

Subject: BMJ - Decision on Manuscript ID BMJ.2016.032072

Body: Dear Prof. GULLIFORD

Manuscript ID BMJ.2016.032072 entitled "Is it safe to reduce antibiotic prescribing for self-limiting respiratory tract infections in primary care? Cohort study using electronic health records"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. 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.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. THERE ARE SEVERAL SUBSTANTIAL AREAS THAT NEED TO BE ADDRESSED, please do so point by point, we appreciate this may take time. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Rubin Minhas
Dr Rubin Minhas
BMJ Associate Editor
rm1000@live.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=5d97b7d9dd144e7eaa0b68a6715bbe32

****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: xxx (chair), yyy (statistician), [and list other eds who took part]

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

*** STATS REPORT**

An interesting research question, well designed, analysed and described.

Very minor stats points. The software hglm is an R package and needs citing. Coefficients in Table 2 per 10 units, inconsistent as RTI per 1000 and AB per 100.

Forest plots need ref (IRR=1) included perhaps as an open blob to show the linear trend. The groups within each diagnosis as currently listed are the wrong way round, with the smallest at the top and largest at the bottom. They need reversing.

P values need only 2 decimal places if $P \geq 0.01$, or 3 if $P < 0.01$ (modified AMA recommendations).

Rates in Table 1 and Figure 1 need 2-3 significant digits, not 2 decimal places.

Useful ref comments, all addressable.

*** PLEASE REMOVE TRACES OF CAUSAL INFERENCE AS THIS IS A GP PRACTICE LEVEL ANALYSIS**

***PLEASE REMOVE THE REFERENCES TO A CLINICAL TRIAL**

*** PLEASE RE-DO THE ANALYSIS, USING MENINGITIS AS THE PREFERRED CLINICAL OUTCOME RATHER THAN CELLULITIS**

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

**** Comments from the external peer reviewers****

Reviewer: 1

Recommendation:

Comments:

Thank you for giving me the opportunity to review this high-quality paper. The study attempts to answer

a long-standing question about how safe reducing the percentage of antibiotics prescribed for respiratory tract infections in the primary care setting is, most of them being unnecessary due to the self-limiting nature of these infections. The present manuscript, carried out by a prestigious group of researchers in the UK, resembles a highly-cited paper published in 2007 also in the BMJ, but some of the present results are quite different (reference number 13). The analysis performed seems sound, and the results obtained are very clear, albeit expected. In addition, the tables and figures provided are very well presented. However, I have some comments:

The use of large datasets of electronic medical records have the drawback of their accuracy – mainly for the diagnostic codes – and, particularly in this paper, this aspect is even more relevant since you considered the diagnosis of different complications. For instance, were pneumonias confirmed radiographically? You should more clearly describe if some of these complications, mainly those attended in the secondary sector such as pneumonia, could have been missed in this cohort study.

Linked to the previous query, it's not clear to me if you also considered the pneumonias admitted to the hospital. About 20% of pneumonias are expected to be managed in the hospital setting, and some of them will have a poor outcome. We all know that the chances of detecting differences in the number of very infrequent complications such as Lemierre's syndrome or intracranial abscess across the different groups are slim, even with the use of large databases. However, the presence of complicated pneumonia, bacteraemia, and death in these diagnoses are not as infrequent as the previous complications. You do not describe the severity of these complications, mainly because the methodology used is not appropriate for that, but did you find any difference in terms of mortality between the highest and the lowest antibiotic prescribing practice groups?

In the Introduction section you mention that Petersen et al observed that the estimated number of patients who would have to be treated with antibiotics to avoid one episode of pneumonia after an upper respiratory tract infection, one quinsy after sore throat and one mastoiditis after otitis media was higher than 4,000. However, you do not mention that the risk of pneumonia in the month after the diagnosis of acute bronchitis in Petersen's study was high and substantially reduced by antibiotic prescription, with this protective effect being greatest in people aged 65 and over (with a NNT of 39 in this group age). When it comes to the number of pneumonias, your results differed considerably from the findings of Petersen et al, since you found that only one extra case of pneumonia would be seen if GPs reduced the antibiotics prescribed by 10%. I miss a clearer discussion about these differences. You standardised the incidence rates of pneumonia by sex and age. However, could you identify the number of extra pneumonias among elderly patients that could have been observed if GPs had reduced the antibiotic prescribing by 10%?

The BMJ is an international journal and from this perspective the lowest quartile of antibiotic prescribing, with a median of 38% of antibiotics prescribed for the respiratory tract infections, might be even higher than the mean antibiotic prescription rate observed in some other countries in Europe such as Sweden or Netherlands (the latter country with 22.5% of antibiotics prescribed for these infections as you mention in reference 8). One might also wonder why you considered quartiles instead of breaking down the different practices into more groups, such as quintiles, sextiles or even deciles. It would permit having groups of practices with really very low antibiotic prescribing rates and some complications might have been more clearly observed in these very low antibiotic prescription practices. Despite the fact that the overall prescription of antibiotics has not dramatically changed over the last years, nowadays there is an increasing number of GPs who are very aware of the threat of the antimicrobial resistance and prescribe very few antibiotics for these self-limiting respiratory tract infections, and these GPs would not be reflected in the lowest quartiles but could have been reflected in the lowest deciles, for instance. You should discuss this point.

You used a cohort of individuals followed up from 2005 to 2014. It would be interesting to have some information about the trend of how the number of consultations for respiratory tract infections and antibiotic prescription for these conditions have changed over this 10-year period in the UK. Linked to the previous query, you should also describe whether the use of rapid tests (CRP for instance) and the rate of delayed prescribing of antibiotics have significantly changed in this period.

It is not clear to me if you were able to identify the percentage of antibiotics not immediately prescribed (delayed). If not, you should make it clearer in the paper. Since some studies have not observed any increase of the number of complications of sore throat when a delayed prescribing of antibiotics was carried out compared to treated patients, provided you have this information, you could specify if the use of the delayed prescribing of antibiotics varied across the different antibiotic prescribing quartiles.

Some tweaks:

You should describe all the acronyms used in the tables and figures. Having to go to the text every time you come across some of them that are not explained as footnotes is really cumbersome.

The vertical line depicting the lack of statistical significance (in number 1) in figures is missing and is crucial for visual impact.

Additional Questions:

Please enter your name: Carl Llor

Job Title: GP and senior researcher

Institution: Institute in Primary Care Research Jordi Gol, Barcelona

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: I report a grant from the Jordi Gol i Gurina Foundation for a research stage at the University of Cardiff in 2013, as well as research grants from the European Commission (Sixth and Seventh Programme Frameworks), Catalan Society of Family Medicine, and Instituto de Salud Carlos III.

Reviewer: 2

Recommendation:

Comments:

Description

This is an enormous study, looking for the rare outcomes of 3 suppurative but treatable infections (cellulitis, peritonsillar abscess, and pneumonia), and 3 more serious infections (mastoiditis, empyema, and Lemierre's Fusobacterium thrombophlebitis of the internal jugular vein). Studying the medical records of 610 UK general practices of around 400,000 patient, and 45,000,000 patient-years of follow-up, they correlated practice visits and antibiotic prescribing for selected acute respiratory infections (ARIs) with these complications.

The study is particularly important in an era of increasing focus on decreasing the antibiotic prescribing in primary care for ARIs, when it is likely that one reason for this over-prescription is anxiety about infective complications of ARI. If right, then the conclusions are that serious infection of the sort that GPs will worry about are so unlikely to occur that these data should provide an enormous level of comfort to GPs and patients alike about a parsimonious antibiotic prescribing approach. This is likely to influence policy and practice, and the paper to be cited extensively. However it will come under scrutiny because the inference is causal, and, coming from observational data, vulnerable to challenge. The paper is very well written. It is slightly long, but this is compatible with the BMJ's 'pico' policy.

Comment

1 The choice of all the 5 respiratory secondary infections that could be 'missed' are uncontroversial. However the inclusion of cellulitis is interesting, and may be something that most GPs would not have thought of, or worried about, since it appears to be unrelated to respiratory infections. Indeed of the 2 references cited to support its inclusion by the Authors, the Zwart 2003 described only one case of impetigo!

This begs the question of what else might have been included as credible, commonly worried-about, infections that might have been avoided by antibiotic use. And they might include meningitis (which GPs really worry about, and although rare, must be more common than Lemierre's disease) and urinary infections. Presumably the data are right there for analysis, although this might be a very unwelcome suggestion for the authors...

Since skin infections are likely only uncommonly and distantly caused by ARIs, presumably the effect on cellulitis must be preventive: if people take antibiotics more often for any reason, they're more likely to be protected against infection of any kind. The causal direction of course may go the other way: perhaps the patients of GPs who prescribe antibiotics commonly for skin infections will also have fewer ARIs. But in any case we are not sure we believe the result because of an inappropriately chosen primary outcome measure (see 3 below).

2 The data for these analyses are highly dependent on GPs' coding (through Read codes) correctly. Coding always has an element of subjectivity (especially with ARIs, which all sit on a variety of spectra). These analyses must assume that GPs who are high antibiotic prescribers code the same away as those who are not. Actually there is some evidence from 45 years ago this is not true in Scotland, and there is nothing to suggest that it might be better today. [Howie JG, Richardson IM, Gill G, Durno D. Respiratory illness and antibiotic use in general practice. J R Coll Gen Pract. 1971;21:657-63.; and also Howie J. Diagnosis--the Achilles heel? JR Coll Gen Pract. 1972;22:310-5.] These data suggest that GP who use antibiotics are more likely to use diagnostic labels of 'antibiotic-justified diagnoses'.

So there should be some speculation about how differences in coding ARIs might have affected the results. This might affect the data about ARI consulting rates, and then secondarily the antibiotic prescribing rates.

Unfortunately we can't see any way to check if this is a problem, unless the organisation holding the electronic medical record database has previously undertaken validity testing of the diagnostic codes independently.

3 Primary Outcome.

The Methods describes "For each CPRD general practice, we estimated the rate of RTI consultations per 1,000 registered patients; the antibiotic prescribing rate for RTI per 1,000 registered patients; and the proportion (%) of RTI consultations with antibiotics prescribed".

The higher the rate of ARI consultations the higher the incidence of infective complications. This is perhaps what would be expected, and therefore is unsurprising.

Also the higher the proportion (percentage) of antibiotics prescribed, also the lower the incidence suppurative complications, supporting the hypothesis that the liberal use of antibiotics suppresses a range of downstream infections. However we know from past work of Little's that high antibiotic prescribers also are associated with high 'returns' with new subsequent RTIs. So the proportion of antibiotics prescribed has to be adjusted for higher consulting rates (working in the opposite direction).

Instead we are provided with the actual rates of antibiotic prescribing, although unfortunately relegated to supplementary information, (as Suppl Fig 1), although reported in Results (p10 li48), but not really explored further.

We actually think this is the least biased data: as the actual rate of antibiotics prescribed per thousand patients, it is free of the consultation rate bias. It shows only one of the potentially downstream infections (pneumonia) is associated with increased antibiotic activity, and this is a very important result.

Chris Del Mar, Amanda McCullough
Centre for Research in Evidence Based Practice
Bond University, Queensland, Australia

Additional Questions:

Please enter your name: Chris Del Mar; and Amanda McCullough

Job Title: Prof Public Health; and Research Fellow

Institution: Bond University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: Funding from Australian NHMRC for research in primary health antibiotic resistance; for a Cochrane Review Group; This pays for Dr McCullough

Reviewer: 3

Recommendation:

Comments:

The question this paper asks is of interest - i.e., are there dangers associated with refraining from prescribing antibiotics for respiratory tract infections, which are primarily of viral origin. They used a rich database, the UK Clinical Practice Research Datalink. On the negative side, when one uses a large dataset, it is relatively easy to see statistically significant findings that have little clinical relevance or importance for the individual practice or patient (1-2 cases a year for cellulitis and pneumonia, 1 case of abscess a decade).

In terms of style, I felt there was too much repetition of the same points about increased risk of cellulitis, pneumonia and peritonsillar abscess. I think it could be shortened without changing the message. Some specific points:

1. In the Introduction, the authors note an earlier study found the overall risk of complications was low and the "number of patients who would have to be treated to avoid one complication was estimated in excess of 4,000." They did not use a similar way to describe their own data, but it would have been of great interest and would put in perspective for the clinician how to interpret this data.
2. They emphasize the significant findings and mention this minimal increased risk is likely offset by the risks of antibiotic treatments that are unnecessary. Some data regarding this would have been very informative, even if just by literature review.
3. There is no breakdown of how individual RTIs were treated, and whether the cases of pneumonia/cellulitis/peritonsillar abscess had any association with patients that actually had an RTI and did or did not get an antibiotic (discussed by the authors, appropriately, as a weakness). If they occurred in a completely different population, can the association be explained by RTI antibiotic treatments? If the excess cases could not be linked to patients with RTIs who were not treated with antibiotics, how should the results be interpreted?
4. The results of infective complications according to quartile of proportion of RTI consultations with antibiotics prescribed, as well as infective complications according to rate of RTI consultations are emphasized and relevant tables/figures included. In contrast, the association between prescribing rate - which takes into account RTI consultation rate and proportion of RTI consultations with antibiotics prescribed - is included only as a supplementary figure, but it seems that this interaction is very important. As discussed, practices with high proportion of antibiotic treatments for RTI consultations encourage more RTI visits than other practices. Perhaps those practices are more experienced with RTI consultations and less likely to miss other diagnoses, or other hypotheses are possible. In any event, this analysis showed only a significant association with pneumonia - less striking results.
5. How does this study help clinicians? It is difficult to see how this information can be practically helpful. Its main benefit is reassurance - reducing antibiotic treatment of RTIs does not have collateral damaging impact. The way the paper is framed, it just doesn't get this across as the major point.

Additional Questions:

Please enter your name: Tamar Barlam

Job Title: Associate Professor of Medicine

Institution: Boston University School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Reviewer: 4

Recommendation:

Comments:

Overall the paper is very well written and easy to understand - addressing a key area of global importance (that is the reduction in AMR through over use of antibiotics - principally in ambulatory care).

This paper shows very clearly that it is safe to reduce antibiotic prescribing for self-limiting diseases with the slight increase in the number of infections the average GP practice may see - offset by reductions in the side-effects of antibiotics as well as associated costs (although the latter not discussed). This is very important in low and middle income countries where often there is 100% co-payment for antibiotics - and increased resistance is leading to increasing use of more expensive antibiotics with implications for access and patients completing the course. Consequently should be published in a high impact journal such as the BMJ.

I do not have major suggestions - only some minor ones for consideration only. These include:

- a) May be good to define Primary Care since in a number of countries this is 'ambulatory care' - so avoid confusion.
- b) Page 3 line 10. Other references for consideration include: (I) Laxminarayan R, Mouton RP et al. Access to effective antimicrobials: a worldwide challenge. *Lancet*. 2016;387(10014):168-75 - as this

gives figures for the appreciable increase in antibiotic use worldwide during recent years and the implications; (ii) taken forward in LMICs by Mendelson M, Rottingen JA et al. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet*. 2016;387(10014):188-98

c) Line 20 page 3 - negligible benefits to whom?

d) Page 3 Lines 38 - 47. Good also to say that interventions are also being targeted at patients to reduce antibiotic prescribing as do mention this on page 13 (lines 42/ 43) and in the French study quoted. Other publications discussing this include Rezal RS, Hassali MA et al. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. *Expert review of anti-infective therapy*. 2015;13(5):665-80. This is because patients themselves are often a source of over use of antibiotics in ambulatory care as mentioned on page 13). This is recognised by typically multicomponent strategies among authorities to reduce inappropriate antibiotic use, e.g. (i) Huttner B et al. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet infectious diseases*. 2010;10(1):17-31; (ii) Dyar OJ, Beovic B et al. How can we improve antibiotic prescribing in primary care? *Expert review of anti-infective therapy*. 2016;14(4):403-13; (iii) Furst J, Cizman M et al. The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings and implications. *Expert review of anti-infective therapy*. 2015;13(2):279-89

e) Page 5 line 38. Not sure every reader outside the UK will be familiar with Read codes as opposed to ICD 10 codes - so a brief explanation may be needed

f) Page 5 lines 50 - 57 - may be good to say why broke the cohorts down into the age groups discussed and not other potential age groups

Additional Questions:

Please enter your name: Brian Godman

Job Title: Professor

Institution: Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Reviewer: 5

Recommendation:

Comments:

The title of the manuscript raises immediate curiosity on the content, where we obviously hope that the answer to the question is yes, having in mind the overuse of antibiotics and the growing threat of bacterial resistance to antibiotics.

The manuscript is easy to read and understand, and the conclusions are clear. As hopefully expected, a lower prescribing rate is only slightly associated with infectious complications. Taken into account the large number of participants in the study, the conclusions are credible and well founded.

Some comments to the manuscript:

1. Are diagnoses for hospital admittance part of the complication diagnoses recorded? If complications with severe courses are not included, the safety of low prescribing rates may still be questioned. On the other hand, there would probably be serious side effects from antibiotic use, demanding hospital admittance.

2. Antibiotic prescribing proportion of 65% in the highest quartile and of 38% in the lowest quartile, with an overall median of 51%, is still high concerning mainly self-limiting infections. Moving from the highest quartile to the level of the lowest would still probably give a prescribing proportion for RTIs that is rather high. In the perspective of antibiotics as limited resources, it would be of a greater interest to know how a 15% or 20% proportion for RTI would affect the complication rate.

3. In a Norwegian study we found that the proportion of broad spectrum antibiotics varied even more than the proportion of treated RTIs. Have the authors looked into the association between narrow-spectrum antibiotics and the rate of complications?

4. The assessment of the consequences of a 10% reduced prescribing proportion of antibiotics is not unproblematic. The individual GP that takes the decision of prescribing while facing the patient, has individual attitudes and experiences that may affect the way the patient is treated and information given. It is not obvious that a shift in prescribing proportion from high to low will give the same complication outcome as the observed association found in this study. Only a randomised, controlled intervention study will be able to verify that assumption.

This is a study of great importance, although with some limitations that the authors have stated. The main conclusion is important knowledge that may contribute to lowering the inappropriate use of antibiotics for RTIs, a target that is widely accepted as necessary in order to slow the progression of bacterial resistance to antibiotics.

Additional Questions:

Please enter your name: Svein Gjelstad

Job Title: Researcher

Institution: University of Oslo

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Reviewer: 6

Recommendation:

Comments:

Morten Lindbæk, professor in general practice, University of Oslo, Antibiotic centre for primary care.

This paper addresses an important question as reduction in antibiotic use for RTIs in primary care is one of the major strategies for reduction in total antibiotic use on a national level. There is clear evidence that this can contribute to reduction of antibiotic resistance. It is of great importance whether a reduction in use can lead to more complications and more hospitalisations.

In general the study is well performed and the results give clear answers to most of the research questions. The study is large with enough power to answer most of the research questions that are raised in the study. Furthermore the cohort probably is representative of UK general practice.

I have some concerns that should be addressed before acceptance:

1. Can the reader be sure that all complications in the cohort have been registered? The authors state that data are gathered from the electronic patient records. But I assume that a number of these complications have been detected outside the practices, such as direct contact with the emergency rooms, out of hours services or direct contact with the hospital. Are the authors sure that all these contacts have been registered in the patient records? If so, are there any quality measurements that this is fulfilled?

2. Why are not doctor factors included in the analysis, such as gender, age, years of practice, degree of work load? Other studies like our own demonstrated that doctor factors can be predictors for antibiotic prescribing. We found that being a specialist and a busy doctor, were significant predictors (ref gjelstad x 2).

3. I miss a more comprehensive discussion on the choice of relevant complications? Why is not necrotising fasciitis included in the complications? It is rare, but I assume still more frequent than Lemierre's syndrom. Furthermore meningitis as a result of otitis media, sinusitis, and orbital cellulitis as a complication to sinusitis. Of course there may be a discussion about the relationship between an RTI and a subsequent complication, but this will be the same as with cellulitis.

4. Is the cohort representative of UK general practice? Can the fact that these practices probably are more academic run, lead to a different cohort of patients? What data are available to clarify this? What about proportion of immigrants on the lists in addition to the deprivation scale?

5. Why did you have to draw a sample from each practice, what were the reasons from the ethical committee. I assume that all data were anonymized or pseudonymized?

So to more specific questions from the editor:

* Originality - does the work add enough to what is already in the published literature? Yes, it adds up to more comprehensive data on complications as compared to previous papers

* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers- Yes it is an important topic for all groups

* Scientific reliability
Research Question - yes, clearly answered.

Overall design of study - adequate - yes

Participants studied - adequately described and their conditions defined? Yes, apart from my comment 1 - whether all complications are included, and why not doctor factors are not included in the analysis

Methods - adequately described? Yes

Results - answer the research question? Yes, well presented.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? Yes, apart from my comments.

References - up to date and relevant? Any glaring omissions? No, just that our study could be mentioned as a reason for including GP factors

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says- Yes.

References:

Gjelstad S, Straand J, Dalen I et al. Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections? *J Antimicrob Chemother* 2011; 66: 2425-33.

Gjelstad S, Høye S, Straand J et al. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ: British Medical Journal* 2013; 347.

Additional Questions:

Please enter your name: Morten Lindbæk

Job Title: xx

Institution: University of Oslo

Reimbursement for attending a symposium?:

A fee for speaking?:

A fee for organising education?:

Funds for research?:

Funds for a member of staff?:

Fees for consulting?:

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?:

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?:

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Information for submitting a revision

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into <http://mc.manuscriptcentral.com/bmj> and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: <http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements> and <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists>).

Items to include with your revision (see <http://www.bmj.com/about-bmj/resources-authors/article-types/research>):

1. What this paper adds/what is already known box (as described at <http://resources.bmj.com/bmj/authors/types-of-article/research>)
2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see <http://resources.bmj.com/bmj/authors/editorial-policies/guidelines>.)
3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).
4. Competing interests statement (see <http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests>)
5. Contributorship statement+ guarantor (see <http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship>)
6. Transparency statement: (see <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/transparency-policy>)
7. Copyright statement/licence for publication (see <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse>)
8. Data sharing statement (see <http://www.bmj.com/about-bmj/resources-authors/article-types/research>)
9. Funding statement and statement of the independence of researchers from funders (see <http://resources.bmj.com/bmj/authors/article-submission/article-requirements>).
10. Patient involvement statement (see <http://www.bmj.com/about-bmj/resources-authors/article-types/research>).
11. Please ensure the paper complies with The BMJ's style, as detailed below:
 - a. Title: this should include the study design eg "systematic review and meta-analysis."
 - b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see <http://resources.bmj.com/bmj/authors/types-of-article/research>). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.
 - c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.
 - d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand

fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines <http://www.equator-network.org/reporting-guidelines/sampl/>. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

- i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
- ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
- iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
- iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
- v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

Online and print publication: All original research in The BMJ is published with open access. Our open access policy is detailed here: <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse>. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at <http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model>). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at <http://resources.bmj.com/bmj/authors/bmj-pico>. Publication of research on bmj.com is definitive and is not simply interim "publication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

Date Sent: 11-Apr-2016