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Pediatric Outpatient Fluoroquinolone Dispensing After EMA/AIFA Safety Restrictions: A Regional Interrupted Time-Series Analysis from Southern Italy

Maurizio Aricò [1], Cataldo Procacci [2,*], Pasquale Stefanizzi [1], Claudia Palmieri [1] and Silvio Tafuri [1]

[1] Interdisciplinary Department of Medicine, Aldo Moro University of Bari, 70121 Bari, Italy
[2] Pharmaceutical Department, Barletta-Andria-Trani Local Health Authority, 76125 Trani, Italy
* Correspondence: aldo.procacci@aslbat.it; Tel.: +39-3451537844

Abstract

Background/Objectives: Pediatric fluoroquinolone use is restricted because of safety concerns and antimicrobial-stewardship priorities. We described outpatient dispensing trends in Apulia, Italy, during 2019–2024 and examined whether the June 2023 EMA/AIFA safety reminder coincided with an additional change in utilization. Methods: This regional population-based drug-utilization study analysed reimbursed outpatient fluoroquinolone dispensing records among residents aged 0–14 years. Annual rates were expressed per 1000 pediatric residents; defined daily doses (DDDs) were secondary measures. Monthly dispensing-record rates were analysed by segmented interrupted time-series regression, using June 2023 as the interruption and Newey–West standard errors (maximum lag 3). Results: Dispensing records fell from 786 in 2019 to 509 in 2024 (−35.2%), and standardized rates decreased from 1.51 to 1.08 per 1000 pediatric residents (−28.2%). DDD per 1000 residents decreased from 8.30 to 5.65. The estimated pre-reminder monthly slope was negative but not statistically significant ($\beta = -0.000522$; $p = 0.305$). Neither the immediate level change ($\beta = +0.013316$; $p = 0.415$) nor the post-reminder slope change ($\beta = -0.000150$; $p = 0.852$) was statistically significant. Results for all fluoroquinolones were robust to sensitivity analyses addressing seasonality and the COVID-19 pandemic; for ciprofloxacin, two exploratory specifications yielded nominally significant level increases. Conclusions: Pediatric outpatient fluoroquinolone dispensing in Apulia decreased over six years, although its trajectory was not monotonic. The interrupted time-series analysis detected no statistically significant additional level or slope change following the June 2023 reminder. These findings describe utilization within an evolving regulatory and stewardship context but cannot establish the effects of earlier restrictions or assess the clinical appropriateness of individual dispensings.

Keywords: antimicrobial stewardship; child; drug utilization; pharmacoepidemiology; pharmacovigilance

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1. Introduction

Fluoroquinolones are broad-spectrum antibacterial agents with high oral bioavailability and activity against several Gram-negative and selected Gram-positive pathogens. Despite these pharmacological advantages, their role in pediatric practice has remained restricted for decades because of concerns regarding cartilage toxicity, arthropathy, tendinopathy, and other potentially severe adverse reactions. These concerns originally derived largely from

preclinical observations showing quinolone-associated cartilage injury and arthropathy in juvenile animals [1].

Early pediatric clinical experience suggested a more nuanced picture. In a worldwide compassionate-use series of ciprofloxacin in children, Chyský et al. specifically evaluated joint-related safety because of the arthropathogenic potential observed in juvenile animals [2]. The subsequent pediatric literature has continued to support a cautious but not absolute approach. Severe musculoskeletal toxicity appears uncommon in children, but uncertainty regarding long-term safety has contributed to restricting systemic fluoroquinolone use to selected situations in which other effective agents are unavailable or inappropriate [3–5].

The rationale for restricting fluoroquinolone use has progressively evolved from concerns focused primarily on cartilage toxicity toward a broader assessment of rare but serious, disabling, long-lasting, and potentially irreversible adverse reactions involving multiple organ systems. In Europe, the European Medicines Agency and the Italian Medicines Agency introduced major restrictions on systemic and inhaled fluoroquinolones following a European safety review completed in 2018 and implemented in 2019 [6,7]. These recommendations were reinforced in 2023, when EMA and AIFA issued a further reminder because fluoroquinolones continued to be prescribed outside recommended indications [8,9]. In Italy, the fluoroquinolone-containing medicines addressed by AIFA safety communications included ciprofloxacin, levofloxacin, moxifloxacin, pefloxacin, prulifloxacin, rufloxacin, norfloxacin, and lomefloxacin [10]. These agents differ in their approved indications and age-related restrictions; their inclusion in regulatory communications does not imply authorization for routine pediatric use.

A similar risk-management trajectory has occurred in the United States. The U.S. Food and Drug Administration progressively strengthened fluoroquinolone safety warnings, expanding concerns from tendon-related toxicity to peripheral neuropathy, neuropsychiatric effects, dysglycaemia, and vascular complications, while recommending more restrictive use in situations where alternative treatment options are available [11]. Additional FDA communications subsequently reinforced warnings on mental health effects, serious hypoglycaemia, and the risk of aortic aneurysm or dissection in selected high-risk patients [12,13]. These U.S. regulatory actions are relevant to the interpretation of European prescribing trends because they indicate that fluoroquinolone restriction is part of a broader international pharmacovigilance signal rather than an isolated EMA/AIFA position.

Evidence from other settings suggests that regulatory restrictions may not be uniformly translated into clinical practice. A recent Brazilian drug-utilization study reported a substantial increase in quinolone prescriptions among children aged 0–10 years between 2014 and 2019, exceeding the growth observed in the overall population [14].

In Italy, antibiotic utilization is systematically monitored by the Italian Medicines Agency through the National Observatory on Medicines Utilization (OsMed), which integrates pharmaceutical dispensing data and publishes national and regional reports. The annual national report on antibiotic use includes analyses by age group, healthcare setting, and antibiotic class, providing a framework for interpreting regional pediatric dispensing patterns [15].

Against this background, we evaluated outpatient pediatric fluoroquinolone dispensing in Apulia, Southern Italy, during 2019–2024. Our primary aim was to quantify population-standardized utilization trends; our secondary aim was to evaluate whether the June 2023 EMA/AIFA reminder was temporally associated with additional changes in dispensing, overall and for ciprofloxacin. Because observation began in 2019, the study was not designed to estimate the effect of the original 2019 restrictions.

2. Results

2.1. Annual Utilization Trends

Between 2019 and 2024, pediatric outpatient fluoroquinolone dispensing records in Apulia decreased from 786 to 509, corresponding to a 35.2% reduction in absolute counts. Over the same period, the total volume of dispensed fluoroquinolones, expressed in defined daily doses (DDD), decreased from 4319.5 to 2655.5 DDD, corresponding to a reduction of 38.5%. Population-standardized dispensing-record rates decreased from 1.51 to 1.08 per 1000 pediatric residents, corresponding to a relative reduction of 28.2%, while DDD-based rates decreased from 8.30 to 5.65 per 1000 residents aged 0–14 years (Table 1; Figure 1A,B).

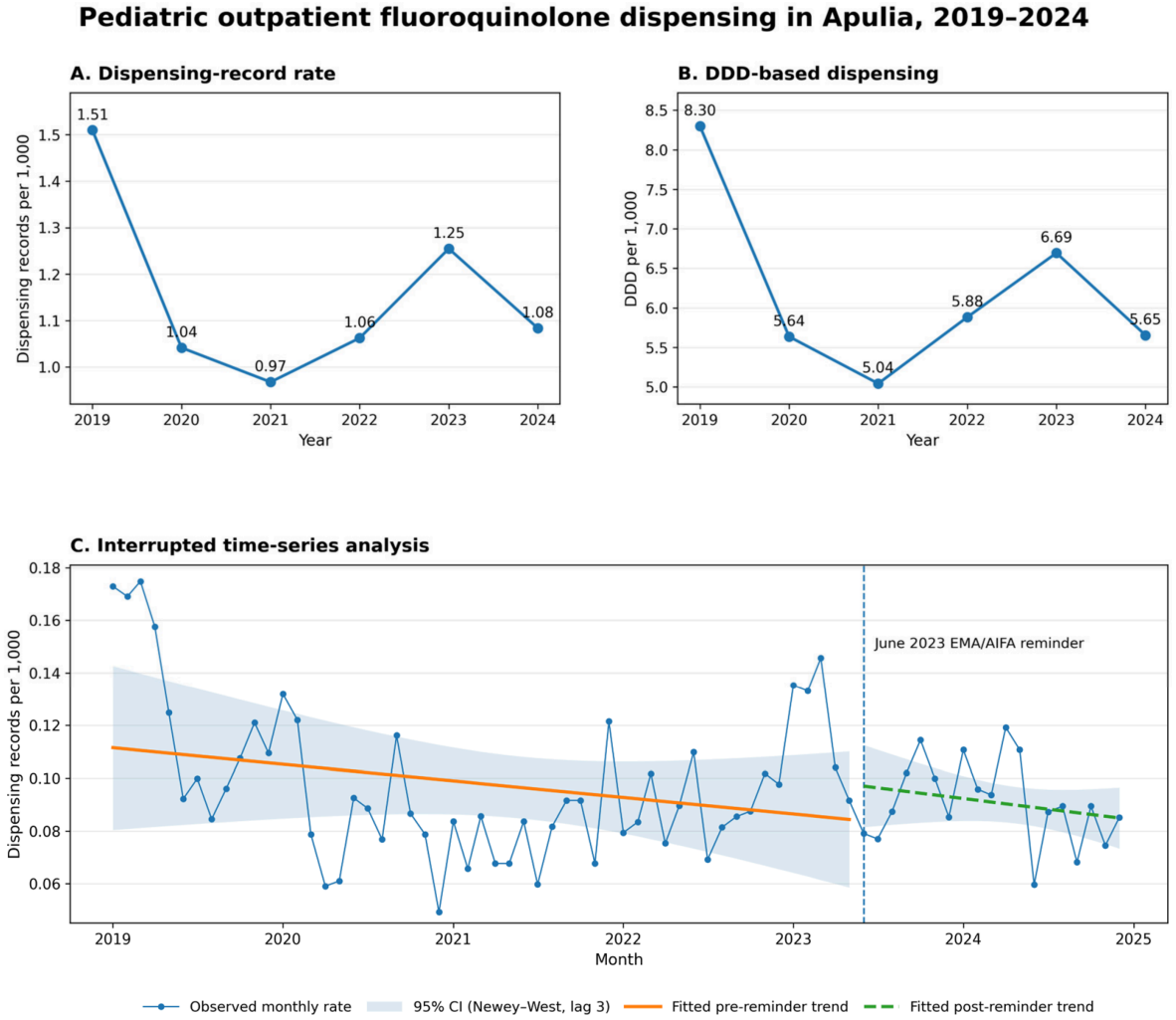


Figure 1. Pediatric outpatient fluoroquinolone use in Apulia, 2019–2024. (**A**) Annual outpatient fluoroquinolone dispensing-record rates per 1000 pediatric residents aged 0–14 years. (**B**) Annual dispensed fluoroquinolone volume expressed as defined daily doses (DDD) per 1000 pediatric residents aged 0–14 years. (**C**) Interrupted time-series analysis of monthly dispensing-record rates per 1000 pediatric residents. The vertical dashed line marks the June 2023 EMA/AIFA reminder. Solid and dashed fitted lines represent the pre-reminder and post-reminder segmented trends, respectively; shaded areas indicate 95% confidence intervals. Segmented linear regression models were estimated using Newey–West heteroskedasticity- and autocorrelation-consistent standard errors with a maximum lag of 3 months.

Table 1. Annual pediatric fluoroquinolone dispensing and DDD-based utilization indicators, Apulia, 2019–2024.

Indicator	2019	2020	2021	2022	2023	2024
Pediatric population aged 0–14 years	520,560	507,823	502,136	491,274	480,548	469,662
Dispensing records, n	786	529	486	522	603	509
Dispensing records per 1000 pediatric residents	1.51	1.04	0.97	1.06	1.25	1.08
Total DDD	4319.5	2862.0	2532.0	2890.0	3217.0	2655.5
DDD per 1000 pediatric residents	8.30	5.64	5.04	5.88	6.69	5.65

DDD, defined daily doses. Rates were calculated using the annual resident population aged 0–14 years in Apulia as denominator. Dispensing records refer to outpatient pharmaceutical dispensing records captured in the regional administrative database.

The annual pattern was not monotonic. After an initial decline between 2019 and 2021, both dispensing records and DDD-based utilization increased in 2022 and 2023, followed by a renewed decrease in 2024. Total DDD reached a minimum of 2532.0 in 2021, increased to 2890.0 in 2022 and 3217.0 in 2023, and declined to 2655.5 in 2024. Dispensing records showed a similar pattern, decreasing to 486 in 2021, increasing to 603 in 2023, and subsequently declining to 509 in 2024 (Table 1).

Most fluoroquinolone dispensing records involved children aged 3–14 years, whereas dispensing among children aged 0–2 years remained uncommon throughout the observation period. In 2023, 585 dispensing records were observed among children aged 3–14 years, compared with 18 among children aged 0–2 years; in 2024, the corresponding values were 485 and 24, respectively. Dispensing-record rates in children aged 0–2 years remained very low, ranging from 0.53 per 1000 residents in 2019 to 0.23–0.31 per 1000 in subsequent years. Among children aged 3–14 years, rates decreased from 1.71 per 1000 residents in 2019 to 1.24 per 1000 in 2024, with an intermediate increase to 1.46 per 1000 in 2023.

The reduction in total dispensed fluoroquinolone DDD mainly involved ciprofloxacin, levofloxacin, and prulifloxacin. Ciprofloxacin DDD decreased from 2751.0 in 2019 to 1615.5 in 2024, corresponding to a 41.3% reduction, while levofloxacin declined from 1262.5 to 867.0 DDD, a 31.3% reduction. Prulifloxacin decreased from 255.0 to 125.0 DDD, corresponding to a 51.0% reduction. Moxifloxacin increased from 20.0 to 35.0 DDD, but its dispensed volume remained very low throughout the study period.

2.2. Interrupted Time-Series Analysis Results

In the interrupted time-series analysis of monthly fluoroquinolone dispensing-record rates, the estimated pre-reminder trend was negative but was not statistically significant after accounting for autocorrelation (β −0.00052 dispensing records per 1000 pediatric residents per month; Newey–West SE 0.00051; 95% CI −0.00152 to 0.00047; $p = 0.305$). No statistically significant immediate level change was observed following the June 2023 EMA/AIFA reminder (β +0.0133 per 1000; Newey–West SE 0.0163; 95% CI −0.0187 to 0.0453; $p = 0.415$). Similarly, the post-reminder slope did not differ significantly from the preceding trend (slope change β −0.00015 per 1000 per month; Newey–West SE 0.00080; 95% CI −0.00173 to 0.00143; $p = 0.852$) (Table 2; Figure 1C).

In the ciprofloxacin-specific interrupted time-series analysis, the estimated pre-reminder trend was also negative but not statistically significant (β −0.00030 dispensing records per 1000 pediatric residents per month; 95% CI −0.00080 to 0.00020; $p = 0.243$). Neither the immediate level change following the June 2023 reminder (β +0.0143 per 1000; 95% CI −0.0037 to 0.0323; $p = 0.119$) nor the subsequent slope change (β −0.00077 per 1000 per month; 95% CI −0.00175 to 0.00020; $p = 0.119$) was statistically significant (Table 2).

Table 2. Interrupted time-series analysis of monthly pediatric fluoroquinolone dispensing-record rates before and after the June 2023 EMA/AIFA reminder.

Model	Parameter	Estimate	Newey–West SE	95% CI	*p* Value
All fluoroquinolones	Pre-reminder monthly trend	−0.000522	0.000508	−0.001518 to 0.000475	0.305
	Immediate level change	+0.013316	0.016323	−0.018676 to 0.045308	0.415
	Post-reminder slope change	−0.000150	0.000804	−0.001727 to 0.001426	0.852
Ciprofloxacin	Pre-reminder monthly trend	−0.000299	0.000256	−0.000800 to 0.000203	0.243
	Immediate level change	+0.014306	0.009166	−0.003660 to 0.032271	0.119
	Post-reminder slope change	−0.000774	0.000496	−0.001745 to 0.000198	0.119

Estimates are expressed as changes in dispensing records per 1000 pediatric residents aged 0–14 years. Segmented linear regression models included time, a post-reminder indicator beginning in June 2023, and time after the reminder. Heteroskedasticity- and autocorrelation-consistent Newey–West standard errors were calculated using a maximum lag of 3 months. The pre-reminder trend represents the monthly slope before June 2023; the immediate level change represents the discontinuity at the intervention point; and the post-reminder slope change represents the difference between the post- and pre-reminder monthly slopes. CI, confidence interval; SE, standard error.

Sensitivity analyses incorporating calendar-month fixed effects, early-lockdown exclusions, or a pandemic-period indicator did not identify statistically significant post-reminder level or slope changes for overall fluoroquinolone dispensing (Table S2). The corresponding principal sensitivity models for ciprofloxacin were also nonsignificant. However, two additional exploratory specifications combining seasonal adjustment with the exclusion of pandemic-affected months yielded nominally significant positive immediate level changes for ciprofloxacin ($p = 0.033$ and $p = 0.047$), without significant slope changes. These findings were sensitive to modelling choices, and the reported p values were not adjusted for multiple comparisons. Across the primary and sensitivity models, 2 of 32 reminder-related coefficients were nominally significant ($p < 0.05$), compared with approximately 1.6 expected under the nominal 5% threshold if all null hypotheses were true. However, these estimates were correlated across overlapping model specifications, and this comparison should not be interpreted as a formal multiple-testing assessment. Both nominally significant coefficients indicated higher, rather than lower, ciprofloxacin dispensing after the reminder.

2.3. Seasonal Variation

Monthly data showed modest seasonal variation, with fluoroquinolone use generally higher during the colder months. Using equal-duration six-month periods (October–March vs. April–September), the cold-to-warm DDD ratio ranged from 1.02 to 1.39 across the study period. Seasonal differences were most evident in 2019 and 2023 and were minimal in 2024, when cold- and warm-season DDD totals were nearly comparable (Table S1).

3. Discussion

In this regional population-based study, pediatric outpatient fluoroquinolone dispensing in Apulia decreased substantially between 2019 and 2024, both in absolute dispensing records and in population-standardized DDD-based utilization. The annual trajectory was not monotonic, with a partial rebound in 2022–2023, but utilization in 2024 remained markedly below that observed in 2019. Interrupted time-series analysis did not identify a statistically significant immediate level change or slope change following the June 2023 EMA/AIFA reminder. Although the estimated pre-reminder monthly slope was negative, it was not statistically significant after accounting for autocorrelation.

The absence of a detectable discontinuity in June 2023 is compatible with gradual changes in utilization but does not establish that earlier regulatory restrictions or stewardship initiatives caused the observed reduction. The 2023 communication reiterated

measures introduced in 2019 [6–9], and the present series has no untreated comparator. Previous studies have documented the potential of pediatric antimicrobial stewardship interventions to reduce broad-spectrum antibiotic use [16] and substantial variability in antibiotic use across children's hospitals [17]. Changes in pediatric antibiotic prescribing during the COVID-19 pandemic have also been reported in Italy [18]. These observations provide relevant context but cannot explain the regional trends observed in our study.

Restrictions on fluoroquinolones reflect longstanding pediatric safety concerns, initially focused on cartilage and joint toxicity and subsequently encompassing potentially serious multisystem adverse reactions [1–13,19]. Our earlier magnetic resonance follow-up of fluoroquinolone-exposed children contributes to the safety literature [20]. However, the present administrative dataset contains no adverse-event information and cannot directly connect dispensing changes to clinical risk.

Chronic respiratory conditions, particularly cystic fibrosis, may contribute to a proportion of pediatric fluoroquinolone dispensing. Oral ciprofloxacin has been used in treatment regimens for *Pseudomonas aeruginosa* infection in cystic fibrosis [21], whereas moxifloxacin is not routinely used for antipseudomonal treatment in this setting [22]. The small increase in dispensed moxifloxacin volume (from 20.0 to 35.0 DDD) therefore cannot be attributed to cystic fibrosis on the basis of our data. Moreover, the Italian Cystic Fibrosis Registry indicates that the pediatric population with cystic fibrosis has remained broadly stable in recent years, despite an increase in the adult population [23]. Because clinical indications and treatment courses were unavailable, the contribution of chronic conditions or repeated antibiotic treatment to the observed dispensing trends could not be quantified. Because the pediatric cystic fibrosis population appears broadly stable [23], cystic fibrosis-related use would be expected to contribute a relatively constant component to dispensing; it is therefore unlikely to explain the overall decline, although it could attenuate relative changes.

International findings suggest considerable variation in pediatric quinolone utilization. A Brazilian study reported increasing quinolone prescribing among children during 2014–2019 [14], whereas several regulatory and antimicrobial-resistance initiatives internationally have sought more selective antibiotic use [11–13,24–26]. Different denominators, reimbursement systems and age definitions preclude direct quantitative comparison.

National Italian surveillance provides additional context. The AIFA OsMed report documented a decline in fluoroquinolone utilization beginning in 2019, followed by a partial rebound in 2022–2023 and a renewed decrease in 2024. Other major antibiotic classes showed different post-pandemic trajectories [15]. Although these national patterns are broadly consistent with our regional observations, differences in population coverage and utilization indicators preclude direct quantitative comparisons with our pediatric dispensing-record rates.

The overall decline in fluoroquinolone dispensing may reflect several overlapping influences, including increased awareness of regulatory safety warnings, growing concern about potentially serious adverse reactions, antimicrobial resistance, and more selective use of broad-spectrum antibiotics. However, the present study did not measure individual prescribing indications, clinician decisions, local antimicrobial stewardship interventions, or microbiological resistance patterns. These factors should therefore be regarded as plausible contextual explanations rather than demonstrated determinants of the observed decline. The available data do not permit causal attribution of the observed changes to specific regulatory, stewardship, or pandemic-related influences.

Cold-season DDD modestly exceeded warm-season DDD, with ratios ranging from 1.02 to 1.39 across years (Table S1). Sensitivity analyses incorporating calendar-month fixed effects did not identify a statistically significant post-reminder level or slope change for overall fluoroquinolone dispensing. However, ciprofloxacin-specific level-change estimates

showed some model dependence in exploratory specifications combining seasonal adjustment with pandemic-period exclusions (Table S2). The direction of these estimates—higher rather than lower ciprofloxacin dispensing after the reminder—is not consistent with a restrictive regulatory effect. A plausible explanation is the non-linear 2022–2023 rebound in dispensing (Figure 1C), which a single linear pre-reminder trend cannot fully capture. Given the number of specifications examined, these isolated estimates should be regarded as hypothesis-generating rather than as evidence of a reminder effect.

Several limitations warrant emphasis. Dispensing data lack clinical indications, microbiological results, treatment duration and previous antibiotic exposures, preventing individual-level assessment of appropriateness. Dispensing records should not be interpreted as individual prescriptions, unique treated patients, or actual medication intake. Moreover, DDDs are based on adult maintenance doses and may not accurately reflect pediatric dosing.

Although the source database included a pseudonymous patient identifier, the present analyses did not quantify repeated dispensings per child or distinguish intermittent from prolonged or recurrent treatment courses. A small subset of children with chronic conditions could therefore have contributed disproportionately to dispensing records and DDD totals, with an uncertain influence on estimated temporal trends.

The primary ITS used a single regional series without an untreated comparator. Although sensitivity analyses examined seasonality and pandemic-related perturbations, these adjustments cannot eliminate time-varying confounding. Newey–West standard errors account for autocorrelation and heteroskedasticity but do not address confounding. The nominally significant ciprofloxacin level-change estimates in selected exploratory models warrant cautious interpretation, particularly given multiple comparisons, reduced sample sizes, and dependence on model specification. Nonsignificant coefficients do not demonstrate absence of an effect. Because observation began in January 2019, there was no adequate pre-restriction baseline to estimate reliably the initial impact of the measures introduced during 2019.

The main contribution is a six-year regional description of pediatric outpatient fluoroquinolone dispensing, supported by a cautiously interpreted segmented time-series analysis.

4. Materials and Methods

4.1. Study Design and Setting

We conducted a retrospective, population-based drug-utilization study of outpatient systemic fluoroquinolone use among children aged 0–14 years residing in Apulia, Southern Italy, between January 2019 and December 2024. The study evaluated temporal trends in fluoroquinolone utilization and explored whether the EMA/AIFA safety reminder issued in June 2023 was associated with a measurable change in population-level dispensing patterns. The study was reported with reference to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement, an extension of the STROBE reporting guidelines for observational studies based on routinely collected health data [27]. A RECORD reporting checklist is provided as Supplementary File S1.

4.2. Data Source and Study Population

Data were obtained from the regional administrative flow of National Health Service–reimbursed outpatient pharmaceutical dispensing, established under Article 50 of Decree-Law No. 269/2003, converted into Law No. 326/2003 [28]. Data were extracted from Edotto, the Apulian regional healthcare information system [29], by an authorized pharmacist of LHA BAT within the scope of institutional pharmaceutical monitoring activities.

Records were selected for systemic fluoroquinolones (ATC J01MA) dispensed between January 2019 and December 2024 to residents of Apulia aged 0–14 years, with age determined at the dispensing date. The unit of analysis was the individual dispensing record, corresponding to one medicinal product (AIC code) per prescription, with the number of dispensed packages recorded separately. Analyses were based on the dispensing date. Cancelled or reversed dispensing records were excluded; no duplicate records or records with missing age or residence information were identified.

The dataset included dispensing date, active substance, medicinal product, patient age, local health authority of residence, number of packages, defined daily doses (DDD), and a pseudonymous patient identifier (PILUR). The identifier was used for data-quality checks and age-group verification, without linkage to other administrative or clinical databases. The statistical analyses reported in this study were based on regional monthly and annual aggregates derived from the dispensing-record dataset. Only aggregated, non-identifiable results are presented in the manuscript and Supplementary Materials. Annual population denominators, overall and by age group, were obtained from ISTAT. The study was restricted to children aged 0–14 years, corresponding to the principal age range covered by community pediatric care in the Italian National Health Service.

4.3. Fluoroquinolone Exposure and Utilization Measures

Systemic fluoroquinolones were identified according to Anatomical Therapeutic Chemical (ATC) classification codes within group J01MA. Utilization was assessed both overall and by active substance.

Defined daily doses (DDD) were obtained from the regional administrative dispensing dataset. According to the WHO ATC/DDD methodology, a DDD represents the assumed average maintenance dose per day for a drug used for its main indication in adults [30]. Because pediatric doses vary substantially with age, body weight, and clinical indication, DDD-based estimates may not accurately represent actual pediatric exposure or treatment duration. Therefore, the primary utilization measure was the number of outpatient dispensing records per 1000 pediatric residents. Secondary measures included total DDD, DDD per 1000 pediatric residents, age-group distribution, molecule-specific utilization, and monthly dispensing-record rates. DDD were retained as standardized measures of dispensed drug volume to facilitate longitudinal comparisons, rather than as estimates of the number of children treated or days of therapy.

4.4. Annual and Age-Specific Analyses

Annual dispensing-record and DDD-based rates were calculated using the corresponding annual resident population aged 0–14 years as denominator. Age-specific analyses were conducted for children aged 0–2 and 3–14 years using the respective annual population denominators. Changes over the study period were expressed as absolute and relative differences between years. The analysis was restricted to the 0–14-year age group, and the same age boundaries were applied consistently to dispensing records and population denominators. This age range broadly corresponds to the traditional organization of pediatric primary care in Italy, where adolescents generally transition from family pediatricians to general practitioners after the age of 14 years, although exceptions are possible. Adolescents aged 15–17 years were not included; therefore, the findings should not be extrapolated to the entire population younger than 18 years.

4.5. Seasonal Analysis

Seasonal utilization was examined descriptively by dividing each calendar year into two equal six-month periods: a cold season comprising January–March and October–December,

and a warm season comprising April–September. For each period, total DDD and dispensing records were calculated, together with cold-to-warm utilization ratios. Seasonality was examined descriptively in the primary analysis and was additionally accounted for through calendar-month fixed effects in ITS sensitivity models (Section 4.6).

4.6. Interrupted Time-Series Analysis

To evaluate whether the June 2023 EMA/AIFA reminder was associated with a change in fluoroquinolone utilization, an interrupted time-series analysis was performed using monthly dispensing-record rates per 1000 pediatric residents from January 2019 through December 2024 (72 monthly observations).

Segmented linear regression included: (1) a continuous time variable estimating the pre-reminder monthly trend; (2) a binary indicator for the period beginning in June 2023, estimating the immediate level change; and (3) a post-reminder time variable estimating the change in slope after the intervention. June 2023 was included in the post-reminder period.

Heteroskedasticity- and autocorrelation-consistent Newey–West standard errors were calculated using a maximum lag of 3 months. Results are reported as regression coefficients (β), Newey–West standard errors, 95% confidence intervals, and two-sided p values. An analogous model was fitted separately for ciprofloxacin, the most frequently dispensed fluoroquinolone. Given the observational design and absence of an external control series, ITS estimates were interpreted as temporal associations rather than causal effects.

To assess the robustness of the primary ITS results, sensitivity analyses were performed by introducing calendar-month fixed effects, excluding March–May 2020 to account for the initial COVID-19 lockdown period, and introducing an indicator for March 2020–December 2021 as a proxy for pandemic-related perturbations. Additional exploratory specifications combined seasonal adjustment with pandemic-period indicators or exclusions. All models retained the original calendar-time index and June 2023 interruption and used Newey–West standard errors with a maximum lag of 3 months. Analyses were repeated for all fluoroquinolones and ciprofloxacin separately (Table S2). In specifications excluding months, Newey–West standard errors were estimated on the remaining observations in chronological order, so that months bordering the excluded interval were treated as adjacent; this limitation applies particularly to the exclusion of March 2020–December 2021. Analyses were performed in Python (version 3.13.5) using the statsmodels package (version 0.14.6).

4.7. Statistical Analysis

Analyses were primarily descriptive. Annual dispensing-record counts and total DDD were summarized overall and by active substance, and population-standardized rates were calculated using the corresponding pediatric population denominators. Absolute and relative changes were calculated between years. Age-specific analyses and descriptive seasonal comparisons were conducted as detailed in Sections 4.4 and 4.5, respectively. Interrupted time-series models and their statistical specifications are described in Section 4.6. Statistical significance for the ITS coefficients was defined as a two-sided p value < 0.05.

4.8. Generative AI Assistance

ChatGPT (OpenAI; GPT-6 Sol, accessed October–November 2026) was used to assist with manuscript drafting, methodological discussion, and editorial revision. Its output was critically reviewed by the authors. The primary analysis estimates were retained from the original study analyses. For the sensitivity analyses reported in Table S2, ChatGPT was also used to assist in generating and executing Python code; the code was reviewed and the resulting estimates were independently verified by the authors. The sensitivity analyses were performed using aggregated monthly time-series data.

5. Conclusions

Pediatric outpatient fluoroquinolone dispensing in Apulia decreased between 2019 and 2024, despite an intermediate rebound. The primary ITS did not identify a statistically significant immediate level or slope change following the June 2023 EMA/AIFA reminder. Sensitivity analyses yielded consistently nonsignificant post-reminder findings for overall fluoroquinolone dispensing, although exploratory ciprofloxacin level-change estimates varied across model specifications. The data cannot establish causal effects of regulatory actions or stewardship activities and do not permit patient-level appropriateness assessment. Further surveillance incorporating clinical indications and comparator series may help clarify utilization patterns.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics15111151/s1, Table S1, Seasonal distribution of pediatric outpatient fluoroquinolone use in Apulia, 2019–2024; Table S2, Interrupted time-series sensitivity analyses of pediatric outpatient fluoroquinolone dispensing in Apulia, 2019–2024; Supplementary File S1, RECORD reporting checklist; Figure S1, Observed pediatric outpatient fluoroquinolone dispensing-record rates in Apulia com-pared with three hypothetical, author-defined utilization ranges. Shaded bands represent non-validated scenarios and do not establish EMA/AIFA concordance or individual clinical appropriateness.

Author Contributions: M.A.: conceptualization, methodology, supervision, validation, writing—original draft, writing—review & editing. C.P. (Cataldo Procacci): conceptualization, methodology, data curation, formal analysis, investigation, software, visualization, writing—original draft, writing—review & editing. P.S.: conceptualization, methodology, supervision, validation, writing—review & editing, project administration. C.P. (Claudia Palmieri): investigation, validation, writing—review & editing. S.T.: methodology, formal analysis, validation, writing—review & editing. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The data used in this study originated from routine institutional pharmaceutical monitoring activities conducted by the Health Department of the Apulia Regional Government. Pseudonymized individual community-pharmacy records were analyzed exclusively by an authorized investigator within his institutional setting, and only aggregated results were shared with the other authors. No directly identifying patient information was made available to the other investigators. No patient contact or intervention was involved. No formal Ethics Committee approval or exemption determination was obtained for this study.

Informed Consent Statement: Not applicable. The study used pseudonymized administrative dispensing data processed within the institutional pharmaceutical monitoring activities of the Apulia Regional Health Department; no patient contact or intervention was involved, and only aggregated, non-identifiable results were analyzed and reported by the authors.

Data Availability Statement: The data supporting the findings of this study are held by the Regional Health Authority of Apulia and are not publicly available because they comprise restricted administrative health data. Requests for access are subject to authorization by the relevant institutional data custodian and applicable data-protection requirements.

Acknowledgments: During the preparation and revision of this manuscript, the authors used ChatGPT (OpenAI) to support scientific writing, manuscript organization, methodological discussion, and assistance with generating and executing Python code for the sensitivity analyses. The authors reviewed and edited the output, independently verified the reported statistical results and references, and take full responsibility for the content of this publication.

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

Abbreviations

The following abbreviations are used in this manuscript:

AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
DDD	Defined daily dose
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ITS	Interrupted time series
PILUR	Pseudonymous patient identifier
SE	Standard error

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