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Impact of the US Food and Drug Administration warning regarding increased risk of aortic aneurysms or aortic dissections on fluoroquinolone prescribing trends

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ABSTRACT

Background The US Food and Drug Administration (FDA) issued a warning in December 2018 regarding an increased risk of aortic aneurysms and aortic dissections associated with fluoroquinolone (FQ) use. This warning specifically targeted older adults and patients with conditions such as hypertension, Marfan syndrome, Ehlers-Danlos syndrome, atherosclerosis, peripheral vascular disease and history of aneurysms.

Objective To evaluate the impact of the safety warning on prescribing trends of FQs in the targeted population.

Methods This cross-sectional study with an interrupted time series (ITS) analysis (January 2018–December 2019) used a 25% random sample of IQVIA PharMetrics® Plus for Academics health plan claims database. The impact of the warning on FQ utilisation was quantified among the targeted population and a non-targeted population.

Results From 2018 to 2019, both study populations saw a decrease in the year-over-year percent change of FQ prescriptions per 100 000 beneficiaries (–11%, from 14 227 to 12 662, targeted; –15%, from 5227 to 4446, non-targeted) and proportion of FQ use versus other antibiotics (from 15.6% to 13.8%, targeted; from 9.4% to 8%, non-targeted). In the targeted population, the ITS analysis did not show a significant trend change, a change in level or postwarning trend in the monthly rate of FQ prescriptions per 1000 beneficiaries. A positive trend change was observed in the non-targeted population (0.07, <0.01–0.13), but there were no significant changes in level or post-warning trend.

Conclusion We did not find a change in FQ prescription rates after the warning. The utility of safety advisories as a primary tool for mitigating FQ use in high-risk populations should be revisited.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have reported a significant decrease in prescription fills for fluoroquinolones (FQ) from 2008 to 2020 in the general population, but these declines were most strongly associated with warnings or label changes announced prior to the December 2018 warning.

WHAT THIS STUDY ADDS

⇒ This is the first study to focus on the high-risk patient population that was specifically targeted by the December 2018 Food and Drug Administration warning.

⇒ The FQ warning did not have a discernible effect on reducing FQ utilisation among targeted patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests the need to reassess the effectiveness of safety advisories as the main strategy for mitigating the use of FQs and other high-risk medications in specific populations.

INTRODUCTION

Fluoroquinolones (FQs) are one of the most frequently prescribed classes of antibiotics in North America.[1–3] Their pharmacokinetic properties and broad-spectrum antibacterial coverage make them a desirable option against numerous infectious diseases, including urinary tract infections and bacterial pneumonia.[1–3]

Despite their clinical value, FQs are associated with potential adverse effects ranging from minor side effects such as gastrointestinal upset (eg, diarrhoea, nausea) and headaches[4] to more severe safety concerns that have become increasingly well-characterised over the past few decades.[5] Safety concerns reported in epidemiological studies[6–9] show a potential association between FQs and increased risk of bulges or tears in the aorta blood vessel known as aortic aneurysms (AA) and aortic dissections (AD).

Initially, the US Food and Drug Administration (FDA) announced in May 2017 that findings from the published studies and patient cases identified by the FDA did *not* support

reports that these medicines may result in AA or AD.[10] However, on 20 December 2018, the FDA updated and reversed its earlier decision, stating that, 'FQs should not be used in patients at increased risk unless there are no other treatment options available'.[11]

The population that was targeted by the warning included patients with known aneurysms or history of aneurysms, certain genetic disorders that involve blood vessels (eg, Marfan syndrome, Ehlers-Danlos syndrome), peripheral atherosclerotic vascular diseases, hypertension and older adults. Following the FDA update, a study published in 2019 that used the WHO's Vigibase database of individual case safety reports, similarly found that FQ use was associated with a higher risk of AA or AD (OR 2.13, 95% CI 1.03 to 4.37).[12] Additionally, a meta-analysis concluded that, compared with non-users or with users of comparator antibiotics, FQ users had a significantly increased risk of AA or AD (OR 2.23, 95% CI 1.80 to 2.77),[13] and subsequent meta-analysis have also demonstrated a similar association.[14]

Previous studies have reported a significant decrease in prescription fills for FQ from 2008 to 2020 in the general population, but these declines were most strongly associated with warnings or label changes announced prior to the December 2018 warning (online supplemental eTable 1).[5 15 16] To our knowledge, changes in FQ prescription utilisation following the December 2018 warning in the target patient population have not been characterised. Thus, the main objective of this study was to evaluate the impact of the December 2018 FDA warning on FQ prescribing trends among those targeted by the warning and among those who were not the intended target (ie, patient populations who did not have risk factors included in the warning).

METHODS

Data source

We used a 25% random sample of enrollees within the IQVIA PharMetrics® Plus[17] for Academics data from 2018 to 2019. The data include fully adjudicated health plan claims data and enrolment information for mostly commercial individuals with a subset of Medicare Advantage/Cost and Managed Medicaid in the US. Insurance beneficiaries have unique encrypted identifiers for longitudinal follow-up across medical and pharmacy records.

Study design

We used medical claims data to identify the targeted and non-targeted population and prescription claims data to identify prescription drug utilisation. Beneficiaries in the prewarning period were required to be continuously enrolled from January 2018 through December 2018, while beneficiaries in the postwarning period were required to be continuously enrolled from January 2019 through December 2019 (online supplemental eFigure 1). We did not extend the ITS analysis to 2020 because the use of antibiotics was significantly disrupted by the COVID-19 pandemic (online supplemental eFigure 2).[18]

Study population

The study included two populations of beneficiaries: a targeted population and a non-targeted population. Beneficiaries in the targeted population were required to be ≥65 years of age and/or have at least one International Classification of Diseases, Tenth Revision (ICD-10) code in their medical claims for hypertension, Marfan syndrome, Ehlers-Danlos syndrome, atherosclerosis, peripheral vascular disease, aneurysmal disease or AA/AD during the required continuous enrolment period (online supplemental eTable 2). Within the targeted population, we further stratified beneficiaries into subpopulations: one comprising beneficiaries most vulnerable to AA/AD (ie, with evidence of presence of Marfan syndrome, Ehlers-Danlos syndrome and AA/AD), and another including those with other risk factors (ie, with evidence of presence of hypertension, atherosclerosis, peripheral vascular disease and no evidence of presence of Marfan syndrome, Ehlers-Danlos syndrome and AA/AD).

Beneficiaries in the non-targeted population were required to be age <60 years and have no evidence of the ICD-10 codes for the aforementioned risk factors that constitute the targeted population during the continuous enrolment period. Since the purpose of using a non-targeted population is to serve as a falsification sample (with the expectation that this patient group is unlikely to be substantially affected by the warning), we hypothesised that using <60 years instead of <65 years as a cut-off may reduce potential spill-over effects that could have impacted prescribing decisions for beneficiaries aged 60–65 years. We excluded beneficiaries who were <18 or >84 years during the study period. We flagged, then quantified and compared the cross-sectional period prevalence of co-occurring clinical conditions (diabetes, arrhythmias, epilepsy, depression, anxiety, diabetic neuropathy, other neuropathic pain), in the prewarning and postwarning period. These conditions can increase the risk of FQ-associated adverse events and may impact prescribing decisions.[19 20]

Drugs of interest

We identified all FQ products (oral or intravenous) in the pharmacy claims, including levofloxacin, ciprofloxacin, moxifloxacin, delafloxacin and ofloxacin. We excluded topical, optic and otic formulations since safety concerns related to AA or AD have been limited to systemic formulations. For comparison, prescriptions for other antibiotic classes including cephalosporins, macrolides, penicillins and sulfonamides, as well as fluconazole (used as a non-antibiotic comparator) were also identified.

Year-over-year percent change and proportion of antibiotic use

Using prescription rates per 100 000 beneficiaries from 2018 and 2019, we analysed the percent change in the

use of FQs and non-FQ antibiotics from the prewarning period year to the postwarning period year. We also used multinomial proportions (with simultaneous 95% CIs)[21] to compare the proportion of FQs (and other antibiotics) in relation to all other antibiotics in 2018 and 2019 (eg, proportion of FQs in relation to cephalosporins, sulfonamides, macrolides, penicillins).

Monthly drug use measure

Monthly FQ, cephalosporin and fluconazole prescription rates per 1000 beneficiaries were used in the interrupted time series (ITS) analysis. We selected cephalosporins as a comparator antibiotic because cephalosporins have a similar prescribing profile to FQs and are not known to have a causal effect on AA or AD. Because use of other antibiotics can indirectly be affected by declining FQ use, fluconazole (antifungal) was used as a falsification test. Fluconazoles were chosen on the basis that prescribing trends for antifungal agents would not be affected by the drug safety communication, and that fluconazoles are also given for an acute infection (non-bacterial) and have the same route (oral and intravenous). Prescription rates per 1000 beneficiaries for each monthly interval were calculated separately for the targeted and non-targeted population. The numerator for monthly rates is the overall number of prescriptions dispensed (FQ, cephalosporins or fluconazole) in a month for all beneficiaries (targeted or non-targeted) who are continuously enrolled in the 12-month preperiod or postperiod. The denominator is all beneficiaries (targeted or non-targeted) who are continuously enrolled in the 12-month preperiod or postperiod.[22]

Statistical analysis

An ITS analysis was conducted using segmented ordinary least-squares regression to evaluate the change in trends from January 2018 to November 2018 and January 2019 to December 2019, and the immediate change (level change) after the warning in FQ, cephalosporin and fluconazole monthly prescription rates for both populations (online supplemental eMethods 1). The regression model was augmented with an autoregressive model for random error to account for the violation of the assumption of independent errors using the Yule-Walker method.[23 24]

In secondary analyses, we examined whether there was evidence that changes in FQ utilisation following the FDA warning occurred differentially between targeted older adults and targeted non-older adults, and between those who are most vulnerable to AA/AD (Marfan syndrome, Ehlers-Danlos syndrome and AA/AD) and those with other risk factors (hypertension, atherosclerosis, peripheral vascular disease). We carried out all analyses and data visualisation in SAS statistical software (V.9.4; SAS Institute).

Sensitivity analysis

In sensitivity analysis, we expanded the length of the time segments of the preperiod and postperiod by 12 and 3 months, respectively. Additionally, joinpoint regression, a permutation method developed by the National Cancer Institute, was used to detect naturally occurring break points without prespecified hypotheses over the study period.[25] Moreover, to evaluate the robustness of our model, we required full insurance eligibility during the entire study period (January 2018–December 2019) to reduce the possible impact of varying participation in insurance plan that might affect cohort characteristics.

Patient and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this project.

RESULTS

Table 1 summarises demographic and clinical characteristics of the two populations (targeted and non-targeted) in both periods. The distribution of sex, age and clinical comorbidities within each population were similar in the prewarning and postwarning periods. In the targeted population, we identified 58 280 FQ prescriptions for 409 646 unique adults in the prewarning period, and 47 696 FQ prescriptions for 376 685 unique adults in the postwarning period. In the non-targeted population, we identified 36 687 FQ prescriptions for 701 810 unique adults in the prewarning period, and 28 010 FQ prescriptions for 629 988 unique adults in the postwarning period.

Comparing the prewarning period with the postwarning period in the targeted population, prescription rates for FQs registered the clearest decrease, followed by macrolides and sulfonamides. Prescription rates for cephalosporins saw the greatest increase, followed by penicillins. A similar trend was observed in the non-targeted population, where prescription rates decreased for FQs, macrolides and sulfonamides, but increased for cephalosporins and penicillins (table 2).

The proportion of prescriptions for FQs in relation to all other antibiotics saw a statistically significant decrease from the prewarning period to the postwarning period in both populations. The proportion of prescriptions for cephalosporins in relation to all other antibiotics increased significantly from the prewarning period to the postwarning period in both populations. The proportion of prescriptions for macrolides, penicillins and sulfonamides did not significantly change from the prewarning to the postwarning period in both populations (online supplemental eFigure 3).

The ITS analysis showed that in the targeted population, the initial prescription rate (intercept) for FQs in January 2018 was 13.19 per 1000 beneficiaries. There was a decreasing monthly trend before the warning announcement (slope: −0.23 prescriptions per 1000 beneficiaries, 95% CI −0.39 to −0.06) that flattened after the warning. There was no change in level or trend for FQs in the targeted population (figure 1, table 3). When stratifying the targeted population based on age, the initial

Table 1 Demographic and clinical characteristics of the targeted and non-targeted population before and after the FDA warning*

	Targeted population†			Non-targeted population‡		
	No. (%)		Absolute standardised difference§	No. (%)		Absolute standardised difference§
	Prewarning (January 2018–December 2018)	Postwarning (January 2019–December 2019)		Prewarning (January 2018–December 2018)	Postwarning (January 2019–December 2019)	
Unique adults (continuously enrolled for 12 months (denominator)), total no.	409646	376 685	NA	701 810	629988	NA
Unique adults prescribed FQ, no. (%)	40012 (9.77%)	32818 (8.71%)	NA	29497 (4.20%)	22372 (3.55%)	NA
FQ episodes, total no.¶**	58280	47696	NA	36687	28 010	NA
Age, median (IQR), year	63 (54–71)	63 (54–71)	0.04	38 (28–48)	38 (29–49)	0.04
Female	203236 (49.61%)	187049 (49.66%)	<0.01	404677 (57.66%)	359920 (57.13%)	0.01
High-risk conditions, no. (% unique adults with condition)††						
Age ≥65 years	185789 (45.35%)	176355 (46.82%)	0.03	NA	NA	–
Hypertension	247246 (60.36%)	224913 (59.71%)	0.01	NA	NA	–
Marfan syndrome or Ehlers-Danlos syndrome	502 (0.12%)	523 (0.14%)	<0.01	NA	NA	–
Atherosclerosis	22476 (5.49%)	20926 (5.56%)	<0.01	NA	NA	–
Peripheral vascular disease	5323 (1.30%)	5226 (1.39%)	0.01	NA	NA	–
Aneurysmal disease	769 (0.19%)	655 (0.17%)	<0.01	NA	NA	–
Aortic aneurysm, aortic dissection, iliac artery aneurysm, other abdominal aneurysm or other aneurysm	2936 (0.72%)	2915 (0.77%)	0.01	NA	NA	–
Other comorbidities‡‡						
Diabetes	60755 (14.83%)	57002 (15.13%)	0.01	8694 (1.24%)	8404 (1.33%)	0.01
Arrhythmias	17774 (4.34%)	17052 (4.53%)	0.01	5455 (0.78%)	5285 (0.84%)	0.01
Epilepsy	917 (0.22%)	935 (0.25%)	0.01	1469 (0.21%)	1329 (0.21%)	<0.01
Depression	11852 (2.89%)	12137 (3.22%)	0.02	19142 (2.73%)	19450 (3.09%)	0.02
Anxiety	17081 (4.17%)	17246 (4.58%)	0.02	30386 (4.33%)	30751 (4.88%)	0.03
Diabetic neuropathy	4389 (1.07%)	4698 (1.25%)	0.02	296 (0.04%)	303 (0.05%)	<0.01
Other neuropathic pain	8597 (2.10%)	8486 (2.25%)	0.01	12046 (1.72%)	11152 (1.77%)	<0.01

*25% random sample of IQVIA PharMetrics® Plus for Academics, January 2018–December 2019.
†The targeted population includes beneficiaries with 1 year of continuous enrolment, with a claim for hypertension, Marfan syndrome, Ehlers-Danlos syndrome, atherosclerosis, peripheral vascular disease, aneurysms and/or are aged ≥65 years.
‡The non-targeted population includes beneficiaries with 1 year of continuous enrolment, have no evidence of a high-risk diagnosis claim and are aged <60 years.
§A standardised difference of <0.1 denotes negligible imbalance between groups.
¶Beneficiaries may have multiple prescriptions.
**Each prescription fill for an FQ constitutes an episode.
††These conditions are not mutually exclusive.
‡‡These are conditions that can increase the risk of FQ-associated adverse events and may impact prescribing decisions.
FDA, Food and Drug Administration; FQ, fluoroquinolone; NA, not applicable.

Table 2 Rates of antibiotic prescriptions per 100 000 beneficiaries in the prewarning and postwarning periods among the targeted and non-targeted populations*

	Prewarning period (January 2018–December 2018)	Postwarning period (January 2019–December 2019)	Year-over-year % change in prescription rate (2018–2019)
Targeted population			
Fluoroquinolone	14 227	12 662	−11.00
Cephalosporin	19 516	22 413	14.84
Macrolide	18 013	17 359	−3.63
Penicillin and combinations	30 413	30 498	0.28
Sulfonamide	9083	8889	−2.14
Non-targeted population			
Fluoroquinolone	5227	4446	−14.95
Cephalosporin	9766	10 692	9.48
Macrolide	13 464	13 017	−3.32
Penicillin and combinations	22 521	22 722	0.89
Sulfonamide	4819	4606	−4.42

The numerator for rates is the overall number of prescriptions dispensed (FQ or non-FQ antibiotics) in a year for all beneficiaries (targeted or non-targeted) who are continuously enrolled in the 12-month preperiod or postperiod. The denominator is all beneficiaries (targeted or non-targeted) who are continuously enrolled in the 12-month preperiod or postperiod.
*25% random sample of IQVIA PharMetrics® Plus for Academics, January 2018–December 2019.
FQ, fluoroquinolone.

(intercept) for FQs in January 2018 was 14.84 and 11.18 per 1000 targeted older adults and targeted non-older adults, respectively. Among targeted older adult beneficiaries, there was a decreasing monthly trend for FQs before the warning (slope: −0.26 prescriptions per 1000 beneficiaries, 95% CI −0.45 to −0.07) that flattened after the warning. Among targeted non-older adults, there was a decreasing monthly trend for FQs before the warning (slope: −0.18 prescriptions per 1000 beneficiaries, 95% CI −0.32 to −0.04) that flattened after the warning. There were no other statistically significant trends or changes in levels or trends for FQs in the targeted population by age (figure 2, online supplemental eTable 3). In the secondary analysis stratified by clinical risk group, there was no statistically significant level change or change in trend among the most vulnerable group. There was a statistically significant trend change among those with other risk factors after the warning (slope change: 0.19 prescriptions per 1000 beneficiaries, 95% CI 0.04 to 0.34), but the level change was not significant (figure 2, online supplemental eTable 3).

For the non-targeted population, the initial prescription rate (intercept) for FQs in January 2018 was 4.81 per 1000 beneficiaries. There was a decreasing monthly trend before the warning announcement (slope: −0.07 prescriptions per 1000 beneficiaries, 95% CI −0.12 to −0.03) that flattened after the warning. Although the level change was not significant, the trend change was significant (slope change: 0.07 prescriptions per 1000 beneficiaries, 95% CI <0.01 to 0.13) (figure 1, table 3).

For cephalosporins, monthly trends (slope) were flat before the warning and remained flat after the warning in both targeted and non-targeted populations. There were no significant trends or changes in levels or trends for cephalosporins (figure 1, table 3). Fluconazole showed no change in trend or level of use following the warning in the targeted population. In the non-targeted population, however, there was a drop in the level of fluconazole use, with no observed change in trend (figure 1, table 3).

Sensitivity analysis

Our sensitivity analysis that expanded the prewarning period by 1 year and the postwarning period by 3 months confirmed the primary analysis (online supplemental eFigure 4). Additionally, joinpoint regression did not identify any significant break points in the entire study period for FQs in the targeted population (online supplemental eFigure 5A–D). Moreover, the sensitivity analysis with the reconstructed denominators where we required full insurance eligibility during the entire study period confirmed no statistically significant difference in the level change or trend change between the postwarning and prewarning periods (online supplemental eFigure 6).

DISCUSSION

Our findings show that the FDA safety warning for FQs issued in December 2018 was not associated with a statistically significant immediate or sustained decrease in FQ prescription rates in the targeted population. We found a

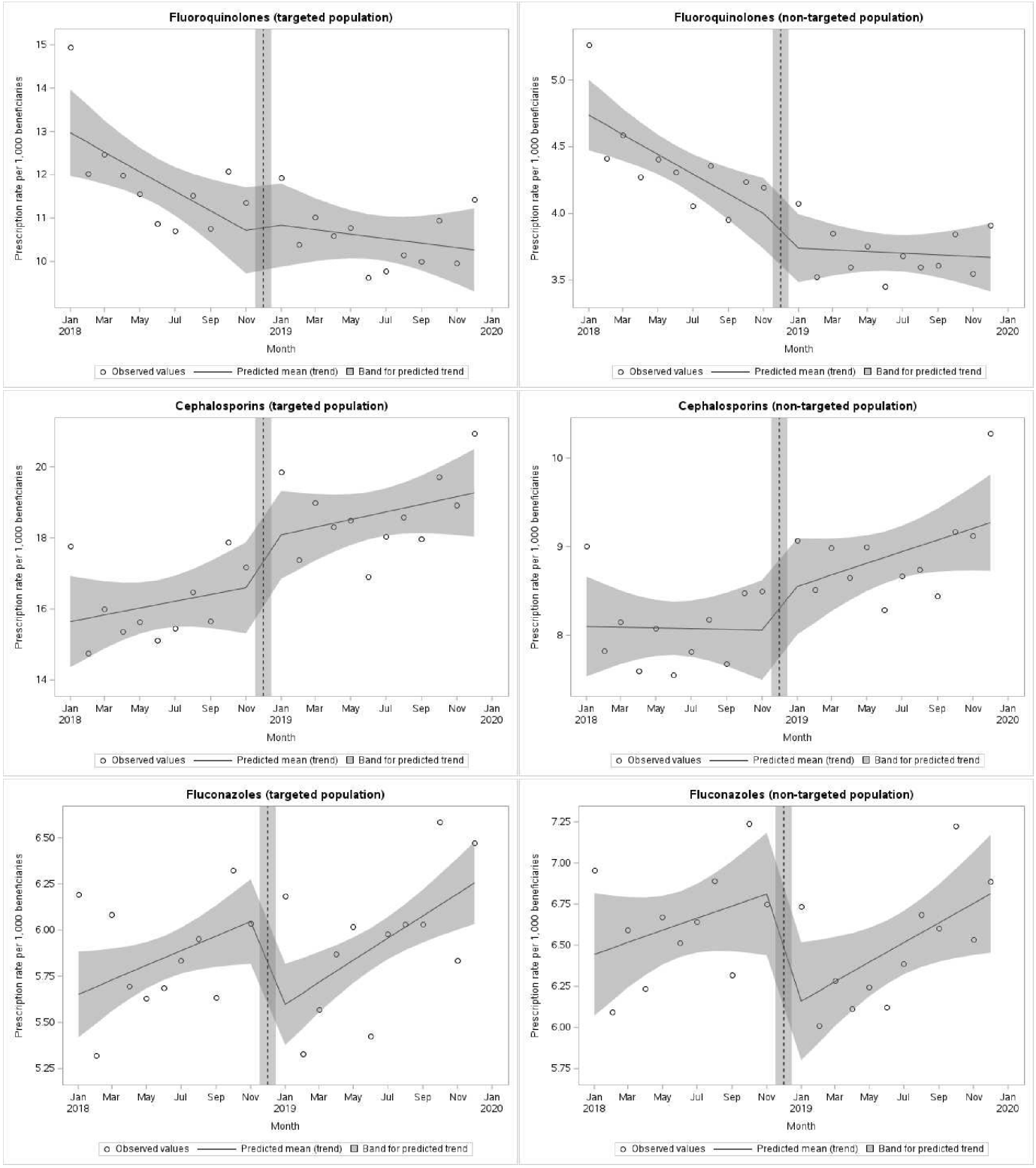

Figure 1 Monthly prescription rates (per 1000 beneficiaries) of fluoroquinolones, cephalosporins and fluconazoles in the targeted and non-targeted populations, January 2018–December 2019.[a] [a]25% random sample of IQVIA PharMetrics® Plus for Academics, 2018–2019. The month of December 2018 (warning announcement) was excluded from the interrupted time series analysis. Limited to oral and intravenous formulations.

decrease in the rate of FQ prescriptions and the proportion of FQs in comparison with other antibiotics from 2018 to 2019 across the targeted and non-targeted population. However, our findings indicate that this decrease was not associated with the December 2018 warning and was rather due to a downward trend in FQ use that preceded the warning. These findings are important because FQs remain a widely used antibiotic class in patients at high

Table 3 Results of interrupted time series analysis of monthly fluoroquinolone, cephalosporin and fluconazole utilisation rates per 1000 beneficiaries before and after the FDA warning

	Utilisation rate at start of period (95% CI)	Trend before FDA warning (January 2018–November 2018)		Level change after FDA warning*		Trend after FDA warning (January 2019–December 2019)		Trend change after FDA warning	
		Trend (95% CI)	P value	Rate change (95% CI)	P value	Trend (95% CI)	P value	Trend change (95% CI)	P value
Targeted population									
Fluoroquinolones	13.19 (12.08 to 14.30)	−0.23 (−0.39 to -0.06)	0.01	0.39 (−1.14 to 1.93)	0.61	−0.05 (−0.20 to 0.09)	0.47	0.17 (−0.04 to 0.39)	0.12
Cephalosporins	15.55 (14.12 to 16.98)	0.10 (−0.12 to 0.31)	0.37	1.29 (−0.69 to 3.27)	0.20	0.11 (−0.08 to 0.29)	0.25	0.01 (−0.27 to 0.29)	0.93
Fluconazoles	5.71 (5.30 to 6.13)	0.02 (−0.04 to 0.09)	0.45	−0.42 (−1.00 to 0.16)	0.15	0.06 (0.01 to 0.11)	0.05	0.03 (−0.05 to 0.16)	0.42
Non-targeted population									
Fluoroquinolones	4.81 (4.51 to 5.10)	−0.07 (−0.12 to -0.03)	0.003	−0.18 (−0.59 to 0.23)	0.38	−0.006 (−0.04 to 0.03)	0.74	0.07 (0.01 to 0.13)	0.03
Cephalosporins	8.10 (7.47 to 8.73)	−0.004 (−0.10 to 0.09)	0.93	0.43 (−0.44 to 1.30)	0.32	0.07 (−0.02 to 0.15)	0.12	0.07 (−0.05 to 0.19)	0.27
Fluconazoles	6.41 (5.99 to 6.82)	0.04 (−0.02 to 0.10)	0.24	−0.75 (−1.32 to -0.17)	0.02	0.06 (0.01 to 0.11)	0.04	0.02 (−0.06 to 0.10)	0.58

The month of December 2018 (warning announcement) was excluded from the interrupted time series analysis, and the month of January 2019 was considered the first time point of the postwarning period.
*Level change reflects the predicted change in prescription rates per 1000 between the last month of period 1 (November 2018) and the first month of period 2 (January 2019).
FDA, Food and Drug Administration.

risk for developing AA or AD despite the safety concerns raised in published literature that ultimately led to the issue of the FDA safety warning.

A study reported by Buerhle *et al*[5] on FQ prescribing patterns in the general population provides some support to our findings. The authors used IQVIA's National Prescription Audit® to measure the impact of FDA advisories on monthly outpatient prescription fills of FQs using an ITS model. The authors combined the period from May 2016 to June 2018 into a single period called 'first warning period', and July 2018 to February 2020 into a second period called 'second warning period'. The first warning period includes the May 2016 advisory (restrict use) and the July 2016 advisory (tendons, muscles, joints, nerves and central nervous system). The second warning period includes the July 2018 advisory (blood glucose and mental health) and December 2018 advisory (AA and AD). According to their findings, FQ prescription fills decreased significantly in May 2016 and throughout the first warning period. However, the decreasing trend in the second warning period did not significantly differ from the first warning period, suggesting that while the FQ warnings released in July 2018 and December 2018 did not *accelerate* downward trends, they may have helped *maintain* them.

Another study by Umarje *et al*[15] that used IQVIA's National Disease and Therapeutic Index examined trends and variations in outpatient prescribing of FQs by infection type and prescriber characteristics. The authors reported a reduction in the proportion of FQ prescriptions in relation to other antibiotics from 2015 to 2019. In line with the findings from Buerhle *et al*, their analysis using joinpoint regression confirmed significant break points coinciding with the May 2016 and July 2016 advisories, with no break points detected in 2018 or 2019. These studies were limited in that investigators only examined trends in the general population, without regard to patient-specific risk factors that constituted the target of the warning and which we focus on in the present study.

There are several possible explanations for why we did not find an immediate or sustained decrease in FQ prescription rates after the warning. First, prescribers might be weighing the overall risk-benefit ratio in each patient. Second, it is possible that the advisory was successful in communicating the uncertainties about FQ use in high-risk patients but insufficient to change antibiotic prescribing behaviours and decisions. Previous research that has examined other FDA safety warnings has noted the possibility that while clinicians may not change their prescribing behaviour, they may make greater effort to monitor patients they perceive to be at high risk.[26] Third, even if the safety warning was successful in communicating risk, prescribers might have been unconvinced of the causal association between FQ use and AA or AD. It is also possible that the prewarning decline in FQ use, motivated by relevant high-impact publications in major journals[6–8] combined with overlap in targeted populations from previously announced warnings

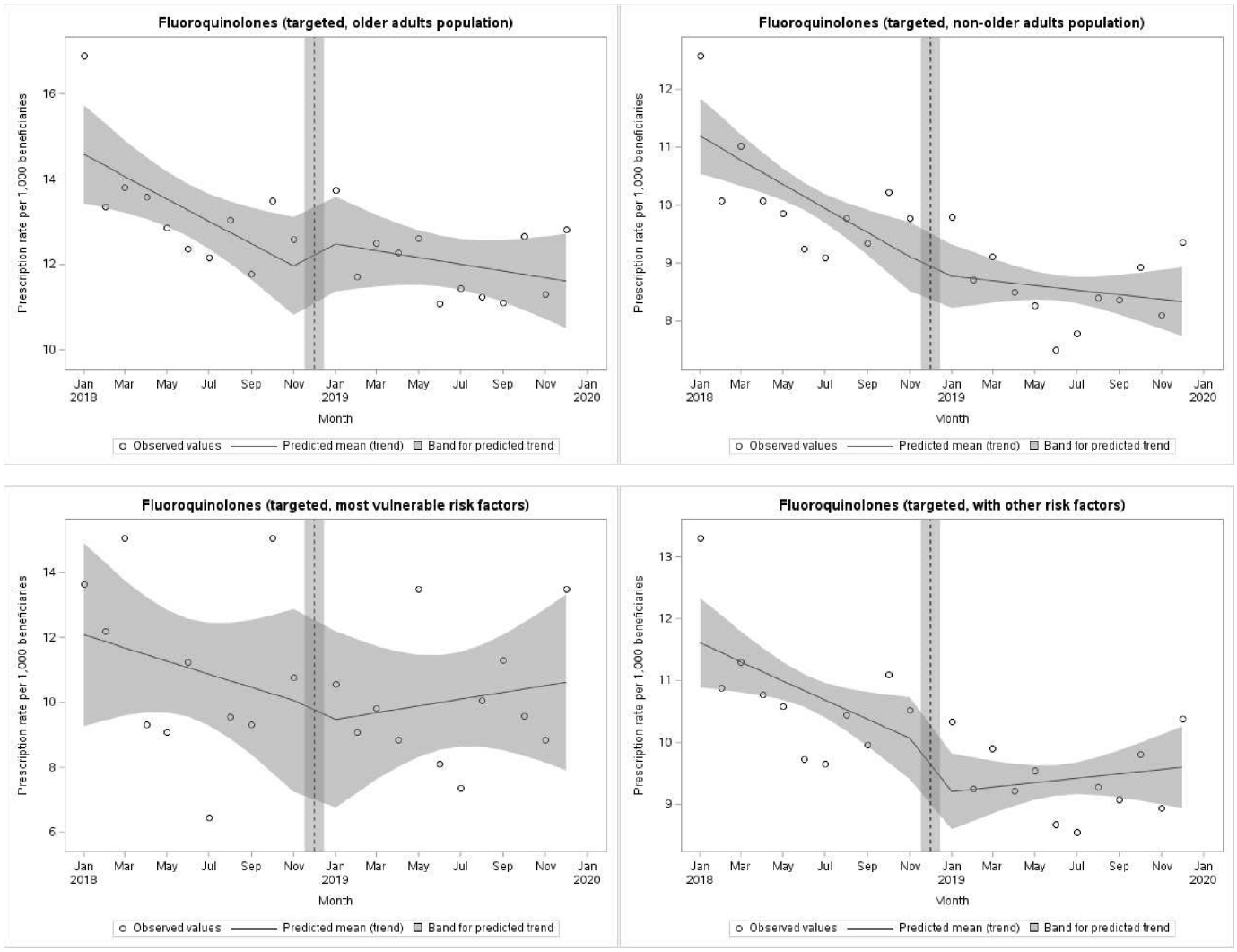

Figure 2 Monthly prescription rates (per 1000 beneficiaries) of fluoroquinolones (FQs) among the targeted population stratified by age and clinical risk group, January 2018–December 2019.[a] [a]25% random sample of IQVIA PharMetrics® Plus for Academics, 2018–2019. The targeted older adult population is composed of beneficiaries who are aged 65 years or older with or without high-risk conditions. The targeted non-older adult population is composed of beneficiaries who are aged <65 and have a high-risk condition. The most vulnerable group includes beneficiaries with claims for Marfan syndrome, Ehlers-Danlos syndrome and aneurysmal disease/other aneurysms. The group with other risk factors includes those with claims for hypertension, peripheral vascular disease and atherosclerosis, and no claims for Marfan syndrome, Ehlers-Danlos syndrome and aneurysmal disease/other aneurysms. The month of December 2018 (warning announcement) was excluded from the interrupted time series analysis. Limited to oral and intravenous FQ formulations.

(online supplemental eTable 1), led to a plateau in FQ use.[6–8] Finally, it is possible that the advisory simply did not reach the target prescriber audience or communicate risk information effectively.

In many cases, there are alternative antibiotics to FQs that could be used instead. While substitutes for FQs are common, there may still be instances where an FQ remains the preferred choice despite associated risks. This is particularly true as quinolones are the sole class of orally administered agents providing coverage of *Pseudomonas*,[27] and their favourable pharmacokinetic/pharmacodynamic profile offers an oral option when parenteral alternatives are the only option. We would anticipate such scenarios to be relatively much less common, with alternative agents typically feasible for substitution. However, our study did not observe the anticipated immediate and sustained decrease in FQ utilisation, suggesting complexities in prescribing behaviours beyond the availability of alternatives.

The continued use of FQs among those with high-risk factors raises the question of the effectiveness of FDA advisories in discouraging use of high-risk medications and whether and how their utility could be increased. FDA advisories have previously been shown to be successful in decreasing prescribing of atypical antipsychotics, antidepressants and rosiglitazone,[28] but less successful with attention-deficit/hyperactivity disorder medications.[26] Market segmentation strategies[29] that involve tailoring safety information to the appropriate patient and physician segments have been proposed as a potential element

to improve the effectiveness of the FDA warning. These strategies could also help assess the impact of FDA advisories on prescribers' behaviour by allowing for monitoring and feedback mechanisms. Reinforced, targeted communication based on comorbidity risk may offer additional opportunity to further communicate risks of FQ use.

In addition to strengthening the dissemination of evidence-based advisories, we support initiatives that augment safety advisories with practical interventions. For instance, integrating decision support tools into electronic health records tailored for high-risk populations could provide personalised guidance to clinicians. Such tools would highlight the specific risks associated with FQs in patients vulnerable to AA or AD, and recommend alternative treatment options suitable for high-risk populations, thereby aiding clinicians in weighing the risks and benefits effectively. Moreover, fostering a culture of continuous quality improvement within healthcare settings may promote regular review and adaptation of prescribing practices in light of emerging safety concerns.[30]

There are some limitations to our study. First, information on indications for antibiotic therapy is lacking in our dataset. Currently, there are no universally standardised documentation requirements for antibiotic indications.[31–35] Second, the prevalence of high-risk factors that constitute the targeted population may be underestimated due to undiagnosed or inadequately documented conditions. Third, claims data have inherent limitations because they represent healthcare claims adjudicated through insurance, which may not definitively indicate receipt of care. Fourth, we elected not to extend the ITS analysis to 2020 because the use of antibiotics was significantly disrupted by the COVID-19 pandemic. Finally, our interpretation does not solely regard these findings as indicative of the advisories' ineffectiveness. Rather, we emphasise the complexity of factors influencing prescribing behaviours, including clinical judgement and varying levels of awareness among healthcare providers. Moving forward, further research is warranted to better understand the nuanced responses to safety advisories among different user groups. This includes exploring healthcare provider decision-making processes and identifying effective strategies to enhance the implementation and impact of regulatory warnings.

Despite these limitations, we supported our results using a falsification sample of non-targeted beneficiaries, antibiotic and non-antibiotic comparators, a sensitivity analysis that expanded the length of the time segments and a joinpoint regression analysis which did not detect break points that overlapped with the hypothesised break point associated with the FDA warning. Our results add to the literature by exploring FQ trends among a population that was explicitly targeted by the FDA advisory.

CONCLUSION

In conclusion, the FDA warning was not associated with a reduction in the use of FQs in the targeted population. While we found a decrease in FQ prescription rates and proportion of FQ relative to non-FQ antibiotics in the postwarning period, our analysis suggests this decline was part of a prewarning downward trend in FQ use, and thus not associated with the December 2018 warning. The volume of FQ prescribing continues to be high among those at high risk of developing AA or AD, raising concerns regarding the potential for continued use of these agents in settings where they may have an unfavourable risk-benefit balance. Reinforced targeted communication, coupled with programme evaluation based on clearly defined clinical metrics, may help reduce potentially inappropriate FQ use among high-risk patients. Additionally, the utility of safety advisories as a primary tool for mitigating FQ use in high-risk populations should be revisited.

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