Reviewer’s report

Title: Consecutive antibiotic use in the outpatient setting: an extensive, longitudinal descriptive analysis of antibiotic dispensing data in the Netherlands

Version: 0 Date: 05 Apr 2018

Reviewer: Mette Reilev

Reviewer's report:

Overall

Thank you for the opportunity to read this article.

Evaluating the trends in consecutive antibiotic use and switching in antibiotics within treatment episodes is very relevant. Such studies may help us to point out serious misuse of antibiotics and thereby to avoid increasing antibiotic resistance, which is a major public health concern. The concise aim and objectives of the present study is, however, unclear and the authors have left me with some considerations.

Major comments

In the abstract the authors state that they present an in depth analysis of consecutive antibiotic use. However, the concise aim or objectives of the study is not presented or specified in the introduction. It is thus unclear whether the authors aim to quantify treatment failure (or other reasons to switch?), adherence to guidelines or simply to provide an overview to inform policy makers? I think it would be helpful to clarify the motivation for doing the study and further, to include the specific aim and objectives of the study (and present/prioritize findings and conclusion accordingly).

Consecutive prescriptions are defined as two prescription durations separated by three days or less. However, prescriptions with a start date prior to the end date of the first prescription seem to be excluded. The reasons for this exclusion is unclear - please specify. It seems reasonable to argue, that switching occurring immediately after the start date of the first prescription may be as relevant as a switching occurring immediately after the end date of a first prescription. In case of treatment failure, I assume that for many patients the need for switching will be recognized before the end date of the first prescription since a large proportion of switches caused by treatment failure presumably occur from 3–4 days after initiation of the first antibiotic.
Minor comments

Please specify/describe the study population in the methods and state how many individuals were included in the study. 40 mill prescriptions issued to how many individuals? How extensive is the use of antibiotics in the Netherlands?

Table 2. The authors present the nine most commonly used antibiotics. It is stated that pheneticillin represents 3% of the total single prescriptions and therefore seems to be more commonly used than trimethoprim and fosfomycin (2%). Yet, trimethoprim and fosfomycin are presented separately, but not pheneticillin - why?

Figure 2: Please specify in the text and figure legend whether the figure concerns switching to or from the given antibiotic.

Figure 4: The Sankey diagram is very useful to describe switching patterns. However, it becomes a bit overwhelming with increasing number of categories. A very high-quality figure is needed to distinguish the thinner lines illustrating flow. Including fewer categories could also be considered.

Do the authors have any information about the distribution of infectious diseases for which antibiotics are prescribed in an outpatient setting in the Netherlands? This would improve the readers understand of the prescribing patterns of antibiotics.

The authors highlight in principal findings that "…the great majority of antibiotics, including antibiotics that are generally considered as second or third-line treatment, are prescribed as first in antibiotic…" and "… initial choice is not in line with recommendations in guidelines". Please, discuss this finding (is it the aim of the study to evaluate adherence to guidelines?). Importantly, it may seem contradicted by the paragraph on page 11, line 221-228 were the following is stated: " This is in line with the Dutch guidelines for the treatment of urinary tract infections".

Please elaborate on the finding ("… annual increase in second prescriptions in a switch that was seen for …") discussed on page 11, line 229-230.

Please specify whether switching to or from doxycycline and ciprofloxacin is subject for the discussion on page 10, line 213-220.

Page 11, line 234-235: Is this study only based on patients with subsequent fillings of antibiotics in the same pharmacy? If so, please state this in the methods section and describe to which extend patients are not linked to the one pharmacy only (if known).

The purpose of the paragraph on page 12, line 261-264 is unclear ("The dataset could be enriched by linking pharmacy data with…"). I agree that it would be nice to have indications for prescribing, so why haven’t this linking been done? Further, I think the article would benefit from a description of the implications of the study (based on the aim).
Please also see a recent Danish study, also focusing on switching patterns (though only in Children) (https://www.ncbi.nlm.nih.gov/pubmed/29474259).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Acceptable

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