PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with antibiotic prescribing in patients with acute respiratory tract complaints in Malta: a one-year repeated cross-sectional surveillance study
AUTHORS	Saliba-Gustafsson, Erika; Dunberger Hampton, Alexandra; Zarb, Peter; Orsini, Nicola; Borg, Michael; Lundborg, Cecilia

VERSION 1 - REVIEW

REVIEWER	Minyon Avent The University of Queensland, Australia
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	Dear Editor, Thank you for asking me to review the manuscript entitled 'Factors associated with antibiotic prescribing in patients with acute respiratory tract complaints in Malta: a one-year repeated cross-sectional surveillance study'. Overall the manuscript has been well written. I have the following suggestions for the manuscript Abstract The objective should be more clearly written. The conclusion should also be re-phrased i.e. 'but' changed to 'by'. Introduction Would suggest limiting the use of abbreviations such ABR. Define what is meant by 'broad spectrum' antibiotics Methods Include a statement addressing research ethics approval Results Table 2. Please check percentage AB prescribed by age

REVIEWER	Morten Lindbæk Antibiotic centre for primary care, dept of general practice, HELSAM, University of Oslo Norway
REVIEW RETURNED	02-Oct-2019

GENERAL COMMENTS	General comments.

	This is an important study, since it is the first one from Malta, one of the highest prescribing countries in Europe. The study is prospective with registrations from acute respiratory infections in primary care and is relatively large. The methods seem to be appropriate, using a multivariate logistic regression. As I understood, the authors have performed one large model, presented in 3 tables where it is stated what is controlled for. The findings are interesting and confirm the high antibiotic use in Malta. Furthermore it confirms that age and gender of both prescriber and patient are associated in addition to clinical variables. It is interesting that cultural factors such as uncertainty avoidance is discussed in the paper. I have a few critical points: 1. In the methods, it is described that the authors have chosen symptoms rather than diagnoses as independent variables. There may be pros and cons which should be more discussed. With only symptoms, it is not so easy to compare with results from other studies using diagnoses. 2. In the questionnaire it is also stated what type of antibiotic is prescribed, but this is not used in the paper. It is of course interesting to evaluate whether narrow or broad spectrum is prescribed and also if the prescription is according to guidelines (if they exist). But maybe these data are saved for another paper, this should be stated. 3. It could also be of interest if resistance data are available, and then compare the appropriateness of the prescribing according to the local resistance data. Especially pneumococci and Hæmophilus and Strep A would be of interest. 4. I miss a central reference which is Gjelstad et al in JAC 2011 from Norway (ref), using much of the same methodology to describe predictors for antibiotic prescribing and for broad- vs narrow spectrum antibiotics. In this study consultation rates was significantly associated with antibiotic prescriptions 5. OR for predictors should be stated in the abstract, only 95% CIs are given. 6. It is pointed out that female gender for GP is a predictor, but with only 9 female GPs. Thus this finding is uncertain, should be stated. .Ref: Gjelstad S1, Straand J, Dalen I, Fetveit A, Strøm H, Lindbæk M. Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections? J Antimicrob Chemother. 2011 Oct;66(10):2425-33. doi: 10.1093/jac/dkr295. Epub 2011 Jul 22

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1's comments:

1. "Abstract: The objective should be more clearly written."

 The objective has been re-worded to make it more clear, both in the abstract (lines 21-22) and the main document (lines 107-108).

2. "Abstract: The conclusion should also be re-phrased i.e. 'but' changed to 'by'."

- Line 45: ‘but’ changed to ‘by’.

3. “Introduction: Would suggest limiting the use of abbreviations such ABR.”

- We have now removed abbreviations ABR and RTI throughout the entire manuscript since they were not used as frequently as other abbreviations.

4. “Introduction: Define what is meant by 'broad-spectrum' antibiotics.”

- Lines 103-105 have been re-worded and ‘broad-spectrum antibiotics’ has now been further explained to make it more clear to the reader.

5. “Methods: Include a statement addressing research ethics approval.”

- As per the journal’s formatting requirements, the ethical approval statement is located at the back of the article, separate from the methods section. Kindly see lines 389-395.

6. “Results: Table 2 – Please check percentage AB prescribed by age.”

- Thank you for pointing this error out. It has now been corrected and row percentages for all predictors were also double checked.

Response to reviewer 2’s comments:

1. “As I understood, the authors have performed one large model, presented in 3 tables where it is stated what is controlled for.”

- As was correctly noted, in this manuscript we present the results of one large model. The univariable and multivariable associations to antibiotic prescription have been presented in three tables, grouped as follows: GP-, practice- and consultation-level factors (Table 1), patient sociodemographic factors (Table 2), and clinical factors (Table 3).

2. “In the methods, it is described that the authors have chosen symptoms rather than diagnoses as independent variables. There may be pros and cons which should be more discussed. With only symptoms, it is not so easy to compare with results from other studies using diagnoses.”

- Other articles have indeed considered diagnoses as a variable, although there are some that have used signs and symptoms too. While we did take into consideration whether we should include the diagnoses rather than the signs and symptoms, we opted to only include signs and symptoms. The main reason that we chose to exclude diagnoses from the multivariable model was that since GPs were being observed, it is possible that they adjusted their diagnoses according to their decision

to prescribe antibiotics in order to justify the prescription, and so using signs and symptoms instead was considered more accurate.

 Through our findings we were able to identify key signs and symptoms that play a role in GPs' decision to prescribe antibiotics. These could be targeted in future antimicrobial stewardship activities.

3. "In the questionnaire it is also stated what type of antibiotic is prescribed, but this is not used in the paper. It is of course interesting to evaluate whether narrow or broad spectrum is prescribed and also if the prescription is according to guidelines (if they exist). But maybe these data are saved for another paper, this should be stated."

 Thank you for this important observation. Since we have already published a descriptive study using this data (https://www.ncbi.nlm.nih.gov/pubmed/30624733) we did not re-include our analysis on narrow- to broad-spectrum antibiotic use as well as a more in-depth description of precisely which antibiotics were prescribed by diagnosis. We had already included a sentence in our methods (lines 115-116) showing that we have published data on GPs' antibiotic prescription patterns at baseline (pre-intervention). We have now specified that these results were derived from the same dataset, "An in-depth description of GPs' antibiotic prescribing patterns at baseline, using the same dataset, has been presented elsewhere." We hope that this suffices. As was expected, that study was able to show that broad-spectrum antibiotic use in Malta is extremely high (almost all patients were prescribe broad-spectrum antibiotics) and there was high variability in which antibiotics were prescribed by diagnosis.

 Regarding whether GPs were guideline-adherent, this is also a brilliant suggestion and something that we are considering for a separate paper where we will look at the change in guideline adherence pre- and post- intervention (since this study made part of a larger intervention study). However the data will need to be in further restricted as unfortunately, to-date, guidelines are not available for all the diagnoses listed in this study.

4. "It could also be of interest if resistance data are available, and then compare the appropriateness of the prescribing according to the local resistance data. Especially pneumococci and Hæmophilus and Strep A would be of interest."

 We agree that comparing antibiotic prescription to resistance patterns would certainly be interesting to look into however since this particular paper does not describe individual antibiotic prescribing or comment on the choices of antibiotics prescribed, we do not feel that it is relevant to discuss here.

 Another point worth mentioning is that unfortunately in the outpatient setting in Malta, cultures are rarely performed and those that are, are performed on already severely ill patients giving a rather skewed picture.

5. "I miss a central reference which is Gjelstad et al in JAC 2011 from Norway (ref), using much of the same methodology to describe predictors for antibiotic prescribing and for broad- vs narrow spectrum antibiotics. In this study consultation rates was significantly associated with antibiotic prescriptions."

 We have now included this paper in two separate parts of the discussion (lines 222-226 and lines 253-255).

6. “OR for predictors should be stated in the abstract, only 95% CIs are given.”

 Lines 34-44: ORs have now been included for all predictors as advised.

7. “It is pointed out that female gender for GP is a predictor, but with only 9 female GPs. Thus this finding is uncertain, should be stated.”

 Thank you for raising this issue. We did our utmost to achieve as representative a sample of GPs as possible. There were 32% female GPs on the medical registers at the time of recruitment, and we attained 27% female GPs in our sample. We do believe that this is close to representativeness and that our finding does hold importance although we do believe that further research is needed to better explain this association. Following this comment, we have now included a short discussion (lines 240-247) on the association between GP sex and antibiotic prescription.

VERSION 2 – REVIEW

REVIEWER	Morten Lindbæk Antibiotic centre for primary care Dept of general practice University of Oslo
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	I think the authors have met all the comments given by the reviewers. I would just suggest one change - that the findings from the first paper published in JAC, is cited a bit more. This goes for the diagnoses that gave an antibiotic prescription, and what antibiotics were prescribed for the RTIs.