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Brief Report

An Overview of Antibiotic Consumption in Croatian Counties, 2017–2024: Temporal and Geographic Patterns Before, During, and After the COVID-19 Pandemic

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Abstract

Background/Objectives: Croatia is among the European countries with moderately high antibiotic consumption and correspondingly elevated antimicrobial resistance (AMR) rates. National-level surveillance, however, masks substantial county-level heterogeneity that is relevant for targeted stewardship. This study aimed to (i) quantify and statistically test temporal changes in total antibacterial consumption (J01), beta-lactam antibiotics (J01C), and macrolides/lincosamides/streptogramins (J01F) across all 21 Croatian counties between 2017 and 2024, spanning the pre-pandemic, pandemic, and post-pandemic periods, and (ii) characterize geographic disparities that could inform region-specific stewardship interventions. J01C and J01F were selected because they are, respectively, the most heavily consumed and the most steadily rising antibiotic subgroups in Croatia, and both carry direct relevance to the WHO Access, Watch, Reserve (AWaRe) stewardship framework. **Methods:** A retrospective, registry-based analysis of antibiotic consumption in all 21 Croatian counties was conducted using annual distribution data from the Croatian Agency for Medicinal Products and Medical Devices (HALMED), covering 1 January 2017 to 31 December 2024. Consumption was expressed as defined daily doses per 1000 inhabitants per day (DDD/TID). County-level values for 2017, 2020, 2021, and 2024 were compared using paired Student's *t*-tests (confirmed with Wilcoxon signed-rank tests) and a Friedman test across all four time points; national annual means (2017–2024) were compared descriptively against European Union/European Economic Area (EU/EEA) surveillance benchmarks. **Results:** National J01 consumption declined from 21.16 to 16.96 DDD/TID between 2017 and 2021 (−19.8%) and rebounded to 22.75 DDD/TID by 2024 (+34.1%); the county-level decline and rebound were both statistically significant (paired *t*-tests, $p < 0.001$ for each comparison; Friedman $\chi^2 = 57.97$, $p < 0.001$). J01C followed the same U-shaped pattern, temporally coincident with the COVID-19 pandemic period (12.59 → 5.13 → 9.05 DDD/TID; all comparisons $p < 0.001$), whereas J01F rose continuously throughout the study period, without a corresponding dip during that period (2.81 → 3.49 → 4.43 DDD/TID; $p < 0.001$ for every interval). Croatia's 2024 mean county-level J01 consumption was significantly above the 2024 EU/EEA population-weighted mean of 18.8 DDD/TID (one-sample *t*-test, $p = 0.016$). The sharpest pandemic-era declines and post-pandemic rebounds were concentrated in Adriatic coastal counties (Primorje-Gorski Kotar, Zadar, Šibenik-Knin, and Istria). **Conclusions:** Total and beta-lactam antibi-

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otic consumption in Croatia followed a U-shaped trajectory temporally coincident with the COVID-19 pandemic period, while macrolide, lincosamide, and streptogramin use rose steadily throughout 2017–2024, a pattern of stewardship concern given that this subgroup is predominantly classified as "Watch" under the WHO AWaRe framework. Coastal counties displayed disproportionate fluctuations, plausibly reflecting seasonal population dynamics not captured by resident-population denominators. AWaRe-stratified, tourism-adjusted, county-level surveillance is recommended to guide targeted stewardship.

Keywords: antibiotic consumption; DDD/TID; Croatian counties; AWaRe classification; antimicrobial resistance; COVID-19

1. Introduction

Antimicrobial resistance (AMR) is a direct consequence of the overuse and inappropriate use of antibiotics and is increasingly recognized as a "silent pandemic." Estimates from the World Health Organization (WHO) and the European Union/European Economic Area (EU/EEA) surveillance networks indicate that more than 670,000 infections each year in the EU/EEA are caused by antibiotic-resistant bacteria, with approximately 33,000 associated deaths [1,2]. Antibiotic consumption is the principal modifiable driver of AMR, and its surveillance is a WHO- and ECDC-recommended stewardship tool [1–4].

Croatia is classified among European countries with moderately high antibacterial consumption, and national reports have documented a corresponding rise in resistance rates for several clinically important pathogens [3,4]. In response, a National Control Program for Antimicrobial Resistance has been established, and the National Committee for the Surveillance of Antimicrobial Susceptibility and Resistance has reported a mean annual increase in J01 consumption of 5.8% between 2020 and 2024, driven largely by penicillins (J01C, +7.5%/year), with a further, more gradual, increase documented for macrolides, lincosamides, and streptogramins (J01F) [4]. National figures, however, aggregate 21 counties that differ markedly in population size, healthcare accessibility, age structure, and—for the Adriatic Littoral—seasonal tourist influx, all of which can independently influence per-capita antibiotic use. County-level analysis is therefore needed to identify where stewardship interventions would have the greatest impact, a level of granularity that national aggregate reporting cannot provide.

We focused specifically on J01C (beta-lactam antibiotics, principally penicillins) and J01F (macrolides, lincosamides, and streptogramins) for two reasons. First, these are respectively the most heavily consumed and the most persistently rising antibacterial subgroups in Croatia, together accounting for a large share of total J01 use. Second, both subgroups map onto the WHO Access, Watch, Reserve (AWaRe) stewardship classification in clinically informative ways: J01C is dominated by narrow-spectrum penicillins that largely fall in the "Access" category, whereas J01F—particularly azithromycin and clarithromycin—is predominantly classified as "Watch," reflecting a higher resistance-selection risk [5]. Tracking these two subgroups separately therefore provides an indirect but clinically meaningful proxy for stewardship quality, complementing the aggregate J01 trend.

The COVID-19 pandemic, declared by the WHO on 11 March 2020, provides a further rationale for this study: it constituted a natural, nationwide perturbation of prescribing behavior, allowing before–during–after comparisons that are otherwise difficult to obtain in observational antibiotic-use research. This brief report presents a retrospective, county-stratified analysis of J01, J01C, and J01F consumption in Croatia from 2017 to 2024. Its aim is threefold: (i) to quantify, with formal statistical testing, the magnitude of the decline and rebound observed during and after the pandemic period in each subgroup; (ii) to

characterize which counties departed most from the national pattern; and (iii) to discuss the findings in relation to the WHO AWaRe stewardship targets and EU/EEA benchmarks, with a view to informing regionally targeted antimicrobial stewardship policy in Croatia.

2. Materials and Methods

A retrospective, registry-based analysis of antibiotic consumption in the 21 Croatian counties (including the City of Zagreb) was performed for the period 1 January 2017 to 31 December 2024. Data were obtained from the Croatian Agency for Medicinal Products and Medical Devices (HALMED), which compiles nationwide distribution records from all community pharmacies, hospital pharmacies, and specialized retail outlets for medicinal products.

Consumption was expressed using the WHO-recommended metric of defined daily dose per 1000 inhabitants per day (DDD/TID), calculated according to the Anatomical Therapeutic Chemical (ATC)/DDD index, the international standard for drug utilization studies. Data are reported at ATC level 3 for the overall antibacterials-for-systemic-use group (J01) and for two clinically prioritized subgroups: beta-lactam antibiotics (J01C) and macrolides, lincosamides, and streptogramins (J01F). County-level annual population denominators used by HALMED are official resident-population estimates from the Croatian Bureau of Statistics; these reflect permanent residents and are not adjusted for seasonal tourist influx. This is a relevant limitation for Adriatic coastal counties, where summer population inflows may substantially increase the effective denominator without a corresponding increase in the registered resident population, a point to which we return in the Discussion.

Statistical analysis: For each ATC group, county-level DDD/TID values for 2017, 2020, 2021, and 2024 (n = 21 counties) are summarized as means, standard deviations (SDs), and 95% confidence intervals (CIs). Within-county change over time was tested using paired Student's t-tests for the 2017 vs. 2021 and 2021 vs. 2024 comparisons, with Wilcoxon signed-rank tests performed in parallel as a distribution-free confirmation. A Friedman test (a non-parametric repeated-measures analogue of ANOVA, appropriate given the small, non-normally distributed county-level samples) was used to test for an overall effect of time across all four available years (2017, 2020, 2021, and 2024) simultaneously. Croatia's 2024 county-level mean was additionally compared against the 2024 EU/EEA population-weighted mean (18.8 DDD/TID) using a one-sample t-test. The unit of analysis for this comparison was the individual county (n = 21), with each county contributing a single 2024 DDD/TID value; normality of these 21 values was assessed with the Shapiro–Wilk test, and a one-sample Wilcoxon signed-rank test against the same EU/EEA reference value was performed as a distribution-free confirmation. Statistical significance was set at $p < 0.05$. All analyses were performed in Python 3 (SciPy v1.x).

This study is a limitation-aware ecological (aggregate) analysis: data are reported at ATC level 3 only. A finer, substance-level breakdown (e.g., distinguishing penicillins [J01CA], cephalosporins [J01CE–J01DD], and carbapenems [J01DH] within J01C, or individual macrolides within J01F) was not possible with the aggregated distribution data available for this report and is proposed as a priority for future work, ideally combined with formal AWaRe-category stratification and linkage to county-level antimicrobial resistance surveillance data.

3. Results

3.1. National Trends, 2017–2024

Total antibacterial consumption (J01) in Croatia followed a U-shaped trajectory temporally coincident with the COVID-19 pandemic period (Table 1), decreasing from

21.16 DDD/TID in 2017 to a nadir of 16.96 DDD/TID in 2021 (national, population-weighted values), before rebounding to 22.75 DDD/TID in 2024—the highest value recorded in the study period. Trends for all three ATC groups are shown in Figure 1.

Table 1. National antibiotic consumption of antibacterials for systemic use (ATC group J01), DDD/TID, Croatia, 2017–2024.

ATC	INN	2017	2018	2019	2020	2021	2022	2023	2024
J01	Antibacterial drugs	21.16	18.47	18.66	18.37	16.96	19.58	20.80	22.75

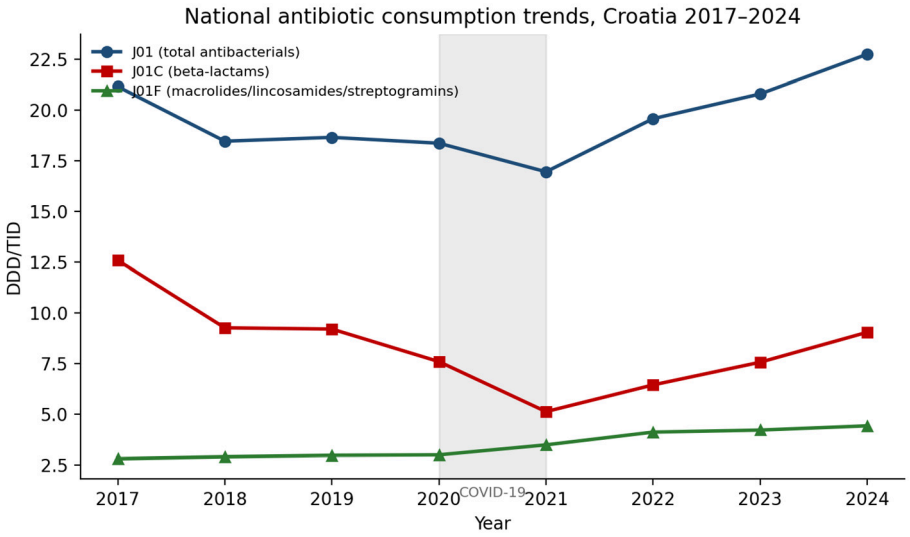

Figure 1. National trend lines for total antibacterials (J01), beta-lactams (J01C), and macrolides/lincosamides/streptogramins (J01F), Croatia, 2017–2024. The shaded band marks 2020–2021 (COVID-19 pandemic).

County-level values underlying the national trend are presented in Table 2. Beta-lactam antibiotics (J01C) mirrored this pattern with a proportionally larger relative amplitude (Table 3), while macrolides, lincosamides, and streptogramins (J01F) rose steadily across the entire period without a corresponding decline during that period (Table 4).

Table 2. Antibiotic consumption (J01), DDD/TID, by county, before (2017), during (2020–2021), and after (2024) the COVID-19 pandemic.

No.	County	2017	2020	2021	2024
1	Zagreb	20.94	14.89	12.99	18.13
2	Krapina-Zagorje	22.59	16.85	15.02	22.39
3	Sisak-Moslavina	20.08	16.04	13.36	19.09
4	Karlovac	21.06	15.35	14.47	18.95
5	Varaždin	20.14	14.47	11.43	17.37
6	Koprivnica-Križevci	18.44	14.06	13.89	19.29
7	Bjelovar-Bilogora	22.57	19.06	15.08	20.56
8	Primorje-Gorski Kotar	22.54	14.47	12.33	20.89
9	Lika-Senj	21.05	15.77	15.53	22.88
10	Virovitica-Podravina	16.55	14.07	12.56	19.38
11	Požega-Slavonia	17.61	14.76	14.03	15.40
12	Brod-Posavina	17.74	15.05	11.51	16.56
13	Zadar	24.16	15.87	13.54	22.08
14	Osijek-Baranja	23.13	18.59	17.42	23.20
15	Šibenik-Knin	27.23	17.62	16.26	22.78

Table 2. *Cont.*

No.	County	2017	2020	2021	2024
16	Vukovar-Srijem	20.48	18.03	16.19	20.45
17	Split-Dalmatia	22.85	17.22	14.55	19.76
18	Istria	24.79	17.57	17.10	24.56
19	Dubrovnik-Neretva	20.39	14.42	14.21	20.14
20	Međimurje	19.63	12.40	12.47	19.20
21	City of Zagreb	22.40	15.82	14.19	19.56

Table 3. Antibiotic consumption of beta-lactam antibiotics (ATC J01C), DDD/TID, Croatia, 2017–2024.

ATC	INN	2017	2018	2019	2020	2021	2022	2023	2024
J01C	Beta-lactam antibiotics	12.59	9.27	9.21	7.60	5.13	6.45	7.57	9.05

Table 4. Antibiotic consumption of macrolides, lincosamides, and streptogramins (ATC J01F), DDD/TID, Croatia, 2017–2024.

ATC	INN	2017	2018	2019	2020	2021	2022	2023	2024
J01F	Macrolides, lincosamides, streptogramins	2.81	2.91	2.98	3.00	3.49	4.12	4.22	4.43

County-level values for beta-lactam antibiotic consumption (J01C) are presented in Table 5.

Table 5. Antibiotic consumption of beta-lactam antibiotics (J01C), DDD/TID, by county, before (2017), during (2020–2021), and after (2024) the COVID-19 pandemic.

No.	County	2017	2020	2021	2024
1	Zagreb	12.83	7.00	4.50	7.99
2	Krapina-Zagorje	13.42	7.66	5.77	9.72
3	Sisak-Moslavina	10.96	6.58	4.19	7.89
4	Karlovac	11.84	6.78	5.17	8.23
5	Varaždin	12.95	7.25	4.37	8.31
6	Koprivnica-Križevci	11.42	7.05	6.02	9.61
7	Bjelovar-Bilogora	13.30	9.56	5.36	9.53
8	Primorje-Gorski Kotar	11.99	6.39	3.67	9.13
9	Lika-Senj	12.18	7.16	5.36	9.79
10	Virovitica-Podravina	10.29	6.99	5.19	9.02
11	Požega-Slavonia	9.43	5.90	3.68	4.91
12	Brod-Posavina	10.78	7.14	3.57	6.76
13	Zadar	14.90	7.49	5.06	9.79
14	Osijek-Baranja	13.77	7.98	6.52	10.46
15	Šibenik-Knin	17.69	9.13	7.15	10.63
16	Vukovar-Srijem	13.05	8.63	6.09	8.78
17	Split-Dalmatia	13.26	7.54	4.32	7.80
18	Istria	13.52	6.81	5.26	9.27
19	Dubrovnik-Neretva	10.31	4.96	3.58	7.36
20	Međimurje	13.63	6.80	6.13	9.72
21	City of Zagreb	12.93	7.22	4.97	7.58

3.2. County-Level Descriptive Statistics and Formal Time Comparisons

Unweighted county-level means (each of the 21 counties given equal weight, in contrast to the population-weighted national figures above) are shown in Table 6, alongside 95% confidence intervals. The unweighted county mean for J01 fell by 33.2% between 2017 and 2021 and rose by 41.8% between 2021 and 2024—a larger relative amplitude than the population-weighted national figures (−19.8% and +34.1%, respectively). This discrepancy indicates that smaller, less populous counties experienced proportionally

sharper declines and rebounds during the pandemic period than the large urban/coastal centers that dominate the population-weighted national average.

Table 6. County-level descriptive statistics (mean DDD/TID [SD]; 95% CI), n = 21 counties.

Group	2017	2020	2021	2024
J01 (total)	21.26 (2.57); 20.09–22.42	15.83 (1.71); 15.05–16.61	14.20 (1.69); 13.43–14.97	20.12 (2.29); 19.08–21.17
J01C (beta-lactams)	12.59 (1.81); 11.77–13.42	7.24 (1.02); 6.78–7.70	5.04 (1.02); 4.58–5.51	8.68 (1.36); 8.06–9.30
J01F (macrolides, etc.)	2.81 (0.52); 2.57–3.05	2.78 (0.49); 2.56–3.00	3.22 (0.63); 2.93–3.51	4.23 (0.67); 3.93–4.54

All within-county changes over time were statistically significant (Table 7). Paired *t*-tests confirmed a significant decline from 2017 to 2021 and a significant rebound from 2021 to 2024 for both J01 and J01C ($p < 0.001$ for all comparisons; Wilcoxon signed-rank tests corroborated each result, $p < 0.001$). For J01F, both the 2017-to-2021 rise ($p < 0.001$) and the 2021-to-2024 rise ($p < 0.001$) were significant, consistent with a continuous upward trend rather than an interruption coincident with the pandemic period. The Friedman test confirmed a significant overall effect of time across all four years for every group (J01: $\chi^2 = 57.97$, $p < 0.001$; J01C: $\chi^2 = 59.91$, $p < 0.001$; J01F: $\chi^2 = 48.60$, $p < 0.001$).

Table 7. Formal statistical comparisons of county-level consumption across time points.

Group	2017 vs. 2021	2021 vs. 2024	Friedman (4 Time Points)
J01 (total)	$t = 15.54$, $p < 0.001$	$t = -17.11$, $p < 0.001$	$\chi^2 = 57.97$, $p < 0.001$
J01C (beta-lactams)	$t = 25.70$, $p < 0.001$	$t = -19.73$, $p < 0.001$	$\chi^2 = 59.91$, $p < 0.001$
J01F (macrolides, etc.)	$t = -4.59$, $p < 0.001$	$t = -10.70$, $p < 0.001$	$\chi^2 = 48.60$, $p < 0.001$

Croatia's 2024 county-level mean J01 consumption (20.12 DDD/TID, unweighted) was significantly higher than the 2024 EU/EEA population-weighted mean of 18.8 DDD/TID (one-sample *t*-test, $t = 2.65$, $p = 0.016$), placing Croatia in the upper-middle portion of the reported EU/EEA country range (9.0–27.8 DDD/TID) [1,2]. The 21 county-level 2024 values did not depart significantly from a normal distribution (Shapiro–Wilk $W = 0.98$, $p = 0.90$), supporting the use of the *t*-test for this comparison; a one-sample Wilcoxon signed-rank test against the same EU/EEA reference value corroborated the result ($W = 46.0$, $p = 0.014$).

3.3. Geographic Patterns

Total antibacterial consumption (J01) by county is shown in Table 2, with beta-lactams (J01C) in Table 5 and macrolides/lincosamides/streptogramins (J01F) in Table 8. County-level percentage change is illustrated in Figure 2.

The three counties with the largest J01 decline from 2017 to 2021 were Primorje-Gorski Kotar (−45.3%), Zadar (−44.0%), and Šibenik-Knin (−40.3%); the three with the largest 2021-to-2024 rebound were Primorje-Gorski Kotar (+69.4%), Zadar (+63.1%), and Istria (+43.6%)—all Adriatic coastal counties. The same coastal counties dominated both the decline and rebound of J01C specifically (e.g., Primorje-Gorski Kotar +148.8% from 2021 to 2024). For J01F, the largest 2017-to-2024 increases were in Virovitica-Podravina (+89.7%), Zadar (+73.9%), and Lika-Senj (+73.5%)—a mixed continental/coastal pattern, in contrast to the coastal concentration seen for J01 and J01C.

Table 8. Antibiotic consumption of macrolides, lincosamides, and streptogramins (J01F), DDD/TID, by county, before (2017), during (2020–2021), and after (2024) the COVID-19 pandemic.

No.	County	2017	2020	2021	2024
1	Zagreb	2.65	2.44	2.63	3.53
2	Krapina-Zagorje	3.48	3.41	3.37	4.86
3	Sisak-Moslavina	3.38	3.17	3.35	4.22
4	Karlovac	3.51	3.38	4.03	4.42
5	Varaždin	2.81	2.69	2.72	3.77
6	Koprivnica-Križevci	2.15	2.18	2.62	3.36
7	Bjelovar-Bilogora	2.52	2.77	3.18	4.02
8	Primorje-Gorski Kotar	2.53	2.45	2.98	3.96
9	Lika-Senj	3.09	3.18	3.91	5.36
10	Virovitica-Podravina	2.23	2.56	2.80	4.23
11	Požega-Slavonia	2.33	2.41	2.70	3.72
12	Brod-Posavina	2.30	2.21	2.38	3.09
13	Zadar	2.87	2.54	2.90	4.99
14	Osijek-Baranja	3.43	3.97	4.33	4.92
15	Šibenik-Knin	2.81	2.51	3.20	4.53
16	Vukovar-Srijem	2.17	2.94	3.22	3.80
17	Split-Dalmatia	2.60	2.90	3.95	4.38
18	Istria	3.88	3.21	4.20	5.64
19	Dubrovnik-Neretva	3.18	2.79	3.87	4.63
20	Međimurje	2.12	1.87	2.05	3.55
21	City of Zagreb	2.99	2.78	3.21	3.90

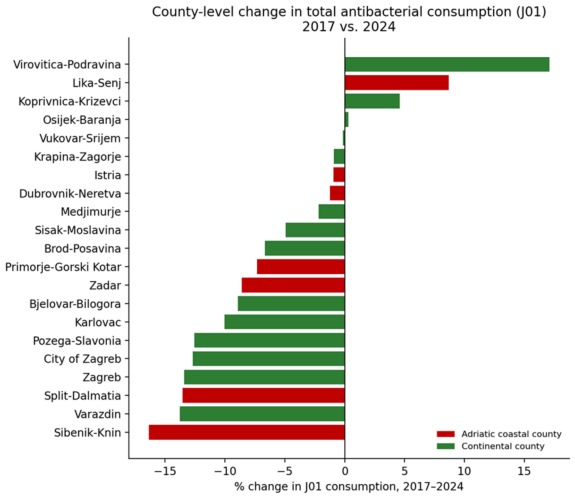

Figure 2. County-level percentage change in total antibacterial consumption (J01), 2017 vs. 2024, ordered by magnitude. Red bars denote Adriatic coastal counties; green bars denote continental counties.

4. Discussion

This is, to our knowledge, the first county-stratified, statistically tested analysis of antibiotic consumption in Croatia spanning the pre-pandemic, pandemic, and post-pandemic periods. Three findings merit discussion: the U-shaped trajectory of total and beta-lactam consumption, temporally coincident with the pandemic; the uninterrupted rise in macrolide/lincosamide/streptogramin use; and the concentration of the largest fluctuations in Adriatic coastal counties. Because our design is ecological and registry-based, this temporal association cannot by itself establish the pandemic as the causal driver of the observed pattern: plausible alternative or contributing explanations include a reduction in non-COVID-related healthcare-seeking during 2020–2021, reduced circulation of other

respiratory pathogens as a result of non-pharmaceutical interventions, restricted in-person access to primary care, and shifts in prescriber risk–benefit judgment for empirical antibiotic use during a period of diagnostic uncertainty; these mechanisms are not mutually exclusive and cannot be disentangled with the aggregate consumption data available to us.

The ECDC Annual Epidemiological Report on antimicrobial consumption in the EU/EEA (ESAC-Net, 28 countries) reported a 2024 population-weighted community mean of 18.8 DDD/TID for J01 (country range 9.0–27.8), with statistically significant increasing trends for both J01C and J01F between 2020 and 2024 across the EU/EEA overall [1,2]. Croatia's 2024 county-level mean (20.12 DDD/TID) was significantly above this EU/EEA mean ($p = 0.016$), placing the country in the upper-middle threshold of the reported EU/EEA range and consistent with its established classification as a moderately high consumer [3,4]. This positions Croatia as a plausible priority for targeted stewardship investment relative to lower-consuming EU/EEA peers.

The rise in J01F is of particular stewardship concern when interpreted through the WHO AWaRe (Access, Watch, Reserve) lens. J01C is dominated by narrow-spectrum penicillins, most of which fall within the "Access" category, whereas J01F—particularly azithromycin and clarithromycin—is predominantly classified as "Watch" [5]. A previously published analysis of Croatian outpatient prescribing (2015–2024) found that azithromycin was the second most prescribed antibiotic overall, accounting for 17.0% of all prescriptions and 84.4% of macrolide use, and that the proportion of Access category antibiotics consistently remained below the WHO target of 60–65% [6]. Our finding of a continuous, pandemic-independent rise in J01F—without the transient dip observed for J01 and J01C—is consistent with that report and suggests that the "Watch" share of Croatian outpatient prescribing has been increasing steadily rather than fluctuating with acute care-seeking behavior. We did not have access to substance-level or AWaRe-coded consumption data to formally quantify the Access/Watch/Reserve proportions at the county level; we identify this as the single most important direction for follow-up surveillance.

A plausible contributor to the sustained rise in J01F is the empirical use of azithromycin for suspected atypical or COVID-19-associated respiratory infections. Bogdanić et al. documented a marked increase in azithromycin consumption in Croatia during the early 2020 pandemic wave, despite subsequently accumulated evidence of limited clinical benefit for viral respiratory infections [7]. Patient and physician preference for a short, well-tolerated three- to five-day macrolide course, together with diagnostic uncertainty in primary care during periods of high respiratory-infection incidence, may have reinforced this pattern beyond the initial pandemic waves, contributing to the sustained increase we observed through 2024 rather than a reversion to pre-pandemic levels.

Geographically, the largest pandemic-era declines and post-pandemic rebounds in J01 and J01C were concentrated in Adriatic coastal counties (Primorje-Gorski Kotar, Zadar, Šibenik-Knin, and Istria). Two non-exclusive explanations are plausible. First, these counties experienced the sharpest reductions in tourism-related population inflow during 2020–2021, which—combined with resident-population denominators that do not adjust for seasonal visitors—could mechanically depress or inflate DDD/TID irrespective of any true change in per-patient prescribing intensity. Second, healthcare-seeking behavior for travel- and tourism-associated infections (respiratory and gastrointestinal) may itself covary with visitor numbers. Because our denominators are resident-population estimates from the Croatian Bureau of Statistics rather than tourism-adjusted effective populations, our data cannot distinguish a true change in prescribing rates from a denominator artifact, and this hypothesis should be treated as such pending population-adjusted follow-up analysis. Notably, the geographic pattern for J01F (Virovitica-Podravina, Zadar, and Lika-Senj) was more mixed between coastal and continental counties than for J01 and J01C, suggesting

that the macrolide trend is less strongly tied to tourism-related denominator effects and more likely reflects a genuine, nationwide prescribing shift.

This study has several limitations. First, it is an ecological, registry-based analysis of aggregate distribution data; no patient-level indication, diagnosis, or prescriber information was available, so individual-level determinants of prescribing cannot be inferred. Second, data are reported at ATC level 3 only; a substance-level breakdown (e.g., penicillins vs. cephalosporins vs. carbapenems within J01C) would allow more targeted stewardship recommendations and is an important direction for future work. Third, county population denominators are not adjusted for seasonal tourism, a limitation that particularly affects the interpretation of the coastal-county findings discussed above. Fourth, we did not have access to county-level antimicrobial resistance surveillance data, which would allow the consumption trends reported here to be directly linked to resistance outcomes.

5. Conclusions

Total and beta-lactam antibiotic consumption in Croatia followed a statistically confirmed U-shaped trajectory, temporally coincident with the COVID-19 pandemic period, between 2017 and 2024, while macrolide, lincosamide, and streptogramin consumption rose continuously and significantly throughout the same period, independent of the pandemic. Because this latter subgroup is predominantly classified as "Watch" under the WHO AWaRe framework, its sustained rise represents a stewardship concern distinct from the pandemic-driven fluctuation seen in beta-lactam use. Croatia's overall consumption in 2024 was significantly above the EU/EEA mean. Adriatic coastal counties showed disproportionately large fluctuations in total and beta-lactam consumption, a pattern that may partly reflect seasonal, tourism-related population dynamics not captured by resident-population denominators, rather than a true difference in per-patient prescribing intensity. We recommend that future national surveillance combine county-level reporting with AWaRe-category stratification, substance-level (ATC level 4/5) breakdowns, and tourism-adjusted population denominators and that stewardship interventions targeting macrolide overuse be prioritized alongside the existing focus on beta-lactams.

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Institutional Review Board Statement: Ethical review and approval were waived for this study. This is a retrospective, ecological analysis of aggregated, county-level antibiotic distribution data routinely compiled by the Croatian Agency for Medicinal Products and Medical Devices (HALMED) for national medicines-utilization surveillance. The dataset contains no patient-level identifiers, individual prescribing or dispensing records, diagnoses, or other protected health information; the unit of observation is the county-year, not the individual patient. The authors had no access to, and no contact with, identifiable patients, prescribers, or medical records at any stage of the study. As the analysis did not involve human participants, identifiable human data, or biological material in the sense covered by institutional or national research-ethics regulations, it fell outside the remit of a formal ethics committee review, consistent with the exemption criteria commonly applied to secondary analyses of routinely collected, non-identifiable administrative data.

Informed Consent Statement: Not applicable. Informed consent was neither required nor obtainable, because the study used only non-identifiable, aggregate, county-level distribution figures obtained from HALMED's national surveillance records; no individual patients were identified, contacted, sampled, or in any way involved in the research, and no individual-level data capable of being linked back to a person were analyzed. The waiver therefore rests on the aggregate, non-identifiable, and secondary (registry-derived) nature of the data, rather than on any determination made about individual participants.

Data Availability Statement: The data analyzed in this manuscript are aggregated annual antibiotic consumption figures, obtained from HALMED [3,4], and are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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