PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4021

ORIGINAL REPORT

Off-label use of oral fluoroquinolone antibiotics in outpatient settings in the United States, 2006 to 2012

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ABSTRACT

Purpose The aim of this study was to evaluate the practice pattern of off-label use of fluoroquinolones (FQs) in ambulatory settings and to identify the related risk factors.

Methods The National Ambulatory Medical Care Surveys from 2006 through 2012 was used to identify subjects who received FQ off-label prescriptions. We defined off-label use as the use of FQs for indications other than those in the FDA-approved drug label. Descriptive statistics were calculated by using a series of weighted chi-squared statistics. Multivariate logistic regression was conducted to identify factors associated with off-label FQ drug use.

Results There were 93 million ambulatory visits in which an FQ was prescribed, and 53.16% of these visits involved the prescribing of FQs in an off-label manner. The percentage of off-label prescriptions was the highest among individuals ≥80 years old (61.6%) and male patients (60.9%). The FQ drug prescribed most for an off-label indication in our study was ciprofloxacin (29.5% of the total visits). The multivariate analysis showed that age of ≥80 years and male patient was significantly associated with off-label use of FQs (adjusted odds ratio (OR) 3.66, 1.72–7.80 and OR 3.26, 2.32–4.56, respectively). Medicaid or private insurance versus Medicare were associated with significantly higher off-label prescribing of FQs (OR 2.53, 1.28–5.01 and 1.77, 1.03–3.03, respectively).

Conclusion The percentage of visits involving off-label FQs in US ambulatory settings is substantial. Efforts are needed consolidate and evaluate what high-quality scientific evidence is available and what is needed to support the safety and effectiveness of such off-label uses.

KEY WORDS—off-label use; prescribing; fluoroquinolones; antibiotics; pharmacoepidemiology; pharmacoepidemiology

Received 16 December 2015; Revised 01 April 2016; Accepted 02 April 2016

INTRODUCTION

The Food and Drug Administration (FDA) requires substantial evidence of efficacy and safety for specific clinical indications for every prescription medication to be approved for marketing. Although the FDA specifies a drug's initial approved indication, the drug's uses are not under control of the FDA after it is on the market.[1] That allows off-label use of medications for indications other than those provided by the manufacturer that has sought approval.[2] It has been estimated that from 40% to 60% of all prescriptions in the USA were used in a different way than described in the FDA-approved drug label.[3] Although off- label use of a medication often represents the most clinical, rational, evidence-based therapies,[4] widespread off-label prescribing can lead to significant deleterious effects by some drugs, especially antibiotics. That is because overuse of antibiotics is associated with increasing the prevalence of resistant bacteria, threatening the ability to treat common infections,[5–9] raising healthcare costs, and placing patients at risk of harm.[10–13] It has been reported that more than 142 000 annual emergency department visits are due to antibiotic-related complications.[14]

In this article, we focus on the fluoroquinolone (FQ) class because it has been one of the most commonly class used in the treatment of bacterial infections in primary care and hospital settings since 1984. In 2002, use of FQ prescriptions tripled from 7 million to 22 million per year and became the most widely prescribed group of antibiotics in the USA among

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adults.[15] According to IMS Health, in 2012, more than 23 million patients received a prescription for an oral FQ, and almost 4 million hospital patients were billed for injectable FQs.[16]

The FQ antibiotics represent an ideal antibiotic because of the favorable characteristics of this drug class. They have longer elimination half-lives, high oral bioavailability, high potency, extensive tissue penetration, and a lower chance of spontaneous bacterial resistance.[17] Furthermore, with their availability 35 years ago, FQs revolutionized the treatment of numerous bacterial infections because of their broad spectrum of activity and effectiveness against gram-negative and gram-positive aerobic bacteria (enterococci, streptococci, and staphylococci), as well as *Mycobacterium*, *Chlamydia*, *Legionella*, and *Mycoplasma* species. Many studies suggest that FQs have a good activity against many bacterial strains that are multiresistant to β-lactam and aminoglycoside antibiotics.[18] As a result, these pharmacological and microbiological profiles encourage physicians' use of FQs for off-label indications.

However, prescribing of FQs in a broader scope or context than those originally approved has led to an increased prevalence of resistant bacteria.[5–8,19] According to the findings of a large national surveillance study, the rate of FQ resistance among gram-negative bacteria tripled in parallel with a threefold increase in the national use of FQs.[9] Moreover, the frequent use of these agents not only increases the risk of antibiotic resistance but also puts the patient at risk of FQ-related adverse events. Recent studies have documented severe adverse effects in individual patients treated with FQs, such as cardiac arrhythmia,[20] kidney injury,[21] tendon rupture,[22] and retinal detachment.[23]

It has been reported that the vast majority of prescriptions of antibiotics occur in the outpatient rather than the inpatient setting and FQs represented the largest proportion of this outpatient antibiotic prescriptions.[24] However, no recent national studies have assessed how often and under what circumstances adult patients are prescribed oral FQ medications off-label at office visits in the USA. There is an urgent need to understand the current patterns and the scope of off-label prescribing of FQs in this setting in order to help guide clinicians and healthcare delivery systems in their efforts to improve use of FQs in ambulatory practice.[25] With this consideration, the purpose of this study was to evaluate the current practice pattern of off-label use of FQs in ambulatory settings and to test what drives it, by using data from the National Ambulatory Medical Care Survey (NAMCS).

METHODS

Data source and design

A trend analysis was performed by using data from a national probability sample survey, NAMCS, from 2006 to 2012, which was conducted annually by the National Center for Health Statistics (NCHS). In a three-stage procedure, the NCHS first sampled geographic areas, then practicing physicians within geographic areas, then patient visits within physician practices. The visits sampled take place during a 1-week period that is randomly assigned for each practice. The NAMCS took a random sample of all US nonfederally employed physicians (excluding anesthesiologists, radiologists, and pathologists) who were primarily engaged in "office-based patient care" as classified by the American Medical Association or the American Osteopathic Association. Physicians completed a one-page patient log for every patient visit, detailing the reason for the visit, diagnoses, services provided, medications prescribed, referral practices, and demographic description. Each individual record in the NAMCS is assigned an inflation factor called the *patient visit weight*. With these weights, nationally representative estimates can be generated from the sampled data to describe the use of ambulatory care services in the USA.[26,27]

The surveys gather physician and office demographics, patient demographics, and visit-specific clinical information. For each visit, the surveys record up to three diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM).[28] The surveys also record up to eight medications that the patient is currently taking or that are prescribed at the visit.

Study population and diagnostic categories

The eligible study population included all patients older than 18 years who received only one of the FQs listed in Table 1 in outpatient settings during the period 2006–2012. ICD-9 CM codes were used to capture the diagnoses in which any FQ was prescribed. Primary, secondary, and tertiary diagnoses for these visits were analyzed. Then visits were grouped into one of five diagnostic categories based on diagnosis assigned at that visit to enable analysis of FQ antibiotic prescribing on the basis of diagnosis. Categories included respiratory tract infections, genitourinary tract infections, intra-abdominal infections, skin infections, and joint or bone infections.

The off-label status for each drug prescribed to each patient was determined by evaluating the indications

DOI: 10.1002/pds

Table 1. Trade names and generic names of FQs used in the USA[30]

Generic name	Trade name	Date introduced	Manufacturer
Ciprofloxacin	Cipro®	22/10/1987	Bayer HealthCare
Gemifloxacin	Factive®	4/4/2003	LG Life Sciences
Levofloxacin	Levaquin®	20/12/1996	Janssen Pharmaceuticals
Moxifloxacin	Avelox®	10/12/1999	Alcon Pharmaceuticals Ltd.
Norfloxacin	Noroxin®	31/10/1986	Merck
Ofloxacin	Floxin®	28/12/1990	Janssen Pharmaceuticals

of therapy that are approved by the FDA.[29] A prescription was considered off label for an indication when none of the visit diagnoses corresponded to an indication that had received FDA approval for FQ use as of 2012.

Food and Drug Administration-approved indication categories for the FQs are provided in Table 2. Those indications were converted to ICD-9 CM codes, which were crossmatched with the NAMCS physician diagnosis variable. To ensure that we included all relevant ICD-9 codes for every indication, in some cases we used a four-digit or three-digit code corresponding to a broader range of indications. To decrease the potential for misclassification, we excluded those office visits in which both potential off-label and on-label indications for a drug prescription are listed.

Analysis

The main outcome variable was off-label prescribing. It was calculated as both the number and the percentage of visits in which an FQ was prescribed. A few categorical variables were created from the original data set to simplify the interpretation of the analyses.

Table 2. Indications for FQ antibiotics labeled by the US FDA by indication category[30]

	Indications	ICD-9-CM codes	Description	Agents
Genitourinary tract infections	Uncomplicated urinary tract infections	595, 597	Cystitis, urethritis	Norfloxacin (Noroxin), ofloxacin (Floxin), ciprofloxacin (Cipro), levofloxacin (Levaquin)
	Complicated urinary tract infections and pyelonephritis	590.0, 590.1, 590.2, 590.3, 595.3	Chronic pyelonephritis, acute pyelonephritis, renal and perinephric abscess, pyeloureteritis cystica, trigonitis	Norfloxacin, ofloxacin, ciprofloxacin, levofloxacin
	Prostatitis	601.0, 601.2, 601.3, 601.8, 601.9	Acute prostatitis, abscess of prostate, prostatocystitis, other specified inflammatory diseases of prostate, prostatitis (unspecified)	Norfloxacin, ofloxacin
Respiratory conditions	Lower respiratory tract infections	466	Acute bronchitis and bronchiolitis	Ofloxacin, ciprofloxacin
	Acute sinusitis	461	Acute sinusitis	Ciprofloxacin, levofloxacin, moxifloxacin (Avelox)
	Acute exacerbations of chronic bronchitis	491.21	Chronic bronchitis with (acute) exacerbation	Levofloxacin, moxifloxacin
	Community-acquired pneumonia	481–486	Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia); other bacterial pneumonia; pneumonia due to other specified organism; pneumonia in infectious diseases classified elsewhere; bronchopneumonia, organism unspecified; pneumonia, organism unspecified	Levofloxacin, moxifloxacin
Skin infections	Skin and skin-structure infections	680–686	Carbuncle and furuncle, cellulitis and abscess of finger and toe, other cellulitis and abscess, acute lymphadenitis, impetigo, pilonidal cyst, other local infections of skin and subcutaneous tissue	Ofloxacin, ciprofloxacin, levofloxacin
Joint or bone infections	Bone and joint infections, gram-negative bacterial infections	730.0–730.3, 730.7–730.9	Osteomyelitis, periostitis, and other infections involving bone; acute osteomyelitis; chronic osteomyelitis; unspecified osteomyelitis; periostitis without mention of osteomyelitis; osteopathy resulting from poliomyelitis; other infections involving bone in disease classified elsewhere; unspecified infection of bone	Ciprofloxacin
Intra-abdominal infections	Infectious diarrhea, typhoid fever	9.2, 2	Infectious diarrhea, typhoid fever	Ciprofloxacin

DOI: 10.1002/pds

The main predictor variables were patient age (18–29, 30–49, 50–64, 65–79, ≥80 years), patient gender, patient race/ethnicity (White, Black, Asian, other), primary payer (private insurance, Medicare, Medicaid, other), physician specialty category (primary care, medical specialist, surgical specialist), and practice type (private practice, community health center (CHC), health maintenance organization (HMO), other).

Categorical data were assessed by using the Pearson chi-squared test or the Fisher exact test. The unit of analysis was the visit. Weighted bivariable logistic regression analyses were performed to determine whether individual patient or physician characteristics were associated with off-label prescribing for a given indication (e.g., 1 = prescribed for off-label indication, 0 = prescribed for on-label indication). A multivariate logistic regression model was then fitted to the data to investigate the relationships of the individual demographic and comorbidity features with the risk of receiving an FQ for an off-label use, when we controlled for the effects of the other predictors. The FQ name variable was not included in the multivariate modeling because the regressions were at the visit level rather than prescription level. An OR and a 95% confidence interval were calculated to evaluate the strength of any association.

The survey data were analyzed by using the sampled visit weight, that is, the product of the corresponding sampling fractions at each stage in the sample design. Analyses were adjusted for clustering, stratification, and visit weight by using the survey design variables provided in the NAMCS dataset.

Finally, variables with sample observations of <30 or a relative standard error of >0.3 were excluded from the analyses as recommended by NCHS.[30] All tests were two sided with a *p*-value of 0.05 considered significant. All statistical analyses were performed by using SAS release 8.0 for IBM PC Windows and SAS Version 9.4 for mainframe computers (SAS Institute Inc., Cary, NC).

RESULTS

Using the NAMCS sample, we extrapolated a weighted national estimate of approximately 93.8 million FQ prescriptions that were dispensed to the adult population during the study period (Table 3). As shown in Figure 1, FQ prescriptions dispensed rose significantly from 11 million in 2006 to 15 million in 2007, a 30.26% change, followed by a 13.64% increase in total number of FQs prescribed in 2008. Compared with 18 million prescriptions in 2008, a significant decrease to reach 13 million prescriptions was seen in 2009. From 2009 to 2012, FQ prescriptions decreased by 12 %.

Fluoroquinolone off-label use increased by 43.68% from 2006 to 2007, while on-label FQ use increased by only 18.8%. Compared with 2008, there was a significant decrease in both on-label and off-label uses in 2009, 15.8% and 26.09%, respectively. The proportion of visits in which FQs were given to patients for on-label use decreased 30.21% from 2010 to 2011, despite the fact that off-label use decreased by only a small percentage (2.55%) for the same period.

Ciprofloxacin (52.4 %) was the most frequently prescribed drug (Figure 2). Of 93 million FQ prescriptions, ciprofloxacin has the largest proportion of off-label use (29.5% of visits). Norfloxacin was excluded from the analysis because there were too few recorded prescriptions for this drug to be statistically reliable. As shown in Table 4, numbers of off-label prescriptions were relatively correlated with numbers of total specific drugs.

Table 5 presents the percentages of visits that involved prescribing of off-label FQ medications. According to the NAMCS data, approximately 53.16% of visits by patients involved prescribing FQs in an off-label manner. According to the predetermined age groups, the percentage of off-label FQ prescriptions were the highest among individuals ≥80 years old than younger adults (61.6%; 95%CI: 53.3–69.8%). Although almost two-thirds of visits resulting

Table 3. Annual office-based visits that involved FQ prescriptions, 2006–2012*

Year	FQ prescriptions	Percent change	Off-label use	Percent change	On-label use	Percent change
2006	11 540 137	–	5 313 712	–	6 226 425	–
2007	15 031 926	30.26	7 634 905	43.68	7 397 021	18.80
2008	17 081 657	13.64	9 618 690	25.98	7 462 967	0.89
2009	13 393 589	−21.59	7 109 493	−26.09	6 284 096	−15.80
2010	13 647 378	1.89	6 552 892	−7.83	7 094 486	12.90
2011	11 336 734	−16.93	6 385 631	−2.55	4 951 103	−30.21
2012	11 783 317	3.94	7 258 347	13.67	4 524 971	−8.61
Total	93 814 738	–	49 873 670	–	43 941 069	–

*Numbers are weighted to reflect population estimates.

DOI: 10.1002/pds

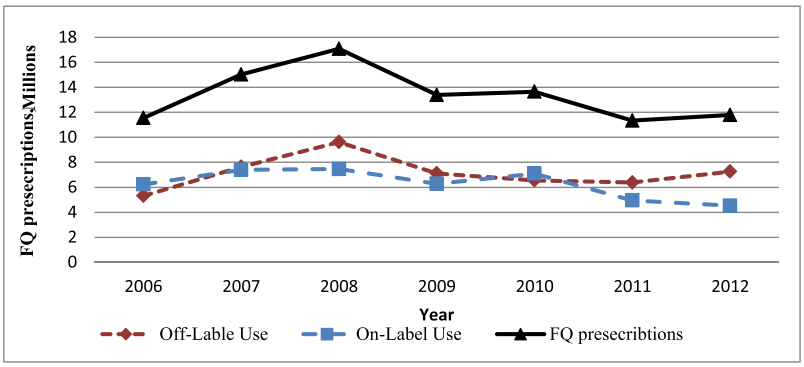

Figure 1. Off-label use and on-label use of FQs medications 2006–2012

in FQ prescriptions were by female patients, the percentage of off-label prescriptions was higher among male patients (60.9%; 95%CI: 56.7–65.1%). Forty-one million visits were by White patients, and 56.2% of them received off-label prescriptions (95%CI: 43.25, 50.60%).

Among the different sources of payment in our data, private insurance and Medicare were associated with the highest number of visits, at 52.5 million and 25.8 million visits, respectively. Off-label prescribing was present in 51.7% and 53.8% of visits covered by private insurance and by Medicare, respectively. Although the estimated total number of visits that resulted in an FQ prescription is much lower among Medicaid beneficiaries (5.5 million visits), the proportion of off-label FQs is the highest in this group compared with those with other payment sources (65.1%).

Substantial variation in off-label use was observed across indication categories. Overall, patients with respiratory infections were prescribed FQ antibiotics at 43.4 million office visits, and 54.8% of these visits involved an off-label prescription. Genitourinary tract infections came in second, accounting for 31.5 million visits. Nearly 57.4% of these visits resulted in an off-label use.

Table 6 presents the results of logistic regression analyses. The results showed that age and sex among patient characteristics had the power to predict FQ off-label prescribing. Patients aged ≥80 years were significantly associated with higher off-label use of an FQ (adjusted odds ratio (OR) 3.665, 95%CI 1.721–7.806, $p = 0.0008$), followed by age groups 50–64 and 65–79 years (OR = 2.056, 95%CI 1.126–3.755, $p = 0.0191$, and OR = 1.018, 95%CI 3.855–0.044,

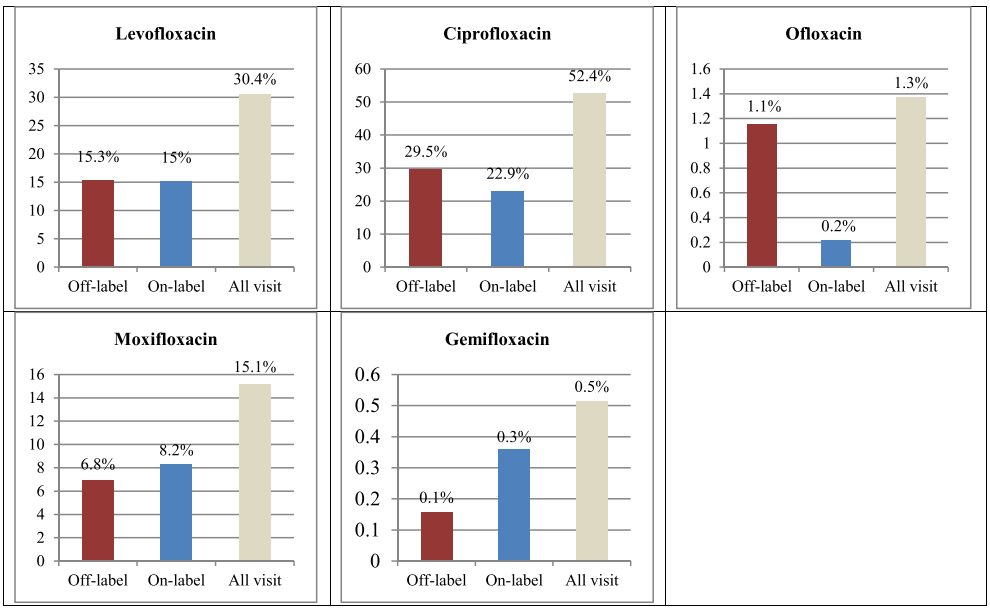

Figure 2. Prescription distribution for the studied FQs (total and off-label, on-label)

DOI: 10.1002/pds

Table 4. FQ medications by annual volume and proportion of off-label prescription

	Ciprofloxacin		Levofloxacin		Moxifloxacin		Ofloxacin		Gemifloxacin	
Year	All	% of off-label	All	% of off-label	All	% of off-label	All	% of off-label	All	% of off-label
2006	4 466 353	56.71	4 741 996	36.75	2 093 635	41.99	81 634	100	156 519	49.52
2007	6 557 619	55.50	4 875 715	49.43	3 337 749	42.74	173 405	91.35	87 438	0
2008	8 279 451	65.23	6 482 322	49.40	2 081 451	43.25	88 752	100	149 681	17.77
2009	7 768 434	48.83	3 564 168	65.60	2 021 430	48.27	2 224	100	37 333	0
2010	7 252 047	47.43	4 097 685	46.65	2 149 899	49.36	147 747	95.31	0	0
2011	7 800 652	59.54	1 610 882	45.22	1 713 495	49.07	186 392	78.61	25 313	100
2012	7 096 941	60.36	3 236 988	65.21	822 451	46.61	602 009	77.13	24 928	65.19
Total	4 922 1497	56.34	28 609 756	50.48	14 220 110	45.47	1 282 163	84.44	481 212	30.27

$p = 0.044$, respectively). The OR for off-label use of FQs is OR = 3.26, 95%CI 2.327–4.567, $p < 0.0001$, among male patients versus female patients. Moreover, compared with patients with Medicare, the odds of receiving an off-label prescription were significantly higher among patients covered by Medicaid and private insurance (OR = 2.539, 95%CI 1.286–5.013, $p = 0.0073$, and OR = 1.774, 95%CI 1.038–3.031, $p = 0.0361$, respectively).

DISCUSSION

This study provides detailed national estimates and rates of off-label use of FQs in ambulatory practice in the USA. Using data from US outpatient physician practices, we found that an estimated 93 million visits involved oral FQ antibiotic prescriptions during the survey years, more than half of which are for off-label indications (53.16%).

Our findings concluded that off-label use of FQs is higher in several patient populations, including men, privately insured and Medicaid enrollees, and patients more than 49 years old. This finding in men may reflect growing FQ use in men with asymptomatic bacteriuria and abacterial prostatitis.[31,32]

In the present study, with Medicaid and privately insured patients, there is a significant association with off-label use of FQs. Overall, the independent contributions of private insurance and Medicaid insurance do suggest that trends in off-label use are at least partially endorsed for economic reasons.

A high percentage of off-label use resulted from physicians working in a private practice setting, where doctors have no antibiotic-selection restrictions and do not want to lose any patients. No difference was found across physicians' specialties. This may suggest that there is no real difference in antibiotic-prescribing behavior among different groups of physicians. Another possible explanation is that all physicians are influenced by patients' demands or expectations.[33,34] Some patients who had previously been prescribed an FQ demand it again, even for conditions that probably are viral, because of the low incidence of side effects and convenient daily dosing. Moreover, because some physicians think that if they hand out prescriptions at the end of the visit, the patients will be satisfied with their health care, especially when they are being prescribed a more effective antibiotic, such as FQs, to treat their condition.[35]

These results suggest several areas for improvement to minimize the increase in FQ off-label prescribing, including increasing targeted education of physicians who prescribe more off-label FQ antibiotics (i.e., general/family practice, internal medicine, and urology). Although previous practice intervention programs[36–39] such as education, treatment guidelines, and decision support systems were implemented to promote judicious antibiotic prescribing, our findings suggest that the impact of these interventions is modest in terms of success. This might suggest the importance of continuing efforts to improve antimicrobial prescribing practice by these physicians. Moreover, efforts must also focus on the management of respiratory tract infections and genitourinary tract infections, which resulted in two-thirds of the total off-label FQ prescriptions by office-based physician practices in the USA during our study period.

It is important to highlight the fact that *off-label* is not synonymous with *inappropriate*. Many off-label FQs have proven clinical value, and some off-label uses may even represent the only therapeutic option available to patients. Even some on-label use may be inappropriate. For example, although one on-label use of FQs is treating patients with sinusitis, FQs are not recommended as first-line agents, and β-lactam antibiotics would be a more appropriate choice.[40]

The problem behind the large extent of off-label use is the lack of harmonization between evidence and on-label use. Therefore, professional bodies should be

DOI: 10.1002/pds

Table 5. Patient and physician characteristics for visits at which an FQ was prescribed in the USA: 2006–2012*

Characteristic	Entire sample, millions	Off-label				
		Total, millions	Visits, weighted %	95%CI		*p*-value
All visits	93.8	49.2	53.16	50.55	55.77	
Age (years)						0.0424
18–29	8.69	3.87	44.5	37.0	52.1	
30–49	28.6	14.8	51.8	47.2	56.4	
50–64	28.9	15.8	54.8	50.7	58.8	
65–79	20.5	10.9	53.3	48.1	58.5	
≥80	7.02	4.32	61.6	53.3	69.8	
Sex						<0.0001
Female	58.2	28.2	48.4	45.3	51.4	
Male	35.5	21.6	60.9	56.7	65.1	
Race/ethnicity						0.8817
White	41.0	23.1	56.2	52.5	60.0	
Black	5.07	2.92	57.5	45.6	69.5	
Asian	2.68	1.41	52.8	38.8	66.8	
Other†	0.43	0.21	48.5	39.3	57.6	
US Census region						0.6002
Northeast	18.9	9.52	50.4	44.4	56.3	
Midwest	19.2	9.95	51.6	45.6	57.7	
South	40.2	21.9	54.6	50.6	58.5	
West	15.4	8.42	54.5	48.8	60.3	
Primary payer						0.0993
Private	52.5	27.1	51.7	48.6	54.7	
Medicare	25.8	13.8	53.8	48.6	59.03	
Medicaid	5.55	3.62	65.1	54.7	75.4	
Self-pay	5.13	2.43	47.5	36.4	58.5	
Other	4.78	2.75	57.6	47.5	67.8	
Practice Type						0.0005
Private practice	85.8	46.6	54.3	51.5	57.02	
Freestanding clinic/urgicenter	5.21	1.90	36.4	26.1	46.8	
HMO	1.29	0.732	56.7	36.4	77.1	
CHC	1.06	0.53	50.5	38.2	62.8	
Other	0.411	0.09	22.6	3.92	41.3	
Site of suspected infection						<0.0001
Respiratory infection	43.4	23.8	54.8	48.3	61.3	
Genitourinary tract infection	31.5	18.1	57.4	50.4	64.5	
Intra-abdominal infection	9.01	4.23	46.9	37.1	56.7	
Joint or bone infection	4.93	1.88	38.1	35.4	40.9	
Skin infection	4.78	2.29	48.1	41.7	54.3	
Physician specialty						<0.0001
General/family practice	37.2	17.5	46.9	42.6	51.3	
Urology	9.26	6.12	66.1	61.5	70.6	
Dermatology	0.32	0.18	57.3	31.2	83.4	
General surgery	1.29	1.03	79.7	68.6	90.7	
Internal medicine	26.3	12.9	49.1	43.1	55.1	
Obstetrics and gynecology	2.13	1.30	61.3	45.9	76.8	
Orthopedic surgery	0.34	0.24	72.3	49.5	95.1	
Otolaryngology	3.06	1.81	59.2	51.7	66.7	
Other specialties	13.7	8.69	63.3	55.03	71.5	

CI, confidence interval; HMO, health maintenance organization; CHC, community health center.
*Based on weighted sample from NAMCS (unweighted $n = 3293$, weighted $n = 93\,814\,738$).
†Includes native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and mixed races.

more proactive and use combined data from off-label drug use clinical trials and data collected from off-label use of drugs in clinical practice to quantify the safety and effectiveness of off-label drug use and implement strategies to ensure patient safety.

There are several limitations that should be acknowledged. First, although the survey data used for this study do not capture the entire universe of ambulatory medical care (e.g., CHCs and federal institutions such as Veterans Administration outpatient clinics are excluded), they do permit nationally reliable estimates of care provided in most US mainstream ambulatory settings. Second, our evaluation is at the visit level, not at the patient level, so the percentages we report are percentage of visits, not percentage of patients. Nonetheless, our findings show trends from the perspective of

DOI: 10.1002/pds

Table 6. Bivariate and multivariate models of factors associated with off-label use of FQs at ambulatory care visits*

	Unadjusted OR	95%CI		*p*-Value	Adjusted OR†	95%CI		*p*-value
Age (years)								
18–29				Referent				Referent
30–49	1.657	1.033	2.659	0.0363	1.583	0.92	2.725	0.097
50–64	2.369	1.404	3.997	0.0013	2.056	1.126	3.755	0.0191
65–79	1.617	0.988	2.649	0.0561	1.982	1.018	3.855	0.044
≥80	2.517	1.357	4.666	0.0034	3.665	1.721	7.806	0.0008
Sex								
Female				Referent				Referent
Male	3.17	2.34	4.27	<0.0001	3.26	2.327	4.567	<0.0001
Race/ethnicity								
White	1.15	0.65	2.02	0.631	1.384	0.794	2.412	0.2504
Black	1.21	0.55	2.64	0.6329	1.485	0.651	3.391	0.3467
Asian				Referent				Referent
Other‡	1.94	0.37	10.17		3.051	0.362	25.709	0.3043
US Census region								
Northeast	1.051	0.658	1.68	0.8353	0.921	0.549	1.545	0.754
Midwest				Referent				Referent
South	1.065	0.702	1.616	0.7672	1.107	0.722	1.696	0.6418
West	1.052	0.661	1.673	0.8319	1.191	0.727	1.95	0.4871
Primary payer								
Private	1.221	0.875	1.704	0.2391	1.774	1.038	3.031	0.0361
Medicare				Referent				Referent
Medicaid	1.512	0.908	2.518	0.1122	2.539	1.286	5.013	0.0073
Self-pay	1.017	0.568	1.822	0.9535	1.386	0.611	3.147	0.4342
Other	1.272	0.668	2.423	0.4641	1.904	0.885	4.097	0.0995
Practice type								
Private practice	1.85	1.043	3.283	0.0355	1.805	0.907	3.589	0.0923
Freestanding clinic/urgicenter				Referent				Referent
HMO	1.396	0.509	3.832	0.5169	1.159	0.362	3.712	0.804
CHC	1.38	0.674	2.825	0.3776	1.563	0.621	3.936	0.3427
Other	0.691	0.208	2.296	0.5459	0.466	0.116	1.861	0.2789
Physician specialty								
General/family practice	0.972	0.297	3.183	0.9623	1.471	0.275	7.875	0.6518
Urology	1.943	0.587	6.433	0.2767	1.825	0.339	9.832	0.4829
Dermatology				Referent				Referent
General surgery	4.176	0.774	22.524	0.0963	6.528	0.919	46.359	0.0606
Internal medicine	0.956	0.275	3.317	0.9431	1.426	0.253	8.046	0.6873
Obstetrics and gynecology	0.968	0.264	3.548	0.9607	2.274	0.385	13.421	0.3635
Orthopedic surgery	2.59	0.361	18.586	0.3435	2.207	0.193	25.257	0.5238
Otolaryngology	1.795	0.421	7.65	0.4284	2.704	0.43	17.021	0.2886
Other specialties	1.825	0.54	6.165	0.3323	3.008	0.556	16.283	0.2006

Bivariable and multivariable logistic regression analyses were used to estimate and report unadjusted and adjusted ORs respectively.
CI, confidence interval; HMO, health maintenance organization; CHC, community health center.
*Based on weighted sample from NAMCS (unweighted $n = 3293$, weighted $n = 93\,814\,738$).
†Includes native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and mixed races.
‡Adjusted for age group, sex, race/ethnicity, and US Census region.

primary care practice. Third, because not all symptoms, diagnoses, and medications are documented in the NAMCS, it is possible that the FQs were actually prescribed for a condition different from that addressed in the visit. Also, physicians may diagnose certain conditions to justify FQ prescriptions for reimbursement purposes; this would lead to an inaccurate estimate of the off-label use of FQs. Fourth, as with many other data sources, the NAMCS lacks detailed clinical information that would be useful to assess physician rationale and decision making. Fifth, we used a four-digit or three-digit ICD-9 code corresponding to a broader indication to ensure we included all relevant ICD-9 codes for every indication, which would result in an underestimation of the number of off-label FQs. Finally, in the logistic regression models, no clustering of patient visits within physicians was accounted for in the analysis, because the number of visits in which patients' off-label FQs were prescribed was distributed across thousands of physicians.

CONCLUSION

In our examination of ambulatory care in the USA, it was shown that FQs are used extensively for indications in which the safety and the efficacy of the drug

DOI: 10.1002/pds

have not been established. To overcome this therapeutic problem, efforts are needed to encourage medical professionals, researchers, and pharmaceutical companies to rigorously consolidate and evaluate what high-quality scientific evidence is available and what is needed to support the safety and effectiveness of such off-label uses. The present results provide additional evidence for the effects of certain patients, providers, and environmental factors on the rates of off-label prescribing that are needed to focus these efforts. Furthermore, our study results point to targets where antibiotic stewardship programs and corrective policies can be implemented to optimize FQ antibiotic use in US ambulatory settings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Off-label use is use of medication for an indication that is not approved by the Food and Drug Administration.
- Of 93 million ambulatory visits in which an FQ was prescribed, over half of prescriptions were off label.
- Off-label prescribing of drugs for adult patients is a continuing public health concern. Efforts are needed consolidate and evaluate what high-quality scientific evidence is available and what is needed to support the safety and effectiveness of such off-label uses.
- Efforts must also focus on the management of respiratory tract infections and genitourinary tract infections, which resulted in two-thirds of the total off-label FQ prescriptions.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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DOI: 10.1002/pds