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Time Series Methods to Assess the Impact of Regulatory Action: A Study of UK Primary Care and Hospital Data on the Use of Fluoroquinolones

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Keywords: autoregressive integrated moving average | fluoroquinolones | impact | interrupted time series | regulatory interventions | risk minimisation measures | segmented regression

ABSTRACT

Purpose: To illustrate the interest in using interrupted time series (ITS) methods, this study evaluated the impact of the UK MHRA's March 2019 Risk Minimisation Measures (RMM) on fluoroquinolone usage.

Methods: Monthly and quarterly fluoroquinolone use incidence rates from 2012 to 2022 were analysed across hospital care (Barts Health NHS Trust), primary care (Clinical Practice Research Datalink (CPRD) Aurum and CPRD GOLD), and linked records from both settings (East Scotland). Rates were stratified by age (19–59 and ≥ 60 years old). Seasonality-adjusted segmented regression and ARIMA models were employed to model quarterly and monthly rates, respectively.

Results: Post-RMM, with segmented regression, both age groups in Barts Health experienced nearly complete reductions (> 99%); CPRD Aurum saw 20.19% (19–59) and 19.29% (≥60) reductions; no significant changes in CPRD GOLD; East Scotland had 45.43% (19–59) and 41.47% (≥60) decreases. Slope analysis indicated increases for East Scotland (19–59) and both CPRD Aurum groups, but a decrease for CPRD GOLD's ≥60; ARIMA detected significant step changes in CPRD GOLD not identified by segmented regression and noted a significant slope increase in Barts Health's 19–59 group. Both models showed no post-modelling autocorrelations across databases, yet Barts Health's residuals were non-normally distributed with non-constant variance.

Abbreviations: ACF, autocorrelation function; ARIMA, autoregressive integrated moving average; CI, confidence interval; CPRD, Clinical Practice Research Datalink; EMA, European Medicines Agency; ITS, interrupted time series; MHRA, Medicines and Healthcare products Regulatory Agency; PACF, partial autocorrelation function; RMM, risk minimisation measures; RR, relative risk; UK, United Kingdom.

Yuchen Guo and Berta Raventós should be considered as joint first authors.

Conclusions: Both segmented regression and ARIMA confirmed the reduction of fluoroquinolones use after RMM across four different UK primary care and hospital databases. Model diagnostics showed good performance in eliminating residual autocorrelation for both methods. However, diagnostics for hospital databases with low incident use revealed the presence of heteroscedasticity and non-normal white noise using both methods.

1 | Introduction

While randomised controlled trials (RCTs) are widely regarded as the gold standard for evaluating interventions, they are not always feasible, especially for population-level policy and program interventions [1]. Interrupted time series (ITS) analysis provides an alternative and is particularly well-suited for assessing the longitudinal effects of interventions when 'natural experiments' occur [2]. Such interventions can be risk minimisation measures (RMM), which aim to prevent or mitigate the occurrence of adverse reactions associated with exposure to medicine or to reduce their severity or impact on the patient if adverse reactions occur [3]. ITS is a quasi-experimental (i.e., non-randomised) design and has been widely applied in public health research [4]. Segmented regression is the most common approach, as it is easy to implement and interpret [5]. However, its limitations in capturing complex data patterns have prompted exploration into alternative methodologies, such as ITS using Autoregressive Integrated Moving Average (ARIMA) models, which can better account for underlying trends, autocorrelation, and seasonality [6, 7].

Fluoroquinolones are effective antibiotics for the treatment of various infections but are associated with rare but serious side effects, including tendon disorders and aortic aneurysm and dissection. In response to these concerns, regulators have strengthened warnings and updated guidelines as new evidence became available [8, 9]. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) introduced RMM in March 2019. These measures aimed to restrict the use of fluoroquinolones to situations where other antibiotics are inappropriate due to antibiotic resistance [10], side effects, or ineffectiveness, particularly emphasising caution for people over 60 years old [11]. These guidelines were communicated to healthcare professionals and patients through updated drug labels and direct notices and were on top of recommendations for the restrictive use of fluoroquinolones to minimise the risk of increasing antibiotic resistance [10].

To the best of our knowledge, only one study commissioned by the European Medicines Agency (EMA) has assessed the impact of the 2018–2019 European RMM on fluoroquinolone prescribing trends in several countries, including the United Kingdom. This study showed no consistent changes in fluoroquinolone prescribing in relation to the intervention [12]. However, it primarily focused on primary care settings and did not account for seasonality. A review of the effectiveness of measures to minimise the risk of potentially long-term adverse reactions led the MHRA to implement tighter restrictions in 2024 [13]. Our study aimed to demonstrate the use of two time series methods for the analysis of RMM effectiveness at the population level. To do this, we illustrated the use of segmented regression and ARIMA and their respective diagnostics by investigating the impact of the 2019 UK RMM on fluoroquinolone use in UK primary care and hospital data.

2 | Methods

2.1 | Data Sources

This study used data from CPRD GOLD (primary care, UK), CPRD Aurum (primary care, England, and Northern Ireland), East Scotland (primary and secondary care, Scotland) and Barts Health NHS Trust data (London hospital data).

2.2 | Study Population

The study included all participants in the databases from 2012 to 2022, with at least 30 days of data availability before the index date (the date they entered the study) and without the use of fluoroquinolones in the previous 30 days. These criteria ensure participants had no recent fluoroquinolone exposure, providing a clear baseline for accurate study outcomes. Age was stratified into two groups: 19–59 and 60 and over. Patients aged 60 and over are at greater risk of tendon rupture so were highlighted as a population of interest in the Drug Safety Update [11].

2.3 | Outcome of Interest

The outcome of interest was the incident use of systemic fluoroquinolones during the study period, where incidence use refers to the first prescription of fluoroquinolones for a patient who meets the above criteria. Database details and IR calculations are available in Supporting Information.

2.4 | Segmented Regression in ITS

Segmented regression, pivotal for ITS, identifies level and trend changes in a time series post-intervention. This approach, dividing the timeline into pre- and post-intervention segments to estimate changes in intercepts and slopes, is crucial for evaluating health interventions' impact [2]. However, it is not applicable when trends are not (or cannot be transformed) to be linear or in the presence of autocorrelation [4]. It is generally recommended to have a minimum of 12 observations pre- and post-intervention [6, 14], making quarterly data suitable for analysing trends over time when limited to a few years of data collection.

For each database and age group, we use quasi-Poisson regression to model event counts, adjusting for person-years to calculate incidence rates (IRs) [2], with the model accounting for step and slope change after RMM, cyclic adjustments for seasonality

Summary

- Impact Analysis (of Regulatory Action) Across Healthcare Settings: We investigated the impact of UK regulatory measures on fluoroquinolone use in both primary care and hospital settings.
- Methodological Diversification: We demonstrated the application of distinct time series methods with different assumptions and modelling strategies, including segmented regression and ARIMA.
- Age Stratification: We provided insights into the effects of regulatory measures on different age groups, aligned with the specifics of the Risk Minimisation Measures (RMM) that apply to all ages but particularly target individuals aged 60 and above.

and lagged values for temporal correlation. Details on modelling and residual diagnostics, including autocorrelation checks (ACF and PACF plots) and tests for normality and homoscedasticity (Q-Q and standardised residual plots), are provided in the Supporting Information.

2.5 | ARIMA Model With Exogenous Variables in ITS

ARIMA models excel by comprehensively addressing autocorrelation and seasonal variations, complementing segmented regression for a thorough evaluation of temporal trends and intervention impacts [7]. The application of ARIMA models typically demands a large dataset, often extending to at least 50 or hundreds of data points to adequately capture patterns in data [2, 5]. Therefore, when employing ARIMA, we used monthly data to fulfil this requirement. Following suggestions by Schaffer et al. [7], ARIMA models were optimised for stationarity and seasonality, selecting the best fit based on the Akaike Information Criterion (AIC). Additional information on modelling and diagnostics is available in the Supporting Information.

For both methods, diagnostics are essential for confirming model reliability. ACF and PACF plots help identify residual correlations, indicating potential model refit. The Q-Q plot checks residual normality, which is important for accurate coefficient estimates, influencing their interpretation and the model's predictive power. The standardised residual plot assesses homoscedasticity, ensuring uniform residual variance, which is essential for consistent coefficient reliability. Failures in diagnostics, such as autocorrelation, non-normality, or heteroscedasticity, compromise coefficient reliability and model credibility, highlighting the need for diagnostic review for robust model performance [15]. All code for this study is available on GitHub: https://github.com/oxford-pharmacoepi/FluroquinolonesTimeSeries.

3 | Results

The databases and their respective numbers of records and numbers of subjects can be found in Supporting Information. All IR results are reported per 100000 persons/year.

Segmented regression revealed statistically significant relative risk (RR) reductions in Barts Health NHS Trust, East Scotland and CPRD Aurum data, but not for CPRD GOLD. ARIMA confirmed the significant step changes in Barts Health NHS Trust and East Scotland, with results nearing significance in CPRD GOLD. However, for CPRD Aurum, ARIMA only found significant step change for the 60 and over 60 years old age group.

In terms of residuals from analysis, segmented regression confirmed white noise distribution of residuals, except in the Barts Health NHS Trust where both age groups showed heteroscedasticity and non-normality in residuals. Details on coefficients and diagnostics, fitted values plots without cyclic splines and lag values are available in Supporting Information. Using ARIMA, residuals from CPRD GOLD, CPRD Aurum and East Scotland databases, displayed a white noise distribution, demonstrating a precise model fit and providing reliable estimates for changes in fluoroquinolone prescribing post-RMM implementation. Barts Health NHS Trust, however, showed non-white noise residuals like findings from segmented regression diagnostics, necessitating further investigation of the pattern in data. All coefficients reported for ARIMA reflect changes in IR per person-year. Model parameters, coefficients and residual diagnostics plots can be found in Supporting Information.

3.1 | Barts Health NHS Trust

Segmented regression revealed statistically significant RR reductions in Barts Health NHS Trust. For the 60 and over 60 years old group, an almost complete step decrease of 99.97% was observed (RR: 0.0003, 95%CI: (10^{-7}, 0.98), p: 0.06). Fluoroquinolone use dramatically reduced after RMM in the 19–59 years old group, achieving a near-total step decrease of 99.98% decrease (0.0002, (10^{-8}, 1.8), p: 0.06). Figure 1 illustrates the IR, both observed (red line) and modelled (blue line), alongside hypothetical (green line) rates had the RMM not been implemented. Given the IR levels across age groups, the y-axis scales are differentiated for clarity. The residual diagnostics after segmented regression in Figure 2 show no remaining autocorrelation. However, the residuals did not show normality and homoscedasticity, which may indicate potential model misspecification or the presence of outliers, impacting the reliability of the model's predictions.

Using ITS with ARIMA, Barts Health NHS Trust also showed significant reductions after RMM. For the 60 and over age group, there was a statistically significant reduction in the IR of fluoroquinolone post-RMM in March 2019, as demonstrated by a step decrease of 62.74 in IR ((48.39, 77.09), $p < 0.01$). For the 19–59 years old group, a marked change in fluoroquinolone use was observed. A step decrease of 46.62 (29.75, 63.48) was observed, which denotes a substantial decrease in IR immediately after the intervention ($P < 0.01$). Moreover, a slope increase of 1.65 was identified ($p < 0.01$), indicating an increase in IR over time after intervention. Results illustrating the observed and fitted IR, alongside hypothetical IR in the absence of intervention, are presented in Figure 3. The predicted increase in the IR without intervention in the green line demonstrates a growing trend. This trend in forecasts for Barts Health NHS Trust, alongside the increasing standardised residuals in Figures B41 and B42 in Supporting Information, signals poor model fit. This indicates an inadequacy in capturing

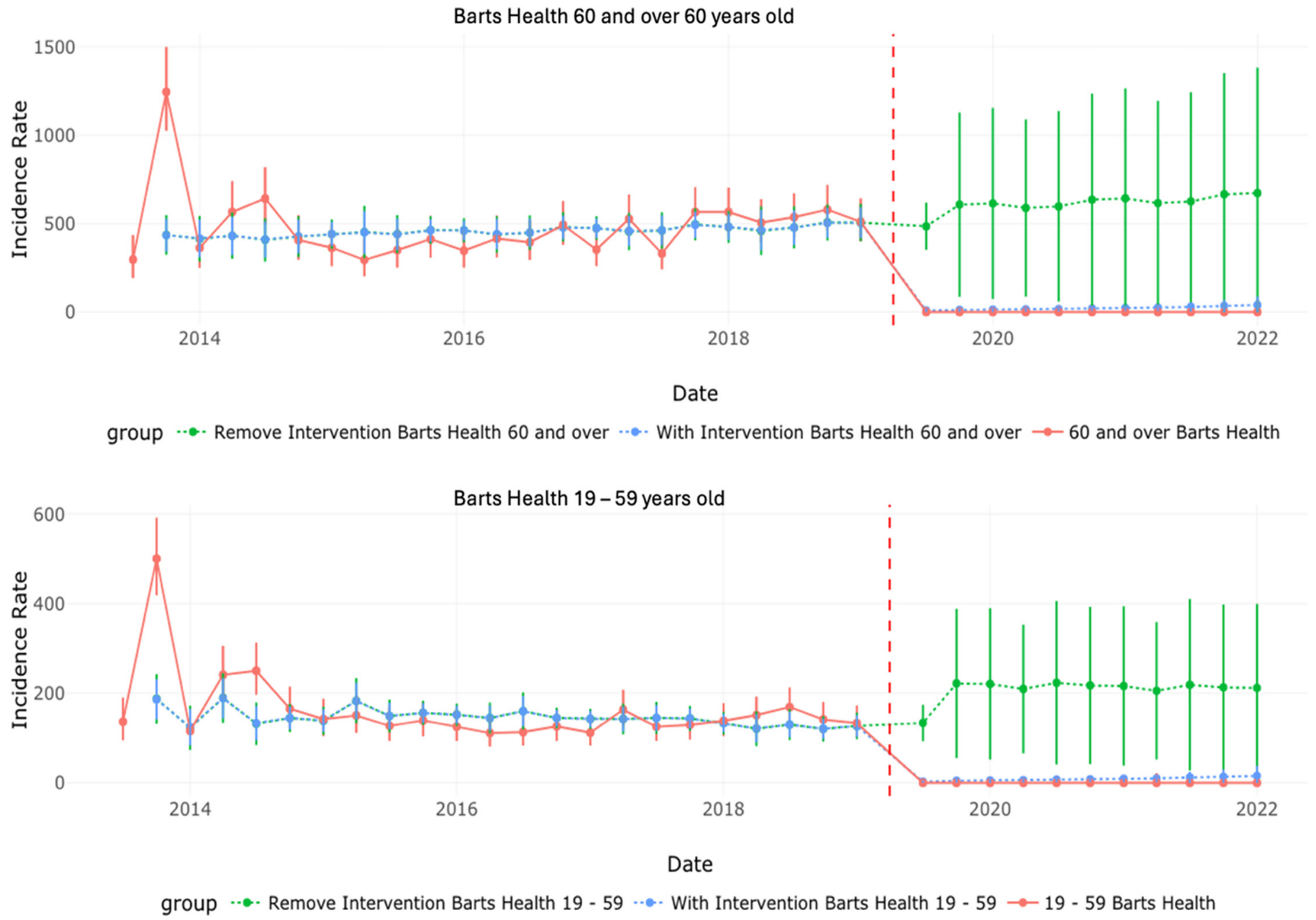

FIGURE 1 | ITS using segmented regression model for Barts Health NHS Trust: Fitted IR with intervention and estimated IR removing intervention.

significant shifts in the data's pattern or external factors impacting the data. The presence of non-white noise residuals suggests underlying patterns in the data that require further exploration.

Residual diagnostics confirmed the absence of residual autocorrelation and demonstrated that the residuals are normally distributed and exhibit homoscedasticity.

3.2 | East Scotland

Segmented regression revealed statistically significant RR reductions in East Scotland after RMM. The 60 and over age group demonstrated a 41.47% step decrease (0.59, (0.40, 0.85), $p < 0.01$). In the 19–59 years old group, a significant step decrease of 45.43% was noted (0.55, (0.40, 0.75), $p < 0.01$), alongside a 0.26% significant slope increase (p: 0.03), indicating the reduction in use over time post-RMM was more gradual compared to the pre-RMM period. The fitted IR (blue) and estimated IR, assuming no RMM (green) are present in Figure 4. Residual diagnostics, available in Supporting Information, showed no remaining autocorrelation and white noise pattern.

Using ARIMA, a significant reduction was also observed in East Scotland after RMM. For the 60 and over 60 years old population, a significant step decrease of 111.19 for IR ((68.65, 153.73), $p < 0.01$) was observed. For the 19–59 years old group, a significant step decrease of 79.39 ((25.13, 133.65). $p < 0.01$) for IR was observed. Results of the observed and fitted IR, in addition to the rates had there been no intervention, are displayed in Figure 5.

3.3 | CPRD Aurum

In CPRD Aurum, significant RR decreases were identified in CPRD Aurum through segmented regression. For the 60 and over age group, a 19.29% (0.81, (0.68, 0.96)) step decrease was noted following the intervention ($p < 0.01$). A slope increase of 0.12% ($p < 0.01$) was observed in these data. The 19–59 years old group showed a significant step decrease of 20.19% (0.80, (0.65, 0.97)) immediately after the intervention ($p = 0.03$), followed by a slope increase of 0.16% ($p = 0.03$). Figure 6 shows the fitted IR with intervention and estimated IR removing RMM. All residual diagnostics available in Supporting Information indicate a white noise pattern, confirming the model's robustness by indicating randomness without uncaptured autocorrelation or seasonality.

Using ARIMA, it was found that only in the 60 and over age group was there a statistically significant immediate reduction in fluoroquinolone use. This group experienced a significant step decrease of 579.20 ((284.45, 873.94), $p < 0.01$). The 19–59 years old group revealed a step decrease of 307.68 (−98.18, 713.53),

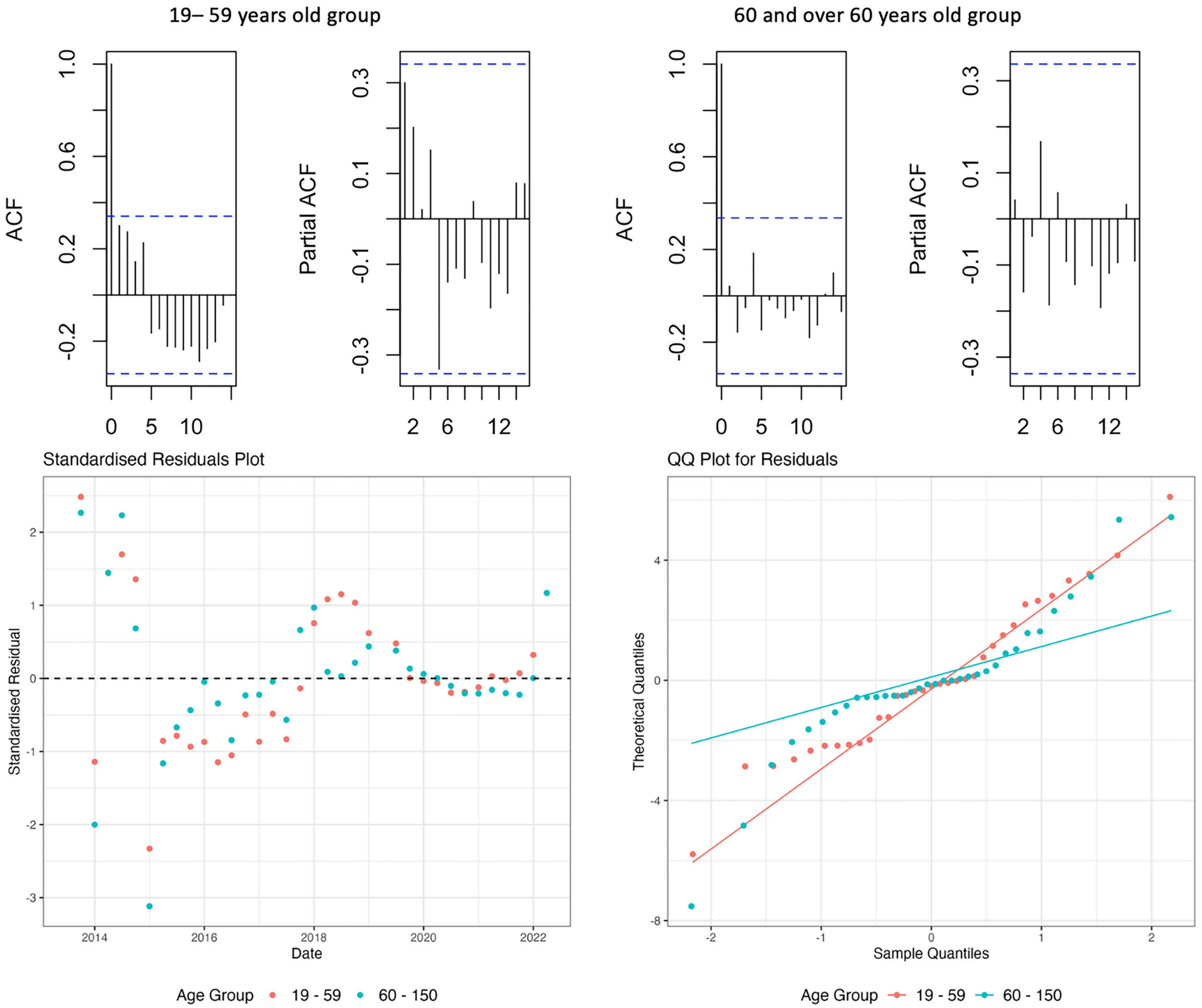

FIGURE 2 | Residual diagnostics plot for ITS using segmented regression for Barts Health NHS Trust.

suggesting a pronounced decrease in IR. However, this observation did not reach statistical significance ($p = 0.14$). Figure B2 in Supporting Information illustrates the observed and fitted IR, alongside estimations without intervention. Residual diagnostics confirmed that the residuals conform to the characteristics of white noise.

3.4 | CPRD Gold

Using segmented regression, no significant step changes were observed for both age groups in CPRD GOLD data. However, for the 60 and over age group, there was a significant slope decrease of 0.37% ($p < 0.01$). Figure B1 in Supporting Information shows the fitted IR with intervention and estimated IR removing intervention. Residuals were found to follow a white noise pattern.

Using ARIMA, the 60 and over age group, an immediate decline in IR was observed, with a step decrease of 161.88 ((−18.15, 341.90), $p = 0.078$). The 19–59 years old group indicates a step decrease of 104.35 (−22.15, 231.20), which neared statistical significance ($p = 0.1069$). Figure 7 presents the ARIMA approach and the estimated IR under the hypothetical scenario of no intervention. Residual diagnostics showed a white noise pattern.

4 | Discussion

Our study employed ARIMA and segmented regression models to assess the impact of 2019 RMM on fluoroquinolone use patterns across various healthcare databases, with a particular focus on contrasting age groups. Both modelling approaches offered unique insights into the immediate and long-term effects of these interventions, though they differed in their approach to account for trends and seasonality. For all databases, segmented regression and ARIMA models had residuals with no autocorrelation, indicating effective model fits. Residuals demonstrated homoscedasticity and normality using both methods across all databases, except for Barts Health NHS Trust, where these conditions were not met.

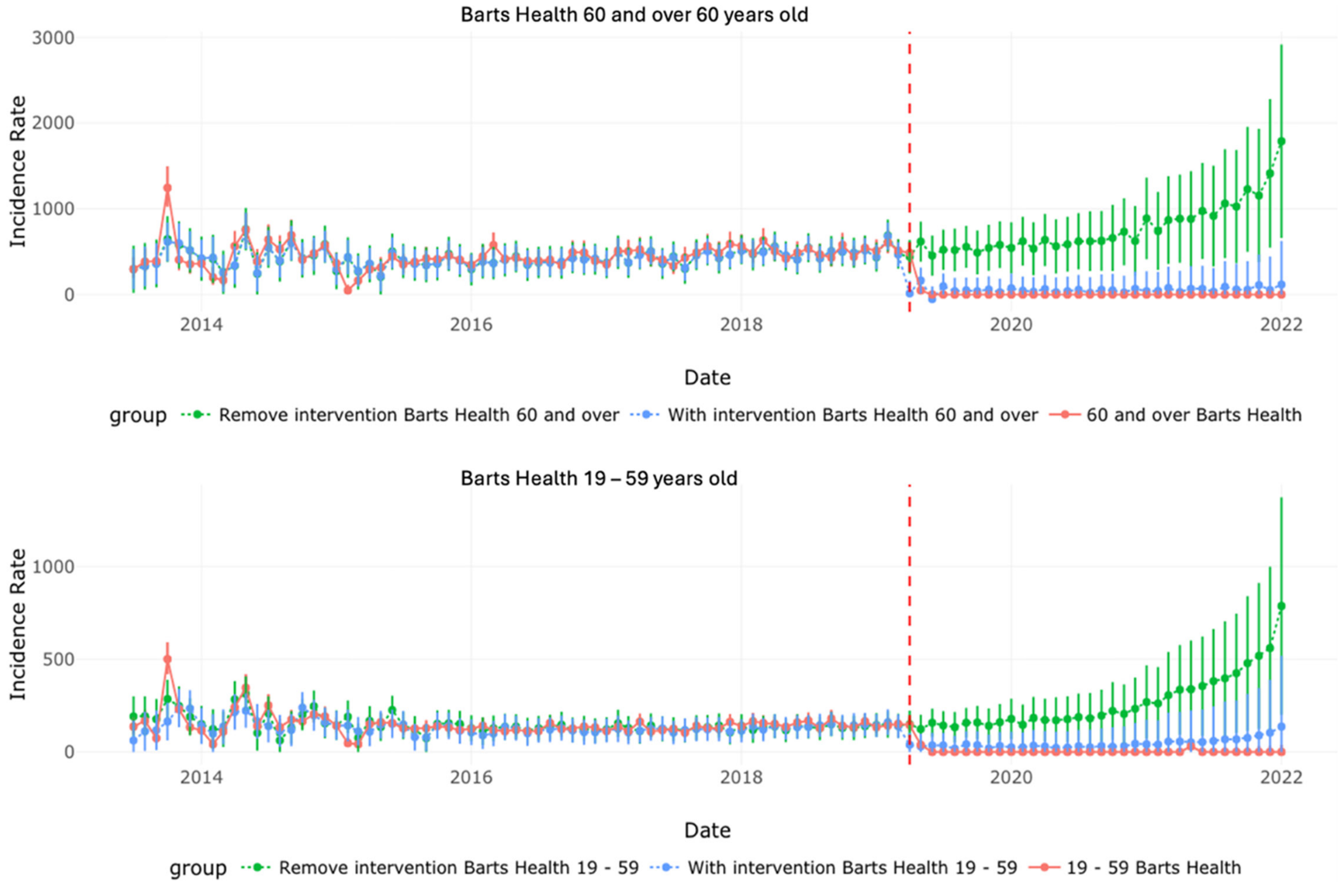

FIGURE 3 | ITS using ARIMA model for Barts Health NHS Trust: Fitted IR with intervention and estimated IR removing intervention.

4.1 | ITS Methods

ARIMA models, applied to monthly data, highlighted subtle IR fluctuations and seasonal patterns, showing a significant, immediate drop in fluoroquinolone use at RMM introduction, especially among older individuals in Barts Health and East Scotland. The effectiveness of ARIMA models in detecting immediate changes with high sensitivity underscores their ability in analysing time-dependent IR trends, especially when data exhibit seasonal patterns.

Segmented regression, applied to quarterly data in this paper, offered a broader perspective, identifying immediate effects through step changes and longitudinal trends through slope alterations. Though less detailed than monthly data analysis, it effectively showcased post-intervention changes' direction and magnitude. The absence of residual autocorrelation confirmed the suitability of this approach for assessing intervention effectiveness.

4.2 | Method Comparisons

Direct comparison between ARIMA and segmented regression is challenging due to their different data inputs and analytical focuses. Nonetheless, both methods demonstrate a notable IR reduction post-intervention. ARIMA is particularly sensitive to immediate changes, detecting significant or near-significant decreases across databases and age groups. However, for Barts Health NHS Trust, ITS analysis with ARIMA predicted an exponential IR increase post-intervention removal, likely due to poor model fit and evident heteroscedasticity in residuals. In contrast, segmented regression in ITS analysis accurately captured the change, offering reliable future trend predictions. A systematic review by Jandoc et al. underscores the growing application of ITS methods in drug utilisation studies, with segmented regression (67%) and ARIMA (16%) being commonly used [16]. Research done by Li et al. [6] also applied both segmented regression and ARIMA in their research, demonstrating the effectiveness of both models in ITS analysis.

Following Li et al.'s [6] suggestion, we explored using the Difference-in-Differences (DiD) approach. However, due to non-parallel pre-intervention trends between the two age groups and the impact of the RMM on both, we excluded DiD from our final analysis. Our decision to use ARIMA models for monthly data and segmented regression for quarterly data was based on literature recommendations regarding sample size and the necessity to capture both immediate and gradual RMM effects, considering the unique characteristics of the data [2, 5].

4.3 | Effect of MHRA 2019 Intervention

We observed significant immediate and long-term changes in fluoroquinolone use patterns following RMM in 2019 in many databases, particularly among older adults. The ARIMA and

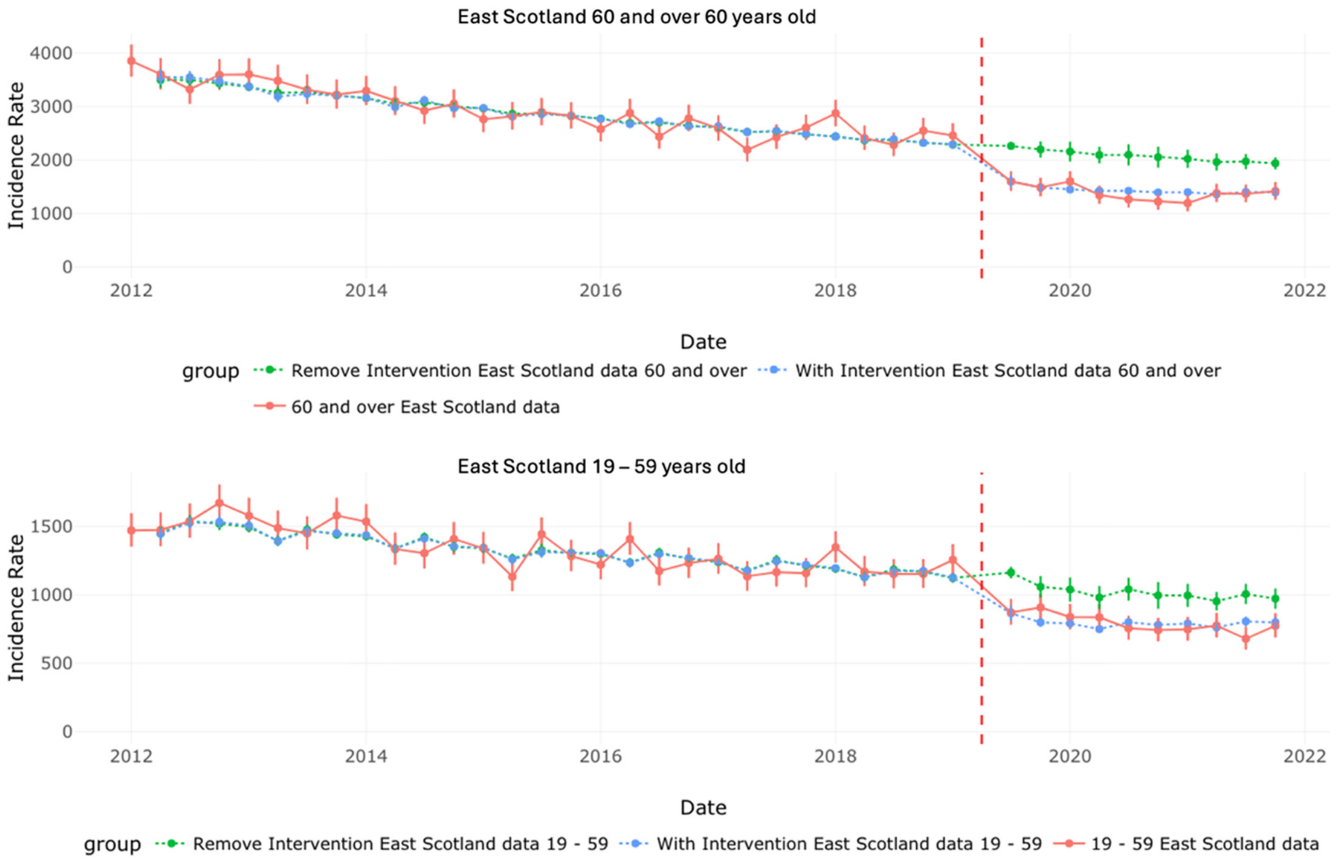

FIGURE 4 | ITS using segmented regression model for East Scotland: Fitted IR with intervention and estimated IR removing intervention.

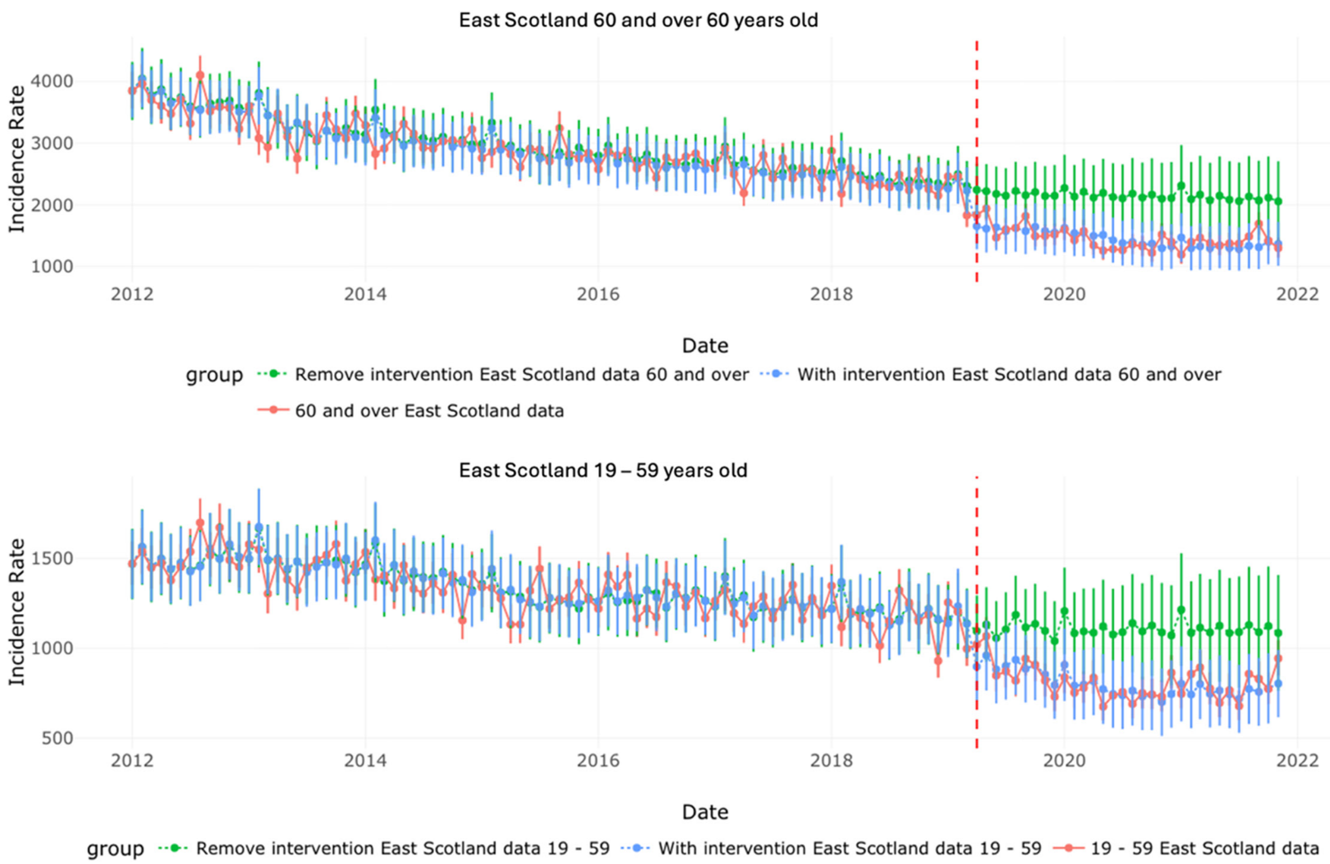

FIGURE 5 | ITS using ARIMA model for East Scotland: Fitted IR with intervention and estimated IR removing intervention.

segmented regression model's detection of a drop, suggests a robust initial response to the intervention. Also, we observed a greater decrease for Barts Health NHS Trust compared to the other datasets. In addition to adhering to MHRA guidelines, Barts Health's significant reduction in fluoroquinolone use can be attributed to internal proactive measures, enhanced patient counselling, and a concerted effort by healthcare providers to recommend alternatives to their prescriptions. Additionally, a more significant change was observed in Scottish data from East Scotland than in CPRD GOLD and Aurum data.

The study by Ly et al. [12] found that regulatory measures aimed at reducing fluoroquinolone use in primary care during 2018–2019 had no significant effect on IR, including data from the United Kingdom, contrasting with our findings. They assessed the impact of EMA regulatory actions from 2016 to 2021 on fluoroquinolone use using segmented regression without predetermined change points. While reductions in IR were noted, they were not consistently aligned with the RMM timeline, indicating these interventions had limited effectiveness in changing IR patterns in primary care, according to their analysis. In contrast, our study provides a more comprehensive evaluation over a decade, incorporating multiple databases from both primary care and hospital settings. Furthermore, our study used multiple databases from primary and hospital care settings. We employed segmented regression and ARIMA models on various datasets, identifying significant post-RMM changes.

The difference in findings could stem from our diverse analytical methods and wider data scope, including hospital records. Our methodology also captures immediate and gradual post-RMM shifts, considering seasonality and autocorrelation.

4.4 | Age Group Comparisons

In our study, using ARIMA and segmented regression approaches, we found that the post-RMM the elderly had a stronger or similarly pronounced decrease in fluoroquinolone use as it did among younger patients. This difference can likely be attributed to the higher initial usage rates of fluoroquinolones among older individuals as well as the fact that this group was particularly targeted by the RMM. Notably, the substantial decrease in fluoroquinolone use within the 60 and over age group highlights the RMM can be adapted to impact prescribing patterns within vulnerable populations. This finding aligns with the MHRA's regulatory action and supports existing literature emphasising the cautious use of fluoroquinolones in older adults due to their heightened risk profile [17, 18].

The significant decrease in fluoroquinolone use among the elderly underscores the efficacy of targeted interventions tailored to high-risk populations, demonstrating the potential of such public health strategies to enhance drug safety outcomes and optimise healthcare resource use. This effect is particularly evident in smaller, controlled settings like hospitals, where these measures

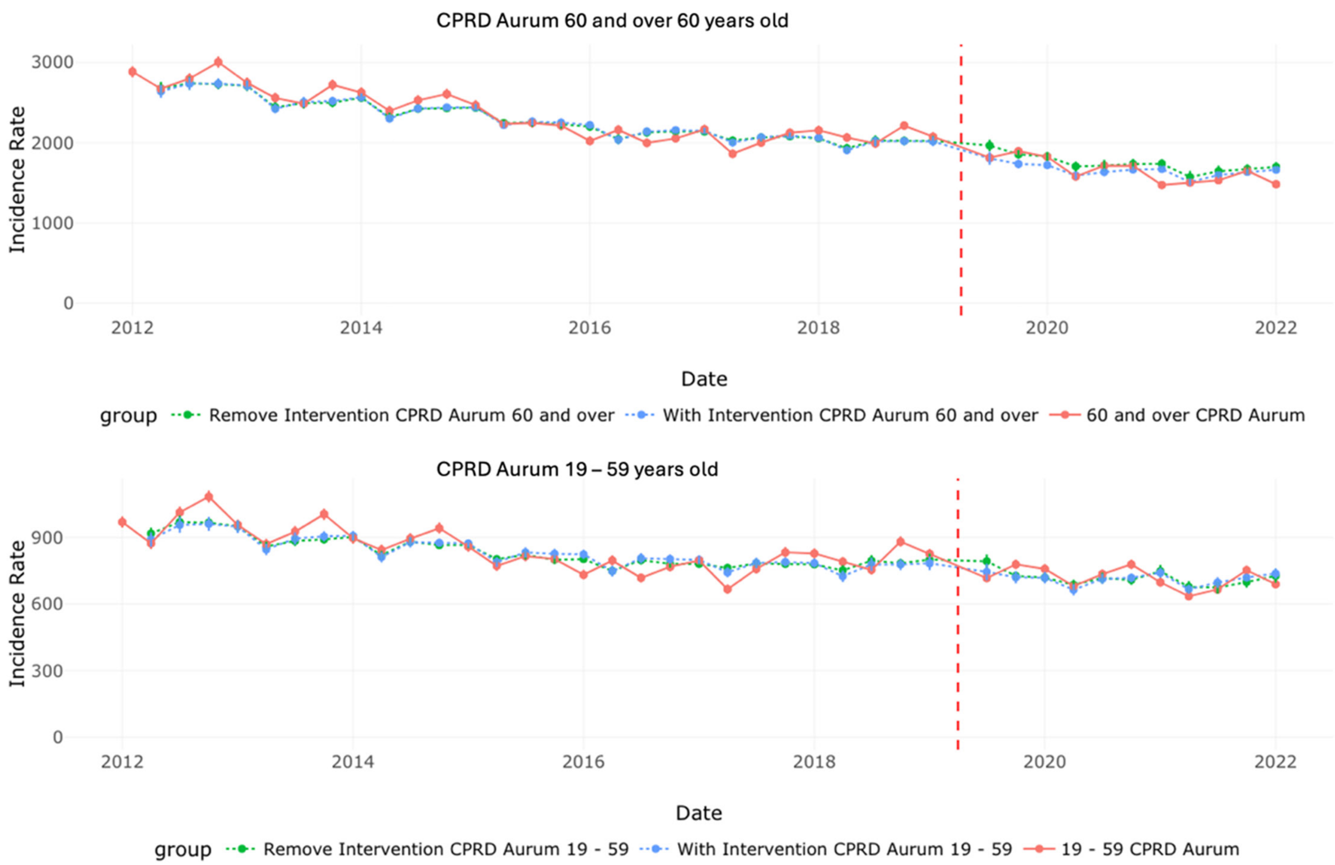

FIGURE 6 | ITS using segmented regression model for CPRD Aurum: Fitted IR with intervention and estimated IR removing intervention.

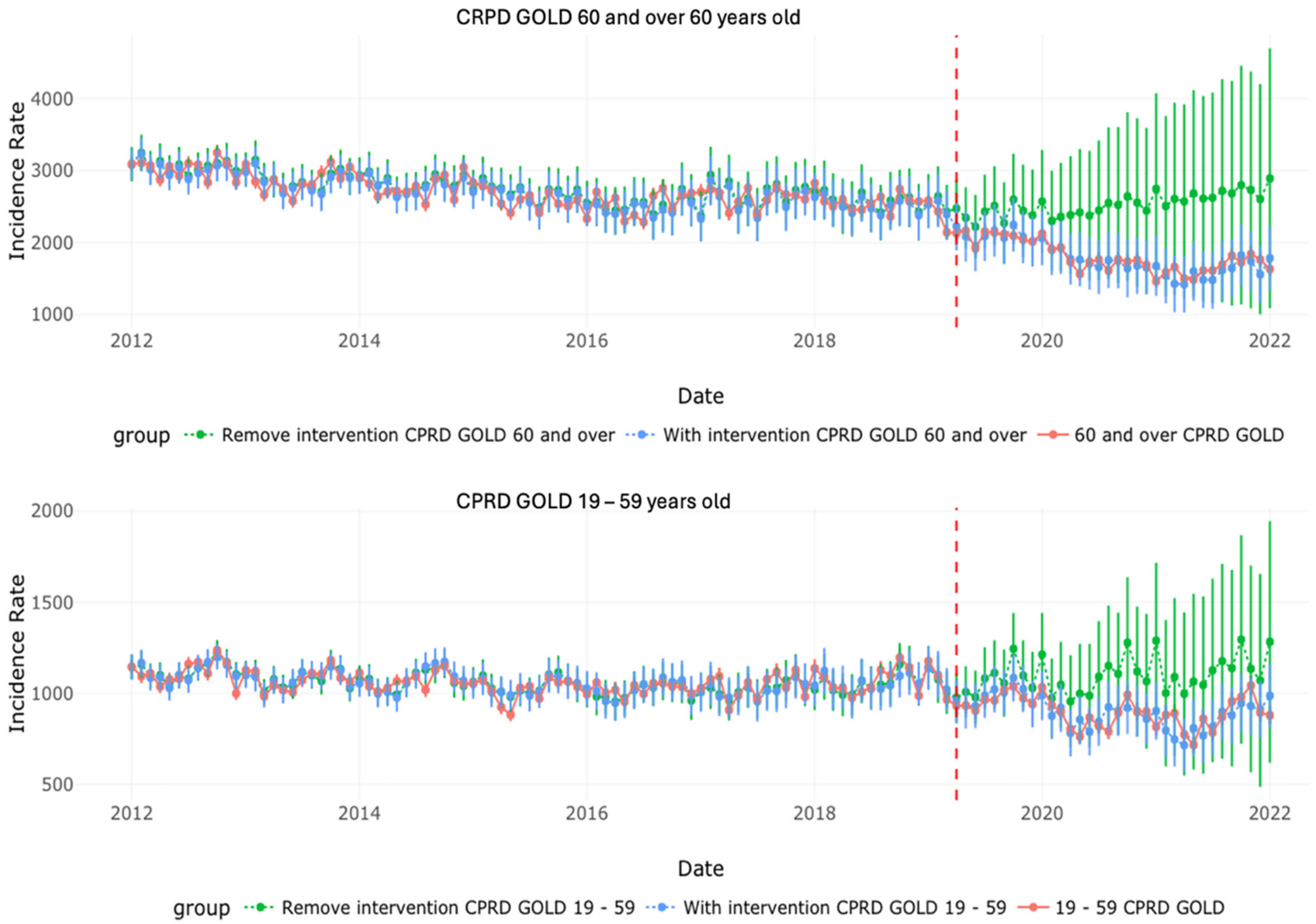

FIGURE 7 | ITS using ARIMA model for CPRD GOLD: Fitted IR with intervention and estimated IR removing intervention.

can be implemented more systematically and monitored more effectively compared to primary care environments.

5 | Strengths and Limitations

Our study illustrates the strengths and limitations of ITS using ARIMA and segmented regression or evaluating the 2019 RMM's impact on fluoroquinolone use. Employing both methods enhances our analysis by addressing trends, seasonality, and age group differences. Segmented regression provides RRs, while ARIMA directly measures IR changes, leading to different interpretative outcomes. The ARIMA model, using monthly data, generally produced residuals closer to white noise compared to segmented regression, suggesting a closer fit to dynamic time series like seasonality and autocorrelation. This suggests that the ARIMA model could capture the data's temporal structure, highlighting the importance of selecting analysis methods that closely match the data's inherent characteristics for more accurate and insightful results. Segmented regression excels in outlining trends and long-term changes, providing a comprehensive view of policy impacts over time [2]. Specifically, our diagnostics revealed considerable heteroscedasticity and non-normality in residuals for Barts Health NHS Trust across both age groups. Particularly, the residuals of the ARIMA model exhibited pronounced heteroscedasticity, resulting in exponentially increasing predictions upon removal of the RMM effect in the model. In addition, another limitation of ITS studies is their inability to account for time-varying factors that are not part of the underlying trend, such as additional interventions or events that occur concurrently with the intervention and may influence the outcome [19]. To the best of our knowledge, no additional events, such as shortages of antibiotics with similar indications, occurred during the study period. Lastly, the COVID-19 pandemic, starting in March 2020, may have influenced trends in fluoroquinolone prescribing, especially in the year following its onset. While the impact of COVID-19 appeared limited in our findings, the influence of the pandemic on these trends was beyond the scope of this study and warrants further investigation.

6 | Conclusions

Using ARIMA and segmented regression for ITS, our study provides an analysis of the impact of 2019 RMM on fluoroquinolone usage. Despite their methodological differences, both models showed statistically significant reductions in usage post-RMM in Barts Health NHS Trust, CPRD Aurum and East Scotland data. ARIMA additionally identified significant changes in CPRD GOLD data. Reductions in fluoroquinolone usage were heterogeneous across databases but were notably observed among individuals aged 60 or over. These findings align with the MHRA's regulatory actions but suggest varying levels of compliance across different settings.

6.1 | Plain Language Summary

This study investigated the effect of 2019 RMM on fluoroquinolone antibiotic uses from 2012 to 2022, using data from various UK healthcare sources. It employed two statistical methods to detect changes in IR over time, considering seasonal effects. The findings showed a significant decrease in fluoroquinolone usage following the RMM, particularly among individuals over 60 years old. This trend was observed across multiple healthcare settings and consistently using different modelling methods.

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Ethics Statement

The protocol for this research was approved by CPRDs Research Data Governance (RDG) (protocol number 23_003263).

Conflicts of Interest

Prof. Daniel Prieto-Alhambra's research group has received grant support from Amgen, Chesi-Taylor, Novartis and UCB Biopharma. His department has received advisory or consultancy fees from Amgen, Astellas, AstraZeneca, Johnson and Johnson, and UCB Biopharma and fees for speaker services from Amgen and UCB Biopharma. Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums and Synapse Management Partners, has supported training programmes organised by DPA's department and open for external participants organised by his department, all unrelated to the submitted work. Christian Cole and Chuang Gao have received research grant funding from AstraZeneca. Albert Prats-Uribe has received consultancy fees from Synapse Management Partners on work for the EHDEN nfp. Barts Bone and Joint Health have received institutional funding for salaries and research support from Barts Charity, NIHR, Chan Zuckerberg Initiative, AO UK, Orthopaedic Research UK and the Academy of Medical Sciences, all unrelated to this work. Funding from the EHDEN consortium supported the development of the Barts Health NHS Trust source.

Data Availability Statement

CPRD GOLD and Aurum: data were obtained under the CPRD multi-study license held by the University of Oxford after Research Data Governance (RDG) approval. Direct data sharing is not allowed. Barts Health NHS Trust: The largest NHS hospital group or Trust in the United Kingdom. Direct data sharing is not allowed. East Scotland: EHR data from the National Health Service (NHS) of Tayside and Fife health board via the Health Informatic Centre (HIC). Direct data sharing is not allowed. For all databases, aggregated incidence rate data are available in: https://dpa-pde-oxford.shinyapps.io/fluroquinoloneTimeSeries/.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.