

Research article

Association between carbapenem resistance in invasive *Klebsiella pneumoniae* and antibacterial consumption in Türkiye: an ecological analysis using national surveillance data

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Abstract

Antimicrobial resistance (AMR) is driven not only by antimicrobial consumption but also by healthcare-associated transmission, the spread of resistant clones, and infection prevention and control practices. In this ecological study, we jointly evaluated consumption of antibacterials for systemic use (ATC group J01) in Türkiye from 2014 to 2023 and carbapenem resistance in invasive *Klebsiella pneumoniae* isolates from 2016 to 2023, with *Acinetobacter* spp., *Pseudomonas aeruginosa*, and *Escherichia coli* described as secondary context. Consumption data were obtained from the WHO Regional Office for Europe Antimicrobial Medicines Consumption (AMC) Network, and resistance data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network and CAESAR-linked national publications, using harmonized definitions. Given the small number of annual observations, trends were assessed using Theil–Sen median slopes with exact Kendall tests, and consumption–resistance associations using exact permutation-based Spearman tests. A potential 2020 breakpoint (onset of the COVID-19 pandemic) was explored for the consumption series only, using segmented regression with HC3 heteroskedasticity-consistent standard errors. Consumption was higher in 2023 than in 2014 (42.7 vs. 34.7 defined daily doses per 1,000 inhabitants per day [DID]), but no monotonic trend was detected over the full period (Theil–Sen slope –0.10 DID/year; 95% CI –1.42 to 1.10; exact Kendall $p = 1.000$). Carbapenem resistance in invasive *K. pneumoniae* rose from 29.5% to 55.0% (Theil–Sen slope +3.83 percentage points/year; 95% CI 2.90 to 4.85; exact Kendall $p < 0.001$). No statistically significant association was found between J01 consumption and *K. pneumoniae* carbapenem resistance in concurrent ($\rho = 0.262$; exact $p = 0.536$), one-year lagged, or first-difference analyses. In the segmented model, the immediate 2020 level change was not significant (–6.47 DID; HC3 $p = 0.184$), whereas the post-2020 slope change was significant (+6.54 DID/year; $p = 0.010$). These findings are consistent with a resistance epidemiology that aggregate J01 consumption alone does not explain, although the short series limits statistical power. Class-specific, sector-specific, and One Health-linked surveillance is needed.

Keywords: Antibiotic consumption, Antimicrobial resistance, Carbapenem resistance, *Klebsiella pneumoniae*, One Health, Türkiye

Introduction

Antimicrobial resistance (AMR) is one of the most significant global health problems of the 21st century, leading to treatment failure, longer hospital stays, higher healthcare costs, and increased mortality. According to a Global Burden of Disease (GBD) analysis, approximately 4.95 million deaths in 2019 were associated with bacterial AMR, of which about 1.27 million were directly attributable to AMR [1]. More recent modeling indicates that in 2021, 4.71 million deaths were associated with AMR, and 1.14 million were directly attributable to AMR. The same study predicts that the annual number of attributable deaths could reach about 1.91 million in 2050 [2].

Carbapenem resistance in Gram-negative pathogens is a particularly critical component of this global burden. The GBD 2021 analysis shows that deaths associated with carbapenem resistance increased from approximately 619,000 in 1990 to 1.03 million in 2021, with carbapenem resistance showing the largest increase among antibiotic classes examined in Gram-negative bacteria [2]. This

increase makes surveillance of microorganisms that play a significant role in healthcare-associated infections, such as *Klebsiella* (*K.*) *pneumoniae*, *Acinetobacter* (*A.*) *baumannii*, *Pseudomonas* (*P.*) *aeruginosa*, and *Escherichia* (*E.*) *coli*, even more crucial.

While antimicrobial use is a primary selective pressure for resistance, the relationship between consumption and resistance is not unidirectional, linear, or synchronous. The antibiotic class consumed, dose and duration, the distribution of community and hospital use, the spread of resistant clones, horizontal gene transfer, patient transfers, infection prevention and control practices, and environmental reservoirs all shape the epidemiology of resistance. Therefore, the antibacterials for systemic use (J01) indicator, representing total systemic antibacterial consumption, should not be expected to explain resistance in a specific pathogen-antibiotic combination alone. The World Health Organization (WHO) has developed the Access, Watch, and Reserve (AWaRe) classification to assess not only the quantity but also the quality of antibiotic use. Access antibiotics include agents

recommended as first- or second-line options for common infections and with relatively lower resistance-promoting potential; the Watch group includes antibiotics requiring close monitoring because of their higher resistance-promoting potential; and the Reserve group includes agents that should be preserved as last-resort options for multidrug-resistant (MDR) infections [3]. The 2024 global AMR policy declaration aimed for at least 70% of antibiotics used in humans to be from the Access group by 2030 [4].

Türkiye has long been among the countries with high antibacterial consumption in the WHO European region. The link between excessive antibiotic consumption and resistance in Türkiye has been previously highlighted [5], and the relatively high use of the Watch group in WHO Europe Antimicrobial Consumption (AMC) Network countries was also documented in the 2014–2018 European Region analyses [6]. A recent study evaluating 1.17 billion prescriptions in Türkiye's primary healthcare services found that between 2011 and 2019, antibiotic-containing prescriptions declined from 34.9% to 23.9%, and primary care antibiotic consumption decreased from approximately 42.3 DID to 31.9 DID [7]. However, because the study ended in 2019, it does not evaluate the pandemic and post-pandemic increase. The comparable 2014–2023 time series presented retrospectively in the WHO European Regional Office's 2023 AMC report shows that systemic antibacterial consumption in Türkiye rose again after a significant decrease in 2020, reaching 42.7 DID in 2023 [8]. During the same period, carbapenem resistance in Türkiye increased significantly, particularly for *K. pneumoniae*. Alhan et al. [9] reported that carbapenem resistance in *K. pneumoniae* rose from 11% in 2013 to 55% in 2023 in the national surveillance curve, while *Acinetobacter* spp. resistance remained at approximately 90% for a long period. Although Türkiye has addressed consumption and resistance separately, limitations remain in evaluating comparable national consumption series alongside invasive carbapenem resistance data using robust methods suitable for small time series within the same analytical framework. This study's unique contribution is not generating new surveillance data, but re-analyzing two independent national surveillance streams and quantitatively testing temporal parallels and divergences.

The primary objective is to assess the overall systemic antibacterial consumption trend in Türkiye from 2014–2023 and the robust temporal trend in invasive *K. pneumoniae* carbapenem resistance during 2016–2023. Secondary objectives include exploratory investigation of same-year, one-year, and two-year lagged relationships between total consumption and *K. pneumoniae* resistance; descriptive presentation of *Acinetobacter* spp., *P. aeruginosa*, and *E. coli* carbapenem resistance series; assessment of the consumption break around 2020 using

robust sensitivity analysis; and interpretation of findings in terms of AWaRe and One Health surveillance objectives.

Materials and methods

Study design and data sources

This retrospective, country-level ecological time-series study is based on secondary analysis of publicly available, aggregated surveillance data. The period 2014–2023 was used for systemic antibacterial consumption; the period 2016–2023, during which annual rates could be independently cross-validated, was used for primary invasive *K. pneumoniae* resistance analysis. Resistance series for other Gram-negative pathogens from 2014–2023 were used as secondary descriptive context. Systemic antibacterial consumption data were obtained from the WHO Regional Office for Europe Antimicrobial Medicines Consumption (AMC) Network reports. For the main time series, a comparable series from 2014–2023, retrospectively presented in WHO's 2025 “AMC data 2023” report [8], was used. Defined daily doses (DDD) per 1,000 inhabitants per day (DID) for systemic antibacterial drugs in the ATC J01 group were used to indicate antibacterial consumption. Population-weighted network averages from the long-term trend table of the same report were used for WHO/AMC comparisons; network averages from different tables were not combined into the same series, as country coverage may vary in annual cross-sectional reports.

The epidemiological framework for carbapenem resistance results was based on the WHO European Regional Office and Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) system. CAESAR reports invasive isolates, primarily blood and cerebrospinal fluid, and standardizes EUCAST/CLSI-based antimicrobial susceptibility data. For antibiotic-group results, CAESAR uses the R→I→S priority; the most resistant category among the agents in the group determines the group result [10]. The primary inference for *K. pneumoniae* was limited to the annual invasive carbapenem resistance percentages from 2016–2023. Because the 2014–2015 *K. pneumoniae* data could not be independently cross-validated across the various CAESAR-linked sources with the same confidence as the 2016–2023 series [9,11–14], we kept them only for descriptive purposes. As a result, major inferential studies were initially limited to the years 2016–2023.

The 2016–2021 rates were cross-validated with Gümüş and Köksal [11], who numerically reported CAESAR/EARS-Net surveillance data, and the official ECDC/WHO regional surveillance report [12]. The late 2022–2023 values were checked against Alhan et al. [9], who reported the WHO/CAESAR national trend. In addition, current CAESAR reports for the data years 2022

and 2023 were examined to verify the current surveillance coverage and Türkiye's participation [13, 14]. Because the annual numerator/denominator isolate series could not be archived completely and consistently for the entire period, we did not establish a model weighted by isolate number. To reduce measurement error and source sensitivity, annual rates from published national surveillance trends for *Acinetobacter* spp., *P. aeruginosa*, and *E. coli* were used only for descriptive purposes and excluded from the key inferential analysis.

Access, Watch, and Reserve (AWaRe) assessment

Türkiye's AWaRe distribution for 2014–2018 was evaluated using country-level data from the WHO Regional Office for Europe AMC Network 2014–2018 report [15]. Consumption volumes for Access, Watch, and Reserve, their percentages of total consumption, and the Access/Watch index were examined. Because the AWaRe analysis used the WHO report's definition, which includes a limited number of antibacterial agents beyond J01, total AWaRe values were not considered directly equivalent to total systemic antibacterial consumption based solely on the J01 group. The Access/Watch index was calculated as Access consumption divided by Watch consumption.

Statistical analysis

Annual data were summarized using baseline-to-end changes and relative percentages. To reduce reliance on assumptions of normality and constant variance in small time series, the main trend analysis was planned to be robust/nonparametric. The Theil–Sen median slope and 95% confidence interval were calculated for total J01 consumption (2014–2023) and invasive *K. pneumoniae* carbapenem resistance (2016–2023); a monotonic trend was assessed using the exact Kendall rank test. Series for the other three pathogens were reported descriptively, and their *p*-values were not included in the main inference.

Spearman rank correlation was used for the relationship between total J01 consumption and invasive *K. pneumoniae* carbapenem resistance. In the initial concurrent analysis ($n = 8$), we used precise two-sided permutation inference with all 40,320 possible permutations of one annual series relative to the other; the *p*-value was the ratio of permutations producing an absolute Spearman coefficient greater than or equal to the observed value. For $n = 8$, an absolute Spearman coefficient of roughly 0.738 is necessary to get a two-sided exact $p < 0.05$, suggesting that the study was particularly sensitive to robust monotonic relationships. In addition to the same-year relationship, we examined one-year- and two-year-lagged values of consumption and annual first differences in the sensitivity analyses. In the lagged analyses, antibacterial consumption in year t was correlated with *K. pneumoniae* carbapenem resistance in year $t + 1$ for the one-year lag and in year $t + 2$ for the two-

year lag. Thus, consumption was temporally arranged to occur before the resistance outcome. These analyses were exploratory and were not interpreted as evidence of a causal relationship.

Segmented linear regression to assess consumption patterns around 2020 was applied only to the J01 consumption series directly from WHO. The year 2020 was established a priori as the central breakpoint since it represented the commencement of the COVID-19 pandemic and considerable simultaneous transformations in health-care use and antibiotic prescribing practices; it was not selected via data-driven optimization. The model included the pre-pandemic slope, the 2020 level change, and the post-2020 slope change. Due to the availability of only 10 years of observations, in addition to classical ordinary least squares (OLS) standard errors, robust heteroskedasticity-consistent type 3 (HC3) standard errors, 95% confidence intervals, and *p*-values, which are more robust to heteroskedasticity in small samples, were calculated; HC3 results were used in the interpretation. This model was considered an exploratory pattern analysis around a predetermined 2020 breakpoint, not a causal pandemic effect analysis. The AWaRe 2014–2018 series was considered only descriptive; no inference was made to the five-year series [15].

Results

Annual trends in systemic antibacterial consumption and carbapenem resistance

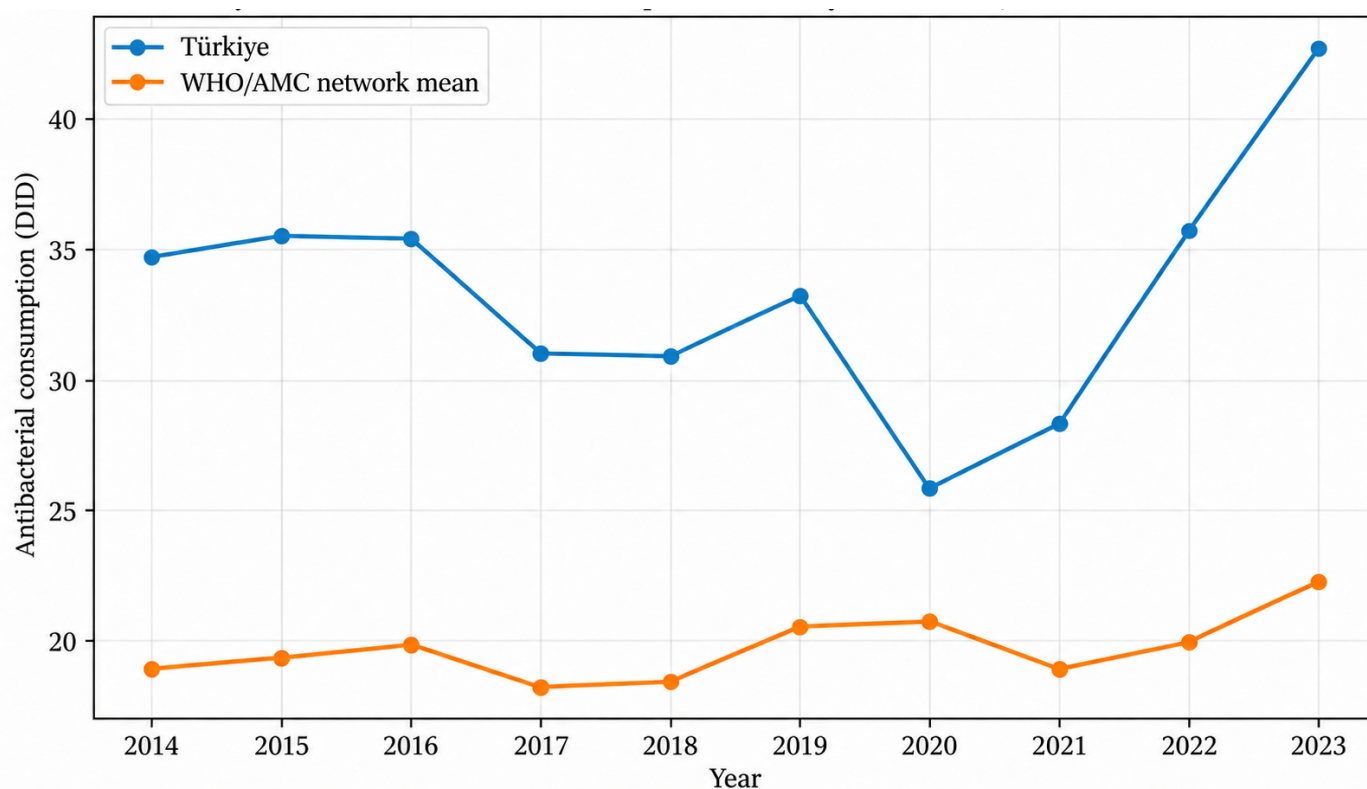
Total systemic antibacterial consumption in Türkiye from 2014 to 2023, the average of the WHO/AMC comparable trend series, and the published context of carbapenem resistance for four Gram-negative pathogens are presented in Table 1. Consumption of J01 decreased from 34.7 DID in 2014 to its lowest level of 25.8 DID in 2020 and then increased to 42.7 DID in 2023. The invasive *K. pneumoniae* rate used for primary resistance analysis was extracted and cross-validated as 29.5% in 2016, 32.5% in 2017, 34.4% in 2018, 39.4% in 2019, 48.2% in 2020, 49.1% in 2021, 52.0% in 2022, and 55.0% in 2023. Annual values for the other three pathogens were retained for descriptive context. Türkiye's consumption level was above the population-weighted average of the WHO/AMC trend series in all years. In 2023, Türkiye's value of 42.7 DID was 1.92 times the network average of 22.2 DID. The temporal trend of Türkiye and the WHO/AMC trend series is shown in Figure 1.

In the descriptive national series, *K. pneumoniae* showed the most pronounced increase in carbapenem resistance, while *Acinetobacter* spp. exhibited a high plateau of approximately 88–92%; *P. aeruginosa* and *E. coli* rates fluctuated at lower levels. Descriptive time series for these four pathogens are shown in Figure 2.

Table 1: Systemic antibacterial consumption, WHO/AMC trend-series mean, and carbapenem resistance among Gram-negative pathogens in Türkiye, 2014–2023.

Year	Türkiye J01 (DID)	WHO/AMC mean (DID)	<i>K. pneumoniae</i> (%)	<i>Acinetobacter</i> spp. (%)	<i>P. aeruginosa</i> (%)	<i>E. coli</i> (%)
2014	34.7	18.9	28.0	88	24	1
2015	35.5	19.3	30.0	88	32	2
2016	35.4	19.8	29.5	91	37	3
2017	31.0	18.2	32.5	90	37	3
2018	30.9	18.4	34.4	91	38	3
2019	33.2	20.5	39.4	89	38	3
2020	25.8	20.7	48.2	92	36	4
2021	28.3	18.9	49.1	92	39	5
2022	35.7	19.9	52.0	90	36	3
2023	42.7	22.2	55.0	90	41	4

J01 = antibacterials for systemic use; DID = defined daily doses per 1,000 inhabitants per day; WHO = World Health Organization; AMC = Antimicrobial Medicines Consumption. *K. pneumoniae* values for 2016–2023 constitute the primary inferential series and were cross-validated in CAESAR-linked publications. The remaining pathogen series are retained for descriptive context only and were not subjected to primary inferential testing.

**Figure 1:** Systemic antibacterial consumption in Türkiye and the population-weighted mean of the comparable WHO/AMC Network long-term trend series (2014–2023). Values are expressed as DID for ATC J01.

The primary inference was applied only to the cross-validated invasive *K. pneumoniae* 2016–2023 series because of its higher source sensitivity.

Linear trends and consumption-resistance correlations

In the robust trend analyses, the Theil–Sen slope for total J01 consumption from 2014 to 2023 was -0.10 DID/year (95% CI -1.42 to 1.10), and no monotonic trend was detected (Kendall $\tau = -0.022$; exact $p = 1.000$). In contrast,

invasive *K. pneumoniae* carbapenem resistance increased every year during 2016–2023. The Theil–Sen median slope was $+3.83$ percentage points/year (95% CI $+2.90$ – $+4.85$), and Kendall $\tau = 1.000$ (exact $p < 0.001$). Main and sensitivity analyses are summarized in Table 2.

No statistically detectable same-year association was observed between total J01 consumption and invasive *K. pneumoniae* carbapenem resistance during 2016–2023 (Spearman $\rho = 0.262$; exact permutation $p = 0.536$). The one-year lagged association was $\rho = -0.107$ (exact $p =$

0.840), the two-year lagged association was $\rho = -0.771$ (exact $p = 0.103$), and the association between annual first differences was $\rho = -0.468$ (exact $p = 0.291$). Despite the magnitude of the coefficient at a two-year lag, only six matched observations were found, so this result was

considered hypothesis-generating and not interpreted as a significant relationship. The different time patterns of J01 consumption and the primary *K. pneumoniae* series are shown in Figure 3.

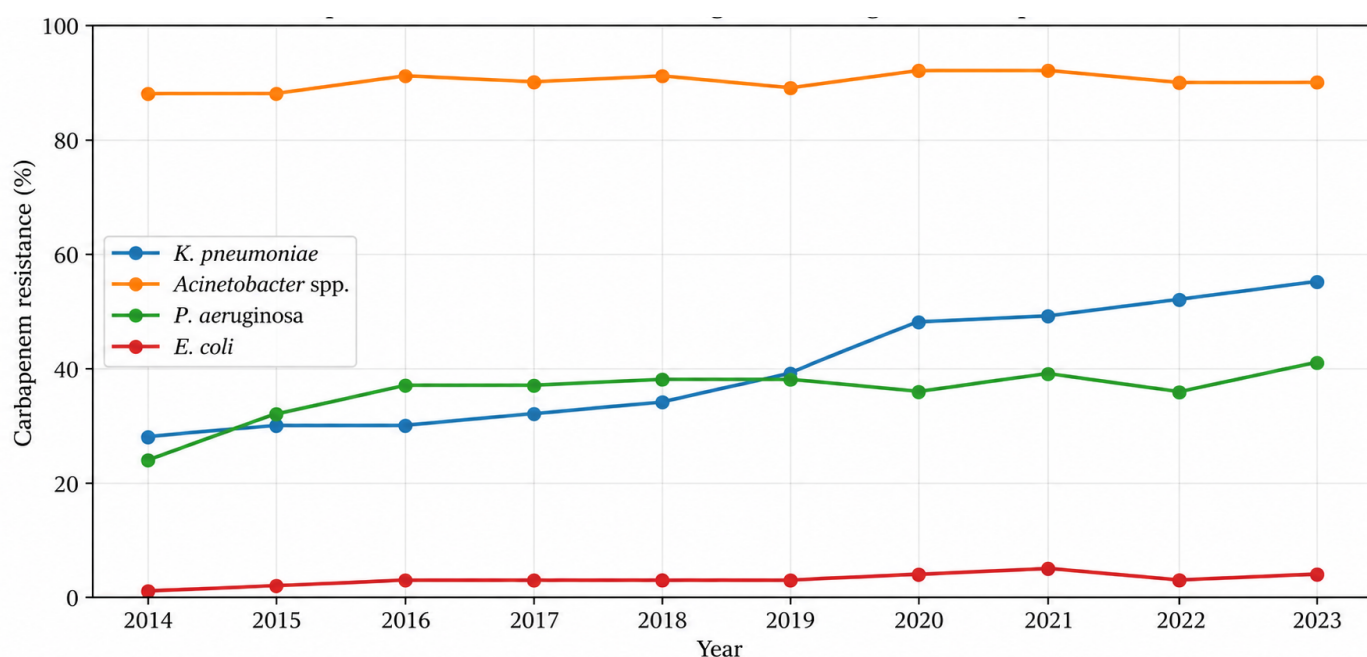


Figure 2: Descriptive time series of carbapenem resistance among major Gram-negative pathogens in Türkiye (2014–2023). The figure provides epidemiological context; primary inference is restricted to the cross-validated *K. pneumoniae* series for 2016–2023. Sources: Alhan et al. [9], Gümüş and Köksal [11], and the ECDC/WHO regional surveillance report [12].

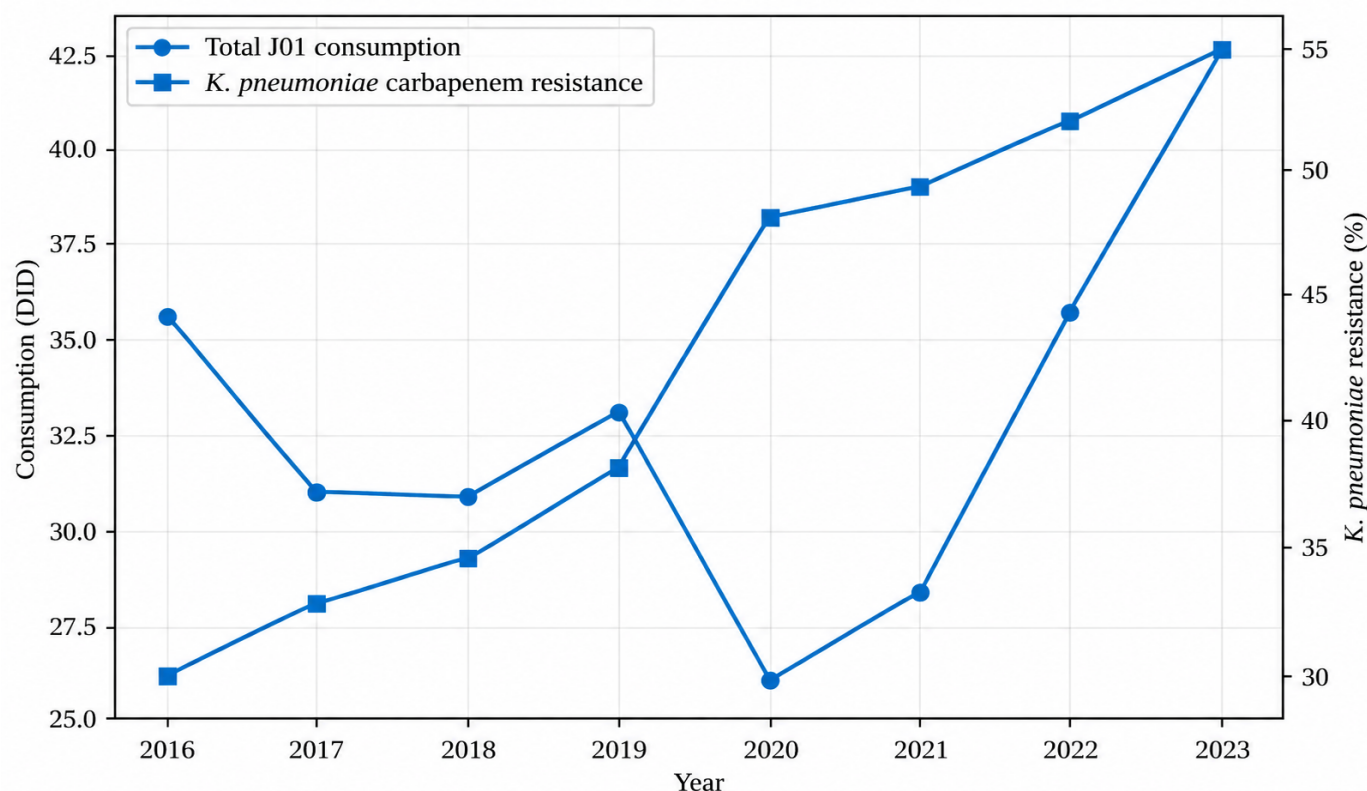


Figure 3: Comparative temporal patterns of total systemic J01 consumption and carbapenem resistance in invasive *K. pneumoniae* in Türkiye (2016–2023). The two series are displayed on separate scales, and visual co-movement should not be interpreted causally.

Table 2: Robust trend analyses and exact-permutation consumption–*K. pneumoniae* association analyses.

Analysis	Period	Estimate	95% CI	Statistic	<i>p</i> -value	Interpretation
Total J01 monotonic trend	2014–2023	Theil–Sen –0.10 DID/year	–1.42 to 1.10	Kendall τ = –0.022	1.000	No monotonic trend detected
Invasive <i>K. pneumoniae</i> trend	2016–2023	Theil–Sen +3.83 percentage points/year	2.90 to 4.85	Kendall τ = 1.000	< 0.001	Strong monotonic increase
Concurrent J01– <i>K. pneumoniae</i>	2016–2023	Spearman ρ = 0.262	—	Exact perm.	0.536	No detectable association
1-year lag	2017–2023	Spearman ρ = –0.107	—	Exact perm.	0.840	No detectable association
2-year lag	2018–2023	Spearman ρ = –0.771	—	Exact perm.	0.103	n = 6; hypothesis-generating
First differences	2017–2023	Spearman ρ = –0.468	—	Exact perm.	0.291	No detectable association

J01 = antibacterials for systemic use; DID = defined daily doses per 1,000 inhabitants per day; CI = confidence interval; n = number of annual observations or matched annual pairs, as applicable; τ = Kendall's tau coefficient; ρ = Spearman's rank correlation coefficient; exact perm. = exact permutation test. *K. pneumoniae* = *Klebsiella pneumoniae*. Because exact tests have a discrete permutation distribution in small samples, exact *p*-values may take coarse values; the *p* = 1.000 result should be interpreted in this context.

AWaRe consumption pattern

In Türkiye's AWaRe distribution between 2014–2018, the relative share of the Access group increased from 44% to 50%, while the share of the Watch group decreased from 54% to 47%, and the Access/Watch index increased from 0.83 to 1.06. However, since only five years of observation are available, a statistical trend test was not performed on this series. Türkiye did not meet the $\geq 60\%$ Access target used at that time in any year of the period. Annual values, obtained from the WHO Regional Office for Europe AMC Network 2014–2018 report [15], are presented in Table 3.

Exploratory analysis of structural change around 2020

In the OLS point estimation of the 2020 break segmented model, the pre-pandemic slope was –0.73 DID/year, the 2020 level change was –6.47 DID, and the post-2020 slope change was +6.54 DID/year. Using HC3 robust standard errors, which are more suitable for small samples, the pre-pandemic slope was not significant (95% CI –2.10–0.63; p = 0.235), and the 2020 sudden level change also remained non-significant (95% CI –17.02–4.08; p = 0.184). In contrast, the post-2020 slope change remained robust (95% CI 2.26–10.82; p = 0.010). Accordingly, the absolute slope after 2020 was calculated as +5.81 DID/year (95% CI 1.75–9.87; p = 0.013). The results are shown in Table 4 and the model in Figure 4.

Table 3: Antibiotic consumption in Türkiye by Access, Watch, and Reserve (AWaRe) category, 2014–2018.

Year	Access DID (%)	Watch DID (%)	Reserve DID (%)	Unclassified DID (%)	Access/Watch index
2014	15.7 (44)	19.0 (54)	0.03 (< 1)	0.6 (2)	0.83
2015	16.3 (44)	19.5 (53)	0.03 (< 1)	0.6 (2)	0.83
2016	16.7 (46)	18.9 (52)	0.04 (< 1)	0.7 (2)	0.88
2017	15.0 (47)	16.0 (50)	0.04 (< 1)	0.8 (3)	0.94
2018	16.0 (50)	15.1 (47)	0.02 (< 1)	0.7 (2)	1.06

The WHO AWaRe denominator includes selected antibacterial agents outside ATC J01; therefore, these totals are not directly interchangeable with the J01-only consumption series. Source: WHO Regional Office for Europe (2021). DID = defined daily doses per 1,000 inhabitants per day. Data presented in this table were obtained from the WHO Regional Office for Europe Antimicrobial Medicines Consumption (AMC) Network report for 2014–2018 [15].

Table 4: Exploratory segmented regression with a 2020 breakpoint: HC3 robust uncertainty estimates.

Outcome	Parameter	β	HC3 95% CI	Robust <i>p</i>
Total J01 consumption	Pre-2020 slope	–0.73 DID/year	–2.10 to 0.63	0.235
Total J01 consumption	Immediate 2020 level change	–6.47 DID	–17.02 to 4.08	0.184
Total J01 consumption	Post-2020 slope change	+6.54 DID/year	2.26 to 10.82	0.010
Total J01 consumption	Absolute post-2020 slope	+5.81 DID/year	1.75 to 9.87	0.013

β = estimated regression coefficient; HC3 = heteroskedasticity-consistent type 3; CI = confidence interval; OLS = ordinary least squares; DID = defined daily doses per 1,000 inhabitants per day. Point estimates were obtained from the segmented OLS model, whereas 95% confidence intervals and *p*-values were calculated using HC3 robust standard errors. The model is exploratory and should not be interpreted as demonstrating a causal effect of the COVID-19 pandemic.

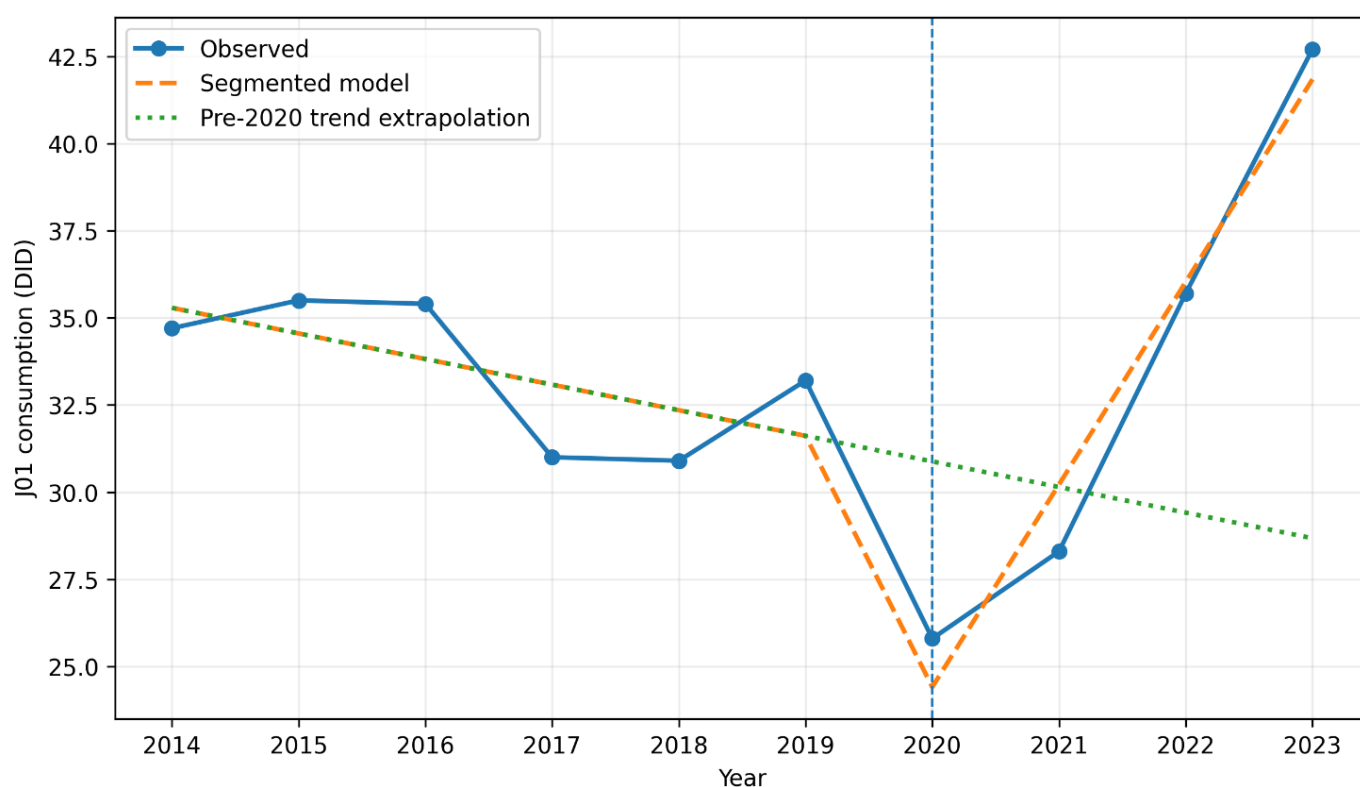


Figure 4: Exploratory segmented analysis of systemic antibacterial consumption in Türkiye with a 2020 breakpoint. Points show observed values, the dashed line shows the segmented model fit, and the dotted line extrapolates the pre-2020 trend for comparison. HC3 robust uncertainty estimates are reported in Table 4.

Discussion

The current ecological analysis reveals three key findings. First, Türkiye's systemic antibacterial consumption has remained high, reaching 1.92 times the WHO/AMC comparable trend average in 2023; however, no robust monotonic trend was detected during 2014–2023. Second, invasive *K. pneumoniae* carbapenem resistance, cross-verified with more sensitive sources, increased strongly and continuously between 2016 and 2023, with a Theil–Sen slope of approximately 3.83 percentage points per year. Third, no statistically detectable relationship was observed between total J01 consumption and this resistance series at the same-year, one-year lagged, or annual change level. This result does not suggest that antibiotic use plays no role in resistance development, but rather that the national total J01 indicator alone does not capture pathogen- and antibiotic class-specific selective pressure. Türkiye's 2023 consumption, approximately 1.92 times the WHO/AMC trend series average, points to an ongoing problem in antimicrobial management. Isler and colleagues previously identified antibiotic overuse in Türkiye as a key area for intervention to combat resistance [5]. Robertson et al. also highlighted high Watch group use in WHO Europe AMC Network countries during 2014–2018 [6].

Türkiye's Access share increased from 44% in 2014 to 50% in 2018, while the Watch share decreased from 54%

to 47%. Although this reflected a favorable shift in antibiotic consumption patterns, the Access share remained below the WHO target of at least 60% established for 2023. The subsequent global target of at least 70% Access antibiotic use by 2030 further emphasizes the importance of improving not only the overall quantity of antibiotic consumption but also antibiotic selection [4].

Primary care prescription data from Türkiye also show a decrease in antibiotic use during 2014–2019. Öztürk and Kayaaslan [7], in their national analysis covering 1.17 billion prescriptions, reported that primary systemic antibiotic consumption decreased from 42.3 DID in 2011 to 31.9 DID in 2019. This study extends the analysis to 2023 and shows a strong rebound after the pandemic. Thus, it becomes clear that the gains observed in the 2010s were not permanent in total consumption. The pattern around 2020 should be interpreted more conservatively, using HC3 robust uncertainty estimates for small samples rather than classical OLS results. In the HC3 robust analysis, the confidence interval for the sudden level change in 2020 includes zero ($p = 0.184$); therefore, the conclusion that "the pandemic caused a statistically significant sudden decrease in antibiotic consumption" is not supported. In contrast, the slope change after 2020 remained positive and statistically detectable with HC3. This finding suggests that the rapid rebound in consumption after the pandemic is the most stable

structural feature within the series. Although Högberg et al. [16] reported a decrease in community antibiotic consumption at the start of the pandemic in Europe, this study does not interpret this temporal correlation as a causal pandemic effect. However, a decrease in total national consumption does not mean that pressure on hospitals for broad-spectrum antibiotics has decreased.

A meta-analysis by Yang et al. [17], which evaluated 173 studies and 892,312 COVID-19 patients, reported that 76.2% of patients received antibiotics and that the prevalence of multidrug-resistant microorganisms was 42.9%. A single-center point-prevalence study in Türkiye also found that 65.9% of hospital antibiotic use was in the Watch group, 5.1% in the Reserve group, and 43.9% was inappropriate [18]. These findings support the idea that the national total J01 indicator may not adequately represent the selective pressure within hospitals.

Among the invasive *K. pneumoniae* series selected as the primary resistance outcome, the strongest AMR finding from a methodological perspective is the observed increase. Annual rates reported in CAESAR/EARS-Net-linked sources from 2016 to 2021 were 29.5%, 32.5%, 34.4%, 39.4%, 48.2%, and 49.1%, respectively [11, 12]; the national trend reached 52% in 2022 and 55% in 2023 [9]. Theil–Sen and exact Kendall results indicate that this increase is not attributable to a single outlier or to linear regression assumptions. Because CAESAR results are based on invasive isolates such as blood and CSF, and the representativeness of national networks may change over time, the rates should not be generalized to all *K. pneumoniae* infections in the population.

The approximately 90% persistent resistance observed in *Acinetobacter* spp. can be considered a “high resistance plateau.” This ceiling effect may also make it statistically difficult to detect correlations with annual changes in total consumption. In a systematic review of the molecular epidemiology of carbapenem-resistant *A. baumannii* in Türkiye, the *bla*OXA-23 gene was reported in 76.4% and *bla*OXA-51-like genes in 98.6% [19]. The persistence of highly resistant clones in hospital environments, their long-term survival on surfaces, horizontal gene transfer, and differences in infection control may contribute to sustained high resistance prevalence, independent of the total national antibiotic volume. The inability to demonstrate a significant relationship between total consumption and *K. pneumoniae* resistance should be interpreted with caution. The statistical power of the eight-year combined series is low. The exact correlation analysis was primarily suited to strong rank correlations and had limited ability to detect moderate associations because of the small number of matched annual observations ($n = 8$). Consequently, rather than saying “no association,” the finding should be stated as “no statistically detectable association was demonstrated at

this data resolution.” Furthermore, the J01 sum combines community and hospital use, different antibiotic classes, and selective pressure densities. Separate consumption of carbapenems, third-generation cephalosporins, fluoroquinolones, and other Watch/Reserve groups; hospital-level usage intensity, infection control indicators, and clonal spread may be more closely associated with resistance. The finding of $\rho = -0.771$ in the two-year lagged analysis, with an exact $p = 0.103$ due to $n = 6$, also underscores the importance of reporting both coefficient magnitude and statistical uncertainty in small sample sizes. Since AWaRe data cover only the period 2014–2018, this section is descriptive, not inferential. While the increase in Access share from 44% to 50% and the decrease in Watch share from 54% to 47% indicate a positive change, Türkiye has not met the $\geq 60\%$ Access target for the period. Not generating a p -value for the five-year series ensures that the results are interpreted in accordance with the data density. For the current 2030 $\geq 70\%$ Access target, reporting national AWaRe shares annually, and separately for hospitals and community, will be particularly important in the future.

This analysis focused solely on human health surveillance data and, as such, should not be interpreted as a complete One Health analysis. The conclusions have implications for upcoming One Health surveillance initiatives. The integrated surveillance system in Türkiye must link hospital and community antimicrobial consumption and resistance data with veterinary antimicrobial use, resistance in foodborne and indicator bacteria, and environmental indicators such as antimicrobial residues and resistome data from hospital, municipal, and surface waters, ideally within consistent temporal and geographic parameters.

The study's strengths lie in its data-source selection, analysis hierarchy, and statistical approach appropriate for small samples. The consumption series was drawn from a single WHO long-term comparable table; the resistance inference was limited to the *K. pneumoniae* series with the highest source sensitivity, and annual rates were cross-validated in independent CAESAR-linked publications. The Theil–Sen, exact Kendall, and exact permutation Spearman methods, appropriate for small samples, reduced reliance on classical parametric assumptions. The use of small-sample-sensitive HC3 standard errors in the 2020 segmented analysis prevented overinterpretation of the “sudden drop” result seen with classical OLS, which is not robust. Reducing the AWaRe and other pathogen series to a descriptive level reduces the risk of multiple weak inferences.

Limitations

The main limitation of the study is its ecological design; total country-level consumption and resistance rates do not establish causality between individual antibiotic

exposure and resistance. Therefore, an ecological fallacy is possible, and country-level correlations should not be interpreted as indicative of individual-level exposure–resistance interactions. Total J01 consumption obscures antibiotic class-specific usage and hospital/community distinctions. The availability of only eight years of observation in the primary *K. pneumoniae* analysis limits the power of correlation and lagged analyses. CAESAR data are based on invasive isolates and therefore do not represent all clinical infections, and the scope of laboratories participating in the surveillance network may vary between years. Because annual isolate numbers at the numerator/denominator level could not be fully and consistently archived for this study, a binomial or isolate-number-weighted model could not be applied as the main analysis; this is a key objective for future updating. The annual statistics for the secondary *Acinetobacter* spp., *P. aeruginosa*, and *E. coli* series were sourced from published national surveillance trends and are used exclusively for descriptive purposes; no inferential trend or correlation *p*-values were produced for these series. The 2020 segmented model is based on only a 10-year consumption series; even with HC3 uncertainty, the model is exploratory and cannot isolate the impact of the pandemic due to concurrent healthcare system changes. Since comparable annual series from Türkiye for the animal and environmental sectors were not included in the analysis, this study is not a complete One Health analysis, but rather an ecological study of human health that generates inferences for One Health surveillance.

Conclusion

In Türkiye, systemic antibacterial consumption reached 42.7 DID in 2023, 1.92 times the average of the WHO/AMC comparable trend series, but showed no significant monotonic trend during 2014–2023. In contrast, invasive *K. pneumoniae* carbapenem resistance increased from 29.5% to 55.0% between 2016 and 2023, showing a strong increase in robust/nonparametric analysis. No statistically significant same-year or one-year-lagged relationship could be demonstrated between total J01 consumption and resistance. While the sharp decrease in consumption in 2020 was not confirmed in the robust HC3 analysis, the rapid increase trend after 2020 emerged as a more stable finding. These results indicate a need for more detailed surveillance that combines antibiotic class, AWaRe group, hospital/community use, infection control, and molecular resistance mechanisms, rather than total antibiotic volume alone. Integrating human health data with animal, food, and environmental AMR data should constitute the next step within the One Health framework.

Declarations and supplementary information

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Author contributions: EOG conceptualized the study, designed the manuscript structure, and supervised the writing process. EOG, OG, SAT, DO and BGG contributed to the literature review, interpretation of the relevant studies, and drafting of the manuscript. EOG and SAT prepared the main manuscript text. OG, DO, and BGG critically reviewed and revised the manuscript for intellectual content.

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Ethics statement: Ethical approval was not required because the study involved no human or animal subjects and used only publicly available aggregated data.

Data accessibility: The antibacterial consumption data analyzed in this study are publicly available in the WHO Regional Office for Europe AMC Network reports “AMC data 2023” and “AMC data, 2014–2018”. Resistance definitions are based on the CAESAR manual version 3.0; annual percentages of invasive *K. pneumoniae* are based on CAESAR/EARS-Net-linked published sources, official regional surveillance reports, and national trend assessments.

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