12-Nov-2017

Dear Dr. Pasternak

Manuscript ID BMJ.2017.040029.R1 entitled "Fluoroquinolone use and risk of aortic aneurysm and dissection: a nationwide cohort study"

Thank you for sending us your paper. We sent it for external peer review again. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

Both our statistician and an outside reviewer have important remaining concerns about the study. We were thus uncertain about whether to proceed with the paper, but do want to give you the opportunity to respond. We cannot guarantee that we will be persuaded by your responses, however, and would understand if you would rather submit the paper elsewhere.

We hope very much that you will be willing and able to revise your paper as explained below in the reviewer's comments, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
BMJ.2017.040029.R1

1. Residual confounding by indication. Patients may be given fluoroquinolone and amoxicillin for very different indications. Your WebTable 5 indicates that patients prescribed fluoroquinolones are almost 65% more likely to have visited an emergency department in the last month, and are 31% more likely to have received a non-study antibiotic in the previous 3 months than those prescribed amoxicillin. Given these differences, it is likely that there are differences in the unobserved confounders as well.
2. Time dependent confounding. Another concern is that these results may suffer from time dependent confounding. One way you could investigate this is by reporting the portion of treatment episodes where the patient was diagnosed with an aortic aneurysm in the 10 days and 60 days *before* their prescription.
3. Negative control analysis. All-cause mortality is a less than ideal control outcome, because aortic aneurysms may lead to differences in mortality, and mortality is very rare. I suggest using a very common outcome, perhaps fractures, or visits to the GP in the 10 days before and after treatment? See

Davies et al. (2016) for an application to IV analysis (the logic of negative controls equally applies to propensity scores).
4. How was censoring of follow-up time handled? Could you report the average follow-up time, after treatment for treatment and control?
5. "On a similar note, if an infection represented indication for treatment with fluoroquinolones, but not amoxicillin, and later led to development of an infectious aneurysm, it would bias results towards increased risk; this too appears unlikely to explain the observed results because infected aneurysms are rare, representing 0.5- 2.5% of all aortic aneurysms, and because patients with infected aneurysm." Infected aneurysms may be a small proportion of aneurysms in the entire population, but it does not follow that they are rare in the population of individuals who have been recently treated with antibiotics.
6. Episodes: Could you present a sensitivity analysis restricted to the first treatment episode? It is important to analyse observational studies as we would randomised controlled trials (Hernan et al. 2008). The results may suffer from immortal time bias, as by definition, patients with multiple treatment episodes cannot have an event in their first treatment episode (Suissa et al. 2008). Hernan argues that observational studies should define exposure on the basis of the first treatment received.
7. Publishing analytic code. Your article is very nicely and clearly written. However, you only have limited space and you cannot possibly explain all of the details and assumptions you've made in your analytic code (nor would most of your readers be interested in these details). However, many researchers will be very interested how you have handled your analysis. Publishing your code helps ensure transparency and allows you to be very precise about the analysis and data cleaning that you've undertaken. See Nosek et al (2015).
8. Preregistration of the study. If the analyses were pre-planned, where was the study registered? Could you include your analysis plan in the supplementary materials?
9. Data sharing. While I understand that you cannot share any individual level patient data, will keep any of the underlying data for archiving purposes?

This study does offer more robust control for confounding than previous studies. However, the reported differences could be due to residual confounding.

Davies NM, Thomas KH, Taylor AE, Taylor GMJ, Martin RM, Munafò MR, et al. How to compare instrumental variable and conventional regression analyses using negative controls and bias plots. International Journal of Epidemiology [Internet]. 2017 Apr 7 [cited 2017 Apr 13]; Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/dyx014

Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, et al. Promoting an open research culture. Science. 2015 Jun 26;348(6242):1422–5.

Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008 Nov;19(6):766–79.

Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol. 2008;167(4):492–9.

Additional Questions:
Please enter your name: Neil Davies

Job Title: Research Fellow

Institution: University of Bristol

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

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Reviewer: 2

Recommendation:

Comments:
I thank the authors for their response and revision. Upon reading both, it triggered some additional comments to address, and I did not fully agree with the completeness of some responses. My thoughts are as follows, and I hope this helps the authors improve their article upon further revision:

Abstract - results: "Fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection (HR 1.66; 95% CI, 1.12-2.46), with an estimated 82 (95% CI, 15-181) additional cases of aortic aneurysm or dissection per 1 million treatment episodes." Please change the last part to tell the reader that (a) the 82 additional cases when using fluoro assumes causality (as the language infers causality the way I read it), and (b) the time-point you refer to (i.e. 82 additional cases by what time after treatment? 60 days?). Same applies to the what this study adds text, and the end of paragraph 1 of the discussion. The authors have added the 60 days time-scale into their results, in response to my previous comment, but it remains missing in many other places.

Abstract results - interesting comment about increased outcome events in first 10 days. Rather than, or in addition to, giving the HR for the first 10 days, would it be better to give the overall probability of the outcome by 10 days in each group? This is more informative to the BMJ reader I imagine. The HR may still be a constant over time, but the baseline hazard rate may be coming down. Indeed, is there really a difference between the overall HR and the HR by 10 days? I don't think so, as the authors test for non-proportional hazards and there is no strong evidence to support it.

Therefore, there is a tension in the article: no evidence of non-proportional hazards, and yet different HRs obtained over intervals. This is most dramatic in Figure 3, where the HR for first 60 days in shown, and then HRs for intervals by 10 days shown.
In their response, the authors stand by this decision, but it still feels rather over-analysing the data when there really is no strong evidence of a difference. As mentioned, assuming a common HR over time, and giving us S(t) values at 10 days, 20 days, etc seems more complete, and would give you the information you want to convey (i.e. slower increase in having risk of event after first 10 days).

- 'What this study adds' – the authors say there is a 66% increased risk, but this is more correctly a 66% increased rate.

- the handling of missing data via the inclusion of a missing data category is perhaps sub-optimal compared to multiple imputation, but with the small amount of missing data (0.1%) I do not expect this to be an issue.

Methods: the authors say that the individuals who contributed more than once are independent, as they could not have had an event previously. Therefore, I am more reassured by this response.

Methods: can the authors explain the use of (HR-1)x(incidence rate of amoxicillin group) to calculate the absolute risk difference at 60 days? Sorry, it is not clear what assumptions the authors are making to get this absolute risk difference at 60 days. Is it the HR for the main analysis being used, or that restricted to 60 days? What not simply take the S(t) values (e.g. from Kaplan Meier curve) for each group and take the difference? Does this simple approach not give the same answer?

Methods: Why is age dichotomised at 65 years in the subgroup analysis? A better approach is to consider linear or non-linear trends for age, as this is more realistic if there is indeed a difference across the age range. Table 2 should also provide the actual interaction estimates (differences between groups) and their CIs, not just the p-value for homogeneity.

Figure 2: numbers by what time-point (as noted above) are shown?

Best wishes, Richard Riley

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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