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Original Research

Impact of the Italian antimicrobial resistance National Action Plan on antibiotic consumption in primary care: An interrupted time series analysis from 1999 to 2024

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ABSTRACT

Objectives: Antimicrobial resistance (AMR) is a major global health threat, largely driven by inappropriate and excessive antibiotic use. Italy has historically reported antibiotic consumption rates above the European average, especially in primary care. In 2017, Italy implemented the National Action Plan on Antimicrobial Resistance (NAP-AMR), including targets for reducing overall community antibiotic and fluoroquinolone use. This study evaluated the impact of NAP-AMR on antibiotic consumption trends in Italian primary care from 1999 to 2024.
Study design: Quasi−experimental interrupted time series study.
Methods: Annual ECDC data were expressed as defined daily doses (DDD) per 1000 inhabitants per day. Total antibiotic consumption was analyzed for 1999–2024 and fluoroquinolone consumption for 2005–2024. Segmented linear regression with Newey−West standard errors estimated post−2017 changes in level and trend. Total systemic antibiotic consumption was the primary outcome, and fluoroquinolone consumption was the secondary outcome.
Results: Total antibiotic consumption showed a significant pre−intervention upward trend, increasing annually by 0.10 DDD per 1000 inhabitants per day (annual change = 0.096; p = 0.032; 95% CI: 0.014 to 0.178). NAP-AMR implementation was associated with a significant immediate reduction in total antibiotic use (mean level difference = −4.940; p = 0.003; 95% CI: −7.864 to −2.016), while the post−intervention slope change was not significant (annual change = 0.126; p = 0.606; 95% CI: −0.346 to 0.599). Fluoroquinolone consumption showed a significant pre−intervention upward trend (annual change = 0.039; p = 0.016; 95% CI: 0.011 to 0.066) and a significant immediate reduction (mean level difference = −1.079; p = 0.023; 95% CI: −1.910 to −0.248). The post−intervention trend was negative but not significant (annual change = −0.219; p = 0.096; 95% CI: −0.459 to 0.021).
Conclusions: NAP-AMR was associated with immediate reductions in total antibiotic and fluoroquinolone consumption, but sustained trend changes were not statistically significant. No significant long-term trend change was observed, underscoring ongoing surveillance and future evaluation.

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1. Introduction

Antimicrobial resistance (AMR) represents a major public health issue, with severe health and economic consequences. Globally, 1.14 million deaths attributable to AMR and 4.71 million deaths associated with AMR were estimated in 2021.[1] Within the European Union/-European Economic Area (EU/EEA), AMR contributed to approximately 35,800 deaths in 2020, with a slight decrease compared to the previous year (about 38,700 deaths), but still an increase compared to 2016, when around 30,700 deaths were reported. A particularly high burden was observed in Italy,[2] with just under one third of all deaths (about 11, 000) recorded in the EU/EEA and nearly double the number of cases compared with an EU country of similar size, such as France.[3] Economically, worse projections indicate a loss of 3.8% of the annual GDP by 2050 worldwide, with an annual shortfall of $3.4 trillion by 2030.[4]

Resistance is primarily driven by the inappropriate and excessive use of antimicrobial agents.[5] It may develop intrinsically or through acquired genetic mutations and is driven by multifactorial influences at individual, clinical, and population levels. Key contributors include the over-prescription of antibiotics, inappropriate use in livestock production, suboptimal infection prevention and control (IPC) measures, limited availability of new antibiotics, inadequate diagnostic capabilities, and poor hygiene practices.[6] Inappropriate antibiotic use exerts selective pressure that accelerates the emergence and dissemination of resistant strains.[7] Furthermore, AMR is driven not only by antibiotic use in humans and animals and by the spread of resistant pathogens and resistant genes in the environment, but also by broader, social, governance and economic factors.

In Italy, approximately 90% of antibiotics for systemic use are prescribed in primary care settings; local data indicate that broad-spectrum antibiotic prescriptions exceed the European average by more than threefold, and these agents are associated with a higher risk of promoting AMR compared to narrow-spectrum antibiotics.[8–10] The use of broad-spectrum antibiotics is often associated with empirical therapy, particularly when diagnostic turnaround times are prolonged.[11] Empirical treatments and self-medication further contribute to resistance's development.[12]

In response to the growing global threat posed by AMR, the World Health Organization (WHO) launched in 2015 the Global Action Plan on Antimicrobial Resistance (GAP-AMR), which urged all member states to formulate and implement National Action Plans (NAPs-AMR).[13] The GAP-AMR promotes a One Health approach, recognizing the interconnectedness of human, animal, and environmental health in tackling AMR. The EU's commitment to combating AMR was further reinforced by the 2017 One Health Action Plan and Regulation (EU) 2022/2370, which mandates updated AMR reporting every three years.

Italy introduced the first NAP-AMR (Piano Nazionale di Contrasto all'Antimicrobico Resistenza - PNCAR) in 2017, with a timeline set to end in 2020, and later extended to 2021 due to the COVID-19 pandemic.[14] This plan emphasized actions in surveillance of AMR, antibiotic use and Healthcare Associated Infections (HAIs), prevention of infections caused by antibiotic-resistant microorganisms, antimicrobial stewardship, diagnostics, healthcare workforce training, public awareness, and research.

This study aims to evaluate the impact of the Italian NAP-AMR 2017–2020 on antibiotic consumption in the primary care setting, to detect changes in trends associated with the policy's implementation.

2. Methods

2.1. Study design

A quasi-experimental design was used, applying an interrupted time series (ITS) approach to evaluate the impact of the Italian NAP-AMR on trends in total antibiotic consumption and on fluoroquinolone use in primary care. ITS relies on regularly collected outcome data before and after an intervention, enabling identification of changes in level or slope at the implementation point. This method quantifies both immediate and sustained effects while accounting for underlying pre-intervention trajectories. As randomized controlled trials are often impractical in public health settings, ITS provides a robust alternative, yielding strong evidence of intervention effects through comparison of pre- and post-implementation periods.[15] Fluoroquinolones were analyzed separately, as they represent a key NAP-AMR indicator and their use is frequently associated with inappropriate prescribing.

2.2. Intervention

The Italian NAP–AMR 2017–2020 is a coordinated One Health strategy integrating human, veterinary, food-safety, agricultural, and environmental sectors to reduce the epidemiologic and economic burden of antimicrobial resistance. It defines joint actions in resistance and antibiotic-use surveillance, HAI prevention and control, antimicrobial stewardship in community and hospital settings, diagnostic strengthening, workforce training, public communication, and research, all embedded within a national–regional governance system with explicit monitoring and accountability.

More specifically, the Plan is structured around three main pillars, including surveillance, infection prevention and control, and appropriate antimicrobial use, supported by cross-cutting actions on governance, communication, training, and research. It establishes a coordinated framework of responsibilities at national and regional levels, with designated focal points, technical coordination groups, implementation timelines, and annual monitoring mechanisms to assess progress and support periodic updating of actions and targets. In the human sector, it aims to reduce systemic antibiotic use by more than 10% in the community and by more than 5% in hospitals compared with 2016, with additional reductions targeted for fluoroquinolones in both settings. It also sets explicit targets for reducing the prevalence of key resistant pathogens, including methicillin-resistant *Staphylococcus aureus* and carbapenemase-producing Enterobacterales, while expanding regional surveillance coverage. In the veterinary sector, it promotes reduced use of antibiotics overall, oral formulations, and critically important antimicrobials, including colistin, alongside improved traceability and monitoring. Overall, the NAP combines measurable targets, structured governance, and periodic evaluation to support sustained implementation and ensure accountability. The main components and selected numerical targets of the Italian NAP-AMR 2017–2020 are reported in Supplementary Material Table S1. These quantitative objectives operationalize prudent prescribing and ensure consistent regional evaluation, enabling iterative policy adjustments to maintain effectiveness during and beyond the 2017–2020 period.

2.3. Data collection

Data on total antibiotic consumption in Italian primary care from 1999 to 2024 and on fluoroquinolones from 2005 (first year available) to 2024 were obtained from the ECDC database.[16] The first analysis examined community use of antibiotics in ATC group J01, while the second focused specifically on fluoroquinolones (ATC J01MA), both within the primary care setting. The dataset covers all age groups and both sexes, providing a comprehensive picture of systemic antibacterial use in the general population. Consumption was measured in defined daily doses (DDD) per 1000 inhabitants per day,[17] the WHO-recommended standardized unit that enables robust cross-national comparability and reliable temporal trend assessment by normalizing usage to population size and standardized dosing.[18]

2.4. Statistical analyses

The ITS analysis was performed using a segmented linear regression

model with Newey–West robust standard errors,[15,19] accounting for residual autocorrelation up to two previous time points (lag = 2) and heteroscedasticity, while allowing estimation of intervention-related level and slope changes. Newey–West corrections ensure consistent variance–covariance estimates even when residuals display serial correlation or non-constant variance. The model included a continuous time trend, a dummy variable marking the intervention, and an interaction term capturing the post-intervention slope change, specified as:

$$Yt = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t$$

where Y_t is antibiotic consumption in DDD per 1000 inhabitants per day, T is time, and X_t indicates pre- (0) and post-intervention (1) periods. β_0 represents the baseline level, β_1 the underlying secular trend, β_2 the immediate post-intervention shift, and β_3 the change in trend thereafter. A secondary exploratory analysis of total antibiotic use applied the same modelling approach but excluded 2020–2021, treating these pandemic-affected years as outliers. Model assumptions were assessed through residual diagnostics: heteroscedasticity via the Breusch-Pagan test, stationarity via the KPSS test[20] and normality via QQ plots, both confirming appropriate specification. The intervention effect was expressed as the absolute difference between observed and counterfactual consumption with 95% confidence intervals, and results were considered significant when intervals excluded zero. All analyses were conducted in R 4.4.1.

3. Results

3.1. Descriptive analysis

During the study period, the highest levels of antibiotic consumption in Italy were recorded in 2009, 2008, and 2013 (23.727, 23.595, and 23.323 DDD per 1000 inhabitants per day, respectively), whereas the lowest values were observed in 2017, 2020, and 2021 (19.015, 16.499, and 15.991 DDD per 1000 inhabitants per day, respectively) (Table 1). Overall consumption decreased by about 4.4% between 1999 and 2024 and by 11% between 1999 and the introduction of the NAP-AMR in 2017. The minimum levels coincided with the COVID-19 pandemic years, followed by an increase in 2022–2023 toward values similar to those observed before 2017. Between 2016 and 2020, annual antibiotic consumption decreased by 5.337 DDD per 1000 inhabitants per day (−24.44%), compared with a more modest reduction of 1.395 DDD per 1000 inhabitants per day (−6.39%) between 2016 and 2024. Over the study period, fluoroquinolone consumption in DDD per 1000 inhabitants per day showed an initial increase from 3.096 in 2005 to a peak of 3.879 DDD per 1000 inhabitants per day in 2013, followed by a sustained decline, particularly after 2015. The highest consumption was observed in 2013, whereas the lowest value was recorded in 2021, at 1.770 DDD per 1000 inhabitants per day. In 2024, consumption was 1.781 DDD per 1000 inhabitants per day, corresponding to a 42.5% decrease compared with 2005, indicating an overall marked downward trend over the study period. From 2016 to 2020, annual fluoroquinolone consumption decreased by 1.729 DDD per 1000 inhabitants per day (−48.0%), with a similarly marked reduction observed through 2024 (−50.56%).

Table 1
Annual antibiotic consumption in primary care in Italy from 1999 to 2024.

Year	Overall Antibiotic Consumption (DDD per 1000 inhabitants/day)	Fluoroquinolone Consumption (DDD per 1000 inhabitants/day)
1999	21.382	-
2000	20.952	-
2001	22.095	-
2002	20.921	-
2003	21.801	-
2004	21.053	-
2005	22.095	3.096
2006	22.311	-
2007	22.872	3.594
2008	23.595	3.733
2009	23.727	-
2010	23.024	3.781
2011	23.097	3.770
2012	22.515	3.800
2013	23.323	3.879
2014	22.626	3.786
2015	22.383	3.801
2016	21.836	3.602
2017	19.015	3.054
2018	19.497	2.996
2019	19.798	2.241
2020	16.499	1.873
2021	15.991	1.770
2022	20.048	1.974
2023	21.182	1.932
2024	20.441	1.781

3.2. Impact of NAP-AMR on antibiotic consumption in primary care

Following implementation of the NAP-AMR in 2017, antibiotic use in primary care showed a statistically significant reduction (Fig. 1). Before the intervention, consumption was increasing over time ($\beta = 0.096$, 95% CI [0.014, 0.178], $p = 0.032$), corresponding to an estimated annual change of 0.096 DDD per 1000 inhabitants per day (+0.4% yearly increase of consumption). The intervention produced a marked immediate drop, corresponding to an estimated mean level difference of −4.940 DDD per 1000 inhabitants per day (95% CI [−7.864, −2.016], $p = 0.003$), equivalent to approximately 5 DDD per 1000 inhabitants per day in the year after implementation (−21.4% immediate reduction of consumption). The post-intervention slope was not significant ($\beta = 0.126$, 95% CI [−0.346, 0.599], $p = 0.606$), indicating no further sustained change in trend beyond the initial decline. Residual diagnostics supported model adequacy: the KPSS test showed level stationarity (KPSS = 0.068, $p > 0.10$), and the QQ plot indicated approximate normality, with only two right-tail observations deviating from expectation, a pattern consistent with small-sample residual analyses. These findings reinforce the temporal association between NAP-AMR implementation and the observed reduction in antibiotic consumption (Table 2).

3.3. Impact of NAP-AMR on antibiotic consumption excluding COVID-19 pandemic years

When 2020–2021 were excluded, the pre-intervention trajectory remained significantly increasing ($\beta = 0.096$, 95% CI [0.014, 0.178], $p = 0.033$), corresponding to an annual rise of about 0.1 DDD per 1000 inhabitants per day (+0.4% yearly increase in consumption) (Fig. 2). The policy was associated with a sharp and highly significant immediate decline ($\beta = -4.033$, 95% CI [−5.087, −2.979], $p < 0.0001$), of roughly 4 DDD per 1000 inhabitants per day (−17.4% immediate reduction in consumption). Thereafter, the slope became significantly positive ($\beta = 0.135$, 95% CI [0.021, 0.249], $p = 0.031$), indicating that consumption increased over time following the initial drop, at a rate exceeding the pre-intervention growth, with an annual increase of approximately 0.14 DDD per 1000 inhabitants per day (+0.7% yearly increase in consumption). Model checks confirmed reliability: the Breusch–Pagan test did not detect heteroskedasticity (BP = 3.568, $p = 0.312$), the KPSS test supported level stationarity (KPSS = 0.113, $p \geq 0.10$), and the QQ plot showed approximately normal residuals (Table 2).

3.4. Impact of NAP-AMR on fluoroquinolone consumption in primary care

The pre-intervention period showed a modest but significant upward trend ($\beta = 0.039$, 95% CI [0.011, 0.066], $p = 0.016$), corresponding to an annual increase of 0.039 DDD/1000 inhabitants/day (+1.0% yearly

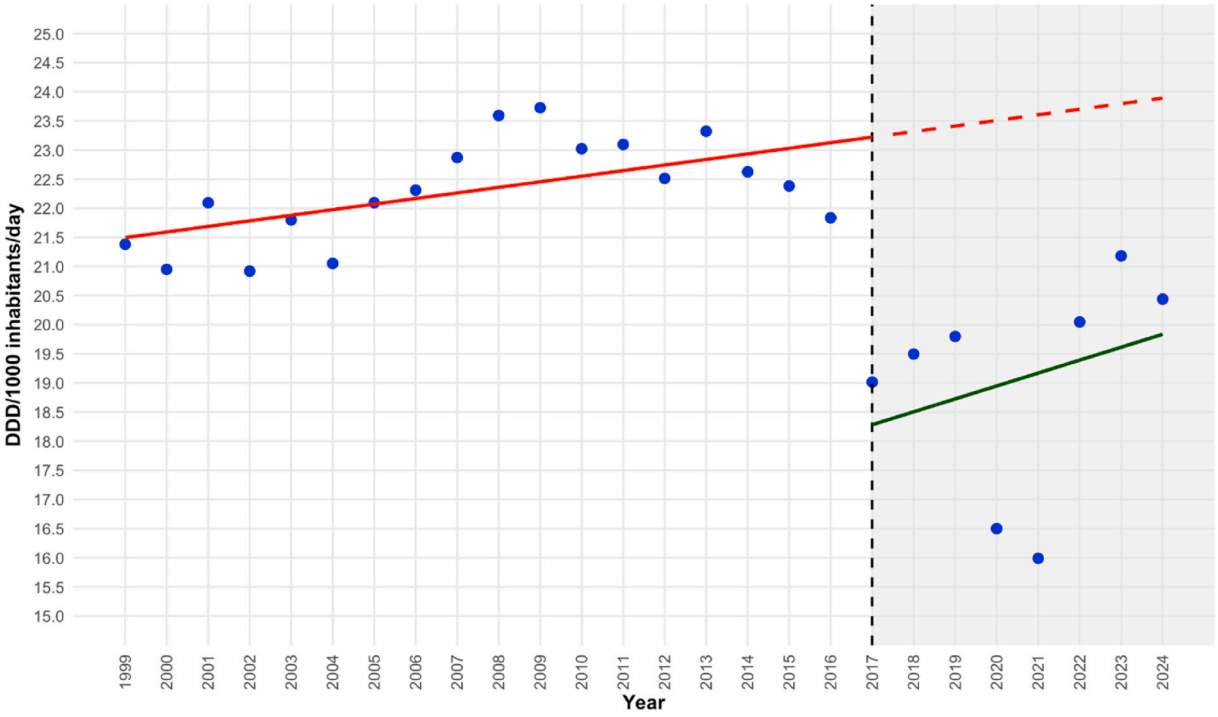


Fig. 1. Interrupted Time Series Analysis of Total Antibiotic Consumption - Observed values and model-based predictions under intervention and counterfactual scenarios from 1999 to 2024.

Table 2
Summary of segmented ITS models and sensitivity analyses across outcomes.

Outcome	Model	Pre-intervention trend beta (95% CI); p-value	Level change beta (95% CI); p-value	Post-intervention slope change beta (95% CI); p-value
PNCAR 2017-2020 antibiotic consumption analysis (all classes) over the entire historical series	Linear ITS (Newey–West estimator)	0.096 (0.014 to 0.178); p = 0.032	−4.940 (−7.864 to −2.016); p = 0.003	0.126 (−0.346 to 0.599); p = 0.606
PNCAR 2017-2020 antibiotic consumption analysis (all classes) over the entire historical series (excluding 2020-2021)	Linear ITS (Newey–West estimator)	0.096 (0.014 to 0.178); p = 0.033	−4.033 (−5.087 to −2.979); p < 0.001	0.135 (0.021 to 0.249); p = 0.031
PNCAR 2017-2020 antibiotic consumption analysis (fluoroquinolones only) over the entire historical series	Linear ITS (Newey–West estimator)	0.039 (0.011 to 0.066); p = 0.016	−1.079 (−1.910 to −0.248); p = 0.023	−0.219 (−0.459 to 0.021); p = 0.096

increase in consumption). As shown in Fig. 3, the introduction of the NAP-AMR was associated with a significant immediate reduction in use (β = −1.079, 95% CI [−1.910, −0.248], p = 0.023), reflecting an abrupt level decrease of 1.079 DDD/1000 inhabitants/day in fluoroquinolone consumption (−27.6% immediate decrease in consumption). In the subsequent period, the slope turned slightly negative (β = −0.219, 95% CI [−0.459, 0.021], p = 0.096), suggesting a tendency toward continued gradual decline that did not reach conventional statistical significance. Diagnostic tests indicated an adequate model: the Breusch–Pagan test did not suggest heteroskedasticity (BP = 5.40, p = 0.145), the KPSS test showed level-stationary residuals (KPSS = 0.077, p ≥ 0.10), and QQ plot indicated approximately normal residuals with mildly lighter tails than expected under perfect normality (Table 2).

4. Discussion

4.1. Main findings and interpretation

We observed a steady and structural increase in antibiotic consumption in the period prior to the implementation of the NAP-AMR, suggesting that, in the absence of regulation, prescribing tends to follow a self-perpetuating pattern. This increase is consistent with previously reported evidence of inappropriate prescribing, limited awareness, insufficient stewardship, diagnostic barriers, and weak centralized surveillance,[21] which contribute to clinical and economic risks, longer hospitalizations, complications, and reliance on costly second- and third-line therapies, undermining primary care and contributing to avoidable hospital admissions.[22,23]

The 2017 NAP-AMR introduced coordinated measures to reduce consumption and contain resistance. However, despite a significant reduction in consumption at the intervention point, which may reflect an immediate NAP-AMR effect, this impact did not persist, suggesting a transient policy response, often described as “legislative shock” or “policy fade-out”.[24] We observed a sharp decline in antibiotic consumption in 2020–2021, mirroring EU/EEA trends[25] and coinciding with the COVID-19 pandemic, during which containment measures were shown to reduce the spread of respiratory infectious diseases and antibiotic prescribing.[26,27] Overall consumption dropped by almost 25% from 2016 to 2020, exceeding the NAP-AMR target of a >10% reduction. However, once the external pressure of the pandemic subsided, a rebound toward pre-2017 values was observed in 2022-2023. This pattern is further supported by the sensitivity analysis: when the period 2020-2021 is excluded, the post-intervention trend becomes significantly positive, with antibiotic use increasing faster than before,

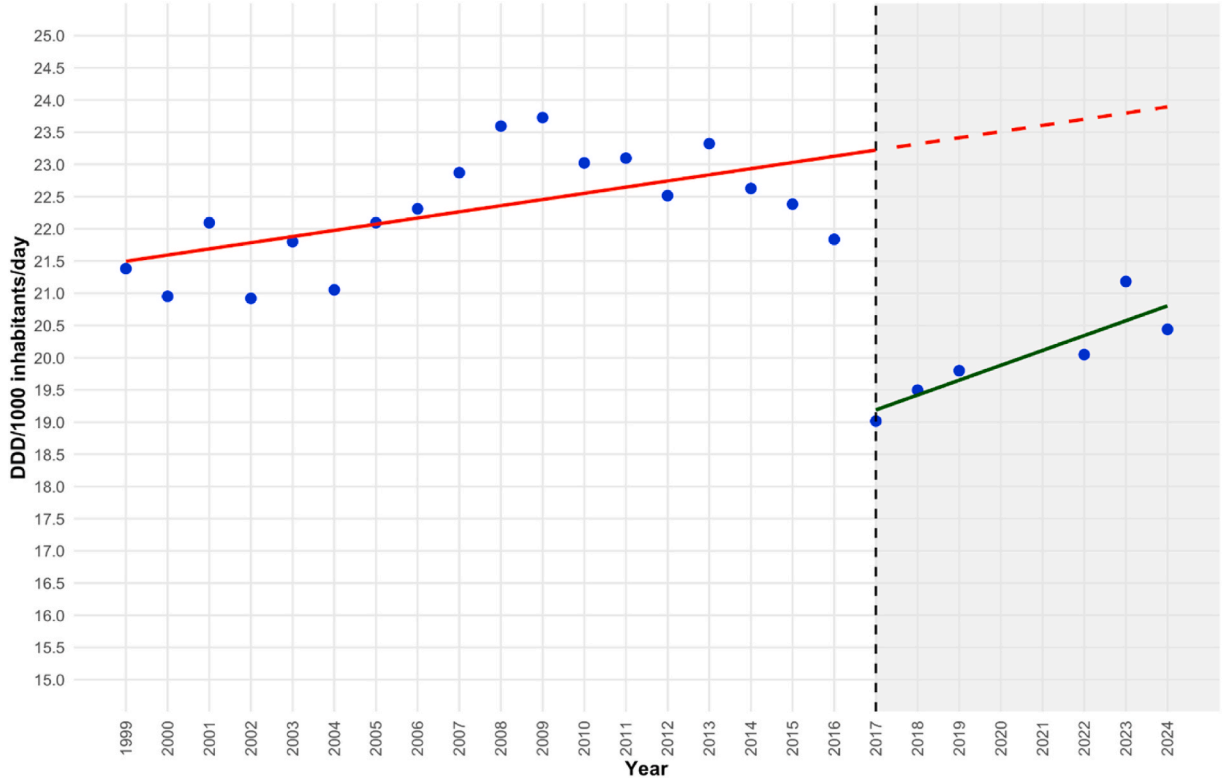


Fig. 2. Interrupted Time Series Analysis of Antibiotic Consumption – Observed values and model-based predictions under intervention and counterfactual scenarios from 1999 to 2024, excluding data for 2020 and 2021.

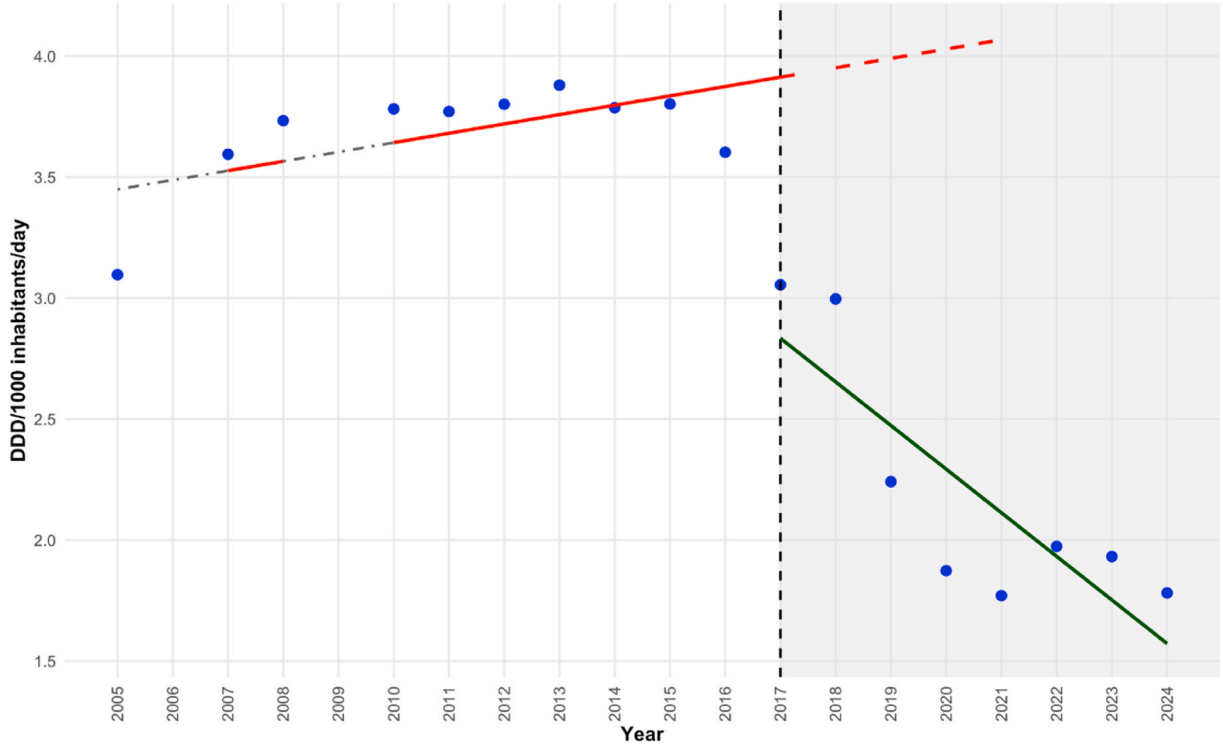


Fig. 3. Interrupted Time Series Analysis of Fluoroquinolones Consumption - Observed values and model-based predictions under intervention and counterfactual scenarios from 2005 to 2024.

suggesting that the pandemic partially masked an underlying increase in consumption following the initial policy-associated decline. Between 2016 and 2024, total antibiotic consumption declined by 6.39%, confirming that the sharp reduction recorded in 2020 was not consolidated into a structural change in prescribing practice, and underscoring the need for continued strategies and actions, including prevention,

monitoring and assessment.[28]

Considering fluoroquinolone trends, we found a reduction of approximately 48% between 2016 and 2020, above the national target of a >10% target, and remained nearly unchanged through 2024 (−50.56%), suggesting that the policy was effective. This is particularly relevant given that fluoroquinolones exert high selective pressure, promoting resistance in *E. coli*, *K. Pneumoniae*, and *N. gonorrhoeae*, and are linked to adverse events such as *C. difficile* infection.[29–31] Their classification in the WHO AWaRe group "Watch"[32] further underscores why sustained reductions in their use represent a meaningful indicator of stewardship progress.

4.2. Policy implications

These findings highlight the need to translate policy into real and lasting implementation, through sustained changes in prescribing and patient behavior, rather than one-off regulatory interventions. Italy's NAP score of 72% on EU criteria, higher than Spain (51%) and much higher than the Netherlands (37%), illustrates that planning quality alone may not guarantee implementation effectiveness.[33]

Since around 90% of antibiotics in Europe are prescribed in primary care,[10] strengthening stewardship in this setting is a priority.[34–36] Even moderate reductions in prescribing can reverse resistance trends within a few years,[37] and community-based interventions combining rational prescribing, patient education, point-of-care diagnostics, and audit-feedback have consistently demonstrated reductions in unnecessary antibiotic use.[38–40] An integrated approach combining proactive IPC measures with coordinated communication between primary and hospital care can further enhance the sustainability of these gains.

After the end of the NAP-AMR 2017–2020, Italy adopted the NAP-AMR 2022–2025,[28] which represents a more operational and integrated strategy, strengthening the One Health approach, expanding surveillance and monitoring across human, animal and environmental sectors, and placing greater emphasis on prevention, stewardship, regional benchmarking and integration of prescription data with AMR surveillance systems. The NAP-AMR 2022-2025 also sets more explicit targets for reducing antimicrobial use, including selected critical classes (such as fluoroquinolones), although recent evidence suggests that antibiotic use in Italy remains above the EU average and unevenly distributed across regions.[41] Rigorous evaluation of this plan will be essential to determine whether more structured implementation can achieve durable reductions in prescribing.

4.3. Limitations

This study has several limitations. First, the short post-intervention period limits assessment of long-term sustainability, a constraint further compounded by the inclusion of the COVID-19 outliers (2020-2021). Second, aggregated ECDC data lack stratification by age, sex, region or antibiotic class (beyond fluoroquinolones), potentially masking heterogeneity; hospital data fragmentation precluded inclusion. Third, the interrupted time series design was conducted without a control group, so observed changes should be interpreted as temporal associations rather than causal effects of the NAP-AMR and may reflect seasonality, regional initiatives, regulatory changes, public awareness, surveillance changes, or secular trends. Future studies should incorporate subnational data, genomic surveillance and stewardship compliance metrics.

4.4. Conclusion

The implementation of the public health actions included in the Italian NAP-AMR 2017–2020 was associated with a significant immediate reduction in primary care antibiotic consumption, although no sustained change in the post-intervention trend was observed. The subsequent rebound during the COVID-19 pandemic further suggests that this early reduction was not maintained over time. Beyond planning, rigorous implementation is needed: antimicrobial stewardship for prudent prescribing, IPC multimodal strategies to curb infections, integrated One Health surveillance, and continuous training and education for primary care providers. Ongoing NAP 2022–2025 evaluation and cross-country ITS are essential for scalable AMR strategies.

Author contributions

All authors contributed to study conception and design. Material preparation and data collection were performed by MB, SM and FP. MB and MCN performed statistical analysis. The first draft of the manuscript was written by MB, SM, FP and LV. PL, AS, AA, PP, LV and WR commented on the latest version of the manuscript. LV and WR supervised the study. All authors read and approved the final version of the manuscript.

Ethics approval

This study does not require ethical approval as it exclusively utilizes aggregate data and does not involve the collection or analysis of any personal information pertaining to individual participants.

Declaration of generative AI in scientific writing

Generative AI and AI-assisted technologies were used exclusively during the writing process to enhance the readability and language of the manuscript, under human oversight and control.

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Declaration of competing interest

The authors declare no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2026.106391.

Data availability

Antibiotic consumption data are publicly available; analytical datasets can be provided upon reasonable request.

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