Author’s response to reviews

Title: Prevalence of antibiotic prescription in pediatric outpatients in Italy: the role of local health districts and primary care physicians in determining variation. A multilevel design for healthcare decision support

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Author’s response to reviews:

Dear Editor,

dear Reviewers,

the suggested corrections are highlighted in yellow throughout the paper text, while the cancellations are in ‘Strikethrough’ font. Moreover, the sequence of the references has been modified. Our “point-by-point” responses are as follows below.

Tanmay Mahapatra (Reviewer 1)

Abstract

Information provided in the background and methods appeared to be inadequate. The authors should mention the study area under background information. The use of the term "causal link" in the first paragraph appeared strong. Information regarding data sources and recruitment of the eligible subjects should be provided in methods.

The authors totally agree with the referee's comment. We modified the abstract (both “Background” and “Methods” sections) according to referee's suggestions. The word 'causal' has been deleted.

Main text
Background

Rationale and public health implications of conducting this research need to be strong and should be described in Italian contexts. Authors need to perform an exhaustive literature review for establishing the rationale of the current paper.

As suggested by the referee, we revised the “Background section” (page 3, lines 11 to 14 and page 3, lines 28 to 34), focusing on the public health implications of conducting this study. Furthermore, the bibliography has been expanded.

Methods

Sampling, recruitment of study subjects and measurement of drug exposure are confusing and lacked scientific merits. The estimation process of the prescription prevalence needs a proper citation. The methods the authors validate this estimation process should also be mentioned. It is not clear how authors did time-trend analysis?

As requested by the referee, the “recruitment” of study subjects, and the health information systems used to retrieve information - including drug exposure data - were now described in more details. Moreover, a citation related to the “prescription prevalence” estimation was now included (Methods, “Data sources” section, page 5, lines 3 to 8, and lines 12 to 14; Methods, “Study population and drug exposure” section, page 5, line 18). In addition, more details and results were provided on the time-trend analysis (Methods, “Study population and drug exposure” section, page 5, lines 20 to 22; Methods, Statistical methods and analysis of variation” section, page 6, lines 5 to 7; Results section, page 7, lines 6-7).

Discussion

This section is too sketchy and comparison of the study findings with other contemporary literature seemed inadequate. Authors should also highlight other sources of bias as the study limitations for example information bias, etc.

According to the reviewer's comments, the whole “Discussion” section was revised (pages 8-9) and some new, contemporary references were added to this section. Moreover, the “study limitation section” was expanded. We have highlighted that our health information systems do not collect data on indications for which antibacterials are prescribed (“Discussion” section, page 9, lines 27 to 33).

Charles (Chad) M Heilig (Reviewer 2)

This manuscript evaluates how the prevalence of antibacterial prescriptions for children varies across the Lazio region of Italy. It includes a temporal component and a spatial component in separate analyses. The use of median odds ratio is especially intriguing. The description of the
data, the analysis, and the conclusions seem to leave out useful details that would aid a reader. I have 3 major concerns with this manuscript.

1. The source data should be more clearly described within the body of the manuscript. In addition, the characteristics of the children and their physicians should be more clearly described.

2. The manuscript should clearly distinguish the 2015 analysis from the 2007-2015 analysis, with more details about model search (that is, variables considered) within each analysis.

3. The authors should more clearly distinguish conclusions that are supported by the data in this analysis from those that are speculative or supported by other sources.

Our “point-by-point” responses are as follows below.

In the declarations section, the authors write that "this is a retrospective, observational, population-based study, which included more than 636,900 people. … Patient data were anonymous, and results were reported in aggregate form only." The manuscript states that children were "recruited" (page 5, line 5) and "enrolled" (page 6, line 44, plus the abstract). I recommend that the data sources section explicitly mention that this is a retrospective, observational, population-based study.

As suggested by the referee, the “Data sources” section now explicitly mentions the characteristics of the study design (Methods, “Data sources” section, page 5, lines 3 to 5). Moreover, after reading the referee’s comment, we think the words ‘recruited’ and ‘enrolled’ may be misleading. Therefore, we revised this wording, according to the observational nature of the study (Methods, “Study population and drug exposure” section, page 5, line 18; “Results” section, page 7, line 2).

It would be useful to know which characteristics of children and physicians were available to the analysts, to be described in either the methods, the results, or a supplement. Limited information is available in the results section: children's sex and age, physician's practice type (pediatric vs general) and health district and an apparently partial list for which the reader is further referred to reference 11. The reader should be able to tell which characteristics were evaluated within the analysis reported in this manuscript.

As suggested by the reviewer, the full list of evaluated characteristics was now provided and described in details (Methods, “Statistical methods and analysis of variation” section, page 6, lines 27 to 29). Moreover, information about children’s and physicians’ characteristics was now provided throughout the “Results” section (pages 7-8).

Within the 2015 analysis, can a child have been prescribed more than 1 antibacterial class? Is any information available on medical indications for these prescriptions? For example, the implications are quite different for otitis media versus upper respiratory infection.
Unfortunately, information on medical indications for antibiotic prescriptions is not present in our regional health information systems. The absence of this information was now explicitly stated in the “study limitations” section of the paper (“Discussion” section, page 9, lines 27 to 33).

Is the same data source used for the 2015 analysis as for the 2007-2015 analysis? In other words, is longitudinal information available on each child? If so, how does the temporal analysis account for birth cohort effects and the fact that many children in this analysis were born after 2006? Can a child be included as both having a pediatrician and later a general practitioner? If not, what data source is used for the temporal analysis (the Drug Claims Register?), and how does that data source relate to that source for the 2015 analysis?

In the temporal analysis, individuals were not followed across calendar years. In fact, the same enrollment criteria were independently applied to each year, in order to describe the “cross-sectional” antibiotic prescription patterns over time. Moreover, drug information was collected from the Drug Claims Register for both the main analysis (2015) and the temporal analysis (2007-2014). After reading the referee’s comment, we realized that the temporal analysis was poorly described and confusing. Therefore, all sections related to temporal analysis (including “Data sources”, “Study population”, “Statistical methods”, and “Results”) were completely revised (Methods, “Data sources” section, page 5, lines 12 to 14; Methods, “Study population and drug exposure” section, page 5, lines 20 to 22; Methods, “Statistical methods and analysis of variation” section, page 6, lines 5 to 7; “Results” section, page 7, lines 6-7).

What software was used for this analysis?

“All analyses were performed using SAS statistical software (version 9.2)”. According to the comment of the referee, this sentence was now included in the manuscript (Methods, “Statistical methods and analysis of variation” section, page 6, lines 33-34).

Page 6, line 51: "The time-trend analysis indicated a slight decrease in the last three years for the 0-13 and 0-5 age groups." Is this observation based on a formal statistical assessment? If so, by what method?

In the first version of the paper, there was no statistical assessment for the “slight decrease in the last three years”. However, thanks to the referee's comment, a global chi-square test was performed in order to check for differences in antibiotic prescription prevalence during the cited period. The decrease over time was statistically significant (p-value less than 0.001) in both age groups (Methods, “Statistical methods and analysis of variation” section, page 6, lines 5 to 7; “Results” section, page 7, lines 6-7).

Page 7, line 9: "We found that this correlation was positive and statistical significant." What is the magnitude of this correlation? Is the statistical inference based on a post hoc analysis?

As suggested by the reviewer, the magnitude of the cited correlation was now provided (“Results” section, page 7, lines 23 to 26). As regards the statistical analysis, variables were clearly defined “a priori”, i.e. the “antibiotic prescription prevalence” and the “propensity of
prescribing cephalosporins”. In order to analyze this association, we used the standard linear regression model for bounded-range dependent variables (Methods, “Statistical methods and analysis of variation” section, page 6, lines 10 to 14).

Page 7, on 33: What is meant by “geographic gradient”? If this is shorthand for apparently increasing prevalence as one moves away from Rome, then it is recommended to state that explicitly.

As suggested by the reviewer, the meaning of “geographic gradient” was now explicitly described (“Results” section, page 8, lines 5-6).

Page 7, lines 36-58 and page 10, table 1: The text contains nearly all the information that appears in the table, and both the text and the table omit potentially important details. In particular, the results mention "inclusion of variables reflecting physicians' characteristics” without providing the full list; it is not clear if the list in the methods section includes all characteristics evaluated.

As suggested by the referee, the full list of variables was now provided (“Results” section, page 8, lines 14-15, and 20-21). Moreover, the full list of physician characteristics evaluated was now reported and clearly stated in the methods section (Methods, “Statistical methods and analysis of variation” section, page 6, lines 27 to 29).

Were characteristics included in the presence of a few additional variables, or did the analysis include a large multivariate model?

The first-step model is an “intercept only” model (Table 1). In the second step, physician characteristics were included into the model, in order to assess their association with antibiotic prescribing. In order to clarify this aspect, more details on the performed logistic multilevel models were now provided (Methods, “Statistical methods and analysis of variation” section, page 6, line 15; Table 1, page 11).

The absolute AIC values do not provide any value and could safely be omitted.

The authors prefer not to remove the AIC values, in order to underline the very slight improvement in the “model goodness to fit” after the inclusion of physician characteristics.

Where duration of clinical practice experience is reported, the discussion section should describe whether these quantified differences are practically significant. To what extent can the authors conclude that other variables were not significant because there was no association to be found versus other reasons related to study design?

According to our opinion, the duration of clinical practice experience may suggest a diagnostic uncertainty problem. This could be “moderated” by specific training courses for primary care physicians. This topic is discussed in the “Discussion” section (page 9, line 16; lines 20 to 23; reference number 19). Moreover we think that the study design is valid and that multilevel modeling is the best way for evaluating second-level or, more in general, higher-level characteristics, where data are hierarchical and correlations within groups exist (Hox, 2002).
However, the study limitations were discussed and expanded after reading the referees’ comments (“Discussion” section, page 9, lines 27 to 33).

In the discussion section, the authors make several statements that seem to go beyond the data presented in this analysis. Page 8, line 11: "slight improvement, probably due to the information campaign". Can the "slight improvement" be distinguished from chance? What leads the authors to attribute the change to the 2010 information campaign?

The authors cannot be sure this relation is causal. In fact, we used a cautious wording: “probably due to” (“Discussion” section, page 8, line 29). However, the “slight improvement” can be distinguished from chance. In fact, the decrease over time was statistically significant (p-value less than 0.001) in both age groups (Methods, “Statistical methods and analysis of variation” section, page 6, lines 5 to 7; “Results” section, page 7, lines 6-7).

Page 8, line 29: The word "unwarranted" is rather strong, such that the description of "unwarranted geographic variation" requires more explanation of the variation that is observed. For example, is there anything about the patient case mix, access to care (denser vs sparser population areas), or other reasons? The authors go on to raise these possibilities. They also state, "we must take into account" other considerations, which weakens the claim that the variation is unwarranted.

The authors perfectly agree with the reviewer. The word “unwarranted” is rather strong, and it was deleted throughout the manuscript.

Page 8, line 40: In discussing physician characteristics, the authors attribute one difference to duration of clinical experience based on the only characteristic besides geographic variation found to be statistically significant. Was the measured difference practically significant? Where the authors propose education or training (line 58 for physicians, page 9, line 3 for parents), they do not make the case for this particular intervention, nor do they suggest other possible interventions. Is there evidence within this study or other sources to support the appeal to education? Are other interventions possible?

The issue raised by the referee is very relevant and controversial. Our objective was to detect, to measure, and to underline geographic variation. In fact, this variability stresses the lack of therapeutic protocols shared at regional level and raises equity issues in access to optimal care. Therefore, variation should be taken into account by health policy-makers, in order to improve the use of antibiotics and mitigate the effect of “contextual” variables. Unfortunately, most of these geographic, “contextual” variables are unmeasurable, so we cannot evaluate their contribution, and we cannot control for their effects. With regard to potential interventions, we cited and proposed the most commonly used interventions, based on our experience and based on international scientific literature (e.g. Horwood 2016, Cantarero-Arévalo 2017, Filippini 2006, and Piovani 2013). After all, the detection of the most effective or cost-effective interventions aimed to improve the use of antibiotics (e.g. by means of pre-post designs, comparing drug use before and after specific interventions implemented in clinical practice) is not an objective of this study. We would like to underline that most of the cited references was added to the manuscript thanks to the comments and suggestions of the referees (“References” section, pages 13-14).
Time trends: Can these data establish how the decrease in prescribing prevalence of cephalosporins and macrolides offset the increase in penicillin prescribing prevalence? In other words, are penicillins prescribed more where the other classes would have been if patterns had not shifted?

We are not sure to have completely understood what the referee is asking. However, we think our “observed” data cannot provide answers to this “counterfactual” question.

Geographic trends: What could account for the observed “geographic gradient”?

The question of the referee is very relevant and interesting. However, we can only formulate hypotheses which are not supported by the study results. It may depend by cultural factors related to parents, by the different organization of LHDs and their propensity to organize training courses, by the lower number of pediatricians observed in peripheral areas… However, further studies based on different health information systems are needed to concretely support these hypotheses. Therefore, in the discussion of this paper we were very cautious.

Page 9, lines 7-16: It is not clear what the reader is meant to infer from the reported population size (lines 9-11). This information might support internal validity, but it does not address external validity. Further limitations to this analysis might include a lack of information on indications for which antibacterials are prescribed (which could go more directly to whether prescriptions are above acceptable levels) and case mix of primary care practices.

We completely agree with the referee. Reporting the population size in that context was misleading. Therefore, we “deleted” the population size data from that section (“Discussion” section, page 9, line 30). Moreover, the “study limitations” section was expanded, according to the reviewers’ comments (“Discussion” section, page 9, lines 27 to 33).

Consider rendering Figures 1, 2, and 3 as line graphs rather than bar charts. The patterns over time might be more readily apparent.

We comprehend the referee’s suggestion, however, we would like to maintain the original bar charts. Our choice, which is just a preference, is mainly related to “figure 2” that shows how each antibiotic “category” contributes to the total. We think a line graph representation might be more confusing and less clear in describing this kind of data. On the other hand, we would like to use the same graph representation for Figures 1-3, because they all deal with changes over time. After all, in scientific literature, bar charts are often used for showing changes over time.