PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Influenza-like illness and antimicrobial prescribing in Australian general practice from 2015 to 2017: a national longitudinal study using the MedicineInsight dataset
AUTHORS	Bernardo, Carla; Gonzalez-Chica, David; Stocks, Nigel

VERSION 1 - REVIEW

REVIEWER	Koen Pouwels Public Health England
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	This study describes the frequencies of ILI and associated antibiotic and viral prescribing between 2015 and 2017 in Australian general practices. This is an interesting and important area of research. However I do have a couple of comments that should ideally be addressed before the manuscript would be considered acceptable for publication: 1. Abstract: The median age was 37 years. Isn't this a bit low compared to the median age observed in other studies? If so, is that because similar to New Zealand, the working force need a note from the doctor for sick leave, while in other countries this is not necessary? 2. Abstract and throughout the manuscript: It seems the authors are a bit liberal with the terms rate. If I understand it correctly, the 'ILI rate' is the proportion of total consultations that is for ILI and is factually not a rate (it can't go above 1 or equivalently 1000/1000). Expressing the burden of ILI in this way is a bit confusing, as the ILI 'rate' does not only depend on the number of people consulting with ILI, but also on the number of people consulting with other conditions. The observation that people with comorbidities or mental health issues showed lower ILI 'rates' than their counterparts is likely mainly explained by the fact that such people more frequently consult for other reasons than healthy people. In fact, it is quite likely that the number of ILI consultations per persontime/registered patient is actually higher among patients with comorbidities. To make the analysis less dependent on other types of consultations and easier to interpret I suggest the authors express the ILI rate as a true rate, i.e. the number of ILI consultations per 1000 registered persons (with comorbidities) or 1000 personyears. If it is not known how many of the registered people have such comorbidities, I would suggest to be much

	clearer that the 'ILI rate' is not a rate but a proportion/percentage and is dependent on the rate of 'other reason' consultations. 3. Introduction. '…. Prevention … of influenza in primary health care settings for higher risk groups are essential when treating more severe cases.' If the authors mean severe cases of influenza, prevention is not treating a severe case, but preventing it right? 4. Introduction. It would be good to also add findings from recent data from English primary care, where the percentage of patients with ILI receiving an antibiotic was compared in both patients with and without comorbidity: https://academic.oup.com/jac/article/73/suppl_2/19/4841820. That paper found that 18% of ILI patients without comorbidities received an antibiotic, while this was 28% for patients with comorbidities (for same-day prescriptions). 5. Outcomes section. The use of anti-influenza medications were also coded as positives for ILI, even in the absence of any diagnosis. This likely leads to an overestimation of use, as this modifies the numerator (patients receiving the antiviral), but not the denominator (patients with ILI). This could even bias the trend if there is a trend in coding quality (such trends do exist in other countries, is it known whether this might also be true for Australia?). Also, because this bias is not introduced for antibiotics, as different methodology is used, one will overestimate the viral/antibiotic use ratio. 6. Re definition of use: 'when it was prescribed within 14 days of the original ILI diagnosis' (does this include prescriptions 14 days before as well, or only those prescribed within 14 days after the diagnosis? 'No other reasons for that prescription was identified in the database' is that also assessed during the entire 14 (or 28) day period? 7. How was clustering within practices/patients taken into account? Did the authors use a multi-level model using random or fixed effects or were robust standard errors calculated that took into account potential clustering effects? 8. Why is there a much lower number of encounters in 2017? Were some practices dropped from the analysis or is the data incomplete for 2017? Could the reason possibly bias the results? 9. 'Thirdly, the characteristics of the practice were more strongly associated with the diagnosis of ILI and medication prescribing than patients' characteristics.' Is it possible to add the amount of deviance explained or some form of pseudo R2 (conditional and marginal in case of mixed effects model) by both groups of characteristics? 10. Discussion. A comparison with the English data would also be helpful: https://academic.oup.com/jac/article/73/suppl_2/19/4841820. (see also comment 4). It has been noted before in England patients with comorbidity are more likely to receive antibiotics for ILI than patients without such comorbidities (28% vs 18%. When looking at same day prescriptions) 11. In addition, it would be helpful to discuss to what extent the gender difference for antibiotic prescribing has been observed in other studies focusing on ILI (and other conditions). For example, a recent study from England, also observed higher antibiotic prescribing for females for various conditions including ILI: https://bmjopen.bmj.com/content/8/2/e020203?cpetoc=&utm_source=TrendMD&utm_medium=cpc&utm_campaign=BMJOp_TrendMD-0

	12. This paper found that there was more frequent prescribing in higher socioeconomic areas and states that this is in line with other countries. While this may be true for some countries, this correlation is in the opposite direction in other countries, such as the UK: https://www.bmj.com/content/351/bmj.h6117 & https://www.ncbi.nlm.nih.gov/pubmed/24176983. Moreover, as already discussed in this paper, correlations with ethnicity and probably also socioeconomic status is highly context dependent: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2751935/. The latter paper shows that practices with more white patients prescribe more antibiotics.

REVIEWER	Dominik Glinz University Hospital Basel, Switzerland
REVIEW RETURNED	16-Oct-2018

GENERAL COMMENTS	You have an interesting database, but you need to be careful with the interpretation of the results. You assess a year to year variation, you cannot conclude any trends. your data is descriptive, you don't have to test significance for everything. a general rule, the more you test, the more significant p-values you get. But this doesn't makes sense and is wrong. you would need to adjust for multiple testing. but you don't need that your database itself is interesting enough. But you need to present it correctly. I did not check references, and STROBE checkliste. The discussion has to be redone after you have adapted the methods and results section. I suggest to have a careful read of the discussion after you have revised the manuscript. Regards Title: - remove “trends”, your data is limited to three years, this is simply too short to call it trends. A trend is a general direction in which something is developing or changing - I suggest you call “antibiotic and antiviral” antimicrobials - Add design in title, please also consult the STROBE checklist - Rather describe the data source (MedicineInsight) than 4.5 Mio patients Page 2 line 10: Delete “open”, I don’t understand why this should be relevant, there is no intervention line 17: remove median age, but add % of children? line 28: entire results section, give total numbers instead of percentages line 36: what should be the causal relation of mental disease with ILI? This looks like you ran several tests for significancy and report significant finding, irrespective of there causal relationship. Results and conclusion: you observed different ILI rates for the three years. Call it year-to-year variation. Most likely, this has affected prescribing patterns of these three years. ILI was higher in 2017, antiviral prescribing was higher (and not increased), antibiotic prescribing was lower (and not decreased). You need to rephrase carefully your results and conclusions. Page 3 Line 4: 4.2 million or 4.5?

	Line 11: rephrase: the association of comorbidities with antimicrobial prescribing was assessed Line 16: what does “vary” mean? Vary between GPs? Regions? On day-to-day basis, depending on the GPs workload?! Please be more specific Line 18: “can be” or were? Page 4 Line 30: Here you jump from influenza and antivirals to uncomplicated respiratory infections. Antibiotics are not recommendate because they have no benefit and cause antibiotic resistance. Financial cost shouldn’t be the first reasoning. Line 42: continue? You mean prescription rates are still high? Line 44: why are the number of US relevant for your publication? Delete Line 48-50: unclear, what is the relation to bronchitis? Rephrase Line 54: you didn’t assess trends, rephrase Page 5: Line 33: some? To be clear just say: Routinely collected data includes …. Line 44: why “open”? it is not a intervention study… Page 6 Line 3-4: this is the reason why you shouldn’t include the number in the title, it depends on the definition… Line 9-19: this is unclear? Why is this under outcome? This describes your data source right? And how you prepared the data set, but not how you assessed the outcomes. Line 9-42: what does this mean? The GP registered a diagnosis and in addition you search for other influenza specific terms within this database? Why was the diagnosis of the physician insufficient? Did you also search for spelling mistake? Which program did you use? Was there a systematic approach? Line 29: fever alone is not influenza specific. So you searched for fever or whether GP has reported body temperature above 38C? Did you count a patient as ILI patient if he received an antiviral but no influenza specific symptoms were reported by the physician? In how many cases? This might have led to increase number of prescribing rates, for instant if you have missed through influenza patient who did no receive antivirals… Line 54: antivirals should be prescribed within the first three days of symptoms… why did you choose 14 days? In your Chapter “Outcome”, you should explain the outcome. How was ILI exactly defined (you tried, but it is still not clear to me, see comments above). How was prescribing rate defined? How will you present summary measures? You describe this further below in statistical analysis, but there, you should describe the comparative methods (log regression and so…). Page 7 Line 41-44: why would you include mental health? Influence medication prescription? What does this mean? Line 48-51: move to outcomes Page 8 Line 45: major cities, remote, does this sum up? Line 48: rather present age groups the median Line 50: why you don’t stratify by comorbidities for instance for immunosuppressed patients?

	Page 9 Line 3: this is not surprising, isn't it? Patients with comorbidities and mental disease have in general a closer relation to their treating physicians. They see their GP in regular intervals. And the gap to seek help is lower. Discuss. Line 10: 63% is misleading the readers! What is the difference between 2.3, 2.7 or 4.4 ILIs per 1000 consultations?! Present only absolut numbers and state the ILI rate was higher in 2017, but don't present the year to year variations as 63% increase. Line 30: no, it did not decrease, it was lower in 2017, rephrase Line 33: lower compared to what? Table 1: Superscript a: it doesn't makes sense to test significant difference if compared to total because the compared group is part of the total. Only test what makes sense and is actually relevant. In your case, this is only descriptive, no need for testing. Superscript b: what test was used? Superscript c: can you display the different co-morbidities? Page 11 Line 5: describe antivirals only prescription rate, antibiotic only prescription rate and antiviral in combination with antibiotic prescription rate Line 8: it did not increase, it is higher. Adapt throughout your manuscript! And you can't calculate percentage on percentages! This is misleading in this context!!! The prescription rate was higher in 2017 than in 2015, 29.7% vs. 20.6% Table 2 You have to display three groups: describe antivirals only prescription rate, antibiotic only prescription rate and antiviral in combination with antibiotic prescription rate. Redo table. The same comment to the superscript account here as for Table 1. Only test what makes sense and is actually relevant. In your case, this is only descriptive, no need for testing. I haven't read the discussion, the authors need first to adapt their finding and interpretations. After this major revision, including the Discussion, I will give my inputs to the Discussion. General questions: - Are antivirals reimbursed by health insurance? - Trial registry number? CT.gov or so? - Do you have information on which influenza strain was predominant in each year?

VERSION 1 – AUTHOR RESPONSE

Comments by Referee 1:

Reviewer Name: Koen Pouwels

Institution and Country: Public Health England

This study describes the frequencies of ILI and associated antibiotic and viral prescribing between 2015 and 2017 in Australian general practices. This is an interesting and important area of research.

A: We appreciate all reviewer's contribution and time spent reading our manuscript. Antibiotic stewardship has received a lot of attention recently but antiviral use in general practice may be increasing and this needs to receive similar interest. We believe all suggestions have been incorporated into the paper in one form or another.

However, I do have a couple of comments that should ideally be addressed before the manuscript would be considered acceptable for publication:

1. Abstract: The median age was 37 years. Isn't this a bit low compared to the median age observed in other studies? If so, is that because similar to New Zealand, the working force need a note from the doctor for sick leave, while in other countries this is not necessary?

A: The study included participants of all age groups, not only adults. Based on that, our sample resembles the structure of the whole Australian population (i.e. according to the Australian Bureau of Statistics, the median age in Australia is 37.3 years). In any case, we have included a statement in the abstract and result section indicating the sample included individuals of all age groups (Page 2 Line 16; Page 9, Line 14). The reviewer is correct in saying that workers in Australia often require a medical certificate for work absences. More recently pharmacists have been able to provide such certification. Therefore GP attendance for 'working age' adults with respiratory conditions will tend to be higher than in other countries without this requirement. This may affect the ILI rate for these age groups. Of course many other factors affect attendance to medical practitioners including availability and cost, however we do not have space to comment on these issues.

2. Abstract and throughout the manuscript: It seems the authors are a bit liberal with the terms rate. If I understand it correctly, the 'ILI rate' is the proportion of total consultations that is for ILI and is factually not a rate (it can't go above 1 or equivalently 1000/1000). Expressing the burden of ILI in this way is a bit confusing, as the ILI 'rate' does not only depend on the number of people consulting with ILI, but also on the number of people consulting with other conditions. The observation that people with comorbidities or mental health issues showed lower ILI 'rates' than their counterparts is likely mainly explained by the fact that such people more frequently consult for other reasons than healthy people. In fact, it is quite likely that the number of ILI consultations per persontime/registered patient is actually higher among patients with comorbidities. To make the analysis less dependent on other types of consultations and easier to interpret I suggest the authors express the ILI rate as a true rate, i.e. the number of ILI consultations per 1000 registered persons (with comorbidities) or 1000 personyears. If it is not known how many of the registered people have such comorbidities, I would suggest to be much clearer that the 'ILI rate' is not a rate but a proportion/percentage and is dependent on the rate of 'other reason' consultations.

A: We appreciate and agree with your comment than an ILI rate (or ILI "attack" rate) refers to the number of cases per patient (individual as the denominator). Nonetheless, in this case we refer to ILI "consultation" rates, and this definition follows recommendations from the European Centre for Disease Prevention and Control (https://ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/facts-indicators) and the Australian National Influenza Surveillance Scheme (http://www.health.gov.au/internet/main/publishing.nsf/Content/cdi4104-f). Therefore, to avoid any

misinterpretation and preserve comparability with other reports/papers available in the literature, we opted to change the term “ILI rate” to “ILI consultation rate” throughout the manuscript and provide a clarification about the definition in the methods section (Page 7, Line 13). In addition, we have highlighted in the discussion section that the use of “consultation” rates may lead to misinterpretation of the relationship between comorbidity and ILI (Page 14, Line 20).

3. Introduction. ‘…. Prevention … of influenza in primary health care settings for higher risk groups are essential when treating more severe cases.’ If the authors mean severe cases of influenza, prevention is not treating a severe case, but preventing it right?

A: Suggestion accepted. The text has been amended.

4. Introduction. It would be good to also add findings from recent data from English primary care, where the percentage of patients with ILI receiving an antibiotic was compared in both patients with and without comorbidity: https://academic.oup.com/jac/article/73/suppl_2/19/4841820. That paper found that 18% of ILI patients without comorbidities received an antibiotic, while this was 28% for patients with comorbidities (for same-day prescriptions).

A: We appreciate your suggestion and have included a sentence in the introduction section (Page 4, Line 49) and the respective reference.

5. Outcomes section. The use of anti-influenza medications were also coded as positives for ILI, even in the absence of any diagnosis. This likely leads to an overestimation of use, as this modifies the numerator (patients receiving the antiviral), but not the denominator (patients with ILI). This could even bias the trend if there is a trend in coding quality (such trends do exist in other countries, is it known whether this might also be true for Australia?). Also, because this bias is not introduced for antibiotics, as different methodology is used, one will overestimate the viral/antibiotic use ratio.

A: Secondary databases such as MedicineInsight are based on ‘real world’ information recorded by GPs into a health informatics system during the consultation. Therefore, its quality, accuracy, and completeness of recording may vary by clinician and the electronic medical record used in each general practice (i.e. non-mandatory fields, free-text for coding, system coding vocabularies). It is likely that this will result in some under-reporting of clinical information such as diagnoses or reasons for encounter. For that reason, it has been widely recommended in the literature that prescribed medication be used to increase the accuracy of the information1-3, especially when the medication is specific for that condition (i.e. antivirals for influenza). In this sense, the same individual was first included in the denominator (positive for ILI even in the absence of ILI diagnosis in the respective field – data quality improvement recommendation) and in the numerator (using antivirals), thus this strategy was not intended to “overestimate” the proportion but to correct under-coding of ILL by busy general practitioners and improve data quality. In any case, of the total number of ILI cases identified in the database using this method was only 7% (n=6,922) Cases were classified based exclusively on the use of antivirals but not on a registered diagnosis (see Supplementary Figure 1 for details). Therefore, although the same procedure was not applied for antibiotic use (i.e. an antibiotic prescription can be used to treat conditions other than influenza), it is unlikely that the pattern observed over time could be explained by this methodological approach, as the percentage of individuals classified as an ILI case based only on the use of antivirals remained steady (7% in 2015, 7% in 2016, and 8% in 2017). This information has been incorporated in the manuscript (Page 6, Line 41).

1. Tu K, Manuel D, Lam K, et al. Diabetics can be identified in an electronic medical record using laboratory tests and prescriptions. J Clin Epidemiol 2011;64(4):431-5. doi: 10.1016/j.jclinepi.2010.04.007

2. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from the UK Biobank Stroke Outcomes Group. PLoS One 2015;10(10):e0140533. doi: 10.1371/journal.pone.0140533

3. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885

6. Re definition of use: 'when it was prescribed within 14 days of the original ILI diagnosis' (does this include prescriptions 14 days before as well, or only those prescribed within 14 days after the diagnosis? 'No other reasons for that prescription was identified in the database' is that also assessed during the entire 14 (or 28) day period?

A: Suggestion accepted. We included prescriptions within 14 days "after" the diagnosis, and the same period (14 days) was considered for "no other reasons". We have now clarified this information in the text.

7. How was clustering within practices/patients taken into account? Did the authors use a multi-level model using random or fixed effects or were robust standard errors calculated that took into account potential clustering effects?

A: We performed logistic regression with robust standard errors. We have now included this information in the Methods section (Page 8, Line 19).

8. Why is there a much lower number of encounters in 2017? Were some practices dropped from the analysis or is the data incomplete for 2017? Could the reason possibly bias the results?

A: As stated in the methods (Page 5, Line 52), the dataset included data collected between January 2015 and November 2017. However, as the influenza season in Australia occurs between June-October, it is unlikely that it biased the results as December corresponds to a period of interseason levels of ILI with few cases being reported according to other surveillance systems in the country (http://www.health.gov.au/internet/main/publishing.nsf/Content/cdi4104-f).

9. 'Thirdly, the characteristics of the practice were more strongly associated with the diagnosis of ILI and medication prescribing than patients' characteristics.' Is it possible to add the amount of deviance explained or some form of pseudo R2 (conditional and marginal in case of mixed effects model) by both groups of characteristics?

A: We appreciate your suggestion and added this information to the text (Page 14, Line 10).

10. Discussion. A comparison with the English data would also be helpful: https://academic.oup.com/jac/article/73/suppl_2/19/4841820. (see also comment 4). It has been noted before in England patients with comorbidity are more likely to receive antibiotics for ILI than patients without such comorbidities (28% vs 18%. When looking at same day prescriptions)

A: Suggestion accepted (Page 4, Line 49; Page 16, Line 50).

11. In addition, it would be helpful to discuss to what extent the gender difference for antibiotic prescribing has been observed in other studies focusing on ILI (and other conditions). For example, a recent study from England, also observed higher antibiotic prescribing for females for various conditions including ILI: https://bmjopen.bmj.com/content/8/2/e020203?cpetoc=&utm_source=TrendMD&utm_medium=cpc&utm_campaign=BMJOp_TrendMD-0

A: Suggestion accepted. Results regarding gender differences in antibiotic prescription for ILI treatment are discrepant, as some studies have found no association (Page 15, Line 26).

12. This paper found that there was more frequent prescribing in higher socioeconomic areas and states that this is in line with other countries. While this may be true for some countries, this correlation is in the opposite direction in other countries, such as the UK: https://www.bmj.com/content/351/bmj.h6117 & https://www.ncbi.nlm.nih.gov/pubmed/24176983. Moreover, as already discussed in this paper, correlations with ethnicity and probably also socioeconomic status is highly context dependent: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2751935/. The latter paper shows that practices with more white patients prescribe more antibiotics.

A: Suggestion accepted (Page 15, Line 57).

Comments by Referee 2:

Reviewer Name: Dominik Glinz

Institution and Country: University Hospital Basel, Switzerland

You have an interesting database, but you need to be careful with the interpretation of the results.

A: We are grateful for all the suggestions and comments provided by the reviewer.

You assess a year to year variation, you cannot conclude any trends.

A: We agree that it would be necessary a longer assessment period to consider oscillatory fluctuations over time. We now refer to our results as “higher” or “lower” across the text (or some synonym accepted in the literature) when comparing different years.

Your data is descriptive, you don't have to test significance for everything. A general rule, the more you test, the more significant p-values you get. But this doesn't makes sense and is wrong. You would need to adjust for multiple testing. But you don't need that your database itself is interesting enough. But you need to present it correctly.

A: We appreciate this comment. However, due to the large amount of information in the study (comparison according to independent variables and comparison across years), we haven’t included 95%CIs, which allow readers to identify those groups where these differences can be considered statistically significant. Therefore, to help readers identify these differences, we have opted to retain these p-values. We agree multiple comparisons in the same study increase the probability of type-1 error. However, such adjustments are recommended only when you have multiple outcomes and you assume they are not correlated (see Bland M, 2015. An Introduction to Medical Statistics - http://www-users.york.ac.uk/~mb55/intro/bonf.htm). In studies like ours where you assume tests will be highly correlated (i.e. series of observations over time or observational studies with different explanatory variables), multiple test adjustment such as the Bonferroni method are inappropriate as they are considered to be very conservative and may lead to missing real differences between groups. Furthermore, our study showed results that are consistent with patterns identified in other studies.

I did not check references, and STROBE checklist.

A: BMJ open requires all authors check the STROBE checklist before submission. Therefore, our paper follows the stablished requirements for presenting the study.

The discussion has to be redone after you have adapted the methods and results section. I suggest to have a careful read of the discussion after you have revised the manuscript.

A: We may have missed the point, but there was no any recommendation suggesting a change to the analysis or methods based on the comments by this reviewer. As previously stated, the inclusion or omission of the p-values would not affect the main conclusions and discussion in the original paper. Furthermore, the first reviewer did not suggest any analytical changes that could potentially affect our results/conclusions however some additional comments and references have been added in response to their suggestions.

Title:

- remove “trends”, your data is limited to three years, this is simply too short to call it trends. A trend is a general direction in which something is developing or changing.

- I suggest you call “antibiotic and antiviral” antimicrobials.

- Add design in title, please also consult the STROBE checklist.

- Rather describe the data source (MedicineInsight) than 4.5 Mio patients.

A: Suggestions accepted.

Page 2

line 10: Delete “open”, I don’t understand why this should be relevant, there is no intervention

A: Suggestion not accepted. This is not an intervention study but a cohort. It is therefore important to define the kind of cohort we have data on. In this case “an open cohort” is dynamic, meaning that members can leave or be added over time. Rothman gives the example of a state cancer registry. Subjects are continually added when they are diagnosed with cancer, so new subjects are continually added. Subjects can also leave the cohort by moving to a new state or dying” (http://sphweb.bumc.bu.edu/otlt/MPH-modules/EP/EP713_CohortStudies/EP713_CohortStudies_print.html). Also see “Rothman KJ, 2012. Epidemiology: An introduction”. Moreover, the same definition has been used in other papers with a similar methodology also published in BMJ Open (e.g. https://bmjopen.bmj.com/content/8/4/e020572 , https://bmjopen.bmj.com/content/5/3/e007825).

line 17: remove median age, but add % of children?

A: Suggestion partially accepted. We have included the information on the percentage of children, but also kept the median age of the sample, as this is important for comparison with other studies. See response to reviewer one.

line 28: entire results section, give total numbers instead of percentages

A: Suggestion not accepted. Presenting total numbers are not recommended in statistical or epidemiological terms (see Rothman KJ, 2012. Epidemiology: An introduction), as they do not allow comparison between years or with results from other published studies. Therefore accepting this recommendation would compromise interpretation by readers. Presenting both, absolute numbers and percentages would be also be inappropriate, as the former can be estimated based on the percentages and total numbers already shown in the table for each year. Therefore, we believe the results are appropriately presented.

line 36: what should be the causal relation of mental disease with ILI? This looks like you ran several tests for significancy and report significant finding, irrespective of there causal relationship.

A: All variables included in the study were selected based on theoretical frameworks and findings from previous studies. Mental health conditions, especially depression and anxiety, have been associated with higher antibiotic prescribing for acute respiratory infections (Mehta N, et al. Antibiotic prescribing in patients with self-reported sore throat. https://www.ncbi.nlm.nih.gov/pubmed/27999063), as already referred in our text. Furthermore, other studies have also shown that mental health can interfere in decisions GP's make when managing other health conditions (e.g. Voigt et al. Why do family doctors prescribe potentially inappropriate medication to elderly patients? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957869/; Smolders et al. Depressed and a co-morbid condition: more psychotropics prescribed! https://www.tandfonline.com/doi/full/10.1080/13814780701855724). These studies have shown that medical decisions are affected when doctors are under perceived patient pressure, so it can be part of the explanation. Therefore we believe that mental health should remain in the study as one of the variables for analysis.

Results and conclusion: you observed different ILI rates for the three years. Call it year-to-year variation. Most likely, this has affected prescribing patterns of these three years. ILI was higher in 2017, antiviral prescribing was higher (and not increased), antibiotic prescribing was lower (and not decreased). You need to rephrase carefully your results and conclusions.

A: We agree that it would be necessary a longer assessment period to consider oscillatory fluctuations over time. In any case, we opted for referring to our results as "higher" or "lower" across the text (or some synonym accepted in the literature) when comparing different years, except in our conclusion, when we explain that the results appear to be a trend to be confirmed with further investigations.

Page 3

Line 4: 4.2 million or 4.5?

A: The total number of patients in the MedicineInsight is 4.5 million, although 4.2 million had at least one encounter during the investigation period. We excluded "4.5 million" of the title to clarify the information.

Line 11: rephrase: the association of comorbidities with antimicrobial prescribing was assessed

A: We rewrote the sentence following the suggestion.

Line 16: what does "vary" mean? Vary between GPs? Regions? On day-to-day basis, depending on the GPs workload?! Please be more specific

A: Suggestion accepted. Data-recording quality may vary between and within GPs. This information has been incorporated into the manuscript.

Line 18: "can be" or were?

A: Suggestion accepted. We changed it to "could have been" to reflect the appropriate sense in this sentence.

Page 4

Line 30: Here you jump from influenza and antivirals to uncomplicated respiratory infections. Antibiotics are not recommendate because they have no benefit and cause antibiotic resistance. Financial cost shouldn't be the first reasoning.

A: We appreciate your comment and rewrote the sentence according to your suggestion (Page 4, Line 33).

Line 42: continue? You mean prescription rates are still high?

A: The information presented in the paragraph shows that studies conducted in the US, England and Australia in 2015 reported that between 18% and 85% of patients with uncomplicated respiratory infections were prescribed antibiotics.

Line 44: why are the number of US relevant for your publication? Delete

A: We disagree. One of the most important recommendations in papers like this is to provide current international evidence to support the need for a study and improve external validity of results. According to the information stated on the BMJ Open website, the introduction section should "Explain the rationale for the study and what evidence gap it may fill. Appropriate previous literature should be referenced, including relevant systematic reviews". In this case, that study and the paper from England suggested by reviewer 1 represent current data, pertinent for the topic, involve highly important studies in the field and are relevant to our study.

Line 48-50: unclear, what is the relation to bronchitis? Rephrase

Line 54: you didn't assess trends, rephrase

A: Suggestions accepted. We changed the sentences.

Page 5:

Line 33: some? To be clear just say: Routinely collected data includes ….

A: We replaced the sentence as requested.

Line 44: why "open"? it is not a intervention study…

A: As mentioned above, we believe there is a misunderstanding regarding the study design. This is an observational study and it is important to clarify that people could enter the cohort anytime during the whole period of study, just as detailed in the methods section.

Page 6

Line 3-4: this is the reason why you shouldn't include the number in the title, it depends on the definition…

A: We excluded the number in the title as suggested.

Line 9-19: this is unclear? Why is this under outcome? This describes your data source right? And how you prepared the data set, but not how you assessed the outcomes.

A: Suggestion accepted. The manuscript now includes two subtitles: Data extraction and Outcomes.

Line 9-42: what does this mean? The GP registered a diagnosis and in addition you search for other influenza specific terms within this database? Why was the diagnosis of the physician insufficient? Did you also search for spelling mistake? Which program did you use? Was there a systematic approach?

A: All information was extracted following a systematic process, as detailed in the methods section. Although GPs can record the diagnosis of ILI according to a medical coding system, they could also record synonyms of ILI (e.g. "influenza", "flu-like illness", "flu") or their symptoms (i.e. fever, cough and fatigue) as free text when registering the fields diagnosis and reason for encounter for each

consultation. Therefore to improve data quality and identify all possible cases, we prepared an extraction algorithm using the statistical software Stata using all these potential terms, and misspellings as well. The same algorithm was used to find ILI cases in different fields of MedicineInsight dataset. Secondary databases such as MedicineInsight are based on 'real world' information recorded by GPs into a health informatics system during the consultation. Therefore, its quality, accuracy, and completeness of recording may vary by clinician and health systems used in each general practice (i.e. non-mandatory fields, free-text for coding, system coding vocabularies). It is likely that this will result in some under-reporting of clinical information under the "diagnosis" field. For that reason, it has been widely recommended in the literature that the use of other fields such as reason for encounter, clinical measurements, or prescribed medications can be used to increase the accuracy of the information1-3, especially when the medication is specific for that condition (i.e. antivirals for influenza).

1. Tu K, Manuel D, Lam K, et al. Diabetics can be identified in an electronic medical record using laboratory tests and prescriptions. J Clin Epidemiol 2011;64(4):431-5. doi: 10.1016/j.jclinepi.2010.04.007

2. Woodfield R, Grant I, Group UKBSO, et al. Accuracy of Electronic Health Record Data for Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from the UK Biobank Stroke Outcomes Group. PLoS One 2015;10(10):e0140533. doi: 10.1371/journal.pone.0140533

3. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885

Line 29: fever alone is not influenza specific. So you searched for fever or whether GP has reported body temperature above 38C?

A: Yes, we agree and the text in the manuscript was reworded to avoid any misunderstanding (Page 6, Line 30). When the diagnosis of ILI was not reported as a diagnosis, the concomitant report of fever, cough and fatigue was used as indicative of ILI, as this is the definition used in Australia for surveillance purposes (Varghese et al. Epidemiology of viral respiratory infections in Australian working-age adults (20-64 years): 2010-2013. https://www.cambridge.org/core/journals/epidemiology-and-infection/article/epidemiology-of-viral-respiratory-infections-in-australian-workingage-adults-2064-years-20102013/F1026FC6CD310703CAB70FAF660D7D67). We searched for records of fever (diagnosis and reason for encounter) or body temperature ≥ 38 C° (in clinical measurements).

Did you count a patient as ILI patient if he received an antiviral but no influenza specific symptoms were reported by the physician? In how many cases? This might have led to increase number of prescribing rates, for instant if you have missed through influenza patient who did no receive antivirals…

A: As shown in our Supplementary Figure 1, a total of 6,922 ILI cases (7% of all ILI cases) were found only in the medication field and this percentage remained steady over the years. Thus, it is unlikely this decision biased the results (also see answer to reviewer 1). According to previous studies on influenza management (Hardelid et al. Prescribing of neuraminidase inhibitors for influenza in UK primary care since the 2009 pandemic. http://www.ncbi.nlm.nih.gov/pubmed/26364671 and Hooiveld et al. Prescription of antiviral drugs during the 2009 influenza pandemic: an observational study using electronic medical files of general practitioners in the Netherlands. https://doi.org/10.1186/2050-6511-14-55

https://bmcpharmacoltoxicol.biomedcentral.com/track/pdf/10.1186/2050-6511-14-55), the prescription of medication without a diagnosis of ILI commonly happens (up to 50% of prescriptions can be issued

to people without a record of ILI diagnosis). Therefore, this decision was made to improve data quality and accuracy in the identification of patients with ILI.

Line 54: antivirals should be prescribed within the first three days of symptoms… why did you choose 14 days?

A: We agree with the reviewer. Some doctors may delay the treatment until they get a laboratory confirmation, patients develop complications over time or present all symptoms of the disease, especially fever (Sopirala et al. Effect of fever on hospital presentation, diagnosis, and treatment in patients with H1N1/09 influenza, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4271823/). For these reasons, we considered the use of antivirals on the same day of diagnosis and within a period of 14 days after the first ILI diagnosis as the period to consider the patient was treated with that medication.

In your Chapter “Outcome”, you should explain the outcome. How was ILI exactly defined (you tried, but it is still not clear to me, see comments above). How was prescribing rate defined? How will you present summary measures? You describe this further below in statistical analysis, but there, you should describe the comparative methods (log regression and so…).

A: Suggestion accepted (Page 7, Line 13).

Page 7

Line 41-44: why would you include mental health? Influence medication prescription? What does this mean?

A: We have already provided an explanation for this decision previously and the paper already includes two references to support such decision. Due to the limited number of words allowed by the journal, we decided not to expand the explanations regarding this issue.

Line 48-51: move to outcomes

A: Suggestion accepted.

Page 8

Line 45: major cities, remote, does this sum up?

A: The categories used to identify rurality/remoteness follow the current classification used by the Australian Bureau of Statistics (see http://www.abs.gov.au/geography), so all individuals are classified in some of these categories.

Line 48: rather present age groups the median

Line 50: why you don’t stratify by comorbidities for instance for immunosuppressed patients?

A: We appreciate your comments, and we added information about age groups. However, the stratification according to the use of immunosuppressive drugs is out of the scope of this paper.

Page 9

Line 3: this is not surprising, isn’t it? Patients with comorbidities and mental disease have in general a closer relation to their treating physicians. They see their GP in regular intervals. And the gap to seek help is lower. Discuss.

A: Suggestion accepted. We have highlighted in the discussion section the use of “consultation” rates may lead to misinterpretation of the relationship between comorbidity and ILI (Page 14, Line 20).

Line 10: 63% is misleading the readers! What is the difference between 2.3, 2.7 or 4.4 ILIs per 1000 consultations?! Present only absolut numbers and state the ILI rate was higher in 2017, but don't present the year to year variations as 63% increase.

Line 30: no, it did not decrease, it was lower in 2017, rephrase

A: Suggestion not accepted. Results from epidemiological investigations can be presented as absolute differences, ratios, or proportional differences between groups (Rothman KJ, 2012. Epidemiology: An introduction). In this sense we believe the results are appropriately presented.

Line 33: lower compared to what?

A: We included information about the comparison group in the sentence.

Table 1:

Superscript a: it doesn't makes sense to test significant difference if compared to total because the compared group is part of the total. Only test what makes sense and is actually relevant. In your case, this is only descriptive, no need for testing.

Superscript b: what test was used?

Superscript c: can you display the different co-morbidities?

A: Suggestion not accepted. This recommendation is related to the third commentary on the use of p-values and the explanations for such decisions were previously detailed. In fact, comparison between years for consultation rates or medication use did not include a comparison with the "overall" total, as this would be inappropriate. Furthermore, we have included variables based on a theoretical framework, thus it would be inappropriate to include/exclude variables based on the statistical significance. Including all comorbidities would extend the length of the table, this affecting readability of the manuscript. However, we can submit a supplementary table with all comorbidities analysed individually if the editors consider it is relevant.

Page 11

Line 5: describe antivirals only prescription rate, antibiotic only prescription rate and antiviral in combination with antibiotic prescription rate

A: Suggestion not accepted. We appreciate your comments. However, our main objective is to compare antiviral and antibiotic prescribing for influenza according to patient and practice's characteristics over the three years, we only include results on the use of both medications together to allow comparison with previous studies, but this is not part of our main objective. We believe the results are clearer as they are presented.

Line 8: it did not increase, it is higher. Adapt throughout your manuscript! And you can't calculate percentage on percentages! This is misleading in this context!!! The prescription rate was higher in 2017 than in 2015, 29.7% vs. 20.6%

A: Suggestion partially accepted. As previously detailed, epidemiological results can be presented as absolute differences, ratios, or proportional differences between groups (Rothman KJ, 2012. Epidemiology: An introduction). Other studies in this field published in BMJ Open and other journals have used similar methods to present their results. In any case, we have revised the manuscript to avoid words indicating trends.

Table 2

You have to display three groups: describe antivirals only prescription rate, antibiotic only prescription rate and antiviral in combination with antibiotic prescription rate. Redo table.

A: Suggestion not accepted. As mentioned above, our main objective is to show results for antivirals and antibiotics separately. We have included results on the use of both medications only for comparison/discussion purposes.

The same comment to the superscript account here as for Table 1. Only test what makes sense and is actually relevant. In your case, this is only descriptive, no need for testing.

A: Suggestion not accepted. See previous answer regarding the use of tests for statistical significance.

I haven't read the discussion, the authors need first to adapt their finding and interpretations.

After this major revision, including the Discussion, I will give my inputs to the Discussion.

A: We may have missed the point, but there was no any recommendation suggesting a change to the analysis or methods based on the comments by this reviewer. As previously stated, the inclusion or omission of the p-values would not affect the main conclusions and discussion in the original paper. Furthermore, the first reviewer did not suggest any analytical changes that could potentially affect our results/conclusions however some additional comments and references have been added in response to their suggestions.

General questions:

- Are antivirals reimbursed by health insurance?

A: Anti-influenza antivirals are not available on the Pharmaceutical Benefit Scheme in Australia. Only private prescriptions are available, and the cost in a popular drugstore is AUD$43.39 for Tamiflu 75mg for 10 capsules and AUD$47.39 for Relenza 5mg Rotadisc 20.

- Trial registry number? CT.gov or so?

A: We do not understand the reason for requesting such kind of information. As stated in the paper, this is an observational study and not a randomized controlled trial.

- Do you have information on which influenza strain was predominant in each year

A: We do not have access to information on influenza strains in this dataset and the study did not intend to ascertain the answer.

VERSION 2 – REVIEW

REVIEWER	Koen Pouwels Public Health England, UK
REVIEW RETURNED	23-Nov-2018

GENERAL COMMENTS	I only have one additional minor suggestion:

	1. Could the total number of cases (and for each year) be added to table 2? This makes it much easier to make calculations with the percentages.

REVIEWER	Dominik Glinz Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel
REVIEW RETURNED	28-Nov-2018

GENERAL COMMENTS	The authors have addressed my points and carefully justified. Most of the reasoning I can accept and I thank the authors for their explanations. Also, I feel the manuscript is much clearer now. However, there are still some point you should address and revise. General issues: Statistics: in the Tables they report differences between time points, but it seems not that the authors formally tested whether 2017 was higher than 2016 or 2015. I agree that it seems obvious that 2017 was different, but it would be wrong to put such interpretation when not formally tested. The authors need to sprecify what was tested exactly. Table should be revised as suggested below. Figure 1 is apparently wrong (vaccine rates?!) Conclusion need to be revised, see suggestion below. :: Page 2, line 49: You repeat the results in the first sentence of the conclusions and in the following you repeat the results in another form. Please provide an interpretation of your results. What is the key message of your Manuscript? My suggestion for your conclusion (and please see my comment further below to understand how I come up with this conclusion): “Our observation suggest that flu intensity (here described as an increased number of ILI consultation) might (I use subjunctive because you did not assess causality) have affect the prescribing pattern of antivirals and antibiotics. Page 5 Line 31: why did you not use the total number of 656 GPs. You might explain here line 53: personal preference, but you might consider to write “January 2015” instead of January/2015 Line 58: in case of double encounter, under which criteria you decided to delete one of them. Page 6, line 24: Introduce the abbreviation GP further up in the text. Page 7, line 7: “no other reason” Does this mean, within the identified ILI population receiving antibiotics, you then actively searched for other reasons? What would then you criteria be? This should be further elaborated. Line 15: I suggest to remove the brackets for “for any reason”. Page 8, line 34-38: I am not sure whether I understand this sentence correctly. There is twice ILI diagnosis mentioned. Could you rephrase. Page 9,

	Line 21: please add also children below 18 years, How many were above 65ys? Line 39, The authors insist to present difference of ILI consultations in 2017 as 63% higher. In the point-by-point respone they refer to the introduction chapter by Rothman. As trained and experienced epidemiology I ignore this hint. However, I insist that this relative increase is misleading, but I suggest a compromise, could you present the relative increase of 63% together with the absolute difference you have observed (1.7 per 1000 consultations) as a compromise. Line 45, please specify “per 1000 consultations” Table 1: Move the total numbers either up to the first row (example in brackets behind the year like 2015 (31,882 = n of ILI cases), or below the last row. Add information which test was applied, the table should stand alone. Again, I don’t see the need to test each raw because the total is already significant (although the significance was only described in the text and could be added in the table two). The total was higher in 2017 than in the years before. Hence, in such a large database, as you have, you should expect that it will be different for each variable. It would be surprised if not. Putting b into the last column is misleading, because “fast readers” might interpret that 2017 is different from 2015 and 2016, but “it is actually “difference between years”. Put the b to the variable names in the first column. Table 2: Again, I don’t see the need to test each raw. The total was higher in 2017 than in the years before. Hence, in such a large database, as you have, you should expect that it will be different for each variable. It would be surprised if not. Putting b into the last column is misleading, because “fast readers” might interpret that 2017 is different from 2015 and 2016, but “it is actually “difference between years”. Put the b to the variable names in the first column. Page 13, line 59: “Firstly,…” okay, but this was not you aimed for to find. This is an observation you might discuss as a strength (but only if the Australien surveillance system did not base its observations on the same database as you did. Page 14, line 5: “secondly,…” No, you are assuming again a trend! The only thing you know is: ILI was more frequent in 2017, with more antiviral use, but antibiotics were less frequently prescribed. There are seasonal difference, therefore you can not conclude that there was a change. It was just different. This is also a question of causality, but this you can’t answer with you information from your database. Line 9: “thirdly,…” put the results to the results section. Add to the methods how you assessed the differences between practice and patient characteristics. Add results in the results section. Mention it as aim. Although, in epidemiology it is well known that socioeconomic aspects are very strong drivers, and I don’t see the need of testing it here, seems to be out of your scope. I would summarize your findings: firstly, ILI was more frequent in 2017, with more antiviral use, but antibiotics were less frequently prescribed. Secondly, socioeconomic/regional and comorbidities (chronic medical conditions and mental health problems) are associated with higher ILI consultatinos.

	Page 16, line 54: a strength would be that your results are consistent with other surveillance systems in Australia, you may add this Page 17, line 5, is it possible that you overestimated the antiviral treatment? Line 30: do you intend to assess this trend? If not, then delete sentence. You observed a difference of ILI intensity and this affected the prescribing pattern. From your data I would not conclude that in the next year more antivirals will be prescribed (except you change guidelines…) Figure 1: represents the vaccine rate and not ILI consultation. Please add correct figure

VERSION 2 – AUTHOR RESPONSE

Comments by Referee 1: Koen Pouwels

1. Could the total number of cases (and for each year) be added to table 2? This makes it much easier to make calculations with the percentages.

Authors: Suggestion accepted. We included the information in the table.

Comments by Referee 2: Dominik Glinz

The authors have addressed my points and carefully justified. Most of the reasoning I can accept and I thank the authors for their explanations. Also, I feel the manuscript is much clearer now. However, there are still some point you should address and revise.

General issues: Statistics: in the Tables they report differences between time points, but it seems not that the authors formally tested whether 2017 was higher than 2016 or 2015. I agree that it seems obvious that 2017 was different, but it would be wrong to put such interpretation when not formally tested. The authors need to specify what was tested exactly. Table should be revised as suggested below. Figure 1 is apparently wrong (vaccine rates?!). Conclusion need to be revised, see suggestion below.

A: We appreciate your comments and changed the text according to your suggestions, as specified in each answer below.

We would like to be clear that we decided to present the results for antibiotic and antiviral prescribing for each year in the results and abstract. We have not used the term “trend” and because this is one of main findings, we hope the reviewer understands why this is important to include. “Antiviral prescribing increased from 20.6% in 2015, to 23.7 in 2016 and 29.7% in 2017, while antibiotic prescribing decreased from 30.3% to 28.0% and 26.7%, respectively ($p<0.05$ in both cases).” Page 2, Line 32.

We have ‘formally tested’ these differences. “Logistic regression models were also used to test differences in ILI rates and medication use between 2015 and 2017 in each category of the explanatory variables.” Page 8, Line 34.

Page 2, line 49: You repeat the results in the first sentence of the conclusions and in the following you repeat the results in another form. Please provide an interpretation of your results. What is the key message of your Manuscript? My suggestion for your conclusion (and please see my comment further

below to understand how I come up with this conclusion): “Our observation suggest that flu intensity (here described as an increased number of ILI consultation) might (I use subjunctive because you did not assess causality) have affect the prescribing pattern of antivirals and antibiotics.

A: Suggestion partially accepted. We agree that in years when infection with influenza is common and the illness is severe that prescribing patterns may change. Perhaps due to heightened media reports and health warnings by Departments of Health. This is somewhat supported by the results for 2017 in Western Australia. However, it does not explain the differences between 2015 and 2016 that were relative similar in flu “intensity”. Clearly we need more data, which we are collecting now. We have re-written our conclusion focusing on the importance of targeting high-risk individuals when managing ILI cases with antivirals.

Page 5 Line 31: why did you not use the total number of 656 GPs. You might explain here

A: The total number of 656 practices included all general practices with any data in the MedicineInsight database. However, to ensure high quality data, practices must follow acceptability criteria for inclusion in analyses or extracts. Only practices established for at least two years before the analysis period and those which had no interruptions of six weeks or more in practice data were included in data extraction. We included this information in the Sample Selection.

line 53: personal preference, but you might consider to write “January 2015” instead of January/2015

A: Suggestion accepted.

Line 58: in case of double encounter, under which criteria you decided to delete one of them.

A: We saved all information regarding both encounters (reason for encounter, diagnosis, medication) in only one encounter and deleted the duplicate. We added a sentence to the Sample Selection to explain it.

Page 6, line 24: Introduce the abbreviation GP further up in the text.

A: Suggestion accepted.

Page 7, line 7: “no other reason” Does this mean, within the identified ILI population receiving

antibiotics, you then actively searched for other reasons? What would then you criteria be? This should be further elaborated.

A: Suggestion accepted. We included a sentence in Data Extraction explaining that any illness requiring the use of antibiotics 1, such as pneumonia, streptococcus infection, bacterial infection, chronic sinusitis, urinary tract infection and cholecystitis, triggered a negative categorisation for ILI treatment.

1 Antibiotic Expert Groups. Therapeutic Guidelines: Antibiotic. Melbourne: Therapeutic Guidelines Limited 2014.

Line 15: I suggest to remove the brackets for “for any reason”.

A: Suggestion accepted.

Page 8, line 34-38: I am not sure whether I understand this sentence correctly. There is twice ILI diagnosis mentioned. Could you rephrase.

A: Suggestion accepted.

Page 9, Line 21: please add also children below 18 years, How many were above 65ys?

A: Suggestion accepted.

Line 39, The authors insist to present difference of ILI consultations in 2017 as 63% higher. In the point-by-point response they refer to the introduction chapter by Rothman. As trained and experienced epidemiology I ignore this hint. However, I insist that this relative increase is misleading, but I suggest a compromise, could you present the relative increase of 63% together with the absolute difference you have observed (1.7 per 1000 consultations) as a compromise.

A: Suggestion accepted.

Line 45, please specify “per 1000 consultations”

A: Suggestion accepted.

Table 1: Move the total numbers either up to the first row (example in brackets behind the year like 2015 (31,882 = n of ILI cases), or below the last row. Add information which test was applied, the table should stand alone. Again, I don’t see the need to test each raw because the total is already significant (although the significance was only described in the text and could be added in the table two). The total was higher in 2017 than in the years before. Hence, in such a large database, as you have, you should expect that it will be different for each variable. It would be surprised if not. Putting b into the last column is misleading, because “fast readers” might interpret that 2017 is different from 2015 and 2016, but “it is actually “difference between years”. Put the b to the variable names in the first column.

A: Suggestion partially accepted. We included information about the test performed and move the ‘b’ to the first column, but we believe the clearer way to show the total number of ILI cases is still in the last row before the total. We also added it to the second table as requested by the other reviewer.

Table 2: Again, I don’t see the need to test each raw. The total was higher in 2017 than in the years before. Hence, in such a large database, as you have, you should expect that it will be different for each variable. It would be surprised if not. Putting b into the last column is misleading, because “fast readers” might interpret that 2017 is different from 2015 and 2016, but “it is actually “difference between years”. Put the b to the variable names in the first column.

A: Suggestion accepted.

Page 13, line 59: “Firstly,…” okay, but this was not you aimed for to find. This is an observation you might discuss as a strength (but only if the Australian surveillance system did not base its observations on the same database as you did.

A: Suggestion accepted.

Page 14, line 5: “secondly,…” No, you are assuming again a trend! The only thing you know is: ILI was more frequent in 2017, with more antiviral use, but antibiotics were less frequently prescribed. There are seasonal difference, therefore you can not conclude that there was a change. It was just different. This is also a question of causality, but this you can’t answer with you information from your database.

A: Suggestion accepted.

Line 9: “thirdly,…” put the results to the results section. Add to the methods how you assessed the differences between practice and patient characteristics. Add results in the results section. Mention it as aim. Although, in epidemiology it is well known that socioeconomic aspects are very strong drivers, and I don’t see the need of testing it here, seems to be out of your scope.

I would summarize your findings: firstly, ILI was more frequent in 2017, with more antiviral use, but antibiotics were less frequently prescribed. Secondly, socioeconomic/regional and comorbidities (chronic medical conditions and mental health problems) are associated with higher ILI consultations.

A: Suggestion partially accepted. We moved some sentences from the Discussion to Methods and Results according to your suggestion, as well as rephrased the main findings. However we maintained four main topics as it seemed appropriate to discuss some points in separate sentences, such as the association between comorbidities with lower ILI consultation rates, which demanded further explanation to clarify the finding.

Page 16, line 54: a strength would be that your results are consistent with other surveillance systems in Australia, you may add this

A: Suggestion accepted.

Page 17, line 5, is it possible that you overestimated the antiviral treatment?

A: Considering antivirals were searched for specific brand names and medicine active ingredients which are specific for ILI treatment, it is unlikely we overestimate their use. Although MedicineInsight is based on information recorded by GPs during the consultation and it can result in some under-reporting of clinical information such as diagnoses or reasons for encounter (ILI diagnosis, for instance), our ILI results are consistent when compared to other surveillance systems.

Line 30: do you intend to assess this trend? If not, then delete sentence. You observed a difference of ILI intensity and this affected the prescribing pattern. From your data I would not conclude that in the next year more antivirals will be prescribed (except you change guidelines…)

A: We indeed intend to assess the patterns in ILI diagnosis and prescriptions in future years. This was our first attempt to assess the consistency of data extracted from MedicineInsight in order to use the dataset as an ILI surveillance system in Australia. Whilst we acknowledge that ILI intensity may affect prescribing patterns, we cannot assume causality. For instance, ILI intensity does not explain changes in prescribing between 2015 and 2016. There may be many other factors that could affect prescribing by GPs and we have mentioned them in the discussion. We also indicate that data from future years will be valuable/necessary to confirm if a trend emerges.

Figure 1: represents the vaccine rate and not ILI consultation. Please add correct figure

A: We apologize for the mistake and corrected it.