years (from January 2015 to December 2019), while in the second study it was just two years (from March 2018 to February 2020). In addition, the COVID-period was different in our two studies, in the first, it lasted from January 2020 to March 2022, while in the second, it lasted from March 2020 to February 2022. In the *EU/EEA countries* a temporary decrease in antibiotic consumption was observed during the pandemic, however, community antibiotic use increased from 14.98 DID in 2021 to 18.04 DID in 2022, returning to levels close to those before the pandemic [77]. This rebound could be explained by the decrease in strict social restrictions as the pandemic faded, which allowed infectious disease incidence rates and daily life to return to normal. In *Switzerland* 9.36 DID for mean monthly antibiotic consumption during their pre-pandemic period (January 2018-February 2020) was observed. After the start of the pandemic period (March 2020- March 2022) this decreased to 7.29 DID, a trend similar to our findings. However, after the pandemic (April 2022-December 2023) the antibiotic utilisation returned to pre-pandemic levels [91]. Based on an article examining outpatient antibiotic prescription data from six European countries (*France*, *Belgium*, *Germany*, *Italy, the UK, and Poland*), after the pandemic, continuous increase was observed in five countries (except *Poland*) in the annual number of patients with ≥1 antibiotic prescription during 2021-2023. In 2022, the number of patients receiving antibiotics increased significantly in all countries compared to 2021. This increase ranged from +12% to +39% in different countries. In 2023, growth slowed down, with lower increases observed in several countries. *Poland* was the only country which showed a slight decrease in 2023 (-2.2%). In 2024, *France*, *Germany*, and the *United Kingdom* showed an increase in the number of patient with antibiotic prescription again, while *Belgium*, *Italy*, and *Poland* showed a slight decrease [92].

Table 10. Annual number of patients with antibiotic prescriptions in six European countries (2021-2024) [92]

Country	Number of patients (in Millions)			
	2021	2022	2023	2024
France	10.95	12.27	12.28	12.44
Belgium	0.86	1.20	1.24	1.18
Germany	9.66	12.18	13.85	14.20
Italy	7.12	8.65	9.72	9.57
UK	8.12	10.24	10.81	11.34
Poland	11.64	15.26	14.92	14.97

5.2.2.2 WHO AWaRe classification

The WHO's 13th General Programme of Work (2019–2023) established a global target for at least 60% of total systemic antibiotic consumption to consist of "Access" group antibiotics. In addition, the most recent ECDC ESAC-Net 2024 report aims for a more ambitious 65% target, which EU Member States should achieve by 2030, based on the "Council of the European Union Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach (2023/C 220/01)" [52,93]. In Hungary, this aim was not achieved during any of the study periods (Before COVID: 49.51%, COVID: 51.63%, After COVID: 50.80%). In contrast, several countries, including *Denmark*, *Finland*, and the *Netherlands*, have already successfully achieved the target, as reported in the ESAC-Net 2024 report [52]. Applying the WHO AWaRe classification to analyze systemic antibiotic use (J01), we found that the use of Watch antibacterials showed consistent usage across the periods, they represented around 50% of the total antibiotic use. Addressing antibiotic resistance globally requires tackling the improper use of Watch antibacterials. It was a positive observation, that, throughout the whole study period, the use of Reserve group antibiotics remained marginal (almost negligible) in Hungarian ambulatory care. We were only able to compare AWaRe's classification analysis with one country. In *Switzerland*, during the pandemic period (March 2020-March 2022), a significant decrease (-1.33 DID) was observed in the use of Access antibiotics compared to the pre-pandemic period (approximately 6.0 DID between January 2018-February 2020), while after the pandemic (April 2022-December 2023), the use of this group returned to pre-pandemic levels. The usage of Watch antibiotics in *Switzerland* showed a slight decrease during the pandemic, with 0.78 DID compared with the pre-pandemic period (approximately 3.5 DID), and this lower usage continued after the pandemic. The Reverse group had marginal use , similarly to the Hungarian data [91].

5.2.3 International Benchmarking: Pattern of Antibacterial Utilization

5.2.3.1 Antibiotic subgroup and substance level

Analysis of Penicillins (J01C) use

Hungarian studies have consistently highlighted the significant role of beta-lactam antibiotics (penicillins, cephalosporins) in outpatient antibiotic use [94,95]. Our results support these findings by showing that, across all three study periods, beta-lactam antibiotics remained the most often used antibiotics, making up almost 50% of outpatient antibiotic consumption. The penicillins (J01C) use in Hungary increased slightly during the Before and After COVID periods, which pattern was also observed in the *UK* [96]. In *Switzerland*, during the pandemic (March 2020-March 2022), the most significant decrease was observed in the use of penicillins combinations (including beta-lactamase inhibitors, J01CR) - 0.76 DID compared with the pre-pandemic period (January 2018-February 2020), however, this returned after the pandemic (April 2022-December 2023) to the pre-pandemic levels [91]. The most commonly used penicillin group in Hungary in all three periods was this group, combined with beta-lactamase inhibitors (J01CR). This group was dominated by amoxicillin-clavulanic acid (co-amoxiclav), with over 150,000 patients exposed each month in the After COVID period corresponding to an exposure of 1.800.000 patients per year. However, because Hungarian clinical guidelines restrict its use (e.g., co-amoxiclav is recommended only second-line treatment for acute bacterial rhinosinusitis, community acquired pneumonia, etc.), the frequent use of co-amoxiclav is inadequate [97,98]. In contrast, despite national guidelines favoring the utilization of penicillins with extended spectrum (J01CA), their use has remained persistently low and continued to decline. In Hungary, 93.2% of *Streptococcus pneumoniae* (the primary causative agent of bacterial respiratory tract infections) isolates from ambulatory care samples remained susceptible to aminopenicillins according to national resistance data [99]. This validates the Hungarian guidelines' recommendation that amoxicillin should be used as the first empirical treatment for e.g. pneumonia, bacterial sinusitis, and acute otitis media [97,98,100]. Furthermore, according to the WHO's 23rd Model List of Essential Medicines, amoxicillin is the first-line treatment for a variety of bacterial illnesses [101]. Similarly, to Hungary, co-amoxiclav dominated the antibiotic prescriptions in *France* and in *Belgium*, making up 70-79% of all prescriptions. In *France*, a continuous increase in the use of co-amoxiclav after the pandemic was observed. In *Germany*, the relative use of co-amoxiclav continued to increase after the pandemic (from 44.0% in 2021 to 54.4% in 2024), but it still accounted for a much lower proportion of all antibiotic prescriptions compared with *France* or *Belgium*. Similar usage data for co-amoxiclav was observed in *Italy* in the post-pandemic period (relative share increased from 54.1% in 2021 to 59.5% in 2024). In contrast, in *Poland*, co-amoxiclav accounted for only about 30% of all antibiotics prescriptions in the post-pandemic period (from in 2021:28.0%, to in 2022: 32.3%, in 2023: 33.9% and in 2024: 30.7%) [92]. The use of beta-lactamase-sensitive penicillins (J01CE) declined significantly during the COVID period compared to the before COVID level and continued to drop afterward in Hungary, largely due to limited product availability in Hungary. Previously, phenoxymethylpenicillin was widely available through multiple products, but only one brand remained on the Hungarian market, often affected by drug shortages. This decrease is worrying because resistance surveillance data of *Streptococcus pyogenes* have demonstrated 100% sensitivity to phenoxymethylpenicillin; therefore it should remain the first-line treatment for bacterial tonsillopharyngitis [99,102]. According to WHO guidance, phenoxymethylpenicillin is listed as first line agent for mild to moderate community-acquired pneumonia, pharyngitis, and progressive apical dental abscess [101].

Analysis of Cephalosporins (J01D) use

In Hungary, the decrease in the overall use of cephalosporins (J01D) that was seen during the pandemic continued in the After COVID period. On the other hand, after the COVID-19 pandemic, cephalosporin use increased slightly in the *UK*; nevertheless, direct comparisons are limited by methodological variations. [96]. The second-generation cephalosporins (J01DC) was the most frequently used cephalosporin in Hungary. Cefprozil was 10th in the top 10 antibacterial list during the After COVID period, while the use of cefuroxime decreased, dropped to the 5th place (see Table 7) on the top list. Supply challenges, including shortages of the often-prescribed 500 mg dose of cefuroxime following the pandemic, might partly explain this change, however, cefuroxime remained the most frequently used cephalosporin agent. In *Germany* the proportional use of cefuroxime showed a downward trend (2021: 14.9%, 2022: 15.3%, 2023: 16.4%, 2024: 13.1%). In *Poland* a similar trend was observed, but lower proportional use of this agent (2021: 6.2%, 2022: 6.3%, 2023: 6.8%, 2024: 5.5%) [92]. Additionally, an increase in the use of third-generation cephalosporins (J01DD) was observed in Hungary, with cefixime entering the top 10 list. Cefixime has few primary care indications. It is primarily recommended as a first-line treatment for acute uncomplicated pyelonephritis in outpatients; therefore, its increased use is alarming, because of the increasing rate of the ESBL pathogens. [103]. In *Italy*, the proportional use of cefixime increased after the pandemic (2021: 13.6% - 2024: 17.0%) [92].

Analysis of Fluoroquinolones (J01M) use

The continuing decrease in quinolone (J01M) usage in Hungary's outpatient sector should be regarded as a positive change during our study periods. The usage of quinolones showed a decreasing trend during the pandemic, without revert to pre pandemic levels (see Table 6.). Following a review on disabling and potentially long-lasting, irreversible side effects associated with quinolone use, the European Medicines Agency (EMA) recommended firstly in 2018 (and reiterated several times because of additionally identified side effects) that quinolone usage should be restricted [104–106]. Furthermore, national resistance data from 2022 indicated that the susceptibility of the two most prevalent uropathogens, *Escherichia coli* and *Klebsiella pneumoniae*, to fluoroquinolones was below 80%, which limits the empirical use of these antibacterials in Hungary [99]. Similarly, in *Switzerland* the use of fluoroquinolones (J01MA) was decreased during the pandemic (-0.18 DID), which trend continued in the post-pandemic period [91].

Analysis of Macrolides and lincosamides (J01F) use

In terms of macrolide consumption, Hungary experienced a significant increase in use firstly during the pandemic, which continued in the After COVID period. Patterns varied by country: the *UK* reported a slight reduction in macrolide consumption in 2022 compared to 2019, while 12 other nations, including Hungary, reported increasing use [89,96]. While in *Switzerland*, similarly to the *UK* data, the use of macrolides (J01FA) showed a decreasing trend (-0.37 DID) [91]. Since the pandemic, the relative share of macrolide use (J01FA) has dramatically increased in Hungary. During the pandemic, azithromycin emerged as the second most often used antibacterial agent in Hungary and continued to hold this position. This is surprising, because, according to Hungarian guidelines, azithromycin should only be used as a first-line empirical treatment for atypical pneumonia or in case of severe penicillin allergies [98,102,107]. Azithromycin's practical features, which include a once-daily dosage schedule and a brief 3-day course of treatment, and a favorable safety profile (ie. low risk of medication interactions), may explain its widespread use. Its use in patients with persistent coughing may also be influenced by Hungary's increasing pertussis incidence [107]. Similarly, to Hungary, in *France* and *Belgium* azithromycin was the second most commonly used antibiotic during and after the pandemic, with an increasing trend in relative share in *France* from 10.2% in 2021 to 14.7% in 2024 and in *Belgium* from 17.3% in 2021 to 23.6% in 2024. In *Germany*, the proportional use of azithromycin also increased from 9.9% in 2021 to 18.2% in 2024. In contrast, in *Italy* and *Poland*, the proportional use of azithromycin showed a downward trend in 2024 [92].

5.2.4 Seasonal Variation in Antibiotic Use

A previous Hungarian study highlighted significant seasonal variation in systemic antibiotic use in ambulatory care, with notably higher consumption during winter months [95]. An EU/EEA-wide study assessing the quality of antibiotic use in the community sector found that Hungary had one of the highest seasonality indexes in 2017 (J01_SV%: 51.31%), compared to *Denmark* (10.56%), the *UK* (11.07%), and *Finland* (12.73%) [64]. In our study, the seasonality index for systemic antibacterials remained consistently high across all three periods, though it was slightly lower in the post pandemic period (Before COVID: 46.86%, COVID: 53.42%, After COVID: 39.68%). While no comparable seasonality index data from other countries were available regarding the pandemic's impact, *Portugal* reported nearly a 40% decrease in antibiotic use during the winter months of 2020 compared to the average of the previous two years [70]. The pronounced seasonal variation in Hungary suggests that antibiotics are frequently prescribed for self-limiting viral respiratory tract infections (RTIs) [108].

6. LIMITATIONS

We have to acknowledge the limitations of this research. First, the findings of our research may lack generalizability to other contexts due to the significant variability in the implementation of limitations (i.e. social restrictions) during the COVID-19 pandemic in other countries. Second, we were unable to apply interrupted time series analysis and analyze antibiotic use for certain infection types because we lacked access to weekly level and indication linked data and antibiotic use data. Third, we were unable to quantify the number of prescriptions per inhabitant since we employed an aggregated dataset of reimbursed systemic antibiotic prescriptions. Also, we were unable to differentiate between prescriptions based on telemedicine versus in-personal consultations. Finally, we were unable to compare prescription trends and pattern changes at the individual level because we lacked detailed data on individual patients.

7. 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. We found that overall the After pandemic antibiotic use has returned to levels similar to those observed before pandemic levels. However, several alarming patterns regarding the quality of prescriptions emerged during and after the pandemic. Broad-spectrum penicillin combinations (J01CR) became more widely used, while the use of narrow-spectrum beta-lactamase-sensitive penicillins (J01CE) and second-generation cephalosporins (J01D) decreased. Meanwhile, the use of third-generation cephalosporins (J01DD) and macrolides (J01F) significantly increased.

In the future, healthcare practitioners will need to adopt evolving evidence-based recommendations more rapidly. Telemedicine should be integrated into standard care, especially for the diagnosis of illnesses that do not require laboratory tests or physical examinations, such as acute cystitis. 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. The long-term impacts of the COVID-19 pandemic on antibiotic use require additional research. Since the pandemic caused significant modifications in healthcare services and prescribing procedures, additional research is necessary to determine if these changes have contributed to changes in antibiotic use. Our findings underscore the urgent need to assess the pandemic's effects on both the quantity and quality of antibiotic prescribing in primary care settings across countries, supporting the development of specific antimicrobial stewardship interventions.

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