

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study
AUTHORS	Hashimoto, Hideki; Matsui, Hiroki; Sasabuchi, Yusuke; Yasunaga, Hideo; Kotani, Kazuhiko; Nagai, Ryoza; Hatakeyama, Shuji

VERSION 1 - REVIEW

REVIEWER	Katherine Fleming-Dutra, MD Centers for Disease Control and Prevention, Atlanta, Georgia, United States
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	<p>Overall, this is a nice paper describing outpatient antibiotic use by class, diagnoses, and patient and facility characteristics in a population of national health insurance beneficiaries in a prefecture in Japan. The authors do a very nice job of interpreting their results to identify clear targets for outpatient antibiotic stewardship in this population. However, additional clarifications on the data source, the population included, and how these findings relate to Japanese recommendations would allow readers to better interpret the results of this nice study.</p> <ol style="list-style-type: none">1. Additional description of the population the included is needed. What percentage of the Kumamoto prefecture has national or late elder's health insurance? The authors should include a traditional table 1 with a description of the population. Are there any biases based on who is eligible for or enrolls in this health insurance that the reader should be aware of?<ol style="list-style-type: none">a. On page 3, line 38, did the individuals have to "join" this insurance during April 2012-March 2013, or just be beneficiaries during that time? Please clarify.2. I was actually unsure until the discussion as to whether these prescriptions only were for outpatients or included inpatient antibiotic use. This should be clearly defined in the abstract, objective, methods, and results. It becomes especially confusing when you discuss differences among visits to clinics versus hospitals of various sizes. Does this mean free-standing clinics versus hospital-based clinics? Please clarify this throughout the manuscript.3. It would be very useful to include rates of prescriptions per 1000 population, as other countries have done, to put these raw numbers into context.4. Also, is the main outcome measure the number of patients who had any antibiotic prescriptions or the total number of antibiotic prescriptions per enrollee? I can't tell. Based on the first sentence of the results, I think this means that the authors captured 87 antibiotic prescriptions per 1000 enrollees. That is very low, but contrast in the U.S. it is 830 per 1000 population, versus Sweden
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	<p>which is around 300 per 1000 population. Alternatively, the authors may be trying to say that 8.7% of people received at least one antibiotic prescription during this time frame, but again I can't tell. Please check that these numbers are right and then clarify the descriptions in the paper. If it is that low, please describe why—is it a data issue? How does this compare to other Japanese studies?</p> <p>5. How did you link the antibiotics to the diagnoses? Was there a prescriber identifier on the prescription and visit or did you link it via a time window? Please describe those methods in more detail.</p> <p>6. Also, do you have any ideas why only 65% of prescriptions were able to be linked to a visit? If this is correct, it should be addressed in the discussion and limitations.</p> <p>7. It would be very helpful to put the selection patterns and percent prescribing by condition into context of the national guidelines—how well are they being followed?</p> <p>a. For example, the authors state that quinolones are not recommended for children under 10, which makes sense. However, it looks like there were basically the same number of quinolone prescriptions in children <10 years old as penicillins. Do the authors have any hypotheses why?</p> <p>8. All of the tables would benefit from adding percentages to the rows with total numbers of prescriptions. I would favor % of each class by age group or diagnosis (e.g. column percents in Tables 1 and 2). It would help tremendously with the interpretation.</p>
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REVIEWER	Annelies Colliers University of Antwerp, Belgium
REVIEW RETURNED	28-Sep-2018

GENERAL COMMENTS	<p>Thank you for the opportunity to review this article.</p> <p>Line 35. The aim of your study is not to reduce inappropriate AB use, but to guide future interventions to reduce inappropriate prescribing.</p> <p>Line 43 The percentages with your diagnoses, unclear on what they mean? Do you mean of all oral antibiotics prescribed?</p> <p>Line 55 What do you mean by small-sized institution groups?</p> <p>Line 93. You use a claims database, however it also consists of diagnoses. So it is also dependent on registrations? Who registers the contacts (physicians?)? How do they do that? What about missing data?</p> <p>Introduction or discussion: organization of outpatient care In Europe almost 80 % of antibiotics are prescribed in ambulatory care. How is the Japanese health care system organised? Is there a strong ambulatory care, are there general practitioners? Is it divided in first line, or also secondary and third line care? What type of physicians are included in your study? You speak about outpatients (line117). Does the patient choose freely where to go?</p>
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Are there guidelines on antibiotic prescribing? National campaigns? Feedback for physicians? Interventions?

Line 101

What is the population of Japan?

Line 102-105

Are the patients in the database representative for the general population?

Line 131

Penicillin. What about broadspectrum penicillins such as amoxiclav? There is an important difference in using narrow spectrum or broad-spectrum.

Line 141

Why did you choose these ones, and not UTI or skin infections?

Line 159

Does this mean 682 822 unique patients. What if they visited more than once in one year?

Line 162

See remark on organization of outpatient care.

Line 169

Why was it not possible to link all antibiotic prescriptions with diagnosis? See comment on registering? Do all physicians make use of an electronic medical file? How is your registration done?

Line 171

It would be more interesting to do it the other way around, like in table 5. To look at the consults with for example bronchitis, and to see if there was an antibiotic prescribed, and which one? Because now it says something about the prevalence of diagnoses, and not on the prescribing quality.

Example: Adriaenssens N, Coenen S, Tonkin-Crine S, et al. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. *BMJ Qual Saf* 2011;20:764–72

22 % of prescriptions was made for viral URI. 45 % with viral URI got an antibiotic prescription. That really astonishes me. Please comment on this or state an hypothesis in the discussion.

Line 181

I suppose if you say male gender was associated with more antibiotic prescription, you mean the patient and not the prescriber? Why is this?

Do you have gender information on the prescriber?

Line 182 -186

The results on antibiotic prescribing and age are something unexpected for me. I would have expected more in the children's age group and the elderly; Please comment

Line 191

Prescribing antibiotics for gastrointestinal infections seems common in Japan? What about guidelines? Why is there unadherence?

Line 208

See previous comment on broad spectrum penicillin's.

Line 224.

It is indeed suprisingly that so many antibiotics are prescribed for viral URI, but not rally that it was the most frequent infection associated with AB prescribing because I expect that the incidence was really high.

Line 250

I think you have already found some interesting targets to focus on for future interventions. Please state and summarize the implications or suggestions for practice/further research of your study.

Line 257

For your statement of type of prescribers you refer to an American study. Is this the same in Japan?

Line 272

Do you have an hypothesis why this is different in Japan?

Line 281

Out-of-hour , should be out-of-hours

Line 281

What are non-physician practitioners? Can they prescribe antibiotics?

Line 282

Is black race relevant for Japan? Which minorities group are there in Japan? Is there relationship with quality of care?

Line 285

"we found no follow-up visit ..." I'm not sure I understand what you mean by this. Please explain.

Discussion

I really miss some information on the health care context in Japan.

Who are your prescribers in this study, what type of physicians? Are some prescribers "better" prescribers than others?

Are there any qualitative studies available in Japan that could explain these results? With patients or with physicians? Why are so many antibiotics prescribed for viral URI and gastro-intestinal infections?

There are much more interesting results in the tables than you discussed in your article.

Table 1

What about amoxicillin with b lactamase inhibitor?

	<p>Table 3 Please explain or comment: Bacterial pneumonia only 45,7% antibiotic prescribing. I would expect almost 100%? Same for PID and urinary tract infection Influenza, almost 38% antibiotic prescribing.</p> <p>Table 4 What is 'clinic". Only ambulant care? Something like general practice?</p> <p>Table 5 What is your denominator in your percentage of antibiotic prescription</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer reports:

Katherine Fleming-Dutra, MD (Reviewer 1):

Overall, this is a nice paper describing outpatient antibiotic use by class, diagnoses, and patient and facility characteristics in a population of national health insurance beneficiaries in a prefecture in Japan. The authors do a very nice job of interpreting their results to identify clear targets for outpatient antibiotic stewardship in this population. However, additional clarifications on the data source, the population included, and how these findings relate to Japanese recommendations would allow readers to better interpret the results of this nice study.

1) Additional description of the population the included is needed. What percentage

of the Kumamoto prefecture has national or late elder's health insurance? The authors should include a traditional table 1 with a description of the population. Are there any biases based on who is eligible for or enrolls in this health insurance that the reader should be aware of?

Author's response: In 2012, 780,000 residents (44% of the population living in Kumamoto) were beneficiaries of the national or late elder's health insurance.

The national health insurance system is for self-employed or unemployed people, and the late elder's health insurance is for individuals over 75 years old. Employed workers and their dependents are not included. Therefore, insurance beneficiaries of this study are older than the general Japanese population. We added this information to the Methods section (lines 102–105 and 111–113).

Regrettably, we could not present a traditional Table 1 because the detailed information (such as sex and age composition) of the population included in this study was not available.

a. On page 3, line 38, did the individuals have to "join" this insurance during April 2012-March 2013, or just be beneficiaries during that time? Please clarify.

Authors' response: The individuals were just beneficiaries of these insurance systems during April 2012–March 2013. We have modified the sentences in lines 39 and 111.

2) I was actually unsure until the discussion as to whether these prescriptions only were for outpatients or included inpatient antibiotic use. This should be clearly defined in the abstract, objective, methods, and results.

Author's response: In accordance with the reviewer's comment, we have added the word "outpatient" in the revised manuscript (lines 41, 53, 59, 93, and 169).

3) It becomes especially confusing when you discuss differences among visits to clinics versus hospitals of various sizes. Does this mean free-standing clinics versus hospital-based clinics? Please clarify this throughout the manuscript.

Authors' response: As the reviewer indicated, "hospitals" indicates "hospital-based clinics". Similarly, "clinics" indicates "free-standing clinics". We have modified the information in the manuscript (lines 51, 177–179, 199–201, and 210–212).

4) It would be very useful to include rates of prescriptions per 1000 population, as other countries have done, to put these raw numbers into context.

Authors' response: We thank the reviewer on this point. Accordingly, we have added the information on rates of antibiotic prescriptions per 1000 population to the manuscript (lines 42 and 170–171). Unfortunately, we cannot calculate the age and sex-standardized prescription rate because information about age and sex compositions of the enrollees are not available in this study: We are now investigating in this point in another claims database.

5) Also, is the main outcome measure the number of patients who had any antibiotic prescriptions or the total number of antibiotic prescriptions per enrollee? I can't tell. Based on the first sentence of the results, I think this means that the authors captured 87 antibiotic prescriptions per 1000 enrollees. That is very low, but contrast in the U.S. it is 830 per 1000 population, versus Sweden which is around 300 per 1000 population. Alternatively, the authors may be trying to say that 8.7% of people received at least one antibiotic prescription during this time frame, but again I can't tell. Please check that these numbers are right and then clarify the descriptions in the paper. If it is that low, please describe why—is it a data issue? How does this compare to other Japanese studies?

Author's response: Our main outcome measure was the total number of visits with antibiotic prescriptions. We have modified the expression in the manuscript to clarify this point (lines 41 and 169–191). We have calculated rates of antibiotic prescriptions per 1000 population (in accordance with point #4 above) and have added the information (lines 42 and 170–171). In this study, the rate of antibiotic prescriptions was 860 per 1000 population, which is comparable to the US study.

6) How did you link the antibiotics to the diagnoses? Was there a prescriber identifier on the prescription and visit or did you link it via a time window? Please describe those methods in more detail.

Author's response: We linked the antibiotics to the infectious diagnoses in each patient's claims when both the code of antibiotics and the code of diagnoses were recorded in the same month. We have added this information to the manuscript (lines 145–147).

7) Also, do you have any ideas why only 65% of prescriptions were able to be linked to a visit? If this is correct, it should be addressed in the discussion and limitations.

Author's response: We appreciate the reviewer's comment on this point. Because we could not capture follow-up visit data of a single illness episode, antibiotics were linked to infectious diseases only when antibiotics were prescribed at the first visit for an illness episode in this study. In addition, approximately 3–5% of medical claims that included diagnostic codes and 0.1% of pharmacy claims that included prescription (medication) codes were registered in non-digital format. As non-digital insurance claims were not included in our database, approximately 3–5% of antibiotic prescriptions were not linked to diagnoses. We have added this information to the Discussion section (lines 315–322).

8) It would be very helpful to put the selection patterns and percent prescribing by condition into context of the national guidelines—how well are they being followed?

Author's response: We agree that the reviewer's suggestion would be valuable. We are now analyzing a more comprehensive claims database to investigate this point and intend to report it in a later paper.

a. For example, the authors state that quinolones are not recommended for children under 10, which makes sense. However, it looks like there were basically the same number of quinolone prescriptions in children <10 years old as penicillins. Do the authors have any hypotheses why?

Author's response: This may be because that the oral fluoroquinolone tosufloxacin is approved for children to treat otitis media and pneumonia in Japan. Since the approval of quinolones in 2010, despite the recommendation to prescribe quinolones carefully for children, many physicians prescribed tosufloxacin to children in expectation of clinical effectiveness. We have added this information to the Discussion section (lines 233–238).

9) All of the tables would benefit from adding percentages to the rows with total numbers of prescriptions. I would favor % of each class by age group or diagnosis (e.g. column percents in Tables 1 and 2). It would help tremendously with the interpretation.

Author's response: Accordingly, we have added percentages to the rows in Tables 1, 2, and 3.

Annelies Colliers (Reviewer 2)

Thank you for the opportunity to review this article.

1) Line 35.

The aim of your study is not to reduce inappropriate AB use, but to guide future interventions to reduce inappropriate prescribing.

Authors' response: Per the reviewer's suggestion, we have modified the sentence in the revised manuscript (lines 35–36).

2) Line 43

The percentages with your diagnoses, unclear on what they mean? Do you mean of all oral antibiotics prescribed?

Author's response: The percentages indicate the proportion of each diagnosis to all diagnoses with antibiotic prescription.

3) Line 55

What do you mean by small-sized institution groups?

Author's response: Small-size institutions include free-standing clinics and small-scale hospital-based clinics. We modified the term "small-sized" to "small-scale" throughout the revised manuscript (lines 51, 57, 178, 179, 198–211, and 330).

4) Line 93.

You use a claims database, however it also consists of diagnoses. So it is also dependent on registrations? Who registers the contacts (physicians)? How do they do that? What about missing data?

Author's response: As the reviewer stated, diagnoses in the medical claims are dependent on registrations. At the end of each month, claims are registered from each medical facility. Most were registered in digital format, but a few medical claims are registered in non-digital format (approximately 3–5% of the whole claims) and are thus missing in the database. Diagnoses on the claims were recorded by physicians of the medical facility. We added this information to the Methods and Discussion section (lines 118–120 and 319–322).

5) Introduction or discussion: organization of outpatient care

In Europe, almost 80 % of antibiotics are prescribed in ambulatory care.

How is the Japanese health care system organised? Is there a strong ambulatory care, are there general practitioners? Is it divided in first line, or also secondary and third line care? What type of physicians are included in your study? You speak about outpatients (line117). Does the patient choose freely where to go?

Author's response: In Japan, as stated in lines 77–81, oral antibiotics prescribed mainly in ambulatory care account for more than 90% of the total antibiotic consumption. Patients can go to any clinic (either free-standing or hospital-based) of their choice. All physicians working at any free-standing or hospital-based clinic can provide primary care and prescribe antibiotics. Therefore, our study includes any type of physician. We have added this information to the Methods section (lines 105–107).

6) Are there guidelines on antibiotic prescribing? National campaigns? Feedback for physicians? Interventions?

Author's response: The Japanese guideline concerning antimicrobial stewardship was adopted in 2017. We stated the guideline in the manuscript (lines 96–97).

7) Line 101

What is the population of Japan?

Author's response: The population of Japan was estimated to be 127 million. We have added this information to the revised manuscript (line 101).

8) Line 102-105

Are the patients in the database representative for the general population?

Author's response: The participants in this study are self-employed or unemployed people including retired people (please also see our responses to Reviewer #1, point 1). Employed workers and their dependents are not included. Therefore, patients in the database may be older than the general population of Japan. We have added this information to the revised manuscript (lines 101–107 and 112–113). The patients in this study are not necessarily representative of the general population because detailed information (such as sex and age composition) of the population included in this study was not available. We are now analyzing a more comprehensive claims database to investigate this point and intend to report it in a later paper.

9) Line 131

Penicillin. What about broad-spectrum penicillins such as amoxiclav? There is an important difference in using narrow spectrum or broad-spectrum.

Author's response: We appreciate the reviewer's interest in additional information on penicillin. However, because the proportion of penicillins to all antibiotics was low in Japan, we extracted broad-spectrum penicillins and narrow-spectrum penicillins together from the database in this study. We

therefore wish to retain the original text on this point. Instead, we have deleted the sentence "penicillin, a representative narrow-spectrum antibiotic" (line 221).

10) Line 141

Why did you choose these ones, and not UTI or skin infections?

Author's response: We focused on acute respiratory tract infections and gastrointestinal infections because these infections were the main targets of the Japanese antimicrobial stewardship guideline. We stated this point in lines 94–97.

11) Line 159

Does this mean 682 822 unique patients. What if they visited more than once in one year?

Author's response: We intended to state 682,822 "visits", not "unique patients". To clarify this point, we have modified the sentences throughout the revised manuscript (lines 41 and 169–191).

12) Line 162

See remark on organization of outpatient care.

Author's response: Please see point 5 above. We have added this information in the revised manuscript (lines 105–107).

13) Line 169

Why was it not possible to link all antibiotic prescriptions with diagnosis? See comment on registering? Do all physicians make use of an electronic medical file? How is your registration done?

Author's response: Registration is completed by physicians. Most physicians register claims in digital format. However, there are a few missing medical claims registered in non-digital form (approximately 3–5% of all claims), and diagnoses on the missing medical claims were not linked to antibiotic prescriptions. Additionally, we were able to link antibiotics to infectious diagnosis only when antibiotics were prescribed at the first visit of the illness episode, therefore we could not link all antibiotic prescriptions to the diagnoses (please also see point 4 above and Reviewer #1, point 7). We have added this information to the Discussion section (lines 315–322).

14) Line 171

It would be more interesting to do it the other way around, like in table 5. To look at the consults with for example bronchitis, and to see if there was an antibiotic prescribed, and which one? Because now it says something about the prevalence of diagnoses, and not on the prescribing quality.

Example: Adriaenssens N, Coenen S, Tonkin-Crine S, et al. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. *BMJ Qual Saf* 2011; 20: 764–72

Author's response: We agree the reviewer's suggestion that the information on the prescribing quality would be valuable. We have referred the quality indicators above and described the antibiotic prescribing quality in the Discussion section (lines 275–280). We would like to add the reference (reference 23 in the revised manuscript). Please also see our responses to reviewer 1 comment #8.

15) 22 % of prescriptions was made for viral URI. 45 % with viral URI got an antibiotic prescription. That really astonishes me. Please comment on this or state a hypothesis in the discussion.

Author's response: We agree with the reviewer's comment on this point. However, this tendency was observed in other administrative database studies, as we described in the manuscript (lines 252–256). We suppose that physicians frequently prescribe antibiotics for viral URI as prophylaxis for secondary bacterial infections. In addition, some previous studies from the UK analyzed reasons for frequent antibiotic prescribing for sore throats and revealed that patient demand for antibiotics and physician pressure to meet patient demand are associated with antibiotic prescription. However, these have not been clarified in Japan, and qualitative research is needed. We have commented on this in the Discussion section (lines 270–274).

16) Line 181

I suppose if you say male gender was associated with more antibiotic prescription, you mean the patient and not the prescriber? Why is this? Do you have gender information on the prescriber?

Author's response: We meant that male sex of the patient was associated with more antibiotic prescription. We have clarified this point throughout the manuscript (lines 50–51, 193, 205, 206, and 298). The reason for the patient sex difference in antibiotic prescribing remains to be clarified, and controversial results were observed in various studies. We have discussed this point in the Discussion section (lines 297–301). In addition, we modified the word "gender" to "sex" for consistency throughout the manuscript. Information on prescriber sex was not available in this study.

17) Line 182 -186

The results on antibiotic prescribing and age are something unexpected for me. I would have expected more in the children's age group and the elderly; Please comment

Author's response: We agree with the reviewer's comment on this point. This tendency was observed in other studies, as we discussed in the manuscript (lines 293–295). However, the reason for frequent antibiotic prescription in young patients remains to be clarified. Sex and age-standardized antibiotic prescription rates need to be assessed in Japan (lines 300–302).

18) Line 191

Prescribing antibiotics for gastrointestinal infections seems common in Japan? What about guidelines? Why is there unadherence?

Author's response: Antibiotics are often prescribed for gastrointestinal infections in Japan. The Japanese guideline recommends not to prescribe antibiotics for most patients, but the guideline was not created in 2012 (the study period).

19) Line 208

See previous comment on broad spectrum penicillin's.

Author's response: As we described above (please see point 9 above), we did not extract the prescription of broad-spectrum penicillin (amoxicillin/clavulanate) and other narrow-spectrum penicillins separately in this study. We have deleted the sentence "penicillin, a representative narrow-spectrum antibiotic" from the text (line 221).

20) Line 224.

It is indeed surprisingly that so many antibiotics are prescribed for viral URI, but not rally that it was the most frequent infection associated with AB prescribing because I expect that the incidence was really high.

Author's response: We appreciate the reviewer's comment on this point. This tendency was observed in other administrative database studies, as we described in the manuscript (lines 252–255). We suppose that physicians frequently prescribe antibiotics for viral URI as prophylaxis for complicating secondary bacterial infections (please also see point 15 above).

21) Line 250

I think you have already found some interesting targets to focus on for future interventions. Please state and summarize the implications or suggestions for practice/further research of your study.

Author's response: This should be investigated in future studies because we were unable to calculate age and sex-standardized antibiotic prescription rate in this study. We have added this information to the Discussion section (lines 301–303). We are now analyzing it and intend to report it in a later paper.

22) Line 257

For your statement of type of prescribers you refer to an American study. Is this the same in Japan?

Author's response: We suppose that the type of prescribers who prescribe antibiotics frequently may be similar between in the US and Japan; nonetheless, this has not been verified.

23) Line 272

Do you have a hypothesis why this is different in Japan?

Author's response: We think geographical diversity in antibiotic prescribing may be present because there are geographical variations in age and gender-composition of population and number of doctors per population in Japan, although Japan is a homogeneous society. Now we are analyzing a more comprehensive claims database to investigate this point and intend to report it in a later paper.

24) Line 281

Out-of-hour, should be out-of-hours

Authors' response: We have modified the sentence accordingly (lines 66 and 312).

25) Line 281

What are non-physician practitioners? Can they prescribe antibiotics?

Author's response: Non-physician practitioners include nurse providers and physician assistants. These positions are approved in the United States but do not yet exist in Japan. We have deleted this information from the revised manuscript (line 312).

26) Line 282

Is black race relevant for Japan? Which minorities group are there in Japan? Is there relationship with quality of care?

Author's response: Black race is associated with inappropriate antibiotic prescribing in the US study, but black population is quite rare in Japan. We have deleted this information from the revised manuscript (line 312).

27) Line 285

"we found no follow-up visit ..." I'm not sure I understand what you mean by this. Please explain.

Author's response: We intend to mean that we could not capture follow-up visit data when patients had multiple visits for a single infection episode in this study. We have modified the sentence (lines 317–319).

Discussion

28) I really miss some information on the health care context in Japan.

Who are your prescribers in this study, what type of physicians? Are some prescribers “better” prescribers than others?

Author's response: Please see point 5 and 21 above. All physicians working at any free-standing or hospital-based clinic can prescribe antibiotics; therefore, our study includes any type of physician. The type of physicians with frequent prescription has not been clarified thoroughly in Japan, and additional studies are needed.

29) Are there any qualitative studies available in Japan that could explain these

results? With patients or with physicians? Why are so many antibiotics prescribed for viral URI and gastro-intestinal infections?

There are much more interesting results in the tables than you discussed in your article.

Author's response: We appreciate the reviewer's interest in this point. We suppose that physicians in Japan prescribe antibiotics for viral URI and gastrointestinal infections as prophylaxis for complicating secondary bacterial infections (please see point 15 and 20). However, we could not deduce the reason from this claims database study. Another study is needed to assess this point.

30) Table 1

What about amoxicillin with beta-lactamase inhibitor?

Author's response: Amoxicillin with beta-lactamase inhibitor was included in the group “penicillins”. Please also see points 8 and 18 above.

31) Table 3

Please explain or comment:

Bacterial pneumonia only 45,7% antibiotic prescribing. I would expect almost 100%? Same for PID and urinary tract infection

Influenza, almost 38% antibiotic prescribing.

Author's response: We agree with the reviewer's comment. This may be because diagnostic accuracy was not validated owing to the use of the administrative claims database. We stated this point in the Discussion section (lines 307–308). However, a similar tendency was observed other administrative database studies. For example, 61% of patients with pneumonia received antibiotics in a US study.

32) Table 4

What is ‘clinic’. Only ambulant care? Something like general practice?

Author's response: Clinic indicates a free-standing clinic. General practice is provided in both free-standing clinics and hospital-based clinics (please see Reviewer #1, point 3). We have modified the expression in Tables 4 and 5.

33) Table 5

What is your denominator in your percentage of antibiotic prescription

Author's response: All visits with gastrointestinal infections (with or without antibiotic prescription) are stratified by characteristics in each column; this is used as the denominator. Regrettably, some errors were made concerning the number of visits with antibiotic prescriptions in the group "patient sex". We corrected the mistakes in Table 5.

VERSION 2 – REVIEW

REVIEWER	Annelies Colliers University of Antwerp, Faculty of Medicine and Health Sciences, Department of General Practice – Primary and Interdisciplinary Care Belgium
REVIEW RETURNED	14-Dec-2018

GENERAL COMMENTS	Thank you for answering my questions. I have 2 remarks left: -You use "patient sex of (fe)male", I think this is not a standard English term. - line 279 : You talk about reasons for not adhering to the guidelines for antibiotic prescribing. You only talk about (perceived!) patient pressure. But the reasons to prescribe are much more complicated than this. There are many more studies on this topic, which are more recent and relevant. Brookes-Howell L, Hood K, Cooper L, et al. Understanding variation in primary medical care: a nine-country qualitative study of clinicians' accounts of the non-clinical factors that shape antibiotic prescribing decisions for lower respiratory tract infection. <i>BMJ Open</i> 2012;2(4) doi: 10.1136/bmjopen-2011-000796 O'Connor R, O'Doherty J, O'Regan A, et al. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. <i>Irish J Med Sci</i> 2018;187(4):969-86. doi: 10.1007/s11845-018-1774-5 Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. <i>J Antimicrob Chemother</i> 2011;66(10):2215-23. doi: 10.1093/jac/dkr279
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VERSION 2 – AUTHOR RESPONSE

Reviewer reports:

Annelies Colliers (Reviewer 2)

Thank you for answering my questions.

I have 2 remarks left:

1) You use "patient sex of (fe)male", I think this is not a standard English term.

Authors' response: We have modified the sentences in the revised manuscript (lines 193, 205-206, and 300-301).

2) line 279: You talk about reasons for not adhering to the guidelines for antibiotic prescribing. You only talk about (perceived!) patient pressure. But the reasons to prescribe are much more complicated than this. There are many more studies on this topic, which are more recent and relevant.

Brookes-Howell L, Hood K, Cooper L, et al. Understanding variation in primary medical care: a nine-country qualitative study of clinicians' accounts of the non-clinical factors that shape antibiotic prescribing decisions for lower respiratory tract infection. *BMJ Open* 2012;2(4) doi: 10.1136/bmjopen-2011-000796

O'Connor R, O'Doherty J, O'Regan A, et al. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. *Irish J Med Sci* 2018;187(4):969-86. doi: 10.1007/s11845-018-1774-5

Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. *J Antimicrob Chemother* 2011;66(10):2215-23. doi: 10.1093/jac/dkr279

Author's response: Thank you for your suggestion. We have referred these studies and described additional information about factors associated with antibiotic prescribing in the revised manuscript (lines 274-277).