

1 **The association between oral fluoroquinolone use and the development of**
2 **retinal detachment: a systematic review and meta-analysis of observational**
3 **studies**

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13 **Running title:** Meta-analysis on fluoroquinolones and retinal detachment

14 **Keywords:** Fluoroquinolones, Retinal detachment, adverse drug reaction,
15 pharmacoepidemiology, meta-analysis

16

17 **Abstract**

18 **Background:** Several observational studies were published investigating the association
19 between oral fluoroquinolone use and the development of retinal detachment; however, the
20 findings are not concordant. This study is a meta-analysis of the existing literature and estimates
21 the overall absolute risk of such an event.

22 **Methods:** Electronic databases were searched for observational studies on the association
23 between oral fluoroquinolone and retinal detachment up to August 2014. Studies that did not
24 meet the criteria for meta-analysis were narratively reviewed. Cases of retinal detachment during
25 current fluoroquinolone use were also extracted for absolute risk calculation.

26 **Results:** Seven observational studies were included. Three (case-control and self-controlled case
27 series studies) were eligible for meta-analysis and four (cohort studies) were narratively
28 reviewed. The rate ratio of the case-control studies was 1.82 (95% CI 0.67-4.93), $I^2=96%$ and the
29 incidence rate ratio of the self-controlled case series was 1.03 (95% CI 0.84-1.27), $I^2=36%$.
30 Three of the four cohort studies found no significant association between oral fluoroquinolone
31 use and the development of retinal detachment. The pooled absolute risk of retinal detachment
32 whilst on current oral fluoroquinolone treatment is estimated to be 4.85 per 1,000,000
33 prescriptions (95% CI 0.78 – 8.91).

34 **Conclusion:** The findings of this systematic review and meta-analysis do not support an
35 association between oral fluoroquinolone use and the development of retinal detachment. Given
36 the low absolute risk, such an event would be rare if there were an association. The current
37 prescribing practice for fluoroquinolones should not be altered because of a previously suggested
38 potential risk of retinal detachment.

39 **Introduction**

40 Etminan *et al.*¹ reported a significant association between the current use of oral
41 fluoroquinolones (FQ) and the development of retinal detachment (RD) (i.e. an RD event
42 occurring within the prescription period of FQ). This study caused the US, Canadian and
43 European regulatory authorities to place FQ on their alert list²⁻⁴ and since then more
44 observational studies have been published. This systematic review and meta-analysis evaluates
45 these observational studies and the potential for increased risk of RD with oral FQ use.

46 **Method**

47 A systematic literature search was conducted using keywords, MeSH and Emtree terms.
48 Records were retrieved from databases including Pubmed, CINAHL and EMBASE in August
49 2014. The search terms included were fluoroquinolones AND (retinal detachment OR retinal*).
50 This study was conducted in accordance with the Preferred Reporting Items for Systematic
51 reviews and Meta-Analyses (PRISMA)⁵ and the Meta-analysis of Observational Studies in
52 Epidemiology⁶ to ensure clear and comprehensive reporting.

53 **Inclusion and exclusion criteria**

54 Observational studies that investigated the association between FQ use and the
55 development of RD were included. Animal studies were excluded.

56 **Quality assessment**

57 The included studies were assessed for methodological quality using the Newcastle-
58 Ottawa Scale (NOS) as recommended by the Cochrane Collaboration.⁷ CSLC and LYLW

59 independently reviewed and scored each of the studies. Study quality is indicated by the number
60 of stars with a maximum allocation of 9 stars.

61 **Data extraction**

62 Data on the outcome of interest, which is the risk or odds of developing RD whilst on FQ
63 treatment, were extracted for analysis. Statistics presenting the period up to 10 days from the first
64 day of prescription were selected. Studies where such statistics could not be extracted or
65 included in the meta-analysis were summarised in the narrative review.

66 **Statistical analysis**

67 A random-effects model⁸ was used in the meta-analysis to account for heterogeneity
68 between studies. Statistical analyses were conducted using Review Manager 5.2 (Cochrane
69 Collaboration, 2012).

70 The number of RD cases that occurred whilst on FQ treatment was extracted from the
71 original list of articles and the absolute risk was estimated using a method previously described.⁹
72 The 95% CI was calculated using the Wilson score interval.¹⁰ The analysis was performed using
73 SAS 9.3 (SAS Inc, USA).

74 **Results**

75 A total of 695 citations were retrieved from the literature search. CSLC and LYLW
76 screened and reviewed relevant articles independently. Seven observational studies were relevant
77 (Figure 1). The quality of the methodology was assessed and the results are presented in Table 1
78 and 2.

79 *Case-control*

80 Two case-control studies were included in the meta-analysis. Etminan *et al.*¹ reported a
81 positive association between FQ use and the development of RD in a cohort, nested among
82 patients who had visited an ophthalmologist, using The British Columbia Linked Health
83 Database.¹¹ Cases were defined as those with an RD-related procedure 14 days after the
84 diagnosis date. Cases in FQ users and non-FQ users were compared and the rate ratio (RR) was
85 adjusted for sex, previous history of cataract surgery, myopia, diabetes, number of visits to
86 ophthalmologist, and number of prescription drugs used. In an attempt to replicate the study of
87 Etminan *et al.*, Fife *et al.*¹² conducted a similar analysis in the US using the MarketScan
88 Commercial Claims and Encounters and the Optum ClinFormatics database. The results are
89 presented as Fife 2014 (CCAEC-CC) and Fife 2014 (Optum-CC) respectively in the meta-analysis.
90 Meta-analysis of the three databases did not show a significant association with an odds ratio
91 (OR) of 1.82(95% CI 0.67-4.93), $I^2=96\%$ (Figure 2). There was no significant change to the RR
92 [1.25(95%CI 0.95-1.65)], I^2 of 0%, following removal of Etminan *et al.* study from the
93 sensitivity analysis.

94 *Self-controlled case series*

95 Two studies using four different databases were included in this meta-analysis. Neither
96 study found a significant association between oral FQ use and the development of RD. Of these,
97 one study⁹ was done using the Hong Kong Clinical Data Analysis and Reporting System
98 (CDARS) and Taiwan National Health Insurance Research Database (NHIRD). The incident RR
99 (IRR) was adjusted for age, history of diabetes and cataract surgery. The meta-analysis results of
100 Hong Kong and Taiwan database are presented as Chui 2014 (HK) and Chui 2014 (TW),

101 respectively. Fife *et al.*¹² also conducted a self-controlled case series study in the US. Unlike the
102 case-control analysis, ophthalmology visits were not an inclusion criterion. Cases were defined
103 as those with RD 30 days after the beginning of FQ exposure. The RRs are presented as Fife
104 2014 (CCAE-SCCS) and Fife 2014 (Optum-SCCS). Meta-analysis of the four databases gave a
105 statistically non-significant IRR of 1.03(95% CI 0.84-1.27), $I^2=36\%$ (Figure 3).

106 *Narrative review*

107 Four cohort studies¹³⁻¹⁶ were also included in this review. However, their study designs
108 were very different and therefore, are not appropriate for meta-analysis.

109 Pasternak *et al.*¹³ used the Central Person Register to identify adults living in Denmark
110 from 1997 to 2011. RD cases were defined as incident diagnosis of RD with a related procedure
111 performed within 14 days of the diagnosis date. They reported 5 cases of RD among current FQ
112 users (1-10 days post first day of treatment) with a corresponding RR of 1.29(95% CI 0.53-3.13)
113 compared to non-FQ use. RR for recent use (11-30 days) was 0.97(95% CI 0.46-2.05), past use
114 (31-60 days) was 1.37(95% CI 0.80-2.35) and distant use (61-180 days) was 1.27(95% CI 0.93-
115 1.75). The crude incidence rate was 25.3 cases per 100,000 person-years in current users. The
116 authors concluded that oral FQ use was not associated with an increased risk of RD.

117 Kuo *et al.*¹⁴ identified FQ and amoxicillin users from the NHIRD between 1998 and 2010.
118 They compared FQ users with amoxicillin users and estimated an adjusted hazard ratio (HR) of
119 2.07(95% CI 1.45-2.96) in a 90 day follow-up period. The adjusted HR was 10.68(95% CI 3.28-
120 34.82) for ciprofloxacin, 2.41(95% CI 0.76-7.68) for levofloxacin, 2.00(95% CI 1.06-3.79) for
121 norfloxacin, 1.17(95% CI 0.59-2.31) for ofloxacin and 1.48(95% CI 0.25-8.84) for lomefloxacin.
122 The median interval between the beginning of the FQ prescription and the index date of RD

123 diagnosis was 35.5 days. RD cases were defined as diagnosis with RD within 90 days of the
124 follow-up period. The authors concluded that oral FQ was associated with subsequent occurrence
125 of RD. The FQ risk was independent of age, sex, diabetes, indications for antimicrobials, and
126 underlying ophthalmic conditions.

127 Kapoor *et al.*¹⁵ examined whether there was an associated increase in subsequent RD and
128 symptomatic retinal breaks and oral FQ. They included adult residents of Olmsted County,
129 Minnesota, who were prescribed oral FQ from 2003 to 2011, from the Rochester Epidemiology
130 Project. Patients prescribed oral FQ were compared to those prescribed oral macrolide and β -
131 lactam antibiotics. Cases were defined as procedures recorded within 1 year of the first
132 prescription. RD repair procedures were performed within 365 days of the first prescription in
133 0.03% (95% CI 0.01-0.06) of the FQ group, 0.02% (95% CI 0.01-0.03) of the macrolide group,
134 and 0.03% (95% CI, 0.02-0.05) of the β -lactam group ($P>0.05$). There were no significant
135 differences in treatment rates within 7, 30, and 90 days of the first prescription between the
136 groups. Kapoor *et al.*¹⁵ concluded that oral FQ use was not associated with an increased risk of
137 RD or symptomatic retinal breaks in their study.

138 Eftekhari *et al.*¹⁶ investigated whether oral FQ use would increase the risk of RD and
139 retinal tear in the UK using The Health Improvement Network database (THIN). Patients
140 prescribed FQ between 1994 and 2012 were compared with those prescribed β -lactam. Cases
141 were defined as those with a procedure related to retinal break during the observation period. No
142 case was observed 7 days after the prescription among FQ users; therefore it was not possible to
143 estimate the HR. The adjusted HR was 0.78 (95% CI 0.02-4.74) 30 days after prescription, 1.26
144 (95% CI 0.40-3.06) at 90 days, and 1.35 (95% CI 0.85-2.06) at 365 days. A sensitivity analysis
145 included only cases with a retinal break diagnosis within 30 days of the procedure with no

146 findings of increased risk. Eftekhari *et al.*¹⁶ concluded that no increased risk of retinal break was
147 observed using the THIN database.

148 *Absolute risk of RD whilst on current FQ treatment*

149 The absolute risks of developing RD whilst on current FQ treatment among the included
150 studies are presented in Table 2. No RD cases in current FQ users were reported in Kapoor *et*
151 *al.*¹⁵ and Eftekhari *et al.*¹⁶ The total number of FQ prescriptions was not reported by Etminan *et*
152 *al.*¹ and Fife *et al.*;¹² therefore the absolute risk cannot be estimated. The pooled absolute risk of
153 the five database analyses is estimated to be 4.85 per 1,000,000 prescriptions (95% CI 0.78–8.91)
154 (Figure 4).

155 **Discussion**

156 The results of this meta-analysis do not support an association between oral FQ use and
157 the development of RD. Three of the four cohort studies^{13, 15, 16} in the narrative review do not
158 support an association either. Although two studies^{1, 14} reported significant results, they do not
159 concur. Etminan *et al.*¹ reported that the effect of FQ on RD is of an acute nature, i.e. current FQ
160 users. However, Kuo *et al.*¹⁴ report that the median interval between the prescription and the
161 index date of RD diagnosis was 35.5 days, i.e. not acute.

162 Farioli and Kriebel¹⁷ estimated the incidence rate of RD in the study of Kuo *et al.*¹⁴ to be
163 218.5 per 100,000 patient-years with a mean age of 47 years. The incidence of RD is age-
164 dependent with <19–27 cases per 100,000 person-years in the sixth decade of life¹⁸. They
165 questioned the validity of the findings of Kuo *et al.* since the study's incidence rate was much
166 higher with a lower mean age. This discrepancy may be explained by significant differences in

167 the RD case definition in the study of Kuo *et al.*,¹⁴ where procedure codes were not required to
168 confirm RD cases.

169 It is worth noting that the RR reported by Etminan *et al.*¹ was much higher than that
170 reported by other included studies. Fife *et al.*¹² replicated the analysis using two datasets from
171 two databases and estimated an OR of almost 1. Since both studies had similar settings, it is
172 unclear why this discrepancy occurred. However, differences in clinical practice and the coding
173 system may account for this. Fife *et al.*¹² validated their results with additional analyses; however,
174 they did not find a significant association, which concurs with the findings of this meta-analysis.

175 The meta-analysis for self-controlled case series gave an RR of almost 1 [1.03(95% CI
176 0.84-1.27)] with moderate variability among the studies from different countries ($I^2=36\%$). With
177 such a narrow confidence interval around 1, the results clearly reject an association between the
178 use of FQ and RD. Finally, it is important to note that the pooled absolute risk of developing RD
179 whilst on FQ treatment was minimal (Figure 4). Such an event would be very rare if there were
180 an association.

181 *Strength and limitation*

182 Disease codes such as ICD-9 were used to identify cases among the included studies.
183 Although the case definitions varied, all (except Kuo *et al.*¹⁴) included a procedure code to
184 confirm the RD case. The codes of the included databases have been validated in other
185 settings,¹⁹⁻²¹ thus ensuring the quality of the analysed data. In addition, the study designs of all
186 the included studies are of satisfactory quality, obtaining more than 6 of 9 stars from the NOS
187 quality assessment.

188 The results of this meta-analysis are compiled from available observational studies and
189 attempts to draw a conclusion on the potential for increased risk of RD with oral FQ use.
190 Variability may have an effect on heterogeneity, which is demonstrated in the meta-analysis of
191 the case-control studies. However, the result remains non-significant in the sensitivity analysis
192 with reduced heterogeneity. Furthermore, the heterogeneity of the self-controlled case series
193 studies analyses was not significant and supports the validity of the conclusion.

194 **Conclusion**

195 The results of the meta-analysis do not support an association between oral FQ use and
196 the development RD. However, if there were an association, such events would be rare given the
197 small absolute risk estimated in the available literature. Based on the evidence from this meta-
198 analysis, the use of oral FQ should not be precluded.

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206 included studies.

207 **Author contributions:** CSLC, EWC, LYLW and ICKW had the original idea for this study and
208 contributed to the development of the idea and the study design. CSLC and LYLW

209 independently conducted a systematic review and reviewed the literature for relevance. CSLC,
210 EWC and ICKW undertook the primary analysis. CSLC, EWC and ICKW contributed to the
211 interpretation of the analysis. CSLC, EWC and LYLW wrote the first draft of the paper. EWC,
212 LYLW and ICKW critically reviewed the paper. EWC and ICKW provided oversight of all
213 aspects of this project. CSLC and ICKW are the guarantors. All authors had full access to all the
214 data in the study and take responsibility for the integrity of the data and the accuracy of data
215 analysis.

References

1. Etminan M, Forooghian F, Brophy JM *et al.* Oral fluoroquinolones and the risk of retinal detachment. *JAMA : the journal of the American Medical Association* 2012; **307**(13):1414-1419.
2. U.S. Food and Drug Administration. Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between April - June 2012
[\[http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adverse_drug_effects/ucm324020.htm\]](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adverse_drug_effects/ucm324020.htm) (5 May 2014, date last accessed).
3. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the Meeting - 29-31 October 2012
[\[http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/12/WC500135712.pdf\]](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/12/WC500135712.pdf) (5 May 2014, date last accessed).
4. Health Canada. Canadian Adverse Reaction Newsletter, Volume 23 - Issue 3 - July 2013
[\[http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v23n3-eng.php#article1\]](http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v23n3-eng.php#article1) (5 May 2014, date last accessed).
5. Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj* 2009; **339**:b2535.
6. Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**(15):2008-2012.
7. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [www.cochrane-handbook.org] (date last accessed).
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986; **7**(3):177-188.
9. Chan EW, Liu KQ, Chui CS *et al.* Adverse Drug Reactions - Examples of detection of rare events using databases. *British journal of clinical pharmacology* 2014.
10. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927; **22**(158):209-212.
11. Population Data BC. [<https://www.popdata.bc.ca/home>] (24 April 2014, date last accessed).
12. Fife D, Zhu V, Voss E *et al.* Exposure to oral fluoroquinolones and the risk of retinal detachment: retrospective analyses of two large healthcare databases. *Drug safety : an international journal of medical toxicology and drug experience* 2014; **37**(3):171-182.
13. Pasternak B, Svanstrom H, Melbye M *et al.* Association between oral fluoroquinolone use and retinal detachment. *JAMA : the journal of the American Medical Association* 2013; **310**(20):2184-2190.
14. Kuo SC, Chen YT, Lee YT *et al.* Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **58**(2):197-203.
15. Kapoor KG, Hodge DO, St Sauver JL *et al.* Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study. *Ophthalmology* 2014; **121**(6):1269-1273.

16. Eftekhari K, Ghodasra DH, Haynes K *et al.* Risk of retinal tear or detachment with oral fluoroquinolone use: a cohort study. *Pharmacoepidemiology and drug safety* 2014; **23**(7):745-752.
17. Farioli A, Kriebel D. Incidence rates of retinal detachment in 2 cohorts of patients treated with oral fluoroquinolones or amoxicillin. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **58**(10):1489-1490.
18. Mitry D, Charteris DG, Fleck BW *et al.* The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. *Br J Ophthalmol* 2010; **94**(6):678-684.
19. Hsieh CY, Chen CH, Li CY *et al.* Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2013.
20. Denburg MR, Haynes K, Shults J *et al.* Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 2011; **20**(11):1138-1149.
21. Holland-Bill L, Christiansen CF, Ulrichsen SP *et al.* Validity of the International Classification of Diseases, 10th revision discharge diagnosis codes for hyponatraemia in the Danish National Registry of Patients. *BMJ open* 2014; **4**(4):e004956.

Table 1. Study characteristics and quality

Study	Data Source	Study period	Region	Study design	Inclusion criteria	Exclusion criteria	Outcome definition	Newcastle-Ottawa Scale ^{a,b}		
								Selection	Comparability	Exposure/ Outcome
Etminan 2012 ¹	British Columbia Linked Health Database	01/2000-12/2007	Canada	CC	Had an ophthalmologist visit	History of RD diagnosis or procedures; endophthalmitis; intravitreal injection or vitreous biopsy	RD procedure (British Columbia procedure codes) received within 14 days after RD diagnosis (ICD-9)	*	**	***
Kuo 2013 ¹⁴	NHIRD	1998-2010	Taiwan	C	Aged >18 years; prescribed >3 consecutive doses of oral FQ/amoxicillin	Treated with FQ or amoxicillin during the prior 90 days; hospitalised 90 days prior to enrollment; history of RD diagnosis or procedure; blindness; procedure for enucleation or evisceration of eyes	RD diagnosis (ICD-9) within 90 days of follow-up	***	**	***
Pasternak 2013 ¹³	Central Person Register, The National Prescription Registry, The Danish National Patient Registry	1/1/1997-31/12/2011	Denmark	C	Aged ≥18 years; prescribed FQ; no history of RD or retinal break; did not use FQ in the last 180 days; had lived in Denmark for minimum of 2 years; had filled at least 1 prescription for	History of endophthalmitis, intravitreal injection, or choroidal; retinal or vitreal biopsy; cataract surgery; major eye surgery or eye trauma 30 days before RD	RD procedure received within 14 days after RD diagnosis	****	**	***

					any medication in the last year; no history of hospitalisation in the last 30 days					
Chui 2014 ⁹	CDARS, NHIRD	HK: 1/1/2001- 31/12/2012 Taiwan: 1/1/2000- 31/12/2010	HK, Taiwan	SCCS	Prescribed FQ	Head or eye injury 30 days before RD; history of endophthalmitis, RD diagnosis or procedure.	RD procedure during FQ prescription (ICD- 9)	***	**	***
Eftekhari 2014 ¹⁶	THIN	06/1994- 01/2012	UK	C	Had prescription for FQ or β - lactam; registered with GP for at least 365 consecutive days prior prescription date	History of RD or retinal tear; FQ and β -lactam prescribed on the same day; history of intraocular surgery or diagnosis of endophthalmitis within 90 days of prescription.	RD or retinal tear procedure (Medcodes) within 7, 30, 90 and 365 days after the FQ prescription	****	*	***
Fife 2014 ^{12c}	CCAЕ, Optum	CCAЕ: 1/1/2000- 31/1/2012 Optum: 1/9/2005- 31/3/2012	USA	CC	Had an ophthalmologist visit and at least 1 year in the cohort	History of RD diagnosis or procedure; endophthalmitis or related procedures such as vitreous biopsy or intravitreal injection; RD event happened during hospitalisation or within 10 days after being discharged	RD procedure received within 14 days after RD diagnosis	*	**	***

				SCCS	Ophthalmologist visit not required	Exclusion criteria in CC; history of inflammatory, infectious, or traumatic retinitis; index date of RD event happened during current or recent use of multiple antibiotic prescription (FQ and/or β -lactam); hospitalisation between cohort entry and event date	Restricted to codes associated with rheumatogenous retinal detachment and within 30 days after the beginning of FQ prescription	***	**	***
Kapoor 2014 ¹⁵	REP	1/1/2003-30/6/2011	USA	C	Prescribed FQ, macrolides or β -lactam	History of endophthalmitis, necrotising retinitis, ipsilateral intraocular surgery; severe ocular/head trauma within 90 days of RD; treated with serous/ exudative retinal detachment or diabetic retinopathy-related tractional RD.	RD procedure (Current Procedure Terminology) within 7, 30, 90 and 365 days after the FQ prescription	****	*	***

Abbreviations: CC=Case-control study; RD=retinal detachment; ICD-9= International Classification of Diseases, Ninth Revision; NHIRD=National Health Insurance Research Database; C=Cohort study; FQ=fluoroquinolones; CDARS=Clinical Data Analysis and Reporting System; HK=Hong Kong; SCCS=Self-controlled case series; THIN=The Health Improvement Network; UK=United Kingdom;

CCAЕ=MarketScan Commercial Claims and Encounter database; Optum=Optum ClinFormatics database; USA=United States of America; REP=Rochester Epidemiology Project.

^a Quality assessment of the methodology of the included studies. The assessment guideline for case-control studies was used for self-controlled case series studies.

^b Study quality was indicated by a higher number of stars. Each study could be allocated a maximum of 9 stars.

^c Replication case-control and self-controlled case series analyses.

Table 2. Summary of the results of included studies and estimated absolute risk

Study	Sample size	Closest “Current use” definition	Number of cases in “current FQ use”	Result of current FQ use	Absolute risk of RD whilst on FQ treatment (up to 10 days from the first day of prescription) ^a
Etminan 2012 ¹	RD case: 4,384 Control: 43,840	Within prescription period	145	Rate Ratio: 4.50(95% CI 3.56-5.70)	Data not available
Kuo 2013 ¹⁴	FQ prescriptions: 178,179 AMX prescriptions: 178,179	Patients were followed up for 90 days after they entered the cohort	96	Hazard Ratio: 2.07(95% CI 1.45-2.96)	Data not available
Pasternak 2013 ¹³	FQ episodes: 748,792 Control episodes: 5,520,446	1-10 days starting from the first day of prescription	5	Rate Ratio: 1.29(95% CI 0.53-3.13)	5 cases out of 748,792 prescriptions =6.7 per 1,000,000 prescriptions
Chui 2014 ⁹	FQ prescriptions ^b : HK: 260,198 TW: 1,098,086	Within prescription period	HK: 2 ^b TW: 7 ^b	Incidence rate ratio: HK: 0.82(95% CI 0.20-3.36) TW: 1.45(95% CI 0.68-3.10)	HK: 2 cases out of 260,198 prescriptions =7.7 per 1,000,000 prescriptions TW: 7 cases out of 1,098,086 prescriptions =6.4 per 1,000,000 prescriptions
Eftekhari 2014 ¹⁶	FQ prescriptions: 290,393 β-lactam prescriptions: 6,314,030	1-7 days after the prescription	0	Data not available	0 case out of 290,393 prescriptions
Fife 2014 ^{12c}	Case control: CCAE: RD case: 7,844 Control: 77,654 Optum: RD case: 3,059 Control: 30,230 Self-controlled case series (case only): CCAE: 19,101 Optum: 6,896	Case control: Within prescription period Self-controlled case series: 30 days after start of FQ prescription	Case control: CCAE: 66 Optum: 13 Self-controlled case series: CCAE: 74 Optum: 18	Odds ratio (Case control): CCAE: 1.33(95% CI 0.99-1.80) Optum: 0.93(95% CI 0.48-1.81) Rate Ratio (Self-controlled case series): CCAE: 1.13(95% CI 0.99-1.29) Optum: 0.85(95% CI 0.66-1.09)	Data not available

Kapoor 2014 ¹⁵	FQ prescriptions: 92,130 Macrolide prescriptions: 107,086 β-lactam prescriptions: 178,352	Within 7 days after the prescription	0	0%(95% CI 0-0.01)	0 case out of 92,130 prescriptions
Overall absolute risk					4.85 case out of 1,000,000 prescriptions (95% CI 0.78-8.91)

Abbreviations: FQ=fluoroquinolones; RD=retinal detachment; AMX=Amoxicillin; HK=Hong Kong; TW=Taiwan; CCAE=MarketScan Commercial Claims and Encounters database; Optum=OptumClinFormatics database.

^a Absolute risk of RD whilst on FQ treatment = number of RD cases whilst on FQ treatment divided by total number of FQ prescriptions included in the study

^b Unpublished data, requested from authors

^c Replication case-control analysis

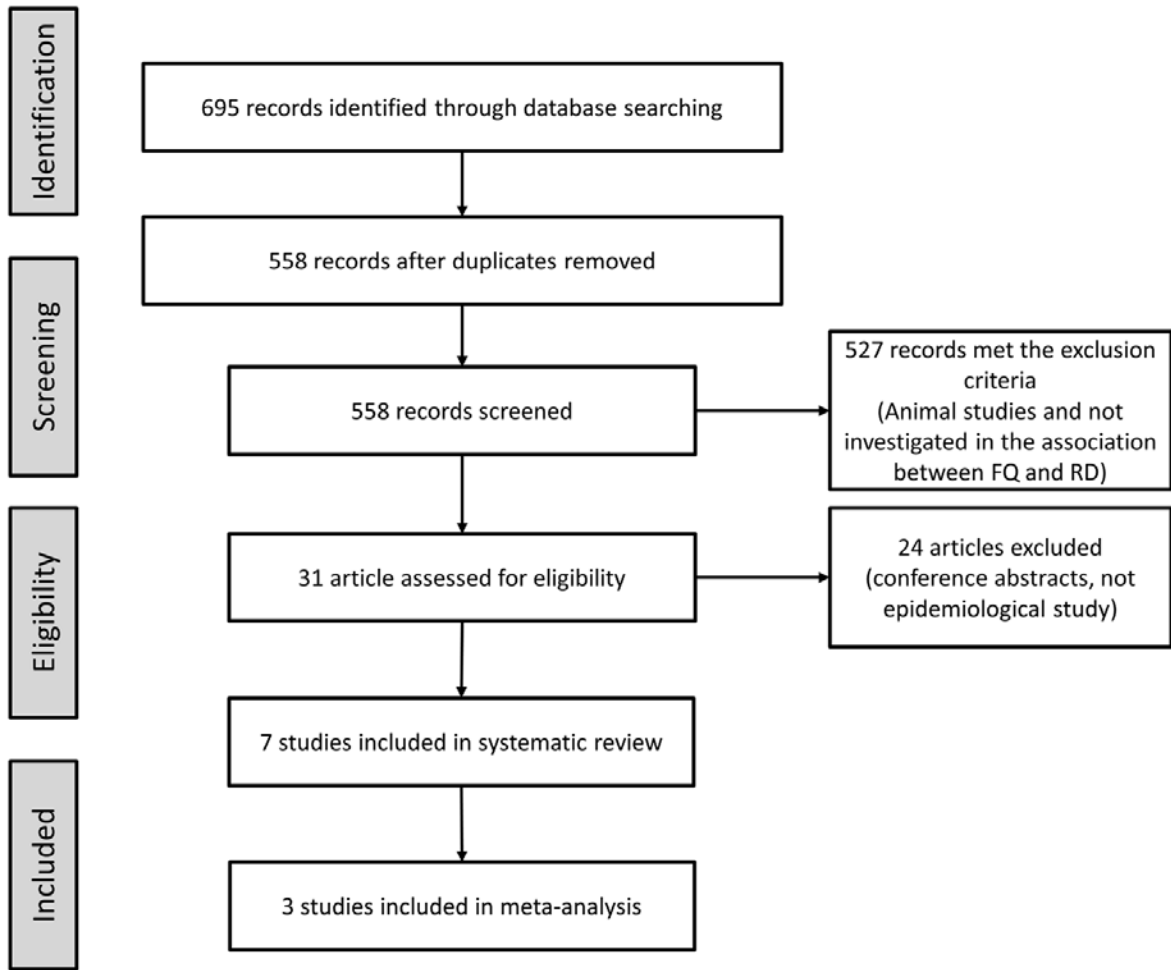
Figure legend:

Figure 1. PRISMA flowchart

Figure 2. Meta-analysis of case-control studies

Figure 3. Meta-analysis of self-controlled case series studies

Figure 4. Meta-analysis of absolute risk of retinal detachment whilst on oral fluoroquinolone treatment



Abbreviations: FQ=oral fluoroquinolones; RD=retinal detachment.

Figure 1. PRISMA flowchart

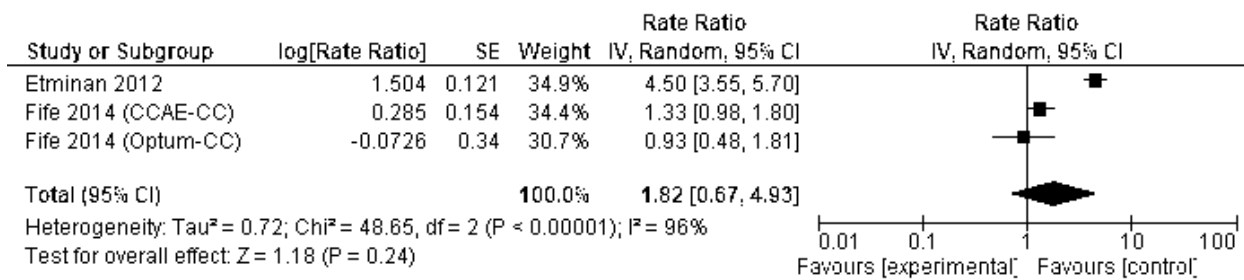


Figure 2. Meta-analysis of case-control studies

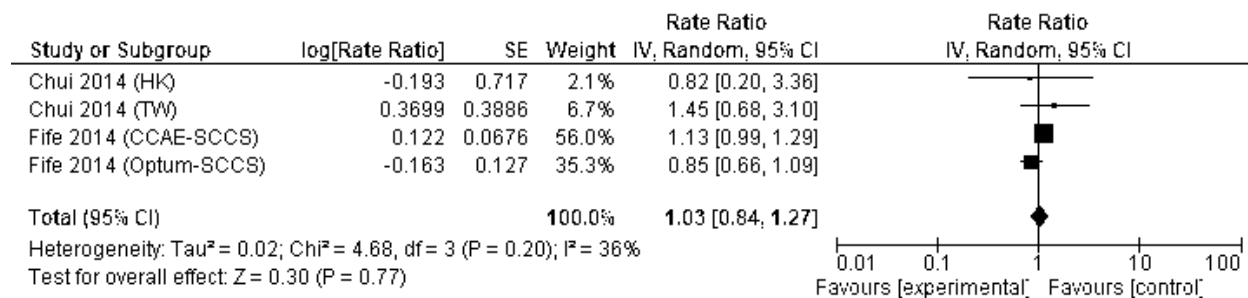


Figure 3. Meta-analysis of self-controlled case series studies

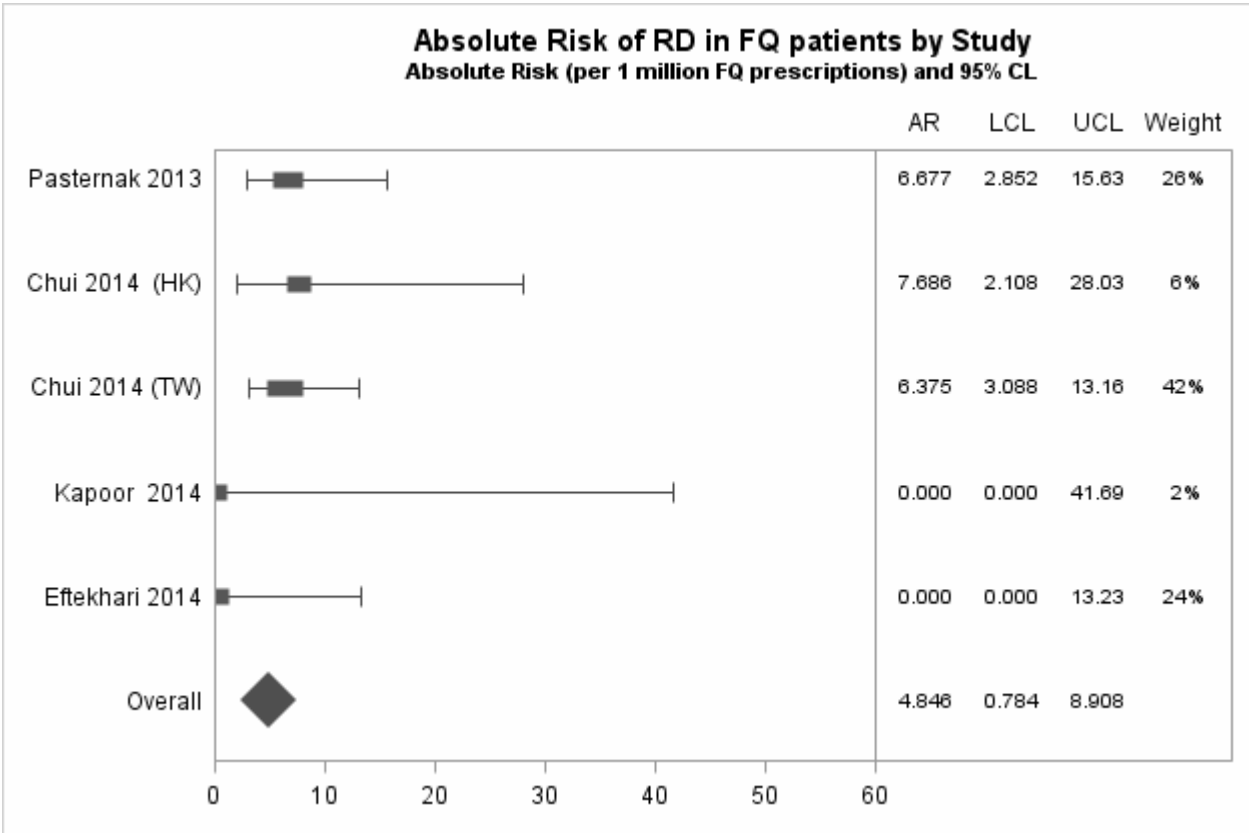


Figure 4. Meta-analysis of absolute risk of retinal detachment whilst on oral fluoroquinolone treatment

Abbreviations: RD=retinal detachment; FQ=oral fluoroquinolones; CL=confidence Limit; AR=absolute risk; LCL=Lower 95% Confident Limit; UCL=Upper 95% Confident Limit; HK=Hong Kong; TW=Taiwan.