Fluoroquinolone Antibiotics and Tendon Injury in Adolescents

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abstract

OBJECTIVES: To estimate the association between fluoroquinolone use and tendon injury in adolescents.

METHODS: We conducted an active-comparator, new-user cohort study using population-based claims data from 2000 to 2018. We included adolescents (aged 12–18 years) with an outpatient prescription fill for an oral fluoroquinolone or comparator broad-spectrum antibiotic. The primary outcome was Achilles, quadricep, patellar, or tibial tendon rupture identified by diagnosis and procedure codes. Tendinitis was a secondary outcome. We used weighting to adjust for measured confounding and a negative control outcome to assess residual confounding.

RESULTS: The cohort included 4.4 million adolescents with 7.6 million fills for fluoroquinolone (275 767 fills) or comparator (7 365 684) antibiotics. In the 90 days after the index antibiotic prescription, there were 842 tendon ruptures and 16 750 tendinitis diagnoses (crude rates 0.47 and 9.34 per 1000 person-years, respectively). The weighted 90-day tendon rupture risks were 13.6 per 100 000 fluoroquinolone-treated adolescents and 11.6 per 100 000 comparator-treated adolescents (fluoroquinolone-associated excess risk: 1.9 per 100 000 adolescents; 95% confidence interval −2.6 to 6.4); the corresponding number needed to treat to harm was 52 632. For tendinitis, the weighted 90-day risks were 200.8 per 100 000 fluoroquinolone-treated adolescents and 178.1 per 100 000 comparator-treated adolescents (excess risk: 22.7 per 100 000; 95% confidence interval 4.1 to 41.3); the number needed to treat to harm was 4405.

CONCLUSIONS: The excess risk of tendon rupture associated with fluoroquinolone treatment was extremely small, and these events were rare. The excess risk of tendinitis associated with fluoroquinolone treatment was also small. Other more common potential adverse drug effects may be more important to consider for treatment decision-making, particularly in adolescents without other risk factors for tendon injury.

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Ms Ross conceptualized and designed the study, conducted the analysis, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Kinlaw conceptualized and designed the study, supervised the analysis, interpreted the data, and critically reviewed and revised the manuscript; Drs Herzog and Jonsson Funk contributed to the design of the study, interpreted the data, and critically reviewed and revised the manuscript; Dr Gerber conceptualized and designed the study, interpreted the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: A 2008 US Food and Drug Administration warning notes an elevated risk of tendon rupture and tendinitis after fluoroquinolone antibiotics. The authors of a 2002 epidemiological analysis of this potential adverse effect in children did not observe an elevated risk.

WHAT THIS STUDY ADDS: In this analysis of 7.6 million antibiotic prescription fills for US adolescents, tendon rupture and tendinitis after exposure were rare. Fluoroquinolone was associated with small excess risk for tendon rupture and tendinitis, which may not be clinically meaningful.

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Antibiotics are the most common medication class used in children and are associated with a significant burden of adverse events.[1] Children, when compared with adults, are particularly vulnerable to adverse drug reactions because of limited dosing and pharmacokinetic data, common off-label prescribing,[2,3] and scarce postmarketing surveillance studies, which are needed to identify rare harmful effects.

Fluoroquinolone antibiotics are commonly prescribed to adults because of convenient dosing, broad-spectrum coverage, high bioavailability, and favorable tolerability.[4–7] Additionally, oral fluoroquinolones may be important alternatives to parenteral antibiotics when equivalent oral antibiotics are unavailable.[7,8] Pediatric use of fluoroquinolones, however, has been more limited[4,9] because of safety concerns extrapolated from animal studies revealing cartilage damage in weight-bearing joints.[10,11]

In multiple studies in adults, fluoroquinolone use has been associated with increased risk of tendon injury,[12–21] which causes disability, pain, and need for surgery.[22] Evidence suggests that fluoroquinolones may impact tendons and cartilage in the load-bearing joints of the lower limbs through collagen degradation, necrosis, and disruption of the extracellular matrix.[23–25] Fluoroquinolones have an affinity for connective tissue,[25] and upregulation of tenocytes caused by fluoroquinolone use has been shown to negatively affect collagen fibrils in tendons, leading to an increased risk of tendon rupture and tendinitis.[24] In some studies, it was found that age modified the association with the highest increased risk among older adults.[13,14,19,25] In 2008, the US Food and Drug Administration (FDA) issued a boxed warning regarding fluoroquinolone-associated elevated risk of tendon injury.[26,27]

One study has been conducted in children, published in 2002,[28] in which fluoroquinolone use was examined, and tendon and joint injury was a composite outcome. Although no association was observed, there was a limited sample size and potential confounding bias. Although restrictions of fluoroquinolone use for children have recently been relaxed,[8] low fluoroquinolone prescribing rates in children compared with adults suggests ongoing safety concerns.[5,9] To improve on this evidence base, we examined the association between fluoroquinolone use and tendon rupture and tendinitis among millions of adolescents over 2 decades.

METHODS

Study Design and Data Source

We implemented an active-comparator, new-user[29,30] cohort study using IBM Watson Health MarketScan Commercial Claims and Encounters data (IBM Watson Health; Armonk, NY).[31] MarketScan includes beneficiaries enrolled in employer-sponsored private insurance across the United States and with adjudicated claims data on outpatient and inpatient health services and outpatient pharmacy dispensing. The University of North Carolina Institutional Review Board reviewed and exempted this study (19-2483).

Study Cohort

We included adolescents (aged 12–18 years) with an outpatient pharmacy claim for a dispensed prescription (henceforth, "index fill") for oral formulations of fluoroquinolone or comparator antibiotics between 2000 and 2018. The cohort was restricted to this age group to improve comparability across treatment groups because fluoroquinolone dispensing is rare for children aged <12 years (1 fill per 1000 person-years in this database) as compared with comparator antibiotic dispensing (319 fills per 1000 person-years).[32]

In Fig 1 and Supplemental Fig 5,[33] we illustrate cohort inclusion and exclusion criteria. To restrict to new users of these antibiotics, we required ≥100 days of continuous prescription drug coverage before their index fill. We excluded adolescents with a systemic fluoroquinolone or comparator fill in that 100-day washout period on the basis of our hypothesis that prophylactic antibiotic prescriptions would not exceed a 90-day supply. To assess baseline covariates, we required continuous fee-for-service insurance coverage for ≥180 days before the index fill. We also excluded adolescents who experienced an outcome before 2 days post index fill (explained below).

Treatments

Treatment was defined by using outpatient pharmacy dispensing data for oral antibiotics (fluoroquinolones and comparators). Fluoroquinolones included ciprofloxacin, levofloxacin, moxifloxacin, and gatifloxacin; comparator antibiotics included amoxicillin-clavulanate, azithromycin, cefalexin, cefixime, cefdinir, nitrofurantoin, and sulfamethoxazole-trimethoprim. Comparators were chosen because they are broad-spectrum antibiotics used for similar indications, such as urinary tract infections (UTIs), respiratory tract infections, and gastrointestinal infections. To classify medication type, we identified National Drug Codes using generic names in the National Drug Data File Plus (First Databank, South San Francisco, CA; www.firstdatabank.com) and Redbook (IBM Watson Health).

Outcomes

Our primary outcome was tendon rupture of the Achilles, quadricep, patellar, or a tibial tendon. Tendinitis was a secondary outcome. Additionally, we leveraged clavicle fracture as a negative control outcome

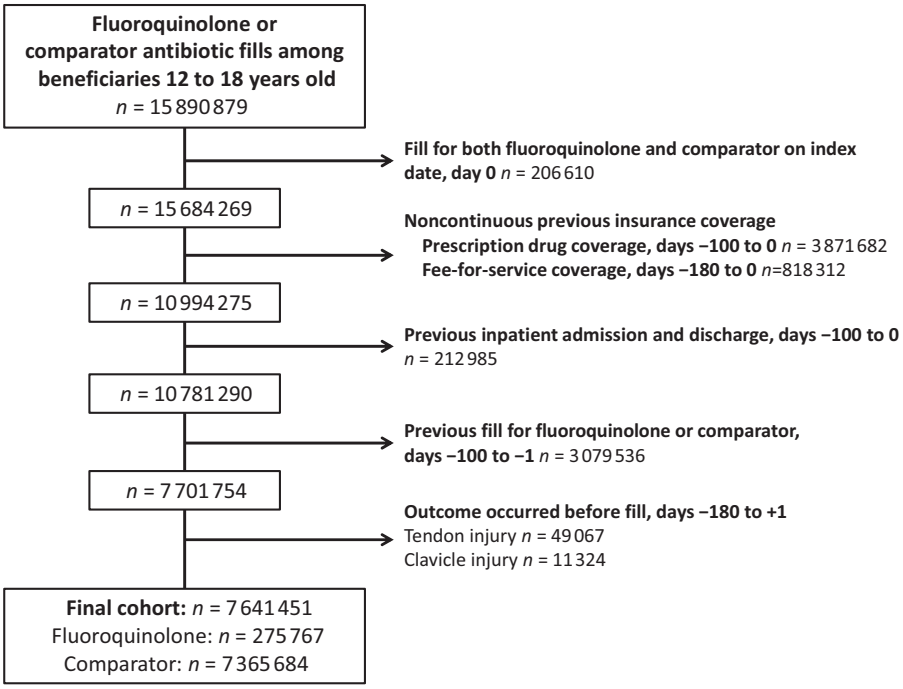

FIGURE 1
Flowchart of cohort creation.

to assess potential uncontrolled confounding; in the absence of confounding, the analysis of this outcome should produce a null result.[34]

To define outcomes, we used *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, 10th Revision, Clinical Modification* diagnosis codes and, for surgical repair of rupture or clavicle fracture, *Current Procedural Terminology* (CPT) codes (Supplemental Table 2). Outcome codes were assessed starting 2 days after the index fill (1) because we hypothesized that antibiotic treatment could not plausibly affect risk of the outcome in less than a day and (2) to reduce the potential for reverse causality, in which the antibiotic is received prophylactically for a procedure to treat the injury.

Confounders

We used a causal diagram to inform our selection of confounders.[35] Demographic factors included age, sex, geographic region of residence, and calendar time of index fill. Indication for the index fill was defined by using diagnosis codes from claims in the 3 days before and on the index fill date. Codes were summarized by using categories developed by Fleming-Dutra et al.[36]

Other baseline covariates included comorbid conditions (complex chronic conditions[37,38]), preindex inpatient and outpatient visit frequency (ie, health care use), preindex fills for other systemic antibiotics (Anatomical Therapeutic Chemical group J01[39]) or systemic corticosteroids (budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone hexacetonide), and systemic corticosteroid fills that occurred on the index fill date (Supplemental Figs 5 and 6, Supplemental Table 3)

Analysis

We estimated the average treatment effect in the treated, which answers the question, "How much would risk of the outcome change among adolescents who received a fluoroquinolone if these adolescents had instead received a comparator antibiotic?" To estimate the average treatment effect in the treated and control for measured confounding,[40] we used standardized mortality ratio (SMR) weighting.[41] In this approach, adolescents treated with a fluoroquinolone have a weight of 1 because they are the target population; adolescents treated with a comparator have a weight equal to their propensity score divided by its complement. The propensity score model parameterization is shown in Supplemental Table 3. We examined balance of measured covariates between treatment groups using standardized mean differences before and after weighting.[42,43]

We used Kaplan-Meier–based methods to estimate the cumulative incidence (ie, risk) of the outcome in each treatment group during follow-up.[44] We implemented 2 primary

analyses: (1) an intention-to-treat (ITT) analysis and (2) a per-protocol analysis.[45] In the ITT analysis, patients were managed until they experienced the outcome, until disenrollment from insurance coverage, until 180 days after the index fill, or until the end of the study period (December 31, 2018), whichever came first. In the per-protocol analysis, the same criteria for follow-up were used, but follow-up was also stopped when the other treatment was dispensed, if that occurred.

We estimated the risk difference for every day of follow-up with 95% confidence intervals (CIs) using nonparametric bootstrap methods. We also calculated the inverse of the risk difference to estimate the number needed to treat to harm (NNTH),[46] which is the number of adolescents who would need to be treated with fluoroquinolones instead of a comparator antibiotic for 1 additional adolescent to experience the outcome, in expectation. Analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

Sensitivity Analyses

To assess the robustness of our results to assumptions, we conducted a number of sensitivity analyses: (1) To reduce confounding by indication, we restricted to adolescents with codes for UTI. (2) To minimize the influence of adolescents with frequent antibiotic use, we restricted to their first eligible follow-up. (3) To mitigate channeling bias[47] and outcome measurement error,[15] we restricted to the time period before the 2008 FDA boxed warning. (4) To reduce the potential obscuring of an association by short-course antibiotic treatment, we restricted to adolescents with index fills with at least a 3-day supply (98.8% of fluoroquinolone group and 98.7% of comparator group). (5) To increase comparability between fluoroquinolone and comparator groups,[48,49] before constructing SMR weights, we implemented asymmetric trimming of the propensity score[50] at the first and 99th percentiles. (6) To reduce potential bias due to missing data on indication (20.5% of the cohort), we used inverse probability-of-missingness weights[51] in combination with refit SMR weights estimated in adolescents with complete data. (7) To examine associations with specific fluoroquinolones, we restricted the fluoroquinolone-treated group to ciprofloxacin (rupture events were too rare to examine other fluoroquinolones alone). Finally, we also conducted a bias analysis to assess the impact of possible differential outcome misclassification (Supplemental Information).

RESULTS

Cohort

There were 15.9 million outpatient fills for an oral fluoroquinolone or comparator antibiotic among adolescents (aged 12–18 years) between 2000 and 2018. In the final study population (Fig 1), 4.4 million unique adolescents experienced a total of 7.6 million eligible antibiotic treatments, including 275 767 (3.6%) for fluoroquinolones. Ciprofloxacin was the most common fluoroquinolone (73%), and azithromycin (45%) and amoxicillin-clavulanate (19%) were the most common comparators; day supply was similar between fluoroquinolones and comparators (Supplemental Table 4).

Table 1 includes the cohort characteristics stratified by treatment. Before weighting (crude), adolescents treated with fluoroquinolones were more likely to be female (69%) and older (median age 17) compared with adolescents treated with the comparator antibiotics (female 54%, median age 15). A greater proportion of fluoroquinolone treatments (32%) than comparator treatments (8%) included a diagnosis that almost always requires an antibiotic (tier 1). As shown in Supplemental Table 5, UTI was the most common indication for fluoroquinolone treatment (29%), followed by gastrointestinal infections (8%) and sinusitis (7%); for comparators, the most common indications were sinusitis (18%), pharyngitis (17%), and skin, cutaneous, and mucosal infections (8%).

Outcomes

We identified 1478 tendon ruptures in the 180 days of follow-up for a crude rate of 0.43 per 1000 person-years (Supplemental Table 6). There were 32 335 tendinitis diagnoses (rate of 9.45 per 1000 person-years). For the negative control outcome, there were 7366 clavicle fractures for a crude rate of 2.15 per 1000 person-years.

Primary Analyses

SMR weights effectively balanced the treatment groups on measured covariates (Table 1, Supplemental Fig 6, Supplemental Table 5). The weighted risk difference per 100 000 adolescents for clavicle fracture and the negative control outcomes from the ITT analysis and the per-protocol analysis are depicted in Supplemental Figure 7. The difference was close to zero (null) before 90 days of follow-up. After 90 days, the difference became negative. Given that it is not biologically plausible that fluoroquinolones are protective against clavicle fracture >90 days after treatment initiation, we believe there is residual bias in this period and restrict presentation of the remaining results to 90 days of follow-up.

Figures 2 and 3 present the crude and weighted risk curves by treatment group and the weighted risk difference for tendon rupture and tendinitis, respectively, from the ITT analysis. The numeric results at 15, 30, and 90 days are presented in

TABLE 1 Demographic and Clinical Characteristics by Treatment Group, Crude and Weighted

	Crude			Weighted[a]	
	Fluoroquinolones (*n* = 275 767)	Comparators[b] (*n* = 7 365 684)	Standardized Mean Difference	Comparators[b] (*n* = 280 168)	Standardized Mean Difference
Region, *n* (%)[c]			0.038		0.004
Northeast	37 331 (13.5)	977 952 (13.3)	—	38 019 (13.6)	—
North central	67 143 (24.3)	1 890 835 (25.7)	—	68 071 (24.3)	—
South	129 936 (47.1)	3 464 911 (47.0)	—	132 236 (47.2)	—
West	38 306 (13.9)	959 147 (13.0)	—	38 683 (13.8)	—
Unknown	3051 (1.1)	72 839 (1.0)	—	3159 (1.1)	—
Sex, *n* (%)			−0.311		0.005
Male	84 950 (30.8)	3 367 759 (45.7)	—	85 689 (30.6)	—
Female	190 817 (69.2)	3 997 925(54.3)	—	194 479 (69.4)	—
Age, y			0.872		0.003
Median (IQR)	17 (16 to 18)	15 (14 to 17)	—	17 (16 to 18)	—
12–13, *n* (%)	13 256 (4.8)	1 824 333 (24.8)	—	13 329 (4.8)	—
14–15, *n* (%)	37 423 (13.6)	1 995 660 (27.1)	—	37 859 (13.5)	—
16–17, *n* (%)	109 504 (39.7)	2 374 101 (32.2)	—	111 416 (39.8)	—
18, *n* (%)	115 584 (41.9)	1 171 590 (15.9)	—	117 564 (42.0)	—
Indication, *n* (%)					
Diagnosis identified[d]					
Tier 1	87 876 (31.9)	590 646 (8.0)	0.625	93 322 (33.3)	−0.031
Tier 2	62 273 (22.6)	3 501 615 (47.5)	−0.542	61 500 (22.)	0.015
Tier 3	47 613 (17.3)	1 781 506 (24.2)	−0.171	46 886 (16.7)	0.014
Diagnosis not identified[e]	78 005 (28.3)	1 491 917 (20.3)	0.145	78 459 (28.0)	0.005
Recent antibiotic, *n* (%)[f]					
Previous 14 d	12 396 (4.5)	236 531 (3.2)	0.067	13 027 (4.6)	−0.007
Previous 30 d	21 814 (7.9)	447 580 (6.1)	0.072	22 747 (8.1)	−0.008
Previous 100 d	46 671 (16.9)	1 049 909 (14.3)	0.074	48 109 (17.2)	−0.007
Recent corticosteroids, *n* (%)[g]					
Same day	9334 (3.4)	423 015 (5.7)	−0.113	9389 (3.4)	0.002
Previous 100 d	10 847 (3.9)	236 543 (3.2)	0.039	11 327 (4.0)	−0.006
Health care use[h]					
Count of outpatient encounters, median (IQR)	3 (2 to 6)	3 (2 to 5)	0.088	3 (2 to 6)	−0.021
Any inpatient admission, *n* (%)	2930 (1.1)	40 867 (0.6)	0.057	3137 (1.1)	−0.006
Comorbid conditions, *n* (%)					
Any complex chronic condition[i]	20 534 (7.4)	400 659 (5.4)	0.082	22 026 (7.9)	−0.016
Neurologic or neuromuscular	2152 (0.8)	40 682 (0.6)	0.028	2410 (0.9)	−0.009
Cardiovascular	2949 (1.1)	64 971 (0.9)	0.019	3051 (1.1)	−0.002
Respiratory	1530 (0.6)	7445 (0.1)	0.079	1867 (0.7)	−0.014
Renal or urologic	1372 (0.50	12 162 (0.2)	0.058	1605 (0.6)	−0.010
Gastrointestinal	3629 (1.3)	24 688 (0.3)	0.109	4395 (1.6)	−0.021
Hematologic or immunologic	1279 (0.5)	21 887 (0.3)	0.027	1405 (0.5)	−0.005
Metabolic	3584 (1.3)	71 998 (1.0)	0.030	3761 (1.3)	−0.004
	3410 (1.2)	105 587 (1.4)	−0.017	3603 (1.3)	−0.004

Supplemental Table 7. The weighted 90-day risk of tendon rupture was higher among the fluoroquinolone-treated adolescents (13.6 per 100 000 adolescents; 95% CI 9.4 to 17.8) compared with those treated with the comparator antibiotics (11.6 per 100 000 adolescents; 95% CI 9.8 to 13.5) for a difference of 1.9 per 100 000 adolescents (95% CI −2.6 to 6.4). The NNTH indicated that 52 632 adolescents would need to be treated with fluoroquinolones instead of a comparator antibiotic for 1 additional adolescent to experience tendon rupture within 90 days. For tendinitis, the 90-day ITT risk difference was 22.7 per 100 000 adolescents (95% CI 4.1 to 41.3) for an NNTH of 4405. The per-protocol analysis results were similar (Supplemental Table 8, Supplemental Fig 8).

Sensitivity Analyses

The 30- and 90-day weighted risk differences per 100 000 adolescents for tendon rupture and tendinitis from each sensitivity analysis and the ITT analysis are presented in Figure 4. The tendon rupture sensitivity analysis estimates for 90-day risk difference per 100 000 adolescents ranged from −1.8 (95% CI −8.6 to 5.0) from the analysis restricted to the first eligible new-user period to 4.2 (95% CI −0.8 to 9.1) from the analysis in which missing data weights were used. The tendinitis sensitivity analysis 90-day estimates

TABLE 1 Continued

	Crude			Weighted[a]	
	Fluoroquinolones (n = 275 767)	Comparators[b] (n = 7 365 684)	Standardized Mean Difference	Comparators[b] (n = 280 168)	Standardized Mean Difference
Other congenital or genetic defect					
Malignancy	4020 (1.5)	93 256 (1.3)	0.017	4087 (1.5)	<0.001
Premature or neonatal	24 (<0.1)	611 (<0.1)	<0.001	26 (<0.1)	−0.001
Transplantation	213 (0.1)	3704 (0.1)	0.011	250 (0.1)	−0.004
Device	1105 (0.4)	14 668 (0.2)	0.037	1335 (0.5)	−0.011

IQR, interquartile range; —, not applicable.

[a] SMR weighting: comparator-treated group weighted to covariate distribution of the fluoroquinolone-treated group.

[b] Comparators: amoxicillin-clavulanate, azithromycin, cefalexin, cefdinir, cefixime, nitrofurantoin, and sulfamethoxazole-trimethoprim.

[c] Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

[d] Codes were obtained from any encounter up to the day of the index fill or 3 d before. Codes were classified by using diagnostic categories developed by Fleming-Dutra et al.[36] Beneficiaries were only counted in the priority category (priority order: tier 1, tier 2, tier 3).

[e] Either no recent codes were available (ie, the child did not have any health care encounters on the day of the antibiotic fill or in the 3 d before) or the diagnoses codes captured during that period were for an unrelated antibiotic or were nonspecific (E-codes and codes for symptoms, signs, or ill-defined health conditions). This category includes all other diagnosis codes that were not included in tier 3.

[f] Any outpatient pharmacy prescription fill for a systemic antibiotic (Anatomical Therapeutic Chemical group J01).

[g] Outpatient pharmacy prescription fill for systemic budesonide, triamcinolone hexacetonide, prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone.

[h] Captured during the 180 d before the index fill. Count of outpatient encounters is the count of unique service and discharge dates. The presence of any inpatient admission during 180 to 101 d before the index fill (exclusion criteria prohibited inpatient admission during the 100 d before).

[i] Feudtner et al.[37,38]

ranged from 8.3 (95% CI −14.9 to 31.4) from the first new-user period analysis to 38.7 (95% CI 7.5 to 70.0) from the analysis restricted to UTI indications. The bias analysis indicated that if differential misclassification of the outcome were present, our primary analysis results would have overestimated the fluoroquinolone-associated excess risk of tendon rupture and tendinitis (Supplemental Table 9).

DISCUSSION

In a cohort of 4.4 million 12 to 18-year-olds with 7.6 million antibiotic fills, we observed an elevated risk of tendon rupture associated with fluoroquinolone antibiotics compared with other broad-spectrum antibiotics. However, tendon rupture was rare, the risk difference was extremely small (even absent in some sensitivity analyses), and our primary results would overestimate the fluoroquinolone-associated excess risk in the presence of differential outcome misclassification. According to these data, on average, >50 000 adolescents would need to be treated with a fluoroquinolone for 1 additional tendon rupture to occur. The fluoroquinolone-associated excess risk was larger for tendinitis but was still small (1 additional event for every 4400 adolescents exposed) and was potentially inflated by differential outcome misclassification.

Few epidemiological studies have been focused on tendon-related adverse effects of fluoroquinolones in children. The first and only large comparative epidemiological study in children was conducted in 2002, and the 60-day risk of a composite outcome of tendon or joint injury was compared between fluoroquinolone and azithromycin treatment in nearly 21 500 children ≤18 years old.[28] The age- and sex-adjusted relative risk was 1.08 (95% CI 0.77 to 1.52), and the authors concluded that fluoroquinolone treatment was not associated with an increased risk. The authors validated outcomes via review of linked medical records, reducing potential bias from outcome misclassification[52]; however, the sample size was small (given the rarity of the outcome), the analysis did not robustly address confounding, and azithromycin alone may not be an appropriate comparator because it is not used for UTI, a common fluoroquinolone indication. In addition, by using a composite outcome, tendon-related adverse effects alone were not examined.

Investigators of multiple large epidemiological studies[12–21] have observed an association between fluoroquinolones and tendon injury or rupture in adults. Because the authors of these studies typically reported odds ratios or risk ratios without presenting adjusted risks, comparison with our results is challenging. Although investigators of some adult studies have observed large associations (eg, relative risk of 6.29[18]), it can be difficult to translate this association into potential harms for treated patients. Of the 3 adult studies in which rate differences were estimated, the excess rate difference for tendon rupture in 60 days of follow-up was 29 cases per 100 000

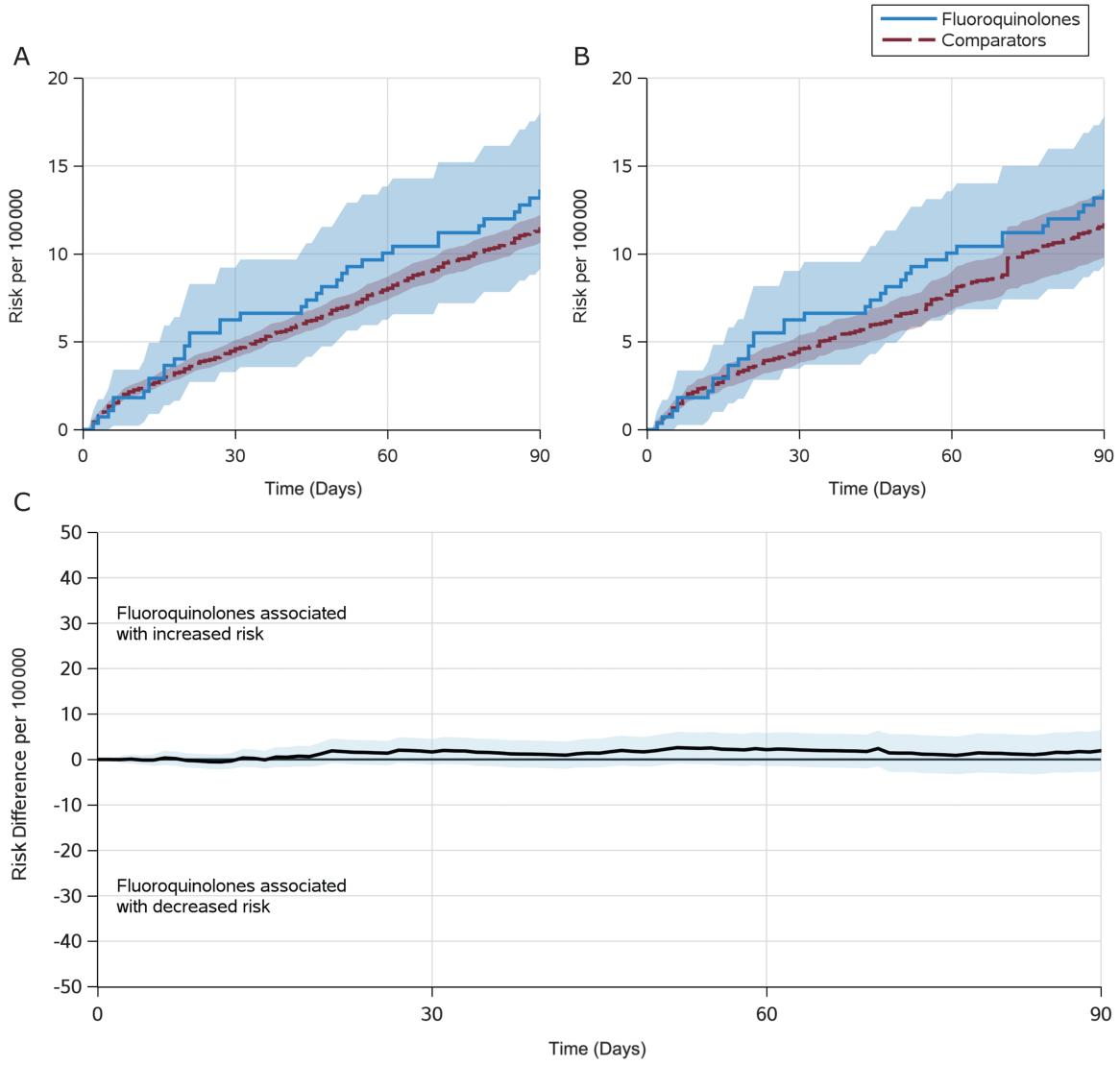

FIGURE 2
ITT analysis results for tendon rupture. A, Crude risk per 100 000 adolescents. B, Weighted risk per 100 000 adolescents. C, Weighted risk difference per 100 000 adolescents. Shaded areas are 95% CIs.

person-years,[21] and rate differences for tendon injury were 320 cases per 100 000 person-years in one study[12] and 1461 cases per 100 000 person-years in another.[13] Although direct comparison of rates and risks requires assumptions (eg, constant rates over follow-up, valid published estimates), it appears that previous published estimates were higher in adults than what we observed in adolescents in this study.

In one adult study, the authors did not observe an association between fluoroquinolones and Achilles tendon rupture and hypothesized that observed associations in other studies may be the result of bias from differential misclassification of the outcome.[15] The authors hypothesized that increased awareness of potential tendon-related adverse effects made providers more likely to include a tendon-related code for patients with recent fluoroquinolone exposure. To address this potential source of bias, we conducted a sensitivity analysis restricted to the time period before the 2008 FDA warning and a bias analysis. Although awareness of tendon-related adverse effects was likely present before the FDA warning, we hypothesize that it would have been lower before the warning than after the warning, which thus provides information on the likely direction of bias. These analyses suggest that our primary analysis, assuming no misclassification, is likely an overestimate of the excess risk due to fluoroquinolones.

Our analysis has a number of strengths. Our cohort includes >7.6 million antibiotic fills for >4 million privately-insured adolescents across the United States over 2 decades. We implemented both an ITT analysis

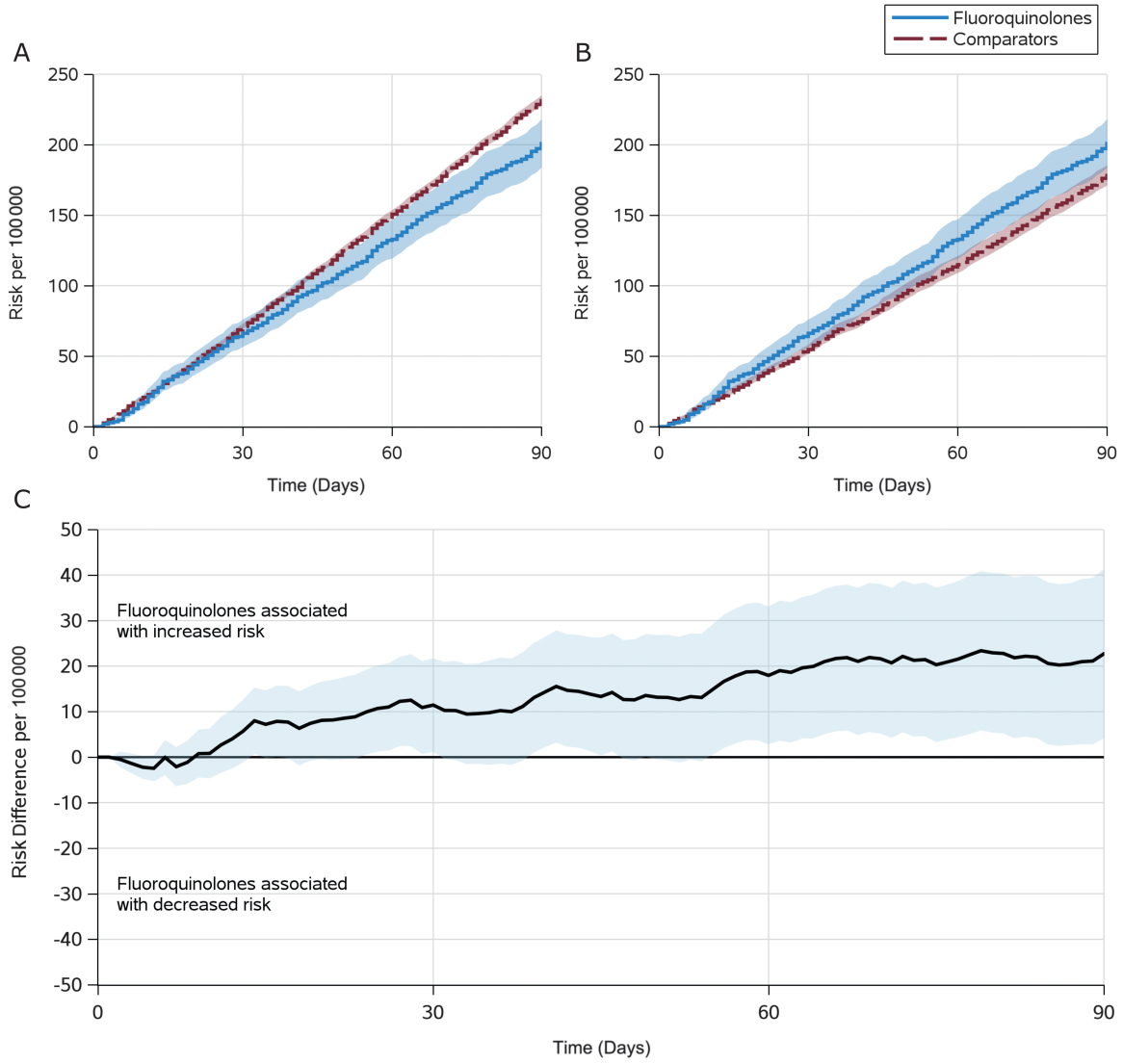

FIGURE 3
ITT analysis results for tendinitis. A, Crude risk per 100 000 adolescents. B, Weighted risk per 100 000 adolescents. C, Weighted risk difference per 100 000 adolescents. Shaded areas are 95% CIs.

and a per-protocol analysis, which accounts for treatment switching and can elucidate potential bias toward the null inherent to ITT designs.[45] We conducted a number of sensitivity analyses and a bias analysis to understand how our study design and analytic decisions might impact results. Importantly, the results of these analyses did not change our interpretations of the findings. Use of comparator broad-spectrum antibiotics that cover the range of potential indications of fluoroquinolones was also a strength, as was our implementation of a weighted analysis to control for measured confounding and estimate marginal risk differences. Lastly, we used a negative control outcome to assess residual confounding.

This study has limitations. Despite the size and scope afforded by MarketScan, including antibiotic prescriptions and injury care across the full spectrum of health care settings, our results may not be generalizable to adolescents outside this database, particularly those on Medicaid or without insurance. Our outcome definition relied on diagnosis and CPT codes, which are susceptible to misclassification. In particular, tendinitis identification may have a low positive predictive value (ie, many false-positives) because of "rule-out" diagnoses and subjectivity of this diagnosis. Results from our bias analysis indicate that differential outcome misclassification likely resulted in upward bias, which would overestimate the excess harm associated with fluoroquinolones. Adolescents who filled a prescription but did not actually take the medication would have been inappropriately included in the analysis, although this would likely be nondifferential with

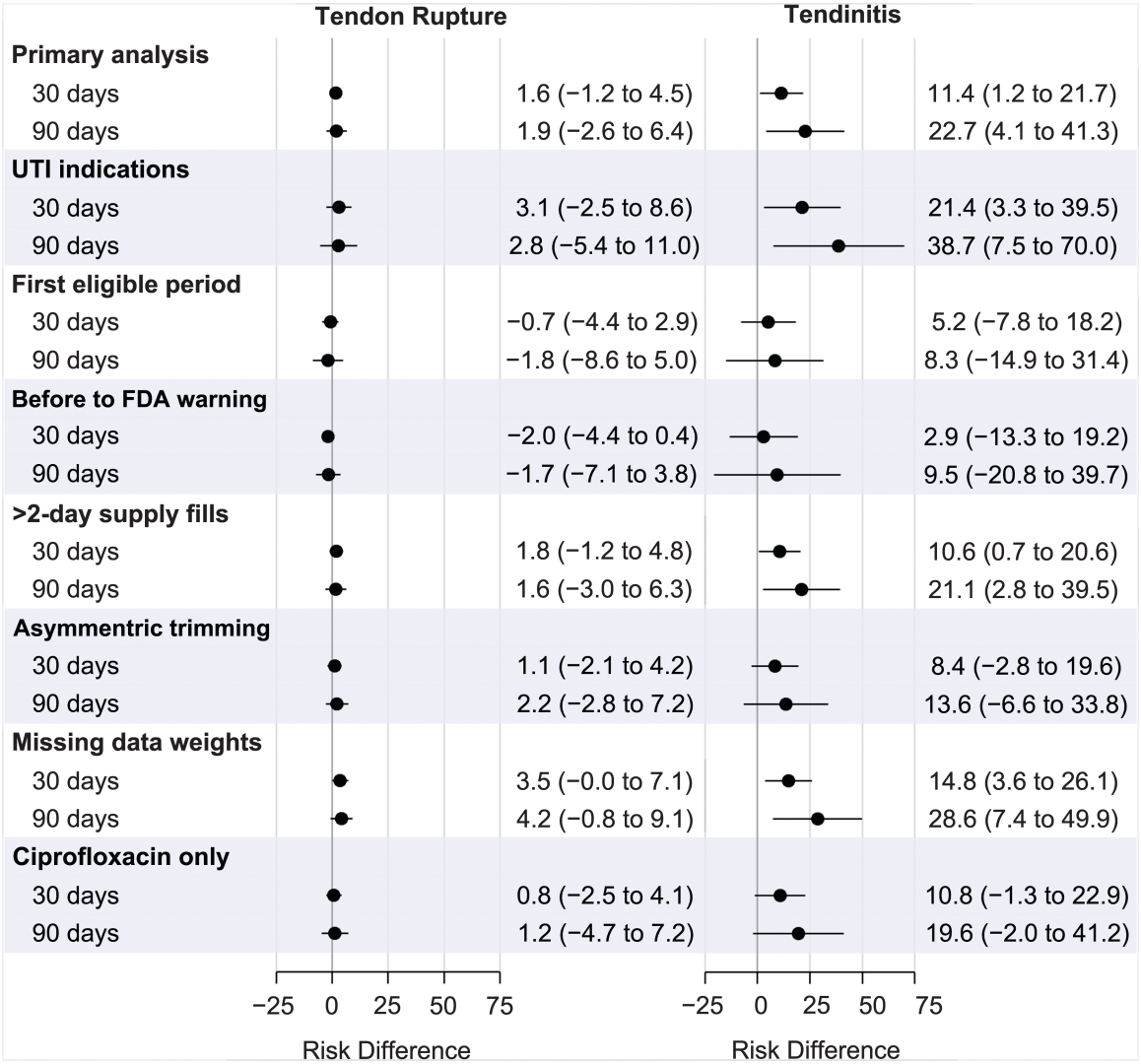

FIGURE 4

Weighted 30- and 90-day risk differences of tendon injury per 100 000 adolescents from sensitivity analyses. Error bars are 95% CIs. Primary analysis n = 7 641 541; UTI only n = 401 652; first eligible period n = 4 364 270; before FDA warning n = 1 858 304; >2-day supply n = 7 545 272; asymmetric trimming n = 6 602 672; missing data weights n = 7 641 541; ciprofloxacin only n = 7 565 647.

respect to the outcome. In our analysis, we assumed that censoring due to disenrollment or treatment switching was random, and if incorrect, our results could be biased.[53] Finally, although our negative control outcome analysis suggested good control of confounding, there could be residual bias related to differences in the confounding structure of tendon injury and clavicle fracture.

CONCLUSIONS

Fluoroquinolone treatment was associated with excess risk of tendon rupture and tendinitis compared with alternate antibiotic therapy. However, these differences were extremely small, and tendon-related adverse events were rare. This analysis provides important context for understanding the risk/benefit ratio of fluoroquinolones for adolescents. Given the rarity of tendon injury and the small excess risks associated with fluoroquinolones, more common adverse drug effects may be more important to consider for treatment decision-making, particularly in adolescents without other risk factors for tendon injury.

ABBREVIATIONS

CI: confidence interval
CPT: *Current Procedural Terminology*
FDA: US Food and Drug Administration
ITT: intention-to-treat
NNTH: number needed to treat to harm
SMR: standardized mortality ratio
UTI: urinary tract infection

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