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ORIGINAL REPORT

# Risk of retinal tear or detachment with oral fluoroquinolone use: a cohort study†

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## ABSTRACT

**Purpose** The aim of this study is to determine if oral fluoroquinolone exposure is associated with an increased hazard for having a retinal tear or detachment.

**Methods** A retrospective cohort study was performed using individuals who met inclusion criteria from The Health Improvement Network database. Cohorts were created for individuals who had a prescription written for either an oral fluoroquinolone or an oral β-lactam antibiotic (comparison group). Subjects were excluded if they had a previous diagnosis of a retinal tear or detachment (hereafter retinal break (RB)), or a procedure code to treat an RB, where in the practice for less than 365 days, had a previous prescription for either antibiotic within 365 days of the index date or had intraocular surgery or a diagnosis of endophthalmitis within 90 days prior to the antibiotic prescription. Covariates of interest were age, gender, diabetes, and year of index. The primary outcome measure of interest was the hazard ratio (HR) of undergoing a procedure to treat an RB within 7, 30, 90, or 365 days after exposure to an oral fluoroquinolone prescription versus an oral β-lactam prescription.

**Results** After exclusions, 6 604 423 prescriptions (290 393 fluoroquinolone; 6 314 030 β-lactam) from 3 413 498 patients (247 073 fluoroquinolone; 3 303 641 β-lactam) and 2685 RB procedures were eligible for analysis (661 retinal tears and 2024 retinal detachments). For fluoroquinolones, 0, 1, 5, and 23 RBs occurred at the 7-, 30-, 90-, and 365-day time points, respectively. For β-lactam prescriptions, 7, 28, 87, and 373 RBs occurred at the 7-, 30-, 90-, and 365-day time points, respectively. Because of zero events occurring in the fluoroquinolone cohort during the 7-day observation period, an unadjusted or an adjusted HR (and subsequent *p*-value or confidence intervals) was unable to be calculated. Univariate and multivariate analyses demonstrated that fluoroquinolones were not significantly associated with RB in the 30-, 90-, or 365-day observation periods (30-day HR = 0.78, $p = 0.80$, 95%CI: 0.11, 5.71; 90-day HR = 1.25, $p = 0.63$, 95%CI: 0.51, 3.08; and 365-day HR = 1.35, $p = 0.16$, 95%CI: 0.89, 2.06).

**Conclusions** Our results do not support an association between oral fluoroquinolone use and subsequent procedures to treat an RB.


KEY WORDS—fluoroquinolones; retinal detachment; retinal tear; retinal break; cohort; Cox regression; pharmacoepidemiology

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## INTRODUCTION

Fluoroquinolones (FQs) are a staple in the armamentarium of antibiotic therapies for infectious disease and, annually, one of the most commonly prescribed antibiotics.[1] While efficacious and generally well tolerated, they are not without adverse effects. Because of their widespread use, the discovery of new adverse effects typically is met with great interest, as was certainly the case when a potentially landmark study performed by Etminan and colleagues found an association between retinal detachments (RDs) and FQ use.[2] Since its publication in mid-2012, two other recent reports have demonstrated conflicting results with one corroborating the findings of Etminan and another refuting.[3,4] Because of the widespread use of FQs and the severity of vision loss possible from RDs, this issue has been of great concern and interest leading to numerous editorial comments regarding the implications for

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patient care.[5–13] These concerning findings are particularly important in ophthalmology, where surgical patients—who are already at higher risk of RD—are frequently given topical FQs postoperatively as prophylaxis against endophthalmitis because of their excellent ocular penetration.[14]

With regard to eye disease, previous case reports have linked FQ use with conditions ranging from corneal perforations to optic nerve disease.[15–17] The mechanism by which oral FQ use would increase the risk of RD is unknown. Etminan *et al*. suggest that the known effect of FQ on collagen dissolution, which is the proposed mechanism for increased risk of Achilles tendon rupture, could lead to early liquefaction of the vitreous gel, premature posterior vitreous detachment, and subsequently increase the rate of RDs.[2]

Along this proposed pathogenic pathway, a necessary intermediate step preceding the rhegmatogenous RD is a retinal tear. When viewed this way, an RD is simply a progression of disease that if diagnosed acutely enough, would be found as a retinal tear. Acute, symptomatic tears are typically treated in the office and, similar to RDs, have their own unique diagnosis and reparative procedure codes that are identifiable in medical administrative databases. Our study aims to examine the relationship between oral FQ use and treatments for retinal breaks—defined as either a retinal tear or detachment—in a population-based medical database from the UK.

## METHODS

### *Data set*

This is a retrospective cohort study using The Health Improvement Network (THIN) database that contains the de-identified electronic medical records of 11.1 million patients (3.7 million active), which currently collects from 562 general medical practices in the UK, covering 6.2% of the UK population. All patients who are registered with one of the 562 practices are included within THIN. The earliest THIN data start in June 1994 and, for this study, are inclusive for data through January 2012. The database contains medical diagnoses, procedures, and laboratory and all outpatient pharmaceutical data. The population within THIN has been found to have good generalizability to the UK population as a whole with similar demographics, systemic disease rates and death rates.[18] Because general practitioners (GPs) in the UK coordinate their patients' care, all medical services delivered by a specialist such as an ophthalmologist generates a notification to the GP specifying the diagnosis for which the patient was seen and any procedures performed at that visit. The GP then inputs the data into the patient's electronic medical record utilizing the Vision software system, which is retrieved by THIN. The National Health Service in the UK also requires that all outpatient prescriptions be administered by the GP, including those requested by specialists. This study was approved by the Scientific Review Committee for the THIN database and was deemed exempt from review by The University of Pennsylvania Institutional Review Board because of the de-identified nature of the data.

### *Cohorts*

Cohorts for this study were defined by having a prescription written for FQs or β-lactam (BL) antibiotics between June 1994 and January 2012. Similar to the previous study, BL antibiotics were chosen as a comparator group because of their similar clinical indications for usage but without concern for the same mechanism of action on collagen, which is suggested to increase the risk of RDs.[2] To meet inclusion criteria, patients had to be registered with their GP for at least 365 continuous days prior to the index date, which was defined as the date that the prescription of interest was written. Index dates for prescriptions with a previous prescription of either class of antibiotics within 365 days were excluded from the analysis. Patients were excluded from the cohort if they had any retinal tear or detachment (RB) diagnosis or procedure code on or before the prescription date. Also, patients who had both classes of antibiotic prescribed on the same index date were excluded. Lastly, any prescriptions written within the 90-day period following an intraocular surgery or a diagnosis of endophthalmitis were excluded because these conditions are known to increase the risk of RD. Patients were allowed to reenter the cohort or even switch cohorts after 365 days assuming that the second episode met the previously mentioned eligibility criteria.

### *Outcomes and covariates of interest*

Outcome events were defined by having a procedure code for an RB repair entered into the THIN database during the observation period of interest. RBs that did not have an associated procedure for a repair were not included in the analysis because of the possibility of an untreated RB being chronic or treated prior to entry into THIN. Also, a strict definition of codes was created to lessen the possibility that a procedure was performed for an RB not associated with a primary rhegmatogenous mechanism (i.e., exudative or tractional RDs). Procedure and diagnosis code lists can be found in Table 1.



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Table 1. Medcodes used for procedure and diagnosis identification

| Medcode* | Procedure category | Procedure description |
|---|---|---|
| 7251.00 | Detachment | Buckling operations for attachment of retina |
| 7251.11 | Detachment | Scleral buckling for attachment of retina |
| 7251200 | Detachment | Buckling of sclera and implant however further qualified |
| 7251300 | Detachment | Buckling of sclera and local encircling |
| 7251400 | Detachment | Buckling of sclera not elsewhere contributed |
| 7251y00 | Detachment | Other specified buckling operation for attachment of retina |
| 7251z00 | Detachment | Buckling operation for attachment of retina NOS |
| 7270.00 | Detachment | Operations on vitreous body for attachment |
| 7270400 | Detachment | Pars plana vitrectomy |
| 7270411 | Detachment | Vitrectomy using pars plana approach |
| 7270600 | Detachment | Internal tamponade of retina using gas |
| 7270700 | Detachment | Internal tamponade of retina using air |
| 7270800 | Detachment | Internal tamponade of retina using liquid |
| 7270900 | Detachment | Internal tamponade of retina using oil |
| 7271.00 | Detachment | Photocoagulation of retina for detachment |
| 7271000 | Detachment | Xenon photocoagulation of retina for detachment |
| 7271100 | Detachment | Laser photocoagulation of retina for detachment |
| 7271y00 | Detachment | Other specified photocoagulation of retina for detachment |
| 7271z00 | Detachment | Photocoagulation of retina for detachment NOS |
| 7273500 | Detachment | Drainage of subretinal fluid through retina |
| 7279000 | Tear | Retinopexy using cryotherapy |
| 7279100 | Tear | Retinopexy using diathermy |
| 7279400 | Tear | Retinopexy not elsewhere contributed |
| 7279.00 | Tear | Fixation of retina |
| 7279y00 | Tear | Other specified fixation of retina |
| 7279z00 | Tear | Fixation of retina NOS |
| **Medcode*** | **Diagnosis category** | **Diagnosis description** |
| F41..00 | Detachment | Retinal detachments and defects |
| F410.00 | Detachment | Retinal detachment with retinal defect |
| F410000 | Detachment | Unspecified retinal detachment with retinal defect |
| F410100 | Detachment | New partial retinal detachment with single defect |
| F410200 | Detachment | New partial retinal detachment with multiple defects |
| F410300 | Detachment | New partial retinal detachment with giant tear defect |
| F410400 | Detachment | New partial retinal detachment with retinal dialysis |
| F410500 | Detachment | Recent total retinal detachment |
| F410600 | Detachment | Recent subtotal retinal detachment |
| F410z00 | Detachment | Retinal detachment with defect NOS |
| F41..11 | Tear | Retinal tears |
| F413.00 | Tear | Retinal defects without detachment |
| F413000 | Tear | Unspecified retinal defect |
| F413200 | Tear | Horseshoe retinal tear without detachment |
| F413300 | Tear | Multiple retinal defects without detachment |
| F413400 | Tear | Retinal break |
| F413z00 | Tear | Retinal defects without detachment NOS |

*Medcodes with zero observations were not included.

In addition to the primary analysis evaluating repair of all retinal breaks in aggregate, secondary analyses were conducted by examining the incidence of procedures for retinal tears and detachments separately during each of the observation periods, as well as an additional analysis focusing on a "high-risk" age cohort consisting only of those 50–70 years old. The high-risk age cohort corresponds to the average age for a posterior vitreous detachment to occur,[19,20] which would be a common precursor lesion for retinal breaks, and therefore, most retinal breaks would expect to be found in this age group in a large cohort. Patients with codes for a reparative procedure and/or for diagnoses for both a retinal tear and detachment had the earliest date taken as the censoring date and were considered to only have an RD in tabulation of totals and for all secondary analyses. Because the THIN database is coded by GPs and not by ophthalmologists, a sensitivity analysis was performed on those RBs with an associated diagnostic (retinal tear or detachment) medcode 30 days before or after the procedure code, with the assumption that any patient with both a procedure code and a known corresponding diagnosis is more likely to truly have had the procedure performed. Possible covariates of interest that were included in the study were age, gender, diabetes, and calendar year of index date.

### *Statistical analysis*

Baseline and demographic characteristics were summarized using descriptive statistics (e.g., means and ranges for continuous variables such as age and percentages for categorical variables). Cox proportional hazard models were used to analyze the time to undergo a procedure to treat an RB in association with an oral FQ use from the prescription index date. The censoring date of eligible patients was defined as the earliest date among the following: occurrence of the event of interest, a code for intraocular surgery (other than for an RB), a prescription for the alternate class of oral antibiotic written after the index date, patient transferred out of the general practice (i.e., no longer followed in THIN), 365 days of follow-up was reached, the latest date that THIN collected data from the practice, or death of the patient. If a patient had a corresponding diagnosis code (retinal tear or detachment) within 30 days prior to the procedure, the date of the diagnosis code was used as the censor date instead of the procedure date. Hazard ratios (HRs) were estimated for four observation periods: days 1–7, 1–30, 1–90, and 1–365 after the index date. Because the unit of observation was one prescription, patients who met entry criteria could be entered into the study more than once. To account for possible nonindependence of multiple observations and also clustering of observations from one patient, robust



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variance estimates were used in all Cox regression analyses.[21] STATA® 12 (College Station, Texas) software was used for all statistical analyses. Results of the analyses were considered statistically significant for $p < 0.05$ (two tailed).

## RESULTS

Included prescriptions were collected from June of 1994 through January of 2012. After exclusions, 6 604 423 prescriptions (290 393 FQs and 6 314 030 BLs) from 3 413 498 patients (247 073 FQs and 3 303 641 BLs) were eligible for analysis (Figure 1). Over 88% of all FQ prescriptions studied were for ciprofloxacin (Table 2). The 290 393 FQ prescriptions represent 3978 to 5569 person years of FQ use (depending on whether a 5- or 7-day prescription duration is assumed). The FQ group consisted of fewer females than the BL group (54.0% FQ vs 55.8% BL, $p < 0.0001$), and the FQ cohort was statistically significantly older than the BL cohort (55.1 years FQ vs 40.0 years BL, $p < 0.0001$). There were 2685 (661 retinal tears/2024 RDs) retinal breaks between both cohorts that occurred after an eligible prescription (Table 3). Of these, zero occurred within 7 days of an FQ prescription and seven occurred within 7 days of a BL prescription. After 30 days, the FQ cohort had 1 RB, and the BL cohort had 28 RBs. At 90 days after the index date, the FQ cohort had 5 RBs, and the BL cohort had 87 RBs. At 365 days from the index date, the FQ cohort had 23 RBs and the BL cohort had 373 RBs (Table 4).

Table 2. Numbers of individual fluoroquinolone prescriptions

| Fluoroquinolone | Number of prescriptions | % of total |
|---|---|---|
| Ciprofloxacin | 256 055 | 88.18 |
| Ofloxacin | 13 488 | 4.64 |
| Norfloxacin | 12 532 | 4.32 |
| Levofloxacin | 5812 | 2.00 |
| All others | 2506 | 0.86 |
| Total | 290 393 | 100.00 |

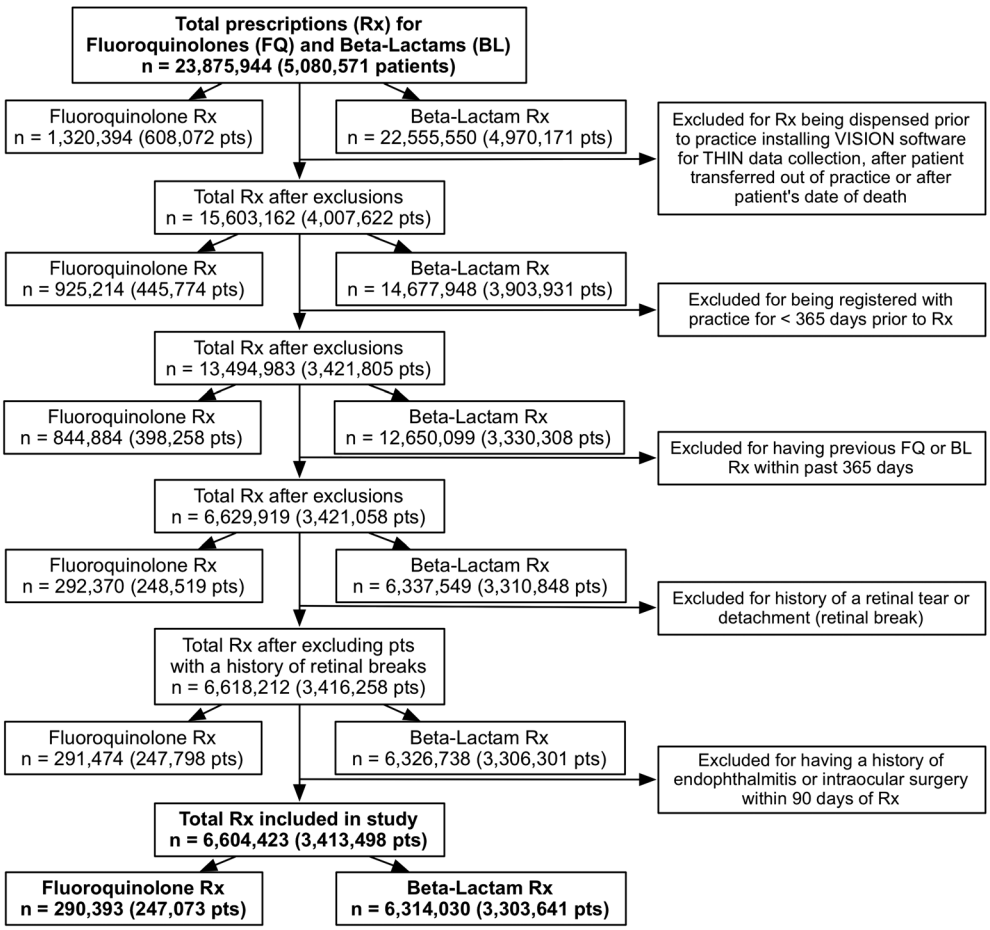


Figure 1. Flow chart depicting numbers of prescriptions and patients after specific exclusion criteria and for final analysis



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Table 3. Baseline characteristics of participants

| Characteristic | Fluoroquinolone recipient | Beta-lactam recipient |
|---|---|---|
| Number of patients | 247 073 | 3 303 641 |
| Number of prescriptions (Rx) | 290 393 | 6 314 030 |
| Age, mean years (range) | 55.1 (1–109) | 40.0 (1–111)* |
| Female gender, percentage | 54.0% | 55.8%* |
| Diabetic (% patients/% Rx) | 10.2/10.2 | 6.0*/6.5* |
| Average year of cohort entry | 2005 | 2005 |
| Total eligible retinal breaks (RT/RD**) | 183 (49/134) | 2502 (612/1890) |

*$p < 0.001$.
**RT = retinal tear and RD = retinal detachment.

Cox univariate analysis showed that gender was not significantly associated with retinal breaks during the 7-day (HR = 0.32, $p = 0.17$, 95%CI: 0.06, 1.63), 30-day (HR = 0.85, $p = 0.66$, 95%CI: 0.41, 1.76) or 90-day (HR = 0.76, $p = 0.19$, 95%CI: 0.50, 1.14) observation periods, but female gender was associated with a protective HR of 0.79 ($p = 0.02$, 95%CI: 0.65, 0.97) at the 365-day period. Older age was not associated with an RB during the 7-day period (HR = 1.01, $p = 0.71$, 95%CI: 0.98, 1.03), but there was an increased HR of 1.03 ($p < 0.001$, 95%CI: 1.02, 1.04), 1.03 ($p < 0.001$, 95%CI: 1.03, 1.04), and 1.04 ($p < 0.001$, 95%CI: 1.04, 1.05) for every 1-year increase in age within the 30-, 90-, and 365-day observation periods, respectively. Univariate analysis of calendar year of index date showed no association with RBs at the 7- or 30-day periods (HR = 1.13, $p = 0.30$, 95%CI: 0.90, 1.43 and HR = 1.10, $p = 0.06$, 95%CI: 0.99, 1.22, respectively), but more recent index year was associated with an 8% (HR = 1.08, $p < 0.01$, 95%CI: 1.02, 1.15) and a 10% (HR = 1.10, $p < 0.01$, 95%CI: 1.07, 1.13) increased hazard for RB in the 90- and 365-day observation windows, respectively. Having a diagnosis of diabetes significantly increased the univariate HR for a retinal break at each time period (7-day HR = 11.3, $p < 0.01$, 95%CI: 2.53, 50.53; 30-day HR = 5.77, $p < 0.001$, 95%CI: 2.56, 13.02; or 90-day HR = 6.68, $p < 0.001$, 95%CI: 4.28, 10.41; and 365-day HR = 6.36, $p < 0.001$, 95%CI: 5.12, 7.91). An HR (and subsequent $p$-value or confidence intervals) was unable to be calculated for the univariate analysis of the antibiotic cohorts at the 7-day observation period because of zero events occurring during that time in the FQ cohort. FQs did not have a significant association with an RB in the 30-, 90-, or 365-day observation periods (30-day HR = 0.78, $p = 0.80$, 95%CI: 0.11, 5.71; 90-day HR = 1.25, $p = 0.63$, 95%CI: 0.51, 3.08; and 365-day HR = 1.35, $p = 0.16$, 95%CI: 0.89 2.06).

Because of the low number of events within the first 7 days after antibiotic prescription, only age was included in the final-reported multiple regression analyses. There was no effect modification or confounding observed on the HR between antibiotics and RB for any observation period for diabetes, calendar year of index, or by either age or gender with inclusion of both variables (data not shown). An interaction term between age and antibiotics also was explored in the multivariable model but did not show relevant association or influence; hence, it was removed from the final models (data not shown). The 7-day period in the multivariable analysis had zero events in the FQ cohort, and therefore, an HR was unable to be calculated. In the 30-, 90-, and 365-day analyses, FQ prescriptions were not associated with increased hazard of RB repair (HRs of 0.56 ($p = 0.57$, 95%CI: 0.08, 4.14), 0.86 ($p = 0.75$, 95%CI: 0.35, 2.12), and 0.89 ($p = 0.60$, 95%CI: 0.58, 1.36), respectively; Table 5). Increasing age was associated with a significant increase in RB—HRs of 1.03 ($p < 0.001$, 95%CI: 1.02, 1.04), 1.03 ($p < 0.001$, 95%CI: 1.03, 1.04), and 1.04 ($p < 0.001$, 95%CI: 1.04, 1.05) per year—in the

Table 4. Retinal break (RB) procedures by antibiotic prescription class (Rx)

| | Fluoroquinolone recipient | | Beta-lactam recipient |
|---|---|---|---|
| Total person years studied (after Rx) | 266 360 | | 5 845 607 |
| RB incidence rate at 365 days† | 8.63 | | 6.38 |
| Number of RB procedures | | | |
| Within 7 days of Rx (RT/RD*) | 0 | | 7 (3 RTs/4 RDs) |
| Incidence rate ratio (FQ/beta) | | 0 (95%CI: 0, 15.20) | |
| Within 30 days of Rx | 1 (0 RT/1 RD) | | 28 (4 RTs/24 RDs) |
| Incidence rate ratio | | 0.78 (95%CI: 0.02, 4.74) | |
| Within 90 days of Rx | 5 (2 RTs/3 RDs) | | 87 (19 RTs/68 RDs) |
| Incidence rate ratio | | 1.26 (95%CI: 0.40, 3.06) | |
| Within 365 days of Rx | 23 (7 RTs/16 RDs) | | 373 (85 RTs/288 RDs)** |
| Incidence rate ratio | | 1.35 (95%CI: 0.85, 2.06) | |

†Per 100 000 person years.
*RT = retinal tear and RD = retinal detachment.
**Those with both a retinal tear and a retinal detachment were only included in the retinal detachment group.



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Table 5. Results of Cox proportional hazard analysis of fluoroquinolone versus β-lactam antibiotic prescription*†

| | Adjusted hazard ratio | *p*-value | 95%CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| 7 Days after prescription | ** | ** | ** | ** |
| 30 Days after prescription | 0.56 | 0.57 | 0.08 | 4.14 |
| 90 Days after prescription | 0.87 | 0.75 | 0.35 | 2.12 |
| 365 Days after prescription | 0.89 | 0.60 | 0.58 | 1.36 |

*Controlled for age.
†Other known associated systemic diseases, Marfan's and Stickler's syndrome, were assessed but found to occur in such small numbers as to be inconsequential to the results of the study and were not included in the final analysis.
**Not able to calculate because of zero events in fluoroquinolone group.

analyses through 30, 90, and 365 days, respectively. However, age was not significantly associated with RB during the 7-day period following antibiotic prescription (HR = 1.01, $p = 0.65$, 95%CI: 0.98, 1.03).

We performed a subset analysis on those aged 50–70 years old to assess whether an association with FQ therapy would be observed in a "high-risk" age cohort similar to that studied by Etminan and colleagues.[2] This subset included 1 510 257 total prescriptions (790 452 FQs and 1 412 977 BLs) from 831 978 patients (82 666 FQs and 97 280 BLs). In this subset, through the 7-, 30-, 90-, and 365-day observation periods, 3 (0 FQ and 3 BLs), 19 (1 FQ and 18 BLs), 48 (1 FQ and 47 BLs), and 204 (9 FQs and 195 BLs) retinal break events were observed, respectively. Again, none of the analyses suggested a higher risk in the FQ group (unable to calculate HR for 7-day, HRs of 0.80 ($p = 0.83$, 95%CI: 0.11, 5.99), 0.30 ($p = 0.23$, 95%CI: 0.04, 2.18), and 0.65 ($p = 0.20$, 95%CI: 0.33, 1.27), through 30, 90, and 365 days' follow-up, respectively). Another secondary analysis performed within the full cohort for associations between FQs and retinal tears or detachments individually was not significant in all four observation periods (HRs: 0.65–1.21, $p > 0.37$ for all analyses).

A sensitivity analysis examining only the retinal break repairs with an associated diagnosis code within 30 days of the procedure code had no events for either cohort in the first 7 days, 3 RBs (0 FQ and 3 BLs) within 30 and 90 days and 54 RBs (3 FQs and 51 BLs) within 365 days. Once again, because of no events occurring during the observation period, HRs were unable to be calculated for the 7-, 30-, and 90-day periods. The 365-day period had an HR of 0.88 ($p = 0.83$), agreeing with the main analysis in finding no increased hazard of retinal break events following exposure to FQs.

## DISCUSSION

In 2002, FQs became the most commonly prescribed antibiotic in the USA,[1] which has been attributed to their ability to treat community-acquired pneumonia and resistant infections. In our cohort study of patients from a UK database using BLs as a comparison group, we did not find an increased hazard of having a procedure to treat a retinal tear or detachment at any time point studied after patients were prescribed an oral FQ.

The root "rhegma" is Greek and means "rent or fissure."[22] By definition then, a rhegmatogenous RD occurs after a break in the retina. Based on this definition and because previous reports suggested that oral FQs may increase the risk of RDs through their effect on collagen turnover,[2,3] we included retinal tears in our study as part of the continuum of RDs. Of the treatments that occurred for retinal breaks in our study, zero occurred within 7 days of the 290 393 index prescriptions for an oral FQ, representing 5569 person years of FQ use. Although direct comparison is difficult because of differences in study design, if the increase in incidence of one additional RD per 2500 person years of use is taken as a benchmark, then there is only a 13% likelihood that our 0/5569 person-years estimate occurred by random chance.[2]

Confounding and the steps taken for its removal are of extreme importance for any observational study. One of the main differences between our study and previous published reports is our inclusion of all forms of intraocular surgery as a possible confounder in addition to cataract surgery. In addition, other studies did not account for the immediacy of the risk of RD after surgery, which is typically highest in the first 90 days.[2,3] We performed an additional analysis to determine the effect of removing our controls for intraocular surgery (IO), and although our results did not reach significance, the point estimates all moved toward finding an association (univariate estimates of 90 and 365 days without IO HR = 1.45 for both vs previous 90- and 365-day univariate estimates of 1.25 and 1.35, respectively; multivariate 90 and 365 days without IO HR = 0.99 and 0.96 vs previous 90and 365 days with IO-included HR of 0.87 and 0.89, respectively).

Additionally, a possible issue exists with the model used to create the propensity scores described by Kuo.[3] One of the components used to create this score was "underlying ophthalmic conditions" that is thought to be associated with RDs. Included under this heading were retinal vein occlusions, proliferative diabetic retinopathy, and vitreous hemorrhages, which are not commonly associated with RDs. Typically, propensity scores even out the variables used to create the score.



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However, their definition of "underlying ophthalmic conditions" was treated as a binary variable and was not separated by individual ophthalmic conditions. Therefore, there is a possibility for imbalance between conditions that are not known to be associated with RD and the established risk factors for RD.

Pasternak and colleagues[4] recently reported a study where they found no association similar to our study. Despite the comparable findings, our study also included retinal tears. Given the mechanism, if there was an association between detachments and FQs, the association should be seen in retinal tears as well. We wanted to be certain that we were only examining procedures to repair RB that is thought to happen by the proposed mechanism of action of FQs. Therefore, we were stricter in defining what constituted a rhegmatogenous RD when compared with that of Pasternak *et al*. who included exudative and tractional detachments, which arise from mechanisms other than vitreous dissolution and a break in the retina.[4]

As is typical for analyses relying on an existing database, there are several limitations of this study. First, prescriptions and the indication for which they were written are not linked within the THIN database, meaning we are unable to identify the specific diagnosis for which each antibiotic prescription was written. We attempted to control for this by comparing the risk for retinal breaks between antibiotic classes with similar indications for use. While we cannot refute with certainty the possibility that the diseases treated by the antibiotic prescription conferred different degrees of risk for retinal breaks, thus obscuring an association with FQs, it is unlikely that differences of this nature existed. Second, the THIN database does not capture inpatient antibiotic use or hospitalizations, which therefore cannot be studied. Third, THIN relies on the GP to report 100% of the codes and does neither occur directly from the specialist nor is required for payment. Either of these issues may have resulted in underreporting or erroneous recording of codes but would be unlikely to be differential between groups. While nondifferential misclassification tends to blunt associations, large negative effects still likely would have been identified; there was no suggestion of any tendency toward higher risk in the FQ group in this analysis. Despite the decrease in "verified" procedures seen in the sensitivity analysis, the 365-day observation period HR was nearly identical for both the full cohort and the "verified" cohort with both a procedure and diagnosis code, suggesting that the GP's diligence in coding was not related to whether a patient received an antibiotic prescription for one of the two classes of interest. Also, we are not able to state with certainty that RBs do not occur more often in patients who take oral FQs because our unit of observation was the RB repair, not the diagnosis. However, it is unlikely that many clinically significant RBs would go untreated given that the standard of care is to repair these lesions. Lastly, we cannot rule out the possibility of unmeasured confounding affecting our results because lattice degeneration and myopia—the two main ocular conditions associated with RB—are typically poorly coded for in administrative databases like THIN, but it is unlikely that systemic antibiotic prescription practices would be altered by these noninfectious ocular factors.

In summary, we did not find a higher risk of undergoing a procedure to treat a retinal tear or detachment in association with oral FQ therapy in a large population-based database. If FQs, in fact, increase the risk of retinal tears or detachments, it would be unlikely that our results would have been observed, raising doubts as to whether such an association exists. Thus, our findings fail to replicate the positive associated observations, reducing the level of confidence that oral FQ use is associated with a higher risk of RD.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

**KEY POINT**

- Our results do not support an association between oral fluoroquinolone use and subsequent procedures to treat a retinal detachment or tear.

## ETHICS STATEMENT

This study was approved by the Scientific Review Committee for the THIN database and was deemed exempt from review by The University of Pennsylvania Institutional Review Board because of the de-identified nature of the data.

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