PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records
AUTHORS	van Bodegraven, Birgitta; Palin, Victoria; Mistry, Chirag; Sperrin, Matthew; White, Andrew; Welfare, William; Ashcroft, Darren; van Staa, Tjeerd

VERSION 1 – REVIEW

REVIEWER	Mark Ashworth King's College London
REVIEW RETURNED	25-Jun-2020

GENERAL COMMENTS	Thank you for asking me to review this paper. Comments: 1) Abstract: Data Sources. The authors have selected an impressive combination of data from both CPRD and SAIL databases. Most studies use just one database. Use of both provides greater validity to the findings. 2) Abstract. Exposures. It is unclear whether the 'rate of antibiotic prescribing' relates to the number of prescriptions or whether the volume of antibiotics prescribed has been standardised. 3) Abstract. Results. The authors describe the association between volume of antibiotic prescriptions and hospital admissions in 'younger patients', but it is unclear what is meant by 'younger'. Under 18's? Under 5's? Under 1's? 4) Methods, pg5: 'READ code' should be written as, 'Read code'. It is not an acronym. 5) Methods, pg6: 'the ICD-10 codes used were reviewed by clinical experts'. This seems a rather simple statement to describe an important process. What clinical experts? Did they include co-authors? Some kind of description of clinical expertise would help. 6) Methods, pg7. The analysis was adjusted for several factors which may have influenced the outcome of infection such as influenza vaccine, smoking, deprivation, Charlson index. However, there are several other potential confounders which may influence infection outcomes which were not included: pneumococcal vaccination, frailty, diabetes. 7) Results, pg8: it seems odd that rates of primary care infective complications should be 1.3 and 4.1 per 1000 person-months in CPRD and SAIL, respectively. Why this large difference? Similarly, for hospital infective admissions, the rates were 1.4 and

	5.1 per 1000 person-months, respectively. Again, why this 3-4 fold difference in the findings from two similar datasets? There were similar, but smaller, differences in the rate of primary care infections between the two databases. The authors attempt to explain this difference in the Discussion pg12, stating that it may have been related to the measles epidemic in Wales. This seems unlikely to be the full explanation. It is more likely to be related to coding behaviour. 8) Discussion: there may be other reasons for the findings. For example, much acute self limiting illness is managed out of hours, and not by the GP practice. The out of hours service usually provides a summary of the consultation. The GP may simply allocate a diagnostic code to that consultation (eg LRTI) but no prescribing code (because the OOH service prescribed the antibiotics) and thus a patient with a more severe infection may appear to have not received an antibiotic prescription. 9) Discussion: there is no mention of the difference between antibiotic prescription and antibiotic dose/volume. Simple measures of prescription number may not be sufficient to capture the relationship between infection and complications. 10) Discussion: age effect. What troubles me is that the association between lower antibiotic prescribing rate and higher primary care/secondary care infection rate was only significant in a younger age population. Intuitively, one might expect cautious antibiotic prescribing in the elderly to be fraught with danger. Is this perhaps because GPs in practice are prescribing more antibiotics to elderly patients? Possibly. But even for this group, there must have been considerable variation in antibiotic prescribing. The authors do attempt an explanation (attenuation of effect of antibiotics), but it is something of a surprise. 11) Overall, the findings present evidence of increased 'complications' arising in practices with low antibiotic prescribing for 6 common infections. This is an important finding. There are questions though about the robustness of the data. I would value an independent statistical analysis too .

REVIEWER	Hannah Lishman University of British Columbia, Canada Imperial College London, UK (honorary)
REVIEW RETURNED	17-Jul-2020

GENERAL COMMENTS	The authors describe a retrospective cohort study utilising primary care data from UK GP practices (CPRD and SAIL) linked with hospital admissions to investigate the association between practice-level antibiotic prescribing rates for common infections and infection-related admissions or re-consultations within 30 days. This is a large piece of work and an important research question: monitoring adverse effects related to the national effort of reducing antibiotic prescribing is crucial. I do, however, have a few points which I think need to be addressed. Intro: Our ecological study on a similar topic might be useful to the authors (https://www.sciencedirect.com/science/article/abs/pii/S0924857918302395?via%3Dihub) Methods: pg 5 - Please include a list of READ codes for common infections in the appendix.

	pg 6 - A flow chart outlining participant numbers based on inclusion and exclusion criteria would be helpful in the appendix. pg 6 - Was only one consultation included per patient or could patients contribute multiple infection episodes? pg 6 - How were deaths during follow up within the 30 day period accounted for in order to accurately calculate person time? pg 6 - Why did the outcome diagnoses differ between hospital admissions and GP consultations? Were UTI and pyelonephritis not included? Perhaps they were the same and this requires clarification. pg 6 - Why was region not adjusted for in the models using CPRD data? pg 6 - Line 56 should be removed. pg 7 - Were data analysed on a complete case basis (i.e. only cases with no missing data before aggregation across all variables of interest)? Please clarify further. Results: pg 8 - Percentages would be helpful - are the URTI, LRTI and UTI breakdowns just based on the CPRD data or CPRD and SAIL pooled? pg 9-10 - The non-standard increases in antibiotic prescribing make comparison of the outcomes difficult to interpret…I don't know if this can be changed? pg 9-10 - Pooling all "infection-related outcomes" makes a causal argument more difficult to make - why did the authors not choose to look at infection outcomes separately (paired with plausible preceding common infections)? It may not be possible to do this at the practice-level but if it were possible, I think it would greatly strengthen the study. I'm finding it difficult to understand why higher antibiotic prescribing for URTIs where antibiotics are rarely beneficial would lead to lower infection-related complications and that this difference would be one of the greatest - some interpretation in the discussion of this result would be welcome. I'm also finding it surprising that gender did not modify effects (for UTI especially) seeing as we see very different treatment patterns based on severity and risk for men and women with UTI - this could benefit from further interpretation. Pg 12 - "A possible hypothesis for this is that increased lifetime exposure and repeatedly using antibiotics could lower their effectiveness in reducing a patient's risk of complications" Are the authors taking about antibiotic resistance? Would this not equate to higher antibiotic exposure leading to higher levels of infection-related complications due to treatment failure? Tables - please shorten the table titles, all other information can be included as a footnote.

REVIEWER	Dr Kate Honeyford Imperial College, UK
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	Abstract The exposure is level of antibiotic prescribing in the practice, the sample is patients who had attended for an appointment for a common infection. The outcome is practice level rates of complication. Summary information of number of patients, prescriptions and admissions. Not clear which infection was the most common? Difficult to interpret results without a bit more context. The abstract does not make it clear that it is an adjusted result. Incidental prescribing – does this have a specific meaning. Introduction In the introduction you discuss the national strategies for reductions in prescribing, but the time period of the study seems a

	bit early in comparison to the interventions. I think this is worth thinking about. Methods I had to read the methods several times to convince myself that it made sense. I think it does, but the order is not logical. Could you check to make it clear that you have sample, exposure, outcome, confounders/adjusting variables. You have tried to do this, but there is some extra detail in the statistical analysis section about the confounders which it would be better to have in a separate section The end of exposure and outcomes has a fragmented sentence - it is not clear what was meant. In terms of sample, patients were included if they have a one-year follow up. But hospital admissions within the previous year led to an exclusion, you will have missed some I think. Please provide some rationale for inclusion of exposure variables. The association of each of the six common infections was then studied against both outcomes separately. The analyses were further stratified by gender and age categories: 0-17, 18-39, 40-59, 60-74, 75+ years old to evaluate the varied prescribing among these risk groups. When you say 'against' do you mean that you ran the model six times with a different cohort of patients in each model? Was each complication attributable to only one infection? Did you run another five models for age, and another two for gender. So in total there were 13 models plus the original model? Or were there 26 - 13 for hospital admissions complication and 13 for follow up primary care appointment. There must be an issue of multiple hypothesis tests! Results The results start with number of consultations, the infections, and prescribing. The sentence on variation in practice prescribing rates is not clear, it would be easier for the reader if you reported it as minimum to maximum, IQR etc. This is a very complicated: "For URTI, 28.6% of the patients received an antibiotic at the 5th percentile practice and 66.4% at the 95th percentile practice." The results sometimes have 95% CIs reported but not always. The phrase 'the largest difference in the incidence of hospital admission' is difficult to understand. Without CIs in the results it is difficult to know if LRTI is significantly different to UTI - the IRs are quite similar. The results do not seem clear to me – the largest difference is LRTI and one IRR is given and then later in the paragraph there are two IRRs given. This needs to be clarified. I am not clear why the antibiotic change is different for different conditions, is it infection specific prescribing? So we have the higher prescribing for UTIs practices compared to low? This needs further clarification. This sentence on its own does not really mean anything: "Patients aged 0-17 had the greatest difference in GP-recorded infection-related complications in CPRD (22%; IRR: 0.780, IQR: 12.05). It just doesn't seem clear what the difference is between." There is a need for the wording in the results to be clarified. A major challenge is that you have so many results it is almost impossible to coherently explain.

	This also impacts on the Discussion – your main result is that lower prescribing practices have higher rates of complications. It is not clear whether the differences between different diseases are important. You quite clearly say in your discussion: Reducing antibiotic prescribing rates may be good for antibiotic resistance, but as shown here could potentially cause more infection-related complications. This is not a sensible conclusion. You could equally argue that practices which miss serious infections have higher rates of complications.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for asking me to review this paper. Comments:
1) Abstract: Data Sources. The authors have selected an impressive combination of data from both CPRD and SAIL databases. Most studies use just one database. Use of both provides greater validity to the findings.

R: Thank you for reviewing our paper and your comments. Please find detailed responses below.

2) Abstract. Exposures. It is unclear whether the 'rate of antibiotic prescribing' relates to the number of prescriptions or whether the volume of antibiotics prescribed has been standardised.

R: Thank you for this comment. We have changed the word ‘rate’ to ‘proportion’ for clarification.

3) Abstract. Results. The authors describe the association between volume of antibiotic prescriptions and hospital admissions in 'younger patients', but it is unclear what is meant by 'younger'. Under 18's? Under 5's? Under 1's?

R: Thank you, we have corrected this to be more specific and now write: “largest in patients aged 18-39 (8.6%; 4.0% to 13.0%) and smallest in the elderly aged 75+”.

4) Methods, pg5: 'READ code' should be written as, 'Read code'. It is not an acronym.

R: We thank the reviewer for spotting this error and have corrected this.

5) Methods, pg6: 'the ICD-10 codes used were reviewed by clinical experts'. This seems a rather simple statement to describe an important process. What clinical experts? Did they include co-authors? Some kind of description of clinical expertise would help.

R: We have emended the text as follows: “The codes for outcomes and infections used were reviewed independently by two clinical epidemiologists”.

6) Methods, pg7. The analysis was adjusted for several factors which may have influenced the outcome of infection such as influenza vaccine, smoking, deprivation, Charlson index. However, there are several other potential confounders which may influence infection outcomes which were not included: pneumococcal vaccination, frailty, diabetes.

R: We thank the reviewer for this comment. There are indeed other potential confounders which were not adjusted for, for some, like pneumococcal vaccination and frailty, this was not possible because of limitations of the data available. We now mention the potential effects of not adjusting for other potential confounders as a limitation in the discussion on page 12. The following text was included: “*In addition, although this analysis attempted to adjust for several available factors which might influence the association investigated. There remains a potential for additional residual confounding by non-adjusted for covariates*.”.

7) Results, pg8: it seems odd that rates of primary care infective complications should be 1.3 and 4.1 per 1000 person-months in CPRD and SAIL, respectively. Why this large difference? Similarly, for hospital infective admissions, the rates were 1.4 and 5.1 per 1000 person-months, respectively. Again, why this 3-4 fold difference in the findings from two similar datasets? There were similar, but smaller, differences in the rate of primary care infections between the two databases. The authors attempt to explain this difference in the Discussion pg12, stating that it may have been related to the measles epidemic in Wales. This seems unlikely to be the full explanation. It is more likely to be related to coding behaviour.

R: Thank you for this comment and your thoughts on an additional explanation to explain the observed difference. We mention variations in coding behaviour in the discussion, page 12, and have extended this to also include as a potential explanation for the difference in complication rates between CPRD and SAIL.

8) Discussion: there may be other reasons for the findings. For example, much acute self limiting illness is managed out of hours, and not by the GP practice. The out of hours service usually provides a summary of the consultation. The GP may simply allocate a diagnostic code to that consultation (eg LRTI) but no prescribing code (because the OOH service prescribed the antibiotics) and thus a patient with a more severe infection may appear to have not received an antibiotic prescription.

R: Thank you for your comment. This is an interesting notion and out of hours prescribing could have had a confounding part in our analysis. However, we believe that given the size of the data set, a large proportion of out of hours prescribing would need to have been recorded incorrectly to have influenced the results. The proportion of patients with routine GP visits is expected to be larger than those with a common infection indication that was managed out of hours. This however can’t be quantified using the current data and further research is needed to understand the role of out of hours prescribing on the association between common infections and infection-related complications.

9) Discussion: there is no mention of the difference between antibiotic prescription and antibiotic dose/volume. Simple measures of prescription number may not be sufficient to capture the relationship between infection and complications.

R: Thank you for your comment. We have indeed not evaluated antibiotic dose, volume, or specific antibiotics. We evaluated a pre-specified hypothesis whether reducing of overall levels of antibiotic prescribing could lead to unintended adverse consequences (some of the UK government policies focus currently on reducing overall levels). Of course, the effects of antibiotics on infection-related complications could vary by type, dose and local resistance levels. We are conducting a separate study evaluating the effects of length of antibiotic courses. We have added the following text to the limitations: "*Incidental antibiotic prescriptions* ***without details on local antibiotic resistance levels*** *were evaluated in this analysis and the results can only be interpreted in this context*."

10) Discussion: age effect. What troubles me is that the association between lower antibiotic prescribing rate and higher primary care/secondary care infection rate was only significant in a younger age population. Intuitively, one might expect cautious antibiotic prescribing in the elderly to be fraught with danger. Is this perhaps because GPs in practice are prescribing more antibiotics to elderly patients? Possibly. But even for this group, there must have been considerable variation in antibiotic prescribing. The authors do attempt an explanation (attenuation of effect of antibiotics), but it is something of a surprise.

R: We agree with the reviewer that this is a surprising finding. We have added some further text and references to recent studies: "*Recent research reported reduced effectiveness of antibiotics with repeated use over several years [21]. A literature review by Costelloe et al. (2010) found that invididuals who were prescribed an antibiotic for respiratory or urinary tract infections develop bacterial resistance that was detectable for up to 12 months [9]. Similar association has been reported recently for resistant blood stream infection after UTI prescribing [22]. However, further research is needed to assess any age effect in the effectiveness of antibiotics. Another reason may be that GPs may be more hesitant to withhold antibiotics from older patients to avoid under-treatment, leading to seeing a greater response in younger patients at higher prescribing rates*." However, we also agree that further research is needed

11) Overall, the findings present evidence of increased 'complications' arising in practices with low antibiotic prescribing for 6 common infections. This is an important finding. There are questions though about the robustness of the data. I would value an independent statistical analysis too.

R: Thank you for this. An experienced statistician is co-author (Matthew Sperrin).

Reviewer 2

The authors describe a retrospective cohort study utilising primary care data from UK GP practices (CPRD and SAIL) linked with hospital admissions to investigate the association between practice-level antibiotic prescribing rates for common infections and infection-related admissions or re-consultations within 30 days. This is a large piece of work and an important research question: monitoring adverse effects related to the national effort of reducing antibiotic prescribing is crucial. I do, however, have a few points which I think need to be addressed.

Intro:
Our ecological study on a similar topic might be useful to the authors (https://www.sciencedirect.com/science/article/abs/pii/S0924857918302395?via%3Dihub)

R: Thank you for reviewing our paper and your comments.

Methods:
pg 5 - Please include a list of READ codes for common infections in the appendix.

R: Thank you for your comment. The following text is now included “All code list used in this analysis are available at clinicalcodes.org”.

pg 6 - A flow chart outlining participant numbers based on inclusion and exclusion criteria would be helpful in the appendix.

R: Thank you for your comment. We used only few inclusion and exclusion criteria. Therefore we feel an additional flowchart is unnecessary in this aggregated analysis.

pg 6 - Was only one consultation included per patient or could patients contribute multiple infection episodes?

R: Thank you for your comment. Yes patients could contribute multiple infection episodes during the study period as long as the consultation was at least 6 months apart from the previous one. We have added an additional clarification of this into the discussion on page 12.

pg 6 - How were deaths during follow up within the 30 day period accounted for in order to accurately calculate person time?

R: Observations were censored in case of death. We have added the following text: “*In case of death or end of data collection within these 30 day periods, observations were censored*.”.

pg 6 - Why did the outcome diagnoses differ between hospital admissions and GP consultations?

Were UTI and pyelonephritis not included? Perhaps they were the same and this requires clarification.

R: We believe this comment relates to the final paragraph of the exposure and outcome section and specifically the following sentences: "*Infection-related hospital admission includes codes for admission for sepsis, endocarditis, acute respiratory tract infection, or bacterial meningitis. Infection-related complications as recorded in the primary care records includes any revisit to the GP for infection-related complications such as pneumonia, sepsis, quinsy, mastoiditis, or meningitis in the 30 day follow-up period*." We apologise if we misunderstood.

The complications listed here are a subset selection for illustrate purposes and do not include all individual outcomes that were included in the evaluated 2 pre-defined outcomes: infection-related hospital admission and GP diagnosed infection-related complication. The full list of complications can be found on clinicalcodes.org.

pg 6 - Why was region not adjusted for in the models using CPRD data?

R: We apologise as region was adjusted for in the CPRD models and appears to mistakenly have been left out in the method of the manuscript. We've now corrected this.

pg 6 - Line 56 should be removed.

R: Thank you, we apologise for this error and this has been removed.

pg 7 - Were data analysed on a complete case basis (i.e. only cases with no missing data before aggregation across all variables of interest)? Please clarify further.

R: Thank you, data was not restricted to complete case only before aggregation up to practice level. This is acknowledged on page 7 and in table 1 where we state "*No imputations or other adjustments were performed for missing characteristics in the covariates*."

Results:
pg 8 - Percentages would be helpful - are the URTI, LRTI and UTI breakdowns just based on the CPRD data or CPRD and SAIL pooled?

R: The numbers of consultations presented at the start of the results section on page 8 are from CPRD. Table 1 gives additional consultation counts for the included common infections for CPRD-HES and SAIL. Data from CPRD and SAIL were not pooled as this is not possible due to data licencing restrictions. Instead the effect estimates were combined as we described in the statistical analysis section of the method.

pg 9-10 - The non-standard increases in antibiotic prescribing make comparison of the outcomes difficult to interpret…I don't know if this can be changed?

R: Thank you for your comment. Because of the scaling we performed the IQR becomes the unit that the effect size is expressed in. This scaling was performed so that our pre-specified hypothesis could be evaluated comparing high to low prescribing. Unfortunately this is a main component of our analyses and cannot be changed.

pg 9-10 - Pooling all "infection-related outcomes" makes a causal argument more difficult to make - why did the authors not choose to look at infection outcomes separately (paired with plausible preceding common infections)? It may not be possible to do this at the practice-level but if it were possible, I think it would greatly strengthen the study.

I'm finding it difficult to understand why higher antibiotic prescribing for URTIs where antibiotics are rarely beneficial would lead to lower infection-related complications and that this difference would be one of the greatest - some interpretation in the discussion of this result would be welcome. I'm also finding it surprising that gender did not modify effects (for UTI especially) seeing as we see very different treatment patterns based on severity and risk for men and women with UTI - this could benefit from further interpretation.

R: Thank you for these two comments. We have performed an additional supplementary paired analysis with URTI and LRTI as common infections and pneumonia and LRTI diagnosed in both primary and secondary care. The results of this can be found in supplement 3. The results are similar to our main analysis and also show an inverse association with lower complications in GP practices with increased prescribing.

We now write (page 11): "*An inverse association was found in an additional sensitivity analysis which paired URTI and LRTI with plausible subsequent infection-related complications, such as pneumonia and hospital admission for LRTI (Supplementary material, appendix 3. In patients who consulted their GP for LRTI, the incidence of a hospital admission with LRTI was 18% (0.820 (0.765 - 0.879)) lower with 8.7% higher antibiotic prescribing (CPRD-HES).*"

Pg 12 - "A possible hypothesis for this is that increased lifetime exposure and repeatedly using antibiotics could lower their effectiveness in reducing a patient's risk of complications" Are the authors taking about antibiotic resistance? Would this not equate to higher antibiotic exposure leading to higher levels of infection-related complications due to treatment failure?

R: Thank you for your comment. We hypothesis here that the association in older patients is less, because they've been exposed to more antibiotics during their lifetimes.

Tables - please shorten the table titles, all other information can be included as a footnote.

R: Thank you for your comment. We prefer to have more informative and therefore longer titles for our tables.

Reviewer 3

The exposure is level of antibiotic prescribing in the practice, the sample is patients who had attended for an appointment for a common infection. The outcome is practice level rates of complication.

Abstract

Summary information of number of patients, prescriptions and admissions. Not clear which infection was the most common? Difficult to interpret results without a bit more context. The abstract does not make it clear that it is an adjusted result.
Incidental prescribing – does this have a specific meaning.

R: Thank you for your comment. We apologise that you felt the abstract is limited in information; we've tried to highlight the main components of our analysis, but are limited by word count regarding more detailed contents. The meaning of incidental prescribing is defined in the method section. Summary information of consultations, rate of outcomes, and proportion of prescribing can be found in the results section. We've added clarification in the abstract that the estimates are adjusted estimates. We now write: "A practice with 10.4% higher antibiotic prescribing (the interquartile range (IQR)) was associated with a 5.7% lower rate of infection-related hospital admissions (Adjusted, 95% Confidence Interval 3.3% to 8.0%)."

Introduction
In the introduction you discuss the national strategies for reductions in prescribing, but the time period of the study seems a bit early in comparison to the interventions. I think this is worth thinking about.

R: Thank you for your comment. It was not our aim or hypothesis to directly evaluate the effect of a specific intervention, which would've required the use of data related to the time period that intervention was used. Instead we evaluate the UK government's general desire to reduce overall prescribing by comparing high prescribing GP practices with low prescribing GP practices and if there was an association with infection-related complications. We hypothesise that indiscriminately reducing antibiotics increases rates of complications, and evaluated this using HER data.

Methods
I had to read the methods several times to convince myself that it made sense. I think it does, but the order is not logical. Could you check to make it clear that you have sample, exposure, outcome, confounders/adjusting variables. You have tried to do this, but there is some extra detail in the statistical analysis section about the confounders which it would be better to have in a separate section

R: Thank you for your comment. We have now created a separate heading for details related to the SES confounder, this can be found on page 7.

The end of exposure and outcomes has a fragmented sentence - it is not clear what was meant.

R: Thank you, we apologise for this error and the fragmented sentence has now been removed.

In terms of sample, patients were included if they have a one-year follow up. But hospital admissions within the previous year led to an exclusion, you will have missed some I think.

R: Thank you for your comment. We excluded patients with either of the outcomes of interest in the six months prior to their GP consultation for common infection.

Please provide some rationale for inclusion of exposure variables.

R: Thank you, we presume that you're referring to our choices in covariates. We apologise if we misunderstood. During the design of this study these covariates were pre-selected as factors that could potentially affect the choice of the physician to prescribe antibiotics for the patient.

The association of each of the six common infections was then studied against both outcomes separately. The analyses were further stratified by gender and age categories: 0-17, 18-39, 40-59, 60-74, 75+ years old to evaluate the varied prescribing among these risk groups. When you say 'against' do you mean that you ran the model six times with a different cohort of patients in each model?

Did you run another five models for age, and another two for gender. So in total there were 13 models plus the original model? Or were there 26 - 13 for hospital admissions complication and 13 for follow up primary care appointment.
There must be an issue of multiple hypothesis tests!

R: We performed an initial main analysis, comparing the combined 6 common infections with the two outcomes (infection-related complication GP recorded and infection-related hospital admission) (Figure 1). We then performed stratified 'by infection' analyses for each 6 infections separately (Figure 2).

Then, the original data was stratified into gender (Figure 3 top) and into age categories (Figure 3 bottom). We did not evaluate separate hypothesis in each stratification nor used previous observations to guide further stratifications.

We did not aim to test a causal hypothesis and have performed a type of analysis (including the stratifications) in the databases that are commonly done. Because of this we do not feel there is any need to correct for multiple comparisons.

Was each complication attributable to only one infection?

R: Thank you for your comment. For each patient with a GP consultation for one of the common infections of interest, complications were assessed up to 30 days post consultation encounter.

Results
The results start with number of consultations, the infections, and prescribing. The sentence on variation in practice prescribing rates is not clear, it would be easier for the reader if you reported it as minimum to maximum, IQR etc. This is a very complicated: "For URTI, 28.6% of the patients received an antibiotic at the 5th percentile practice and 66.4% at the 95th percentile practice."

R: Thank you for your comment. We presented the distribution using the 5th and 95th percentile of prescribing to show variation in prescribing but limit the noise from the very lowest (minimum) and very highest of prescribing (maximum). This is our preference to show the variation in prescribing, table 3 gives additional antibiotic prescribing for the 6 common infections and also reports the 25th and 75th from which the IQR could be worked out.

The results sometimes have 95% CIs reported but not always. Without CIs in the results it is difficult to know if LRTI is significantly different to UTI - the IRs are quite similar.

R: Thank you. We apologise for this and have now added 95% CI's where they were previously missing from the text.

The phrase 'the largest difference in the incidence of hospital admission' is difficult to understand. The results do not seem clear to me – the largest difference is LRTI and one IRR is given and then later in the paragraph there are two IRRs given. This needs to be clarified.

R: Thank you for your comment. We have rephrased the sentence you mention and have rewritten the use of 'largest difference' throughout the manuscript.

We assume you're referring to these two sentences:

1) *"The largest difference in the incidence of hospital admission for the combined analysis was observed in LRTI (IRR: 0.839; 16.1%), …."*

2) *"LRTI was associated with a 14.2% (CPRD-HES, IRR: 0.858) and 18.2% (SAIL-HES, IRR: 0.818) lower incidence for hospital admission when antibiotic prescribing was higher by 8.7% and 15.1%."*

We evaluated infection-related hospital admission in two different databases, CPRD-HES and SAIL-HES. Both these analyses resulted in their own estimate; this is presented in sentence 2. Which database the estimate came from is denoted in the brackets.

These two estimates for LRTI were then combined, as is described in the method section, the combined result is shown in sentence 1. All of these results can also be found in Figure 2.

We apologies for the confusion but have chosen to present both combined effects and database specific (CPRD/SAIL) effect to shown the complete picture of this relationship.

I am not clear why the antibiotic change is different for different conditions, is it infection specific prescribing? So we have the higher prescribing for UTIs practices compared to low? This needs further clarification.

R: Thank you. That is correct, in the stratified "by infection" analyses each infection has its own distribution of prescribing. Which GP practices are high and which are low prescribers differ for these 6 infections, table 3 shows the 25th and 75th from which the IQR derives. For UTI consultations in CPRD, at the 75th percentile 90.98% of practices prescribed. At the 25th percentile 82.96% prescribed antibiotics, the IQR is 8.02%. We find that an increase of 8.02% (the IQR) in prescribing is associated with reduced incidence of GP-recorded infection related complications by 15.6% (IRR: 0.844 (0.770-0.926) (Figure 2).

This sentence on its own does not really mean anything: "Patients aged 0-17 had the greatest difference in GP-recorded infection-related complications in CPRD (22%; IRR: 0.780, IQR:12.05). It just doesn't seem clear what the difference is between."
There is a need for the wording in the results to be clarified.

R: Thank you, we have rephrased the use of "greatest difference" in the manuscript for clarification.

A major challenge is that you have so many results it is almost impossible to coherently explain. This also impacts on the Discussion – your main result is that lower prescribing practices have higher rates of complications. It is not clear whether the differences between different diseases are important.You quite clearly say in your discussion: Reducing antibiotic prescribing rates may be good for antibiotic resistance, but as shown here could potentially cause more infection-related complications. This is not a sensible conclusion. You could equally argue that practices which miss serious infections have higher rates of complications.

R: Thank you for your comment. The results of our analyses show that higher rates of antibiotic prescribing are associated with lower rates of infection-related complications. We also showed this for

multiple common infections. We feel that we have a sensible conclusion that follows directly from the analyses performed.

VERSION 2 – REVIEW

REVIEWER	Mark Ashworth King's College London UK
REVIEW RETURNED	03-Sep-2020

GENERAL COMMENTS	Thank you for asking me to comment further on this paper. The extensive revisions have greatly improved the paper. I have three very minor comments: 1) In response to Reviewer 1, point 8, it would be helpful if the issue of Out of Hours antibiotic prescribing could at least be referred to in the Discussion, however briefly, and how this may have introduced bias. 2) In response to Reviewer 1, point 8, the authors state that they are doing further research on the role of antibiotic dose/volume. However, they do not state this in the Discussion and a brief comment about the relevance of a measure of standardised volume would be of help, and how this may have introduced bias. 3) The Discussion, penultimate para, summarises two Cochrane reviews, stating that complications were 'so low' and 'rare'. If available, the NNTs would give an indication of the relationship between antibiotic prescribing and risk of complications.

REVIEWER	Hannah Lishman University of British Columbia, Canada
REVIEW RETURNED	17-Sep-2020

GENERAL COMMENTS	I thank the authors for their responses to my feedback. Please find below some further comments: Methods: pg 5 - read codes: - please provide the lists of codes you used as there are multiple versions of code lists for each condition on clinicalcodes.org depending on the paper used and it's important for quality assessment and for replication purposes in the future pg 6 - multiple infection episodes: - the clarification should be in the methods, not in the discussion pg 6 - outcome diagnoses: - unfortunately this still does not make it clear what the conditions were and whether they differed between hospital and GP visits, please list them fully for transparency (as opposed to referring to the website) pg 7 - missing data: - please quantify the missing data where it is missing and provide some discussion about what this might mean for the analysis pg 9-10 - infection-related outcomes:

	- I appreciate the extra analyses the authors included and think that they provide more insight into the study - As to my second point, I wonder if they could provide more interpretation of these results (URTI showing the greatest effect) as they seem counterintuitive pg 12 - age effect - Unfortunately I still do not follow this explanation or the rationale behind it

REVIEWER	Dr Kate Honeyford Imperal College, London
REVIEW RETURNED	10-Sep-2020

GENERAL COMMENTS	All comments have been addressed, and minor changes in the wording have made the paper easier to read. The methods still do not include a clear list of confounders - these are in the statistical methods section. I do not feel other confounders have been addressed in the discussion, without thoroughly discussing other possible reasons for the associations you have found (which may be significant by chance given the level of multiple testing) there is too much emphasis on the concept of reducing prescribing rather than lower prescribing. At no point are possible reasons, such as poor care, for low prescribing discussed. This concerns me.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Thank you for asking me to comment further on this paper. The extensive revisions have greatly improved the paper. I have three very minor comments

1) In response to Reviewer 1, point 8, it would be helpful if the issue of Out of Hours antibiotic prescribing could at least be referred to in the Discussion, however briefly, and how this may have introduced bias.

R: Thank you for this comment. We have taken your advice and have added an additional sentence to this effect in the discussion. We now write (page 12): "*In addition, a small proportion of prescribing may be attributable to out of hours prescribing where coding of these consultation or prescriptions into the patient's record is performed afterwards and therefore subject to error and misclassification, potentially leading to an overestimation of the observed association*.".

2) In response to Reviewer 1, point 8, the authors state that they are doing further research on the role of antibiotic dose/volume. However, they do not state this in the Discussion and a brief comment about the relevance of a measure of standardised volume would be of help, and how this may have introduced bias.

R: Thank you. We have made reference to the use of standardised antibiotic measures on page 12. We now write: "*Practice level prescribing proportion as a standardised antibiotic measure allows for comparing the range of GP prescribing within and between datasets with similar inclusion criteria. Other standard measures, such as age- and sex-adjusted STAR-PU prescribing units, are available although the research question here specifically focussed on the reduction of overall antibiotic prescribing levels regardless of patient-mix within a practice.*".

3) The Discussion, penultimate para, summarises two Cochrane reviews, stating that complications were 'so low' and 'rare'. If available, the NNTs would give an indication of the relationship between antibiotic prescribing and risk of complications.

R: Thank you, we have now added complication rates and NNTs were available in this paragraph.

Reviewer: 2

I thank the authors for their responses to my feedback. Please find below some further comments:

Methods: pg 5 - read codes:

- please provide the lists of codes you used as there are multiple versions of code lists for each condition on clinicalcodes.org depending on the paper used and it's important for quality assessment and for replication purposes in the future

R: Thank you, we agree on the importance of reproducibility in research and for this reason we prefer to utilise a code repository for space-saving, simplified and standardised identification of which codes were used for a paper. The codes for this paper intend to be uploaded at time of publication, although for now codes are identical to this publication:
https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/70/

pg 6 - multiple infection episodes:

- the clarification should be in the methods, not in the discussion

R: Thank you for your comment. The sentence has been moved to the methods, subsection selection and eligibility criteria.

pg 6 - outcome diagnoses:

- unfortunately this still does not make it clear what the conditions were and whether they differed between hospital and GP visits, please list them fully for transparency (as opposed to referring to the website)

R: Thank you. We apologise for the confusion on the conditions and whether they differed or not. We have added an additional sentence to this effect. We now write (page7): “The same set of conditions were included in both outcomes.” We prefer to list a subset of conditions in the paper to highlight some conditions and refer to the complete list on the website and in a previous co-author paper (van Staa *et al.* (2020).)

pg 7 - missing data:

- please quantify the missing data where it is missing and provide some discussion about what this might mean for the analysis

R: Thank you, we have added additional clarification on how missing data was handled in the methods (page 8): ” No imputations or other adjustments were performed for missing characteristics in the covariates. Missing data was present for the following covariates; BMI (CPRD: 41.4%), Smoking status (CPRD: 30.4%), and socioeconomic status (CPRD: 37.3%). Also, in the statistical analysis section we now write: “*Models were adjusted for missing data using a covariate specific missing data indicator”.* An additional mention is made in the discussion (page 13): “*In addition, although this analysis attempted to adjust for several available factors which might influence the association investigated, missing data was present in some of the covariates. The analyses accounted for this by using a missing indicator and the presence of missing data in the covariates could have influenced the estimates, although the large sample size and replication of the analysis in a second database (SAIL) gives weight to the interpretation of the results*.”

pg 9-10 - infection-related outcomes:

- I appreciate the extra analyses the authors included and think that they provide more insight into the study

- As to my second point, I wonder if they could provide more interpretation of these results (URTI showing the greatest effect) as they seem counterintuitive

R: Thank you for your comment. However outlined below is why we don’t find our results counterintuitive.

At the time of consultation for a common infection a physician has limited options available, they either prescribe an antibiotic or they do not. The decision to prescribe will be based on the patient’s symptoms, history, and the physician’s assessment on their risk of complications. If a physician makes a correct assessment that their patient has a bacterial infection and would benefit from

antibiotics, even in the case of URTI, then seeing a reduction in that patient's risk of complications is not unexpected, they are after all being treated and the infection is no longer present.

We estimated a NNT of 1164 for URTI in this analysis and although that may be quite large, it shows that some benefit can be had for some patients. Which shows that a reduction in the total number of patients treated will results in less patients without complications (1/1164 = 859/1.000.000 - minus 20% - 687/800.000)

If the patient has a bacterial infection it is logical to assume that antibiotics would improve the symptoms and health of the patient. Conversely, if antibiotic did not improve patient symptoms or had no effect why would they be prescribed?

pg 12 - age effect

- Unfortunately I still do not follow this explanation or the rationale behind it

R: Thank you for your comment. We apologise for the confusion. In this analysis we found that the observed association was less in older patients compared to younger patients. In response to this finding we hypothesise and speculate that antibiotics could be less effective when used more over a lifetime. The elderly are known to have altered pharmacokinetics, mostly relating to kidney and liver function, which can influence drug absorption and distribution. A recent paper by van Staa (2020) evaluated repeated antibiotic use and the effectiveness over several years. We now write (page 13): "*A possible explanation for this is that increased lifetime exposure and repeated use of antibiotics could reduce antibiotic effectiveness, for example due to altered pharmacokinetics*".

Reviewer: 3

All comments have been addressed, and minor changes in the wording have made the paper easier to read.

The methods still do not include a clear list of confounders - these are in the statistical methods section.

R: Thank you for your comment. The list of confounders has been moved from subsection statistical analysis to subsection confounders.

I do not feel other confounders have been addressed in the discussion, without thoroughly discussing other possible reasons for the associations you have found (which may be significant by chance given the level of multiple testing) there is too much emphasis on the concept of reducing prescribing rather than lower prescribing. At no point are possible reasons, such as poor care, for low prescribing discussed. This concerns me.

R: Thank you. This is a good point, and we have made reference to quality of care as other factors on page 13. However, while these factors may have an impact, there's no way for us to evaluate them with the data currently available. However, one assumption here is that lower prescribing equates to poor care, which may or may not be the case. For an individual patient at the time of consultation for a common infection there are limited options for a physician, he either prescribes or he does not. For the population, lower prescribing may be "good care" by slowing the rate of increasing antibiotic resistance, and thus improving antibiotic effectiveness for the those individuals who genuinely need help. For the individual, not prescribing could also be "good care". If the individual would get better without antibiotics, prescribing has no clear benefit except perhaps speed of recovery, but could have unintended side effects. There are also cost-implications, most antibiotics are not free. Also for the individual, if they're getting antibiotics for every little thing, it may not be as effective for when they really need it.

The interpretation of results and their discussion is done in the context of reducing prescribing as we evaluated a pre-specified hypothesis whether reducing overall levels of antibiotic prescribing could lead to adverse consequences.

VERSION 3 – REVIEW

REVIEWER	Mark Ashworth King's College London
REVIEW RETURNED	10-Dec-2020

GENERAL COMMENTS	Thank you for asking me to re-review this paper. It has been considerably reworked since the original submission and is now much stronger (in particular, the sections relating to missing data). I have a couple of points: 1) The authors state in the Discussion: 'Practice level prescribing proportion as a standardised antibiotic measure allows for comparing the range of GP prescribing within and between datasets with similar inclusion criteria. Other standard measures, such as age- and sex-adjusted STAR-PU prescribing units, are available although the research question here specifically focussed on the reduction of overall antibiotic prescribing levels regardless of patient-mix within a practice'. This wording does not emphasise sufficiently the importance of standardised measures of prescribing. A prescription of full dose antibiotics for long duration would count as equivalent in the current study to a prescription of lower dose antibiotics for short duration. Similarly, a GP prescribing several short courses of lower dose antibiotics might appear to be a high antibiotic prescriber but when standardised, the volume of antibiotic prescribing may be relatively small when compared with a prescriber of high dose, long duration antibiotics. The outcome measure was 'infection related

	complications'. Reductions in the numbers of antibiotic prescriptions many be confounded by the standardised volume of antibiotic prescriptions. This should be more fully acknowledged in the Discussion . 2) The authors do now acknowledge the potential importance of missing antibiotic prescribing data, arising from out-of-hours antibiotic prescribing. Patients often bypass primary care with acute self limiting illness, presenting in A&E Departments or Walk-In Centres. These sources of additional antibiotic prescribing should be acknowledged.

REVIEWER	Kate Honeyford Imperial College, UK
REVIEW RETURNED	14-Dec-2020

GENERAL COMMENTS	This is a well written paper which is interesting. It is important to remember that conclusion in the abstract is only one possible explanation of the result.