Systemic quinolones and risk of adverse reactions: Integrating evidence from clinical and epidemiological evidence streams

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Abstract

Quinolones are a group of antibiotics that have gained significant popularity on a global scale since the end of the last century. This popularity was predominantly based on their proven potency, broad coverage against a wide range of bacteria, in addition to possessing a favorable pharmacologic profile. Whereas quinolone-associated adverse reactions are generally tolerable and self-limiting, some reactions have generated heightened concerns due to their serious nature, which have resulted in label changes or even market withdrawal in some instances.

This thesis investigates the association between quinolone antibiotics and two adverse reactions of an acute and serious nature: acute liver failure and retinal detachment. Each adverse reaction is investigated through integrating evidence from three studies utilizing different designs based on data from different sources, with each source offering a unique perspective on this issue.

The first study type (chapter 2 for acute liver failure ‘ALF’ and Chapter 5 for retinal detachment ‘RD’) analyzes spontaneous reports submitted to the US Food & Drug Administration (FDA) adverse event reporting system database. Chapters 3 and 6 systematically identified all relevant (published and unpublished) clinical trials for occurrences of ALF and RD, respectively, among trial participants. Finally, chapters 4 (ALF) and 7 (RD) involved case-control analysis of a major US database of electronic health records for nearly 70 million inpatients admitted to more than 500 hospitals between 2000 and 2016.

The FAERS analysis revealed a positive ALF signal with ciprofloxacin and a marginal signal for RD with moxifloxacin. Examination of the evidence from clinical trials

revealed only two cases of ALF, one associated with gemifloxacin and one with moxifloxacin. No cases of RD were reported in any of the identified clinical trials.

Primary analyses of the Health Facts® data revealed no overall association between quinolones and the risk of ALF or RD. However, elevated risk was identified in some subgroups, including African Americans (ALF, RD), Caucasians (ALF), women (ALF, RD), men (ALF), those ≤60 years of age (ALF) or 56-70 years of age (RD), and those with no or few comorbidities (ALF).

Evidence from analyses of data from spontaneous reports and clinical trials provided some evidence for an elevated risk of ALF or RD following the systemic administration of quinolone antibiotics. Some evidence of elevated risk was also identified in the case-control analyses of inpatient EHR records. Findings from our six epidemiologic studies are in line with current advisories by FDA and Health Canada.

To my wonderful kids

To the souls of my great parents

To all my exceptional teachers and professors

& to the Great Lord who blessed me with all of the above

... and beyond!

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
AHF	Acute hepatic failure
ALF	Acute liver failure
CMI	Comorbidity index (Elixhauser)
CS	Concomitant suspect
DILI	Drug-induced liver injury
EBGM	Empirical Bayesian geometric mean
EHR	Electronic health records
FAERS	FDA adverse event reporting system
FDA	Food and drug administration
IS	Interacting suspect
MedDRA	Medical dictionary for regulatory activities
MGPS	Multi-item gamma Poisson shrinker
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRR	Proportional reporting ratio
PS	Primary suspect
PTs	Preferred terms
RD	Retinal detachment
SRS	Spontaneous reporting systems
SS	Secondary suspect
STROBE	Strengthening the reporting of observational studies in epidemiology statement guidelines

Introduction

Chapter 1: Introduction

Background

Although discovered in the early sixties, it took almost two decades for quinolone antibiotics to become one of the most globally prescribed classes of antibiotics [1-3], with a reported one-sixth of worldwide antibiotic sales of US$ 7 billion in 2009 [4]. An earlier study reported fluoroquinolones as the most commonly prescribed antibiotics in emergency and ambulatory settings in the US between 1995-2002 [5].

Such growth in popularity through four generations of quinolones, particularly their fluorinated agents, was based on progressive improvement in potency, coverage against different types of bacteria (including atypicals), and a reasonable safety profile. Offering features such as excellent bioavailability, good tissue penetration, and longer half-lives allowed for fewer dosing courses and subsequently better patient compliance [2, 6-9].

The first quinolone –nalidixic acid– was derived from the antimalarial drug chloroquine [10]. Subsequent manipulations of the nucleus and side chains led to the development of other quinolone antibiotics [6, 7]. Whereas many of these manipulations enhanced the potency and pharmacological features of quinolones, [1, 8, 11-15], others led to increased risk of certain adverse reactions [1, 11, 13, 16].

Reported adverse drug reactions (ADR) in association with quinolones were found to be largely mild to moderate, self-limiting and mostly reversible [7, 12, 17, 18]. However, other reactions were serious enough to draw considerable attention, including neuropsychiatric [7, 8, 11, 18-21], cardiac [3, 7, 8, 18, 21-26], and tendinopathic [7, 8, 18, 21, 22]

responses. Additional concerns were also raised for two acute diseases, specifically acute liver failure and retinal detachment.

Acute liver failure (ALF) is a serious disease involving *de-novo*, rapid, progressive and possibly severe loss of hepatic cells in patients with no prior liver impairment. Although this condition may sometimes be asymptomatic and reversible, it may also deteriorate quickly leading to death if liver transplantation is not performed in a timely manner [27-31]. While ALF can be caused by many factors [27, 28, 32-36], drug-induced liver injury (DILI) represents the most common reason for both ALF [27, 31, 32, 35, 37, 38], and post-approval medication withdrawal [27, 34, 38, 39] in the US and Europe. In the absence of clear-cut diagnostic criteria, a DILI diagnosis remains predominantly a clinical decision requiring judgment by the attending physician [34-36, 39-41].

Retinal detachment (RD) is a serious disease which involves the development of breaks within the retinal layer of the eye that may result in separation of the retina from the underlying tissues, which may lead to loss of vision in the affected eye [42, 43]. It is relatively common, with an annual population incidence of 1 in 10,000 [43].

Many epidemiologic studies with different designs have been conducted to examine the association of quinolones with these two serious adverse events. In this thesis, we examined and reported on current state of evidence based on our assessment of different data sources and different types of studies that examined the association between use of quinolones and ALF and RD.

Objectives

This thesis aimed at comprehensively investigating the association between systemically administered quinolone antibiotics and risk of ALF and RD. The objectives of this research were to:

1. analyze data of spontaneous reports from the US FDA adverse event reporting system (FAERS) database to identify signals for association of systemically administered quinolone antibiotics with
    a. *acute hepatic failure (chapter 2) and*
    b. *retinal detachment (chapter 5);*
2. conduct a systematic review of original published and unpublished trials where a quinolone antibiotic was tested or used as a comparator to other drugs or drug combinations, for evidence on the association of systemically administered quinolone antibiotics with:
    a. *acute liver failure (chapter 3) and*
    b. *retinal detachment (chapter 6);*
3. conduct a case-control study using electronic health records (EHR) from the Cerner Health Facts database® (Health Facts®) for examining the association of systemically administered quinolone antibiotics with:
    a. *acute liver failure (chapter 4) and*
    b. *retinal detachment (chapter 7).*

Methodology

This thesis comprises eight chapters that detail our comprehensive examination of the association of systemically administered quinolones with two outcomes of interest: ALF and RD. Results for ALF are presented in chapters 2-4 with results for RD provided in chapters 5-7. Chapter 1 provides an introduction to the thesis, with a discussion of the main findings and conclusions given in chapter 8.

Analysis of spontaneous reporting data

Spontaneous reporting systems (SRS) such as FAERS are the most common source used by regulatory authorities to identify signals of possible drug-adverse drug event (ADE) associations that were not initially identified prior to drug approval and release for use by the generally public. These ADE signals may be subsequently targeted for confirmation using more sophisticated pharmacoepidemiological studies, possibly leading to risk mitigation actions if warranted [44-48].

Unless otherwise mandated, ADE reporting is voluntary, depending entirely on the reporter's motivation and/or diligence, which can lead to different types of bias due to missed, under, over, untimely, selective, or incomplete reporting on ADE [44, 46-53]. Moreover, SRS cannot provide information on incidence rates, assessment of risk factors, or comparing of different safety profiles [8, 44-47, 54, 55]. Another disadvantage of SRS is the occurrence of both false positive and false negative associations [48, 52, 54]. When drugs other than the primary drug of interest produce the same ADE of interest at higher rates, they tend to inflate the denominator and undermine the true magnitude of

the drug-ADE association [45, 55]. Despite their limitations, SRS continues to be the cornerstone of drug safety, particularly when integrated with other data sources [44, 56].

FAERS is a large-scale surveillance system operated by the US Food & Drug Administration that captures voluntary reports on ADE associated with certain medications and supplements from the US as well as from other countries. While detailed pharmacoepidemiologic studies may more definitive for confirming or denying such associations, a timely ADE signal is invaluable in identifying priority areas for investigation. In the absence of solid evidence from clinical trials and epidemiologic studies, regulatory authorities may utilize evidence from SRS such FAERS to guide their safety-based responses, even without strong evidence of causality [57-59].

I began the analysis by conducting a rigorous cleaning of the raw data downloaded from the FAERS website. Using our cleansed version of the FAERS data, we examine quinolone-associated reports for the outcomes of interest (AHF and RD) compared to those associated with positive controls and reference antibiotics. For each of our major analyses, we first examined reports where the antibiotic is reported as a primary suspect (PS) only, and then as primary suspect/secondary suspect (SS) combined. The proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS) were used for signal detection, due to their higher sensitivity and specificity, respectively [60-62].

Systematic review of clinical trials

While acknowledging preclinical and clinical trials as the most rigorous tool for assessing drug safety and effectiveness prior to their market authorization, they are

generally not representative of the general population with respect to demographics, lifestyle and other population characteristics. Clinical studies cannot identify all risk factors and underlying disease determinants, determine how the drug will perform under real-world conditions compared to controlled environments of clinical trials, and are highly likely to miss rare or long-term ADR [44, 48, 63-65].

Our comprehensive, multi-step search strategy identified all original studies related to all quinolone antibiotics from multiple bibliographic databases, clinical trial registries, and major grey literature sources such as drug review networks and databases of pharmaceutical companies, relevant national and international agencies and international conference proceedings. Only primary references were assessed for eligibility, with maximum diligence adopted to link all secondary publications reporting on each primary study, if applicable. The search was conducted according to PRISMA guidelines established by the Cochrane Collaboration.

Eligible studies include trials examining a single systemically-administered quinolone antibiotic compared to a placebo, another non-quinolone antibiotic or non-quinolone-containing antibiotic combination. Exclusion criteria include studies testing quinolones against one another, combined together or with other medications, in topical formulations, or when participants had history of liver impairment. Cross-over trials were also excluded to avoid any possible carry-over effect from the initial intervention. Non-original studies, observational studies and trials where no results were available were also excluded. No publication time, language or other filters were imposed to limit the search.

Analysis of the Health Facts® data

Increasingly, data from large administrative databases such as health insurance claims spanning extended periods of time have been used to support pharmacoepidemiologic research. This approach has opened new horizons for assessment of risk factors and major confounders, particularly with late-onset and rare ADR. Nevertheless, having developed for non-research purposes, these databases are prone to different types of bias, confounding, and data integrity issues. A more powerful approach involves examining data from EHR databases, which were created primarily to streamline the flow of patient medical information among service providers across the care continuum. These EHR databases provide extensive patient-related information such as demographics, socioeconomic determinants, comorbidities, medications, investigations, medical, surgical and other procedures as well as patient outcomes.

We analyzed inpatient EHR data from the Health Facts®, which hosts extensive EHR data on for almost 70 million de-identified patients (approximately 21.6% of the US population[1]) that were generated between 2000-2016 via nearly 450 million encounters in more than 500 US hospitals. Health Facts® contains detailed patient information such as demographics, extensive medical care details, healthcare setting and insurance status.

For each of the two outcomes of interest (ALF and RD), I conducted a robust multistep process to identify a pool of eligible cases. Adopting incidence density sampling, I used an optimal variable matching approach to match each case for a maximum of five unique controls without replacement. For the ALF study (chapter 4),

[1] *US population as of December 31, 2016: 324,070,652 (https://www.census.gov)*

inpatient systemic medication exposure was classified into four groups: quinolones, hepatotoxic medications (excluding quinolones), other antibiotics (excluding quinolones and hepatotoxic antibiotics), and other medications combined (excluding all antibiotics and hepatotoxic medications). In the RD study (chapter 7), we identified three medication groups: quinolones, non-quinolone antibiotics and other medications combined. Data on medication exposure was limited to prescriptions filled during inpatient care. As our study examined inpatient EHR data, we used filled prescriptions identified from the internal pharmacy database as proxy for medication administration.

In addition to providing detailed descriptive statistics on the study population, we generated a series of conditional logistic regression models for each medication group, while adjusting for other medication groups and major confounders and risk factors. For each medication group, we fitted a base model with only matching variables and one medication group. This was followed by a minimally adjusted model including base model variables plus all other medication groups. Finally, we fitted a maximally adjusted model extending the minimally adjusted model to include all remaining variables. To identify the individual quinolone(s) with the strongest possible association for the outcome of interest (ALF or RD), we repeated the same series of regression analyses using exposure to individual quinolones, rather than all quinolones as a class, as predictors of the outcome of interest (ALF or RD). I reported on the analyses of the Health Facts® data in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.

Contributions of collaborators

The present thesis is written in manuscript format, with chapters 2 through 7 presented as manuscripts suitable for submission for publication in the scientific literature. The contributions of collaborators on each of these manuscripts is given below.

Analysis of FAERS data (chapters 2 and 5):

The primary author, Mohamed Taher, designed and implemented this study design, statistical analysis, interpretation of findings and drafting of this manuscript. Christopher Gravel, Abdallah Alami, and Derek Tsui contributed to statistical analysis, as well as critical review and approval of two chapters/manuscripts.

Systematic reviews (chapters 3 and 6):

The primary author, Mohamed Taher, designed and implemented the review strategy including search methodology, design of study screening and data abstraction forms, reference collation and full-text acquisition, screening and examination of the identified references, data abstraction and drafting of this manuscript. Mohamed Habsah independently assessed all studies examined in these two chapters/manuscripts.

Analysis of the Health Facts® database (chapters 4 and 7):

The primary author, Mohamed Taher, designed and implemented this study including study design, statistical analysis, interpretation of findings and drafting of this manuscript. James Crispo and Yannick Fortin contributed to statistical analysis, as well as critical review and approval of these two chapters/manuscripts.

PhD thesis committee members:

Douglas McNair and Ryan Moog (Cerner Health Facts®), and thesis committee members Lise Bjerre, Franco Momoli, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of all studies, as well as critical review and approval of all chapters/manuscripts.

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Declaration of Interest

All authors who contributed to all chapters/manuscripts in this thesis report no conflict of interest in relation to the planning for and conducting this study as well as production of all chapters/manuscript.

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Chapter 2 (ALF-FAERS)

Acute liver failure I: FAERS analysis

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

Abstract

Background: 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).

Objective: Data from the US FDA Adverse Event Reporting System (FAERS) were evaluated for signals of AHF in association with systemically administered quinolone antibiotics.

Methods: AHF reports between 1969 and the end of second quarter of 2019 (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 were used to assess the AHF signal: the proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS), which are known for their higher sensitivity and specificity for ADE signal detection, respectively.

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

Conclusion: Further pharmacovigilance studies are required to confirm the association between ciprofloxacin and AHF seen in the present analysis.
Keywords: Quinolones; hepatotoxicity; acute liver failure; acute hepatic failure, FDA Adverse Event Reporting System (FAERS).

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 labelling revision or market withdrawal [2-6].

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 [6-9]. This disease can be caused by many agents, including drugs, toxic substances, nutritional supplements, and bacteria or viruses [7, 8, 10-14].

Drug-induced liver injury (DILI) has been repeatedly reported as the most common cause of AHF [7, 9, 10, 13, 15, 16], and medication withdrawal [7, 12, 16] in the US 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 (ADE) [15]. 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 [8-10, 14]. 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 2,000 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 [15, 17, 18]. 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, 19].

A recent study reported moxifloxacin and levofloxacin-associated AHF at 6.6 and 2.1 reports per 10 million prescriptions, respectively [20]. In the absence of evidence from clinical trials and pharmacovigilance studies, and despite the limitations of spontaneous reporting systems (SRS) reports such as FAERS [1, 21-31], regulators may err on the side of caution and use these reports to guide their safety-based responses, without strong evidence of causality [32-34].

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 US.

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 US and other countries, and currently represents one of the most commonly used sources for early identification and characterization of ADE [25-27, 29, 35-38].

Whereas ADE reporting is mandatory by pharmaceutical companies, it is done on voluntary basis by healthcare providers and consumers [25-27, 29, 31, 35, 36, 38]. SRS-generated signals usually prompt detailed validation studies, which would provide further evidence on product safety under real-world conditions of use [25-27, 29, 37, 39]. 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 [36, 40]. FAERS generates data in a raw format on quarterly basis, which can be downloaded from their website [41]. With drugs listed using both generic and brand names [40, 42], 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 [36, 40].

Based on a recent major review [32] 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.

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

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

ADE are coded in FAERS using the MedDRA (Medical Dictionary for Regulatory Activities) Preferred Terms (PTs) [43]. 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 and colleagues [32]. 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 to 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) [44], due to their higher sensitivity (PRR) and specificity (MGPS) for ADE signal detection [44-46]. 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 [47, 48]. 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 [47, 48].

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 3 reports is considered to be significant evidence of disproportionate reporting [44, 48]. An observed MGPS signal with the value of the lower boundary of EBGM[2] to be higher than 2 with a minimum of 1 report [44] 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 the 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 the Supplementary Material.

Results

The publicly-available FAERS dashboard contains a total of 18,650,676 ADE reports between 1969-2019q2, with almost 76% (14,245,824) reported between 2010-2019q2. 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 2 quarters of 2019.

[2] EBGM: The Empirical Bayesian Geometric Mean value calculated by the MGPS method

Our cleaned version of the FAERS data showed a total of 13,514,601 reports including 6,980 AHF reports (0.05%) between 1969-2019q2, with 5,955 of them (0.04%) reported between 2010-2019q2 (Figure 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).

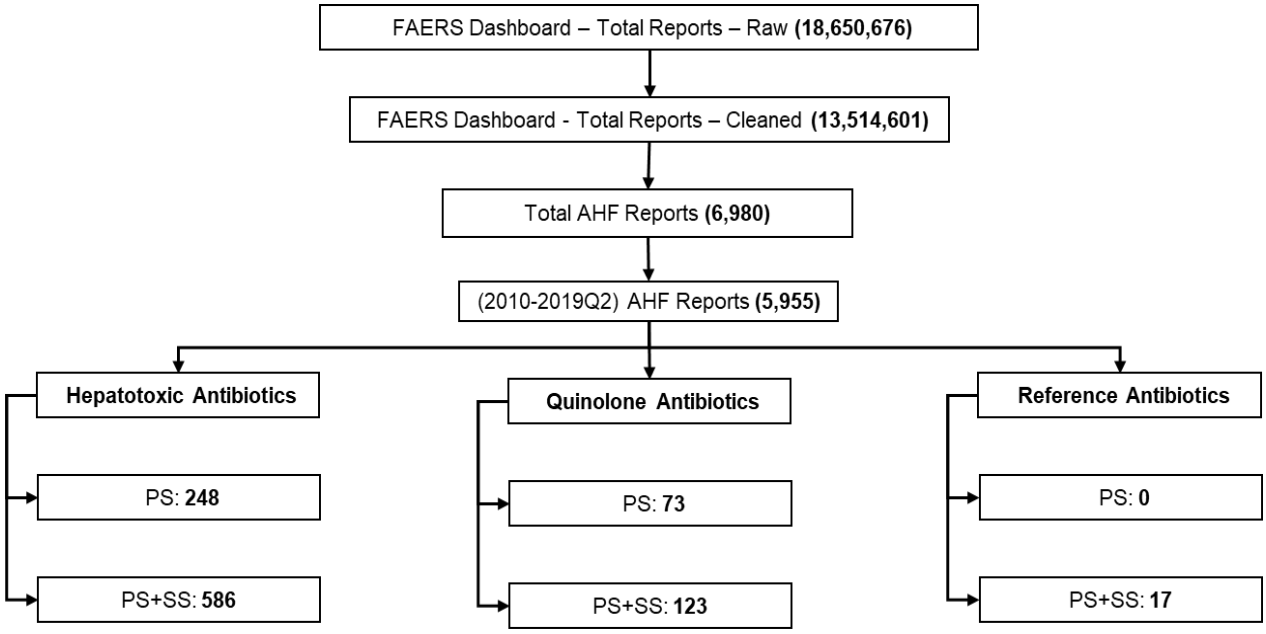

Figure 1: FAERS data cleaning flowchart for identification of 2010-2019Q2 AHF reports

As MedDRA undergoes periodic revisions, this usually involve introduction of new preferred terms (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 1,025 confirmed AHF reports, representing 0.07% of all reports between 2004-2009. Of all AHF reports between 2004-2019q2, quinolones accounted for 206 reports (2.95%) compared to 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.

Table 2: Total and AHF ADE reports from 1969-2019q2 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	6,980	6,980	1,025	5,955
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.

Description of AHF case reports

Our analysis showed that 35% of all AHF reports were submitted from the US, 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 to only 11% by consumers and lawyers. AHF reports between 2010-2019q2 were predominantly in women (48%) compared to men (36%), while sex was unreported in 17% of reports. Reports in the first two decades of life ranged between 5%-7%, which increased to 8%-11% per age group between 3rd-8th decades, with more than 22% of reports missing consumer age.

Table 3 shows a detailed listing of the distribution of AHF report characteristics between 2010-2019q2.

Table 3: Characteristcs of all AHF reports as PS, SS, C and I (2010-2019q2)

Characteristics	Number of reports (%)
Gender	
Women	2,833 (47.57%)
Men	2,131 (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	1,326 (22.27%)
Reported by	
Medical doctors	2,256 (37.88%)

Characteristics	Number of reports (%)
Other Health Professionals	2,549 (42.80%)
Consumers	631 (10.60%)
Pharmacists	285 (4.79%)
Lawyers	35 (0.59%)
Missing	199 (3.34%)
Geographic location	
United States	2,086 (35.03%)
United Kingdom	930 (15.62%)
Japan	192 (3.22%)
Canada	261 (4.38%)
Others	2,346 (39.40%)
Missing	140 (2.35%)

Results (2010 – 2019q2)

Hepatotoxic vs. reference antibiotics

Several AHF reports were reported with eight hepatotoxic (non-quinolone) antibiotics between 2010-2019q2. 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 [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 non-significant 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 2004-2019q2 showed the exact same pattern compared to 2010-2019q2.

Table 4: Reports with AHF signals with hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary suspect (PS) 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)

Quinolones vs. 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 2010-2019q2, 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 non-significant signals.

Ofloxacin produced the highest, though non-significant, 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 2004-2019q2 showed a similar pattern as 2010-2019q2, with a less powerful signal for ofloxacin due to absence of any linked reports between 2004-2009.

As reported earlier [32], and validated in our study, reference antibiotics were not associated with any AHF reports, as PS only, when compared to hepatotoxic or quinolone antibiotics. Table 5 shows results for AHF reports with quinolones compared to reference antibiotics between 2010-1019 (Q2).

Table 5: Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect (PS) 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)

Comparing AHF reports across the three antibiotic groups when reported as a PS vs PS/SS combined did not show a meaningful change in the magnitude of signal or the level of significance except with the anti-tuberculous antibiotics, Ethambutol, Isoniazid and Rifampin. Since AHF as a MedDRA PT was not reported prior to 2006, we analyzed the interval between 1969-2019q2, 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 [19, 49]. Prior to their market withdrawal, there were 2.5 million trovafloxacin prescriptions written annually, with a monthly average of 300,000 [50].

Both norfloxacin and ofloxacin showed weak and non-significant 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 1969-2019q2. A complete listing of AHF reports signals for all antibiotics in the three groups for all time intervals is detailed in the Supplementary Material 2-3.

Table 6: Reports with signals for HF (including AHF) with quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect (PS) 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)

Discussion

Our study is the first to examine the association between quinolones and AHF, covering a wide interval between 1969–2019q2. Our focus on reports between 2010-2019q2 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 results of our primary interval (2010-2019q2).

Only ciprofloxacin flagged a marginally positive and significant AHF signal, whereas moxifloxacin, levofloxacin and ofloxacin showed weak and non-significant signals. No other quinolones showed any signal, despite showing up in some AHF reports.

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

Our identified MedDRA PT of AHF is a precise clinical term that is predominately used by health professionals and pharmaceutical companies, compared to 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.

Studies mining large databases are valuable in generating timely signals for possible ADE [39], 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 [32-34].

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 of a possible drug-drug interactions is limited.

The exploration of multiple possible signals in this chapter raises the question as to whether a formal adjustment for multiple testing should be applied [52]. As the focus of the chapter is the identification of safety signals to be flagged for further investigation and confirmation using more in-depth focused analyses (see chapter 4), such adjustments were not made.

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 [21-29, 39, 53]. 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, 25-27, 30, 31, 37, 39, 53]. As such, significant evidence of disproportionate reporting is primarily thought to be hypothesis generating, requiring confirmation using other data sources, which has been done in part three of this three-part investigation of the association of quinolones with AHF [54].

FAERS does not also give 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.

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 [24, 29, 30, 53]. 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 [31].

Since FAERS does not contain information on comorbidities, including possible liver dysfunction, it is not possible to isolate the potential effect of quinolones on patients with no preexisting liver conditions. However, in a companion paper based on EHR, we are able evaluate the safety of quinolones in patients with no prior liver conditions [54].

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 [32]. However, these results must be interpreted with caution due to the previously described limitations.

Author contributions

The primary author, Mohamed Taher, designed and implemented this study including statistical analysis, interpretation of findings and drafting of this manuscript. Christopher Gravel, Abdallah Alami, and Derek Tsui contributed to statistical analysis, as well as critical review and approval of this manuscript. Lise Bjerre, Franco Momoli, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the study, as well as critical review and approval of the manuscript.

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Declaration of Interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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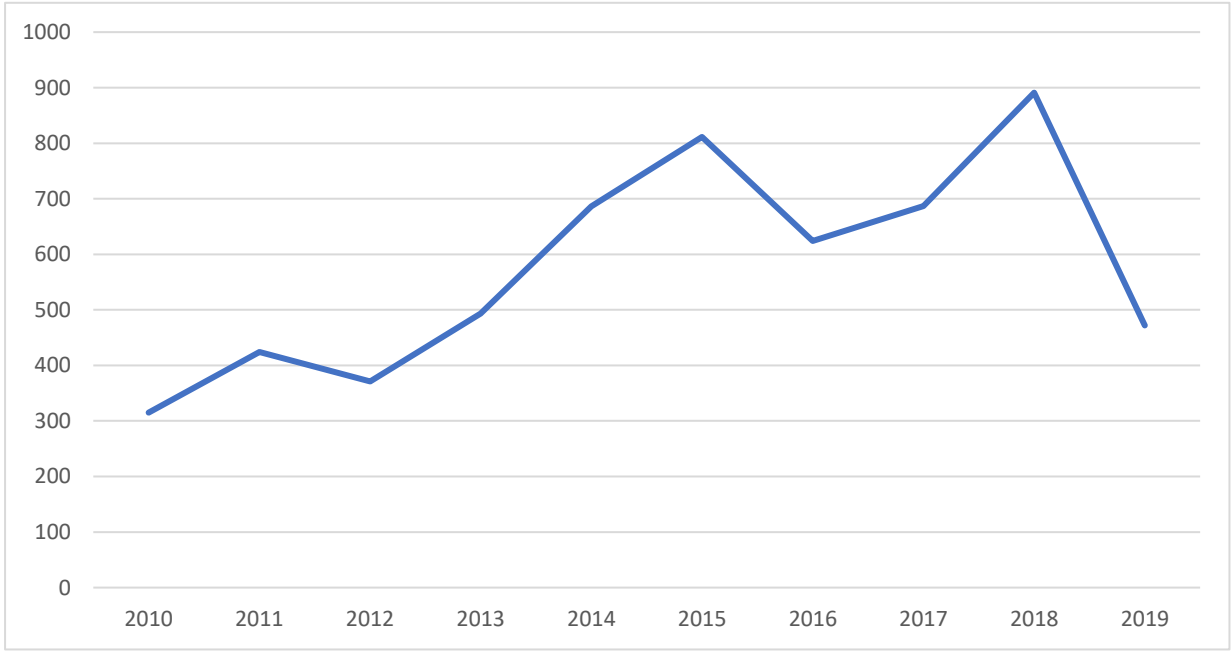
Supplementary Material – Chapter 2

Annual number of AHF reports to FAERS (2010-2019q2)



Drugs reported as primary suspect only

Hepatotoxic antibiotics (Most DILI) vs reference antibiotics (No DILI)

2004 – 2019q2

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary suspect only (2004-2019q2)

Drug	AHF Reports	Expected	PRR (LB-UB)	EBGM (LB-UB)
Isoniazid	80	15.734	**7.27** (5.65-9.34)	**5.71 (4.07-5.86)**
Rifampin	116	38.003	**4.79** (3.82-6.01)	**3.43 (2.55-3.46)**
Nitrofurantoin	16	9.396	*1.96 (1.19-3.24)*	*1.91 (1.06-2.34)*
Ethambutol	6	3.932	*1.73 (0.77-3.87)*	1.71 (0.72-2.41)
Minocycline	14	18.805	0.83 (0.49-1.42)	0.83 (0.49-1.13)
Erythromycin	8	16.511	0.53 (0.27-1.08)	0.54 (0.30-0.86)
Telithromycin	11	27.683	0.43 (0.23-0.78)	0.44 (0.26-0.66)
Sulfasalazine	11	37.441	0.31 (0.17-0.56)	0.33 (0.19-0.49)
Clarithromycin	25	106.999	0.20 (0.13-0.30)	0.26 (0.17-0.33)

2004 – 2009

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary suspect only (2004-2009)

Drug	AHF Reports	Expected	PRR (LB-UB)	EBGM (LB-UB)
Isoniazid	4	1.547	3.46 (1.24-9.64)	0.96 (0.79-2.96)
Rifampin	7	3.539	2.75 (1.23-6.15)	2.47 (0.88-2.57)
Minocycline	6	3.382	2.41 (1.02-5.69)	2.22 (0.77-2.42)
Clarithromycin	10	13.018	0.95 (0.47-1.92)	0.96 (0.49-1.24)
Telithromycin	10	14.371	0.84 (0.41-1.69)	0.87 (0.45-1.14)
Sulfasalazine	2	5.13	0.47 (0.11-1.92)	0.48 (0.24-1.16)

2010 – 2019q2

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary suspect only (2010-2019q2)

Drug	AHF Reports	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)

Quinolone antibiotics vs reference antibiotics (No DILI)

2004 – 2019q2

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect only (2004-2019q2)

Drug	AHF Reports	Expected	PRR (LB-UB)	EBGM (LB-UB)
Ciprofloxacin	34	21.528	*1.95 (1.30-2.91)*	*1.36 (1.14-1.95)*
Moxifloxacin	24	18.473	*1.47 (0.94-2.30)*	1.15 (0.91-1.70)
Ofloxacin	2	1.526	*1.39 (0.34-5.62)*	1.36 (0.51-2.15)
Levofloxacin	27	41.754	0.58 (0.38-0.90)	0.44 (0.49-0.90)

2004 – 2009

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect only (2004-2009)

Drug	AHF Reports	Expected	PRR (LB-UB)	EBGM (LB-UB)
Moxifloxacin	**10**	**6.35**	**2.60 (1.06-6.40)**	1.75 (0.83-2.02)
Ciprofloxacin	4	2.168	2.34 (0.78-7.05)	2.05 (0.67-2.21)
Levofloxacin	4	6.7	0.58 (0.19-1.74)	0.66 (0.39-1.26)

2010 – 2019q2

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect only (2010-2019q2)

Drug	AHF Reports	Expected	PRR (LB-UB)	EBGM (LB-UB)
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)

1969 – 2019q2

Reports with PRR signals for HF (including AHF) with quinolone antibiotics, compared to reference antibiotics (No DILI), as primary suspect drugs only (1969-2019q2)

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

Drugs reported as primary or secondary suspect

Hepatotoxic antibiotics (Most DILI) vs reference antibiotics (No DILI)

2004 – 2019q2

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary or secondary suspect (2004-2019q2)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Ethambutol	138	34.274	**5.16 (4.29-6.21)**	**4.36 (3.41-4.51)**
Isoniazid	195	52.343	**5.16 (4.38-6.08)**	**4.04 (3.24-4.10)**
Rifampin	185	62.85	**3.94 (3.34-4.66)**	3.19 (2.57-3.17)
Nitrofurantoin	24	15.976	*1.65 (1.10-2.48)*	1.63 (1.03-1.98)
Streptomycin	3	2.019	*1.62 (0.52-5.01)*	1.61 (0.53-2.77)
Minocycline	19	23.584	0.87 (0.55-1.37)	0.87 (0.62-1.12)
Telithromycin	11	27.912	0.42 (0.23-0.76)	0.43 (0.25-0.65)
Erythromycin	8	30.268	0.28 (0.14-0.56)	0.29 (0.16-0.48)
Clarithromycin	33	125.862	0.25 (0.18-0.36)	0.28 (0.25-0.35)
Sulfasalazine	17	191.303	0.08 (0.05-0.12)	0.1 (0.06-0.14)

2004 – 2009

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary or secondary suspect (2004-2009)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Minocycline	6	2.971	**2.69 (1.16-6.25)**	2.53 (0.84-2.63)
Isoniazid	10	5.271	**2.64 (1.34-5.20)**	2.37 (0.97-2.49)
Rifampin	7	4.581	*2.03 (0.92-4.46)*	1.91 (0.75-2.19)
Nitrofurantoin	2	1.255	*2.03 (0.50-8.28)*	1.00 (0.49-2.42)
Clarithromycin	10	11.926	*1.06 (0.54-2.08)*	1.05 (0.52-1.33)
Telithromycin	10	12.832	0.97 (0.49-1.91)	0.97 (0.49-1.25)
Ethambutol	2	2.65	0.94 (0.23-3.85)	0.94 (0.36-1.73)
Sulfasalazine	2	5.713	0.42 (0.10-1.71)	0.44 (0.22-1.08)

2010 – 2019q2

Reports with signals for acute hepatic failure due to hepatotoxic antibiotics (Most DILI), compared to reference antibiotics (No DILI), as primary or secondary suspect (2010-2019q2)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Isoniazid	185	47.146	**5.47 (4.62-6.48)**	**4.23 (3.43-4.36)**
Ethambutol	136	32.768	**5.37 (4.45-6.48)**	**4.48 (3.53-4.68)**
Rifampin	178	60.749	**3.95 (3.33-4.68)**	3.16 (2.56-3.28)
Streptomycin	3	2.226	*1.46 (0.47-4.51)*	1.45 (0.49-2.64)
Nitrofurantoin	23	17.24	*1.45 (0.96-2.20)*	1.44 (0.93-1.82)
Minocycline	18	20.939	0.93 (0.58-1.48)	0.93 (0.58-1.24)
Erythromycin	8	30.171	0.28 (0.14-0.56)	0.29 (0.16-0.48)
Clarithromycin	23	115.139	0.19 (0.12-0.28)	0.22 (0.14-0.28)
Sulfasalazine	15	204.4	0.06 (0.04-0.10)	0.08 (0.05-0.11)

Quinolone antibiotics vs reference antibiotics (No DILI)

2004 – 2019q2

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary or secondary suspect (2004-2019q2)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Ciprofloxacin	65	38.424	2.13 (1.59-2.84)	*1.80 (1.34-2.00)*
Ofloxacin	6	4.44	1.45 (0.64-3.26)	1.43 (0.67-2.05)
Moxifloxacin	27	28.928	0.99 (0.66-1.48)	0.99 (0.69-1.25)
Levofloxacin	45	74.463	0.55 (0.40-0.76)	0.64 (0.48-0.78)

2004 – 2009

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary or secondary suspect (2004-2009)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Moxifloxacin	12	9.17	*1.76 (0.87-3.56)*	1.49 (0.77-1.78)
Ciprofloxacin	6	3.588	*2.10 (0.87-5.07)*	1.91 (0.74-2.15)
Levofloxacin	8	10.968	0.78 (0.35-1.72)	0.83 (0.47-1.23)

2010 – 2019q2

Reports with signals for acute hepatic failure due to quinolone antibiotics, compared to reference antibiotics (No DILI), as primary or secondary suspect (2010-2019q2)

Drug	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Ciprofloxacin	65	41.262	**2.03 (1.50-2.74)**	1.67 (1.25-1.87)
Ofloxacin	6	3.304	*1.96 (0.87-4.42)*	1.93 (0.80-2.44)
Moxifloxacin	15	17.568	0.90 (0.53-1.52)	0.91 (0.58-1.26)
Levofloxacin	37	65.089	0.51 (0.35-0.73)	0.60 (0.45-0.75)

1969 – 2019q2

Reports with signals for HF (including AHF) with quinolone antibiotics, compared to reference antibiotics (No DILI), as primary or secondary suspect drugs (1969-2019q2)

Drug	HF Reports	PRR (UB-LB)	EBGM (UB-LB)
Alatrofloxacin	19	4.83 (7.61, 3.07)	4.09 (5.61, 2.56)
Ciprofloxacin	66	1.03 (1.33, 0.80)	0.97 (1.17, 0.77)
Gatifloxacin	5	0.89 (2.14, 0.37)	0.85 (1.44, 0.25)
Gemifloxacin	2	0.64 (2.56, 0.16)	0.66 (1.34, 0.03)
Levofloxacin	112	0.52 (0.63, 0.42)	0.56 (0.65, 0.47)
Moxifloxacin	77	1.01 (1.28, 0.80)	0.95 (1.13, 0.77)
Norfloxacin	19	1.78 (2.81, 1.13)	1.84 (3.76, 0.07)
Ofloxacin	44	1.64 (2.23, 1.21)	1.50 (1.87, 1.13)
Sparfloxacin	3	3.54 (10.98, 1.14)	2.50 (4.69, 0.30)
Trovafloxacin	85	6.52 (8.18, 5.20)	5.35 (6.30, 4.40)

Comparing PRR signal using primary vs primary or secondary suspect

Change in Signal for primay suspect vs. primary or secondary suspect

Duration	Drug	PS PRR (UB-LB)	PS & SS PRR (UB-LB)	△ PRR
Most DILI vs No DILI				
2004-19	Amikacin	NR	0.62 (0.33-1.15)	–
	Clarithromycin	0.20 (0.13-0.30)	0.25 (0.18-0.36)	↑
	Erythromycin	0.53 (0.27-1.08)	0.28 (0.14-0.56)	↓
	Ethambutol	1.73 (0.77-3.87)	5.16 (4.29-6.21)	↑
	Isoniazid	7.27 (5.65-9.34)	5.16 (4.38-6.08)	↓
	Minocycline	0.83 (0.49-1.42)	0.87 (0.55-1.37)	↑
	Nitrofurantoin	1.96 (1.19-3.24)	1.65 (1.10-2.48)	↓
	Penicillin	NR	0.58 (0.22-1.54)	–
	Rifampin	4.79 (3.82-6.01)	3.94 (3.34-4.66)	↓
	Streptomycin	NR	1.62 (0.52-5.01)	–
	Sulfasalazine	0.31 (0.17-0.56)	0.08 (0.05-0.12)	↓
	Telithromycin	0.43 (0.23-0.78)	0.42 (0.23-0.76)	↓
2004-09	Clarithromycin	0.95 (0.47-1.92)	1.06 (0.54-2.08)	↑
	Ethambutol	NR	0.94 (0.23-3.85)	–
	Isoniazid	3.46 (1.24-9.64)	2.64 (1.34-5.20)	↓
	Minocycline	2.41 (1.02-5.69)	2.69 (1.16-6.25)	↑

Duration	Drug	PS PRR (UB-LB)	PS & SS PRR (UB-LB)	△ PRR
	Nitrofurantoin	NR	2.03 (0.50-8.28)	–
	Rifampin	2.75 (1.23-6.15)	2.03 (0.92-4.46)	↓
	Sulfasalazine	0.47 (0.11-1.92)	0.42 (0.10-1.71)	↓
	Telithromycin	0.84 (0.41-1.69)	0.97 (0.49-1.91)	↑
2010-19	Amikacin	NR	0.62 (0.33-1.15)	–
	Clarithromycin	0.12 (0.07-0.20)	0.19 (0.12-0.28)	↑
	Erythromycin	0.54 (0.27-1.10)	0.28 (0.14-0.56)	↓
	Ethambutol	1.77 (0.79-3.96)	5.37 (4.45-6.48)	↑
	Isoniazid	7.17 (5.52-9.32)	5.47 (4.62-6.48)	↓
	Minocycline	0.89 (0.48-1.68)	0.93 (0.58-1.48)	↑
	Nitrofurantoin	1.56 (0.93-2.62)	1.45 (0.96-2.20)	↓
	Penicillin	NR	0.51 (0.19-1.37)	–
	Rifampin	4.65 (3.66-5.91)	3.95 (3.33-4.68)	↓
	Streptomycin	NR	1.46 (0.47-4.51)	–
	Sulfasalazine	0.28 (0.14-0.54)	0.06 (0.04-0.10)	↓
Quinolones vs No DILI				
2004-19	Amikacin	NR	2.63 (1.39-4.95)	–
	Ciprofloxacin	1.95 (1.30-2.91)	2.13 (1.59-2.84)	↑
	Levofloxacin	0.58 (0.38-0.90)	0.55 (0.40-0.76)	↓
	Moxifloxacin	1.47 (0.94-2.30)	0.99 (0.66-1.48)	↓

Duration	Drug	PS PRR (UB-LB)	PS & SS PRR (UB-LB)	△ PRR
	Ofloxacin	1.39 (0.34-5.62)	1.45 (0.64-3.26)	↑
	Penicillin	NR	2.40 (0.89-6.44)	–
	Streptomycin	NR	6.70 (2.15-20.89)	–
2004-09	Ciprofloxacin	2.34 (0.78-7.05)	2.10 (0.87-5.07)	↓
	Levofloxacin	0.58 (0.19-1.74)	0.78 (0.35-1.72)	↑
	Moxifloxacin	2.60 (1.06-6.40)	1.76 (0.87-3.56)	↓
2010-19	Amikacin	NR	2.74 (1.45-5.19)	–
	Ciprofloxacin	1.85 (1.21-2.81)	2.03 (1.50-2.74)	↑
	Levofloxacin	0.57 (0.36-0.91)	0.51 (0.35-0.73)	↓
	Moxifloxacin	1.49 (0.85-2.63)	0.90 (0.53-1.52)	↓
	Ofloxacin	2.20 (0.54-8.91)	1.96 (0.87-4.42)	↓
	Penicillin	NR	2.22 (0.82-5.97)	–
	Streptomycin	NR	6.27 (2.01-19.58)	–

NR: not reported as a primary suspect

Chapter 3 (ALF-SR)

Acute liver failure II: Systematic review of clinical trials

Chapter 3: Systemic quinolones and risk of acute liver failure II: Systematic review of clinical trials

Abstract

Background: Quinolones are a class with four generations of synthetic antibiotics characterized by a unique mechanism of action, broad spectrum, potent pharmacologic properties and reasonable safety profile. Their global and growing popularity has been accompanied by an increase in the emergence of antimicrobial resistance and occurrence of unexpected adverse reactions. Nevertheless, physicians continue to prescribe these drugs on an increasing scale, irrespective of the availability of other treatment alternatives.

Objective: To systematically review all clinical trials where a quinolone antibiotic was tested or used as a comparator to other drugs or drug combinations, for evidence on quinolones' association with ALF risk.

Methods: We examined 4 major bibliographic databases, 8 clinical trial registries, and major grey literature sources including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies. We also examined the bibliographies of publications selected for inclusion in our review for other relevant studies. PROSPERO registration number: CRD42020148742.

Results: We identified 1,370 original clinical trials conducted between 1974 and 2020, in many countries around the world, enlisting men and women from almost all

ethnicities, backgrounds, age groups and with different comorbidity burdens. Only two trials reported a single ALF case with each of gemifloxacin and moxifloxacin.
Conclusion: There is inadequate evidence from clinical trials to implicate quinolone antibiotics as a cause of acute liver failure.
Keywords: Quinolones; acute liver failure; clinical trials; systematic review

Introduction

Quinolones are synthetic antibiotics that continue to gain popularity on a global scale since they were introduced in the mid-1960s [1]. The popularity of quinolones may be attributed to their potency, broad spectrum, unique mechanism of action and strong pharmacologic profile relative to other antibiotic classes [2-8]. Despite the development of adverse events, emergence of resistance, and the availability of other treatment alternatives [2], this favored status persisted. Whereas many researchers consider quinolones as having a reasonable safety profile, with most adverse reactions being mild to moderate and self-limiting, some quinolones have been withdrawn from the market and others have sustained restricted usage advisories [8-11].

Acute liver failure (ALF) is a serious disease involving rapid, progressive and severe loss of hepatic cells without evidence of current or previous liver impairment [12-14]. While this loss is sometimes reversible, it is more likely to progress rapidly to patient death unless liver transplantation is carried out in a timely manner [12-14]. This loss of hepatic cell occurs within 4-6 weeks of a triggering factor [15-17]. These factors including viruses, bacteria, toxins, drugs, and herbal and nutritional supplements [12-14, 18-24]. In the US, a recent study reported ALF incidence between 1-6 per million every year, in

addition to encompassing 7% of liver-related transplants and 6% of liver-related deaths [15].

Drug induced liver injury (DILI) has been repeatedly reported as the most common cause of ALF in Europe and United States, while also representing the most common cause for drug withdrawal by regulatory agencies due to its life-threatening repercussions [12, 18, 20, 21, 24-27].

DILI is a diagnosis of exclusion and depends, due to absence of a credible gold standard, on physician judgment, careful medical and medication histories, and exclusion of all other possible risk factors [20-22, 27-29]. In 2014, the American College of Gastroenterology released their revised criteria for diagnosing DILI, with the hope of establishing a gold standard test for diagnosing this condition [30].

In the absence of solid evidence from clinical trials and pharmacoepidemiology studies, regulators such as FDA and EMA often use spontaneous adverse event and case reports to guide their safety-based responses, irrespective of the existence of solid evidence of causality [2, 31-43].

This review represents the second of three studies that examine the association of systemically administered quinolone antibiotics with the risk of acute liver failure, which focuses on examining results from clinical trials. The first part provides summary of evidence based on data mining of reports recorded in the US FDA adverse event reporting system (FAERS). The third part involves a nested case-control study based on a major US electronic health records database

Table 7: Four generations of quinolone antibotics

Generation	Quinolone Antibiotic
First	Nalidixic acid, cinoxacin, flumequine, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin
Second	Lomefloxacin, norfloxacin, ciprofloxacin, ofloxacin, fleroxacin, pefloxacin, rufloxacin
Third	Levofloxacin, sparfloxacin, temafloxacin, grepafloxacin, balofloxacin, pazufloxacin, tosufloxacin
Fourth	Moxifloxacin, gemifloxacin, trovafloxacin, gatifloxacin, clinafloxacin, garenoxacin, sitafloxacin, prulifloxacin, finafloxacin

Methods

Review strategy

We implemented a comprehensive, multi-step search strategy to identify original studies that examined the association between quinolone antibiotics with the risk of acute liver failure. The search was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and following the specific guidance provided by the Cochrane Collaboration [44].

The search strategy was designed and implemented between April 16-22, 2017, and updated on April 1-3, 2020 to identify all relevant original studies related to each of the 30 members of the quinolone class of antibiotics shown in Table 7.

We searched multiple bibliographic databases, clinical trial registries and major grey literature sources such as drug review networks and databases of pharmaceutical companies, relevant national and international agencies and international conference proceedings. Experts were consulted on all components of the review strategy and implementation. We also inspected the bibliographies of examined studies for additional relevant studies not already identified via the original search. This review has been registered in the international prospective register of systematic reviews PROSPERO under reference number CRD42020148742.

Criteria for considering studies for this review

This review focuses on the safety rather than efficacy of quinolone antibiotics. The outcome measure of interest is the number of cases with a de-novo diagnosis of acute liver failure within 30 days of systemic administration of a quinolone antibiotic in an otherwise liver disease-free individual.

Eligibility criteria for inclusion in this review comprise original clinical trials examining a single systemically-administered quinolone antibiotic compared to a placebo, another non-quinolone antibiotic or non-quinolone-containing antibiotic combination. Trials with multiple arms, which include a single quinolone on one arm and a placebo on one of the other arms, would be considered eligible.

Trials where participants had prior or existing liver impairment, trials testing topical/non-systemically administered quinolones, a combination of quinolones, or a combination of quinolones and other drugs, and trials testing efficacy of different doses of a quinolone antibiotic, or testing a quinolone against another quinolone were excluded from this review. Cross-over trials were also excluded to avoid any possible

carry-over effect from the initial intervention. Non-original studies, observational studies and trials where no results were available were also excluded. We enforced no restrictions on participants' age, sex, racial/ethnicity or any other background characteristics.

Search methods for identification of studies

Bibliographic databases searched included Medline (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present), EMBASE (Embase Classic + Embase 1947 to 2017 May 02), Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL (Cumulative Index to Nursing and Allied Health Literature).

Search terms included medical subject headings and text word search for quinolone antibiotics both as a class and as individual agents, in addition to acute liver failure as the outcome of interest. The search integrated a specialized search algorithm with reported high efficiency for identifying clinical trials in MEDLINE Ovid, EMBASE and CINAHL [45]. We also used another specialized algorithm for identifying adverse reactions [46] with the MEDLINE and EMBASE databases only. No language, time or other filters were used to limit the search output. A detailed description of the used search terms is given in Supplementary Material I. Complete listings of included studies, excluded studies and reason for exclusion are given in Supplementary Material II, III & IV, respectively.

A more extensive search was done for all clinical trials conducted on any of the quinolone antibiotics documented in any of the major international clinical trial registries, including the World Health Organization Clinical Trials Registry (ICTRN) and United

States Clinical Trials Database (Clinicaltrials.gov), as well as similar registries from the European Union, United Kingdom, Netherlands, Japan, China, South Korea, India, Iran, Australia and South Africa.

We also searched major grey literature sources including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies. Some relevant background publications were used to support this review process.

Duplicate screening of titles and abstracts (Level 1) and full-text examination (Level 2) were performed independently by two reviewers (MT and MH) to identify studies eligible for inclusion in the review, based on the predetermined eligibility criteria. Conflicts identified in each step were resolved via consensus between the reviewers or via a panel of senior scientists (FM, LB, DM, DK), prior to moving to the next step.

In the event where multiple publications report on an original study/trial, only the primary publication/record was assessed in the review. All studies which reported on, or have been indexed to a specific original study/trial, were listed under the original study/trial record. Maximum diligence was adopted to include all papers reporting on each of the included clinical trials. A complete listing of original studies and their reporting/indexed publications is included in Supplementary Material IV.

Data collection and analysis

We collated the references identified from all sources using EndNote [47] reference management application version 8.2, which was used to flag potential duplicates, with manual resolution employed to remove actual duplicates.

We used Review Manager application version 5.3.[48] to collate and classify all examined studies, tabulate the reasons for study exclusion, and compile the information required for generating the PRISMA flow diagram [49].

Data abstraction spreadsheets were developed using Microsoft Office Excel, and used to abstract the following information study (design, year, country), tested quinolone antibiotic (name, dose, route of administration, frequency, duration), control agent/group (type, name, dose, route of administration, frequency, duration), participant characteristics (total sample size, age, sex, race), comorbidities (prior liver conditions, diabetes, alcohol abuse), treatment period and follow-up (average, range, years), main result(s), and authors' reported conclusion. Reviewers' comments, if any, are also included.

Results

Flow of studies

The search strategy resulted in retrieval of 3,560 records, including 3,521 records from bibliographic databases and clinical trial registries, 30 records from the databases of pharmaceutical companies, and 1 record from an international conference. Electronic and manual de-duplication resulted in removal of 774 records. An additional 260 non-quinolone-related studies were excluded, leaving 2,526 studies for full-text examination. Examined studies spanned across 5 decades (1974 – 2020), peaking between 2008 – 2012 (Figure 2). These studies were conducted in many countries around the world, enlisting participants from all sexes, ethnicities, age groups and with different types and levels of comorbidities

Whereas only 2 eligible studies reported on the outcome of interest, acute liver failure, 2,709 studies were excluded for different reasons. A summary of the reasons for exclusion in provided in Table 2, with details given in a Supplementary Materials III & IV. A detailed PRISMA flow diagram [49] is shown in Figure 3.

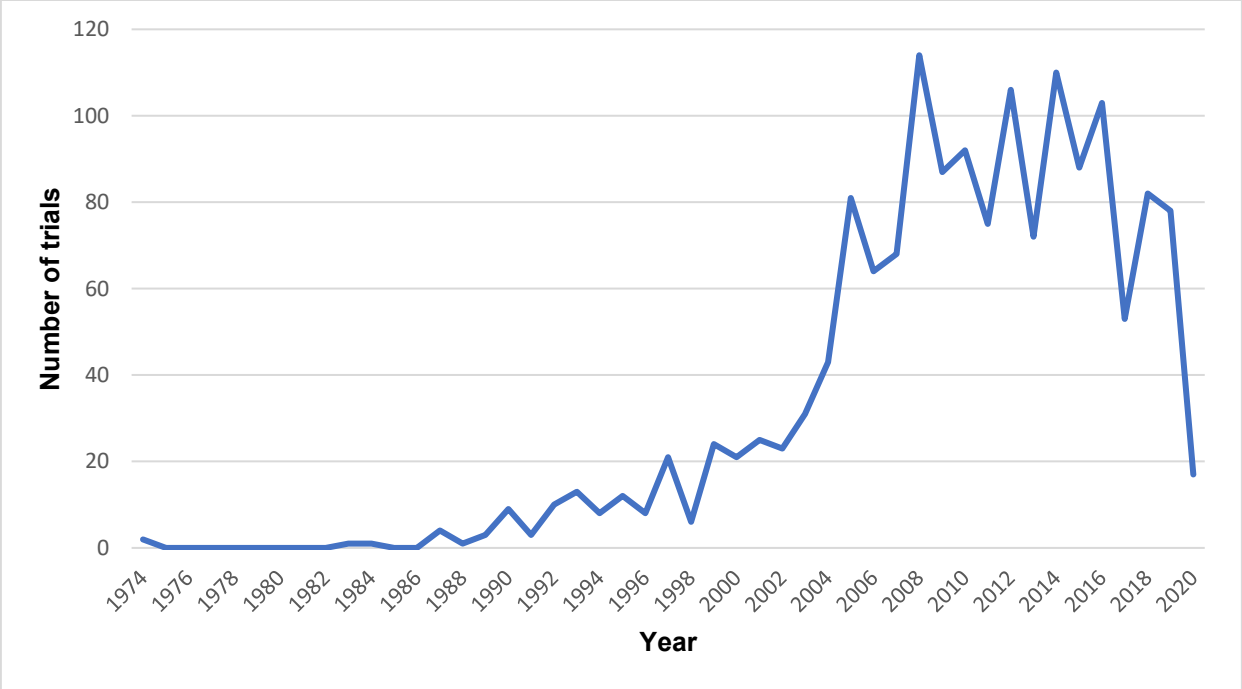


Figure 2: Temporal distribution of clinical trials on quinolone antibiotics

Characteristics of included studies

Among all 1,555 original quinolone-related clinical trials, only 2 trials [50, 51] clearly reported on the incidence of acute liver failure in participants who received a systemically administered mono-quinolone antibiotic, with no history of apparent, current or prior liver conditions/diseases. Accordingly, we were unable to retain enough number of studies to conduct a quantitative analysis. In a 2004 multicenter, randomized, double-blinded trial, 1 case of hepatocellular damage was reported in the gemifloxacin group compared to 2 cases in the amoxicillin/clavulanate (control) group [50].

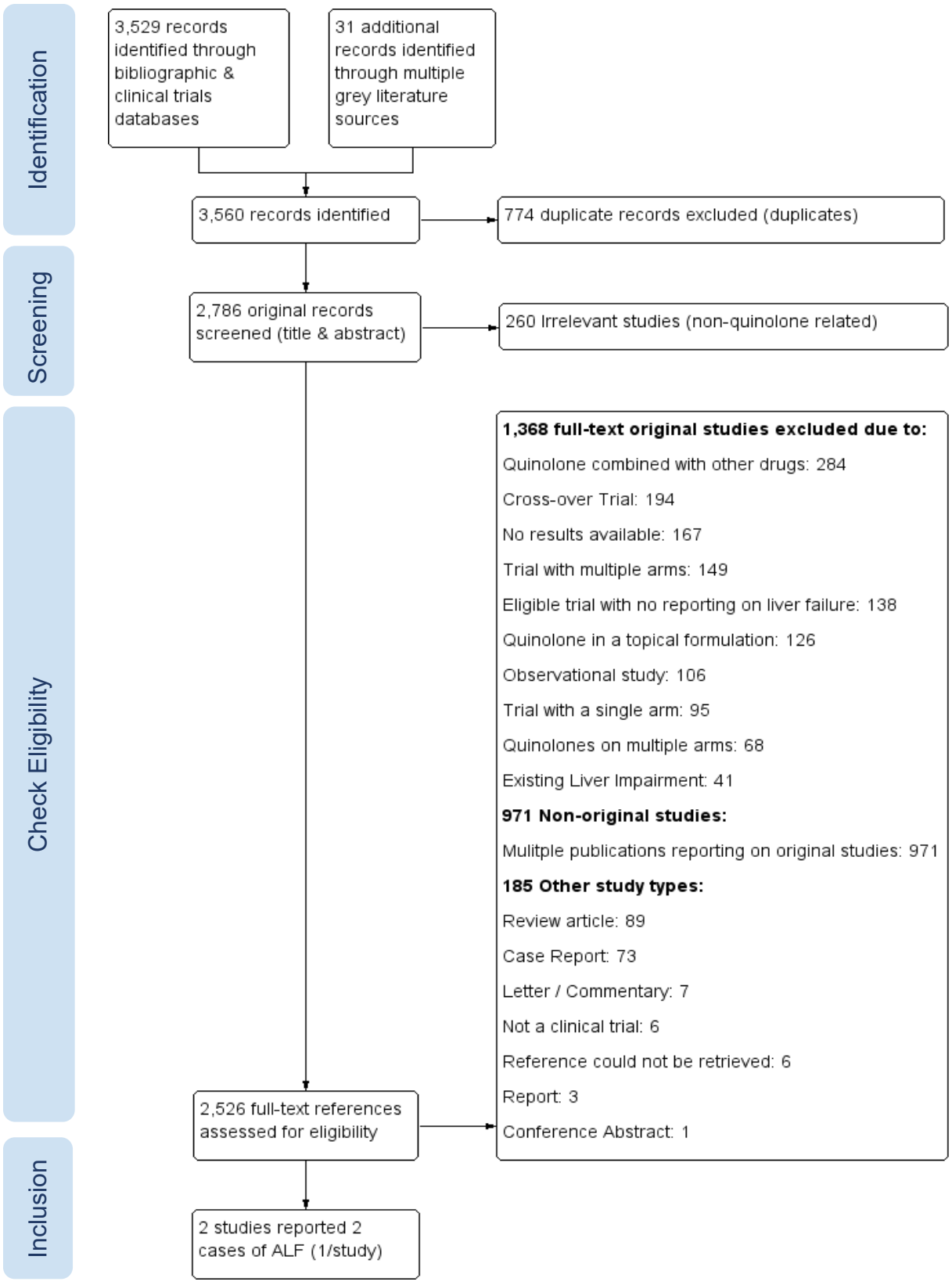


Figure 3: PRISMA flow diagram for studies conducted on/using quinolone antibiotics

Another 2007 prospective, randomized, double-dummy, double-blind, multicenter, non-inferiority trial was conducted in 52 centers in Argentina, Belgium, Bulgaria, Estonia, France, Germany, Greece, Israel, Latvia, Lithuania, Romania, Russia, South Africa, and Spain [51]. This study reported one case of acute liver failure in the moxifloxacin group, compared to none in the ertapenem group. Characteristics of included studies are summarized in Table 8. Further details on these studies, including the Cochrane risk of bias tables, are included in Supplementary Material II.

Summary of excluded studies

Almost all the examined studies (2,524 out of 2,526) were excluded from any further qualitative or quantitative analysis based on the predetermined inclusion criteria. Whenever a trial had more than one reason for exclusion, we reported on the most compelling reason. A summary list of the reasons for exclusion of these trials is shown in Table 9. A detailed listing of the full citations of all excluded studies is given in Supplementary Material III. There were 138 other eligible trials with no reporting on the occurrence of ALF in the systemic mono-quinolone group arm. Results from an additional 167 trials were not available at the time of completion of this review.

Table 8: Characteristics of studies reporting on acute liver failure

Study Name duration, location funding	**Study Design, Sample size** completed study/group total **Follow up**	**Intervention** dose, route, frequency, duration	**Participant Characteristics**	**Age**: mean (SD), [range] **Sex**: number (%) **Race:** number (%)	**Prior liver conditions, alcohol abuse, diabetes**	**ALF** number, (%) Type	**Authors' reported conclusion**
Leophonte 2004 [50] September 1998 - July 1999,	Multicenter, double-blind, randomized, active controlled, parallel-group	**Gemifloxacin** 320 mg, oral, once/day (qd), 7 days	Persons 18 years or older, diagnosed with bacterial community acquired	**Gemifloxacin:** 53.3 (20.4) [18–97] years Men: 107 (64.1%) Caucasian: 138 (82.6%)	Not reported	**Gemifloxacin:** 1 (1%) Hepatocellular damage:	Gemifloxacin is well tolerated and is an effective alternative

	trial	**Amoxicillin/Clavulanic Acid** 1 g/125 mg, oral, 3 times/day (tid), 10 days	pneumonia (CAP), and showing fever and at least 2 of the following: • New or increased cough, • Purulent sputum or a change in sputum characteristics, • Rales and/or evidence of pulmonary consolidation, or • Dyspnea	**Amoxicillin/Clavulanic Acid**: 55.3 (19.8) Range: 18–87 Men: 96 (62.7%) Caucasian: 120 (78.4%)	**Amoxicillin/Clavulanic Acid:** 2 (1%) Hepatocellular damage:	to amoxicillin/ clavulanic acid and offers a more convenient dosing regimen
102 centers in France, Poland and South Africa Funding not reported	**Gemifloxacin**:134/167 **Amoxicillin/Clavulanic Acid**: 120/153 **Follow up:** 24-30 days after end of treatment					

NCT00492726 **2007** [51] July 2006 - February 2009 52 centers in Argentina, Belgium, Bulgaria,	Prospective, randomised, double-dummy, double-blind, multicenter, non-inferiority study **Moxifloxacin:** 408/430	**Moxifloxacin:** 400 mg IV once daily (qd) placebo for 30 min immediately followed by moxifloxacin 400 mg in 250 mL over 60 min every 24 h 5–14 days	Patients who are ≥18 years with a confirmed or suspected complicated intraabdominal infection (cIAI requiring surgery and parenteral antibiotic therapy	**Moxifloxacin:** 46.7 (17.8) Men: 218 (61.9 %) Race: Not reported	Prior liver conditions: No history of severe hepatic insufficiency (Child–Pugh C) Alcohol & diabetes:	**Moxifloxacin:** 1 (0.25%) Acute liver failure	Hepatotoxicity and cardiac toxicity were not observed witheither moxifloxacin or

Estonia, France, Germany, Greece, Israel, Latvia, Lithuania, Romania, Russia, South Africa, and Spain Bayer HealthCare AG	Ertapenem: 380/394 **Follow up:** 21-28 days after end of treatment	**Ertapenem:** 1 gm, IV once daily (qd), 1.0 gm in 50 mL over 30 min, followed by placebo for 60 min every 24 h, for 5–14 days	**Ertapenem:** 46.1 (17.7) Men: 231 (66.6 %) Race: not reported	Not reported	**Ertapenem:** 0 (0.0%) Acute liver failure:	ertapenem therapy.

Table 9: Reasons for study exclusion

Rationale for Exclusion	No. of Studies
Eligible clinical trials with no reporting on acute liver failure	**138**
Original clinical trials excluded	**1,230**
Quinolone combined with other drugs	284
Cross-over trial	194
No results available	167
Trial with multiple arms	149
Quinolone in a topical formulation	126
Observational study	106
Trial with a single arm	95
Quinolones on multiple arms	68
Current or prior liver impairment	41
Other study designs excluded	**185**
Review article	89
Case report / case series	73
Letter / commentary	7
Not a clinical trial	6
Reference could not be retrieved	6
Report	3
Conference abstract	1
All examined original studies	**1,553**

Discussion

Interpretation of findings

Acute liver failure is a serious adverse drug reaction that develops quickly, signaling rapid deterioration of liver function, and requiring immediate medical attention, predominantly, if not exclusively, in hospital and/or emergency room settings. Although ALF may resolve in some cases, this potentially fatal condition is often severe enough to mandate timely liver transplantation. Only 2 original clinical trials reported a single case of acute liver failure, one with gemifloxacin [50] and one with moxifloxacin [51]. This result constitutes an insufficient evidence to implicate systemically administered quinolone antibiotics as being associated with acute liver failure.

Prior reviews

To the best of our knowledge, this is the first systematic review that examined all original studies reporting on clinical trials that tested any of the quinolone antibiotics, in relation to their association with the risk of acute liver failure.

Strengths and limitations of review

This review covers all publicly available original, peer-reviewed publications, as well as other grey literature sources for unpublished clinical trials conducted with quinolone antibiotics. Clinical trials represent the most rigorous assessment of human drug safety, that is used to examine the association between a specific drug(s) and specific adverse reactions (ADRs) [35, 52].

However, clinical trials may be subject to a lack of representativeness since the characteristics of the selected participants will not mirror all possible demographics, risk factors, and underlying determinants in the general population who will be using the approved drug under real-life situations [35, 39, 52-54]. By design, clinical trials might miss rare ADRs such as ALF due to the limited number of participants [35, 39, 52, 55, 56].

Conclusion

As acute liver failure (ALF) is a serious medical emergency that requires immediate medical attention, cases with suspected diagnosis cannot be handled in physician offices and must be immediately admitted to a hospital for further assessment and/or intervention. Although it might not have been one of the outcomes of interest in a clinical trial, any occurrence of ALF in a trial participant cannot go unnoticed. In the event of a case of ALF, treatment must be stopped and the patient managed immediately, while reporting the incident to the relevant regulatory authorities. The unequivocal lack of reporting on incidence of quinolone-related ALF by almost all trials from 1974 to date, across different jurisdictions, enlisting participants from both sets, almost all ethnicities, backgrounds, age groups and with/without different comorbidities, leaves little room for any undetected/unreported incidence of quinolone-associated ALF.

The absence of an abundance of cases of ALF in the clinical trials included in the present review, while reassuring, does not rule out the possibility of an increased risk in the general public under real world conditions of use. Observational Pharmacovigilance studies based on large and diverse patient populations are needed to confidently confirm or reject an association between use of quinolones and increased risk of acute liver failure.

Author contributions

The primary author, Mohamed Taher, designed and implemented the review strategy including search methodology, design of study screening and data abstraction forms, reference collation and full-text acquisition, screening and examination of the identified references, data abstraction and drafting of this manuscript. Mohamed Habsah independently assessed all studies examined in this review. Lise Bjerre, Franco Momoli, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the review design and implementation, as well as critical review and approval of the manuscript.

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Declaration of interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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Supplementary Material – Chapter 3

Supplementary Material I: The literature search strategy

Medline (Ovid)

1. quinolones/
2. quinolones.tw.
3. 4-quinolones/
4. 4-quinolones.tw.
5. fluoroquinolones/
6. fluoroquinolones.tw.
7. nalidixic acid/
8. nalidixic acid.tw.
9. cinoxacin/
10. cinoxacin.tw.
11. flumequine.tw.
12. oxolinic acid/
13. oxolinic acid.tw.
14. piromidic acid/
15. piromidic acid.tw.
16. rosoxacin.tw.
17. lomefloxacin.tw.
18. norfloxacin/
19. norfloxacin.tw.
20. enoxacin/
21. enoxacin.tw.
22. ciprofloxacin/
23. ciprofloxacin.tw.
24. ofloxacin/
25. ofloxacin.tw.
26. fleroxacin/
27. fleroxacin.tw.
28. pefloxacin/
29. pefloxacin.tw.
30. rufloxacin.tw.
31. levofloxacin/
32. levofloxacin.tw.
33. sparfloxacin.tw.
34. temafloxacin.tw.
35. grepafloxacin.tw.
36. balofloxacin.tw.
37. pazufloxacin.tw.

38. tosufloxacin.tw.
39. moxifloxacin.tw.
40. gemifloxacin.tw.
41. trovafloxacin.tw.
42. gatifloxacin.tw.
43. clinafloxacin.tw.
44. garenoxacin.tw.
45. sitafloxacin.tw.
46. prulifloxacin.tw.
47. finafloxacin.tw.
48. or/1-47
49. Aripiprazole.tw.
50. 48 not 49
51. (ae or co or de).fs. or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.
52. Liver Failure/
53. liver failure.tw.
54. hepatic failure.tw.
55. Liver Failure, Acute/
56. acute liver failure.tw.
57. acute hepatic failure.tw.
58. hepatic necrosis.tw.
59. Massive Hepatic Necrosis/
60. massive hepatic necrosis.tw.
61. Hepatic Insufficiency/
62. hepatic insufficiency.tw.
63. severe liver impairment.tw.
64. severe hepatic impairment.tw.
65. liver dysfunction.tw.
66. hepatic dysfunction.tw.
67. fulminant liver failure.tw.
68. severe hepatic impairment.tw.
69. "Chemical and Drug Induced Liver Injury"/
70. drug-induced Liver Injury.tw.
71. or/52-70
72. Randomized Controlled Trials as Topic/
73. randomized controlled trial/
74. Random Allocation/
75. Double Blind Method/
76. Single Blind Method/
77. clinical trial/
78. clinical trial, phase i.pt.

79. clinical trial, phase ii.pt.
80. clinical trial, phase iii.pt.
81. clinical trial, phase iv.pt.
82. controlled clinical trial.pt.
83. randomized controlled trial.pt.
84. multicenter study.pt.
85. clinical trial.pt.
86. exp Clinical Trials as topic/
87. or/72-86
88. (clinical adj trial$).tw.
89. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
90. PLACEBOS/
91. placebo$.tw.
92. randomly allocated.tw.
93. (allocated adj2 random$).tw.
94. or/88-93
95. 87 or 94
96. case report.tw.
97. letter/
98. historical article/
99. or/96-98
100. 95 not 99
101. 50 and 51
102. 50 and 71
103. 50 and 51 and 71
104. 50 and 51 and 71 and 100
105. 50 and 71 and 100

EMBASE

1. quinolone derivative/
2. 4 quinolone derivative/
3. quinolones.tw.
4. fluoroquinolones.tw.
5. nalidixic acid/
6. nalidixic acid.tw.
7. cinoxacin/
8. cinoxacin.tw.
9. flumequine/
10. flumequine.tw.
11. oxolinic acid/
12. oxolinic acid.tw.
13. piromidic acid/
14. piromidic acid.tw.
15. rosoxacin/
16. rosoxacin.tw.
17. lomefloxacin/
18. lomefloxacin.tw.
19. norfloxacin/
20. norfloxacin.tw.
21. enoxacin/
22. enoxacin.tw.
23. ciprofloxacin/
24. ciprofloxacin.tw.
25. ofloxacin/
26. ofloxacin.tw.
27. fleroxacin/
28. fleroxacin.tw.
29. pefloxacin/
30. pefloxacin.tw.
31. rufloxacin/
32. rufloxacin.tw.
33. levofloxacin/
34. levofloxacin.tw.
35. sparfloxacin/
36. sparfloxacin.tw.
37. temafloxacin/
38. temafloxacin.tw.
39. grepafloxacin/
40. grepafloxacin.tw.
41. balofloxacin/
42. balofloxacin.tw.
43. pazufloxacin/
44. pazufloxacin.tw.
45. tosufloxacin/

46. tosufloxacin.tw.
47. moxifloxacin/
48. moxifloxacin.tw.
49. gemifloxacin/
50. gemifloxacin.tw.
51. trovafloxacin/
52. trovafloxacin.tw.
53. gatifloxacin/
54. gatifloxacin.tw.
55. clinafloxacin/
56. clinafloxacin.tw.
57. garenoxacin/
58. garenoxacin.tw.
59. sitafloxacin/
60. sitafloxacin.tw.
61. prulifloxacin/
62. prulifloxacin.tw.
63. finafloxacin/
64. finafloxacin.tw.
65. or/1-64
66. Aripiprazole.tw.
67. 65 not 66
68. (ae or co or de).fs. or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.
69. liver failure/
70. liver failure.tw.
71. hepatic failure.tw.
72. liver insufficiency.tw.
73. hepatic insufficiency.tw.
74. liver dysfunction/
75. liver dysfunction.tw.
76. hepatic dysfunction.tw.
77. acute liver failure/
78. acute liver failure.tw.
79. acute hepatic failure.tw.
80. fulminant hepatic failure/
81. fulminant hepatic failure.tw.
82. fulminant liver failure.tw.
83. severe hepatic impairment/
84. severe hepatic impairment.tw.
85. severe liver impairment.tw.
86. or/69-85
87. Clinical trial/
88. Randomized controlled trial/
89. Randomization/
90. Double blind procedure/

91. Crossover procedure/
92. Placebo/
93. Randomi?ed controlled trial$.tw.
94. Rct.tw.
95. Random allocation.tw.
96. Randomly allocated.tw.
97. Allocated randomly.tw.
98. (allocated adj2 random).tw.
99. Single blind$.tw.
100. Double blind$.tw.
101. ((treble or triple) adj blind$).tw.
102. Placebo$.tw.
103. Prospective study/
104. or/87-103
105. Case study/
106. Case report.tw.
107. Abstract report/ or letter/
108. or/105-107
109. 104 not 108
110. 67 and 68
111. 67 and 68 and 86
112. 67 and 86
113. 67 and 86 and 109
114. 67 and 68 and 86 and 109

Cochrane Central Register of Controlled Trials

1. Quinolones/
2. quinolones.tw.
3. 4-Quinolones/
4. 4-quinolones.tw.
5. Fluoroquinolones/
6. fluoroquinolones.tw.
7. Nalidixic acid/
8. nalidixic acid.tw.
9. Cinoxacin/
10. cinoxacin.tw.
11. flumequine.tw.
12. Oxolinic acid/
13. oxolinic acid.tw.
14. Piromidic acid/
15. piromidic acid.tw.
16. rosoxacin.tw.
17. lomefloxacin.tw.
18. Norfloxacin/
19. norfloxacin.tw.
20. Enoxacin/
21. enoxacin.tw.
22. Ciprofloxacin/
23. ciprofloxacin.tw.
24. Ofloxacin/
25. ofloxacin.tw.
26. Fleroxacin/
27. fleroxacin.tw.
28. Pefloxacin/
29. pefloxacin.tw.
30. rufloxacin.tw.
31. Levofloxacin/
32. levofloxacin.tw.
33. sparfloxacin.tw.
34. temafloxacin.tw.
35. grepafloxacin.tw.
36. balofloxacin.tw.
37. pazufloxacin.tw.
38. tosufloxacin.tw.
39. moxifloxacin.tw.
40. gemifloxacin.tw.
41. trovafloxacin.tw.
42. gatifloxacin.tw.
43. clinafloxacin.tw.
44. garenoxacin.tw.
45. sitafloxacin.tw.

46. prulifloxacin.tw.
47. finafloxacin.tw.
48. or/1-47
49. aripiprazole.tw.
50. 48 not 49
51. Liver Failure/
52. liver failure.tw.
53. hepatic failure.tw.
54. Liver Failure, Acute/
55. acute liver failure.tw.
56. acute hepatic failure.tw.
57. fulminant liver failure.tw.
58. fulminant hepatic failure.tw.
59. severe liver impairment.tw.
60. severe hepatic impairment.tw.
61. liver necrosis.tw.
62. hepatic necrosis.tw.
63. Hepatic Insufficiency/
64. hepatic insufficiency.tw.
65. liver insufficiency.tw.
66. liver dysfunction.tw.
67. hepatic dysfunction.tw.
68. or/51-67
69. 50 and 68

CINAHL (Cumulative Index to Nursing and Allied Health Literature)

1. (MM "Antiinfective Agents, Quinolone+") OR "quinolones"
2. (MM "Antiinfective Agents, Fluoroquinolone+") OR "fluoroquinolones"
3. "nalidixic acid"
4. (MM "Cinoxacin") OR "cinoxacin"
5. "flumequine"
6. "oxolinic acid"
7. "piromidic acid"
8. "rosoxacin"
9. "lomefloxacin"
10. (MM "Norfloxacin") OR "norfloxacin"
11. (MM "Enoxacin") OR "enoxacin"
12. (MM "Ciprofloxacin") OR "ciprofloxacin"
13. (MM "Ofloxacin") OR "ofloxacin"
14. "fleroxacin"
15. "pefloxacin"
16. "rufloxacin"
17. "levofloxacin"
18. "sparfloxacin"
19. "temafloxacin"
20. "grepafloxacin"
21. "balofloxacin"
22. "pazufloxacin"
23. "tosufloxacin"
24. "moxifloxacin"
25. "gemifloxacin"
26. (MM "Trovafloxacin+") OR "trovafloxacin"
27. (MM "Alatrofloxacin")
28. "gatifloxacin"
29. "clinafloxacin"
30. "garenoxacin"
31. "sitafloxacin"
32. "prulifloxacin"
33. "finafloxacin"
34. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
35. (MM "Liver Failure+") OR "liver failure"
36. (MM "Liver Failure, Acute+") OR "acute liver failure"
37. "liver dysfunction"
38. "liver impairment"
39. S35 OR S36 OR S37 OR S38
40. S34 AND S39
41. S34 AND S39 AND S51

Other sources

Other sources include: World Health Organization Clinical Trials Registry (ICTRN), United States Clinical Trials Database (ClinicalTrials.gov). Additionally, major grey literature sources were searched including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies. Names of the individual quinolone antibiotics were the only terms used to search these resources to ensure inclusivity of all possible studies that examined quinolones for all outcomes including those other than the outcome of interest for this current review.

Characteristics of included studies

Leophonte 2004

Study characteristics

Trial	Study	Leophonte, P., File, T., & Feldman, C. (2004). Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. Respir Med, 98(8), 708-720. *[Other: 0954-6111]*
	Year	September 1998 - July 1999
	Design	multicenter, double-blind, randomized, active controlled, parallel-group trial
	Country	102 centers in France, Poland and South Africa.
	Funding	NR
Tested quinolone antibiotic	Quinolone	Gemifloxacin
	Dose	320 mg
	Route	oral
	Frequency	once/day
	Duration	7 days
Control	Type	antibiotic
	Name	amoxicillin/clavulanic acid
	Dose	1 g/125 mg
	Route	oral
	Frequency	3 times/ day
	Duration	10 days
Participant	Sample size (completed/ original)	254 patients completed the study: • Gemifloxacin gp:134/167 • Amoxicillin/clavulanate gp: 120/153
	characteristics	Patients => 18 years diagnosed with bacterial community acquired pneumonia (CAP), with fever and at least two of the following signs and symptoms: new or increased cough, purulent sputum or a change in sputum characteristics, rales and/or evidence of pulmonary consolidation, or dyspnea.
	Age (yrs.)	Gemifloxacin: • Mean (sd): 53.3 (20.4) • Range 18–97 Amoxicillin/clavulanate: • Mean (sd): 55.3 (19.8) • Range: 18–86

	Sex	• Gemifloxacin: male 107 (64.1%) • amoxicillin/clavulanate: male 96 (62.7%)
	Race	• Gemifloxacin: Caucasian: 138 (82.6%) • Amoxicillin/clavulanate: Caucasian 120 (78.4%)
Exclusion	Current condition	• Allergy or severe adverse reactions to carboxyquinolone derivatives, penicillin or other beta-lactam derivatives; pregnancy or lactating • History of tendonitis with fluoroquinolones; phenylketonuria or sensitivity to aspartame; severe respiratory tract infections requiring parenteral antimicrobial therapy; pretherapy • Patients with hospital-acquired or aspiration pneumonia; patients with localized bronchial obstruction or a history of post-obstructive pneumonia • Patients with cystic fibrosis, active tuberculosis, bronchiectasis, or active pulmonary malignancies or any other complicating infection or disease that would compromise treatment evaluation of the study medication • Evidence of significant liver or renal impairment • Concomitant antibacterial agent with a spectrum of activity similar to the study drugs • History of immunocompromising condition • Concomitant sucralfate, probenecid or systemic steroids • Previous therapy with a systemic antibiotic for more than 24 h prior to enrollment.
	Prior liver conditions	No history of significant liver impairment
	Diabetes	NR
	Alcohol abuse	NR
Follow-up	Range	24-30 days
Main result(s)		Hepatocellular damage: • Gemifloxacin group: 1 (1%) • Amoxicillin/ clavulanate group: 2 (1%)
Authors' reported conclusion		Gemifloxacin is well tolerated and is an effective alternative to amoxicillin/clavulanate and offers a more convenient dosing regimen

Authors' comments	• Premature discontinuation: mainly due to adverse events (gemifloxacin: 9.6%; amoxicillin/clavulanate: 9.8%). • Poor compliance, ambiguous clinical outcome, or meeting exclusion criteria; a further 71 patients (39 gemifloxacin; 32 amoxicillin/clavulanate) • A total of 185 patients (95 in the gemifloxacin group and 90 in the amoxicillin/clavulanate group) were excluded from the Bacteriology ITT population as they did not have at least one respiratory pathogen identified at screening. • 135 patients (72 in the gemifloxacin group and 63 patients in the amoxicillin/clavulanate group comprised the Bacteriology ITT population. • 103 patients with a pre-therapy organism identified at pre-therapy were valid for the efficacy analysis (54 in the gemifloxacin group, 49 in the amoxicillin/clavulanate group). These patients comprise the Bacteriology PP population.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Blinding of participants and	Low risk	**Quote:** "double-blind, randomized, active controlled, parallel-group trial"

personnel (performance bias)		**Comment:** Probably done
Blinding of outcome assessment (detection bias)	Low risk	**Quote:** "double-blind, randomized, active controlled, parallel-group trial" **Comment:** Probably done
Incomplete outcome data (attrition bias)	Low risk	**Gemifloxacin gp** · 168 participants were randomized to this group · 167 participants (99%) comprised the intent-to-treat (ITT) population · 1 participant did not receive the first dose and was excluded from the ITT population · 134 participants completed the study · 9.6% of participants have prematurely discontinued the trial due to adverse reactions · Additional 39 participants were excluded from the Clinical PP population as a result of poor compliance with the study medication or visits, treatment with another systemic antibiotic for concurrent illnesses, or an undeterminable clinical outcome · 95 participants were excluded from the Bacteriology ITT population as they did not have at least one respiratory pathogen identified at screening · The remaining 72 participants comprised the Bacteriology ITT population · 54 participants with a pre-therapy identified organism comprised the Bacteriology PP population and were valid for the efficacy analysis. Exclusion from this analysis was determined by the same reasons mentioned with the clinical PP analysis. **Amoxicillin/clavulanate group**

		· 156 participants were randomized to this group · 153 participants (98%) comprised the intent-to-treat (ITT) population · 3 participants did not receive the first dose and was excluded from the ITT population · 120 participants completed the study · 9.8% of participants have prematurely discontinued the trial due to adverse reactions · Additional 32 participants were excluded from the Clinical PP population · 90 participants were excluded from the Bacteriology ITT population · The remaining 63 participants comprised the Bacteriology ITT population · 49 participants with a pre-therapy identified organism comprised the Bacteriology PP population **Comment:** Probably no loss of outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’.
Other bias	Unclear risk	

NCT00492726 2007

Study characteristics

Trial	Study	**Original Record:** NCT00492726. (2007). A prospective, randomized, double-dummy, double-blind, multicenter trial comparing the safety and efficacy of intravenous (IV) moxifloxacin 400 mg IV QD 24 hours to that of ertapenem 1.0 g IV QD 24 hours for 5 to 14 days for the treatment of subjects with complicated intra-abdominal infections (PROMISE study). In Therapy of Complicated Intra-Abdominal Infections With Moxifloxacin or Ertapenem. [Other: Trial ID: 11976] **Publications reporting on this study** De Waele, J.; Tellado, J.; Alder, J.; Reimnitz, P.; Jensen, M.; Hampel, B.; Arvis, P. Randomised clinical trial of moxifloxacin versus ertapenem in complicated intra-abdominal infections: results of the PROMISE study. International Journal of Antimicrobial Agents 2013;41(1):57-64.
	Year	2007
	Design	Prospective, randomised, double-dummy, double-blind, multicenter, non-inferiority study
	Country	52 centers in Argentina, Belgium, Bulgaria, Estonia, France, Germany, Greece, Israel, Latvia, Lithuania, Romania, Russia, South Africa, and Spain
	Funding	Bayer HealthCare AG
Tested quinolone antibiotic	Quinolone	Moxifloxacin (Avelox®, BAY12-8039)
	Dose	400 mg once daily
	Route	Intravenous
	Frequency	Participants received placebo for 30 min immediately followed by moxifloxacin 400 mg in 250 mL over 60 min every 24 h
	Duration	5–14 days
Control	Type	Antibiotic
	Name	Ertapenem
	Dose	1 gm once daily
	Route	Intravenous

	Frequency	Participants received ertapenem 1.0 gm in 50 mL over 30 min followed by placebo for 60 min every 24 h
	Duration	5–14 days
Participant	Total sample size	• Moxifloxacin: 408/430 • Ertapenem: 380/394
	characteristics	Patients who are ≥18 years with a confirmed or suspected complicated intraabdominal infections (cIAI requiring surgery and parenteral antibiotic therapy
	Age (yrs.)	• Moxifloxacin: 46.7 (17.8) • Ertapenem: 46.1 (17.7)
	Sex	• Moxifloxacin: male: 218 (61.9 %) • Ertapenem: male: 231 (66.6 %)
	Race	• Not reported
Exclusion	Current condition	• hypersensitivity to study drugs, pregnancy or breastfeeding, fluoroquinolone-related tendon disorder, clinically relevant cardiac conditions or QT interval prolonging drugs, severe hepatic insufficiency (Child–Pugh C), creatinine clearance ≤30 mL/min/1.73 m2, need for other systemic antibacterial therapy or use for >24 h within 7 days prior to randomisation, indwelling peritoneal catheter or vascular shunt, pre-existing ascites and presumed spontaneous bacterial peritonitis, perforation of the stomach or duodenum (duration <24 h), small or large bowel perforation due to trauma lasting <12 h, all pancreatic processes or an IAI secondary to pancreatitis, liver or splenic abscess, transmural bowel ischaemia or necrosis without perforation or established peritonitis or abscess, non-perforated cholecystitis, acute cholangitis, non-perforated appendicitis, requirement for antibiotic irrigations of the abdominal cavity or surgical wound, treatment with ‘open abdomen’ or marsupialisation, or multiple planned relaparotomies, infections of the female genital tract, perinephric infections, septic shock requiring vasopressors (>12 h), • Known underlying fatal disease (death expected within 6 months), immunological compromise (including drug-induced), and body mass index ≥45 kg/m2.

	Prior liver conditions	No history of severe hepatic insufficiency (Child–Pugh C)
	Diabetes	Not reported
	Alcohol abuse	Not reported
Follow-up	Range	21-28 days after end of treatment
Main result(s)		Acute liver failure: • Moxifloxacin:1 (0.25%) • Ertapenem: 0 (0.0%)
Authors' reported conclusion		Hepatotoxicity and cardiac toxicity were not observed with either moxifloxacin or ertapenem therapy.
Comments		Publication reporting on study (De Waele 2013) did not report on the incidence of 1 case of acute liver failure and 1 case of portal vein thrombosis (as documented on the trial record on ClinicalTrials.Gov)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation code was generated by the Department of Biometry at Bayer HealthCare AG. Investigators called an interactive voice response system for treatment group assignment." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Blinding of participants and personnel (performance bias)	Low risk	Quote:"randomized, double-dummy, double-blind, multicenter, non-inferiority study" Comment: probably done

Blinding of outcome assessment (detection bias)	Low risk	Quote:"randomized, double-dummy, double-blind, multicenter, non-inferiority study" Comment: probably done
Incomplete outcome data (attrition bias)	Low risk	Moxifloxacin group: 410 started the trial, 387 continued until end of treatment, and 360 completed the follow up. Participants who did not complete the treatment in the moxifloxacin gp were 50/410: adverse event (10), death (7), lack of efficacy (0), lost to follow-up (27), physician decision (0), withdrawal by subject (6), and non-compliance with study medication (0). Control group: 394 started the trial, 377 continued until end of treatment, and 358 completed the follow up. Participants who did not complete the treatment in the moxifloxacin gp were 36/394: adverse event (6), death (2), lack of efficacy (2), lost to follow-up (19), physician decision (1), withdrawal by subject (3), and non-compliance with study medication (3). Comment: Probably no loss of outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’.
Other bias	Unclear risk	

Supplementary Material III:

Reasons for study exclusion

(sorted by reason for exclusion)

Case reports

1. Airey 2003
2. Alan 2011
3. Alcalde 1995
4. Alegre 1990
5. Amitrano 1992
6. Assy 2007
7. Barcena 2005
8. Bataille 2002
9. Bhagirath 2008
10. Bjornsson 2000
11. Blum 1991
12. Bussieres 1995
13. Carrascosa 2009
14. Chen 2000
15. Cheung 2004
16. Çoban 2005
17. Coelho 2011
18. Coleman 2002
19. Colucci 2012
20. Contreras 2001
21. Davoren 1993
22. Elliott 2016
23. Figueira-Coelho 2010
24. Franco 2009
25. Fuchs 1994
26. Garcia 2014
27. Garcia-Aparicio 2010
28. Gauffre 1997
29. Goertz 2010
30. Goetz 2003
31. Gonzalez 2000
32. Grassmick 1992
33. Gulen 2015
34. Hautekeete 1995a
35. Heluwaert 2003
36. Henann 2001
37. Hofer 1992
38. Hsu 2014
39. Idilman 2006
40. Karim 2001
41. Khan 2006
42. Kilincalp 2012
43. Lazarczyk 2001
44. Lee 2015
45. Levine 2014
46. Li 2015
47. Lopez-Navidad 1990
48. Lucena 2000
49. Marra 2004
50. Miftode 2008
51. Mitra 2009
52. Nicholson 2002
53. Nisly 2007
54. Nori 2004
55. Odeh 1992
56. Palmero 2013
57. Pubill-Fondevila 2013
58. Puerto 2010
59. Rached-Mohassel 1974
60. Ravenscroft 2005
61. Ridzon 1997
62. Roberts 2011
63. Romero-Gomez 1999
64. Scherer 2005
65. Schwalm 2003

66. Soto 2002
67. Spahr 2001
68. Titos-Arcos 2011
69. Tunuguntla 2005
70. Vazquez 2008
71. Villeneuve 1995
72. Zaidi 2003
73. Zimpfer 2004

B. Conference abstract

74. Prescott 2006

C. Cross-over trial

75. ACTRN12609000544279 2009
76. ACTRN12616001558415 2016
77. Biering-Sorensen 1994
78. CTRI/2009/091/000332 2009
79. CTRI/2012/03/002497 2012
80. EUCTR2008-007647-14-FI 2008
81. EUCTR2009-011044-20-GB 2009
82. EUCTR2013-001976-39-NL 2013
83. Garcia-Calvo 2001
84. Johannesen 2016
85. JPRN-UMIN000005924 2011
86. JPRN-UMIN000007489 2012
87. JPRN-UMIN000009117 2012
88. JPRN-UMIN000015502 2014
89. Kawahara 1995
90. NCT00164112 2005
91. NCT00257452 2005
92. NCT00310596 2006
93. NCT00419783 2007
94. NCT00485667 2007
95. NCT00499642 2007
96. NCT00601432 2008
97. NCT00602589 2008
98. NCT00649155 2008
99. NCT00649662 2008
100. NCT00650351 2008
101. NCT00672399 2008
102. NCT00672984 2008
103. NCT00686179 2008
104. NCT00688493 2008
105. NCT00699504 2008
106. NCT00713336 2008
107. NCT00721344 2008
108. NCT00769041 2008
109. NCT00777595 2008
110. NCT00795145 2008
111. NCT00809289 2008
112. NCT00874237 2009
113. NCT00936871 2009
114. NCT00992329 2009
115. NCT00996021 2009
116. NCT01014247 2009
117. NCT01073891 2010
118. NCT01135680 2010
119. NCT01140425 2010
120. NCT01168895 2010
121. NCT01191723 2010
122. NCT01195675 2010
123. NCT01209026 2010
124. NCT01232413 2010
125. NCT01265641 2010
126. NCT01287793 2011
127. NCT01290900 2011
128. NCT01297062 2011
129. NCT01325415 2011
130. NCT01327066 2011
131. NCT01353729 2011
132. NCT01372345 2011
133. NCT01372358 2011

134. NCT01386593 2011
135. NCT01398293 2011
136. NCT01406262 2011
137. NCT01449188 2011
138. NCT01461460 2011
139. NCT01487135 2011
140. NCT01514929 2012
141. NCT01516372 2012
142. NCT01518699 2012
143. NCT01521377 2012
144. NCT01525394 2012
145. NCT01532115 2012
146. NCT01536951 2012
147. NCT01552928 2012
148. NCT01606436 2012
149. NCT01642485 2012
150. NCT01643889 2012
151. NCT01653990 2012
152. NCT01674218 2012
153. NCT01702376 2012
154. NCT01721135 2012
155. NCT01743677 2012
156. NCT01756495 2012
157. NCT01756521 2012
158. NCT01787357 2013
159. NCT01790087 2013
160. NCT01803399 2013
161. NCT01854710 2013
162. NCT01860703 2013
163. NCT01862887 2013
164. NCT01871701 2013
165. NCT01874314 2013
166. NCT01876316 2013
167. NCT01913002 2013
168. NCT01936480 2013
169. NCT01941446 2013
170. NCT01965431 2013
171. NCT01984827 2013
172. NCT01986894 2013
173. NCT02015507 2013
174. NCT02027454 2014
175. NCT02040987 2014
176. NCT02050802 2014
177. NCT02056392 2014
178. NCT02062203 2014
179. NCT02073084 2014
180. NCT02084953 2014
181. NCT02117830 2014
182. NCT02119091 2014
183. NCT02152332 2014
184. NCT02155205 2014
185. NCT02165332 2014
186. NCT02170987 2014
187. NCT02172144 2014
188. NCT02182310 2014
189. NCT02183467 2014
190. NCT02207699 2014
191. NCT02212795 2014
192. NCT02217930 2014
193. NCT02222324 2014
194. NCT02236026 2014
195. NCT02248883 2014
196. NCT02256735 2014
197. NCT02257398 2014
198. NCT02262546 2014
199. NCT02271438 2014
200. NCT02283788 2014
201. NCT02293148 2014
202. NCT02307864 2014
203. NCT02308748 2014
204. NCT02322619 2014
205. NCT02344303 2015

206. NCT02359331 2015
207. NCT02389036 2015
208. NCT02436486 2015
209. NCT02508753 2010
210. NCT02515864 2015
211. NCT02537288 2015
212. NCT02581072 2015
213. NCT02616913 2015
214. NCT02637193 2015
215. NCT02650479 2016
216. NCT02651623 2016
217. NCT02658825 2016
218. NCT02661594 2016
219. NCT02680080 2016
220. NCT02735603 2016
221. NCT02737605 2016
222. NCT02785770 2016
223. NCT02789579 2016
224. NCT02807207 2016
225. NCT02816853 2016
226. NCT02820311 2016
227. NCT02833831 2016
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229. NCT02911870 2016
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PRISMA Checklist – Chapter 3

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO #: CRD42020148742
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, line 111
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, line 131
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8, line 186
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7, line 172
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, line 175
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplementary Material II
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	- 8, line 186 - Supplementary Material III & IV
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12, table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Material II
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	- 10, line 220 - 11-12, table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14, line 256
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15, line 263
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16, line 292

Chapter 4 (ALF-Health Facts)

Acute liver failure III: Health Facts® analysis

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Taher, M. K., Crispo, J. A. G., Fortin, Y., Moog, R., McNair, D., Bjerre, L. M., Momoli, F., Mattison, D., and Krewski, D. (2021) Systemic quinolones and risk of acute liver failure III: A nested case–control study using a US electronic health records database. *Journal of Gastroenterology and Hepatology*, https://doi.org/10.1111/jgh.15504.

Systemic quinolones and risk of acute liver failure III: A nested case-control study using a US electronic health records database

Abstract

Background: Quinolones are globally popular antibiotics with proven potency, broad coverage and reasonable safety. However, some concerns were raised as to their possible association with acute liver failure (ALF).

Objective: To assess ALF risk within 30 days of receiving a systemically administered quinolone antibiotic, in individuals with no history of liver/diseases**.**

Methods: We conducted a nested case-control study using electronic health records from the Cerner Health Facts®. The initial cohort (n= 35,349,943) included all patients who were admitted between 2000-2016, with no history of liver diseases, and had a minimum medical history of one year. Eligible cases were inpatients who were first diagnosed with ALF between 2010-2015. Using incidence density sampling, each case was matched with up to five unique controls by sex, race, age at index encounter, and period-at-risk. We used conditional logistic regression to calculate the ORs and 95% CI for ALF risk, upon adjusting for exposure to other medications, and major confounders (diabetes mellitus and alcohol abuse). We used the STROBE Statement for reporting on our study.

Results: We identified 3,151 cases and 15,657 controls. Our primary analysis did not reveal an association between quinolones and ALF risk. However, some risk was identified

among those with no or few comorbidities, those ≤60 years of age, women, men, African Americans and Caucasians.

Conclusion: Although our study does not suggest an overall association between quinolones and ALF, elevated risks seen in some subgroups warrant further investigation.

Keywords: Quinolones, acute liver failure, nested case-control, electronic health record.

Introduction

Quinolones are potent antibiotics characterized by broad coverage, favorable pharmacologic properties and a reasonable safety profile [1-12]. These attributes enhanced their popularity against a wide range of infections, despite the development of resistance, adverse reactions, and the availability of other alternatives. Whereas adverse reactions to quinolones are predominantly mild to moderate and self-limiting, some have generated serious safety concerns, resulting in revised labeling and even market withdrawal [7-16].

Drug-induced liver injury (DILI) is reportedly the most common reason for the pre- and post-marketing withdrawal of medications [14, 17-19], and the most common cause of ALF in the US and Europe [14, 19-23], with a reported annual incidence of 44,000 cases in the US alone [24]. As one of the most widely used medication groups, antibiotics, including quinolones, may play a role in the development of DILI [12, 25, 26]

Acute liver failure (ALF) is a serious disease involving rapid, progressive, and likely severe loss of hepatic cells, which may involve transient elevations of liver enzymes up to severe liver damage requiring transplantation *[14-16]*. Such deterioration takes place within 4-6 weeks [27-29] following exposure to different factors such as

medications, nutritional and herbal supplements, bacteria, viruses, and toxins [14, 15, 18, 20, 21, 30, 31]. Annual ALF incidence in the US reportedly ranges between 1-6 per million, while comprising 7% and 6% of liver-related transplants and deaths, respectively [27].

Possible mechanisms for hepatotoxicity include production of reactive metabolites [1, 10, 12, 16, 32], or triggering an immunologic response to the administered quinolone [10, 33]. However, a definitive pathophysiology remains to be confirmed [12, 16].

Whereas quinolone-associated ALF risk has been investigated in some epidemiological studies [12, 16, 34, 35], and spontaneous adverse event reports [12, 14-16, 36], only 2 clinical trials reported such a risk. Our study represents the third part of a multi-pronged investigation of quinolone-associated ALF risk, which analyzes a major US Electronic health records (EHR) database.

Methods

Study design

Using a nested case-control design, we analyzed inpatient EHR data from the Cerner Corporation's Health Facts Datawarehouse® (Health Facts®), Kansas City, Missouri, US. This large surveillance system hosts extensive EHR for almost 70 million deidentified patients (approximately 21.6% of the US population[3]) that were generated between 2000-2016 via nearly 450 million encounters from more than 500 US hospitals. Health Facts® contain detailed patient information such as demographics, extensive medical care details, health care setting and insurance status.

[3] *US population as of December 31, 2016: 324,070,652 (https://www.census.gov)*

Information on number of cases and used ICD codes are shown in Supplementary Material I. All liver diseases leading to exclusion of cases or controls from our study, and a list of hepatotoxic medications are shown in Supplementary Material II & III, respectively. Complete listings of the ORs, 95% CI and p-value for all regression analyses are provided in Supplementary Material IV, V & VI. Characteristics of recent similar studies are detailed in Supplementary Material VII.

Identification of case and matched controls

Upon examining all unique encounters, we were able to identify an initial cohort comprising all registered inpatients who were admitted at any time to any of the Health Facts® participating hospitals, with no history of liver diseases[4].

Using this initial cohort, we excluded all patients with a medical history of less than one year in the Health Facts®. We then restricted our pool to those with the date of index encounter between 2010-2015. This date for a case represents the date of the first encounter where a patient was admitted based on a first-time diagnosis of ALF. Meanwhile, for a control, this date represents the date of the latest inpatient encounter without being diagnosed with ALF.

Subsequently, we excluded all patients with missing or inconsistent information on any of the matching variables (sex, race and age at index encounter). To identify ALF cases, we used specific ICD9[5] and ICD10[6] codes, which were reported earlier as

[4] *Except for acute liver failure (outcome of interest)*
[5] *International Classification of Diseases, Ninth Revision (ICD-9)*
[6] *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*

demonstrating a high positive predictive value for drug-induced hepatotoxicity [34]. We then calculated the period-at-risk for all cases and possible controls, which represents the time spanning between date of the first recorded inpatient encounter, and date of the index encounter.

An optimal variable matching approach [37] was used for matching controls to cases without replacement, where each control was matched to a single case. Each case was matched to up to five controls based on four variables with equal weights: sex, race, age on day of the index encounter (±1 year), and the period-at-risk (±1 year).

Medication exposure

As we are interested in exposure to systemic quinolones, all non-systemic formulations were excluded. Inpatient medication exposure was grouped into four classes: quinolones, hepatotoxic medications (excluding quinolones) [38, 39], other antibiotics (excluding quinolones and hepatotoxic antibiotics), and other medications (excluding all antibiotics and hepatotoxic medications). Data on medication exposure was limited to prescriptions filled during inpatient care.

Data analysis

Descriptive analysis

We reported categorical variables as frequencies and percentages, and continuous variables as means with standard deviations. Categorical variables included sex, race (Caucasian, African American, Asian, Hispanic, other); socioeconomic indicators included census region and division; hospital setting (urban/rural); health insurance (insured, non-insured, missing/unknown); and thirty-day exposure to each of

the four medication groups and individual quinolones (ever/never). Additional variables included ever/never concurrent diabetes mellitus (complicated, uncomplicated), and alcohol abuse.

Continuous variables included age at index encounter and comorbidity status, with the age stratified into 10-year groups (0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90). Comorbidity as measured by the score generated via the Hude Quan version [40] of the Elixhauser comorbidity index (CMI) [41] was stratified into 5 groups according to the CMI score (0, 1-5, 6-10, 11-15, and 16+). The number of inpatient medication prescriptions filled during the thirty-day period preceding the index date was stratified into five groups (0, 1-3, 4-6, 7-10, 11+).

Regression analysis

We generated a series of conditional logistic regression models to identify the best estimate for quinolone-associated ALF risk, upon adjusting for other medication exposures and major confounders. For each medication group, we fitted a base model with only sex, race, age at index encounter, and the selected medication group (ever/never). This was followed by a minimally adjusted model including all variables in the base model plus all other medication groups (ever/ never). Finally, we fitted a maximally adjusted model extending the minimally adjusted model to include all remaining variables. To identify the quinolone(s) with the strongest possible association with ALF risk, we repeated the same series of regression models using exposure to individual quinolones, rather than a class, as predictors of ALF.

Potential confounding

To avoid any possible confounding effect, we a priori excluded all patients with history of any liver disease/condition. We also adjusted for other major confounders, including health status, recognized risk factors (diabetes mellitus and alcohol abuse), socioeconomic status (health insurance and care setting), and concurrent exposure to other medications.

Sensitivity analysis

To isolate the effect of notable differences in comorbidity and inpatient medications between cases and controls, we fitted a third series of regression models to different subgroups of our study population via stratifying by sex, race, comorbidity status (tertiles) and age at index encounter (tertiles).

This study was approved by the Office of Ethics and Research Integrity of the University of Ottawa, Canada (H02-18-05). All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, NC, USA). We hereby report on our study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines [42].

Results

Identification of ALF cases

Upon searching all encounters registered in the entire Health Facts®, we were able to identify a total of 69,117,801 unique patients. By excluding all inpatients with history of liver diseases, we identified an initial cohort of 66,352,931 patients, which included a pool of 17,890 unique ALF cases.

By removing all patients with a medical history of less than one year, we reduced our case pool to 3,820 cases (21.4%), which was then restricted to those with an index date between 2010-2015 (n=3,356, 18.8%). Excluding those with missing or inconsistent data on any of the matching variables resulted in a final pool of 3,151 eligible cases (17.6%). Based on our criteria, we were able to match a total of 15,657 unique controls to the 3,151 eligible cases. A total of 29 cases could not be matched to the maximum of 5 controls sought by our matching algorithm (see Figure 4).

Characteristics of study population

As summarized in Table 10, study population was comprised mainly of Caucasian race (n=2,374; 75.3%), with slightly more women (n=1,677; 53.2%). Incidence of ALF was low (1.1-1.5%) in the early decades of life, increased steadily until the age of 60 years, then plateaued afterwards.

Cases were generally less healthy than controls, with a mean (±SD) CMI score of 7.9 (±3.3) and 3.3 (±3.4), respectively. Most cases (56%) were in the mid-range (CMI: 6-10), with the remainder distributed fairly equally on either side of this middle zone. Only 1.5% of cases showed no comorbidities other than ALF. Whereas most controls (49%) were in a healthier zone (CMI: 1-5), 26% showed no comorbidities (CMI: 0), with the remaining controls (26%) were scattered along the higher zones of the index.

Cases showed a higher prevalence of uncomplicated (44% vs 23%) and complicated (20% vs 8%) diabetes mellitus compared to controls, respectively. Similarly, alcohol abuse in cases (6%) was more than double that in controls (2.5%). Both cases (n=2,695; 85.5%) and controls (n=13,236; 84.0%) were equally covered by health insurance.

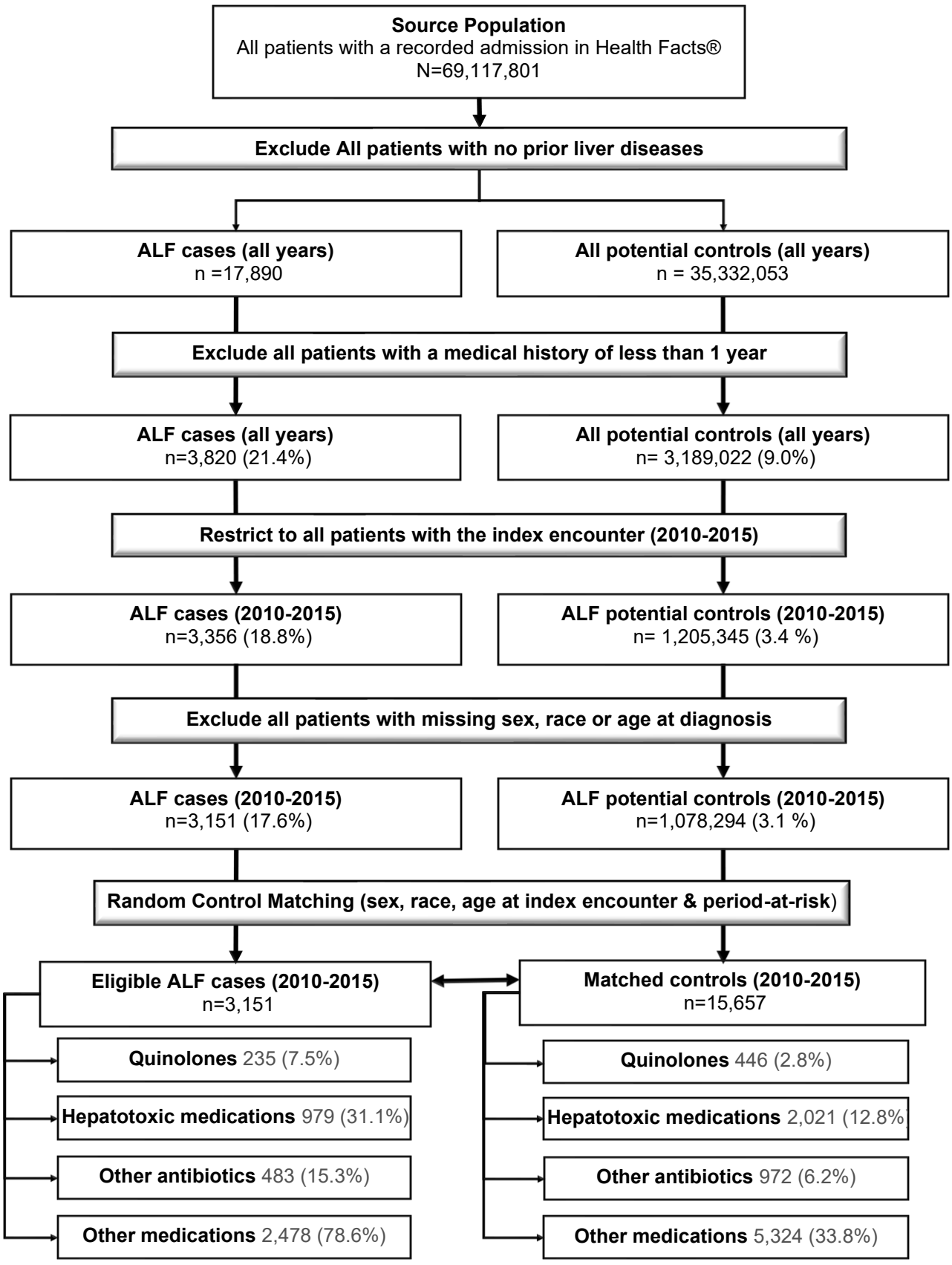

Figure 4: Identification of eligible ALF cases and matching controls (2010-2015)

Table 10: Characteristics of cases and matched controls

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
Total no. of participants	3,151	15,755	
Sex*			**0.97**
Women	1,677 (53.2%)	8,391 (53.3%)	
Men	1,474 (46.8%)	7,364 (46.7%)	
Race class*			**0.98**
Caucasians	2,374 (75.3%)	11,910 (75.6%)	
African Americans	589 (18.7%)	2,925 (18.6%)	
Asians	44 (1.4%)	217 (1.4%)	
Hispanics	10 (0.3%)	41 (0.3%)	
Others	134 (4.3%)	662 (4.2%)	
Age group*			**1.0000**
0 – 10	46 (1.5%)	230 (1.5%)	
11 – 20	35 (1.1%)	175 (1.1%)	
21 – 30	83 (2.6%)	414 (2.6%)	
31 – 40	137 (4.4%)	686 (4.4%)	
41 – 50	228 (7.2%)	1,137 (7.2%)	
51 – 60	526 (16.7%)	2,632 (16.7%)	
61 – 70	707 (22.4%)	3,537 (22.5%)	
71 – 80	758 (24.1%)	3,788 (24.0%)	

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
81 – 90	631 (20.0%)	3,156 (20.0%)	
Census region			**<.0001**
South	1,141 (36.2%)	5,333 (33.9%)	
North East	947 (30.1%)	3,646 (23.2%)	
Midwest	568 (18.0%)	4564 (29.0%)	
West	495 (15.7%)	2207 (14.0%)	
Missing	0 (0.0%)	5 (0.1%)	
Hospital setting			**0.0049**
Urban	2543 (80.7%)	12,358 (78.5%)	
Rural	608 (19.3%)	3,392 (21.5%)	
Missing	0	5 (0.09%)	
Health insurance			**0.0131**
Insured	2,695 (85.5%)	13,236 (84.0%)	
Non-insured	72 (2.3%)	504 (3.2%)	
Unknown/missing	384 (12.2%)	2,015 (12.8%)	
Payer group			**<.0001**
Government	2,090 (66.3%)	8,751 (55.5%)	
HMO/managed care	604 (19.2%)	4,483 (28.5%)	
Self-pay	72 (2.3%)	502 (3.2%)	
Other	1 (0.0%)	4 (0.0%)	

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
Unknown/missing	384 (12.2%)	2,015 (12.8%)	
Comorbidity score	**7.90 (±3.3)**	**3.35 (±3.5)**	**<.0001**
0	65 (2.1%)	4,098 (25.7%)	
1-5	664 (21.1%)	7,710 (49.0%)	
6 – 10	1,753 (55.7%)	3,282 (20.8%)	
11 – 15	647 (20.6%)	689 (4.4%)	
16 – 20	19 (0.6%)	19 (0.12%)	
Confounders			
Diabetes – uncomplicated	1,397 (44.4%)	3,785 (24.0%)	<.0001
Diabetes – complicated	651 (20.7%)	1,372 (8.7%)	<.0001
Alcohol abuse	176 (5.6%)	383 (2.4%)	<.0001

***** Matching variables

During the 30-days preceding the index encounter, average medication prescriptions filled was 2-3 times higher among cases compared to controls for all medication groups, reflecting a less favorable health profile for cases relative to controls. Whereas a large majority of cases (93%) and controls (97%) were prescribed no quinolones during the thirty-day window, they were prescribed other non-quinolone antibiotics (85% vs 93%) or hepatotoxic medications (69% vs 87%) during the same period (Table 11).

Table 11: Thirty-day exposure, by medication group, prior to the index date

Medication group		**Mean (±SD); *p-value*** or No. (%) of filled prescriptions		**p-value**
		Cases	**Controls**	
Quinolones		**0.11 (±0.44); < *.0001***	**0.04 (±0.27); < *.0001***	
	0	2,916 (92.5%)	15,164 (97.2%)	<.0001
	1-3	229 (7.3%)	440 (2.8%)	
	4-6	6 (0.2%)	6 (0.1%)	
	7-10	0 (0%)	0 (0%)	
	11+	0 (0%)	0 (0%)	
Hepatotoxic		**0.76 (±1.59); < *.0001***	**0.27 (±0.91); < *.0001***	
	0	2,172 (68.9%)	13,734 (87.2%)	<.0001
	1-3	777 (24.7%)	1,744 (11.1%)	
	4-6	163 (5.2%)	226 (1.4%)	
	7-10	31 (1.0%)	44 (0.3%)	
	11+	8 (0.3%)	7 (0%)	
Other antibiotics		**0.32 (±0.91); < *.0001***	**0.13 (±0.62); <*.0001***	
	0	2,668 (84.7%)	14,783 (93.8%)	<.0001
	1-3	418 (13.3%)	833 (5.3%)	
	4-6	61 (1.9%)	121 (0.8%)	
	7-10	4 (0.1%)	17 (0.1%)	
	11+	0 (0%)	1 (0%)	
Other medications		**10.11 (±17.50); < .0001**	**3.77 (±11.01); < .0001**	

Medication group		Mean (±SD); *p-value* or No. (%) of filled prescriptions		p-value
		Cases	**Controls**	
	0	673 (21.4%)	10,431 (66.2%)	<.0001
	1-3	1,528 (48.5%)	3,322 (21.1%)	
	4-6	92 (2.9%)	239 (1.5%)	
	7-10	62 (2.0%)	176 (1.1%)	
	11+	796 (25.3%)	1,587 (10.1%)	

Levofloxacin and ciprofloxacin were the most commonly filled quinolones for both cases and controls during the thirty days preceding the index date, whereas moxifloxacin had a remarkably low proportion (Table 12).

Table 12: Thirty-day exposure by the individual quinolones

Medication group	No. (%) of filled prescriptions		p-value
	Cases	**Controls**	
Ciprofloxacin	101 (3.2%)	167 (1.1%)	<.0001
Levofloxacin	125 (4.0%)	262 (1.7%)	<.0001
Moxifloxacin	27 (0.9%)	40 (0.3%)	<.0001

Regression analysis

Entire study population

Primary analysis of the entire study population showed that systemically administered quinolones are not associated with ALF risk [aOR: 1.05 (95% CI: 0.87-1.28)], after adjusting for exposure to other medications, uncomplicated and complicated diabetes mellitus, alcohol abuse, health care setting and insurance status.

Repeating the same regression analyses based on individual quinolones produced similar results to multi-medication model including all quinolones simultaneously. Our risk estimates reported herein were generated using the multi-medication model. Among the individual quinolones, an increased, non-significant ALF risk was detected with moxifloxacin [aOR: 1.46 (95% CI: 0.85-2.50)] and ciprofloxacin [aOR: 1.22 (95% CI: 0.91-1.64)]. A summary of ALF risk estimates for medication groups and individual quinolones is provided in Table 13 and

Table *14*, respectively.

Stratification by Sex

Quinolones showed a marginal, non-significant increase in ALF risk in women [aOR: 1.16 (95% CI: 0.88-1.54)], that was attributable to both moxifloxacin [aOR: 1.43 (95% CI: 0.57-3.61)] and ciprofloxacin [aOR: 1.30 (95% CI: 0.88-1.91)].

Stratification by Race

Quinolones showed a substantial, non-significant increase in ALF risk in African Americans [aOR: 1.43 (95% CI: 0.88-2.30)], that was also attributable to moxifloxacin [aOR: 2.70 (95% CI: 0.96-7.60)]. Additionally, ciprofloxacin showed an increased, non-significant ALF risk in Caucasians [aOR: 1.25 (95%CI: (0.90-1.74)].

Stratification by Age

In the youngest age tertile (0-60), quinolones showed a significant ALF risk [aOR: 1.91 (95% CI: 1.21-3.00)], which was reduced and lost its significance [aOR: 1.30 (95% CI: 0.95-1.78)] in the middle age tertile (61-75). No risk was found in the eldest age tertile (76 years and older). All individual quinolones showed an elevated but non-significant ALF risk in the youngest two tertiles, whereas only moxifloxacin continued to show a non-significant risk in the eldest age group.

Stratification by Comorbidity

By stratifying the study population into tertiles based on their scores, those with the lowest comorbidity burden (CMI: 0-6) showed a significant 156% increase in ALF

risk [aOR: 2.56 (95% CI: 1.54-4.27)] with use of quinolones. In the healthiest group (CMI: 0-6), only ciprofloxacin showed a 4-fold significant increase in ALF risk [aOR: 5.11 (95% CI: 2.39-10.94)]. No quinolones showed any significant ALF risk in the moderate to high CMI groups.

Effect of major confounders

Complicated diabetes mellitus was associated with a significant ALF risk in the primary analysis examining the entire unstratified study population [aOR: 2.09 (95%CI: 1.85-2.36)]. This risk was similar across all races, slightly higher in women, and decreased slightly with advancement of age.

Similarly, alcohol abuse was also associated with a significant ALF risk in the primary analysis [aOR: 1.92 (95%CI: 1.55-2.39)], the healthiest subgroup (CMI: 0-6), women, Caucasians more than African Americans, and in the youngest more than the middle age tertiles.

The adjusted ORs and 95% CI for the primary and subgroup analyses for both confounders are detailed in supplementary material VI. Results for the base and (maximally) adjusted models for the primary analysis examining the entire study population and the subgroup analysis based on comorbidity score are presented in this manuscript in Table 13 for all medication groups, and

Table *14* for the individual quinolones. Detailed results for all regression models for all analyses are provided in the Supplementary Material IV – VI.

Table 13: Base and adjusted odds ratios (aOR) for ALF risk with all medication groups

Population and Medication Group	**Base OR (95% CI)**	***p-value***	**Adjusted aOR (95% CI)**	***p-value***
Entire study population				
Quinolones[7]	2.80 (2.38-3.31)	<.0001	1.05 (0.87-1.28)	0.6075
Hepatotoxic medications[8]	3.17 (2.90-3.48)	<.0001	**1.37 (1.23-1.54)**	**<.0001**
Other antibiotics[9]	2.80 (2.49-3.16)	<.0001	1.03 (0.89-1.20)	0.6528
Non-antibiotics[10]	7.61 (6.91-8.37)	<.0001	**6.52 (5.86-7.25)**	**<.0001**
By comorbidity level (tertiles)				
CMI:0-6				
Quinolones	5.43 (3.58-8.22)	<.0001	**2.56 (1.54-4.27)**	**0.0003**
Hepatotoxic medications	3.05 (2.49-3.73)	<.0001	1.28 (0.99-1.66)	0.0651
Other antibiotics	3.66 (2.82-4.75)	<.0001	1.16 (0.84-1.62)	0.3694
Non-antibiotics	8.35 (7.03-9.93)	<.0001	**7.89 (6.49-9.59)**	**<.0001**
CMI:7-9				

[7] Quinolone antibiotics
[8] Non-quinolone hepatotoxic medications
[9] Non-quinolone, non-hepatotoxic antibiotics
[10] All other medications combined

Population and Medication Group	Base OR (95% CI)	*p-value*	Adjusted aOR (95% CI)	*p-value*
Quinolones	1.27 (0.83-1.94)	0.2799	0.87 (0.54-1.42)	0.5762
Hepatotoxic medications	1.19 (0.92-1.53)	0.1805	0.82 (0.61-1.10)	0.1798
Other antibiotics	1.58 (1.15-2.18)	0.0054	1.31 (0.90-1.92)	0.1605
Non-antibiotics	3.14 (2.37-4.15)	<.0001	**3.03 (2.22-4.13)**	**<.0001**
CMI:10+				
Quinolones	1.12 (0.69-1.83)	1.830	0.80 (0.44-1.44)	0.4567
Hepatotoxic medications	1.52 (1.11-2.06)	0.0084	1.08 (0.73-1.60)	0.7158
Other antibiotics	1.09 (0.73-1.61)	0.6879	0.78 (0.48-1.26)	0.3036
Non-antibiotics	2.62 (1.86-3.70)	<.0001	**2.58 (1.68-3.96)**	**<.0001**

Table 14: Base and adjusted odds ratios (aOR) for acute liver failure in relation to use of individual quinolones

Population and Quinolone Used	**Base OR (95% CI)**	***p-value***	**Adjusted aOR (95% CI)**	***p-value***
Entire study population				
Ciprofloxacin	2.74 (2.12-3.54)	<.0001	1.22 (0.91-1.64)	0.1754
Levofloxacin	2.35 (1.88-2.93)	<.0001	0.90 (0.70-1.15)	0.3966
Moxifloxacin	2.92 (1.75-4.89)	<.0001	1.46 (0.85-2.50)	0.1720
By comorbidity level (tertiles)				
CMI:0-6				
Ciprofloxacin	8.1 (4.32-15.23)	<.0001	**5.11 (2.39-10.94)**	<.0001
Levofloxacin	3.42 (1.89-6.19)	<.0001	1.44 (0.72-2.86)	0.3015
Moxifloxacin	3.45 (0.68-17.44)	0.1346	1.98 (0.35-11.33)	0.4420
CMI:7-9				
Ciprofloxacin	1.58 (0.71-3.48)	0.2604	1.21 (0.51-2.84)	0.6658
Levofloxacin	1.02 (0.61-1.73)	0.9341	0.67 (0.37-1.22)	0.1884
Moxifloxacin	2.09 (0.48-9.00)	0.3240	1.66 (0.37-7.36)	0.5061
CMI:10+				
Ciprofloxacin	0.91 (0.40-2.03)	0.8107	0.69 (0.28-1.72)	0.4261
Levofloxacin	1.10 (0.60-2.02)	0.7584	0.86 (0.43-1.74)	0.6810
Moxifloxacin	3.51 (0.61-20.32)	0.1609	1.26 (0.17-9.32)	0.8240

Discussion

The number of ALF cases identified in the Health Facts® was remarkably low prior to 2010 and after 2015. Whereas we think the former was probably due to the gradual enrollment of participating hospitals, the latter marked the shift of coding from ICD-9 to ICD-10 codes, which could be confirmed by lack of any ICD-10 codes in all identified ALF cases in all years. As such, we decided to focus our study on the interval between 2010 – 2015, which included the bulk of all recorded ALF cases.

By excluding cases or controls with history of liver diseases, and adjusting for major confounders, we aimed at isolating the effect of medications on ALF risk. Our primary analysis of the entire study population showed no evidence of increased ALF risk within 30 days following the 'inpatient' exposure to quinolones. However, a possible risk was seen in those with the lowest CMI score (predominantly driven by ciprofloxacin), and in patients up to 60 years of age (predominantly driven by moxifloxacin. A non-significant ALF risk was identified in both women and men (could be attributed to ciprofloxacin and moxifloxacin), in African Americans (by moxifloxacin and ciprofloxacin), and in Caucasians (by ciprofloxacin). Consistent with earlier studies [43-45], alcohol abuse and complicated diabetes showed increased ALF risk.

Recent pharmacovigilance studies showed closer results [12, 16, 34, 35], despite differences in study design, target population, case definition, case identification and control selection process. Characteristics and results of these studies are summarized in Supplementary Material VII. Earlier observational studies also reported sporadic occurrences of hepatotoxicity with ciprofloxacin [26, 46, 47], moxifloxacin [26, 48-51] and levofloxacin [26, 52-56].

To the best of our knowledge, this is the first large-scale assessment of quinolone-associated ALF using a substantive database with extensive inpatient EHRs for nearly 21% of the US population. We opted for a nested case-control study design rather than a cohort design, due to the former's computational efficiency given its smaller sample size, opportunity for time-based exposure assessment, and accounting for the effects of different potential confounders at different times [57-59]. Moreover, missing observations are expected to have a lesser impact in the nested case-control design, and eventually both designs would be expected reach comparable risk estimates [60-62].

Using inpatient EHRs provided an opportunity for accurately assessing the temporality of association between ALF and prior medication exposure, and also for adjusting for major confounders such as comorbidities, and concurrent medication exposure. Using an inpatient medication management system ensured medication compliance since all filled medications are most likely delivered by hospital staff.

Restricting the inclusion to our study to patients with a minimum of one-year medical history enabled a more extensive assessment of confounding by patients' comorbidity status on ALF risk, although this came at the expense of losing additional ALF cases with short or no medical history.

A major limitation involved the lack of information on outpatient medication history, considering the fact that 50-80% of antibiotics are prescribed in physician offices rather than hospitals [63, 64]. This major limitation should be addressed in future studies. Despite the significant efforts devoted to the cleaning and linking of our data, and similar to other EHR databases [65, 66], our database is subject to limitations such as

misclassification of demographics, comorbidities, medications, outcomes or other clinical details.

Conclusion

Overall, our study did not identify evidence to support an association between ALF and systemically administered quinolones. However, further attention must be paid to quinolone exposure by specific subgroups such as with ciprofloxacin in persons with low CMI score (0-6); moxifloxacin in persons aged 60 years or younger; ciprofloxacin and moxifloxacin in both women and men; moxifloxacin and ciprofloxacin in African Americans and ciprofloxacin in Caucasians. Further studies with additional information on outpatient medication use would be useful in confirming the present findings.

Author contributions

The primary author, Mohamed Taher, designed and implemented this study including statistical analysis, interpretation of findings and drafting of this manuscript. James Crispo and Yannick Fortin contributed to statistical analysis, as well as critical review and approval of this manuscript. Lise Bjerre, Franco Momoli, Ryan Moog, Douglas McNair, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the study design and implementation, as well as critical review and approval of the manuscript.

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Declaration of interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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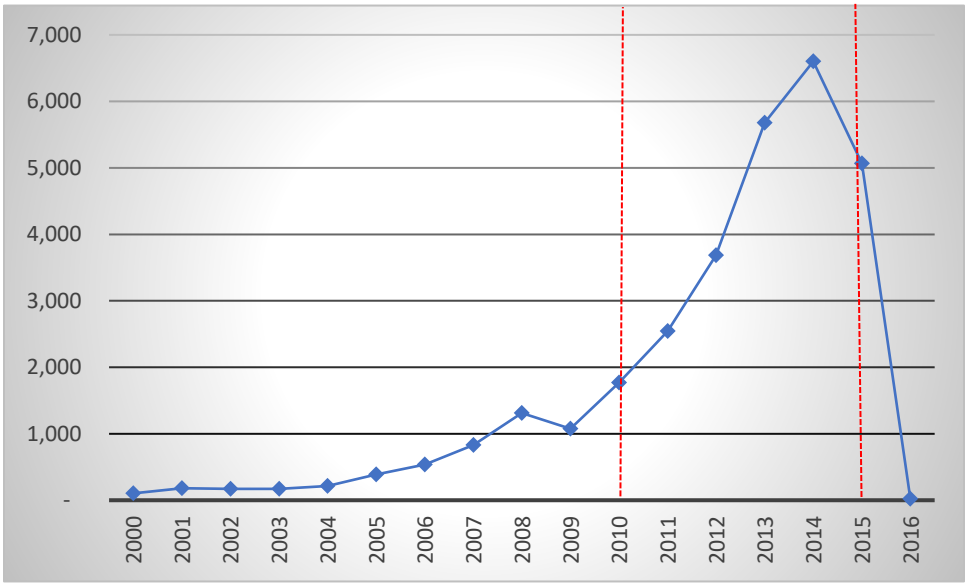
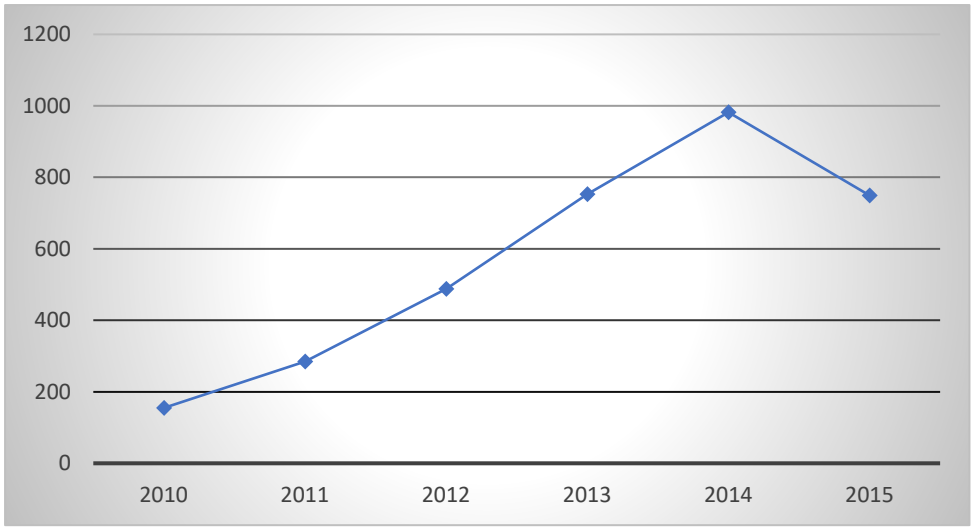
Supplementary Material – Chapter 4

Identifying cases of acute liver failure cases



All new ALF cases recorded in the Healthfacts database, by year (2000-2016)



Final group of fully eligible ALF cases, by year of diagnosis (2010-2015)

ICD codes used for identifying ALF cases and excluding ineligible patients

ICD Type	ICD Code	Details
ICD 9	570	Acute and subacute necrosis of liver
ICD 10-CM	K71	Toxic liver disease
	K71.10	Toxic liver disease with hepatic necrosis, without coma
	K71.11	Toxic liver disease with hepatic necrosis, with coma
	K71.2	Toxic liver disease with acute hepatitis
	K71.6	Toxic liver disease with hepatitis, not elsewhere classified
	K71.9	Toxic liver disease, unspecified
	K72	Hepatic failure, not elsewhere classified
	K72.0	Acute and subacute hepatic failure
	K72.00	Acute and subacute hepatic failure without coma
	K72.01	Acute and subacute hepatic failure with coma
	K72.9	Hepatic failure, unspecified
	K72.90	Hepatic failure, unspecified without coma
	K72.91	Hepatic failure, unspecified with coma

ICD codes for excludable liver conditions

Diagnosis type	Diagnosis code	Diagnosis description
ICD9	70	Viral Hepatitis a with Hepatic Coma
ICD9	70.1	Viral Hepatitis a without Mention of Hepatic Coma
ICD9	70.41	Acute Hepatitis C with Hepatic Coma
ICD9	70.9	Unspecified Viral Hepatitis without Mention of Hepatic Coma
ICD9	211.5	Benign Neoplasm of Liver and Biliary Passages
ICD9	456.1	Esophageal Varices without Mention of Bleeding
ICD9	570	Acute and Subacute Necrosis of Liver
ICD9	571.49	Other Chronic Hepatitis
ICD9	571.6	Biliary Cirrhosis
ICD9	572.2	Hepatic Encephalopathy
ICD9	572.8	Other Sequelae of Chronic Liver Disease
ICD9	573.3	Hepatitis, Unspecified
ICD9	573.9	Unspecified Disorder of Liver
ICD9	789.1	Hepatomegaly
ICD9	V02.6	Carrier or Suspected Carrier of Viral Hepatitis
ICD9	70.2	Viral Hepatitis B with Hepatic Coma, Acute or Unspecified, without Mention of Hepatitis Delta
ICD9	70.21	Viral Hepatitis B with Hepatic Coma, Acute or Unspecified, with Hepatitis Delta

Diagnosis type	Diagnosis code	Diagnosis description
ICD9	70.22	Viral Hepatitis B with Hepatic Coma, Chronic, without Mention of Hepatitis Delta
ICD9	70.23	Viral Hepatitis B with Hepatic Coma, Chronic, with Hepatitis Delta
ICD9	70.3	Viral Hepatitis B without Mention of Hepatic Coma, Acute or Unspecified, without Mention of Hepatitis Delta
ICD9	70.31	Viral Hepatitis B without Mention of Hepatic Coma, Acute or Unspecified, with Hepatitis Delta
ICD9	70.32	Viral Hepatitis B without Mention of Hepatic Coma, Chronic, without Mention of Hepatitis Delta
ICD9	70.33	Viral Hepatitis B without Mention of Hepatic Coma, Chronic, with Hepatitis Delta
ICD9	70.42	Hepatitis Delta without Mention of Active Hepatitis B Disease with Hepatic Coma
ICD9	70.43	Hepatitis E with Hepatic Coma
ICD9	70.44	Chronic Hepatitis C with Hepatic Coma
ICD9	70.49	Other Specified Viral Hepatitis with Hepatic Coma
ICD9	70.51	Acute Hepatitis C without Mention of Hepatic Coma
ICD9	70.52	Hepatitis Delta without Mention of Active Hepatitis B Disease or Hepatic Coma
ICD9	70.53	Hepatitis E without Mention of Hepatic Coma

Diagnosis type	Diagnosis code	Diagnosis description
ICD9	70.54	Chronic Hepatitis C without Mention of Hepatic Coma
ICD9	70.59	Other Specified Viral Hepatitis without Mention of Hepatic Coma
ICD9	70.6	Unspecified Viral Hepatitis with Hepatic Coma
ICD9	155	Malignant Neoplasm of Liver, Primary
ICD9	155.1	Malignant Neoplasm of Intrahepatic Bile Ducts
ICD9	155.2	Malignant Neoplasm of Liver, Not Specified as Primary or Secondary
ICD9	198	Secondary Malignant Neoplasm of Kidney
ICD9	230.8	Carcinoma in Situ of Liver and Biliary System
ICD9	235.3	Neoplasm of Uncertain Behavior of Liver and Biliary Passages
ICD9	456	Esophageal Varices with Bleeding
ICD9	456.2	Esophageal Varices in Diseases Classified Elsewhere
ICD9	571	Alcoholic Fatty Liver
ICD9	571.1	Acute Alcoholic Hepatitis
ICD9	571.2	Alcoholic Cirrhosis of Liver
ICD9	571.3	Alcoholic Liver Damage, Unspecified
ICD9	571.4	Chronic Hepatitis, Unspecified
ICD9	571.41	Chronic Persistent Hepatitis
ICD9	571.5	Cirrhosis of Liver without Mention of Alcohol

Diagnosis type	Diagnosis code	Diagnosis description
ICD9	571.8	Other Chronic Nonalcoholic Liver Disease
ICD9	571.9	Unspecified Chronic Liver Disease without Mention of Alcohol
ICD9	572	Abscess of Liver
ICD9	572.1	Portal Pyemia
ICD9	572.3	Portal Hypertension
ICD9	572.4	Hepatorenal Syndrome
ICD9	573	Chronic Passive Congestion of Liver
ICD9	573.1	Hepatitis in Viral Diseases Classified Elsewhere
ICD9	573.2	Hepatitis in Other Infectious Diseases Classified Elsewhere
ICD9	573.4	Hepatic Infarction
ICD9	573.8	Other Specified Disorders of Liver
ICD9	782.4	Jaundice, Unspecified, Not of Newborn
ICD9	794.8	Nonspecific Abnormal Results of Function Study of Liver
ICD9	996.82	Complications of Transplanted Liver
ICD9	V10.07	Personal History of Malignant Neoplasm of Liver
ICD9	V11.3	Personal History of Alcoholism
ICD9	V42.7	Liver Replaced by Transplant
ICD10-CM	R16.0	Hepatomegaly, not elsewhere classified
ICD10-CM	R16.2	Hepatomegaly with splenomegaly, not elsewhere classified
ICD10-CM	R17	Unspecified jaundice

Diagnosis type	Diagnosis code	Diagnosis description
ICD10-CM	R93.2	Abnormal findings on diagnostic imaging of liver and biliary tract
ICD10-CM	R94.5	Abnormal results of liver function studies
ICD10-CM	I85	Esophageal varices
ICD10-CM	I86.4	Gastric varices
ICD10-CM	K70.0	Alcoholic fatty liver
ICD10-CM	K70.1	Alcoholic hepatitis
ICD10-CM	K70.2	Alcoholic fibrosis and sclerosis of liver
ICD10-CM	K70.3	Alcoholic cirrhosis of liver
ICD10-CM	K70.4	Alcoholic hepatic failure
ICD10-CM	K70.9	Alcoholic liver disease, unspecified
ICD10-CM	K71.0	Toxic liver disease with cholestasis
ICD10-CM	K71.1	Toxic liver disease with hepatic necrosis
ICD10-CM	K71.2	Toxic liver disease with acute hepatitis
ICD10-CM	K71.3	Toxic liver disease with chronic persistent hepatitis
ICD10-CM	K71.4	Toxic liver disease with chronic lobular hepatitis
ICD10-CM	K71.5	Toxic liver disease with chronic active hepatitis
ICD10-CM	K71.6	Toxic liver disease with hepatitis, not elsewhere classified
ICD10-CM	K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
ICD10-CM	K71.8	Toxic liver disease with other disorders of liver
ICD10-CM	K71.9	Toxic liver disease, unspecified

Diagnosis type	Diagnosis code	Diagnosis description
ICD10-CM	K72.0	Acute and subacute hepatic failure
ICD10-CM	K72.1	Chronic hepatic failure
ICD10-CM	K72.9	Hepatic failure, unspecified
ICD10-CM	K73.0	Chronic persistent hepatitis, not elsewhere classified
ICD10-CM	K73.1	Chronic lobular hepatitis, not elsewhere classified
ICD10-CM	K73.2	Chronic active hepatitis, not elsewhere classified
ICD10-CM	K73.8	Other chronic hepatitis, not elsewhere classified
ICD10-CM	K73.9	Chronic hepatitis, unspecified
ICD10-CM	K74.0	Hepatic fibrosis
ICD10-CM	K74.1	Hepatic sclerosis
ICD10-CM	K74.2	Hepatic fibrosis with hepatic sclerosis
ICD10-CM	K74.3	Primary biliary cirrhosis
ICD10-CM	K74.4	Secondary biliary cirrhosis
ICD10-CM	K74.5	Biliary cirrhosis, unspecified
ICD10-CM	K74.6	Other and unspecified cirrhosis of liver
ICD10-CM	K75.0	Abscess of liver
ICD10-CM	K75.1	Phlebitis of portal vein
ICD10-CM	K75.2	Nonspecific reactive hepatitis
ICD10-CM	K75.3	Granulomatous hepatitis, not elsewhere classified
ICD10-CM	K75.4	Autoimmune hepatitis
ICD10-CM	K75.8	Other specified inflammatory liver diseases

Diagnosis type	Diagnosis code	Diagnosis description
ICD10-CM	K75.9	Inflammatory liver disease, unspecified
ICD10-CM	K76.0	Fatty (change of) liver, not elsewhere classified
ICD10-CM	K76.1	Chronic passive congestion of liver
ICD10-CM	K76.2	Central hemorrhagic necrosis of liver
ICD10-CM	K76.3	Infarction of liver
ICD10-CM	K76.4	Peliosis hepatis
ICD10-CM	K76.5	Hepatic veno-occlusive disease
ICD10-CM	K76.6	Portal hypertension
ICD10-CM	K76.7	Hepatorenal syndrome
ICD10-CM	K76.8	Other specified diseases of liver
ICD10-CM	K76.9	Liver disease, unspecified
ICD10-CM	C22.0	Liver cell carcinoma
ICD10-CM	C22.1	Intrahepatic bile duct carcinoma
ICD10-CM	C22.2	Hepatoblastoma
ICD10-CM	C22.3	Angiosarcoma of liver
ICD10-CM	C22.4	Other sarcomas of liver
ICD10-CM	C22.7	Other specified carcinomas of liver
ICD10-CM	C22.9	Malignant neoplasm of liver, not specified as primary or secondary
ICD10-CM	B19.9	Unspecified viral hepatitis without hepatic coma

Diagnosis type	Diagnosis code	Diagnosis description
ICD10-CM	D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts
ICD10-CM	C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
ICD10-CM	D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
ICD10-CM	D13.4	Benign neoplasm of liver
ICD10-CM	B15.0	Hepatitis A with hepatic coma
ICD10-CM	B15.9	Hepatitis A without hepatic coma
ICD10-CM	B16.0	Acute hepatitis B with delta-agent with hepatic coma
ICD10-CM	B16.1	Acute hepatitis B with delta-agent without hepatic coma
ICD10-CM	B16.2	Acute hepatitis B without delta-agent with hepatic coma
ICD10-CM	B16.9	Acute hepatitis B without delta-agent and without hepatic coma
ICD10-CM	B17.0	Acute delta-(super) infection of hepatitis B carrier
ICD10-CM	B17.1	Acute hepatitis C
ICD10-CM	B17.2	Acute hepatitis E
ICD10-CM	B17.8	Other specified acute viral hepatitis
ICD10-CM	B18	Chronic viral hepatitis
ICD10-CM	B18.0	Chronic viral hepatitis B with delta-agent
ICD10-CM	B18.1	Chronic viral hepatitis B without delta-agent
ICD10-CM	B18.2	Chronic viral hepatitis C

Diagnosis type	Diagnosis code	Diagnosis description
ICD10-CM	B18.8	Other chronic viral hepatitis
ICD10-CM	B18.9	Chronic viral hepatitis, unspecified
ICD10-CM	B19.0	Unspecified viral hepatitis with hepatic coma
ICD10-CM	V42.7	Person on outside of car injured in collision with two- or three-wheeled motor vehicle in traffic accident
ICD10-CM	V11.3	Person boarding or alighting a pedal cycle injured in collision with other pedal cycle
ICD10-CM	Z22.50	Carrier of unspecified viral hepatitis
ICD10-CM	Z22.51	Carrier of viral hepatitis B
ICD10-CM	Z94.4	Liver transplant status

List of group A hepatotoxic medications (Source: LiverTox [1, 2])

Generic name	Medication type
Diclofenac	Analgesic
Ibuprofen	Analgesic
Nimesulide	Analgesic
Sulindac	Analgesic
Clavulanate/Amoxicillin	Antimicrobial
Didanosine	Antimicrobial
Efavirenz	Antimicrobial
Erythromycin	Antimicrobial
Flucloxacillin	Antimicrobial
Interferon-a/Peginterferon	Antimicrobial
Isoniazid	Antimicrobial
Ketoconazole	Antimicrobial
Minocycline	Antimicrobial
Nevirapine	Antimicrobial
Nitrofurantoin	Antimicrobial
Pyrazinamide	Antimicrobial
Rifampin	Antimicrobial
Sulfamethoxazole	Antimicrobial
Sulfonamides	Antimicrobial
Telithromycin	Antimicrobial
Busulfan	Antineoplastic

Generic name	Medication type
Floxuridine	Antineoplastic
Flutamide	Antineoplastic
Methotrexate	Antineoplastic
Thioguanine	Antineoplastic
Amiodarone	Cardiovascular
Atorvastatin	Cardiovascular
Hydralazine	Cardiovascular
Methyldopa	Cardiovascular
Quinidine	Cardiovascular
Simvastatin	Cardiovascular
Carbamazepine	CNS
Chlorpromazine	CNS
Dantrolene	CNS
Halothane	CNS
Phenytoin/Fosphenytoin	CNS
Valproate	CNS
Estrogens/Progestins	Endocrine
Propylthiouracil	Endocrine
Steroids	Endocrine
Ticlopidine	Hematologic
Azathioprine/Mercaptopurine	Immunomodulatory
Infliximab	Immunomodulatory

Generic name	Medication type
Interferon-b	Immunomodulatory
Allopurinol	Rheumatologic
Auranofin/Gold	Rheumatologic
Sulfasalazine	Rheumatologic
Disulfiram	Substance abuse

Odds ratios and 95% CI for each medication group, and risk of acute liver failure

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
Entire population						
Quinolones[14]	2.80 (2.38-3.31)	<.0001	1.07 (0.89-1.28)	0.5027	1.05 (0.87-1.28)	0.6075
Hepatotoxic medications[15]	3.17 (2.90-3.48)	<.0001	1.58 (1.42-1.75)	<.0001	**1.37 (1.23-1.54)**	**<.0001**
Other antibiotics[16]	2.80 (2.49-3.16)	<.0001	1.05 (0.92-1.20)	0.4878	1.03 (0.89-1.20)	0.6528
Non-antibiotics[17]	7.61 (6.91-8.37)	<.0001	6.69 (6.05-7.39)	<.0001	**6.52 (5.86-7.25)**	**<.0001**
Comorbidity level						

[11] Base model: age, sex, race variables, and the tested medication group
[12] Minimally adjusted model: base model, and the other medication groups
[13] Maximally adjusted model: minimally adjusted, and complicated diabetes mellitus, alcohol abuse and socioeconomic status (census division, hospital (urban/rural) and insurance)
[14] Quinolone antibiotics
[15] Non-quinolone hepatotoxic medications
[16] Non-quinolone, non-hepatotoxic antibiotics
[17] All other medications combined

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
CMI:0-6						
Quinolones	5.43 (3.58-8.22)	<.0001	2.11 (1.32-3.37)	0.0018	**2.56 (1.54-4.27)**	**0.0003**
Hepatotoxic medications	3.05 (2.49-3.73)	<.0001	1.39 (1.10-1.77)	0.0065	1.28 (0.99-1.66)	0.0651
Other antibiotics	3.66 (2.82-4.75)	<.0001	1.20 (0.88-1.63)	0.2455	1.16 (0.84-1.62)	0.3694
Non-antibiotics	8.35 (7.03-9.93)	<.0001	7.55 (6.32-9.03)	<.0001	**7.89 (6.49-9.59)**	**<.0001**
CMI:7-9						
Quinolones	1.27 (0.83-1.94)	0.2799	0.85 (0.53-1.38)	0.5171	0.87 (0.54-1.42)	0.5762
Hepatotoxic medications	1.19 (0.92-1.53)	0.1805	0.82 (0.62-1.09)	0.1763	0.82 (0.61-1.10)	0.1798
Other antibiotics	1.58 (1.15-2.18)	0.0054	1.30 (0.90-1.88)	0.1589	1.31 (0.90-1.92)	0.1605
Non-antibiotics	3.14 (2.37-4.15)	<.0001	3.23 (2.40-4.34)	<.0001	**3.03 (2.22-4.13)**	**<.0001**
CMI:10+						

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
Quinolones	1.12 (0.69-1.83)	1.830	0.93 (0.55-1.58)	0.7824	0.80 (0.44-1.44)	0.4567
Hepatotoxic medications	1.52 (1.11-2.06)	0.0084	1.02 (0.71-1.46)	0.9222	1.08 (0.73-1.60)	0.7158
Other antibiotics	1.09 (0.73-1.61)	0.6879	0.81 (0.52-1.27)	0.3579	0.78 (0.48-1.26)	0.3036
Non-antibiotics	2.62 (1.86-3.70)	<.0001	2.74 (1.85-4.04)	<.0001	**2.58 (1.68-3.96)**	**<.0001**
Sex						
Women						
Quinolones	3.10 (2.45-3.91)	<.0001	1.13 (0.87-1.47)	0.3505	1.16 (0.88-1.54)	0.2899
Hepatotoxic medications	3.11 (2.74-3.54)	<.0001	1.51 (1.31-1.75)	<.0001	**1.33 (1.14-1.56)**	**0.0003**
Other antibiotics	2.85 (2.42-3.37)	<.0001	1.06 (0.89-1.30)	0.4482	1.04 (0.85-1.27)	0.7119
Non-antibiotics	7.59 (6.66-8.65)	<.0001	6.72 (5.85-7.70)	<.0001	**6.51 (5.63-7.53)**	**<.0001**
Men						

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
Quinolones	2.55 (2.02-3.22)	<.0001	1.00 (0.77-1.30)	0.9803	0.97 (0.73-1.27)	0.8008
Hepatotoxic medications	3.24 (2.84-3.70)	<.0001	1.66 (1.43-1.93)	<.0001	**1.41 (1.20-1.65)**	**<.0001**
Other antibiotics	2.75 (2.31-3.27)	<.0001	1.02 (0.83-1.25)	0.8593	1.00 (0.81-1.24)	0.9694
Non-antibiotics	7.70 (6.68-8.87)	<.0001	6.72 (5.79-7.79)	<.0001	**6.65 (5.69-7.78)**	**<.0001**
Race Class						
Caucasians						
Quinolones	2.59 (2.15-3.12)	<.0001	1.00 (0.81-1.23)	<.0001	0.97 (0.78-1.21)	0.7690
Hepatotoxic medications	3.04 (2.73-3.38)	<.0001	1.52 (1.34-1.71)	<.0001	**1.36 (1.20-1.54)**	**<.0001**
Other antibiotics	2.72 (2.37-3.12)	<.0001	1.05 (0.90-1.23)	0.5596	1.06 (0.90-1.25)	0.4729
Non-antibiotics	7.34 (6.58-8.18)	<.0001	6.56 (5.85-7.35)	<.0001	**6.47 (5.74-7.29)**	**<.0001**
African Americans						

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
Quinolones	3.33 (2.24-4.95)	<.0001	1.31 (0.84-2.05)	0.2283	1.43 (0.88-2.30)	0.1458
Hepatotoxic medications	3.29 (2.67-4.06)	<.0001	1.74 (1.37-2.22)	<.0001	**1.37 (1.05-1.80)**	**0.0215**
Other antibiotics	2.80 (2.11-3.71)	<.0001	1.03 (0.74-1.42)	0.8794	0.88 (0.62-1.25)	0.4624
Non-antibiotics	7.65 (6.10-9.60)	<.0001	6.53 (5.15-8.27)	<.0001	**6.86 (5.25-8.96)**	**<.0001**
Others						
Quinolones	6.35 (2.88-13.98)	<.0001	1.66 (0.70-3.97)	0.2505	1.63 (0.52-5.13)	5.126
Hepatotoxic medications	4.78 (3.29-6.94)	<.0001	1.74 (1.12-2.71)	0.0141	1.16 (0.66-2.06)	0.6006
Other antibiotics	4.31 (2.66-6.99)	<.0001	1.19 (0.66-2.15)	0.5543	1.00 (0.45-2.22)	0.9936
Non-antibiotics	12.09 (7.88-18.56)	<.0001	9.56 (6.08-15.02)	<.0001	**7.46 (4.24-13.13)**	**<.0001**
Age						
0-60						

	Base[11] OR (95% CI)	p-value	Minimally adjusted[12] maOR (95% CI)	p-value	Maximally adjusted[13] aOR (95% CI)	p-value
Quinolones	6.15 (4.32-8.77)	<.0001	1.70 (1.14-2.56)	0.0102	**1.91 (1.21-3.00)**	**0.0053**
Hepatotoxic medications	5.01 (4.17-6.02)	<.0001	2.23 (1.80-2.77)	<.0001	**1.67 (1.31-2.14)**	**<.0001**
Other antibiotics	4.62 (3.65-5.83)	<.0001	1.22 (0.92-1.62)	0.1629	1.22 (0.89-1.67)	0.2280
Non-antibiotics	10.71 (9.00-12.73)	<.0001	8.81 (7.37-10.54)	<.0001	**8.73 (7.15-10.65)**	<.0001
61-75						
Quinolones	3.29 (2.55-4.26)	<.0001	1.24 (0.93-1.66)	<.0001	1.30 (0.95-1.78)	0.0989
Hepatotoxic medications	3.30 (2.84-3.83)	<.0001	1.51 (1.27-1.80)	<.0001	**1.33 (1.11-1.59)**	**0.0025**
Other antibiotics	2.86 (2.34-3.49)	<.0001	1.05 (0.83-1.32)	0.6920	1.03 (0.80-1.31)	0.8420
Non-antibiotics	7.59 (6.44-8.94)	<.0001	6.49 (5.45-7.72)	<.0001	**6.25 (5.21-7.50)**	**<.0001**
76+						
Quinolones	1.45 (1.08-1.95)	0.0124	0.69 (0.51-0.95)	0.0243	0.65 (0.47-0.90)	0.0094

	Base[11] **OR (95% CI)**	**p-value**	**Minimally adjusted[12]** **maOR (95% CI)**	**p-value**	**Maximally adjusted[13]** **aOR (95% CI)**	**p-value**
Hepatotoxic medications	2.24 (1.92-2.61)	<.0001	1.37 (1.15-1.62)	0.0003	**1.29 (1.08-1.54)**	**0.0045**
Other antibiotics	1.97 (1.62-2.40)	<.0001	0.95 (0.76-1.19)	0.6580	0.95 (0.75-1.19)	0.6328
Non-antibiotics	5.37 (4.57-6.32)	<.0001	5.15 (4.34-6.11)	<.0001	**5.16 (4.32-6.16)**	**<.0001**

Odds ratios and 95% CI for the individual quinolones and risk of acute liver failure

	Base[18] OR (95% CI)	p-value	Minimally adjusted[19] maOR (95% CI)	p-value	Maximally adjusted[20] aOR (95% CI)	p-value
Entire population						
Ciprofloxacin	2.74 (2.12-3.54)	<.0001	1.29 (0.98-1.69)	0.0706	1.22 (0.91-1.64)	0.1754
Levofloxacin	2.35 (1.88-2.93)	<.0001	0.89 (0.71-1.13)	0.3497	0.90 (0.70-1.15)	0.3966
Moxifloxacin	2.92 (1.75-4.89)	<.0001	1.43 (0.85-2.42)	0.1799	1.46 (0.85-2.50)	0.1720
Comorbidity level						
CMI:0-6						
Ciprofloxacin	8.11 (4.32-15.23)	<.0001	4.06 (1.99-8.28)	0.0001	**5.11 (2.39-10.94)**	<.0001
Levofloxacin	3.42 (1.89-6.19)	<.0001	1.21 (0.64-2.27)	0.5547	1.44 (0.72-2.86)	0.3015
Moxifloxacin	3.45 (0.68-17.44)	0.1346	1.78 (0.34-9.21)	0.4923	1.98 (0.35-11.33)	0.4420
CMI:7-9						

[18] *Base model: age, sex, race variables, and the tested medication group*
[19] *Minimally adjusted model: base model, and the other medication groups*
[20] *Maximally adjusted model: minimally adjusted, and complicated diabetes mellitus, alcohol abuse and socioeconomic status (census division, hospital (urban/rural) and insurance)*

	Base[18] OR (95% CI)	p-value	Minimally adjusted[19] maOR (95% CI)	p-value	Maximally adjusted[20] aOR (95% CI)	p-value
Ciprofloxacin	1.58 (0.71-3.48)	0.2604	1.19 (0.51-2.77)	0.6839	1.21 (0.51-2.84)	0.6658
Levofloxacin	1.02 (0.61-1.73)	0.9341	0.65 (0.37-1.17)	0.1511	0.67 (0.37-1.22)	0.1884
Moxifloxacin	2.09 (0.48-9.00)	0.3240	1.73 (0.40-7.48)	0.4619	1.66 (0.37-7.36)	0.5061
CMI:10+						
Ciprofloxacin	0.91 (0.41-2.03)	0.8107	0.77 (0.33-1.77)	0.5362	0.69 (0.28-1.72)	0.4261
Levofloxacin	1.10 (0.60-2.02)	0.7584	0.96 (0.51-1.81)	0.8884	0.86 (0.43-1.74)	0.6810
Moxifloxacin	3.51 (0.61-20.32)	0.1609	2.56 (0.44-15.00)	0.2969	1.26 (0.17-9.32)	0.8240
Sex						
Women						
Ciprofloxacin	3.14 (2.24-4.39)	<.0001	1.31 (0.92-1.88)	0.1365	1.30 (0.88-1.91)	0.1833
Levofloxacin	2.40 (1.73-3.33)	<.0001	0.89 (0.63-1.26)	0.5242	0.93 (0.64-1.36)	0.7123
Moxifloxacin	2.40 (1.00-5.76)	0.0491	1.45 (0.61-3.46)	0.4011	1.43 (0.57-3.61)	0.4508
Men						

	Base[18] OR (95% CI)	p-value	Minimally adjusted[19] maOR (95% CI)	p-value	Maximally adjusted[20] aOR (95% CI)	p-value
Ciprofloxacin	2.31 (1.55-3.45)	<.0001	1.25 (0.82-1.91)	0.3002	1.13 (0.72-1.79)	0.5907
Levofloxacin	2.33 (1.73-3.14)	<.0001	0.90 (0.65-1.24)	0.5068	0.89 (0.64-1.25)	0.5051
Moxifloxacin	3.18 (1.68-6.01)	0.0004	1.35 (0.69-2.63)	0.3796	1.43 (0.73-2.82)	0.2988
Race Class						
Caucasians						
Ciprofloxacin	2.82 (2.10-3.78)	<.0001	1.36 (0.99-1.86)	0.0552	1.25 (0.90-1.74)	0.1910
Levofloxacin	2.24 (1.75-2.86)	<.0001	0.85 (0.66-1.11)	0.2283	0.84 (0.64-1.10)	0.2031
Moxifloxacin	1.66 (0.83-3.33)	0.1535	0.74 (0.37-1.51)	0.4120	0.87 (0.43-1.77)	0.7011
African Americans						
Ciprofloxacin	2.44 (1.34-4.46)	0.0037	1.11 (0.59-2.09)	0.7584	1.08 (0.53-2.20)	0.8376
Levofloxacin	2.25 (1.25-4.08)	0.0071	0.94 (0.50-1.75)	0.8355	1.19 (0.60-2.33)	0.6229
Moxifloxacin	5.41 (2.11-13.91)	0.0005	3.49 (1.31-9.30)	0.0124	2.70 (0.96-7.60)	0.0594
Others						

	Base[18] OR (95% CI)	p-value	Minimally adjusted[19] maOR (95% CI)	p-value	Maximally adjusted[20] aOR (95% CI)	p-value
Ciprofloxacin	2.17 (0.63-7.44)	0.2200	0.60 (0.16-2.23)	0.4487	0.61 (0.10-3.66)	3.657
Levofloxacin	11.83 (3.08-45.42)	0.0003	3.94 (0.96-16.14)	0.0571	2.91 (0.56-15.09)	15.091
Moxifloxacin	--	--	--	--	--	--
Age						
0-60						
Ciprofloxacin	4.97 (2.98-8.30)	<.0001	1.72 (0.99-2.99)	0.0547	1.64 (0.87-3.09)	0.1250
Levofloxacin	4.92 (2.98-8.14)	<.0001	1.36 (0.78-2.34)	0.2774	1.62 (0.88-2.97)	0.1218
Moxifloxacin	3.68 (1.17-11.56)	0.0258	1.79 (0.54-5.91)	0.3430	2.36 (0.66-8.49)	0.1870
61-75						
Ciprofloxacin	2.93 (1.95-4.41)	<.0001	1.37 (0.89-2.11)	0.1515	1.38 (0.87-2.20)	0.1768
Levofloxacin	2.98 (2.13-4.17)	<.0001	1.11 (0.77-1.60)	0.5707	1.19 (0.81-1.77)	0.3749
Moxifloxacin	3.22 (1.35-7.70)	0.0085	1.43 (0.58-3.51)	0.4372	1.37 (0.54-3.47)	0.5048
76+						

	Base[18] OR (95% CI)	p-value	Minimally adjusted[19] maOR (95% CI)	p-value	Maximally adjusted[20] aOR (95% CI)	p-value
Ciprofloxacin	1.56 (0.98-2.50)	0.0635	0.88 (0.54-1.44)	0.6052	0.80 (0.48-1.33)	0.3911
Levofloxacin	1.23 (0.84-1.82)	0.2926	0.59 (0.39-0.88)	0.0101	0.54 (0.35-0.82)	0.0036
Moxifloxacin	2.33 (1.06-5.14)	0.0362	1.33 (0.60-2.98)	0.4829	1.42 (0.63-3.22)	0.3999

Odds ratios and 95% CI for complicated diabetes mellitus and alcohol abuse, and risk of acute liver failure

	Diabetes mellitus, complicated	p-value	Alcohol abuse	p-value
Entire population	**2.09 (1.85-2.36)**	**<.0001**	**1.92 (1.55-2.39)**	**<.0001**
Comorbidity score level				
CMI: 0-6	0.92 (0.59-1.42)	0.7050	**2.00 (1.23-3.25)**	**0.0052**
CMI: 7-9	0.76 (0.54-1.05)	0.0939	0.88 (0.47-1.62)	0.6732
CMI: 10+	0.91 (0.64-1.28)	0.5864	0.63 (0.28-1.43)	0.2696
Sex				

	Diabetes mellitus, complicated	p-value	Alcohol abuse	p-value
Women	**2.18 (1.83-2.60)**	**<.0001**	**2.60 (1.79-3.79)**	**<.0001**
Men	**2.03 (1.71-2.42)**	**<.0001**	**1.59 (1.21-2.08)**	**0.0008**
Race				
Caucasians	**2.02 (1.75-2.33)**	**<.0001**	**2.00 (1.54-2.58)**	**<.0001**
African Americans	**2.22 (1.68-2.92)**	**<.0001**	**1.80 (1.14-2.86)**	**0.0122**
Others	**3.02 (1.61-5.65)**	**0.0006**	1.34 (0.44-4.10)	0.6106
Age (tertiles)				
0-60	**2.90 (2.21-3.80)**	**<.0001**	**2.28 (1.64-3.17)**	**<.0001**
61-75	**2.06 (1.70-2.50)**	**<.0001**	**1.92 (1.31-2.80)**	**0.0007**
76+	**1.71 (1.39-2.11)**	**<.0001**	1.31 (0.74-2.33)	0.3561

Results from recent studies on quinolone antibiotics and risk of acute liver failure

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
Alshammari 2014 [3] (USA)	National hospital admissions data on Veterans Affairs	Case-control (population-based)	6.5 years (Jan 2002 - Jun 2008)	• Cases: 7,862 with exposure to quinolones in the 6 months prior to admission • Controls: 45,512 nonexposed controls	58 ± 12.7 years Men: 96.3% Women: 3.7%	ALF • Women • Younger age • Non-Caucasians	• Ciprofloxacin [OR: 1.29 (95% CI: 1.05–1.58)]
Kaye 2014 [4] (USA)	HealthCore Integrated Research Database	Case-control (population-based)	6 years (Jan 2010 - Dec 2015	• Cases: 3,151 inpatients diagnosed with acute liver failure between 2010-2015, with no current or prior liver conditions, minimum of 1 year in the Healthfacts system and no missing data on age or sex	65.2 (±17.9) Men: 46.8% Women: 53.2%	Liver injury (ALF, subacute liver failure, hepatic coma and unspecified hepatitis)	• Levofloxacin [aOR: 3.2 (95% CI: 1.8–5.8)] • Moxifloxacin [aOR: 2.3 (95% CI: 1.1–4.7)]

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
				• Controls: 15,755 (up to 5 controls per case, without replacement), without acute liver failure diagnosis, and under the same inclusion criteria as cases			
Paterson 2012 [5] (Canada)	• Prescriptions: Ontario Drug Benefit Database • Hospital visits: Canadian Institute for Health Information Discharge Abstract Database,	Case-control (population-based	9 years (Apr 2002 - Mar 2011)	• Cases: 144 outpatients 66+ yo, with no history of liver disease, and who were admitted to hospital for acute liver injury within 30 days of receiving a prescription for 1 of 5 broad-spectrum antibiotic agents: moxifloxacin, levofloxacin,	77.4 ± 7.9 years Men: 52.8% Women: 47.2%	ALF 66+ year old	• Moxifloxacin [OR: 2.20 (95% CI: 1.21–3.98)] • Levofloxacin [OR: 1.85 (95% CI, 1.01–3.39)]

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
	• Drug claims: Ontario Health Insurance Plan (OHIP) Database • Demographics: OHIP Registered Persons Database.			ciprofloxacin, cefuroxime axetil or clarithromycin • Controls: 1409 (up to 10 age- and sex-matched to each case), who had received a study antibiotic, without acute liver injury.			
Orman 2011 [6] (USA)	DILIN Study	Cohort (prospective)	5 years, 4 months (Sep 2004 - Jan 2010)	• Cases: 12 of 679 patients enrolled in the DILIN study, who had received a fluoroquinolone (ciprofloxacin, moxifloxacin, levofloxacin, or gatifloxacin) in the last 6	57 years (range: 23–80) Men: 5 (42%) Women: 7 (58%)	ALF	• Ciprofloxacin: 6 • Moxifloxacin: 4 • Levofloxacin: 1 • Gatifloxacin: 1

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
				months and developed hepatotoxicity (in this study: symptoms appeared 1-39 days from quinolone administration)			
This review 2020 (USA)	Cerner Healthfacts EHR database	Case-control (hospital inpatients)	6 years (Jan 2010 - Dec 2015	• Cases: 3,151 inpatients diagnosed with acute liver failure between 2010-2015, with no current or prior liver conditions, minimum of 1 year in the Healthfacts system and no missing data on age or sex	65.2 (±17.9) Men: 46.8% Women: 53.2%	ALF • No overall ALF risk • ≤ 60 years of age • Women • African Americans	**overall ALF risk:** • Quinolones: [aOR: 1.05 (95% CI: 0.87-1.28)] • Moxifloxacin [aOR: 1.46 (95% CI: 0.85-2.50)] • Ciprofloxacin [aOR: 1.22 (95% CI: 0.91-1.64)] **CMI (0-6):** • Quinolones: [aOR: 2.56 (95% CI: 1.54-4.27)]

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
				• Controls: 15,755 (up to 5 controls per case, without replacement), without acute liver failure diagnosis, and under the same inclusion criteria as cases			• Ciprofloxacin [aOR: 5.11 (95% CI: 2.39-10.94)] • Moxifloxacin [aOR: 1.98 (95% CI: 0.35-11.33)] • Levofloxacin [aOR: 1.44 (95% CI: 0.72-2.86)] **Age (0-60):** • Quinolones: [aOR: 1.91 (95% CI: 1.21-3.00)] • Moxifloxacin: [aOR: 2.36 (95% CI: 0.66-8.49)] • Ciprofloxacin: [aOR: 1.64 (95% CI: 0.87-3.09)] • Levofloxacin: [aOR: 1.62 (95% CI: 0.88-2.97)] **Sex (Women):**

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) Sex	Hepatic failure risk	Agent
							• Quinolones: [aOR: 1.16 (95% CI: 0.88-1.54)] • Moxifloxacin: [aOR: 1.43 (95% CI: 0.57-3.61)] • Ciprofloxacin: [aOR: 1.30 (95% CI: 0.88-1.91)] **Race (African Americans):** • Quinolones: [aOR: 1.43 (95% CI: 0.88-2.30)] • Moxifloxacin: [aOR: 2.70 (95% CI: 0.96-7.60)] • Levofloxacin: [aOR: 1.19 (95% CI: 0.60-2.33)] • Ciprofloxacin: [aOR: 1.08 (95% CI: 0.53-2.20)]

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STROBE Statement – Chapter 4

STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) Statement – Checklist of items that should be included in reports of case-control studies

Item	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title (page 1) Abstract (page 2, line 40)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, line 33
Introduction			
Background / rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3, line 63
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3, line 87
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4, line 94
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4, line 109

Item	Item No	Recommendation	Reported on Page No.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 5, line 118
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 5, line 125
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5, line 140
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 4, line 94
Bias	9	Describe any efforts to address potential sources of bias	Page 6, line 169
Study size	10	Explain how the study size was arrived at	Page 7, line 187
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	Page 5, line 140

Item	Item No	Recommendation	Reported on Page No.
		describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6, line 157
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7, line 175
		(*c*) Explain how missing data were addressed	Page 5, line 118
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 5, line 125
		(*e*) Describe any sensitivity analyses	Page 7, line 174
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7, line 187 Page 8, Figure 1
		(b) Give reasons for non-participation at each stage	Page 7, line 187
		(c) Consider use of a flow diagram	Page 8, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	Page 9, line 204

Item	Item No	Recommendation	Reported on Page No.
		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Page 9, Table 1
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Page 12, line 222 Page 12, Table 2 Page 14, line 232 Page 14, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 14, line 241 Page 16, Table 4 Page 17, Table 5
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses	

Item	Item No	Recommendation	Reported on Page No.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 18, line 305
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 20, line 341
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 18, line 305
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 19, line 321
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 21, line 373

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Retinal detachment I: FAERS analysis

Chapter 5: Systemic quinolones and risk of retinal detachment I: Analysis of data from the US FDA adverse event reporting system

Abstract

Purpose: Quinolone are a class of antibiotics that are globally preferred for treating a wide range of bacterial infections due to their potency, broad coverage, favorable pharmacologic profile, easier patient compliance, and mostly mild to moderate adverse reactions. Spontaneous adverse event reports and data from some pharmacoepidemiologic studies raised concerns regarding a possible link between quinolones and risk of retinal detachment (RD). This study examined adverse drug event (ADE) reports submitted to FDA adverse event reporting system (FAERS) for evidence on quinolone-associated RD risk.

Methods: We identified all reports of RD in FAERS between 2010-2019. We compared ADE signals between quinolones and selected medications that were previously associated with RD, and with reference drugs not known to cause RD. For signal detection, we used two disproportionality techniques: the proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS), which are known for their higher sensitivity and specificity for ADE signal detection, respectively [1-3].

Results: Moxifloxacin was the only quinolone with a positive and significant PRR signal for RD, with 20 reports as a primary suspect (PS) between 2010-2019 [PRR: 2.54 (1.60, 4.04); EBGM: 2.21 (1.41, 3.02)]. No positive signals were identified with other quinolones.

Conclusion: Moxifloxacin is the only quinolone with a positive disproportionality signal for RD. Further epidemiologic research is needed to clarify the association between moxifloxacin and the risk of RD.
Keywords: Quinolones; retinal detachment, FDA Adverse Event Reporting System, FAERS, pharmacovigilance, drug safety.

Introduction

Quinolone antibiotics comprise highly preferred treatment options against a wide range of infections worldwide. This globally popular preference is primarily based on their effectiveness against different types of bacteria [4-15]. Whereas their use was associated with predominantly tolerable and reversible adverse drug reactions (ADR), some were serious enough to warrant revised safety warnings or even withdrawal from the market [10-19]. Despite the emergence of resistant bacterial strains, ADR, and availability of other treatment alternatives, quinolones remain one of the most popular choices for the treatment of bacterial infections by physicians worldwide [20-25].

Retinal detachment (RD) is a condition involving the separation of the retinal layer of the eye from the underlying tissues, which may lead to complete loss of vision in the affected eye if not managed immediately [26, 27]. This separation takes one of two forms: the more common rhegmatogenous type or the less common exudative type[26, 27]. The annual incidence of RD ranges from 5-14 cases per 100,000 population based on results from studies conducted in the US, Japan, Finland, Sweden and Croatia [27-29].

In response to safety concerns generated by spontaneous FAERS[21] reports [30, 31] regarding a possible association of quinolone antibiotics with RD risk, and results from a 2012 Canadian study [32], the US FDA[22] issued a safety communication flagging this association. Two more recent studies reported similar findings [27, 33]. Other recent epidemiologic studies reported conflicting results on the association of quinolones with risk of RD [30, 34-41].

This present analysis of FAERS data represents the first of a three-part examination to evaluate the association between quinolones and risk of RD. The second and third parts involve analysis of results from systematic review of clinical trials, and a substantive US electronic health records (EHR) database, respectively.

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 US and other countries, and currently represents one of the most commonly used sources for early identification and characterization of ADE [42-49].

Whereas ADE reporting is mandatory by pharmaceutical companies, it is done on voluntary basis by healthcare providers and consumers [42-45, 47-50]. Spontaneous reporting signals (SRS)-generated signals usually prompt detailed validation studies,

[21] *FAERS: FDA Error Reporting System*
[22] *FDA: Food and Drug Administration*

which would provide further evidence on product safety under real-world conditions of use [42, 44, 46-48, 51]. Timely signal generation is particularly valuable with rare or long-term ADE, or with newly introduced drugs [16].

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 [45, 52]. FAERS generates data in a raw format on quarterly basis, which can be downloaded from the US Food & Drug Administration (FDA) Website [53]. With drugs listed according to both generic and brand names [52, 54], 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 [45, 52].

ADE are coded in FAERS using the MedDRA (Medical Dictionary for Regulatory Activities) Preferred Terms (PTs) [55]. We selected our PT of interest as 'retinal detachment' (RD) for identification of reports relevant to our outcome of interest. For assessing differences in reporting of quinolone-related ADE reports, we searched the literature to identify medications for eligibility for inclusion in one of two groups with either high risk (the "Most RD" group) or no risk of RD (the "No RD" group).

We first identified a number of medications for inclusion as positive controls (Most RD), based on earlier reports linking them to RD. These medications include the anti-malarial chloroquine [56, 57], anti-psychotic thioridazine [58], iron-chelating agent deferoxamine [59], and a number of chemotherapeutic agents/medications [60-64]. To the best of our knowledge, apart from quinolones, no other antibiotics were flagged or reported for possible association with RD risk.

Similarly, based on earlier studies that identified macrolides, β-lactams, and short-acting β-agonists (blood pressure medications) as showing no added RD risk, we selected a number of these antibiotics as our reference group (No RD) [41, 65]. A full list of medications included in each of the three medication groups (quinolones, positive controls, and reference controls) is shown in Table 15.

We extracted ADE reports on RD between the first quarter of 2010 and the last quarter of 2019 for all medications in the three medication groups. Our primary analysis involved RD reports where these medications were flagged as a primary suspect (PS) drugs only to maximize the strength of any potential RD signal and minimize any potential source of bias. Finally, we merged all databases to collate all relevant information for all reports relevant to our investigation. We then repeated the same analysis spanning the same time period considering primary or secondary suspect (PS/SS) drugs combined.

Table 15: Antibiotics investigaged in relation to reports of drug-induced retinal detachment in the FDA event reporting database (FAERS, 2010-2019)

Quinolone antibiotics	Ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin
Reference antibiotics (No RD)	Azithromycin, clarithromycin, erythromycin, fidaxomicin, spiramycin, telithromycin, solithromycin
Positive control medications (Most RD)	Cobimetinib, trametinib, dabrafenib, hyrdoxychloroquine, deferoxamine, nivolumab, atezolizumab, pembrolizumab, ipilimumab

Data analysis

Prior to analysis, the raw FAERS data were subject to 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 version of the FAERS database, we initiated the present analysis by conducting a detailed validation involving examination of RD reports linked to all medications in the different RD groups: positive controls (Most RD), reference controls (No RD) and quinolones [41, 56-65]. We then conducted two primary analyses, the first comparing RD reports linked to the 'Most RD' medications to those linked to the 'No RD' antibiotics, and the second comparing reports linked to quinolone antibiotics with those linked to 'No RD' reference antibiotics.

In analyzing these ADE reports, we used two of the most frequently used data mining techniques for signal detection with spontaneous reporting data: the proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS) [1], chosen because of their higher sensitivity and specificity for ADE signal detection, respectively. Each technique involved 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 [66, 67]. A positive and significant disproportionality measure suggests 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 [66, 67].

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 3 reports is considered to be significant evidence of disproportionate reporting [1, 67]. An observed MGPS signal with the value of the lower boundary of EBGM[23] higher than 2 and a minimum of 1 report [1] is considered to be significant evidence of disproportionate reporting. For each one of our major analyses (quinolones vs. reference antibiotics, and positive controls vs reference antibiotics), we first examined reports where the antibiotic is reported as a PS only, and then as PS/SS combined.

Results

As of December 31, 2019, there were 19,193,312 ADE reports in the FAERS database between 1969 and 2019, as reported on their online dashboard. As the rates of ADE reporting and the quality of reports were of higher rigor from 2010 and onwards, we focused our examination on reports from 2010-2019, which included 74% of all reports submitted to FAERS between 1969-2019 (Table 16). Our cleaned version of the FAERS data showed that all RD-specific reports between 2010-2019 represented only 20% of all RD reports submitted to FAERS between 1969-2019. There were only 12 reports of RD linked to quinolones prior to 2010 compared to 72 between 2010-2019, supporting our decision to focus on the most recent decade of data from FAERS (Figure 1).

[23] EBGM: The Empirical Bayesian Geometric Mean value calculated by the MGPS method

Examining reports linked to each of the individual quinolones and positive controls as PS/SS combined showed that positive controls (3.2%) accounted for double the percentage of reports linked to quinolones (1.6%) between 2010-2019. Considering only PS drugs, the frequency of RD reports was similar for quinolones (1.49%) and positive controls (1.99%).

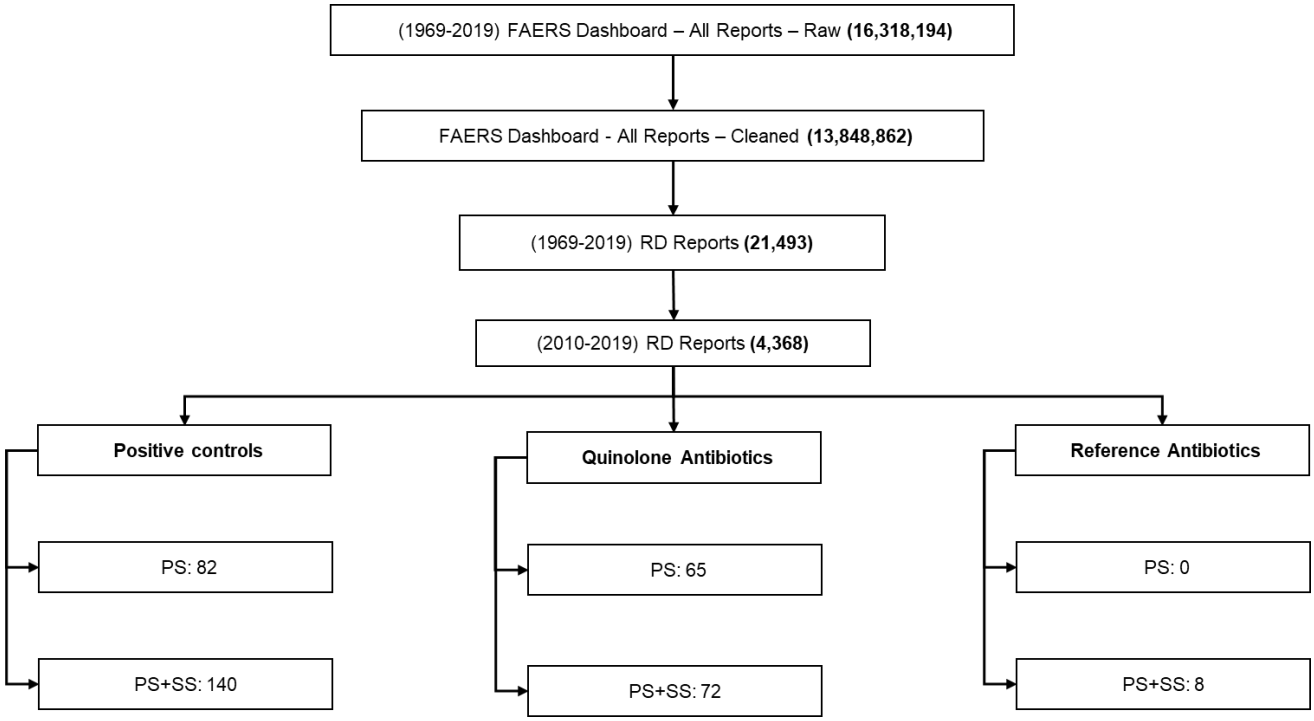

Figure 5: FAERS data cleaning flowchart for identification of RD reports (2010-2019)

Table 16: Total and RD-specific reports from FAERS, 1969-2019

Adverse event reports	**1969-2019**	**1969-2009**	**2010-2019**
FAERS, total number of reports	16,318,194	4,949,058	11,369,136

Adverse event reports	1969-2019	1969-2009	2010-2019
RD, total number of reports	21,493	17,125	4,368
RD, quinolone antibiotics*	84	12	72

** All RD reports linked to study medications as primary (PS) or secondary (SS) suspects.*

Description of RD reports

Analysis of RD reports submitted between 2010-2019 involved more women (53%) then men (38%), with sex either missing or intentionally omitted in 9% of the reports. There were very few reports involving individuals in the first three decades of life (3%) and those older than 80 years old (1%). RD reporting frequency increased gradually in the fourth and fifth decades of age before reaching its peak in the sixth decade (32%), and declining afterwards. Age was missing in 17% of reports.

Reports were predominately submitted by doctors, pharmacists and other health professionals (82%), with only 1% being submitted by lawyers. Most of the reports came from United States (16%), Germany (14%), Canada (12%) and France (11%). Table 17 shows a detailed listing of the distribution of RD report characteristics between 2010-2019.

Table 17: Characteristcs of all RD reports as PS, SS, C and I in FAERS, 2010-2019

Characteristics	Number of reports (%)
Sex	
Women	151 (53%)
Men	108 (38%)

Characteristics	Number of reports (%)
Missing	25 (9%)
Age	
0-10	4 (1%)
11-20	0 (0%)
21-30	7 (2%)
31-40	16 (6%)
41-50	21 (7%)
51-60	90 (32%)
61-70	52 (18%)
71-80	42 (15%)
81+	4 (1%)
Missing	48 (17%)
Reported by	
Medical doctors	124 (44%)
Other Health Professionals	99 (35%)
Consumers	42 (15%)
Pharmacists	8 (3%)
Lawyers	3 (1%)
Missing	8 (3%)
Geographic location	
United States	45 (16%)
Germany	39 (14%)

Characteristics	Number of reports (%)
Canada	34 (12%)
France	32 (11%)
Others	84 (30%)
Missing	50 (18%)

Positive controls vs. reference antibiotics

Reports of RD were identified for only three of the positive controls, with the most powerful signal demonstrated by Cobimetinib, with 13 reports and a strong and significant disproportionality signal [PRR: 14.05 (8.02,24.63); EBGM: 8.81 (4.87,12.76)]. This was followed by two medications with strong and significant PRR signals, although not a significant EBGM signal. Trametinib was mentioned as a PS on 6 reports [PRR: 4.12 (1.83,9.27); EBGM: 3.15 (1.12,5.19)], and Dabrafenib on 12 reports [PRR: 2.32 (1.29,4.16); EBGM: 2.05 (1.09,3.00)]. Results from all examined positive controls compared to reference antibiotics between 2010-2019 are listed in Table 18.

Table 18: Reports with RD signals with positive controls (Most RD), compared to reference antibiotics (No RD), as primary suspect (PS) and primary and secondry suspects combined (PS/SS), FAERS, 2010-2019

Drug	PS/SS	Count	Expected	PRR PS (LB, UB)	EBGM PS (LB, UB)
Cobimetinib	PS	13	1.032	14.05 (8.02,24.63)	8.81 (4.87,12.76)
	PS/SS	33	2.137	19.18 (13.19,27.91)	12.70 (9.09,16.31)
Trametinib	PS	6	1.562	4.12 (1.83,9.27)	3.15 (1.12,5.19)
	PS/SS	16	6.149	2.85 (1.71,4.76)	2.48 (1.48,3.49)
Dabrafenib	PS	12	5.608	2.32 (1.29,4.16)	2.05 (1.09,3.00)
	PS/SS	17	6.423	2.92 (1.77,4.80)	2.53 (1.53,3.52)
Hydroxychloroquine	PS	9	6.256	1.53 (0.78,2.99)	1.41 (0.66,2.16)
	PS/SS	13	33.170	0.36 (0.21,0.64)	0.40 (0.22,0.58)
Deferoxamine	PS	2	0.703	3.00 (0.75,12.07)	2.08 (-0.08,4.24)
	PS/SS	3	1.097	2.86 (0.92,8.96)	2.19 (0.26,4.12)
Nivolumab	PS	23	35.959	0.63 (0.41,0.97)	0.64 (0.43,0.86)
	PS/SS	27	34.272	0.79 (0.52,1.18)	0.79 (0.54,1.04)
Atezolizumab	PS	4	4.246	0.99 (0.37,2.65)	0.95 (0.21,1.68)
	PS/SS	6	4.299	1.46 (0.65,3.30)	1.35 (0.48,2.23)
Pembrolizumab	PS	9	16.608	0.55 (0.28,1.07)	0.56 (0.26,0.85)
	PS/SS	12	16.286	0.75 (0.42,1.34)	0.74 (0.40,1.09)
Ipilimumab	PS	4	10.213	0.40 (0.15,1.07)	0.42 (0.09,0.75)

Drug	PS/SS	Count	Expected	PRR PS (LB, UB)	EBGM PS (LB, UB)
	PS/SS	13	16.510	0.80 (0.46,1.41)	0.79 (0.44,1.15)

Quinolones vs. reference antibiotics

Out of all examined quinolone antibiotics, only moxifloxacin was identified in 20 reports between 2010-2019; analysis of these reports revealed a positive PRR signal with no corresponding EBGM signal [PRR: 2.54 (1.60,4.04); EBGM: 2.21 (1.41,3.02)]. Neither ciprofloxacin nor levofloxacin showed elevated signals, despite being identified in 27 and 18 reports, respectively. No other quinolones were identified in any other FAERS reports during 2010-2019. Table 5 shows the number of RD reports with quinolone antibiotics as a PS or SS drug, compared to reports with reference antibiotics during the interval 2010-1019.

Table 19: Reports with RD signals due to quinolone antibiotics, compared to reference antibiotics (No RD), as primary suspect (PS) and primary and secondry suspects combined (PS/SS), FAERS, 2010-2019

Drug	PS/SS	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
Ciprofloxacin	PS	27	22.470	1.30 (0.87,1.95)	1.20 (0.82,1.57)
	PS/SS	29	20.812	1.61 (1.05,2.46)	1.38 (0.96,1.80)
Levofloxacin	PS	18	31.515	0.56 (0.34,0.91)	0.58 (0.36,0.80)

Drug	PS/SS	Count	Expected	PRR (LB-UB)	EBGM (LB-UB)
	PS/SS	22	30.259	0.70 (0.44,1.11)	0.73 (0.48,0.99)
Moxifloxacin	PS	20	8.768	**2.54 (1.60,4.04)**	2.21 (1.41,3.02)
	PS/SS	21	8.131	**3.08 (1.92,4.96)**	2.49 (1.61,3.37)

Discussion

Our analysis of adverse drug event reports in FAERS between 2010-2019 revealed evidence of disproportionate reporting for moxifloxacin. There was no evidence that any of the other quinolone antibiotics might be associated with RD, despite being included in multiple reports during the same time interval.

In line with the reported evidence, persons in their fifth and sixth decades of life were more likely to report RD compared to other age groups. Women were considerably more likely to report RD than men. Considering the simplicity of diagnosing RD and the finding that 82% of RD reports were submitted by healthcare professionals (including 44% by physicians), leaves little room reporting a wrong diagnosis.

Although it is not uncommon to observe an increase in reporting of ADE upon the release of a new drug, which is known as the Weber Effect [66], our study examines FAERS reports starting in 2010, four years following the release of the latest quinolone. Whereas FAERS does not allow for calculating or comparing incidence rates, our finding that quinolones were involved in 1.49% of RD reports compared to 1.88% with drugs that had been reported earlier for being associated with retinal detachment calls for confirmatory epidemiologic studies.

Our analysis focused on examining FAERS data between 2010-2019 for ADE reports linking quinolones to RD. This period is characterized by the highest reporting rates and highest quality of reported data, which adds power to our findings.
Our findings were in line with recent epidemiologic reviews and studies [27, 31-38] that reported insufficient evidence to implicate quinolones with RD risk, which was later confirmed in safety communications by FDA [67] and Health Canada [68].

Spontaneous reporting systems (SRS) are valuable tools for flagging new or unexpected ADE in a timely manner, particularly those that are rare or life-threatening [48]. However, identification of disproportionate reporting is meant to generate rather than confirm hypotheses of specific ADE associations. Nevertheless, in the absence of analytic pharmacoepidemiologic studies, regulators may use evidence from SRS studies to enforce label changes or even market withdrawal of certain drugs [8, 69, 70]

By design, FAERS, as an SRS, is unable to capture detailed information on ADE risks or compare different safety profiles as it lacks drug utilization details, which is required to assess ADE incidence rates [1, 39, 41, 43, 44, 47, 48, 71, 72]. Furthermore, it is entirely dependent on reporter's skills and motivation, leading to potential reporting bias [39, 41, 44, 45, 48, 72-78]. FAERS does not also show information on risk factors such as current or prior comorbidities or diagnostic test results, which may reveal an underlying cause for the ADE other than the implicated PS or SS drug. False negatives and false positives are not unlikely occurrences with FAERS as it can miss possible associations, or capture associations that will prove to be false, respectively [45, 71, 72, 76]. The present analysis does not explicitly consider the potential for drug-drug interactions, including

interactions among two (or more) drugs within the three groups examined in the present analysis.

Conclusion

With only 20 of 4,368 RD reports for all PS or SS drug suspects identified in FAERS between 2010-2019, moxifloxacin was the only quinolone to show a disproportionality signal for RD. This finding indicates a need for more specialized epidemiologic investigations to verify any possible quinolone-associated RD risk. No other signals were identified with other quinolones. Pending confirmation in analytic pharmacoepidemiologic studies, caution should be exercised in interpreting our study results as reflecting a causal relationship between moxifloxacin and RD.

Author contributions

The primary author, Mohamed Taher, designed and implemented this study including statistical analysis, interpretation of findings and drafting of this manuscript. Christopher Gravel, Abdallah Alami, and Derek Tsui contributed to statistical analysis, as well as critical review and approval of this manuscript. Lise Bjerre, Franco Momoli, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the study, as well as critical review and approval of the manuscript.

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Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa.

Declaration of Interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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Chapter 6 (RD-SR)

Retinal detachment II: Systematic review of clinical trials

Systemic quinolones and risk of retinal detachment II: Systematic review of clinical trials

Abstract

Background: Quinolones represent a popular group of antibiotics favored by physicians worldwide due to their potency, broad spectrum, unique mechanism of action and reasonable safety. The exponential growth in prescription of quinolones, among other antibiotics, has been accompanied by a corresponding increase in antimicrobial resistance and in the occurrence of some adverse reactions. Nevertheless, physicians continue to increasingly prescribe quinolones, despite the availability of other treatment alternatives.

Objective: To assess the association of quinolone antibiotics and risk of retinal detachment based on a systematic review of original clinical trials in which a quinolone antibiotic was tested or used as a comparator.

Methods: We examined 4 major bibliographic databases, 8 clinical trial registries, and grey literature sources including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies. We also examined the bibliographies of publications selected for inclusion in our review for other relevant studies. PROSPERO registration number: CRD42020148747.

Results: We identified 1,554 original studies that examined quinolone antibiotics conducted between 1974 and 2020 on participants of different ages, ethnic/racial backgrounds and health status. Among 145 eligible trials, no cases of retinal detachment were reported.

Conclusion: There was no evidence from clinical trials to question systemically administered quinolone antibiotics as a cause of retinal detachment in patients with no prior history of eye diseases.

Keywords: Quinolones; retinal detachment; clinical trials; systematic review

Introduction

Quinolones are synthetic antibiotics introduced in the mid-1960s that continue to gain popularity on a global scale [1]. The popularity of quinolones may be attributed to their potency, broad spectrum, unique mechanism of action and strong pharmacologic profile relative to other classes of antibiotics [2-8]. Despite the occurrence of adverse reactions, emergence of resistance, and the availability of other treatment alternatives [2], quinolones continue to be widely prescribed. Whereas quinolones are generally considered as having a reasonable safety profile, with most adverse reactions being mild to moderate and self-limiting, some quinolones have been withdrawn from the market and others have sustained restricted usage advisories [8-11].

A number of studies reported ocular adverse reactions in association with use of quinolone antibiotics, including retinal hemorrhage [12], macular degeneration [13], corneal perforation [14] and optic neuropathy [15]. These adverse reactions were reported in association with either systemic or topical quinolone formulations.

The present review focuses on the occurrence of retinal detachment within thirty days following the administration of a single systemically administered quinolone antibiotic. Retinal detachment (RD) is a serious condition involving the separation of the

retinal layer of the eye from its underlying tissues with the subsequent loss of blood and oxygen supply, leading to loss of vision in the affected eye(s) if left untreated [16].

Quinolones are known for having a destructive effect on connective tissues [17], which led to a class warning for association with adverse reactions such as tendon rupture [12, 18]. This may represent a plausible mechanism for causing retinal detachment in humans [19] and animals [20]. Some FDA reports and other epidemiologic studies reported an increased risk of retinal detachment with use of different formulations of quinolones [19, 21-36].

We conducted this systematic review of clinical trials as part of a multipronged strategy to conclusively verify such an association. The first part provides summary of evidence based on data mining of reports recorded in the US FDA Adverse Event Reporting System (FAERS). The third part involves a case-control study based on a major US electronic health records database.

Table 20: Four generations of quinolone antibotics

Generation	Quinolone Antibiotic
First	Nalidixic acid, cinoxacin, flumequine, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin
Second	Lomefloxacin, norfloxacin, ciprofloxacin, ofloxacin, fleroxacin, pefloxacin, rufloxacin
Third	Levofloxacin, sparfloxacin, temafloxacin, grepafloxacin, balofloxacin, pazufloxacin, tosufloxacin

Fourth	Moxifloxacin, gemifloxacin, trovafloxacin, gatifloxacin, clinafloxacin, garenoxacin, sitafloxacin, prulifloxacin, finafloxacin

Methods

Review strategy

We implemented a comprehensive, multi-step search strategy to identify original studies that examined the association between quinolone antibiotics and the risk of retinal detachment. The search was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and following the specific guidance provided by the Cochrane Collaboration [37]. The search strategy was designed and implemented on March 8-9, 2019, and updated on August 2-4, 2020 to identify all relevant original studies related to each of the 30 members of the quinolone class of antibiotics shown in Table 7.

We searched major bibliographic databases and clinical trial registries as well as major grey literature sources such as drug review networks and databases of pharmaceutical companies, relevant national and international agencies and international conference proceedings. Experts were consulted on all components of the review strategy and implementation. We also inspected the bibliographies of examined studies for additional relevant studies not already identified via the original search. This review has been registered in the international prospective register of systematic reviews PROSPERO under reference number CRD42020148747.

Criteria for considering studies for this review

With our focus on the safety of quinolone antibiotics within the present review, the outcome measure of interest is the number of *de novo* cases of retinal detachment

within 30 days of systemic administration of a quinolone antibiotic in patients with no prior history of eye disease.

Clinical trial eligible for inclusion in this review comprise those examining a single systemically-administered quinolone antibiotic compared to a placebo, another non-quinolone antibiotic or non-quinolone-containing antibiotic combination. Trials with multiple arms, which include a single quinolone in one arm and a placebo in one of the other arms, would be considered eligible for inclusion.

Trials where participants had prior or existing eye diseases; trials testing topical/non-systemically administered quinolones, a combination of quinolones, or a combination of quinolones and other drugs; and trials testing efficacy of different doses of a quinolone antibiotic, or testing a quinolone against another quinolone, were excluded from this review. Cross-over trials were also excluded to avoid possible carry-over effects from the initial intervention. Non-original studies, observational studies and trials where no results were available were also excluded. We enforced no restrictions on participants' age, sex, racial/ethnicity or any other background characteristics.

Search methods for identification of studies

Bibliographic databases searched included Medline (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present), EMBASE (Embase Classic + Embase 1947 to 2017 May 02), Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL (Cumulative Index to Nursing and Allied Health Literature).

Search terms included medical subject headings and text word search for quinolone antibiotics both as a class and as individual agents, in addition to retinal

detachment as the outcome of interest. The search integrated a specialized search algorithm with reported high efficiency for identifying clinical trials in MEDLINE Ovid, EMBASE and CINAHL [38]. We also used another specialized algorithm for identifying adverse reactions [39] with the MEDLINE and EMBASE databases only. No language, time or other filters were used to limit the search output. A detailed description of the search terms used is provided in Supplementary Material I. A complete listing of studies considered, with reasons for exclusion of studies not meeting our inclusion criteria, is provided in Supplementary Material II.

An extensive search was conducted to identify all clinical trials conducted on any of the quinolone antibiotics documented in any of the major international clinical trial registries, including the World Health Organization Clinical Trials Registry (ICTRN), United States Clinical Trials Database (Clinicaltrials.gov), as well as similar registries from the European Union, United Kingdom, Netherlands, Japan, China, South Korea, India, Iran, Australia and South Africa. We also searched major grey literature sources including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies.

Duplicate screening of titles and abstracts (Level 1) and full-text examination (Level 2) were performed independently by two reviewers (MT and MH) to identify studies eligible for inclusion in the review, based on the predetermined eligibility criteria. Conflicts identified in each step were resolved via consensus between the reviewers or via a panel of senior scientists (FM, LB, DM, DK), prior to moving to the next step.

In the event where multiple publications report on an original study/trial, only the primary record was assessed in the review. All studies which reported on, or have been

indexed to a specific original study/trial, were listed under the original study/trial record. Maximum diligence was adopted to include all publications reporting on each of the included clinical trials. A complete listing of original studies and associated publications is included in Supplementary Material III.

Data collection and analysis

We collated the references identified from all sources using EndNote [40] reference management application version 8.2, which was used to flag potential duplicates, with manual resolution employed to remove actual duplicates.
We used Review Manager application version 5.3.[41] to collate and classify all examined studies, tabulate the reasons for study exclusion, and compile the information required for generating the PRISMA flow diagram [42].

Data abstraction spreadsheets were developed to abstract the following information: study (design, year, country), tested quinolone antibiotic (name, dose, route of administration, frequency, duration), control agent/group (type, name, dose, route of administration, frequency, duration), participant characteristics (total sample size, age, sex, race), comorbidities (prior eye diseases/conditions, diabetes, alcohol abuse), treatment period and follow-up (average, range, years), main result(s), and authors' reported conclusion. Reviewers' comments, if any, are also included.

Results

Flow of studies

The search strategy resulted in retrieval of 3,461 records, including 3,430 records from bibliographic databases and clinical trial registries, 30 records from the databases of pharmaceutical companies, and 1 record from an international conference. Electronic and manual de-duplication resulted in removal of 787 records.

Examined studies spanned across 5 decades (1974 – 2020), peaking between 2008 – 2016 (Figure 2). These studies were conducted in many countries, with participants from all sexes, ethnicities, age groups and with different types and levels of comorbidity.

Title and abstract screening of 2,674 records resulted in the exclusion of 147 studies due to irrelevancy of exposure (n=23) or publication type (n=124), leaving 2,527 studies for full text examination. An additional 181 trials were not published at the time of completion of this review were also excluded.

Upon full-text examination, we were able to identify 1,554 original and 973 non-original records (duplicate reports on original studies). Only 145 original trials were found to meet the eligibility criteria; however, none of them reported a single case of retinal detachment in persons with otherwise healthy eyes. An additional 1,409 original studies were excluded for different reasons (see Supplementary Material II). A detailed PRISMA flow diagram for studies examined in this review [42] is shown in Figure 3

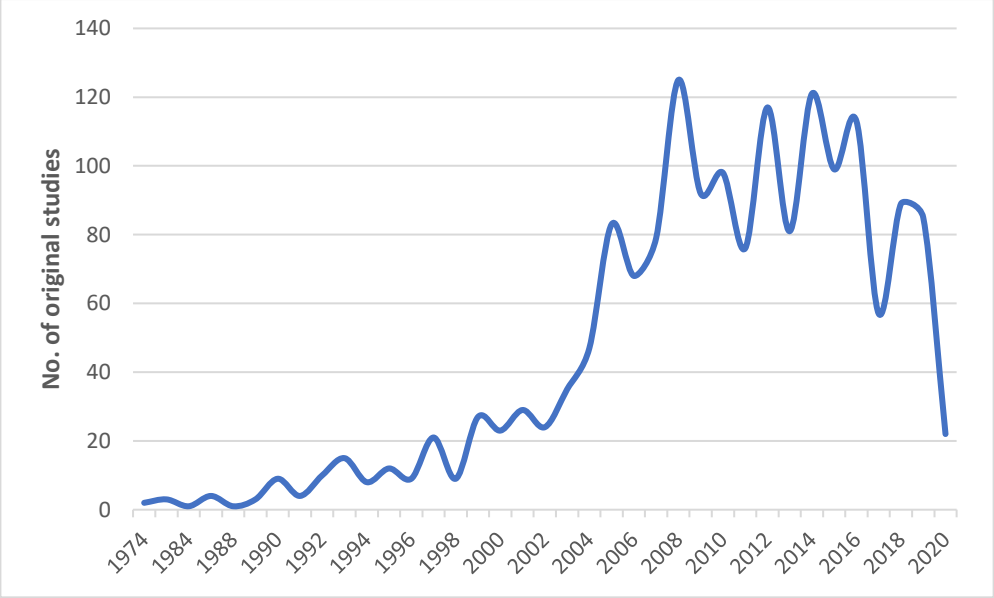

Figure 6: Temporal distribution of clinical trials on quinolone antibiotics

Characteristics of examined studies

None of the identified original clinical trials that met the eligibility criteria in our review reported any cases of retinal detachment during the conduct of these clinical trials. Therefore, we were unable to retain any studies for further qualitative or quantitative analyses.

Whenever a study had more than one reason for exclusion, we reported the study using the most compelling reason. A summary list of the reasons for exclusion of all studies examined in this review is shown in Table 9. A detailed listing of the reason of exclusion for each study and the full citations of original and supporting studies are provided in Supplementary Material II and III, respectively.

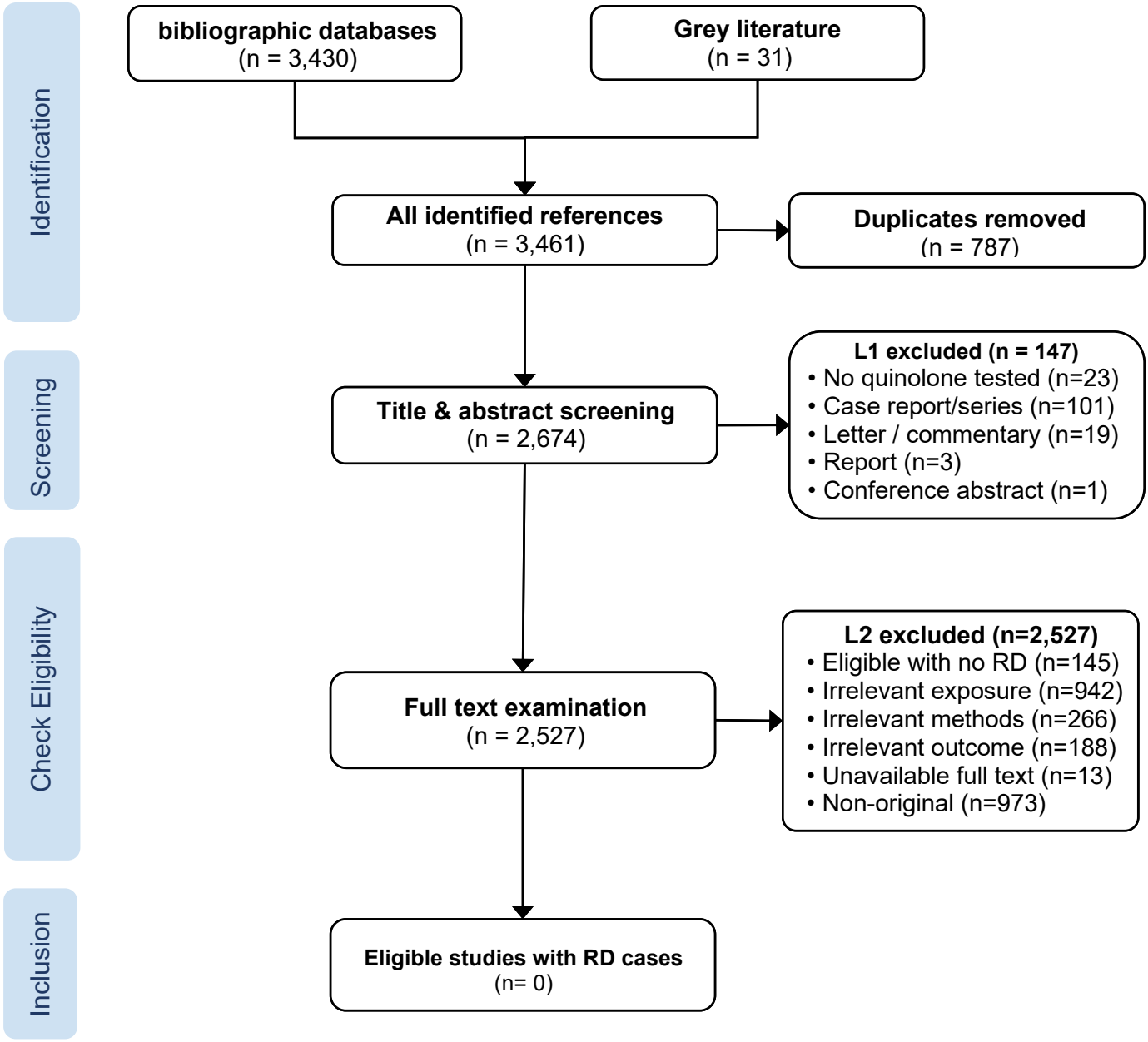

Figure 7: PRISMA flow diagram for studies conducted on/using quinolone antibiotics

Table 21: Reasons for study exclusion

Exclusion group	Reason for exclusion	Records
Level 1: Title and abstract screening (n=147)		
Irrelevant exposure	Irrelevant (no quinolone tested)	23
Irrelevant publication type	Case report/case series	101
	Letter / commentary	19
	Report	3
	Conference abstract	1
Level 2: Full-text examination (n=2527)		
Eligible trial with no RD	Eligible trial with no reporting on RD	145
Irrelevant exposure	Quinolone combined with other drugs	294
	Cross-over trial	196
	Trial with multiple arms	150
	Quinolone in a topical formulation	129
	Trial with a single arm	100
	Quinolones on multiple arms	73
Irrelevant methods	Observational study	147
	Review article	102
	Not a clinical trial	17
Irrelevant outcome	No results available	181
	Current or prior eye disease	7
Unavailable full-text	Reference could not be retrieved	13
Non-original	Additional reports on original studies	973

Discussion

This review covers all publicly available original, peer-reviewed publications, as well as data from clinical trial registries and other grey literature sources for unpublished evidence that were conducted using quinolone antibiotics. There were no reports of retinal detachment in any study participants, with no history of eye diseases, within thirty days of receiving treatment with a single systemically administered quinolone antibiotic in any of the 145 studies included in this review.

Considering its serious nature, the occurrence of retinal detachment would mandate stoppage of treatment and transfer of participant to a hospital/emergency room setting for an immediate medical/surgical intervention to avoid permanent visual loss. Therefore, it is extremely unlikely that there were any undetected/unreported cases of such an adverse reaction.

Clinical trials represent the most rigorous assessment of human drug safety, which is used to examine the association between a specific drug(s) and specific adverse reactions (ADRs) [43, 44]. However, clinical trials may be subject to a lack of representativeness since the characteristics of the selected participants will not necessarily mirror the general population with regards to demographics and other relevant risk factors that may impact how the drug works under real-life situations [43-47]. Because clinical trials typically involve a limited number of patients, it is possible that they might miss rare ADRs such as retinal detachment [43, 44, 46, 48, 49].

To the best of our knowledge, this is the first systematic review that examined all original studies that investigate the association of systemically administered quinolone antibiotics with the risk of retinal detachment.

Conclusion

Although the lack of reporting of a single case of retinal detachment in all trials examined in this review is encouraging, the possibility that use of quinolones could increase the risk of retinal detachment in the general population under real world conditions of use cannot be ruled out. Observational pharmacoepidemiologic studies based on large and diverse patient populations are needed to confidently confirm or reject an association between use of quinolones and increased risk of retinal detachment.

Author contributions

The primary author, Mohamed Taher, designed and implemented the review strategy including search methodology, design of study screening and data abstraction forms, reference collation and full-text acquisition, screening and examination of the identified references, data abstraction and drafting of this manuscript. Mohamed Habsah independently assessed all studies examined in this review. Lise Bjerre, Franco Momoli, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the review design and implementation, as well as critical review the manuscript.

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Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa.

Declaration of interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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Supplementary Material – Chapter 6

Medline (Ovid)

#	Medline query
1	quinolones/
2	quinolones.tw.
3	4-quinolones/
4	4-quinolones.tw.
5	fluoroquinolones/
6	fluoroquinolones.tw.
7	nalidixic acid/
8	nalidixic acid.tw.
9	cinoxacin/
10	cinoxacin.tw.
11	flumequine.tw.
12	oxolinic acid/
13	oxolinic acid.tw.
14	piromidic acid/
15	piromidic acid.tw.
16	rosoxacin.tw.
17	lomefloxacin.tw.
18	norfloxacin/
19	norfloxacin.tw.
20	enoxacin/

21 enoxacin.tw.

22 ciprofloxacin/

23 ciprofloxacin.tw.

24 ofloxacin/

25 ofloxacin.tw.

26 fleroxacin/

27 fleroxacin.tw.

28 pefloxacin/

29 pefloxacin.tw.

30 rufloxacin.tw.

31 levofloxacin/

32 levofloxacin.tw.

33 sparfloxacin.tw.

34 temafloxacin.tw.

35 grepafloxacin.tw.

36 balofloxacin.tw.

37 pazufloxacin.tw.

38 tosufloxacin.tw.

39 moxifloxacin.tw.

40 gemifloxacin.tw.

41 trovafloxacin.tw.

42 gatifloxacin.tw.

43 clinafloxacin.tw.

44 garenoxacin.tw.

45 sitafloxacin.tw.

46 prulifloxacin.tw.

47 finafloxacin.tw.

48 or/1-47

49 Aripiprazole.tw.

50 48 not 49

51 (ae or co or de).fs. or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

52 Retinal Detachment/

53 Retinal Perforations/

54 (retin* adj3 detachment*).tw.

55 (retin* adj3 perforation*).tw.

56 (retin* adj3 injur*).tw.

57 (retin* adj3 tear*).tw.

58 (retin* adj3 break*).tw.

59 (retin* adj3 hole*).tw.

60 or/52-59

61 Randomized Controlled Trials as Topic/

62 randomized controlled trial/

63 Random Allocation/

64 Double Blind Method/

65 Single Blind Method/

66 clinical trial/

67 clinical trial, phase i.pt.

68 clinical trial, phase ii.pt.

69 clinical trial, phase iii.pt.

70 clinical trial, phase iv.pt.

71 controlled clinical trial.pt.

72 randomized controlled trial.pt.

73 multicenter study.pt.

74 clinical trial.pt.

75 exp Clinical Trials as topic/

76 or/61-75

77 (clinical adj trial$).tw.

78 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

79 PLACEBOS/

80 placebo$.tw.

81 randomly allocated.tw.

82 (allocated adj2 random$).tw.

83 or/77-82

84 76 or 83

85 case report.tw.

86 letter/

87 historical article/

88 or/85-87

89 84 not 88

90 50 and 51

91 50 and 51 and 60

92 50 and 51 and 60 and 89

93 50 and 60 and 89

94 50 and 60

EMBASE

#	Embase query
1	quinolone derivative/
2	4 quinolone derivative/
3	quinolones.tw.
4	fluoroquinolones.tw.
5	nalidixic acid/
6	nalidixic acid.tw.
7	cinoxacin/
8	cinoxacin.tw.
9	flumequine/
10	flumequine.tw.
11	oxolinic acid/
12	oxolinic acid.tw.
13	piromidic acid/
14	piromidic acid.tw.
15	rosoxacin/
16	rosoxacin.tw.
17	lomefloxacin/
18	lomefloxacin.tw.
19	norfloxacin/
20	norfloxacin.tw.
21	enoxacin/
22	enoxacin.tw.

23 ciprofloxacin/

24 ciprofloxacin.tw.

25 ofloxacin/

26 ofloxacin.tw.

27 fleroxacin/

28 fleroxacin.tw.

29 pefloxacin/

30 pefloxacin.tw.

31 rufloxacin/

32 rufloxacin.tw.

33 levofloxacin/

34 levofloxacin.tw.

35 sparfloxacin/

36 sparfloxacin.tw.

37 temafloxacin/

38 temafloxacin.tw.

39 grepafloxacin/

40 grepafloxacin.tw.

41 balofloxacin/

42 balofloxacin.tw.

43 pazufloxacin/

44 pazufloxacin.tw.

45 tosufloxacin/

46 tosufloxacin.tw.

47 moxifloxacin/

48 moxifloxacin.tw.

49 gemifloxacin/

50 gemifloxacin.tw.

51 trovafloxacin/

52 trovafloxacin.tw.

53 gatifloxacin/

54 gatifloxacin.tw.

55 clinafloxacin/

56 clinafloxacin.tw.

57 garenoxacin/

58 garenoxacin.tw.

59 sitafloxacin/

60 sitafloxacin.tw.

61 prulifloxacin/

62 prulifloxacin.tw.

63 finafloxacin/

64 finafloxacin.tw.

65 or/1-64

66 Aripiprazole.tw.

67 65 not 66

68 (ae or co or de).fs. or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

69 retina detachment/

70 (retin* adj3 detachmen*).tw.

71 retina tear/

72 (retin* adj3 tear*).tw.

73 retina injury/

74 (retin* adj3 injur*).tw.

75 or/69-74

76 Clinical Trial/

77 Randomized controlled trial/

78 Randomization/

79 Single blind procedure/

80 Double blind procedure/

81 Crossover procedure/

82 Placebo/

83 Randomi?ed controlled trial$.tw.

84 RCT.tw.

85 Random allocation.tw.

86 Randomly allocated.tw.

87 Allocated randomly.tw.

88 (allocated adj2 random).tw.

89 Single blind$.tw.

90 Double blind$.tw.

91 ((treble or triple) adj blind$).tw.

92 Placebo$.tw.

93 Prospective study/

94 or/76-93

95 Case study/

96 Case report.tw.

97 Abstract report/

98 Letter/

99 or/95-98

100 94 not 99

101 67 and 68

102 67 and 68 and 75

103 67 and 68 and 75 and 100

104 67 and 75

105 67 and 75 and 100

CENTRAL[24]

#	CENTRAL query
1	Quinolones/
2	quinolones.tw.
3	4-Quinolones/
4	4-quinolones.tw.
5	Fluoroquinolones/
6	fluoroquinolones.tw.
7	Nalidixic acid/
8	nalidixic acid.tw.
9	Cinoxacin/
10	cinoxacin.tw.
11	flumequine.tw.
12	Oxolinic acid/
13	oxolinic acid.tw.
14	Piromidic acid/
15	piromidic acid.tw.
16	rosoxacin.tw.
17	lomefloxacin.tw.
18	Norfloxacin/
19	norfloxacin.tw.
20	Enoxacin/

[24] Cochrane Central Register of Controlled Trials

21 enoxacin.tw.

22 Ciprofloxacin/

23 ciprofloxacin.tw.

24 Ofloxacin/

25 ofloxacin.tw.

26 Fleroxacin/

27 fleroxacin.tw.

28 Pefloxacin/

29 pefloxacin.tw.

30 rufloxacin.tw.

31 Levofloxacin/

32 levofloxacin.tw.

33 sparfloxacin.tw.

34 temafloxacin.tw.

35 grepafloxacin.tw.

36 balofloxacin.tw.

37 pazufloxacin.tw.

38 tosufloxacin.tw.

39 moxifloxacin.tw.

40 gemifloxacin.tw.

41 trovafloxacin.tw.

42 gatifloxacin.tw.

43 clinafloxacin.tw.

44 garenoxacin.tw.

45 sitafloxacin.tw.

46 prulifloxacin.tw.

47 finafloxacin.tw.

48 or/1-47

49 aripiprazole.tw.

50 48 not 49

51 retinal detachment/

52 (retina* adj3 detachment).tw.

53 retinal perforations/

54 (retina* adj3 perforation*).tw.

55 (retina* adj3 tear*).tw.

56 (retina* adj3 injur*).tw.

57 or/51-56

58 50 and 57

CINAHL[25]

#	CINAHL query
1	(MM "Antiinfective Agents, Quinolone+") OR "quinolones"
2	(MM "Antiinfective Agents, Fluoroquinolone+") OR "fluoroquinolones"
3	"nalidixic acid"
4	(MM "Cinoxacin") OR "cinoxacin"
5	"flumequine"
6	"oxolinic acid"
7	"piromidic acid"
8	"rosoxacin"
9	"lomefloxacin"
10	(MM "Norfloxacin") OR "norfloxacin"
11	(MM "Enoxacin") OR "enoxacin"
12	(MM "Ciprofloxacin") OR "ciprofloxacin"
13	(MM "Ofloxacin") OR "ofloxacin"
14	"fleroxacin"
15	"pefloxacin"
16	"rufloxacin"
17	"levofloxacin"
18	"sparfloxacin"
19	"temafloxacin"
20	"grepafloxacin"

[25] Cumulative Index to Nursing and Allied Health Literature

21 "balofloxacin"

22 "pazufloxacin"

23 "tosufloxacin"

24 "moxifloxacin"

25 "gemifloxacin"

26 (MM "Trovafloxacin+") OR "trovafloxacin"

27 (MM "Alatrofloxacin")

28 "gatifloxacin"

29 "clinafloxacin"

30 "garenoxacin"

31 "sitafloxacin"

32 "prulifloxacin"

33 "finafloxacin"

34 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33

35 (MM "Retinal Detachment") OR "retinal detachment"

37 (MM "Eye Tear")

38 "retinal injury"

39 "retinal perforation"

40 S35 OR S37 OR S38 OR S39

41 MH "Clinical Trials+"

42 PT Clinical Trial

43 TX clinic* n1 trial*

44 TX ((trebl* n1 blind*) or (trebl* n1 mask*))

45 TX ((tripl* n1 blind*) or (tripl* n1 mask*))

46 TX ((doubl* n1 blind*) or (doubl* n1 mask*))

47 TX ((singl* n1 blind*) or (singl* n1 mask*))

48 TX randomi* control* trial*

49 TX randomi$ control trial or rct or clinical trial

50 MH "Random Assignment"

51 TX random* allocat*

52 TX allocat* random*

53 TX placebo*

54 MH "Placebos"

55 MH "Quantitative Studies"

56 (S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55)

57 S30 AND S34

58 S34 AND S40 AND S56

Other Sources

Other sources include: World Health Organization Clinical Trials Registry (ICTRN), United States Clinical Trials Database (ClinicalTrials.gov). Additionally, major grey literature sources were searched including international conference proceedings, drug review networks and databases of pharmaceutical companies for ongoing or unpublished studies. Names of the individual quinolone antibiotics were the only terms used to search these resources to ensure inclusivity of all possible studies that examined quinolones for all outcomes including those other than the outcome of interest for this current review.

Reasons for excluding studies (sorted by reason for exclusion)

A. Case reports/case series

1. Airey 2003
2. Alan 2011
3. Alcalde 1995
4. Alegre 1990
5. Amitrano 1992
6. Assy 2007
7. Barcena 2005
8. Bataille 2002
9. Bhagirath 2008
10. Bjornsson 2000
11. Blum 1991
12. Bussieres 1995
13. Carrascosa 2009
14. Chen 2000
15. Cheung 2004
16. Çoban 2005
17. Coelho 2011
18. Coleman 2002
19. Colucci 2012
20. Contreras 2001
21. Davoren 1993
22. Elliott 2016
23. Figueira-Coelho 2010
24. Franco 2009
25. Fuchs 1994
26. Garcia 2014
27. Garcia-Aparicio 2010
28. Gauffre 1997
29. Goertz 2010
30. Goetz 2003
31. Gonzalez 2000
32. Grassmick 1992
33. Gulen 2015
34. Hautekeete 1995a
35. Heluwaert 2003
36. Henann 2001
37. Hofer 1992
38. Hsu 2014
39. Idilman 2006
40. Karim 2001
41. Khan 2006
42. Kilincalp 2012
43. Lazarczyk 2001
44. Lee S 2015
45. Levine 2014
46. Li X 2015
47. Lopez-Navidad 1990
48. Lucena 2000
49. Marra 2004
50. Miftode 2008
51. Mitra 2009
52. Nicholson 2002
53. Nisly 2007

54. Nori 2004

55. Odeh 1992

56. Palmero 2013

57. Pubill-Fondevila 2013

58. Puerto 2010

59. Rached-Mohassel 1974

60. Ravenscroft 2005

61. Ridzon 1997

62. Roberts 2011

63. Romero-Gomez 1999

64. Scherer 2005

65. Schwalm 2003

66. Soto 2002

67. Spahr 2001

68. Titos-Arcos 2011

69. Tunuguntla 2005

70. Vazquez 2008

71. Villeneuve 1995

72. Zaidi 2003

73. Zimpfer 2004

74. Berrocal 2001

75. Brydak-Godowska 2011

76. Chaudhry 1998

77. Chhablani 2013

78. Chiquet 2007

79. Chui 2014

80. Gangrade 2019

81. Hoffart 2015

82. Hotta 2014

83. Javey 2010

84. Le 1998

85. Lee YW 2020

86. Mancano 2014

87. Ohana 1998

88. Pathengay 2004

89. Pfahler 2009

90. Roy 2013

91. Sharma 2016

92. Shin 2018

93. Silva 2008

94. Singh 2018

95. Sirbat 1983

96. Sirbat 1983a

97. Smiddy 1991

98. Sugiyama 2010

99. Uy 2001

100. Won 2013

101. Yu J 2019

B. Conference Abstract

102. Prescott 2006

C. Cross-over Trial

103. ACTRN12609000544279 2009

104. ACTRN12616001558415 2016

105. Biering-Sorensen 1994

106. Blouin 1992

107. CTRI/2009/091/000332 2009

108. CTRI/2012/03/002497 2012

109. EUCTR2008-007647-14-FI 2008
110. EUCTR2009-011044-20-GB 2009
111. EUCTR2013-001976-39-NL 2013
112. Garcia-Calvo 2001
113. Johannesen 2016
114. JPRN-UMIN000005924 2011
115. JPRN-UMIN000007489 2012
116. JPRN-UMIN000009117 2012
117. JPRN-UMIN000015502 2014
118. Kawahara 1995
119. NCT00164112 2005
120. NCT00257452 2005
121. NCT00310596 2006
122. NCT00419783 2007
123. NCT00485667 2007
124. NCT00499642 2007
125. NCT00601432 2008
126. NCT00602589 2008
127. NCT00649155 2008
128. NCT00649662 2008
129. NCT00650351 2008
130. NCT00672399 2008
131. NCT00672984 2008
132. NCT00686179 2008
133. NCT00688493 2008
134. NCT00699504 2008
135. NCT00713336 2008
136. NCT00721344 2008
137. NCT00769041 2008
138. NCT00777595 2008
139. NCT00795145 2008
140. NCT00809289 2008
141. NCT00874237 2009
142. NCT00936871 2009
143. NCT00992329 2009
144. NCT00996021 2009
145. NCT01014247 2009
146. NCT01073891 2010
147. NCT01135680 2010
148. NCT01140425 2010
149. NCT01168895 2010
150. NCT01191723 2010
151. NCT01195675 2010
152. NCT01209026 2010
153. NCT01232413 2010
154. NCT01265641 2010
155. NCT01287793 2011
156. NCT01290900 2011
157. NCT01297062 2011
158. NCT01325415 2011
159. NCT01327066 2011
160. NCT01353729 2011
161. NCT01372345 2011
162. NCT01372358 2011
163. NCT01386593 2011
164. NCT01398293 2011
165. NCT01406262 2011

166. NCT01449188 2011
167. NCT01461460 2011
168. NCT01487135 2011
169. NCT01514929 2012
170. NCT01516372 2012
171. NCT01518699 2012
172. NCT01521377 2012
173. NCT01525394 2012
174. NCT01532115 2012
175. NCT01536951 2012
176. NCT01552928 2012
177. NCT01606436 2012
178. NCT01642485 2012
179. NCT01643889 2012
180. NCT01653990 2012
181. NCT01674218 2012
182. NCT01702376 2012
183. NCT01721135 2012
184. NCT01743677 2012
185. NCT01756495 2012
186. NCT01756521 2012
187. NCT01787357 2013
188. NCT01790087 2013
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215. NCT02170987 2014
216. NCT02172144 2014
217. NCT02182310 2014
218. NCT02183467 2014
219. NCT02207699 2014
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221. NCT02217930 2014
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234. NCT02344303 2015
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263. NCT03164109 2017
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265. NCT03258515 2017
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268. NCT03432884 2018
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D. Current or prior eye disease

299. Aleman 2019

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365. Kusachi 2012
366. Leibovitz 2000
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376. Navasa 2006
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426. O'Doherty 1997
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1693. NTR4047 2013

1694. Ross 2006

1695. Rugendorff 1987

1696. Salam 1988

1697. Sethi 2004

1698. Shah 1999

1699. Stass 2004

1700. Torres 2008

1701. Vinh 2011

PRISMA Checklist – Chapter 6

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO #: CRD42020148747
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7, line 149
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8, line 164
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8, line 190 - 9, line 200
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9, line 203
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9, line 209
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	- 12, line 248 - Supplementary Material II
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, line 145

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12, line 236
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, line 219 Supplementary Material III & IV
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-14, table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Material II
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	- 12, line 235 - 13-14, table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16, line 291
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16, line 299
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17, line 318

Retinal detachment III: Health Facts® analysis

Systemic quinolones and risk of retinal detachment III: A nested case-control study using a US electronic health records database

Abstract

Purpose: Quinolones are popular antibiotics that are known for their potency, broad coverage, and reasonable safety. Their use has been linked to reports of serious adverse events, including retinal detachment (RD). This study aims at examining the possibility of association between systemically administered quinolone antibiotics and RD risk**.**

Methods: We conducted a nested case-control study using electronic health records (EHR) from the Cerner Health Facts® Database. The initial cohort included all patients who were admitted between 2000-2016, with no history of eye disease, and had a minimum medical history of one year in the Health Facts®. Eligible cases comprised inpatients who were first admitted with a primary diagnosis of RD between 2010-2015. Using incidence density sampling, each eligible case was matched without replacement to five unique controls by sex, race, age at index encounter, and period-at-risk. We used conditional logistic regression to calculate odds ratios and 95% CIs for RD risk, adjusting for exposure to other medications, and major risk factors (diabetes mellitus and alcohol abuse). We used the STROBE Statement for reporting on our study.

Results: We identified 772 cases and 3,860 controls. Whereas our primary analysis of all subjects revealed no quinolone-associated RD risk, elevated but non-significant risks were noted in subgroup analyses of African Americans (ciprofloxacin and levofloxacin), those aged 56–70-year-old (moxifloxacin), and women (ciprofloxacin).

Conclusion: Our study did not identify an elevated RD risk within 30 days following systemic administration of quinolone antibiotics. Suggestions of increased risk observed in some population subgroups warrant further investigation.
Keywords: Quinolones, retinal detachment, nested case-control study, electronic health records, pharmacovigilance, drug safety.

Introduction

Quinolones are a popular class of antibiotics that are heavily prescribed worldwide due to their potency, broad coverage, and reasonable safety [1-12]. Known adverse reactions to quinolones are mainly mild to moderate and self-limiting, although some quinolones have caused serious safety concerns, resulting in either revised labeling or market withdrawal [7-16].

The generous prescription of quinolones, among other antibiotics, is associated with a proportional increase in the emergence of quinolone-resistant bacterial strains [17-22]. However, despite the presence of other alternatives, quinolones continue to maintain their unique status as preferred treatments for a wide range of bacterial infections.

Retinal detachment (RD) is a serious medical condition with an annual incidence of 5-14/100,000 as reported from population studies conducted in Sweden, Finland, Croatia, Japan and United States [23-25]. This involves the creation of breaks in the retinal layer with or without separation from its underlying tissues, with the subsequent loss of blood and oxygen supply, which requires urgent medical attention to avoid loss of vision [24, 26].

A possible mechanism for quinolone involvement in RD involves their ability to destroy the collagen content of the vitreous, with the resulting separation of the retina from the underlying tissues, a mechanism that resembles their damaging effect on collagen and connective tissues in joints and muscles, which led to a class-warning for possible tendon rupture [24, 27-33].

Many epidemiologic studies have examined quinolone-associated RD risk, with conflicting results [24, 33-49]. In 2013, the US FDA[26] flagged a safety signal for quinolone-associated RD risk based on spontaneous reports to FAERS[27] [38, 50]. However, in a 2017 drug safety communication, FDA reported on a lack of evidence of an increased RD risk due to quinolones [51]. Similarly, in 2016, Health Canada concluded that the evidence is insufficient to rule out such an association [52].

This study comprises the third part of a comprehensive examination of systemic quinolones and risk of RD. The first part examines evidence from FAERS data and the second part examines evidence from original clinical trials. The third part described in the present paper uses electronic health records to follow up on safety signals identified in the spontaneous reporting data analyzed in the first part of this series.

Methods

This study was approved by the Office of Ethics and Research Integrity of the University of Ottawa, Canada (H02-18-05). All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, NC, USA). Study results are reported in

[26] *FDA: Food and Drug Administration*
[27] *FAERS: FDA Adverse Event Reporting System*

accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines [53].

Data Source

In this study, we analyzed inpatient EHR data from the Cerner Corporation's Health Facts Data Warehouse® (Health Facts®), Kansas City, Missouri, US. This large database includes detailed EHR for almost 70 million deidentified patients (approximately 21.6% of the US population[28]) that were generated between 2000-2016 via nearly 450 million encounters from more than 500 US hospitals. Health Facts® contains detailed patient information such as demographics, extensive medical care details, health care setting, and insurance status. Information on number of cases and the specific ICD9[29] and ICD10[30] codes used to identify RD cases is provided in Supplementary Materials I and II, respectively. All eye diseases leading to exclusion of cases or controls from our study are defined in Supplementary Material III.

Selection of cases and matched controls

We selected an initial cohort comprising all inpatients who were admitted to any of the Health Facts® participating hospitals with no history of eye disease[31] during the period 2000-2016. To allow for a comprehensive assessment of comorbidity of cases and controls, we excluded all patients with a medical history of less than one year in order to properly characterize the health status of study participants. To ensure

[28] *US population as of December 31, 2016: 324,070,652 (https://www.census.gov)*
[29] *International Classification of Diseases, Ninth Revision (ICD-9)*
[30] *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*
[31] *Except for the outcome of interest, retinal detachment (RD)*

consistency in the control matching process, we removed all patients with missing or inconsistent information on any of the matching variables (sex, race, and age at index encounter).

Finally, we restricted our cohort to inpatients for whom the date of index encounter was between 2010-2015, as preliminary exploration of the database revealed very sparse reporting of RD prior to that period. The index date for a case represents the date of the first encounter where a patient was admitted with a primary RD diagnosis; for a control, this date represents the date of the latest inpatient encounter without being diagnosed with RD. We calculated the period-at-risk, which represent the time interval between date of the first recorded inpatient encounter and date of the index encounter, for both cases and controls.

An optimal variable matching approach [54] was used for matching controls to cases without replacement, where each control was matched to a single case. Each case was matched to five controls based on four variables with equal weights: age on day of the index encounter (±1 year), sex, race, and the period-at-risk (±1 year).

Medication exposure

As we are interested in systemic quinolones, all non-systemic formulations were excluded. Inpatient medication exposure was grouped into three classes: quinolones, other antibiotics (excluding quinolones), and all other medications combined (excluding antibiotics). Data on medication exposure was limited to prescriptions filled during inpatient care.

Data analyses

Descriptive analyses

We reported categorical variables as frequencies and percentages, and continuous variables as means with standard deviations. Categorical variables included sex, race (Caucasian, African American, Asian, Hispanic, other); socioeconomic indicators included census region and division; hospital setting (urban/rural); health insurance (insured, non-insured, missing/unknown); and thirty-day exposure to each of the three medication groups and individual quinolones (ever/never). Additional variables included diabetes mellitus (complicated; ever/never) and alcohol abuse.

Continuous variables included age at index encounter, comorbidity status and the number of medications filled during the thirty-day period preceding the index encounter. Age was stratified into 10-year intervals (0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81-90 years). Comorbidity was measured by the score generated via the Hude Quan version [55] of the Elixhauser comorbidity index (CMI) [56], stratified into 5 categories (CMI = 0, 1-5, 6-10, 11-15, and 16+). The number of inpatient medication prescriptions was stratified into five groups (0, 1-3, 4-6, 7-10, and 11+).

Regression analyses

We generated a series of conditional logistic regression models to identify the best estimate of quinolone-associated RD risk, while adjusting for other medication exposures and major confounders. For each medication group, we fitted a base model including only sex, race, age at index encounter as matching variables, and use (ever/never) of the medication group as the independent variable. We then fit a minimally adjusted model including all variables in the base model as well as all other

medication groups (ever/ never). Finally, we fit a maximally adjusted model, extending the minimally adjusted model to include health insurance, census division, hospital setting/type, diabetes mellitus, and alcohol abuse, as potentially important demographic and socioeconomic covariates. To identify the individual quinolone(s) with the strongest possible association with RD risk, we repeated the same series of regression models using exposure to individual quinolones, rather than a class, as predictors of RD.

To avoid possible confounding, we excluded *a priori* all patients with a history of eye diseases. We also adjusted for other major confounders, including health status, major risk factors (diabetes mellitus and alcohol abuse), and socioeconomic status (health insurance and care setting).

Subgroup analyses

To isolate the effect of notable differences in comorbidity and inpatient medication prescribing between cases and controls, we fitted a third series of regression models to different subgroups of our study population via stratifying by sex, race, comorbidity status (tertiles) and age at index encounter (tertiles).

Results

Identification of RD cases

The entire Health Facts® Data Warehouse contained unique patients who were admitted at least once between 2000-2016 to any of the Health Facts® participating hospitals. By excluding inpatients with prior eye diseases, we identified 67,117,520

potentially eligible patients. By removing all patients with a medical history of less than one year, we were able to identify an initial study cohort of 3,361,592 individuals.

Excluding those with missing or inconsistent data for any of the matching variables restricted this pool to 2,873,591 subjects, which included 845 RD cases and 2,872,746 potential controls. We then removed cases and potential controls with an index date between 2010-2015 to reach a final cohort consisting of 772 cases and 1,465,233 potential controls. Based on our matching algorithm, we were able to match a total of 3,860 unique controls to the 772 cases (see Figure 4).

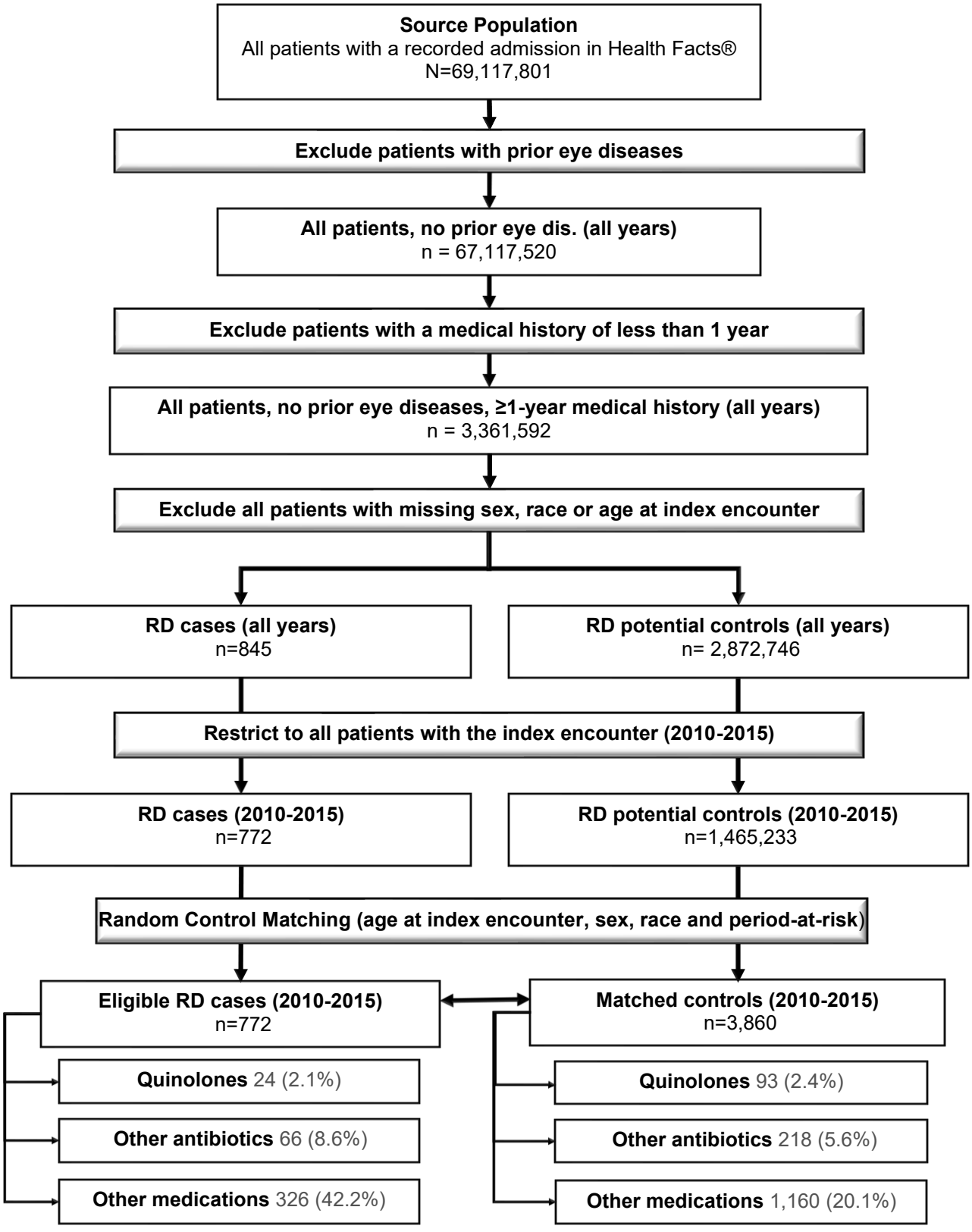

Figure 8: Identification of eligible RD cases and matching controls (2010-2015)

Characteristics of study population

The final study population was predominantly Caucasian (77.6%), and included slightly more men (51%) than women. Incidence of RD ranged from 3-5% in the first four decades of life, doubled twice to 9.3% and 21% in the fifth and sixth decades, respectively, before reaching a plateau afterwards.

Whereas there were more controls than cases with no comorbidities (34% compared to 15%), cases with comorbidities showed consistently higher comorbidities than controls, particularly within the CMI level 1-5 (55% compared to 43%).

A higher prevalence of diabetes mellitus was identified in cases compared to controls at both levels of severity, uncomplicated (33% compared to 21%) and complicated (18% compared to 9%). Alcohol abuse showed no difference in prevalence between the two groups. Further details on the study population are shown in Table 10.

Table 22: Characteristics of cases and matched controls

Characteristics	**No. (%) of patients or Mean (±SD)**		**p-value**
	Cases	**Controls**	
Total no. of participants	772	3,860	
Sex*			**0.89**
Women	378 (49.0%)	1,879 (48.7%)	
Men	394 (51.0%)	1,981 (51.3%)	
Race class*			**0.98**
Caucasian	599 (77.6%)	3,004 (77.8%)	

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
African American	118 (15.3%)	589 (15.3%)	
Asian	9 (1.2%)	37 (1.0%)	
Hispanic	3 (0.4%)	18 (0.5%)	
Other	43 (5.6%)	212 (6.0%)	
Age group*			**1.0000**
0 – 10	46 (5.96%)	229 (5.93%)	
11 – 20	32 (4.15%)	161 (4.17%)	
21 – 30	22 (2.85%)	112 (2.9%)	
31 – 40	43 (5.57%)	213 (5.52%)	
41 – 50	72 (9.33%)	360 (9.33%)	
51 – 60	165 (21.37%)	825 (21.37%)	
61 – 70	174 (22.54%)	870 (22.54%)	
71 – 80	151 (19.56%)	756 (19.59%)	
81 +	67 (8.68%)	334 (8.65%)	
Census region			**<.0001**
South	244 (31.61%)	1113 (28.83%)	
North East	226 (29.27%)	538 (13.94%)	
Midwest	179 (23.19%)	1721 (44.59%)	
West	123 (15.93%)	488 (12.64%)	
Hospital setting			**<.0001**

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
Urban	624 (80.83%)	2694 (69.79%)	
Rural	148 (19.17%)	1166 (30.21%)	
Health insurance			**0.0096**
Insured	642 (83.16%)	3347 (86.71%)	
Non-insured	27 (3.50%)	139 (3.60%)	
Unknown/missing	103 (13.34%)	374 (9.69%)	
Payer group			**0.0143**
HMO[32]/managed care	417 (54.02%)	2035 (52.72%)	
Free, research	225 (29.15%)	1309 (33.91%)	
Self-pay	26 (3.37%)	137 (3.55%)	
Other	1 (0.13%)	5 (0.13%)	
Unknown/missing	103 (13.34%)	374 (9.69%)	
Comorbidity score	**4.12 (± 3.57)**	**3.08 (± 3.7)**	**<.0001**
0	112 (14.51%)	1315 (34.07%)	
1-5	422 (54.66%)	1674 (43.37%)	
6 – 10	190 (24.62%)	660 (17.09%)	
11 – 15	44 (5.71%)	194 (5.02%)	
16 +	4 (0.52%)	17 (0.45%)	
Confounders			

[32] HMO: Health Management Organizations

Characteristics	No. (%) of patients or Mean (±SD)		p-value
	Cases	Controls	
Diabetes – uncomplicated	252 (32.64%)	824 (21.35%)	<.0001
Diabetes – complicated	140 (18.13%)	328 (8.50%)	<.0001
Alcohol abuse	36 (4.66%)	171 (4.43%)	0.7747

***** Matching variables

The average number of quinolone prescriptions per patient filled during the 30 days preceding the index date was comparable between cases (0.044 ± 0.28) and controls (0.037 ± 0.26). However, prescribing of other non-quinolone medications was higher in cases compared to controls (Table 11).

Table 23: Thirty-day exposure, by medication group, prior to the index date

Medication group	Mean (±SD) or No. (%) of filled prescriptions		p-value
	Cases	Controls	
Quinolones	**0.044 (±0.28)**	**0.037 (±0.26)**	**<0.001**
0	748 (96.89%)	3767 (97.59%)	0.2791
1-3	23 (2.98%)	92 (2.38%)	
4-6	1 (0.13%)	1 (0.03%)	
Other antibiotics	**0.22 (±0.92)**	**0.11 (±0.52)**	**<0.001**
0	706 (91.45%)	3643 (94.38%)	<.0013
1-3	53 (6.87%)	194 (5.03%)	
4-6	11 (1.42%)	22 (0.57%)	
7+	2 (0.26%)	1 (0.03%)	
Other medications	**4.90 (±14.43)**	**3.04 (±10.02)**	**<0.001**
0	446 (57.77%)	2700 (69.95%)	<.0001
1-3	207 (26.81%)	774 (20.05%)	
4-6	14 (1.81%)	63 (1.63%)	
7-10	10 (1.30%)	36 (0.93%)	
11+	95 (12.31%)	287 (7.44%)	

Each of ciprofloxacin, levofloxacin and moxifloxacin were similarly prescribed among cases and controls during the thirty days preceding the index date, with

moxifloxacin being prescribed only once for a single case and once for each of three controls (Table 12).

Table 24: Thirty-day medication exposure by the individual quinolones

Medication group	No. (%) of filled prescriptions		p-value
	Cases	Controls	
Ciprofloxacin	12 (1.55%)	37 (0.96%)	0.14
Levofloxacin	11 (1.42%)	56 (1.45%)	0.96
Moxifloxacin	1 (0.13%)	3 (0.08%)	0.66

Regression analysis

Entire study population

Our primary analysis of the entire study population showed that exposure to systemically administered quinolone antibiotics was not associated with an increased risk of RD [(aOR: 0.75 (95% CI: 0.43-1.32)], upon adjusting to exposure to non-quinolone antibiotics and other medications combined, as well as major risk factors for this outcome.

Repeating the same analysis based on individual quinolones produced similar results to the multi-medication model including all quinolones simultaneously. The risk estimates reported in Table 13 for the two medication groups comprised of quinolones and other non-quinolone antibiotics and in

Table *14* for individual quinolones were generated using the multi-medication model.

Stratification by comorbidity status

Upon stratifying the study population into tertiles (0-1, 2-4, 5+) based on their comorbidity status (CMI score), neither quinolones nor other antibiotics showed any RD risk upon adjusting to major confounders.

Stratification by Race

Quinolone antibiotics showed an almost 2-fold non-significant increase in RD risk in African Americans [aOR: 2.88 (95% CI: 0.43-19.33)]. This risk was driven by ciprofloxacin [aOR: 2.09 (95% CI: 0.11-41.09)] and levofloxacin [aOR: 1.85 (95% CI: 0.08-42.88)].

Stratification by Sex

Whereas quinolones showed no difference in RD risk between men and women, ciprofloxacin showed a marginal, non-significant increased risk in women [aOR: 1.34 (95% CI: 0.34-5.22)].

Stratification by Age

Upon stratifying the study population by age into tertiles (0-55, 56-70, 71+ years), quinolones were not associated with an increased risk in any age group. However,

moxifloxacin was associated with a more than 4-fold, but highly uncertain, increase in RD risk in the (56-70) year-old group [aOR: 5.36 (95% CI: 0.30-97.21)]

Effect of major confounders

Our primary analysis of the entire study population showed an increased RD risk in association with complicated diabetes mellitus [aOR: 2.19 (95% CI: 1.68-2.86)]. Upon stratifying the study population, a similar pattern was identified in population subgroups, particularly in the healthiest comorbidity tier (CMI: 0-1): 14.08 (95% CI: 1.40-141.93)]. An increased risk was also noted in women [aOR: 2.69 (1.82-4.00)] more so than men [aOR: 1.82 (95% CI: 1.26-2.63)], and in African Americans [aOR: 5.85 (95% CI: 2.70-12.65)] more so than Caucasians [aOR: 1.69 (95% CI: 1.24-2.30)]. A 5-fold risk was also noted in the youngest age tertile (0-55): [aOR: 6.18 (95% CI: 3.65-10.46)], which declined and became non-significant in the older age tertiles. In contrast to diabetes, alcohol abuse showed no elevated RD risk in either the entire study population or population subgroups.

Results for the base and maximally adjusted models for the primary analysis examining the entire study population and the subgroup analysis based on comorbidity score are presented in this manuscript for all medication groups and for the individual quinolones in Table 13 and

Table *14*, respectively. Complete listings of the ORs, 95% CI and p-value for all regression analyses are provided in Supplementary Materials IV-VI.

Table 25: Base and adjusted odds ratios (aOR) for risk of retinal detachment with quinolones compared to non-quinolone antibiotics

Population and medication group	Base model[33] OR (95% CI)	p-value	Maximally adjusted model[34] aOR (95% CI)	p-value
Entire population				
Quinolones	1.27 (0.80-2.01)	0.3055	0.75 (0.43-1.32)	0.3184
Non-quinolone antibiotics	1.54 (1.15-2.06)	0.0036	0.86 (0.58-1.26)	0.4259
Comorbidity level				
CMI:0-1				
Quinolones	1.40 (0.25-7.79)	0.6984	0.70 (0.05-9.74)	0.7914
Non-quinolone antibiotics	2.66 (1.00-7.08)	0.0503	1.12 (0.28-4.44)	0.8777
CMI:2-4				
Quinolones	0.46 (0.09-2.29)	0.3420	0.35 (0.05-2.42)	0.2872
Non-quinolone antibiotics	0.62 (0.22-1.79)	0.3782	0.49 (0.12-1.92)	0.3053
CMI:5+				
Quinolones	0.87 (0.45-1.66)	0.6624	0.49 (0.21-1.17)	0.1094
Non-quinolone antibiotics	1.46 (0.91-2.33)	0.1173	1.15 (0.55-2.38)	0.7155

[33] Base model: age, sex, race variables, and the tested medication group
[34] Maximally adjusted model: minimally adjusted, and complicated diabetes mellitus, alcohol abuse and socioeconomic status (census division, hospital (urban/rural) and insurance)

Table 26: Base and adjusted odds ratios (aOR) for risk of retinal detachment in relation to use of individual quinolones

Population and individual quinolone	Base model OR (95% CI)	p-value	Maximally adjusted model aOR (95% CI)	p-value
Entire Population				
Ciprofloxacin	1.60 (0.83-3.07)	0.1588	0.87 (0.39-1.97)	0.7415
Levofloxacin	0.94 (0.48-1.81)	0.8411	0.61 (0.29-1.30)	0.1984
Moxifloxacin	1.67 (0.17-16.02)	0.6582	1.07 (0.10-11.08)	0.9535
Comorbidity level				
CMI:0-1				
Ciprofloxacin	2.78 (0.38-20.39)	0.3157	1.00 (0.05-19.93)	0.9987
Levofloxacin	<0.001 (<0.001->999.999)	0.9826	<0.001 (<0.001->999.999)	0.9905
Moxifloxacin	N/A	N/A	N/A	N/A
CMI:2-4				
Ciprofloxacin	0.40 (0.04-3.75)	0.4239	0.15 (0.01-2.05)	0.1546
Levofloxacin	0.54 (0.05-5.47)	0.5981	1.07 (0.08-13.78)	0.9577
Moxifloxacin	N/A	N/A	N/A	N/A
CMI:5+				
Ciprofloxacin	1.24 (0.44-3.43)	0.6858	0.74 (0.19-2.91)	0.6606
Levofloxacin	0.70 (0.29-1.74)	0.4455	0.46 (0.16-1.39)	0.1691
Moxifloxacin	0.65 (0.07-6.60)	0.7190	0.14 (0.01-3.59)	0.2369

Discussion

Examining our entire study population revealed no evidence of an increased RD risk within thirty-days of a systemically administered quinolone antibiotic. However, quinolones showed a nearly 2-fold non-significant increase in RD risk in African Americans that was attributable to ciprofloxacin and levofloxacin. Moxifloxacin showed more than 4-fold non-significant increase in RD risk in those 56-70 years of age. Ciprofloxacin showed also a marginal and non-significant increase in RD risk in women. An overall low consumption of medications, particularly antibiotics, reflects a relatively healthy population demonstrating minimal to moderate comorbidity.

Complicated diabetes mellitus showed a consistently increased RD risk in all analyses. Alcohol abuse showed an increased and non-significant RD risk only in Caucasians, women, and those ≥ 71 years of age. A complete listing of risk estimates for all analyses involving diabetes mellitus and alcohol abuse is provided in Supplementary Material VI.

Similar to an earlier study that utilized Health Facts® data for a different outcome, the total number of RD cases was exceptionally low except, between 2010-2015. Prior to 2010, this may have been attributable to gradual enrollment into Health Facts®, whereas 2016 marked the adoption of the new ICD10 coding with a subsequent drop in recorded cases. Accordingly, our study examined data of the 2010-2015 interval only.

To examine the association between quinolones and RD risk, we excluded all inpatients with prior eye diseases to avoid possible confounding of the association. We also adjusted for two major risk factors, complicated diabetes mellitus and alcohol abuse. Since the study subjects were inpatients, we used medication filling orders as

proxy for medication administration with high confidence that the medications were consumed by patients while in hospital.

In this study, we opted in for the nested case-control rather than cohort design since the former offers similar benefits, but with greater computational efficiency than the cohort design [57-59]. The nested case-control design allows for matching on age and calendar time, rather than adjusting for these effects as covariates in a cox regression model widely used in the analysis of cohort data [57-59]. Missing observations may also have a lesser impact in a nested case-control analysis compared to the cohort design [60-62].

We compared our results to those of recent major epidemiologic studies that examined the association of quinolones with RD risk. This included eight original studies [24, 33-39], three systematic reviews [40-42] and one umbrella review [43]. Whereas all reviews [40-43] and five original studies [33-36, 38] reported no association between oral quinolone administration and RD risk, t three studies [24, 37, 39] reported an increased RD risk with use of quinolone antibiotics. These inconsistencies may be due to differences in factors such as study design, target population, and sampling frame (further details of these studies are provided in Supplementary Material VII).

A major strength for our study is its use of a major EHR database, which provided a great opportunity for studying large patient populations over long period of time, thereby supporting meaningful investigation of a rare adverse drug reaction such as RD [63, 64]. With the availability of comprehensive patient-related information such as demographics, diagnoses, clinical assessments, diagnostic, medical and surgical procedures, and patient outcomes, it was possible to assess the temporality of

association of between exposure (quinolone antibiotics) and outcome (RD), adjusting for medication exposure and major risk factors [63-66].

Limiting our pool of cases and possible controls to those with a medical history of one-year at a minimum allowed for a better assessment of the health status of the examined study population. Finally, using prescriptions filled for our study population and delivered by nursing staff as proxy for medication administration provided more confidence in patients' medication compliance compared to medications prescribed on an outpatient basis.

Similar to other EHR databases, Health Facts® was primarily created for the purpose of supporting a seamless exchange of patients' medical information among providers across the care continuum. However, despite all robust data cleaning techniques, EHR databases are subject to data integrity issues such as misclassification of demographics, comorbidities, medications, outcomes or other clinical care details [67, 68]. Additionally, Health Facts® lacked information on outpatient or consumption of over-the-counter medication consumption, precluding a comprehensive examination of possible polypharmacy effects [66].

Considering the fact that 50-80% of antibiotics are prescribed in physician offices rather than hospitals [17, 69], records of antibiotic use in Health Facts® are necessarily incomplete. However, prescriptions filled during hospital stay may reflect outpatient prescription patterns to a large extent. If outpatient and inpatient prescribing patterns differed notably, this would lead to exposure misclassification, which, if random, would be expected to bias the risk estimates towards the null value of no effect.

Conclusion

Our study provided no evidence of an increased quinolone-associated RD risk. Care should be exercised in interpreting the results of this study due to small number of filled quinolone prescriptions during the 30-day window prior to case ascertainment. Further attention should be directed at quinolone exposure within certain population subgroups such as women, those 56-70 years old, and African Americans. Further studies with additional information on outpatient medication use would be also complement the present findings.

Author contributions

The primary author, Mohamed Taher, designed and implemented this study including study design, statistical analysis, interpretation of findings and drafting of this manuscript. James Crispo and Yannick Fortin contributed to statistical analysis, as well as critical review and approval of this manuscript. Lise Bjerre, Franco Momoli, Ryan Moog, Donald Mattison and Daniel Krewski provided guidance and feedback on all aspects of the study design and implementation, as well as critical review and approval of the manuscript.

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Declaration of interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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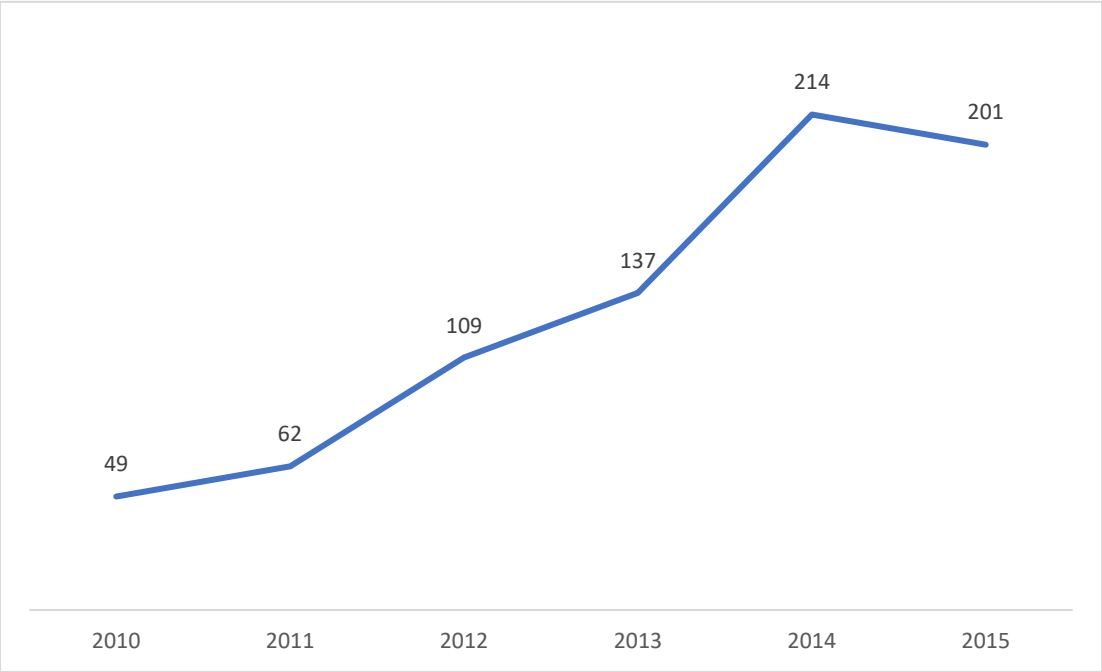
Supplementary Material – Chapter 7

Annual recording of cases of retinal detachment (RD)



Final group of eligible RD cases, by year of diagnosis (2010-2015)

List of ICD-9/ICD-10 codes for identifying cases of retinal detachment (RD)

ICD Type	ICD Code	Details
ICD 9	361.03	Recent Retinal Detachment, Partial, with Giant Tear
	361.89	Other Forms of Retinal Detachment
	361	Retinal Detachment with Retinal Defect
	361	Retinal Detachment with Retinal Defect, Unspecified
	361.01	Recent Retinal Detachment, Partial, with Single Defect
	361.02	Recent Retinal Detachment, Partial, with Multiple Defects
	361.04	Recent Retinal Detachment, Partial, with Retinal Dialysis
	361.05	Recent Retinal Detachment, Total or Subtotal
	361.06	Old Retinal Detachment, Partial
	361.07	Old Retinal Detachment, Total or Subtotal
	361.2	Serous Retinal Detachment
	361.8	Other Forms of Retinal Detachment
	361.9	Unspecified Retinal Detachment
	361.03	Recent Retinal Detachment, Partial, with Giant Tear
ICD 10-CM	H33	Retinal detachments and breaks, Excl.: detachment of retinal pigment epithelium (H35.7)
	H33.0	Retinal detachment with retinal break (Rhegmatogenous retinal detachment)
	H33.1	Retinoschisis and retinal cysts
	H33.2	Serous retinal detachment

ICD Type	ICD Code	Details
	H33.3	Retinal breaks without detachment

List of eye diseases leading to exclusion of cases

ICD type	ICD code	Details
ICD9	91.51	Syphilitic Chorioretinitis (Secondary)
ICD9	94.83	Syphilitic Disseminated Retinochoroiditis
ICD9	130.2	Chorioretinitis Due to Toxoplasmosis
ICD9	190	Malignant Neoplasm of Eyeball, Except Conjunctiva, Cornea, Retina, and Choroid
ICD9	190.5	Malignant Neoplasm of Retina
ICD9	224	Benign Neoplasm of Eyeball, Except Conjunctiva, Cornea, Retina, and Choroid
ICD9	224.5	Benign Neoplasm of Retina
ICD9	228.03	Hemangioma of Retina
ICD9	239.81	Neoplasm of Unspecified Nature of Retina and Choroid
ICD9	361	Retinal Detachments and Defects
ICD9	361.01	Recent Retinal Detachment, Partial, with Single Defect
ICD9	361.02	Recent Retinal Detachment, Partial, with Multiple Defects
ICD9	361.03	Recent Retinal Detachment, Partial, with Giant Tear
ICD9	361.04	Recent Retinal Detachment, Partial, with Retinal Dialysis
ICD9	361.05	Recent Retinal Detachment, Total or Subtotal
ICD9	361.06	Old Retinal Detachment, Partial
ICD9	361.07	Old Retinal Detachment, Total or Subtotal
ICD9	361.1	Retinoschisis and Retinal Cysts
ICD9	361.13	Primary Retinal Cysts

ICD type	ICD code	Details
ICD9	361.14	Secondary Retinal Cysts
ICD9	361.19	Other Retinoschisis and Retinal Cysts
ICD9	361.3	Retinal Defects without Detachment
ICD9	361.3	Retinal Defect, Unspecified
ICD9	361.31	Round Hole of Retina without Detachment
ICD9	361.32	Horseshoe Tear of Retina without Detachment
ICD9	361.33	Multiple Defects of Retina without Detachment
ICD9	361.81	Traction Detachment of Retina
ICD9	362	Other Retinal Disorders
ICD9	362.1	Other Background Retinopathy and Retinal Vascular Changes
ICD9	362.13	Changes in Vascular Appearance of Retina
ICD9	362.14	Retinal Microaneurysms Nos
ICD9	362.15	Retinal Telangiectasia
ICD9	362.16	Retinal Neovascularization Nos
ICD9	362.18	Retinal Vasculitis
ICD9	362.3	Retinal Vascular Occlusion
ICD9	362.3	Retinal Vascular Occlusion, Unspecified
ICD9	362.31	Central Retinal Artery Occlusion
ICD9	362.32	Retinal Arterial Branch Occlusion
ICD9	362.33	Partial Retinal Arterial Occlusion
ICD9	362.34	Transient Retinal Arterial Occlusion
ICD9	362.35	Central Retinal Vein Occlusion

ICD type	ICD code	Details
ICD9	362.36	Venous Tributary (Branch) Occlusion of Retina
ICD9	362.37	Venous Engorgement of Retina
ICD9	362.4	Separation of Retinal Layers
ICD9	362.4	Retinal Layer Separation, Unspecified
ICD9	362.42	Serous Detachment of Retinal Pigment Epithelium
ICD9	362.43	Hemorrhagic Detachment of Retinal Pigment Epithelium
ICD9	362.5	Degeneration of Macula and Posterior Pole of Retina
ICD9	362.5	Macular Degeneration (Senile) of Retina, Unspecified
ICD9	362.51	Nonexudative Senile Macular Degeneration of Retina
ICD9	362.52	Exudative Senile Macular Degeneration of Retina
ICD9	362.53	Cystoid Macular Degeneration of Retina
ICD9	362.54	Macular Cyst, Hole, or Pseudohole of Retina
ICD9	362.55	Toxic Maculopathy of Retina
ICD9	362.56	Macular Puckering of Retina
ICD9	362.57	Drusen (Degenerative) of Retina
ICD9	362.6	Peripheral Retinal Degenerations
ICD9	362.6	Peripheral Retinal Degeneration, Unspecified
ICD9	362.61	Paving Stone Degeneration of Retina
ICD9	362.62	Microcystoid Degeneration of Retina
ICD9	362.63	Lattice Degeneration of Retina
ICD9	362.64	Senile Reticular Degeneration of Retina
ICD9	362.65	Secondary Pigmentary Degeneration of Retina

ICD type	ICD code	Details
ICD9	362.7	Hereditary Retinal Dystrophies
ICD9	362.7	Hereditary Retinal Dystrophy, Unspecified
ICD9	362.71	Retinal Dystrophy in Systemic or Cerebroretinal Lipidoses
ICD9	362.72	Retinal Dystrophy in Other Systemic Disorders and Syndromes
ICD9	362.74	Pigmentary Retinal Dystrophy
ICD9	362.75	Other Dystrophies Primarily Involving the Sensory Retina
ICD9	362.76	Dystrophies Primarily Involving the Retinal Pigment Epithelium
ICD9	362.77	Retinal Dystrophies Primarily Involving Bruch's Membrane
ICD9	362.8	Other Retinal Disorders
ICD9	362.81	Retinal Hemorrhage
ICD9	362.82	Retinal Exudates and Deposits
ICD9	362.83	Retinal Edema
ICD9	362.84	Retinal Ischemia
ICD9	362.85	Retinal Nerve Fiber Bundle Defects
ICD9	362.89	Other Retinal Disorders
ICD9	362.9	Unspecified Retinal Disorder
ICD9	363	Chorioretinal Inflammations, Scars, and Other Disorders of Choroid
ICD9	363	Focal Chorioretinitis and Focal Retinochoroiditis
ICD9	363	Focal Chorioretinitis, Unspecified
ICD9	363.01	Focal Choroiditis and Chorioretinitis, Juxtapapillary
ICD9	363.03	Focal Choroiditis and Chorioretinitis of Other Posterior Pole

ICD type	ICD code	Details
ICD9	363.04	Focal Choroiditis and Chorioretinitis, Peripheral
ICD9	363.05	Focal Retinitis and Retinochoroiditis, Juxtapapillary
ICD9	363.06	Focal Retinitis and Retinochoroiditis, Macular or Paramacular
ICD9	363.07	Focal Retinitis and Retinochoroiditis of Other Posterior Pole
ICD9	363.08	Focal Retinitis and Retinochoroiditis, Peripheral
ICD9	363.1	Disseminated Chorioretinitis and Disseminated Retinochoroiditis
ICD9	363.1	Disseminated Chorioretinitis, Unspecified
ICD9	363.11	Disseminated Choroiditis and Chorioretinitis, Posterior Pole
ICD9	363.12	Disseminated Choroiditis and Chorioretinitis, Peripheral
ICD9	363.13	Disseminated Choroiditis and Chorioretinitis, Generalized
ICD9	363.14	Disseminated Retinitis and Retinochoroiditis, Metastatic
ICD9	363.15	Disseminated Retinitis and Retinochoroiditis, Pigment Epitheliopathy
ICD9	363.2	Other and Unspecified Forms of Chorioretinitis and Retinochoroiditis
ICD9	363.2	Chorioretinitis, Unspecified
ICD9	363.3	Chorioretinal Scars
ICD9	363.3	Chorioretinal Scar, Unspecified
ICD9	363.32	Other Macular Scars of Retina
ICD9	363.33	Other Scars of Posterior Pole of Retina
ICD9	363.34	Peripheral Scars of Retina

ICD type	ICD code	Details
ICD9	363.35	Disseminated Scars of Retina
ICD9	363.4	Choroidal Degenerations
ICD9	363.4	Choroidal Degeneration, Unspecified
ICD9	363.5	Hereditary Choroidal Dystrophies
ICD9	363.5	Hereditary Choroidal Dystrophy or Atrophy, Unspecified
ICD9	363.54	Central Choroidal Atrophy, Total
ICD9	363.6	Choroidal Hemorrhage and Rupture
ICD9	363.61	Choroidal Hemorrhage, Unspecified
ICD9	363.62	Expulsive Choroidal Hemorrhage
ICD9	363.63	Choroidal Rupture
ICD9	363.7	Choroidal Detachment
ICD9	363.7	Choroidal Detachment, Unspecified
ICD9	363.71	Serous Choroidal Detachment
ICD9	363.72	Hemorrhagic Choroidal Detachment
ICD9	365	Glaucoma
ICD9	365	Borderline Glaucoma [glaucoma Suspect]
ICD9	365.02	Anatomical Narrow Angle Borderline Glaucoma
ICD9	365.03	Steroid Responders Borderline Glaucoma
ICD9	365.06	Primary Angle Closure without Glaucoma Damage
ICD9	365.1	Open-Angle Glaucoma
ICD9	365.1	Open-Angle Glaucoma, Unspecified
ICD9	365.11	Primary Open Angle Glaucoma

ICD type	ICD code	Details
ICD9	365.12	Low Tension Glaucoma
ICD9	365.13	Pigmentary Glaucoma
ICD9	365.14	Glaucoma of Childhood
ICD9	365.15	Residual Stage of Open Angle Glaucoma
ICD9	365.2	Primary Angle-Closure Glaucoma
ICD9	365.2	Primary Angle-Closure Glaucoma, Unspecified
ICD9	365.21	Intermittent Angle-Closure Glaucoma
ICD9	365.22	Acute Angle-Closure Glaucoma
ICD9	365.23	Chronic Angle-Closure Glaucoma
ICD9	365.24	Residual Stage of Angle-Closure Glaucoma
ICD9	365.3	Corticosteroid-Induced Glaucoma
ICD9	365.31	Corticosteroid-Induced Glaucoma, Glaucomatous Stage
ICD9	365.32	Corticosteroid-Induced Glaucoma, Residual Stage
ICD9	365.4	Glaucoma Associated with Congenital Anomalies, Dystrophies, and Systemic Syndromes
ICD9	365.41	Glaucoma Associated with Chamber Angle Anomalies
ICD9	365.42	Glaucoma Associated with Anomalies of Iris
ICD9	365.43	Glaucoma Associated with Other Anterior Segment Anomalies
ICD9	365.44	Glaucoma Associated with Systemic Syndromes
ICD9	365.5	Glaucoma Associated with Disorders of the Lens
ICD9	365.51	Phacolytic Glaucoma
ICD9	365.52	Pseudoexfoliation Glaucoma

ICD type	ICD code	Details
ICD9	365.59	Glaucoma Associated with Other Lens Disorders
ICD9	365.6	Glaucoma Associated with Other Ocular Disorders
ICD9	365.6	Glaucoma Associated with Unspecified Ocular Disorder
ICD9	365.61	Glaucoma Associated with Pupillary Block
ICD9	365.62	Glaucoma Associated with Ocular Inflammations
ICD9	365.63	Glaucoma Associated with Vascular Disorders
ICD9	365.64	Glaucoma Associated with Tumors or Cysts
ICD9	365.65	Glaucoma Associated with Ocular Trauma
ICD9	365.7	Glaucoma Stage
ICD9	365.7	Glaucoma Stage, Unspecified
ICD9	365.71	Mild Stage Glaucoma
ICD9	365.72	Moderate Stage Glaucoma
ICD9	365.73	Severe Stage Glaucoma
ICD9	365.74	Indeterminate Stage Glaucoma
ICD9	365.8	Other Specified Forms of Glaucoma
ICD9	365.81	Hypersecretion Glaucoma
ICD9	365.82	Glaucoma with Increased Episcleral Venous Pressure
ICD9	365.89	Other Specified Glaucoma
ICD9	365.9	Unspecified Glaucoma
ICD9	368.34	Abnormal Retinal Correspondence
ICD9	377.03	Papilledema Associated with Retinal Disorder
ICD9	377.13	Optic Atrophy Associated with Retinal Dystrophies

ICD type	ICD code	Details
ICD9	743.53	Chorioretinal Degeneration, Congenital
ICD9	743.56	Other Retinal Changes, Congenital
ICD9	794.11	Nonspecific Abnormal Retinal Function Studies
ICD9	V19.11	Family History of Glaucoma
ICD9	V80.1	Screening for Glaucoma
ICD10-CM	H30	Chorioretinal inflammation
ICD10-CM	H31.0	Chorioretinal scars
ICD10-CM	H31.1	Choroidal degeneration
ICD10-CM	H31.101	Choroidal degeneration, unspecified, right eye
ICD10-CM	H31.102	Choroidal degeneration, unspecified, left eye
ICD10-CM	H31.103	Choroidal degeneration, unspecified, bilateral
ICD10-CM	H31.109	Choroidal degeneration, unspecified, unspecified eye
ICD10-CM	H31.22	Choroidal dystrophy (central areolar) (generalized) (peripapillary)
ICD10-CM	H31.3	Choroidal hemorrhage and rupture
ICD10-CM	H31.32	Choroidal rupture
ICD10-CM	H31.321	Choroidal rupture, right eye
ICD10-CM	H31.322	Choroidal rupture, left eye
ICD10-CM	H31.323	Choroidal rupture, bilateral
ICD10-CM	H31.329	Choroidal rupture, unspecified eye
ICD10-CM	H31.4	Choroidal detachment
ICD10-CM	H32	Chorioretinal disorders in diseases classified elsewhere

ICD type	ICD code	Details
ICD10-CM	H33	Retinal detachments and breaks
ICD10-CM	H33.0	Retinal detachment with retinal break
ICD10-CM	H33.01	Retinal detachment with single break
ICD10-CM	H33.011	Retinal detachment with single break, right eye
ICD10-CM	H33.012	Retinal detachment with single break, left eye
ICD10-CM	H33.013	Retinal detachment with single break, bilateral
ICD10-CM	H33.019	Retinal detachment with single break, unspecified eye
ICD10-CM	H33.02	Retinal detachment with multiple breaks
ICD10-CM	H33.021	Retinal detachment with multiple breaks, right eye
ICD10-CM	H33.022	Retinal detachment with multiple breaks, left eye
ICD10-CM	H33.023	Retinal detachment with multiple breaks, bilateral
ICD10-CM	H33.029	Retinal detachment with multiple breaks, unspecified eye
ICD10-CM	H33.03	Retinal detachment with giant retinal tear
ICD10-CM	H33.031	Retinal detachment with giant retinal tear, right eye
ICD10-CM	H33.032	Retinal detachment with giant retinal tear, left eye
ICD10-CM	H33.033	Retinal detachment with giant retinal tear, bilateral
ICD10-CM	H33.039	Retinal detachment with giant retinal tear, unspecified eye
ICD10-CM	H33.04	Retinal detachment with retinal dialysis
ICD10-CM	H33.041	Retinal detachment with retinal dialysis, right eye
ICD10-CM	H33.042	Retinal detachment with retinal dialysis, left eye
ICD10-CM	H33.043	Retinal detachment with retinal dialysis, bilateral
ICD10-CM	H33.049	Retinal detachment with retinal dialysis, unspecified eye

ICD type	ICD code	Details
ICD10-CM	H33.3	Retinal breaks without detachment
ICD10-CM	H34	Retinal vascular occlusions
ICD10-CM	H34.23	Retinal artery branch occlusion
ICD10-CM	H34.231	Retinal artery branch occlusion, right eye
ICD10-CM	H34.232	Retinal artery branch occlusion, left eye
ICD10-CM	H34.233	Retinal artery branch occlusion, bilateral
ICD10-CM	H34.239	Retinal artery branch occlusion, unspecified eye
ICD10-CM	H35.04	Retinal micro-aneurysms, unspecified
ICD10-CM	H35.041	Retinal micro-aneurysms, unspecified, right eye
ICD10-CM	H35.042	Retinal micro-aneurysms, unspecified, left eye
ICD10-CM	H35.043	Retinal micro-aneurysms, unspecified, bilateral
ICD10-CM	H35.049	Retinal micro-aneurysms, unspecified, unspecified eye
ICD10-CM	H35.05	Retinal neovascularization, unspecified
ICD10-CM	H35.051	Retinal neovascularization, unspecified, right eye
ICD10-CM	H35.052	Retinal neovascularization, unspecified, left eye
ICD10-CM	H35.053	Retinal neovascularization, unspecified, bilateral
ICD10-CM	H35.059	Retinal neovascularization, unspecified, unspecified eye
ICD10-CM	H35.06	Retinal vasculitis
ICD10-CM	H35.061	Retinal vasculitis, right eye
ICD10-CM	H35.062	Retinal vasculitis, left eye
ICD10-CM	H35.063	Retinal vasculitis, bilateral
ICD10-CM	H35.069	Retinal vasculitis, unspecified eye

ICD type	ICD code	Details
ICD10-CM	H35.07	Retinal telangiectasis
ICD10-CM	H35.071	Retinal telangiectasis, right eye
ICD10-CM	H35.072	Retinal telangiectasis, left eye
ICD10-CM	H35.073	Retinal telangiectasis, bilateral
ICD10-CM	H35.079	Retinal telangiectasis, unspecified eye
ICD10-CM	H35.6	Retinal hemorrhage
ICD10-CM	H35.60	Retinal hemorrhage, unspecified eye
ICD10-CM	H35.61	Retinal hemorrhage, right eye
ICD10-CM	H35.62	Retinal hemorrhage, left eye
ICD10-CM	H35.63	Retinal hemorrhage, bilateral
ICD10-CM	H35.81	Retinal edema
ICD10-CM	H35.82	Retinal ischemia
ICD10-CM	H36	Retinal disorders in diseases classified elsewhere
ICD10-CM	H40	Glaucoma
ICD10-CM	H40.0	Glaucoma suspect
ICD10-CM	H40.3	Glaucoma secondary to eye trauma
ICD10-CM	H40.30	Glaucoma secondary to eye trauma, unspecified eye
ICD10-CM	H40.30X0	Glaucoma secondary to eye trauma, unspecified eye, stage unspecified
ICD10-CM	H40.30X1	Glaucoma secondary to eye trauma, unspecified eye, mild stage

ICD type	ICD code	Details
ICD10-CM	H40.30X2	Glaucoma secondary to eye trauma, unspecified eye, moderate stage
ICD10-CM	H40.30X3	Glaucoma secondary to eye trauma, unspecified eye, severe stage
ICD10-CM	H40.30X4	Glaucoma secondary to eye trauma, unspecified eye, indeterminate stage
ICD10-CM	H40.31	Glaucoma secondary to eye trauma, right eye
ICD10-CM	H40.31X0	Glaucoma secondary to eye trauma, right eye, stage unspecified
ICD10-CM	H40.31X1	Glaucoma secondary to eye trauma, right eye, mild stage
ICD10-CM	H40.31X2	Glaucoma secondary to eye trauma, right eye, moderate stage
ICD10-CM	H40.31X3	Glaucoma secondary to eye trauma, right eye, severe stage
ICD10-CM	H40.31X4	Glaucoma secondary to eye trauma, right eye, indeterminate stage
ICD10-CM	H40.32	Glaucoma secondary to eye trauma, left eye
ICD10-CM	H40.32X0	Glaucoma secondary to eye trauma, left eye, stage unspecified
ICD10-CM	H40.32X1	Glaucoma secondary to eye trauma, left eye, mild stage
ICD10-CM	H40.32X2	Glaucoma secondary to eye trauma, left eye, moderate stage
ICD10-CM	H40.32X3	Glaucoma secondary to eye trauma, left eye, severe stage
ICD10-CM	H40.32X4	Glaucoma secondary to eye trauma, left eye, indeterminate stage
ICD10-CM	H40.33	Glaucoma secondary to eye trauma, bilateral

ICD type	ICD code	Details
ICD10-CM	H40.33X0	Glaucoma secondary to eye trauma, bilateral, stage unspecified
ICD10-CM	H40.33X1	Glaucoma secondary to eye trauma, bilateral, mild stage
ICD10-CM	H40.33X2	Glaucoma secondary to eye trauma, bilateral, moderate stage
ICD10-CM	H40.33X3	Glaucoma secondary to eye trauma, bilateral, severe stage
ICD10-CM	H40.33X4	Glaucoma secondary to eye trauma, bilateral, indeterminate stage
ICD10-CM	H40.4	Glaucoma secondary to eye inflammation
ICD10-CM	H40.40	Glaucoma secondary to eye inflammation, unspecified eye
ICD10-CM	H40.40X0	Glaucoma secondary to eye inflammation, unspecified eye, stage unspecified
ICD10-CM	H40.40X1	Glaucoma secondary to eye inflammation, unspecified eye, mild stage
ICD10-CM	H40.40X2	Glaucoma secondary to eye inflammation, unspecified eye, moderate stage
ICD10-CM	H40.40X3	Glaucoma secondary to eye inflammation, unspecified eye, severe stage
ICD10-CM	H40.40X4	Glaucoma secondary to eye inflammation, unspecified eye, indeterminate stage
ICD10-CM	H40.41	Glaucoma secondary to eye inflammation, right eye
ICD10-CM	H40.41X0	Glaucoma secondary to eye inflammation, right eye, stage unspecified

ICD type	ICD code	Details
ICD10-CM	H40.41X1	Glaucoma secondary to eye inflammation, right eye, mild stage
ICD10-CM	H40.41X2	Glaucoma secondary to eye inflammation, right eye, moderate stage
ICD10-CM	H40.41X3	Glaucoma secondary to eye inflammation, right eye, severe stage
ICD10-CM	H40.41X4	Glaucoma secondary to eye inflammation, right eye, indeterminate stage
ICD10-CM	H40.42	Glaucoma secondary to eye inflammation, left eye
ICD10-CM	H40.42X0	Glaucoma secondary to eye inflammation, left eye, stage unspecified
ICD10-CM	H40.42X1	Glaucoma secondary to eye inflammation, left eye, mild stage
ICD10-CM	H40.42X2	Glaucoma secondary to eye inflammation, left eye, moderate stage
ICD10-CM	H40.42X3	Glaucoma secondary to eye inflammation, left eye, severe stage
ICD10-CM	H40.42X4	Glaucoma secondary to eye inflammation, left eye, indeterminate stage
ICD10-CM	H40.43	Glaucoma secondary to eye inflammation, bilateral
ICD10-CM	H40.43X0	Glaucoma secondary to eye inflammation, bilateral, stage unspecified
ICD10-CM	H40.43X1	Glaucoma secondary to eye inflammation, bilateral, mild stage

ICD type	ICD code	Details
ICD10-CM	H40.43X2	Glaucoma secondary to eye inflammation, bilateral, moderate stage
ICD10-CM	H40.43X3	Glaucoma secondary to eye inflammation, bilateral, severe stage
ICD10-CM	H40.43X4	Glaucoma secondary to eye inflammation, bilateral, indeterminate stage
ICD10-CM	H40.5	Glaucoma secondary to other eye disorders
ICD10-CM	H40.50	Glaucoma secondary to other eye disorders, unspecified eye
ICD10-CM	H40.50X0	Glaucoma secondary to other eye disorders, unspecified eye, stage unspecified
ICD10-CM	H40.50X1	Glaucoma secondary to other eye disorders, unspecified eye, mild stage
ICD10-CM	H40.50X2	Glaucoma secondary to other eye disorders, unspecified eye, moderate stage
ICD10-CM	H40.50X3	Glaucoma secondary to other eye disorders, unspecified eye, severe stage
ICD10-CM	H40.50X4	Glaucoma secondary to other eye disorders, unspecified eye, indeterminate stage
ICD10-CM	H40.51	Glaucoma secondary to other eye disorders, right eye
ICD10-CM	H40.51X0	Glaucoma secondary to other eye disorders, right eye, stage unspecified

ICD type	ICD code	Details
ICD10-CM	H40.51X1	Glaucoma secondary to other eye disorders, right eye, mild stage
ICD10-CM	H40.51X2	Glaucoma secondary to other eye disorders, right eye, moderate stage
ICD10-CM	H40.51X3	Glaucoma secondary to other eye disorders, right eye, severe stage
ICD10-CM	H40.51X4	Glaucoma secondary to other eye disorders, right eye, indeterminate stage
ICD10-CM	H40.52	Glaucoma secondary to other eye disorders, left eye
ICD10-CM	H40.52X0	Glaucoma secondary to other eye disorders, left eye, stage unspecified
ICD10-CM	H40.52X1	Glaucoma secondary to other eye disorders, left eye, mild stage
ICD10-CM	H40.52X2	Glaucoma secondary to other eye disorders, left eye, moderate stage
ICD10-CM	H40.52X3	Glaucoma secondary to other eye disorders, left eye, severe stage
ICD10-CM	H40.52X4	Glaucoma secondary to other eye disorders, left eye, indeterminate stage
ICD10-CM	H40.53	Glaucoma secondary to other eye disorders, bilateral
ICD10-CM	H40.53X0	Glaucoma secondary to other eye disorders, bilateral, stage unspecified

ICD type	ICD code	Details
ICD10-CM	H40.53X1	Glaucoma secondary to other eye disorders, bilateral, mild stage
ICD10-CM	H40.53X2	Glaucoma secondary to other eye disorders, bilateral, moderate stage
ICD10-CM	H40.53X3	Glaucoma secondary to other eye disorders, bilateral, severe stage
ICD10-CM	H40.53X4	Glaucoma secondary to other eye disorders, bilateral, indeterminate stage
ICD10-CM	H40.6	Glaucoma secondary to drugs
ICD10-CM	H40.60	Glaucoma secondary to drugs, unspecified eye
ICD10-CM	H40.60X0	Glaucoma secondary to drugs, unspecified eye, stage unspecified
ICD10-CM	H40.60X1	Glaucoma secondary to drugs, unspecified eye, mild stage
ICD10-CM	H40.60X2	Glaucoma secondary to drugs, unspecified eye, moderate stage
ICD10-CM	H40.60X3	Glaucoma secondary to drugs, unspecified eye, severe stage
ICD10-CM	H40.60X4	Glaucoma secondary to drugs, unspecified eye, indeterminate stage
ICD10-CM	H40.61	Glaucoma secondary to drugs, right eye
ICD10-CM	H40.61X0	Glaucoma secondary to drugs, right eye, stage unspecified
ICD10-CM	H40.61X1	Glaucoma secondary to drugs, right eye, mild stage
ICD10-CM	H40.61X2	Glaucoma secondary to drugs, right eye, moderate stage

ICD type	ICD code	Details
ICD10-CM	H40.61X3	Glaucoma secondary to drugs, right eye, severe stage
ICD10-CM	H40.61X4	Glaucoma secondary to drugs, right eye, indeterminate stage
ICD10-CM	H40.62	Glaucoma secondary to drugs, left eye
ICD10-CM	H40.62X0	Glaucoma secondary to drugs, left eye, stage unspecified
ICD10-CM	H40.62X1	Glaucoma secondary to drugs, left eye, mild stage
ICD10-CM	H40.62X2	Glaucoma secondary to drugs, left eye, moderate stage
ICD10-CM	H40.62X3	Glaucoma secondary to drugs, left eye, severe stage
ICD10-CM	H40.62X4	Glaucoma secondary to drugs, left eye, indeterminate stage
ICD10-CM	H40.63	Glaucoma secondary to drugs, bilateral
ICD10-CM	H40.63X0	Glaucoma secondary to drugs, bilateral, stage unspecified
ICD10-CM	H40.63X1	Glaucoma secondary to drugs, bilateral, mild stage
ICD10-CM	H40.63X2	Glaucoma secondary to drugs, bilateral, moderate stage
ICD10-CM	H40.63X3	Glaucoma secondary to drugs, bilateral, severe stage
ICD10-CM	H40.63X4	Glaucoma secondary to drugs, bilateral, indeterminate stage
ICD10-CM	H40.81	Glaucoma with increased episcleral venous pressure
ICD10-CM	H40.811	Glaucoma with increased episcleral venous pressure, right eye
ICD10-CM	H40.812	Glaucoma with increased episcleral venous pressure, left eye
ICD10-CM	H40.813	Glaucoma with increased episcleral venous pressure, bilateral
ICD10-CM	H40.819	Glaucoma with increased episcleral venous pressure, unspecified eye
ICD10-CM	H42	Glaucoma in diseases classified elsewhere
ICD10-CM	H59.81	Chorioretinal scars after surgery for detachment

ICD type	ICD code	Details
ICD10-CM	H59.811	Chorioretinal scars after surgery for detachment, right eye
ICD10-CM	H59.812	Chorioretinal scars after surgery for detachment, left eye
ICD10-CM	H59.813	Chorioretinal scars after surgery for detachment, bilateral
ICD10-CM	H59.819	Chorioretinal scars after surgery for detachment, unspecified eye

Odds ratio and 95% CL for quinolones and other medication groups, and risk of retinal detachment

Population and medication group	Base[35] OR (95% CI)	p-value	Minimally adjusted[36] maOR (95% CI)	p-value	Maximally adjusted[37] aOR (95% CI)	p-value
Entire population						
Quinolones	1.27 (0.80-2.01)	0.3055	0.84 (0.51-1.38)	0.4907	0.75 (0.43-1.32)	0.3184
Non-quinolone antibiotics	1.54 (1.15-2.06)	0.0036	1.18 (0.85-1.64)	0.3117	0.86 (0.58-1.26)	0.4259
Comorbidity level						
CMI:0-1						
Quinolones	1.40 (0.25-7.79)	0.6984	0.72 (0.12-4.39)	0.7212	0.70 (0.05-9.74)	0.7914
Non-quinolone antibiotics	2.66 (1.00-7.08)	0.0503	2.09 (0.72-6.05)	0.1753	1.12 (0.28-4.44)	0.8777
CMI:2-4						
Quinolones	0.46 (0.09-2.29)	0.3420	0.48 (0.09-2.50)	0.3842	0.35 (0.05-2.42)	0.2872

[35] *Base model: age, sex, race variables, and the tested medication group*
[36] *Minimally adjusted model: base model, and the other medication groups*
[37] *Maximally adjusted model: minimally adjusted, and complicated diabetes mellitus, alcohol abuse and socioeconomic status (census division, hospital (urban/rural) and insurance)*

Population and medication group	Base[35] OR (95% CI)	p-value	Minimally adjusted[36] maOR (95% CI)	p-value	Maximally adjusted[37] aOR (95% CI)	p-value
Non-quinolone antibiotics	0.62 (0.22-1.79)	0.3782	0.63 (0.21-1.90)	0.4149	0.49 (0.12-1.92)	0.3053
CMI:5+						
Quinolones	0.87 (0.45-1.66)	0.6624	0.60 (0.29-1.24)	0.1641	0.49 (0.21-1.17)	0.1094
Non-quinolone antibiotics	1.46 (0.91-2.33)	0.1173	1.19 (0.67-2.11)	0.5635	1.15 (0.55-2.38)	0.7155
Gender						
Women						
Quinolones	1.22 (0.60-2.46)	0.5860	0.90 (0.41-1.95)	0.7894	0.89 (0.36-2.23)	0.8042
Non-quinolone antibiotics	1.23 (0.78-1.94)	0.3812	0.90 (0.54-1.50)	0.6759	0.62 (0.34-1.15)	0.1307
Men						
Quinolones	1.44 (0.79-2.64)	0.2367	0.89 (0.46-1.73)	0.7309	0.72 (0.34-1.51)	0.3826
Non-quinolone antibiotics	1.84 (1.26-2.69)	0.0018	1.43 (0.93-2.19)	0.1059	1.10 (0.66-1.82)	0.7198

Population and medication group	Base[35] OR (95% CI)	p-value	Minimally adjusted[36] maOR (95% CI)	p-value	Maximally adjusted[37] aOR (95% CI)	p-value
Race Class	Race Class					
Caucasians	Caucasians					
Quinolones	1.12 (0.67-1.89)	0.6638	0.75 (0.42-1.32)	0.3145	0.67 (0.36-1.24)	0.2013
Non-quinolone antibiotics	1.55 (1.13-2.14)	0.0071	1.30 (0.91-1.87)	0.1558	1.06 (0.70-1.59)	0.8005
African Americans						
Quinolones	3.57 (1.13-11.25)	0.0297	2.53 (0.69-9.28)	0.1609	2.88 (0.43-19.33)	0.2758
Non-quinolone antibiotics	1.66 (0.74-3.76)	0.2213	0.77 (0.30-1.98)	0.5916	0.13 (0.03-0.58)	0.0076
Others						
Quinolones	0.71 (0.08-6.18)	0.7565	0.45 (0.03-6.19)	0.5481	0.001 (<0.001-0.147)	0.0062
Non-quinolone antibiotics	1.15 (0.31-4.22)	0.8369	1.29 (0.25-6.54)	0.7588	13.16 (0.75-230.14)	0.0776
Age Stratum						

Population and medication group	Base[35] OR (95% CI)	p-value	Minimally adjusted[36] maOR (95% CI)	p-value	Maximally adjusted[37] aOR (95% CI)	p-value
0-55						
Quinolones	4.01 (1.78-9.05)	0.0008	2.13 (0.88-5.14)	0.0924	0.87 (0.26-2.93)	0.8156
Non-quinolone antibiotics	2.51 (1.50-4.19)	0.0004	1.50 (0.85-2.66)	<.0001	0.76 (0.32-1.79)	0.5337
56-70						
Quinolones	1.03 (0.46-2.35)	0.9360	0.92 (0.37-2.29)	0.8516	0.90 (0.34-2.41)	0.8404
Non-quinolone antibiotics	1.07 (0.62-1.83)	0.8179	0.85 (0.46-1.59)	0.6112	0.68 (0.34-1.36)	0.2733
71+						
Quinolones	0.66 (0.27-1.57)	1.5680	0.41 (0.16-1.05)	0.0622	0.42 (0.16-1.15)	0.0916
Non-quinolone antibiotics	1.47 (0.91-2.37)	0.1172	1.34 (0.78-2.29)	0.2852	1.13 (0.61-2.08)	0.7021

Odds ratio and 95% CL for individual quinolones and risk of retinal detachment

Population and individual quinolone	Base OR (95% CI)	p-value	Minimally adjusted maOR (95% CI)	p-value	Maximally adjusted aOR (95% CI)	p-value
Entire Population						
Ciprofloxacin	1.60 (0.83-3.07)	0.1588	1.07 (0.54-2.14)	0.8399	0.87 (0.39-1.97)	0.7415
Levofloxacin	0.94 (0.48-1.81)	0.8411	0.62 (0.32-1.24)	0.1774	0.61 (0.29-1.30)	0.1984
Moxifloxacin	1.67 (0.17-16.02)	0.6582	1.25 (0.13-12.06)	0.8474	1.07 (0.10-11.08)	0.9535
Comorbidity level						
CMI:0-1						
Ciprofloxacin	2.78 (0.38-20.39)	0.3157	1.45 (0.18-11.48)	0.7233	1.00 (0.05-19.93)	0.9987
Levofloxacin	<0.001 (<0.001->999.999)	0.9826	<0.001 (<0.001->999.999)	0.9825	<0.001 (<0.001->999.999)	0.9905
Moxifloxacin	N/A	N/A	N/A	N/A	N/A	N/A
CMI:2-4						
Ciprofloxacin	0.40 (0.04-3.75)	0.4239	0.41 (0.04-3.88)	0.4344	0.15 (0.01-2.05)	0.1546
Levofloxacin	0.54 (0.05-5.47)	0.5981	0.59 (0.05-6.43)	0.6657	1.07 (0.08-13.78)	0.9577
Moxifloxacin	N/A	N/A	N/A	N/A	N/A	N/A

Population and individual quinolone	Base OR (95% CI)	p-value	Minimally adjusted maOR (95% CI)	p-value	Maximally adjusted aOR (95% CI)	p-value
CMI:5+						
Ciprofloxacin	1.24 (0.44-3.43)	0.6858	0.83 (0.27-2.52)	0.7355	0.74 (0.19-2.91)	0.6606
Levofloxacin	0.70 (0.29-1.74)	0.4455	0.49 (0.19-1.27)	0.1397	0.46 (0.16-1.39)	0.1691
Moxifloxacin	0.65 (0.07-6.60)	0.7190	0.57 (0.06-5.66)	0.6335	0.14 (0.01-3.59)	0.2369
Gender						
Women						
Ciprofloxacin	1.65 (0.60-4.56)	0.3304	1.25 (0.43-3.71)	0.6820	1.34 (0.34-5.22)	0.6726
Levofloxacin	0.90 (0.34-2.39)	0.8358	0.68 (0.25-1.86)	0.4507	0.68 (0.22-2.15)	0.5150
Moxifloxacin	N/A	N/A	N/A	N/A	N/A	N/A
Men						
Ciprofloxacin	1.84 (0.77-4.39)	0.1676	1.18 (0.47-2.93)	0.7281	0.86 (0.30-2.48)	0.7855
Levofloxacin	1.00 (0.41-2.44)	0.9963	0.61 (0.24-1.56)	0.3027	0.52 (0.18-1.48)	0.2176
Moxifloxacin	1.67 (0.17-16.02)	0.6582	1.22 (0.13-11.83)	0.8657	1.12 (0.11-11.46)	0.9211
Race Class						

Population and individual quinolone	Base OR (95% CI)	p-value	Minimally adjusted maOR (95% CI)	p-value	Maximally adjusted aOR (95% CI)	p-value
Caucasians						
Ciprofloxacin	1.38 (0.63-3.02)	0.4225	0.92 (0.41-2.10)	0.8492	0.80 (0.32-2.02)	0.6364
Levofloxacin	0.96 (0.48-1.92)	0.9156	0.65 (0.32-1.34)	0.2441	0.60 (0.27-1.33)	0.2117
Moxifloxacin	<0.001 (<0.001->999.999)	0.9786	<0.001 (<0.001->999.999)	0.9779	<0.001 (<0.001->999.999)	0.9796
African Americans						
Ciprofloxacin	3.69 (0.79-17.17)	0.0960	3.07 (0.56-16.75)	0.1953	2.09 (0.11-41.09)	0.6268
Levofloxacin	1.12 (0.10-12.48)	0.9281	0.72 (0.07-7.93)	0.7883	1.85 (0.08-42.88)	0.7006
Moxifloxacin	5.00 (0.31-79.94)	0.2551	3.23 (0.20-51.95)	0.4081	0.84 (0.04-20.04)	0.9139
Others						
Ciprofloxacin	1.15 (0.12-10.97)	0.9030	0.72 (0.05-10.27)	0.8070	#VALUE!	0.0437
Levofloxacin	<0.001 (<0.001->999.999)	0.9904	<0.001 (<0.001->999.999)	0.9901	<0.001 (<0.001->999.999)	0.9972
Moxifloxacin	N/A	N/A	N/A	N/A	N/A	N/A
Age Stratum						

Population and individual quinolone	Base OR (95% CI)	p-value	Minimally adjusted maOR (95% CI)	p-value	Maximally adjusted aOR (95% CI)	p-value
0-55						
Ciprofloxacin	5.91 (1.76-19.84)	0.0040	3.29 (0.93-11.69)	0.0657	0.83 (0.15-4.52)	0.8282
Levofloxacin	2.34 (0.73-7.47)	0.1514	1.28 (0.39-4.22)	0.6827	0.93 (0.18-4.95)	0.9343
Moxifloxacin	<0.001 (<0.001->999.999)	0.9938	<0.001 (<0.001->999.999)	0.9938	<0.001 (<0.001->999.999)	0.9944
56-70						
Ciprofloxacin	0.84 (0.19-3.75)	0.8163	0.79 (0.17-3.78)	0.7660	0.84 (0.15-4.72)	0.8418
Levofloxacin	0.92 (0.31-2.69)	0.8765	0.78 (0.25-2.42)	0.6640	0.71 (0.21-2.38)	0.5827
Moxifloxacin	5.00 (0.31-79.94)	0.2551	4.50 (0.28-73.18)	0.2904	5.36 (0.30-97.21)	0.2558
71+						
Ciprofloxacin	1.08 (0.37-3.21)	0.8865	0.67 (0.22-2.09)	0.4910	0.64 (0.18-2.26)	0.4891
Levofloxacin	0.36 (0.08-1.60)	0.1791	0.24 (0.05-1.08)	0.0622	0.27 (0.06-1.29)	0.1009
Moxifloxacin	<0.001 (<0.001->999.999)	0.9906	<0.001 (<0.001->999.999)	0.9907	<0.001 (<0.001->999.999)	0.9907

Odds ratios and 95% CI for complicated diabetes mellitus and alcohol abuse, and risk of retinal detachment

	Diabetes mellitus, complicated	p-value	Alcohol abuse	p-value
Entire population	2.19 (1.68-2.86)	<.0001	1.03 (0.67-1.58)	0.8872
Comorbidity score level				
CMI: 0-1	14.08 (1.40-141.93)	0.0249	0.69 (0.01-90.55)	0.8825
CMI: 2-4	0.46 (0.11-1.98)	0.0654	0.55 (0.14-2.13)	0.2999
CMI: 5+	1.94 (1.19-3.18)	0.0083	0.82 (0.38-1.77)	0.6098
Sex				
Women	2.69 (1.82-4.00)	<.0001	1.56 (0.67-3.59)	0.2999
Men	1.82 (1.26-2.63)	0.0014	0.99 (0.59-1.64)	0.9644
Race				
Caucasians	1.69 (1.24-2.30)	0.0008	1.23 (0.76-1.97)	0.3986
African Americans	5.85 (2.70-12.65)	<.0001	0.90 (0.26-3.16)	0.8728
Others	21.84 (4.25-112.28)	0.0002	<0.001 (<0.001->999.999)	0.9932

	Diabetes mellitus, complicated	p-value	Alcohol abuse	p-value
Age (tertiles)				
0-55	6.18 (3.65-10.46)	<.0001	1.02 (0.46-2.27)	0.9633
56-70	1.24 (0.80-1.92)	0.3453	0.99 (0.52-1.89)	0.9750
71+	1.60 (0.94-2.71)	0.0830	1.79 (0.74-4.33)	0.1978

Results from recent studies on quinolone antibiotics and risk of retinal detachment

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) years Sex (%)	RD risk (formulation)	Agent Risk ratio (95% CI)
Gatti 2020 [1]		Umbrella review (3 systematic reviews)				No association (systemic)	
Yu 2019 [2]		Systematic review (8 studies)				No association with current use (systemic)	Current use (1-30 days) OR: 1.25 (1.01–1.53) Past use (31-365 days) OR: 1.27 (1.09–1.47)
Choi 2018 [3] (South Korea)	Korean National Health Insurance Service National Sample Cohort (KNHIS-NSC)	Nested case-control (population-based)	2002 - 2013	Cases: 1,151 Controls: 11,470	NR Men: 56.4%	No association (oral)	aOR: 1.00 (0.81-1.24), P = 0.99
Alves 2016 [4]		Systematic review (10 studies)				No association (systemic)	RR: 1.47 (0.95–2.27) I_2 = 92.8%, p = 0.09

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) years Sex (%)	RD risk (formulation)	Agent Risk ratio (95% CI)
Raguideau 2016 [5] (France)	French National Interscheme Health Insurance Information System database (SNIIRAM)	Case-crossover (population-based)	1 Jul 2010 - 31 Dec 201	27,540 adults with RD	61.5 ± 13.6 Men: 57%	Increased risk for current but not recent use (oral)	Current use (10 days): aOR: 1.46 (1.15-1.87) Recent use (11-30 days): aOR: 0.94 (0.78-1.14)
Chui 2015 [6]		Systematic review (7 studies)				No association (systemic)	Current use: Overall absolute risk: 4.85 cases / 1 million prescriptions (95% CI: 0.78–8.91)
Eftekhari 2014 [7] (UK)	The Health Improvement Network (THIN) database	Cohort study (population-based)	Jun 1994 – Jan 2012	Patients who were prescribed fluoroquinolones or beta-lactam antibiotics	Quinolones: 55.1 years (1-109) Beta-lactams: 40 years (1-111)	No association (oral)	≥ 30-days: HR= 0.78 (0.11–5.71) 31-90 days: HR= 1.25 (0.51–3.08) 91-365 days: HR= 1.35 (0.89–2.06).

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) years Sex (%)	RD risk (formulation)	Agent Risk ratio (95% CI)
					Men: 44%		
Fife 2014 [8] (USA)	MarketScan Commercial Claims and Encounters database (CCAE)	Case-control study	Jan 2000 – Jan 2012			No association (oral)	Current use: OR: 1.33 (0.99-1.80) Recent use (7 days) OR: 1.19 (0.81-1.76)
	Optum ClinFormatics database	Case-control study	Sep 2005 – Mar 2012			No association (oral)	Current use: OR: 0.93 (0.48-1.81) Recent use (7 days) OR: 0.74 (0.33-1.63)
	MarketScan Commercial Claims and Encounters database (CCAE)	Self-controlled case series	Jan 2000 – Jan 2012			No association (oral)	30-day risk period: IRR 1.13 (0.99-1.29)

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) years Sex (%)	RD risk (formulation)	Agent Risk ratio (95% CI)
	Optum ClinFormatics database	Self-controlled case series	Jan 2005 – Mar 2012			No association (oral)	30-day risk period: IRR: 0.85 (0.66-1.09)
Kapoor 2014 [9] (USA)	Medical record linkage system Rochester Epidemiology Project (REP)	Cohort study (population-based)	1 Jan 2003 – 30 Jun 2011	Adult residents of Olmsted County, Minnesota who were prescribed oral fluoroquinolones	50.6 ± 19.6 Men: 39%	No association (oral)	Recent use (30 days) * RR: 1.82 (0.11-29.03) Past use (90 days) * RR: 1.08 (0.26-4.56)
Kuo 2014 [10] (Taiwan)	Taiwan National Health Insurance Research Database	Cohort study (population-based)	1998 – 2010	Adults (aged >18 years) who were prescribed >3 consecutive doses of an oral fluoroquinolone or amoxicillin) on study entry. Fluoroquinolones cohort: 178,179	47.2 ± 18.3 Men: 40.8%	Increased risk (oral)	Quinolones: aHR: 2.07 (1.45–2.96). Ciprofloxacin: aHR: 10.68 (3.28–34.82) Levofloxacin: aHR: 2.41 (0.76–7.68) Norfloxacin: aHR: 2.00 (1.06–3.79)

Study (Country)	Database	Design (Type)	Duration	Population	Age (mean ±SD) years Sex (%)	RD risk (formulation)	Agent Risk ratio (95% CI)
				Amoxicillin cohort: 178,179			Ofloxacin aHR: 1.17 (0.59–2.31)
Pasternak 2013 [11] (Denmark)	The Central Person Register of Denmark	Cohort study (population-based)	1 Jan 1997 – 31 Dec 2011	Adults (aged >18 years) with no prior RD 748,792 episodes of fluoroquinolone use (ciprofloxacin: 88%)	57.7 ± 19.9 Men: 38%	No association (oral)	(10 days): aRR: 1.29 (0.53 – 3.13) (11-30 days): aRR: 0.97 (0.46 – 2.05)
Etminan 2012 [12] (Canada)	British Columbia Linked Health Database	Nested case-control	1 Jan 2000 – 31 Dec 2007	Cases: 4,384 Controls: 43,840	61.1 ± 16.6 Men: 58.2%	Increased risk (oral)	Current use (overlaps index date): aRR: 4.50 (3.56-5.70) Recent use (1-7 days): aRR: 0.92 (0.45-1.87) Past use (8-365 days): aRR: 1.03 (0.89-1.19]

aHR: *adjusted hazard ratio****; aOR:*** *adjusted odds ratio,* ***aRR:*** *adjusted rate ratio,* ***HR****: hazard ratio,*

** Unadjusted estimates calculated from crude rates: as reported by Raguideau et al. [5]*

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STROBE Statement – Chapter 7

STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) Statement – Checklist of items that should be included in reports of case-control studies

Item	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title (page 1) Abstract (page 2, line 37)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, line 31
Introduction			
Background / rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3, line 59
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2, line 35
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4, line 93
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5, line 100

Item	Item No	Recommendation	Reported on Page No.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 5, line 112
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 6, line 129
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6, line 134
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7, line 143
Bias	9	Describe any efforts to address potential sources of bias	Page 8, line 172
Study size	10	Explain how the study size was arrived at	Page 9, line 184
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	Page 7, line 143

Item	Item No	Recommendation	Reported on Page No.
		describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8, line 160
		(*b*) Describe any methods used to examine subgroups and interactions	Page 8, line 177
		(*c*) Explain how missing data were addressed	Page 5, line 113
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 6, line 129
		(*e*) Describe any sensitivity analyses	Page 8, line 177
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9, line 184 Page 8, Figure 1
		(b) Give reasons for non-participation at each stage	Page 9, line 184
		(c) Consider use of a flow diagram	Page 8, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	Page 11, line 198

Item	Item No	Recommendation	Reported on Page No.
		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Page 11, Table 1
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Page 15, line 222 Page 15, Table 2 Page 16, line 232 Page 16, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 17, line 226 Page 19, Table 4 Page 21, Table 5
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses	

Item	Item No	Recommendation	Reported on Page No.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 22, line 288
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 24, line 342
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 22, line 288
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 23, line 320
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 26, line 375

Discussion

Discussion and conclusions

Overview

This thesis comprises a comprehensive strategy for investigating the association between quinolones, one of the most globally popular class of antibiotics, and the risk of two adverse reactions - acute liver failure (ALF) and retinal detachment (RD) - of an acute and serious nature that requires urgent medical attention. For each outcome of interest, this strategy comprised assessing the evidence generated from multiple data sources with different designs, target populations, strengths, limitations and data quality.

Chapters 2 (ALF) and 4 (RD) involved examining one of the most substantive spontaneous error reporting systems (SRS) in the world, the US FAERS database, which included nearly 15 million reports on adverse events (ADE) suspected of being associated with medications and supplements. Studies involving this type of data aim mainly at generating hypothesis for possible medication-ADE pair associations, which would direct more detailed pharmacoepidemiologic studies. However, in the absence of these more detailed studies, national regulators may use the evidence generated from ADE reports to guide their safety-based medication regulatory decisions.

Chapters 3 (ALF) and 6 (RD) comprised examination of results from all published and unpublished original clinical trials that examined quinolone antibiotics, for evidence on cases of *de-novo* diagnosis of ALF or RD following the administration of a quinolone antibiotic in an otherwise liver disease-free (ALF, chapter 3) or eye disease-free (RD, chapter 6) individuals, respectively.

Chapters 4 (ALF) and 7 (RD) comprised case-control analysis of inpatient data from a major US electronic health records (EHR) database that include extensive medical and

demographic information on more than 70 million patients, comprising 21% of the US population.

Methodology

Analysis of FAERS data

As part of the investigation of the association of quinolones with AHF/ALF[38] (chapter 2) and RD (chapter 5), and following a rigorous cleaning stage of FAERS data, I examined adverse drug event (ADE) reports to identify safety signals of associated with quinolone antibiotics compared to selected medications representing both reference and positive controls.

In chapter 2, I identified three groups of antibiotics: quinolones, non-quinolone antibiotics with known drug-induced liver injury (DILI) which constituted positive controls ('Most DILI'), and non-quinolone antibiotics with no known DILI potential ('No DILI') as reference controls.

In the investigation concerning quinolone-associated RD risk (chapter 5), I identified three groups: quinolones, non-quinolone medications with reported association with RD (positive controls, 'Most RD'), and non-quinolone antibiotics with no known association with RD (reference antibiotics, 'No RD').

The analysis was predominantly focused on ADE reports linking our identified medications as primary suspects (PS) or as primary suspects and secondary suspects combined (PS/SS) to either AHF or RD. Analysis was also focused on reports submitted

[38] ALF is the medical term describing acute liver failure (as listed in the MedDRA dictionary), that is reported in FAERS as acute hepatic failure (AHF)

during the interval between 2010-2019, which marked the interval with both highest reporting rates to FAERS and highest quality of ADE reports.

For identifying disproportionality signals between quinolones and each of positive controls or reference controls, I tallied all reports linked to each of the examined medications and quantified the signal for each using two data mining techniques: the proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS), which are known for their higher sensitivity and specificity for ADE signal detection, respectively. ADE reports are generally considered hypothesis generating rather than hypothesis testing: identifying a significant disproportionality signal for a medication may suggest higher reporting of the ADE without constituting a basis for inferring causality, which requires detailed pharmacoepidemiologic investigation.

Systematic reviews

I designed a multi-step search strategy for identifying relevant original studies through examination of four bibliographic databases (MEDLINE, EMBASE, CENTRAL and CINAHL), eight international clinical trial registries, and major grey literature sources such as drug review networks and databases of pharmaceutical companies, relevant national and international agencies and international conference proceedings. I have also inspected the bibliographies of examined studies for additional relevant studies not previously identified via the original search.

Searching for medical subject headings, and text words and word combinations related to all known quinolones and the outcome of interest (ALF/RD). The search employed specialized search algorithms with validated efficiency for identifying clinical trials, without applying any language, time or other filters to limit the search output. This strategy was

conducted in accordance with the PRISMA guidelines and the specific guidance of the Cochrane Collaboration. Screening and full-text examination of identified references was completed independently by me (MT) and my coauthor (MH), based on predetermined eligibility criteria. Conflicts identified at each level were resolved prior to moving to the next level.

Analysis of the Health Facts® data

In this study, I preferred the nested case-control over a cohort design since the former offers similar benefits, with greater computational efficiency [1-3]. The nested case-control design allows for matching on age and calendar time, rather than adjusting for these effects as covariates in a cox regression model widely used in the analysis of cohort data [1-3]. Missing observations may also have a lesser impact in a nested case-control analysis compared to the cohort design [4-6].

The eligibility criteria for identifying cases and controls included being admitted at least once to any of the hospitals contributing to the Health Facts® database, with a minimum recorded medical history of one year prior to the day of the index encounter, having complete and consistent information on the matching variables, and no history of current or prior liver diseases (ALF, chapter 4), or eye diseases (RD, chapter 7).

Summary of the main findings

Acute liver/hepatic failure (ALF/AHF)

FAERS analysis

Our results showed that out of four quinolones that were reportedly linked to ALF, only ciprofloxacin showed a marginally positive and significant AHF signal, whereas moxifloxacin, levofloxacin and ofloxacin showed weak and/or non-significant signals. Cumulative analysis of the FAERS data between 2004-2019 showed a similar pattern to that obtained from our primary analysis interval (2010-2019q2), with a less powerful signal for ofloxacin as a result of the absence of any AHF reports between 2004-2009.

Systematic review

Through a detailed search strategy, I was able to identify 3,714 records from four bibliographic databases and eight clinical trial registries, 30 records from the databases of pharmaceutical companies, and one record from an international conference. Upon removal of duplicates and irrelevant studies, I was able to retain 2,971 studies for full-text examination, including 1,370 original and 1,601 non-original[39] studies. No results were reported at the time of production of this thesis on 167 of the identified original studies. Using our inclusion/exclusion criteria, and out of 140 eligible original studies, only two studies reported one ALF case with each of moxifloxacin and gemifloxacin.

Health Facts® analysis

Following a detailed identification process, I compiled a pool of 3,151 eligible cases who were first diagnosed with ALF between 2010-2015. Using incidence density matching algorithm, I was able to match these cases for up to five unique controls each for a total of

[39] Here, the term 'non-original studies' refers to all publications, other than the original trial record, that report on or had been indexed to an original clinical trial. All non-original studies are listed under the corresponding original trial in the Supplementary Material for chapter 3 (ALF) and Chapter 6 (RD).

15,657 unique controls. Matching of cases and controls was based on four variables with equal weights: sex, race, age on day of the index encounter (±1 year), and the period-at-risk (±1 year).

The study population was predominately Caucasian (75%) with slightly more women (53%) than men. Incidence of ALF was low in the early decades of life, increased steadily until the age of 60 years, then plateaued afterwards. Cases were generally less healthy than controls, with a higher prevalence of diabetes mellitus (both uncomplicated and complicated) and alcohol abuse compared to controls. Both cases and controls were equally covered by health insurance. During the 30-day window prior to the index encounter, and on average, prescriptions filled to cases were 2-3 times higher than that for controls for all medication groups.

Results from our primary conditional logistic regression for the entire study population revealed no association between systemically-administered quinolones as a class and ALF risk, after adjusting for exposure to other medications, uncomplicated and complicated diabetes mellitus, alcohol abuse, health care setting and insurance status. Examining the individual quinolones showed an elevated, but non-significant, risk with moxifloxacin and ciprofloxacin.

Secondary analyses for the different subgroups revealed some evidence of ALF risk in some subgroups. Quinolones revealed a marginal, non-significant ALF risk in both men and women (attributable to both moxifloxacin and ciprofloxacin). Non-significant ALF risk was also observed in African Americans (due to ciprofloxacin and moxifloxacin), and in Caucasians (attributable to ciprofloxacin). A significant quinolone class-ALF risk was identified only in the 0-60 years of age group, with all individual quinolones showing a non-significant ALF risk in the 0-60- and 61–75-year-old groups. The subgroup analysis based on health status revealed

that quinolones had a significant ALF risk for the healthiest group (CMI: 0-6) that was attributable to ciprofloxacin.

Complicated diabetes mellitus was associated with a significant ALF risk in the primary analysis, across all races, in women more so than men, and decreased slightly with advancement of age. Alcohol abuse was also associated with a significant ALF risk in the primary analysis, in the healthiest subgroup (CMI: 0-6), in women, in Caucasians more so than African Americans, and in the youngest more than the middle age tertiles. Despite having different designs and target populations, results from recent major epidemiologic studies were similar to results from the current study.

Retinal Detachment

FAERS analysis

Analysis of FAERS data for ADE reports between 2010-2019 revealed a total of 4,368 reports of RD that were linked to all types of medications, including PS, SS, concomitant (C) or interacting (I) medications. Results identified a total of 20 reports, which generated a significant PRR disproportionality signal for RD with moxifloxacin. No such signals were identified with other quinolones during the same time interval.

Systematic Review

Following the same strategy for acute liver failure, I was able to identify 3,461 records, which included 3,430 records from bibliographic databases and clinical trial registries, 30 records from the databases of pharmaceutical companies, and 1 record from an international conference. Screening of titles and abstracts then full-text examination resulted in the

identification of only 145 original studies that met the eligibility criteria. There were no reports of retinal detachment in any of the study participants with no history of prior eye diseases

Health Facts® analysis

Based on the case identification strategy mentioned earlier, I was able to identify an eligible pool of 772 RD cases with no history of eye diseases with medical history of one or more years and no missing or inconsistent data for the matching variables. Using the same matching algorithm, each eligible case was successfully matched to five unique controls, which totaled to 3,860 controls based on sex, race, age on day of the index encounter (±1 year) and the period-at-risk (±1 year).

The study population was mainly Caucasian (77.6%) with near equal sex distribution (51% men). The incidence of RD was very low early up until the age of 40, following which it doubled twice to 9.3% and 21% in the fifth and sixth decades of life, respectively, before reaching a plateau afterwards. Cases showed a higher prevalence of comorbidities compared to controls, particularly with respect to diabetes mellitus. No appreciable differences were identified regarding health insurance or hospital setting. Thirty-day prescriptions of quinolones were similar between cases and controls, while cases were prescribed more non-quinolone medications compared to controls.

Our primary conditional regression analysis did not identify any association between systemically administered quinolones, either as a class or as individual agents, with RD risk after adjusting for exposure to non-quinolone antibiotics, other medications combined, major risk factors and confounders. Race-based subgroup analysis flagged an almost 2-fold non-significant increase in RD risk in African Americans that was attributable to ciprofloxacin and levofloxacin. Whereas quinolones showed no associated RD risk at any specific age group,

moxifloxacin showed more than 4-fold, non-significant increase in RD risk in the 56–70-year-old group. Ciprofloxacin showed a marginal and non-significant risk in women. No other quinolones showed evidence of an increase in RD risk in any other subgroup analysis. Complicated diabetes mellitus was associated with a significant RD in the primary and almost all subgroup analyses, with African Americans at higher risk than Caucasians, in women more so than in men, and in those 55 years of age or younger. In contrast, alcohol abuse showed no such increase in risk in either primary or secondary subgroup analyses.

Strengths and limitations

Analysis of FAERS data

FAERS is a large-scale spontaneous reporting system (SRS) that captures reports on ADE that are submitted by health professionals and consumers from the US and other countries. These reports contain detailed information on patient demographics, medication/supplement, indications, ADE and treatment outcome.

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 [7, 8].

As reporting is voluntary, it depends on the reporters' motivation and/or professional skills and judgment, which makes SRS such as FAERS prone to different types of reporting bias. FAERS has an inherent limitation of generating many false positive and false negative results, in addition to lacking detailed information relevant on risk factors such as comorbidities or results of diagnostic tests.

While the FAERS analyses were primarily focused on associations where drugs were reported as primary suspects (PS), I did not consider drug-drug interactions among multiple drugs from the examined medication groups when considering drugs reported as primary suspect/secondary suspect (PS/SS) combined. However, incidents in the latter scenario accounted for less than 5% of the total number of cases, thus limiting any possible impact of drug-drug interactions on the overall results.

Despite their major limitations, national regulators use SRS for early identification and characterization of early signals of ADE, particularly rare or long-term ADE. Results from SRS-based studies are traditionally used to identify serious adverse outcomes or high-priority areas for conducting more detailed confirmatory studies.

Systematic reviews

Clinical trials are considered to represent the most robust tool for assessing clinical effectiveness and safety of medications prior to their release for use by the public. These assessments are carried out via strict protocols, using healthy volunteers, under strictly controlled testing environments, which make clinical trials time- and cost-prohibitive. However, these trials are still subject to certain limitations.

A major limitation of clinical trials involves the lack of representativeness with the general public due to difference in risk factors and other underlying health determinants between trial participants and the general public, as well as between the controlled trial environment and real-life situations. Another limitation involves the limited power to detect rare or long-term ADE due to the limited number of trail participants and limited durations of most trials.

Analysis of Health Facts® data

EHR databases such Health Facts® were initially created for facilitating efficient and seamless flow of medical information among service providers throughout the medical care continuum. They comprise a high-value source of data on patient profiles, which include clinical, demographic and other types of patient-related information. Additionally, they offer a less time- and resource-exhaustive opportunity to examine and compare the risks of different ADR in large patient populations under real-world conditions of use, particularly rare or long-term ADR.

However, as with other large databases, Health Facts® is prone to different data integrity issues such as misclassification of demographics, comorbidities, medications, outcomes or other clinical details. Since Health Facts® provides primarily inpatient-related information, information on outpatient medications is incomplete. Although 50-80% of antibiotics are prescribed on an outpatient basis and may not be captured in an inpatient-based database as Health Facts®, in-patient prescriptions are expected to reflect out-patient prescription patterns to a large extent. If outpatient and inpatient prescribing patterns differed notably, this would lead to exposure misclassification, which, if random, would be expected to bias the risk estimates towards the null value of no effect. I also used medication prescription orders filled by each hospital pharmacy as a proxy for medication exposure, which offered more confidence in patient compliance compared to medications filled for outpatients where patient compliance could not be guaranteed.

Following the eligibility criteria for this study, the pool of eligible cases was reduced to include only those with a medical history of at least one year to allow for assessing the impact of previous comorbidities on the association under investigation.

Results from recent major reviews and original epidemiologic studies that examined the association between quinolones and both outcomes are predominantly in line with our results, despite the variation in factors such as study design, target population, and identification of cases and controls.

Contributions to the advancement of knowledge

To the best of my knowledge, this is the first comprehensive attempt to conduct a multi-pronged investigation of associations between a broad medication class and ADR using multiple evidence streams. The two investigations of the association between use of quinolones and the risk of ALF and RD were conducted through an innovative approach incorporating different study designs, with each one offering a different value and depth to the investigation process. While acknowledging each design has its own limitations, they collectively support a comprehensive assessment of the questioned associations (ALF/RD), and provided suggestions for future research. This multi-pronged approach provides a more solid evidence-base for supporting better decision-making regarding possible drug-ADR associations than relying on any one evidence stream alone.

Conclusion

During the proceedings of this thesis, I conducted six epidemiologic studies to investigate the association of quinolones with two serious ADR, with each association being investigated through examining and analyzing data from three different sources: published and unpublished original clinical trials, spontaneous reports from the US FAERS database, and a case control analysis of the substantive US-based Health Facts® EHR database.

The analysis of the association of quinolone antibiotics with ALF represented the first robust and multi-pronged assessment of a serious DILI issue, where DILI represents the most common cause of post-marketing medication withdrawal by national regulators. Results from the case-control analysis were compatible with results from other recent pharmacovigilance studies, despite the difference in study designs and target population. Examining results from clinical trials in conjunction with FAERS reports represented the first time this approach has been used to address quinolone-associated ALF risk.

Similarly, the investigation for quinolone-associated RD was the first to examine results from clinical trials and spontaneous reports to FAERS. Results from the case-control analysis of the Health Facts® database were in alignment with the latest FDA advisories and results from almost all recent major reviews and other pharmacovigilance studies that examined this association. Whereas I could not identify an overall class-based association of quinolone antibiotics with either ALF or RD, an increased risk with some quinolones was identified in certain sub-populations such as women, men, certain age-groups, African Americans and Caucasians.

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