Association between initiation of fluoroquinolones and hospital admission or emergency department visit for suicidality: population based cohort study

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ABSTRACT

OBJECTIVE
To evaluate the association between initiation of fluoroquinolones and hospital admission or emergency department visit for suicidality.

DESIGN
Population based cohort study.

SETTING
IBM MarketScan database, USA.

PARTICIPANTS
2 756 268 adults (≥18 years) who initiated an oral fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, gatifloxacin, norfloxacin, lomefloxacin, besifloxacin) or comparator antibiotic (January 2003 to September 2015) and had at least six months of continuous health plan enrollment and a diagnosis of pneumonia or urinary tract infection (UTI) three days or less before the drug initiation date. Comparator antibiotics were azithromycin in the pneumonia cohort and trimethoprim-sulfamethoxazole in the UTI cohort. Participants were matched 1:1 within each cohort on a propensity score, calculated from a multivariable logistic regression model that included 57 baseline covariates.

MAIN OUTCOMES MEASURE
Primary outcome was hospital admission or emergency department visit for suicidal ideation or self-harm within 60 days after treatment initiation. Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals.

RESULTS
The pneumonia cohort included 551 042 individuals, and the UTI cohort included 2 205 526 individuals. During the 60 day follow-up, 181 events were observed in the pneumonia cohort and 966 in the UTI cohort. The adjusted hazard ratios for fluoroquinolones were 1.01 (95% confidence interval 0.76 to 1.36) versus azithromycin in the pneumonia cohort and 1.03 (0.91 to 1.17) versus trimethoprim-sulfamethoxazole in the UTI cohort. Results were consistent across sensitivity analyses and subgroups of sex, age, or history of mental illnesses.

CONCLUSION
Initiation of fluoroquinolones was not associated with a substantially increased risk of admission to hospital or emergency department visits for suicidality compared with azithromycin or trimethoprim-sulfamethoxazole.

Introduction

Fluoroquinolones are a family of antibiotics that have been widely used as treatment for acute respiratory infections and uncomplicated urinary tract infections (UTIs).[1-3] Partly owing to their desirable pharmacokinetic properties, excellent oral availability, and broad spectrum of antimicrobial activity, fluoroquinolones were the third most commonly prescribed antibiotic class in the United States in 2011.[4] Despite their attractive profile as anti-infective agents, the toxic effects of fluoroquinolones on gastrointestinal, dermatological, cardiovascular, and nervous systems have been well established.[1 5 6] However, the risks of serious associated adverse effects on mental health remain uncertain.

Although a range of mental health side effects from fluoroquinolone use has been reported,[7] suicidal ideation is of concern. People attempting or completing suicide and suicidal ideation have been reported after initiation of fluoroquinolones.[8-11] A review of US Food and Drug Administration reports of suicidal behaviors associated with all FDA approved fluoroquinolones suggested these events could occur even in people with no previous psychiatric illness.[12] In 2016, after a review of the adverse event reports and case reports, the FDA revised the boxed warning for all oral and injectable fluoroquinolones because of the potential risks of serious side effects, including suicidal thoughts.[7]

Several neurobiological mechanisms have been proposed to explain the association between fluoroquinolones and central nervous system (CNS) events, which include suicidality.[13-15] Given the similarity of the structure of fluoroquinolones to γ-aminobutyric acid (GABA) agonists, it is believed that fluoroquinolones may bind to brain GABA receptors, leading to neurotoxicity.[6 13-15] It has also

WHAT IS ALREADY KNOWN ON THIS TOPIC

The US Food and Drug Administration's revised boxed warning on fluoroquinolones in 2016 suggested an increased risk of suicidal thoughts associated with use of fluoroquinolones

No population-wide cohort study has investigated the association

WHAT THIS STUDY ADDS

In this population based study the short term use of outpatient oral fluoroquinolones for pneumonia or urinary tract infections was not associated with an increased risk of admission to hospital or an emergency department for suicidality compared with azithromycin or combined trimethoprim and sulfamethoxazole

The absolute risk of hospital admissions for suicidality was low

been suggested that fluoroquinolones may stimulate the excitatory N-methyl-d-aspartate (NMDA) and adenosine receptors, which on sufficient penetration of the CNS could manifest in observable CNS symptoms.[13] [14] Finally, fluoroquinolone induced reduction in serotonin levels, oxidative stress and lowered antioxidant levels, and alterations of various microRNAs may also contribute to neuropsychiatric adverse effects.[13]

Given the limitations of adverse event case reports and the broad use of fluoroquinolones, we evaluated the risk of hospital admission and emergency department visits for suicidal behaviors in a large cohort of people and quantified the magnitude of any increase in risk. We compared the rates of suicidality between fluoroquinolones and clinically appropriate comparators in patients with pneumonia or UTI; two of the most common indications for treatment with fluoroquinolones.

Methods

Data source and study cohort

The study data were derived from health insurance claims between 1 January 2003 and 30 September 2015, obtained from a national commercial US health insurance claims database (IBM MarketScan). The database contains person level data on healthcare use and expenditures for people enrolled in private insurance plans through a participating employer, health plan, or government organization. IBM MarketScan includes the MarketScan Commercial Claims and Encounters database, as well as the MarketScan Medicare Supplemental database that includes Medicare eligible retirees with employer sponsored Medicare Supplement plans. In addition to personal information and enrollment status, the database provides longitudinal records of reimbursed medical services. Information on inpatient and outpatient encounters includes diagnoses and procedures coded using ICD-9 (international classification of diseases, ninth revision) and CPT (Current Procedural Terminology) codes, as well as corresponding dates of service. For pharmacy claims, the database provides details such as national drug code, date of dispensing, quantity dispensed, and day's supply for prescription drugs dispensed in the outpatient setting.

The study cohort included adults aged 18 years and older who initiated an oral fluoroquinolone or a comparator antibiotic between 1 January 2003 and 30 September 2015, and who had at least 180 days of continuous medical and prescription drug coverage enrollment before the drug initiation date (cohort entry date; fig 1). We defined initiation as the absence of dispensings for any fluoroquinolones or comparator antibiotics in the 180 days before the cohort entry date.

To control for confounding by indication and bias due to differential surveillance, we restricted the eligible study population to individuals with specific treatment indications and used an active comparator design. In particular, we restricted to those with a diagnosis of pneumonia or a UTI within three days
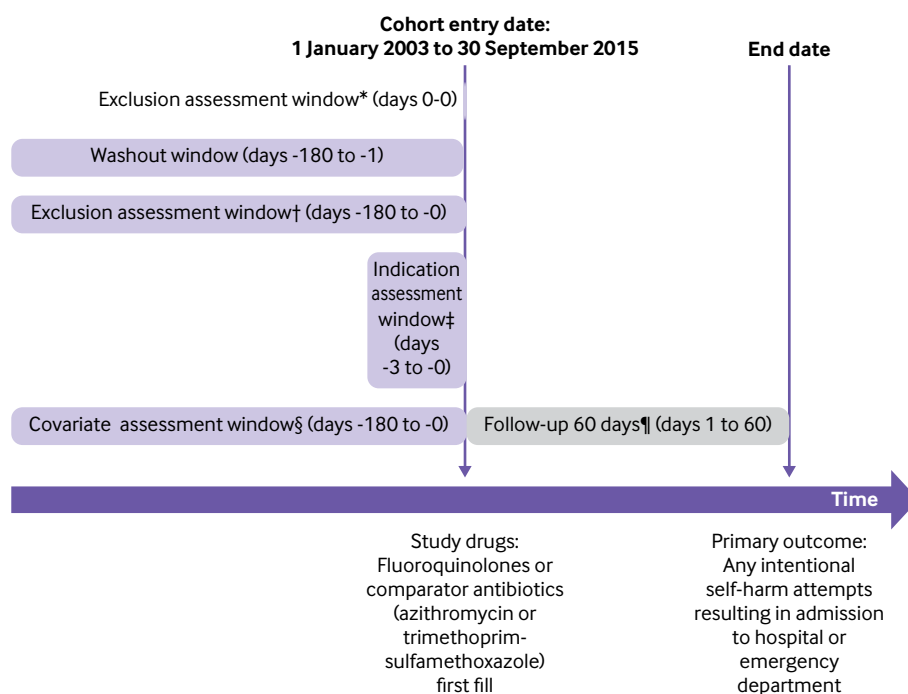

Fig 1 | Study design. *Age <18 years, antibiotics other than study drugs, nursing home or hospital stay. †History of intentional self-harm, any hospital admission >28 days, any diagnosis of HIV infection or cancer. ‡Diagnosis of pneumonia or urinary tract infection. §Demographic information, calendar year, other covariates (mental disorders, neurological disorders, other comorbidities, medication use, healthcare utilization). ¶Censoring criteria: occurrence of study outcome, death, nursing home or hospice admission, end of continuous health plan enrollment, end of study period (30 September 2015)

before and including the cohort entry date. We chose azithromycin as the comparator antibiotic for the pneumonia cohort and combined trimethoprim and sulfamethoxazole for the UTI cohort.[16] Supplementary table 1 provides definitions of pneumonia and UTI.

We excluded patients if they received antibiotics other than the study drugs (fluoroquinolones or a comparator) on the cohort entry date; had a diagnosis of attempted suicide, cancer, or HIV; had a prolonged hospital stay (length of stay >28 days) within the six months preceding the cohort entry date; or were in a hospital or nursing home on the cohort entry date. Supplementary table 2 presents definitions of exclusion criteria. For patients with multiple eligible cohort entries, we selected the first one.

Assessment of drug use
The fluoroquinolones of interest included ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, gatifloxacin, norfloxacin, lomefloxacin, and besifloxacin. We chose azithromycin and trimethoprim-sulfamethoxazole as the comparator drugs for the pneumonia and UTI cohorts, respectively, because they represented alternative treatment options for the infections of interest during the study period.[17 18] Use of fluoroquinolones and comparator drugs was identified using pharmacy dispensing data.

Outcome and follow-up
The study outcome, suicidality, was defined as any hospital admission or emergency department visit with ICD-9 codes V62.84 (suicidal ideation) or E950.x-E958.x (suicide and self-inflicted injury) at any position.[19] We also conducted a sensitivity analysis limiting the outcome definition to primary discharge diagnosis for hospital admissions and any emergency department visit (emergency department records do not differentiate between primary and other diagnoses).

Follow-up started on the day after the antibiotic was dispensed, and continued for a maximum of 60 days regardless of changes to treatment, until the occurrence of a study outcome, death, nursing home or hospice admission, end of continuous health plan enrolment, or end of the study period (30 September 2015), whichever came first (fig 1). Since the exact biological mechanism behind the association between fluoroquinolones and CNS symptoms is not established, but the usual course of fluoroquinolone treatment is short,[20] we varied the duration of follow-up in sensitivity analyses.

Covariates
We assessed patient characteristics from 180 days before cohort entry and through the cohort entry date (day of antibiotic initiation). In addition to personal information (age, sex, region) and calendar year, conditions that may be associated with suicidality and the choice of study antibiotic were identified through ICD-9 codes and CPT-4 codes for comorbidities, and through pharmacy dispensings for drug use. These covariates included psychiatric disorders, such as anxiety disorder, depression, psychotic disorders, delirium, and substance misuse, and other comorbidities, such as neurological disorders, Parkinson's disease, migraine, multiple sclerosis, diabetes mellitus, stroke, ischemic heart disease, skin disorders, renal dysfunction, and liver disease (see supplementary table 3 for full list). To ensure comparability between study groups, we measured indicators for healthcare utilization, including previous hospital admissions, office visits, and total number of unique drugs used. The combined comorbidity index and a validated, claims based frailty index were included as proxies for overall disease state and care intensity.[21 22] Supplementary table 3 presents definitions for covariates.

Statistical analysis
To account for baseline differences between the study drug groups, we matched patients initiating fluoroquinolones with those initiating the comparator antibiotic on their predicted probability of drug use (propensity score) in a 1:1 ratio, using a nearest neighbor algorithm and a caliper of 0.05 on the propensity score scale. Propensity scores were estimated separately within each cohort using logistic regression and all predefined covariates (listed in supplementary tables 4 and 5). Standardized mean differences were used to examine the balance of covariates within the matched cohorts; a standardized difference greater than 0.1 was considered to show imbalance between groups.[23] In each propensity score matched cohort, we estimated hazard ratios and corresponding 95% confidence intervals using Cox proportional hazards regression models.

To evaluate the robustness of the primary results we conducted several sensitivity analyses. First, we varied the follow-up period to 14 days, 30 days, and 90 days in sensitivity analyses. Additionally, we conducted a high dimensional propensity score analysis that included an additional 200 empirically identified proxies for confounders to further control for potential residual confounding,[24] an analysis that included people with cancer, HIV, and a history of suicidality while adjusting for these risk factors, and an analysis using a more restrictive outcome definition.

Finally, we conducted several subgroup analyses. Analysis was stratified by age (age 18-24, 25-44, 45-64, ≥65 years), since the susceptibility for bacterial infections and suicidality may vary by age.[25 26] The analysis was also stratified by sex (men and women) in light of potential sex differences in certain bacterial infections.[27] Finally, the rate of hospital admission for self-harm within 60 days was assessed among subgroups of patients with or without a history of mental illness at baseline. All statistical analyses were performed on Aetion, platform version 4.20,[28] with R, version 3.1.2.

Patient and public involvement
No patients were involved in setting the research question or study design nor in the interpretation

of results, owing to training restrictions and budget constraints.

Results

Study population

A total of 825 420 patients with pneumonia and 3 463 500 patients with UTI satisfied the inclusion criteria and were eligible for study inclusion (fig 2).

Before propensity score matching, fluoroquinolone initiators compared with azithromycin initiators in the pneumonia cohort were older (mean age 56.23 v 48.55 years), had a greater burden of comorbidities, and had a higher prevalence of characteristics suggestive of frailty (see supplementary table 4). Similarly, fluoroquinolone initiators compared with trimethoprim-sulfamethoxazole initiators in the UTI cohort were older (48.08 v 43.70 years), had a higher prevalence of characteristics suggestive of frailty (mean 0.13 (standard deviation 0.04) v 0.12 (0.03)), and were more likely to be men (15.4% v 8.1%) (see supplementary table 5).

After propensity score matching, the final study populations included 275 521 matched pairs in the pneumonia cohort and 1 102 613 matched pairs in the UTI cohort (fig 2). Both pneumonia and UTI cohorts were adequately balanced on all measured covariates across drug use and reference groups (table 1). Supplementary table 6 presents the median (interquartile range) duration of index prescription, as measured by days' supply recorded by the pharmacy,

and the distribution of individual fluoroquinolone agents. The most common fluoroquinolone used by the pneumonia cohort was levofloxacin (73.1% of patients using fluoroquinolones), whereas the most common fluoroquinolone used by the UTI cohort was ciprofloxacin (86.3% of patients using fluoroquinolones).

Admissions for suicidality

Supplementary table 7 presents the median duration of follow-up and reasons for censoring. Most of the patients (92.3% in the pneumonia cohort and 93.0% in the UTI cohort) completed the 60 day follow-up. Overall, 91 (0.03%) fluoroquinolone initiators and 90 (0.03%) azithromycin initiators in the pneumonia cohort and 491 (0.04%) fluoroquinolone initiators and 475 (0.04%) trimethoprim-sulfamethoxazole initiators in the UTI cohort were admitted to hospital or an emergency department for suicidality during follow-up (see supplementary figure for cumulative incidence curves). The adjusted hazard ratio for use of fluoroquinolones and hospital admission for suicidality was 1.01 (95% confidence interval 0.76 to 1.36) in the pneumonia cohort and 1.03 (0.91 to 1.17) in the UTI cohort (table 2).

The results were similar in the overall cohorts before propensity score matching. The crude hazard ratio for suicidality was 1.06 (95% confidence interval 0.84 to 1.35) in the pneumonia cohort and 0.98 (0.88 to 1.09) in the UTI cohort (see supplementary table 8).
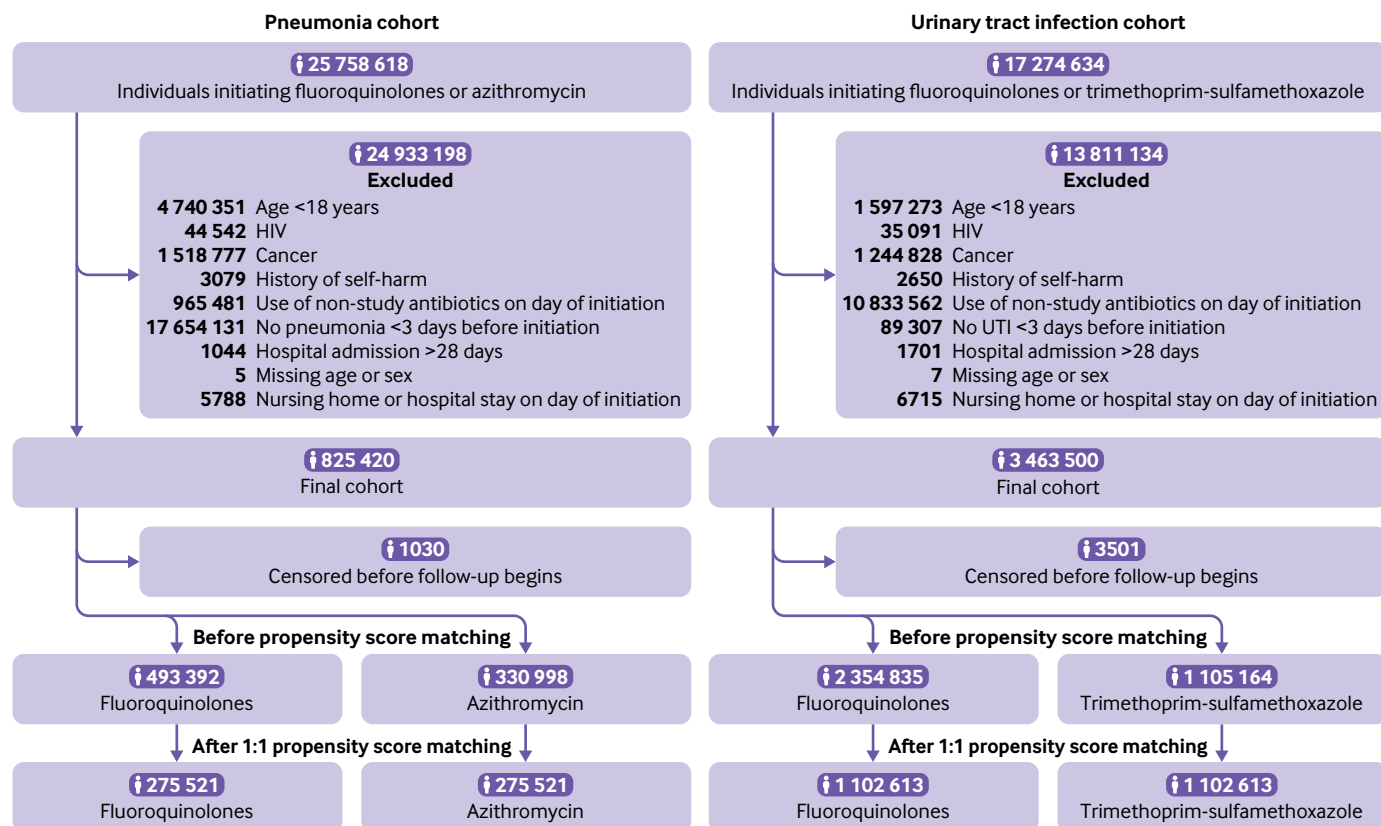

Pneumonia cohort

| 👤 25 758 618 |
| Individuals initiating fluoroquinolones or azithromycin |

| 👤 24 933 198 |
| **Excluded** |
| 4 740 351 Age <18 years |
| 44 542 HIV |
| 1 518 777 Cancer |
| 3079 History of self-harm |
| 965 481 Use of non-study antibiotics on day of initiation |
| 17 654 131 No pneumonia <3 days before initiation |
| 1044 Hospital admission >28 days |
| 5 Missing age or sex |
| 5788 Nursing home or hospital stay on day of initiation |

| 👤 825 420 |
| Final cohort |

| 👤 1030 |
| Censored before follow-up begins |

Before propensity score matching

| 👤 493 392 | 👤 330 998 |
| Fluoroquinolones | Azithromycin |

After 1:1 propensity score matching

| 👤 275 521 | 👤 275 521 |
| Fluoroquinolones | Azithromycin |

Urinary tract infection cohort

| 👤 17 274 634 |
| Individuals initiating fluoroquinolones or trimethoprim-sulfamethoxazole |

| 👤 13 811 134 |
| **Excluded** |
| 1 597 273 Age <18 years |
| 35 091 HIV |
| 1 244 828 Cancer |
| 2650 History of self-harm |
| 10 833 562 Use of non-study antibiotics on day of initiation |
| 89 307 No UTI <3 days before initiation |
| 1701 Hospital admission >28 days |
| 7 Missing age or sex |
| 6715 Nursing home or hospital stay on day of initiation |

| 👤 3 463 500 |
| Final cohort |

| 👤 3501 |
| Censored before follow-up begins |

Before propensity score matching

| 👤 2 354 835 | 👤 1 105 164 |
| Fluoroquinolones | Trimethoprim-sulfamethoxazole |

After 1:1 propensity score matching

| 👤 1 102 613 | 👤 1 102 613 |
| Fluoroquinolones | Trimethoprim-sulfamethoxazole |

Fig 2 | Formation of study cohort

Table 1 | Selected baseline characteristics in propensity score matched pneumonia cohort and urinary tract infection cohort. Values are numbers (percentages) unless stated otherwise

Characteristics	Pneumonia cohort			Urinary tract infection cohort		
	Fluoroquinolones* (n=275 521)	Azithromycin (n=275 521)	Standardized difference	Fluoroquinolones* (n=1 102 613)	TMP-SMX (n=1 102 613)	Standardized difference
Personal characteristics						
Mean (SD) age (years)	51.44 (16.93)	51.69 (17.00)	0.01	43.66 (17.41)	43.76 (17.49)	0.01
Age categories (years):						
18-24	15 748 (5.7)	14 228 (5.2)	−0.02	195 010 (17.7)	189 810 (17.2)	−0.01
25-44	83 467 (30.3)	82 206 (29.8)	−0.01	395 123 (35.8)	396 915 (36.0)	0.00
45-64	120 455 (43.7)	123 594 (44.9)	0.02	388 695 (35.3)	392 357 (35.6)	0.01
≥65	55 851 (20.3)	55 493 (20.1)	0.00	123 785 (11.2)	123 531 (11.2)	0.00
Men	133 903 (48.6)	134 269 (48.7)	0.00	92 621 (8.4)	89 254 (8.1)	−0.01
Psychiatric comorbidities						
Anxiety disorder	12 103 (4.4)	11 872 (4.3)	0.00	57 931 (5.3)	58 236 (5.3)	0.00
Depression	19 531 (7.1)	19 034 (6.9)	−0.01	88 256 (8.0)	88 806 (8.1)	0.00
Sleep disorder	9703 (3.5)	9676 (3.5)	0.00	30 924 (2.8)	30 920 (2.8)	0.00
Psychotic disorder	1806 (0.7)	1682 (0.6)	−0.01	5314 (0.5)	5161 (0.5)	0.00
Mania	2657 (1.0)	2564 (0.9)	−0.01	11 079 (1.0)	11 072 (1.0)	0.00
Delirium	2096 (0.8)	1736 (0.6)	−0.02	4554 (0.4)	4344 (0.4)	0.00
Dementia	4492 (1.6)	4130 (1.5)	−0.01	10 892 (1.0)	10 583 (1.0)	0.00
Substance misuse	16 530 (6.0)	16 186 (5.9)	0.00	30 116 (2.7)	30 050 (2.7)	0.00
Other mental disorder	3028 (1.1)	2977 (1.1)	0.00	14 027 (1.3)	14 066 (1.3)	0.00
Neurological comorbidities						
Seizure or epilepsy	2697 (1.0)	2594 (0.9)	−0.01	8423 (0.8)	8383 (0.8)	0.00
Neuropathy or neuropathic pain	11 348 (4.1)	11 104 (4.0)	−0.01	34 793 (3.2)	34 891 (3.2)	0.00
Migraine	5063 (1.8)	4964 (1.8)	0.00	30 016 (2.7)	30 486 (2.8)	0.01
Parkinson's disease	906 (0.3)	867 (0.3)	0.00	2348 (0.2)	2267 (0.2)	0.00
Other comorbidities						
Congestive heart failure	12 552 (4.6)	11 453 (4.2)	−0.02	11 554 (1.0)	10 921 (1.0)	0.00
Ischemic heart disease	21 533 (7.8)	20 463 (7.4)	−0.02	32 282 (2.9)	31 478 (2.9)	0.00
Any stroke	6332 (2.3)	5916 (2.1)	−0.01	13 534 (1.2)	13 104 (1.2)	0.00
Atrial fibrillation	10 624 (3.9)	10 182 (3.7)	−0.01	14 788 (1.3)	14 423 (1.3)	0.00
Autoimmune disorder	10 973 (4.0)	10 927 (4.0)	0.00	33 987 (3.1)	34 204 (3.1)	0.00
Diabetes	33 149 (12.0)	32 909 (11.9)	0.00	83 932 (7.6)	84 031 (7.6)	0.00
Skin disorder	37 778 (13.7)	37 218 (13.5)	−0.01	147 370 (13.4)	148 296 (13.4)	0.00
Renal dysfunction	12 016 (4.4)	11 079 (4.0)	−0.02	22 927 (2.1)	21 465 (1.9)	−0.01
Liver disease	5631 (2.0)	5343 (1.9)	−0.01	14 419 (1.3)	14 253 (1.3)	0.00
Asthma or COPD	81 428 (29.6)	80 907 (29.4)	0.00	139 285 (12.6)	140 578 (12.7)	0.00
Mean (SD) combined comorbidity index	0.38 (1.14)	0.34 (1.13)	−0.04	0.10 (0.73)	0.09 (0.73)	−0.01
Mean (SD) frailty index	0.14 (0.04)	0.14 (0.04)	0.00	0.12 (0.03)	0.12 (0.03)	0.00
Drug use						
Opioid	80 621 (29.3)	80 738 (29.3)	0.00	243 198 (22.1)	244 455 (22.2)	0.00
Lithium	648 (0.2)	641 (0.2)	0.00	2649 (0.2)	2666 (0.2)	0.00
Antipsychotic	5603 (2.0)	5432 (2.0)	0.00	18 838 (1.7)	18 792 (1.7)	0.00
Antidepressant	55 432 (20.1)	55 238 (20.0)	0.00	228 466 (20.7)	230 432 (20.9)	0.00
NSAID	39 201 (14.2)	39 355 (14.3)	0.00	163 022 (14.8)	164 539 (14.9)	0.00
Benzodiazepine	30 314 (11.0)	29 932 (10.9)	0.00	116 039 (10.5)	116 818 (10.6)	0.00
Migraine product	4401 (1.6)	4466 (1.6)	0.00	28 652 (2.6)	29 254 (2.7)	0.01
Antiparkinsonian agent	3141 (1.1)	3093 (1.1)	0.00	8628 (0.8)	8748 (0.8)	0.00
Dementia drug	3526 (1.3)	3396 (1.2)	−0.01	8418 (0.8)	8332 (0.8)	0.00
Muscle relaxant	19 897 (7.2)	19 856 (7.2)	0.00	84 960 (7.7)	85 729 (7.8)	0.00
Anticonvulsant	19 354 (7.0)	19 004 (6.9)	0.00	66 726 (6.1)	66 997 (6.1)	0.00
CNS stimulant	2396 (0.9)	2390 (0.9)	0.00	13 105 (1.2)	13 272 (1.2)	0.00
Other anxiolytic or hypnotic	19 113 (6.9)	18 894 (6.9)	0.00	73 809 (6.7)	74 585 (6.8)	0.00
Health services utilization						
Mean (SD) No of office visits	4.11 (4.37)	4.05 (4.18)	−0.01	3.83 (3.78)	3.83 (3.80)	0.00
Mean (SD) No of unique psychotropics	0.98 (1.49)	0.97 (1.48)	−0.01	0.88 (1.42)	0.88 (1.43)	0.00
Mean (SD) No of unique drugs	6.22 (4.34)	6.18 (4.37)	−0.01	5.09 (3.73)	5.11 (3.76)	0.01
Mean (SD) No of hospital admissions	0.17 (0.44)	0.16 (0.44)	−0.02	0.07 (0.28)	0.06 (0.29)	−0.04
Mean (SD) No of emergency department visits	0.56 (1.08)	0.54 (0.98)	−0.02	0.33 (0.78)	0.32 (0.83)	−0.01

TMP-SMX=trimethoprim and sulfamethoxazole; SD=standard deviation; COPD=chronic obstructive pulmonary disease; NSAID=non-steroidal anti-inflammatory drug; CNS=central nervous system.
*Ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, gatifloxacin, norfloxacin, lomefloxacin, or besifloxacin.

Sensitivity and subgroup analyses

The high dimensional propensity score matched analysis (table 2) produced results consistent with those of the main analyses in both the pneumonia cohort (hazard ratio 1.02, 95% confidence interval 0.76 to 1.38) and the UTI cohort (1.05, 0.92 to 1.19). When the follow-up period was varied to 14 days, 30 days, or 90 days the results became qualitatively consistent with

Table 2 | Association between fluoroquinolone initiation and hospital admission or emergency department visit for suicidality

| | Pneumonia cohort | | | | Urinary tract infection cohort | | | |
| | Propensity score matching | | High dimensional propensity score matching | | Propensity score matching | | High dimensional propensity score matching | |
Analyses	Fluoroquinolones* (n=275 521)	Azithromycin (n=275 521)	Fluoroquinolones* (n=269 625)	Azithromycin (n=269 625)	Fluoroquinolones* (n=1 102 613)	TMP-SMX (n=1 102 613)	Fluoroquinolones* (n=1 098 770)	TMP-SMX (n=1 098 770)
No (%) of admissions	91 (0.03)	90 (0.03)	86 (0.03)	84 (0.03)	491 (0.04)	475 (0.04)	492 (0.04)	470 (0.04)
Risk/1000 patients	0.33	0.33	0.32	0.31	0.45	0.43	0.45	0.43
Hazard ratio (95% CI)	1.01 (0.76 to 1.36)	Reference	1.02 (0.76 to 1.38)	1 (Reference)	1.03 (0.91 to 1.17)	Reference	1.05 (0.92 to 1.19)	1 (Reference)

TMP-SMX=trimethoprim and sulfamethoxazole; CI=confidence interval.
*Ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, gatifloxacin, norfloxacin, lomefloxacin, or besifloxacin.

the primary findings (see supplementary tables 9-11), as did the analysis that included people with cancer, HIV, or a history of suicidality (see supplementary table 12), and the sensitivity analysis using a more restrictive outcome definition (see supplementary table 13).

Results were similar in subgroup analyses (fig 3). In both cohorts, we found no evidence of effect modification by age, sex, or history of mental illness, although some subgroups were small (see supplementary table 14 for number of patients and events in each subgroup), which led to limited statistical precision and wide confidence intervals.

Discussion
Principal findings
In this nationwide cohort study of more than a million US patients treated with fluoroquinolones for either pneumonia or UTI, we observed no increased risk of suicidality associated with short term use of fluoroquinolone compared with azithromycin or trimethoprim-sulfamethoxazole, as measured by hospital admissions and emergency department visits for suicidal ideation or self-harm. The lack of association persisted across several sensitivity and subgroups analyses. Moreover, the absolute risks of admission to hospital admission or an emergency

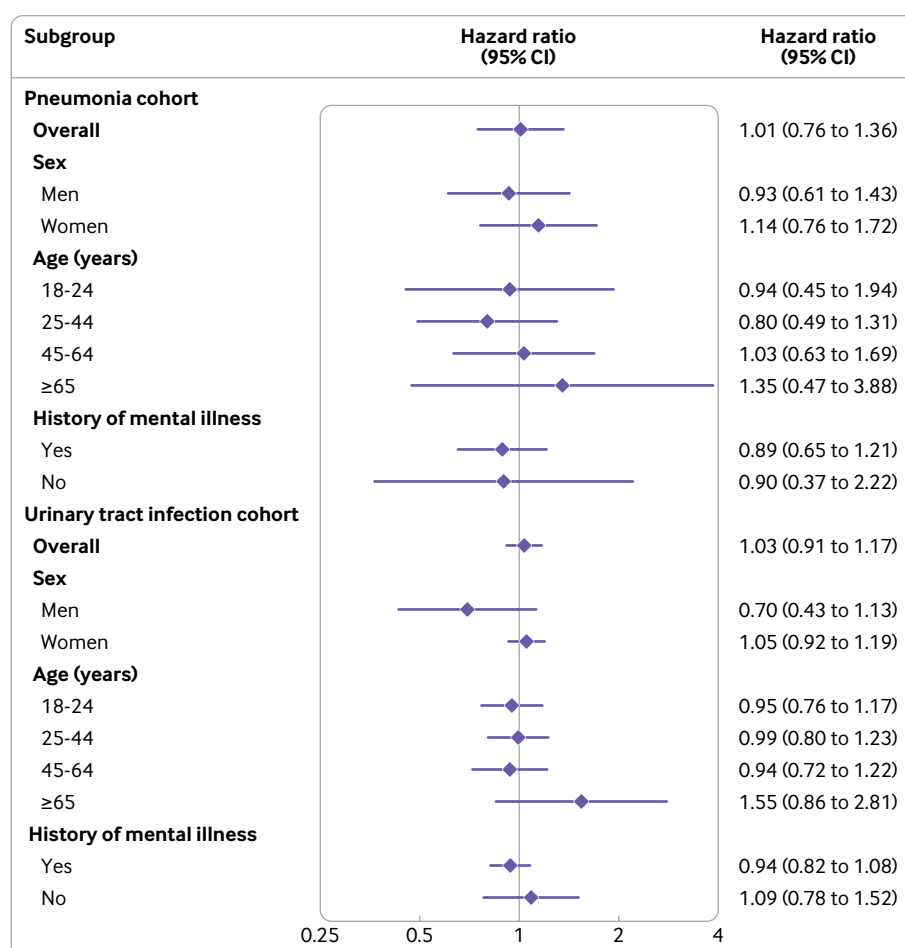| Subgroup	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Pneumonia cohort		
Overall		1.01 (0.76 to 1.36)
Sex		
Men		0.93 (0.61 to 1.43)
Women		1.14 (0.76 to 1.72)
Age (years)		
18-24		0.94 (0.45 to 1.94)
25-44		0.80 (0.49 to 1.31)
45-64		1.03 (0.63 to 1.69)
≥65		1.35 (0.47 to 3.88)
History of mental illness		
Yes		0.89 (0.65 to 1.21)
No		0.90 (0.37 to 2.22)
Urinary tract infection cohort		
Overall		1.03 (0.91 to 1.17)
Sex		
Men		0.70 (0.43 to 1.13)
Women		1.05 (0.92 to 1.19)
Age (years)		
18-24		0.95 (0.76 to 1.17)
25-44		0.99 (0.80 to 1.23)
45-64		0.94 (0.72 to 1.22)
≥65		1.55 (0.86 to 2.81)
History of mental illness		
Yes		0.94 (0.82 to 1.08)
No		1.09 (0.78 to 1.52)

Fig 3 | Subgroup analyses of association between fluoroquinolone use and suicidality

department for suicidality were low in both cohorts (<0.1%) and consistent with the numbers reported in the general population.[29]

Comparison with other studies

Two previous studies have provided conflicting results.[13 30] In a nested case-control study that included 348 people with attempted or completed suicide or suicidal ideation and 808 controls, Jick et al found that the use of quinolone antibiotics was not associated with an increased risk of suicidal behaviors.[30] In contrast with this finding, the disproportionality analyses by Samyed et al using a global adverse drug reaction database, including 608 quinolone related suicidal behaviors, reported an increase in reporting of suicidal behaviors associated with quinolone use.[13]

Despite differences in data sources and design and analysis methods, our findings are consistent with those of Jick et al's case-control study,[30] which compared fluoroquinolone users with antibiotic non-users. The findings of our study, which used an active comparator design to tackle differences in individuals who did and did not use an antibiotic, bolster the findings of Jick et al's study.[16] Although Samyed et al's analyses of suicidality associated with quinolone use also compared quinolone users with those receiving other antibiotics,[13] the findings of this study should be interpreted in the context of the under-reporting and selective reporting of spontaneous adverse drug events.[15] For example, factors such as experience of the reporter, local patterns of utilization, specificity of the adverse reaction, and knowledge about safety profile of the drug can affect reporting patterns of adverse drug reactions to pharmacovigilance systems, which can limit the interpretation of disproportionality studies.[15 31]

Strengths and limitations of this study

We used several approaches to ensure the validity of findings and to minimize bias that can affect non-randomized studies of treatments. Restricting the study cohorts to people with pneumonia or UTI, identifying comparable treatment alternatives within each indication, and implementing propensity score based adjustment for covariates increased our ability to control for confounding. An incident user, active comparator design enabled us to align time zero (start of follow-up) for the fluoroquinolone and comparator antibiotic groups and to avoid time related biases or selection bias due to depletion of individuals susceptible to the outcome.[32-34] A large sample size allowed us to evaluate a rare outcome and to exclude a substantial increase in risk.

Our study does, however, have several limitations. First, our findings should be interpreted in the context of the limitations inherent to the nature of claims data, as such data are generated for administrative purposes and are generally limited to information relevant for billing. Administrative claims data lack information on certain patient characteristics that could affect the risk of suicidality, such as socioeconomic status and lifestyle factors, if they are different between the drug groups. To ensure robust control of confounding, we implemented multiple approaches, such as a clinically exchangeable comparator and adjustment for multiple variables measured in claims, many of which serve as proxies for unmeasured characteristics. Nevertheless, residual confounding cannot be completely excluded.

Second, as our outcome definition was based on hospital admissions and emergency department visits with billed ICD-9 codes, the observed absolute risks could underestimate the true incidence of suicidality in antibiotic users as our outcome definition only captured those who were admitted to hospital or obtained emergency care. Electronic healthcare records were not available to confirm outcomes, and outcomes among individuals with suicidal thoughts who were not admitted to hospital or did not seek emergency care, such as those who called their doctors, social workers, or hotlines, would have been missed in our study. Inasmuch as the degree of outcome misclassification is similar between the groups compared, relative risks remain unbiased.[35] However, we cannot rule out that fluoroquinolone use might be associated with suicidal thoughts that do not lead to hospital admission. Future work, preferably using data that contain information on mental health services, including those not billed to medical insurance, may shed more light on this question. In addition to not capturing less extreme cases, our outcome definition would have also missed people who completed suicide and therefore did not attend a hospital. Outpatient deaths are not recorded in administrative claims data. Nevertheless, the percentages of individuals who died (in a hospital) or had their insurance terminated (which would happen after death) were almost identical between the antibiotic groups.

The results of our study should also be interpreted in the context of study inclusion criteria and study design choices. Our study included commercially insured individuals treated for pneumonia or UTI in an outpatient setting who are typically prescribed a treatment regimen that lasts less than two weeks; thus, our results may not be generalizable to patients who require long term use of fluoroquinolones, or require systemic fluoroquinolones. Although we did not find evidence of effect measure modification in subgroup analyses, it is possible that analysis was underpowered in these subgroups. Our results need to be confirmed in populations that may be underrepresented in our study cohort, such as older people who are eligible for Medicare in the US. We compared fluoroquinolones to therapeutically comparable antibiotics—namely, azithromycin and trimethoprim-sulfamethoxazole. If comparators are associated with suicidality, then our findings do not necessarily reflect an absence of risk associated with fluoroquinolones. To our knowledge, neither azithromycin nor trimethoprim-sulfamethoxazole are known to cause suicidal thoughts.

The study period was also limited to years before 2016 to avoid bias due to differential surveillance

after the FDA labeling change in 2015. In the US, where transition to ICD-10 codes occurred in October 2015, only ICD-9 codes were in place during the study period. It is possible that suicidal coding changed with the introduction of the ICD-10 codes, and the rates we observed in our study are not generalizable to more recent years.

Next, although we had sufficient statistical power to exclude a substantial increase in risk associated with fluoroquinolone use in the overall study population, we cannot exclude a small increase in risk, particularly in individuals treated for pneumonia. Some of our subgroup analyses were also limited by the low number of events; thus, our study might have been underpowered to detect effect heterogeneity across subgroups. Finally, since individual fluoroquinolones differ in their pharmacokinetic properties, including brain tissue penetration, it is possible that some agents may be more likely to cause CNS adverse events, including suicidality. Most patients in our cohort were taking ciprofloxacin and levofloxacin, both of which are known to have poor to limited CNS penetration.[36] Further work is needed to evaluate fluoroquinolones known to achieve good CNS penetration.

Conclusion

No substantially increased risk of hospital admission or emergency department visit for suicidality was observed among people treated for pneumonia or UTI with a fluoroquinolone, compared with those receiving azithromycin or combined trimethoprim and sulfamethoxazole. We cannot, however, exclude a small increase in risk, or an effect on suicidal thoughts that do not lead to hospital admission or emergency department visit.

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Supplementary information: additional tables 1-14 and figure