Dear Dr. Llewelyn

BMJ.2017.037542 entitled "“Complete the antibiotic course to avoid resistance”; non-evidence-based dogma which has run its course?"

Thank you for sending us this paper and giving us the chance to consider your work.

We sent it out for external peer review and discussed it at the Analysis manuscript committee meeting (present: Peter Doshi, Prashant Jha, Navjoyt Ladher, Emma Rourke).

If you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

1) Editors thought your paper covered an important and interesting clinical topic. The comments here are intended to strengthen your argument and broaden the appeal to our international readership.

2) We thought that some additional background about the "complete the course" gospel would be helpful to make clear that this is standard of care, particularly taking in to account the recommendations from other organisations and guideline bodies (for example the CDC). It would also be helpful to know how commonly this occurs - is it possible to quantify prescribing activity/guidance?

3) We also thought it would be helpful to be clearer about the evidence guiding a rationale for change. Is there a sufficient evidence base to reach a tipping point and change practice? This doesn't come through clearly enough in the paper, and adding more on this would help make your argument more convincing

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks.When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again

for review.

Once you have revised your manuscript, go to https://mc.manuscriptcentral.com/bmj and login to your Author Center. Click on "Manuscripts with Decisions," and then click on "Create a Resubmission" located next to the manuscript number. Then, follow the steps for resubmitting your manuscript.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely

Navjoyt Ladher
nladher@bmj.com

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
This paper is an interesting commentary regarding the often-given counseling advice by healthcare professionals to patients receiving an antibiotic to finish the course completely to prevent antibiotic resistance.

The history of the advice is laid out well in the paper as well as considerations and indications for when this advice is warranted. The authors do make a compelling argument for healthcare professionals to avoid this advice (due to lack of evidence) in most circumstances and cite recent clinical trials that focus on shorter durations of antibiotics. Overall, the authors make a good case to de-emphasize this message and, in turn, promote the message to view antibiotics as a finite natural resource.

Specific comments:
1. For the 'Standfirst' statement, consider adding to end of sentence 'vs. completing the course' or changing to '. . . . should drop the message that completing the course prevents antibiotic resistance', as in most cases this is the specific counseling advice offered.
2. page 5, paragraph starting with 'This belief . . ', please modify first 2 sentences, adding 'a' between is and barrier in first sentence and adding comas after 'In primary care', and before and after 'for example'.
3. End of page 5, consider removing content related to patient consent as this touches upon other broad areas related to clinical trials and could be considered distracting from main points of paper.
4. Consider expanding the last paragraph regarding 'What should we

advise patients . . .’ to include what message to substitute in cases where a shorter course of antibiotics has not been demonstrated or prescribed. Given that there is not yet evidence for patients determining an appropriate and effective antibiotic duration based on their self-reported symptoms, it seems that if the usual message regarding completing course is dropped, that a new message needs to be substituted.

Additional Questions:
Please enter your name: Amy Pakyz

Job Title: Associate Professor of Pharmacy

Institution: Virginia Commonwealth University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 2

Recommendation:

Comments:
Hi, this is Julia from St. Georges. Many thanks for giving me the opportunity to review this manuscript. I fully agree with you that the "finish the course to avoid antimicrobial resistance" recommendation is an important misconception to address and that a BMJ Analysis piece is appropriate to do this. I have only a few comments to make:

- In general, I would steer away from saying "more" or "less" antibiotic treatment. What is being discussed here is duration, i.e. "longer" or "shorter". More treatment could also refer to the dose of antibiotics being administered (or the dosing regimen in general, e.g. BID vs TID). The relationship of antimicrobial resistance selection with dose is likely to be complex, but in terms of dose sometimes more may be better.
- Please could you cite evidence to support the following statement: "the longer the antibiotic exposure these 'opportunist' bacteria are subjected to, the greater the pressure to select for antibiotic resistance in them."
-Could you explain why you feel that the different pharmacological properties of antibiotics being compared in the (few) existing studies comparing shorter and longer treatment
durations make the assessment of optimal treatment duration more complex (p4, l11)?
- I don't feel that failure to stop antibiotics at 48-72 hours in hospitalised patients relates to the discussion of duration of treatment being presented here. In this situation, it seems to me that the problem isn't as much physicians wanting to complete a standard course, as lack of physician confidence about absence of infection.
- Perhaps suggesting that we would want to formally consent patients for receiving antibiotics is taking it a bit far? I guess the point that much of antibiotic prescribing is experimental in that it is not based on robust evidence (especially where duration is concerned) is valid. Patients are unlikely to be aware of this.

- change take to taking in line 47/48, p. 4
- This belief is a barrier - line 33/34, p. 5

Additional Questions:
Please enter your name: Julia Bielicki

Job Title: Paediatric Infectious Diseases Consultant

Institution: St George's University of London

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

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Date Sent: 01-May-2017