## ORIGINAL ARTICLE

# Systemic quinolones and risk of acute liver failure I: Analysis of data from the US FDA adverse event reporting system

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## Abstract

**Background and Aim:** Quinolones are a potent and globally popular group of antibiotics that are used to treat a wide range of infections. Some case reports have raised concern about their possible association with acute hepatic failure (AHF). Data from the US FDA Adverse Event Reporting System were evaluated for signals of AHF in association with systemically administered quinolone antibiotics.

**Methods:** AHF reports between 1969 and 2019q2, with a focus on 2010–2019q2, were analyzed. Specifically, AHF reports linked to non-quinolone antibiotics of known hepatotoxicity were compared to reports with non-quinolone, non-hepatotoxic (reference) antibiotics; and AHF reports with quinolones were also compared to reports with the same group of reference antibiotics. Two disproportionality signal detection techniques (proportional reporting ratio, PRR, and empirical Bayes geometric mean, EBGM) were used to assess the AHF signal for both analyses.

**Results:** Only ciprofloxacin showed a marginal and significant AHF signal (PRR: 1.85 [1.21, 2.81]; EBGM: 1.54 [1.06, 1.81]); moxifloxacin, levofloxacin, and ofloxacin showed weak and nonsignificant signals.

**Conclusion:** Further pharmacovigilance studies are required to confirm the association between ciprofloxacin and AHF seen in the present analysis.

## Introduction

Quinolones are a globally popular class of antibiotics that have been marketed since the 1960s for treatment of a wide range of infection due to their strength, broad coverage, and reasonable safety.[1–5] Nevertheless, this popularity was accompanied by the emergence of resistance and some adverse reactions, which led to safety-based labeling revision or market withdrawal.[2–6]

Acute hepatic failure (AHF) is a serious disease involving rapid, progressive, and possibly severe loss of hepatic cells without evidence of chronic liver impairment. Although this disease may sometimes be asymptomatic and reversible, it may reflect

severe deterioration of hepatic function leading to death if liver transplantation is not undertaken in a timely manner.[6–8] This disease can be caused by many agents, including drugs, toxic substances, nutritional supplements, and bacteria or viruses.[7–13]

Drug-induced liver injury (DILI) has been repeatedly reported as the most common cause of AHF,[7–9,12,14,15] and medication withdrawal[7,11,15] in the United States and Europe. An earlier report by the US National Institute of Diabetes and Digestive and Kidney Diseases reported that AHF comprises 3–9% of all reported adverse drug events (ADEs).[14] DILI may be idiosyncratic (unpredictable, not dose-dependent) or non-idiosyncratic (predictable, dose-dependent), with recovery primarily dependent on timely removal of the causative agent and the capacity of liver to regenerate.[8,9,13] In the absence of a gold standard, diagnosing DILI depends primarily on medical history, exclusion of other relevant causes, and the physician's judgment.

Of an estimated 2000 AHF cases in the US annually, DILI accounted for 60% of these cases.[8] The incidence of DILI per 100 000 inhabitants reportedly ranged from as low as 2.3 (Sweden) and 2.4 (England), to 13.1 (France) and 19.1 (Iceland), up to 24 in other parts in the world.[14,16,17] Concerns over quinolone-associated AHF led the FDA and other regulators to issue safety updates, and order market withdrawal such as with alatrofloxacin and trovafloxacin.[7,8,18]

A recent study reported moxifloxacin and levofloxacin-associated AHF at 6.6 and 2.1 reports per 10 million prescriptions, respectively.[19] In the absence of evidence from clinical trials and pharmacovigilance studies, and despite the limitations of spontaneous reporting systems (SRS) reports such as US FDA Adverse Events Reporting System (FAERS),[1,20–30] regulators may err on the side of caution and use these reports to guide their safety-based responses, without strong evidence of causality.[3,31,32]

This review represents the first of three studies that comprehensively examine the association of systemically administered quinolones with AHF risk. Subsequent studies will examine results from clinical trials, and electronic health records of a large patient population from the United States.

## Methods

***Data source.*** FAERS is a large-scale, publicly available surveillance system that captures unsolicited reports on ADE associated with medications and supplements. Since its launch in 1969, FAERS has collected such information from multiple sources in the United States and other countries, and currently represents one of the most commonly used sources for early identification and characterization of ADE.[24–26,28,33–36]

Whereas ADE reporting is mandatory by pharmaceutical companies, it is done on voluntary basis by healthcare providers and consumers.[24–26,28,30,33,34,36] SRS-generated signals usually prompt detailed validation studies, which would provide further evidence on product safety under real-world conditions of use.[24–26,28,35,37] Timely signal generation is particularly valuable with rare or long-term ADE, or with newly introduced drugs.[6]

FAERS comprises seven databases that collate detailed and anonymous information on patient demographics, drug/supplement, ADE, patient outcomes, report sources, drug therapy start and end dates, and indications for use/diagnosis.[34,38] FAERS generates data in a raw format on quarterly basis, which

**Table 1** Antibiotics investigated in relation to reports of drug-induced acute hepatic failure in the FDA event reporting database (FAERS, 2010–2019q2)

| Antibiotic groups | Identified antibiotics |
| --- | --- |
| Hepatotoxic antibiotics (Most DILI) | Sulfathiazole, isoniazid, clarithromycin, erythromycin, ethambutol, minocycline, nitrofurantoin, rifampin, sulfasalazine, and telithromycin |
| Reference antibiotics (No DILI) | Amikacin, penicillin, polymyxin, neomycin, paromomycin, streptomycin, kanamycin, bacitracin, and chloramphenicol |
| Quinolone antibiotics | Ciprofloxacin, moxifloxacin, levofloxacin, and ofloxacin |

DILI, drug-induced liver injury.

can be downloaded from their website.[39] With drugs listed using both generic and brand names,[38,40] each ADE report points out to a specific drug as a primary suspect (PS), and to others as secondary (SS), concomitant (C), or interacting (I) suspects, whenever applicable.[34,38]

Based on a recent major review[31] that classified drugs according to their hepatotoxicity signals, we used non-quinolone antibiotics with confirmed positive DILI signal (termed "Most DILI") as positive controls, and non-quinolone antibiotics with no such signal ("No DILI") as reference controls (Table 1).

We then extracted all ADE reports for the identified antibiotics between 1969 and the second quarter of 2019 (2019q2). In our study, we focused primarily on reports for PS drugs to maximize the strength of any potential DILI signals and minimize any potential source of bias. We then repeated the same analyses considering drugs as PS/SS combined to make maximum use of all relevant data. We then linked these reports to the different FAERS databases to obtain all relevant information.

ADEs are coded in FAERS using the MedDRA (Medical Dictionary for Regulatory Activities) Preferred Terms (PTs).[41] We selected our PT of interest as "acute hepatic failure" (AHF) and not "hepatic failure" (HF) for identification of reports relevant to our outcome of interest. AHF is a scientific term that is used specifically and predominantly by health professionals when reporting adverse events in FAERS, which increases the reliability of such reports for examining possible AHF–drug associations. Reports using HF are only examined as a sensitivity analysis encompassing the interval 1969–2019q2.

***Data analysis.*** We conducted a rigorous data cleaning, including but not limited to deleting duplicate reports, correction of misspelled drug names, removal of reports with no suspected drug, and mapping and linking its different components. Using our cleaned data, we started the present analysis by conducting a detailed validation of the antibiotics in the different DILI groups identified earlier by Chen et al.[31] The first analysis compared AHF reports that are linked to the "Most DILI" antibiotics to those linked to the "No DILI" antibiotics. The second analysis compared quinolone antibiotics with the same group of reference antibiotics; "No DILI."

In analyzing these reports, we used two of the most frequently used data mining techniques: the proportional reporting

ratio (PRR) and multi-item gamma Poisson shrinker (MGPS),[42] due to their higher sensitivity (PRR) and specificity (MGPS) for ADE signal detection.[42–44] Each technique involves comparing the proportion of ADE reports described in conjunction with each drug in the group of interest to that reported in the comparison/reference group.[45,46] A positive and significant observed disproportionality measure may signify higher reporting of the ADE in question than would be expected. This elevated reporting rate may be considered a drug safety signal, which merits further investigation.[45,46]

A higher number of reports or a higher value of the disproportionality signal do not automatically flag a real signal. An observed PRR with a value of 2 or more, a 95% confidence interval above 1, and a minimum of three reports is considered to be significant evidence of disproportionate reporting.[42,46] An observed MGPS signal with a lower boundary of the EBGM[1] higher than 2 with a minimum of 1 report[42] is considered to be significant evidence of disproportionate reporting.

For each one of our major analyses (hepatotoxic *vs* reference antibiotics, and quinolones *vs* reference antibiotics), we first examined reports where the antibiotic is reported as a PS only, and then as PS/SS combined. Only results based on the PS are shown in this manuscript; with other results provided in Supplementary Material.

Since both the level of reporting of ADE and quality of reports were of lesser rigor prior to 2010, we reported primarily on results for the time interval 2010–2019q2. However, to make use of all relevant data, we conducted sensitivity analyses using the same strategy for three additional time intervals: 2004–2009, 2004–2019q2, and 1969–2019q2. Only results from the 2010–2019q2 interval were reported in this manuscript, with all other results provided in Supplementary Material.

## Results

The publicly available FAERS dashboard contains a total of 18 650 676 ADE reports between 1969 and 2019q2, with almost 76% (14 245 824) reported between 2010 and 2019q2. In 2010, there were nearly 700 000 ADE reported in FAERS, which increased gradually to more than 2 million in 2018, besides an additional 1.8 million reports during the first two quarters of 2019.

Our cleaned version of the FAERS data showed a total of 13 514 601 reports including 6980 AHF reports (0.05%) between 1969 and 2019q2, with 5955 of them (0.04%) reported between 2010 and 2019q2 (Fig. 1). The annual number of AHF reports increased from around 300 in 2010 to a high of 700–900 reports annually afterwards (Supplementary Material 1).

As MedDRA undergoes periodic revisions, this usually involves introduction of new PTs, removing earlier terms, or changing the hierarchy of existing terms. According to the current version, the term "AHF" was reported in FAERS for the first time in 2006. Accordingly, there were only 1025 confirmed AHF reports, representing 0.07% of all reports between 2004 and 2009. Of all AHF reports between 2004 and 2019q2, quinolones accounted for 206 reports (2.95%) compared with hepatotoxic

and reference antibiotics, with 749 (10.73%) and 29 (0.12%) reports, respectively. Table 2 provides a detailed listing of AHF reports, for all time-intervals, that are linked to drugs as primary (PS), secondary (SS), concomitant (C), or interacting (I) suspects.

**Description of AHF case reports.** Our analysis showed that 35% of all AHF reports were submitted from the United States, followed by the UK (15%), Japan (3%), and Canada (4%); 39.4% were reported from other countries and 2.4% had no reported country. Eighty six percent (86%) of all AHF reports were submitted by health professionals, compared with only 11% by consumers and lawyers. AHF reports between 2010 and 2019q2 were predominantly reported in women (48%) compared with men (36%), while sex was unreported in 17% of the reports. AHF Reports in the first two decades of life ranged between 5 and 7%, which increased to 8–11% per decade between third and eighth decades, with more than 22% of reports missing consumer age. Table 3 shows a detailed listing of the distribution of AHF report characteristics between 2010 and 2019q2.

### Results (2010–2019q2)
*Hepatotoxic versus reference antibiotics.* Several AHF reports were reported in association with eight hepatotoxic (non-quinolone) antibiotics between 2010 and 2019q2. Despite having the second highest number of reports (76), isoniazid demonstrated the most powerful signal (PRR: 7.17 [5.52, 9.32]; EBGM: 5.49 [3.86, 5.61]), compared to rifampin with the second most powerful signal (PRR: 4.65 [3.66, 5.91]; EBGM: 3.22 [2.39, 3.27]), while having the highest number of reports (109).

Both ethambutol and nitrofurantoin produced weak and nonsignificant signals, whereas the remaining four antibiotics produced no signal at all, despite having some reports linking them to risk of AHF. Table 4 shows all results for the examined antibiotics during 2010–2019q2. Cumulative analysis of AHF reports between 2004 and 2019q2 showed the exact same pattern compared with 2010–2019q2.

*Quinolones versus reference antibiotics (non-quinolone, non-hepatotoxic).* Only four quinolones were linked to at least one AHF report. Ciprofloxacin showed the highest number of reports (34) between 2010 and 2019q2, followed by levofloxacin (23), moxifloxacin (14), and ofloxacin (2). Only ciprofloxacin showed a marginally positive and significant AHF signal (PRR: 1.85 [1.21–2.81]; EBGM: 1.54 [1.06–1.81]), whereas moxifloxacin, levofloxacin, and ofloxacin showed weak and/or nonsignificant signals.

Ofloxacin produced the highest, though nonsignificant, signal (PRR: 2.20 [0.54–8.91]; EBGM: 2.17 [0.59–2.40]), with only two reports during 2010–2019q2. Cumulative analysis of AHF reports between 2004 and 2019q2 showed a similar pattern as 2010–2019q2, with a less powerful signal for ofloxacin due to the absence of any linked reports between 2004 and 2009.

As reported earlier,[31] and validated in our study, reference antibiotics were not associated with any AHF reports, as PS only, when compared with hepatotoxic or quinolone antibiotics. Table 5 shows the results for AHF reports with quinolones compared to reference antibiotics between 2010 and 1019 (Q2).

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1. EBGM: empirical Bayes geometric mean value calculated by the MGPS method.
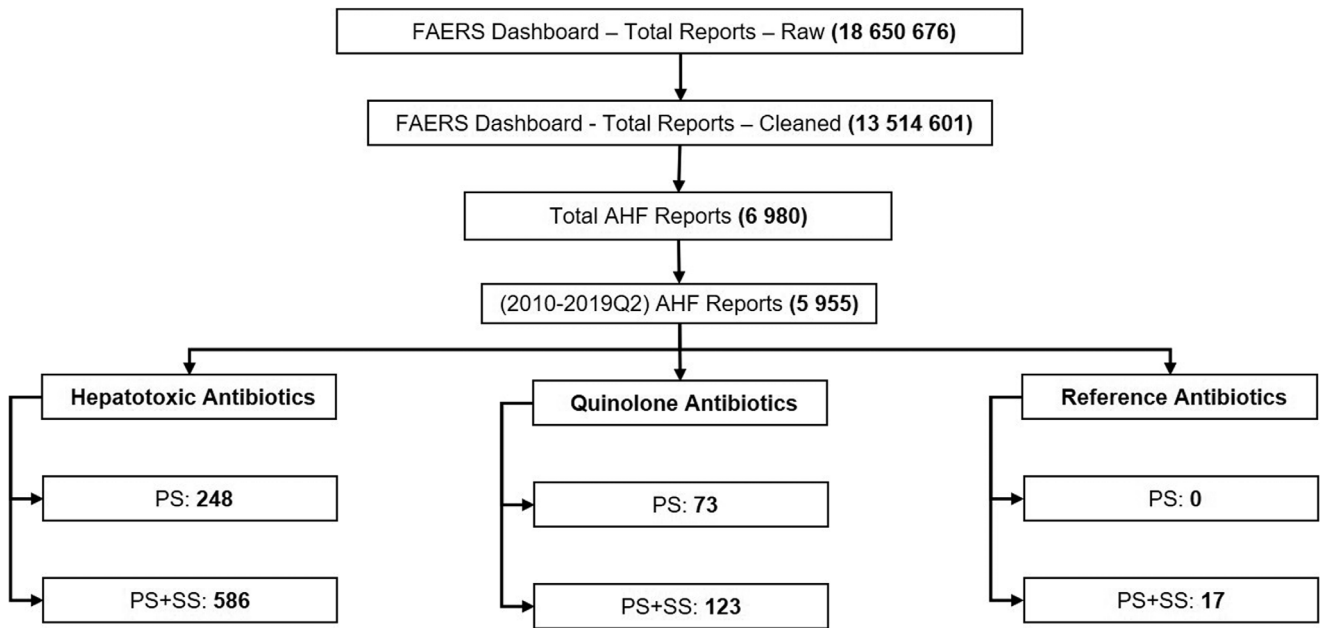
**Figure 1** US FDA Adverse Event Reporting System data cleaning flowchart for identification of acute hepatic failure (AHF) reports (2010–2019q2). PS, primary suspect; SS, secondary suspect.

**Table 2** Total and AHF reports from 1969 to 2019q2 using cleaned FAERS data

| Adverse event reports | 1969–2019 | 2004–2019 | 2004–2009 | 2010–2019 |
| --- | --- | --- | --- | --- |
| FAERS, total number of reports | 13 514 601 | 11 082 677 | 1 589 090 | 9 493 587 |
| AHF, total number of reports | 6980 | 6980 | 1025 | 5955 |
| AHF, hepatotoxic antibiotics | N/A† | 749 | 65 | 684 |
| AHF, quinolone antibiotics | N/A† | 206 | 50 | 156 |
| AHF, reference antibiotics | N/A† | 29 | 3 | 26 |

†N/A: Since AHF was first reported as a MedDRA preferred term (PT) in 2006.
AHF, acute hepatic failure; FAERS, US FDA Adverse Event Reporting System.

Comparing AHF reports across the three antibiotic groups when reported as a PS *versus* PS/SS combined did not show a meaningful change in the magnitude of signal or the level of significance except with the antituberculous antibiotics, ethambutol, isoniazid, and rifampin. Since AHF as a MedDRA PT was not reported prior to 2006, we analyzed the interval between 1969 and 2019q2, as a sensitivity analysis, using the more generic HF term instead.

Compared to reference antibiotics, analysis of data during 1969–2019q2 revealed strong signals for hepatic failure (including AHF) for both trovafloxacin (PRR: 6.06 [9.71, 2.27]) and its prodrug alatrofloxacin (PRR: 3.31 [8.27, 2.11]), which were both withdrawn from the market in 2001 due to hepatotoxicity concerns.[18,47] Prior to their market withdrawal, there were 2.5 million trovafloxacin prescriptions written annually, with a monthly average of 300 000.[48]

Both norfloxacin and ofloxacin showed weak and nonsignificant HF signals. No other quinolones showed a similar signal, despite having more AHF reports. Table 6 lists the number of HF reports and the corresponding PRR signal linked to any of the quinolone antibiotics as PS only between 1969 and 2019q2. A complete listing of AHF reports signals for all

antibiotics in the three groups for all time intervals is detailed in the Supplementary Materials 2 and 3.

## Discussion

Our study is the first to examine the association between quinolones and AHF based on reports in FAERS between 1969 and 2019q2. Our focus on reports between 2010 and 2019q2 covered the interval with the highest quality data, and reporting rates to date (76% of all types of reports and 86% of all AHF reports) added more power to our results. Our sensitivity analyses of three additional intervals (2004–2019q2, 2004–2009, and 1969–2019q2) did not reveal any conflicts with the results of our primary interval (2010–2019q2). Only ciprofloxacin has been flagged as showing a marginally positive and significant AHF signal, whereas moxifloxacin, levofloxacin, and ofloxacin showed weak and nonsignificant signals.

In a companion study of real-world electronic health records, ciprofloxacin showed evidence of a possibly increased AHF risk in persons with low comorbidity.[49] No other

quinolones showed a significant signal, despite showing up in some AHF reports. The results of an ongoing systematic review of quinolone-associated ALF/AHF in clinical trials involving quinolone antibiotics will be reported separately.[50]

Consistent with current evidence, women were more likely than males to experience AHF. Those younger than 10 or older than 90 years of age were less likely to experience AHF than the other age groups. While FAERS does not allow the calculation of incidence rates, the fact that quinolones were recorded as the PS drug in 1% of reports, compared to 4% with antibiotics of known hepatotoxicity, flags a need for additional epidemiologic investigation.

Our identified MedDRA PT of AHF is a precise clinical term that is predominately used by health professionals and pharmaceutical companies, compared with HF, which is a general term encompassing a wide range of diseases that do not necessarily match our outcome of interest. This was confirmed by our analysis, which revealed that 80% of our results were reported by health professionals. Whereas FAERS reporting might habitually exhibit a spike upon launch of a new drug: the Weber Effect,[51] this is not of any concern in our study since the latest quinolone was launched in 2006, prior to our primary interval (2010-2019q2). Additionally, AHF is a serious disease that must be immediately reported, irrespective of the suspected drug or its release/approval date.

The present analysis does not explicitly consider the potential for drug–drug interactions, including interactions among two (or more) drugs within the three antibiotic groups examined in the present analysis. Of the 726 reports of AHF between 2010 and 2019, there were only 32 reports in which more than one drug from the three antibiotic groups was mentioned as either a PS or SS on the same report; as this represents only 4.4% of the total number of AHF cases, the concern about possible drug–drug interactions is limited.

A major limitation for FAERS relates to its dependency on the reporter's motivation and skills, which generates bias due to missed, under-, over-, untimely, selective, variable, or incomplete reporting of ADE.[20–28,37,52] Additionally, FAERS cannot provide information on incidence rates since reports lack the required information on drug utilization, which precludes an assessment of ADE risks, or a comparison of safety profiles for multiple drugs.[1,24–26,29,30,35,37,52] As such, significant evidence of disproportionate reporting is primarily thought to be hypothesis generating, requiring confirmation using other data sources. This has been done in our companion paper, which investigated the association of quinolones with AHF in a large EHR database for reference 49.

FAERS does not actively solicit information on important risk factors such as comorbidities, or results of laboratory and other confirmatory investigations. An AHF case report might in reality reflect an acute exacerbation to an already ailing liver, rather than a de novo case of drug-induced AHF. Since FAERS does not contain validated information on comorbidities,

**Table 3** Characteristics of all acute hepatic failure reports as primary suspect, secondary suspect, concomitant (C), and interacting suspect (I) (2010–2019q2)

| Characteristics | Number of reports (%) |
|---|---|
| **Sex** | |
| Women | 2833 (47.57%) |
| Men | 2131 (35.79%) |
| Missing | 991 (16.64%) |
| **Age** | |
| 0–10 | 324 (5.44%) |
| 11–20 | 412 (6.92%) |
| 21–30 | 562 (9.44%) |
| 31–40 | 636 (10.68%) |
| 41–50 | 676 (11.35%) |
| 51–60 | 664 (11.15%) |
| 61–70 | 655 (11.00%) |
| 71–80 | 484 (8.13%) |
| 81–90 | 199 (3.34%) |
| 91+ | 17 (0.29%) |
| Missing | 1326 (22.27%) |
| **Reported by** | |
| Medical doctors | 2256 (37.88%) |
| Other Health Professionals | 2549 (42.80%) |
| Consumers | 631 (10.60%) |
| Pharmacists | 285 (4.79%) |
| Lawyers | 35 (0.59%) |
| Missing | 199 (3.34%) |
| **Geographic location** | |
| United States | 2086 (35.03%) |
| United Kingdom | 930 (15.62%) |
| Japan | 192 (3.22%) |
| Canada | 261 (4.38%) |
| Others | 2346 (39.40%) |
| Missing | 140 (2.35%) |

**Table 4** Reports with acute hepatic failure signals with hepatotoxic antibiotics (most drug-induced liver injury [DILI]), compared to reference antibiotics (no DILI), as primary suspect only (2010–2019q2)

| Drug | Count | Expected | PRR (LB, UB) | EBGM (LB, UB) |
|---|---|---|---|---|
| Isoniazid | 76 | 15.603 | 7.17 (5.52, 9.32) | 5.49 (3.86, 5.61) |
| Rifampin | 109 | 38.137 | 4.65 (3.66, 5.91) | 3.22 (2.39, 3.27) |
| Ethambutol | 6 | 3.87 | 1.77 (0.79, 3.96) | 1.74 (0.73, 2.49) |
| Nitrofurantoin | 15 | 11.055 | 1.56 (0.93, 2.62) | 1.52 (0.86, 1.94) |
| Minocycline | 10 | 12.565 | 0.89 (0.48, 1.68) | 0.89 (0.48, 1.29) |
| Erythromycin | 8 | 16.217 | 0.54 (0.27, 1.10) | 0.55 (0.30, 0.88) |
| Sulfasalazine | 9 | 33.826 | 0.28 (0.14, 0.54) | 0.29 (0.17, 0.47) |
| Clarithromycin | 15 | 100.412 | 0.12 (0.07, 0.20) | 0.16 (0.10, 0.23) |

LB, lower boundary; PRR, proportional reporting ratio; UB, upper boundary.

**Table 5**  Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (no drug-induced liver injury), as primary suspect only (2010-2019q2)

| Comparator | Drug | Count | Expected | PRR (LB, UB) | EBGM (LB, UB) |
| --- | --- | --- | --- | --- | --- |
| Quinolone antibiotics | Ofloxacin | 2 | 0.972 | 2.20 (0.54, 8.91) | 2.17 (0.59, 2.40) |
| | Ciprofloxacin | 34 | 23.275 | 1.85 (1.21, 2.81) | 1.54 (1.06, 1.81) |
| | Moxifloxacin | 14 | 10.414 | 1.49 (0.85, 2.63) | 1.41 (0.84, 1.82) |
| | Levofloxacin | 23 | 35.975 | 0.57 (0.36, 0.91) | 0.67 (0.49, 0.92) |

LB, lower boundary; PRR, proportional reporting ratio; UB, upper boundary.

**Table 6**  Reports with signals for HF (including acute hepatic failure [AHF]) with quinolone antibiotics, compared to reference antibiotics (no drug-induced liver injury), as primary suspect only (1969–2019q2)

| Antibiotic | HF reports | PRR (LB, UB) | EBGM (LB, UB) |
| --- | --- | --- | --- |
| Alatrofloxacin | 19 | 5.24 (3.31, 8.29) | 4.38 (2.75, 6.01) |
| Ciprofloxacin | 62 | 1.29 (0.99, 1.69) | 1.19 (0.94, 1.43) |
| Gatifloxacin | 4 | 1.01 (0.38, 2.71) | 0.97 (0.22, 1.72) |
| Gemifloxacin | 2 | 0.72 (0.18, 2.90) | 0.73 (0.03, 1.50) |
| Levofloxacin | 78 | 0.51 (0.40, 0.65) | 0.57 (0.46, 0.67) |
| Moxifloxacin | 67 | 1.11 (0.86, 1.44) | 1.04 (0.83, 1.25) |
| Norfloxacin | 13 | 1.99 (1.15, 3.46) | 1.81 (1.00, 2.62) |
| Ofloxacin | 33 | 1.72 (1.21, 2.45) | 1.57 (1.12, 2.01) |
| Trovafloxacin | 85 | 7.69 (6.07, 9.73) | 5.91 (4.86, 6.96) |

HF, hepatic failure; LB, lower boundary; PRR, proportional reporting ratio; UB, upper boundary.

including possible liver dysfunction, it is not possible to isolate the potential effect of quinolones on patients with no preexisting liver conditions. However, in our companion paper based on EHR data, we are able evaluate the safety of quinolones in patients with no prior liver conditions.[49]

As an SRS, FAERS have an inherent capacity to generate many false positives, since not all captured drug-ADE associations will prove to be true, as well as false negatives as SRS data are imperfect and would miss some true associations.[23,28,29,52] A common confounder; known as the "innocent bystander effect," where all medications that are prescribed together for treatment of a specific disease, will inherit the same causal association with an ADE, irrespective of their actual contributions.[30]

Studies mining large databases are valuable in generating timely signals for possible ADE,[37] without providing solid evidence of causality. However, in cases of severe or life-threatening ADE, regulators may use these signals to enforce label changes in the absence of more in-depth epidemiologic evidence.[3,31,32]

In conclusion, although a marginal and significant AHF signal was detected with ciprofloxacin, this signal requires confirmation using additional epidemiologic investigation. Otherwise, we found no evidence of significant signals for quinolone-induced AHF. Our findings on AHF signals with the "Most DILI" antibiotics are in line with previous research.[31] However, these results must be interpreted with caution due to the previously described limitations.

## Acknowledgments

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Appendix S1** Supporting information.