1. Akuffo KO, Nolan JM, Stack J, et al. The impact of cataract, and its surgical removal, on measures of macular pigment using the Heidelberg Spectralis HRA+OCT multicolor device. *Invest Ophthalmol Vis Sci*. 2016;57(6):2552-2563.

2. Mayne ST, Cartmel B, Scarmo S, et al. Noninvasive assessment of dermal carotenoids as a biomarker of fruit and vegetable intake. *Am J Clin Nutr*. 2010;92(4):794-800.

3. Chew EY, Clemons TE, Sangiovanni JP, et al; Age-Related Eye Disease Study 2 (AREDS2) Research Group. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol*. 2014;132(2):142-149.

4. Bernstein PS, Li B, Vachali PP, et al. Lutein, zeaxanthin, and *meso*-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog Retin Eye Res*. 2016;50:34-66.

5. Espaillat A, Aiello LP, Arrigg PG, Villalobos R, Silver PM, Cavicchi RW. Canthaxanthine retinopathy. *Arch Ophthalmol*. 1999;117(3):412-413.

6. Sarraf D, Ceron O, Rasheed K, Drenser KA, Casey R. West African crystalline maculopathy. *Arch Ophthalmol*. 2003;121(3):338-342.

COMMENT & RESPONSE

Oral Fluoroquinolone Use and Retinal Detachment

To the Editor We read with interest the recent article by Raguideau et al[1] on the association between the use of fluoroquinolone antibiotics and retinal detachment. The authors chose to use 2 self-controlled study designs to address this question: first, the case crossover method,[2] and, second, the self-controlled case series.[3] The 2 methods appear to give similar answers, suggesting a roughly 50% increased risk of retinal detachment following exposure to a fluoroquinolone. However, we have some concerns about the method underpinning the study.

First, in the case-crossover study, Raguideau et al[1] excluded people who had been exposed to any fluoroquinolone during the intermediate-risk period, and they also excluded all people exposed twice to a fluoroquinolone within any 50-day period during the control period. We believe this may have introduced an important bias, whereby people exposed during the control period were disproportionately excluded. As a consequence, patients would appear to be more likely exposed during the risk period close to the date of retinal detachment, potentially creating a spurious association. This approach is analogous to conducting a case-control study and selecting patients based on prior knowledge of the exposure of interest, which can cause serious bias. We note that 331 of the 994 fluoroquinolone-exposed cases were excluded from the main analysis for this reason, a substantial proportion of the informative cases in this study. It would be helpful to see the results of an analysis with no exclusions.

Second, a recent cohort study[4] with the same question used a "control" exposure to demonstrate that an effect size of similar magnitude may be driven by bias and confounding; the authors found that fluoroquinolone and amoxicillin had similar associations with the risk of retinal detachment. Although self-controlled designs are less susceptible to individual-level time-invariant confounding than traditional cohort studies, other biases (in particular, indication bias) are not avoided, and a similar control exposure, not hypothesized to be associated with retinal detachment, would have been helpful in the study by Raguideau et al[1] to help exclude such biases.

Finally, the detailed methods used for the self-controlled case series are not presented in the study or the online supplementary material. Correctly implementing this design requires a careful choice of observation and risk periods.[5] Is it possible for the authors to provide further details on how the self-controlled case-series analysis was performed? This additional information would be helpful in the interpretation of the conclusions.

Ian J. Douglas, PhD
Adrian Root, MBBS
Bhaskaran Krishnan, PhD

Author Affiliations: Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, England.

Corresponding Author: Ian J. Douglas, PhD, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England (ian.douglas@lshtm.ac.uk).

Published Online: October 20, 2016. doi:10.1001/jamaophthalmol.2016.3477

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Krishnan reports receiving grants from Wellcome Trust, the Royal Society, the National Institute for Health Research, the Medical Research Council, the Michael J Fox Foundation, the British Heart Foundation, and the Royal National Institute for the Blind. No other disclosures are reported.

1. Raguideau F, Lemaitre M, Dray-Spira R, Zureik M. Association between oral fluoroquinolone use and retinal detachment. *JAMA Ophthalmol*. 2016;134(4):415-421.

2. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133(2):144-153.

3. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768-1797.

4. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5(11):e010077.

5. Douglas IJ, Langham J, Bhaskaran K, Brauer R, Smeeth L. Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink. *BMJ*. 2013;346:f1936.

In Reply Our main analysis focused on the immediate acute effects of fluoroquinolones. Therefore, as is usually done, we excluded patients exposed during the intermediate risk period. Because the intermediate risk period is not associated with an increased risk, this exclusion is unlikely to have affected the odds ratio. Individuals with a fluoroquinolone prescription during the 10 days preceding retinal detachment (RD) and exposed during the intermediate risk period (ie, during the 50 prior days) were not considered exposed during the risk period. Consistently, individuals with 2 fluoroquinolone prescriptions dispensed within 50 days in the control period were not considered exposed either.

In a complementary analysis, we included the 331 patients exposed during the intermediate risk period. As anticipated, the results were unchanged; exposure to fluoroquinolones remained significantly associated with the occurrence of RD during the 10-day risk period, with an adjusted odds ratio of 1.46 (95% CI, 1.17-1.81).

A potential confounding bias of the systemic disease for which fluoroquinolones may be prescribed is possible. Other studies[1-5] previously managed this issue using another antibiotic as reference. The cohort study performed by Kuo et al[2] reported, contrarily to the one performed by Daneman et al,[1]

a significant association of fluoroquinolone use with RD after they compared the prescriptions of patients in the fluoroquinolone cohort with those of propensity score–matched adults treated with amoxicillin. Moreover, the study design that we used ensures the minimization of confusion by indication. Indeed, the self-matched design implies that time-invariant multiplicative confounders are necessarily adjusted for. Given the short observation period of our study (180 days), the clinical situations of the patients may be considered fixed during the control and risk periods. Therefore, the prescription of fluoroquinolones for an underlying respiratory, inflammatory, or infectious disease may occur in a nondifferential manner within control or risk periods. In addition, in our study, we excluded all patients who had been hospitalized within 6 months prior to the RD. This likely resulted in excluding patients with severe chronic diseases, including inflammatory diseases, and thus minimizing confounding by indication. Lastly, to control for potential residual bias, we conducted a sensitivity analysis excluding patients with long-term infectious or inflammatory conditions and respiratory failure. Exposure to fluoroquinolones remained significantly associated with the occurrence of RD over the 10-day period, with an adjusted odds ratio of 1.43 (95% CI, 1.11-1.84).

In the self-controlled case series design, we also looked at first event, and we used the same short observation period. The risk period was defined as the 10-day period after each fluoroquinolone prescription had been dispensed, whereas the risk-free period included all other periods when patients were considered to be at baseline risk. Individuals exposed to fluoroquinolones during the intermediate risk period (11-60 days) were excluded.

The incidence rate ratio and its 95% CIs were estimated by comparing the incidence of RD during the risk and risk-free periods using a conditional Poisson regression model with a logarithmic link function, taking the duration of the different study periods into account. Given the study observation period (180 days), age and comorbidities were considered to be "fixed" during the study period. Corticosteroid treatment was taken into account as a time-dependent variable.

Fanny Raguideau, PharmD, MSc
Rosemary Dray-Spira, MD, PhD
Mahmoud Zureik, MD, PhD

Author Affiliations: Department of Epidemiology of Health Products, The French National Agency for Medicines and Health Products Safety, Saint-Denis, France.

Corresponding Author: Fanny Raguideau, PharmD, MSc, Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety, 143-147 Blvd Anatole France, F-93285 Saint-Denis, France (fanny.raguideau@ansm.sante.fr).

Published Online: October 20, 2016. doi:10.1001/jamaophthalmol.2016.3479

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5(11):e010077.

2. Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis*. 2014;58(2):197-203.

3. Eftekhari K, Ghodasra DH, Haynes K, Chen J, Kempen JH, VanderBeek BL. Risk of retinal tear or detachment with oral fluoroquinolone use: a cohort study. *Pharmacoepidemiol Drug Saf*. 2014;23(7):745-752.

4. Kapoor KG, Hodge DO, St Sauver JL, Barkmeier AJ. Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study. *Ophthalmology*. 2014;121(6):1269-1273.

5. Fife D, Zhu V, Voss E, Levy-Clarke G, Ryan P. Exposure to oral fluoroquinolones and the risk of retinal detachment: retrospective analyses of two large healthcare databases. *Drug Saf*. 2014;37(3):171-182.