PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	How patients' experiences of respiratory tract infections affect healthcare seeking and antibiotic use: Insights from a cross sectional survey in rural Anhui, China
AUTHORS	Diao, MengJie; Shen, Xingrong; Cheng, Jing; Chai, Jing; Feng, Rui; Panpan, Zhang; Rongyao, Zhou; Lambert, Helen; Wang, DeBin

VERSION 1 – REVIEW

REVIEWER	Ingrid Keilegavlen Rebnord Uni Research
REVIEW RETURNED	15-Oct-2017

GENERAL COMMENTS	Background: Page 2, Line 4: Wrong writing: To investigate… Page 3: 1 paragrah: The authors use the first paragraph to describe the costs of RTIs in terms of sickness absence and school absence. These are not matters that the article will take care of, so it gets unnecessarily large space in the introduction. Sick leave in the number of days would be an interesting variable to have included in this study but as long as it is not mentioned later in the article, it becomes distracting to describe so in the beginning. Line 45: The abbreviation OTC is not explained Page 4: 1 paragraph: I think this is unclear and maybe not correct; there exist studies also about the patients' decisions about self or professional care. But it may vary a lot, especially after how much antibiotics is used in the community. This fact is not discussed or mentioned in the article. 2 paragraph: I find the objective in the main article unclear. There is no clear objective or hypothesis. I lack a description of what this study really describes: The course of the symptoms of respiratory tract infections in a population that mainly uses antibiotics in almost all infections. Methods: The design is not mentioned in the article, only in the abstract. Page 5, line 3: buying medicines from medicines shop: It is not clear enough what type of medication is asked for here? Antibiotics or NSAID/paracetamol or for cough? Results: Page 5, line 47. 68% female is rather high if the selection was random. Should be discussed more.

	Page 6: Figure 2: Generally I think there is to many variables that has its one diagram and with very little difference in results. Rhinorrhea with and without pus could be one variable, cough also. Table 1: This table is too big with too many numbers, and no bold text or other marks. B is not explained and not Exp(B) (Odds Ratio). I think some variables should be added together, and use bold text for significant values, and remove some columns (B). Figure 4: What is the difference between getting medicines from the shop and getting antibiotics from the shops? Not clearly defined. The figure shows no demographic variables as the text in the article says. And gender was not significant associated with any difference so I think this figure is not interesting. Looking at the figure it seems like more than 90 % have got antibiotics at 7 days or more, totally? If that is correct it should have been mentioned in the article text. Discussion Page 7 First paragraph: My main objection to the article is that it claims to describe the course of respiratory infections using symptoms and that this is essential for clinicians and patients as it can provide information that is useful for predicting the course and explaining expectations. When more than 80% of the study population has used antibiotics, this will not be any longer interesting or correct. The majorities of respiratory infections are viral or mixed infections. It is becoming very weak to say that this is normal course of illness without specifying what treatment is given. The one article referred to here is also only done on children (ref 6), while the study performed here is only adults. The conclusion must be reformed and include these assumptions. It is less useful and transferable to populations with lower antibiotic use as described now. Page 9, 2 paragraph: Limitations: here it also should be mentioned the limitation that high rate of antibiotics give to the study.

REVIEWER	Hasse Melbye Department of Community Medicine Faculty of Health Sciences UIT the Arctic Universirty of Norway
REVIEW RETURNED	24-Oct-2017

GENERAL COMMENTS	This is a study of symptoms and help-seeking behavior in RTI in a general Chinese population, based on interviews/retrospective data-collection. The study demonstrates an alarming high use of antibiotics, which often are bought in shops or are left-overs. The study includes a detailed presentation of clinical course of the common RTI symptoms. Main concerns: The time interval between the last RTI and the data collection is not shown. Anyway, it is not likely that the patients can remember the appearance and duration of each symptom. The symptom peaks after 1, 3 and 7 days strongly indicate the influence of guessing. I would recommend to drop all the figures with symptom trajectories. Presence and number of symptoms are probably more reliable. Minor points Page 4 lines 12-12. I dot understand how a yearly incidence of 84-121% is the same as 2-4 cases per person per year. And further, hjw can a country with less than 2 billion people have 16 billion cases a year? (Maybe I misunderstand, I am not sure about the meaning of “person-times”.

	Page 5, line 5. Medicine shops, is this the same as pharmacies, can you explain? Page 5, lines 53-55. It should be made clear that the 20.8% who did nothing was excluded before calculating the use of antibiotics. Page 9, limitations. The frequency of seeking help for RTI was high, is it possible that mild RTIs have been forgotten by the respondents?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment 1
Page 2, Line 4: Wrong writing: To investigate…
Response: Amended to "To investigate the occurrence". (Page 2, line 2)

Comment 2
Page 3,1 paragraph: The authors use the first paragraph to describe the costs of RTIs in terms of sickness absence and school absence. These are not matters that the article will take care of, so it gets unnecessarily large space in the introduction. Sick leave in the number of days would be an interesting variable to have included in this study but as long as it is not mentioned later in the article, it becomes distracting to describe so in the beginning.
Response: We have cut details of costs and absenteeism due to RTIs in this paragraph. Given that the manuscript is already quite lengthy, we did not include days of sick leave in this analysis. We may do so in a separate manuscript focusing on the costs of RTIs. (Page 3, lines 1-14)

Comment 3
Line 45: The abbreviation OTC is not explained
Response: Omission has been corrected by adding 'over-the-counter (OTC)'. (Page 3, line 25)

Comment 4
Page 4: 1 paragraph: I think this is unclear and maybe not correct; there exist studies also about the patients' decisions about self or professional care. But it may vary a lot, especially after how much antibiotics is used in the community. This fact is not discussed or mentioned in the article.
Response: Thanks for this useful comment. We expanded our search terms and found several recent publications relating to patients' decisions about self or professional care. We have removed the last sentence of the paragraph and added a couple of references. (Page 3, line 28-34)

Comment 5
Page 4:2 paragraph: I find the objective in the main article unclear. There is no clear objective or hypothesis. I lack a description of what this study really describes: The course of the symptoms of respiratory tract infections in a population that mainly uses antibiotics in almost all infections.
Response: Thanks again for pointing out this important omission. In addition to the Objective stated in the Abstract, we have modified our account of the existing literature in the 'Background' section and added a sentence explaining the rationale for the study. (Page 4, line 8-10) We have also explained further the purpose and underlying hypothesis of the study in the Abstract Conclusions and Discussion section of the paper.

Comment 6
Methods: The design is not mentioned in the article, only in the abstract.
Response: We have now specified the study design in the methods sections as following "The study used a cross sectional retrospective household survey design." (Page 4, line 13)

Comment 7
Page 5, line 3: buying medicines from medicines shop: It is not clear enough what type of medication is asked for here? Antibiotics or NSAID/paracetamol or for cough?
Response: By “buying medicines from medicine shop” we mean all kinds of medicines. In order to prevent potential misunderstandings, we have added a sentence in our revised manuscript to explain that ‘In China, almost all medicine shops sell both OTC and non-OTC medicines, including antibiotics; although they may be displayed in separate cabinets, in practice non-OTC medicines are frequently sold without prescription and customers generally do not distinguish these two types of medicines.” (Page 5, line 2-6)

Comment 8
Results: Page 5, line 47. 68% female is rather high if the selection was random. Should be discussed more.
Response: The selection was random. The reason why female respondents counted for 68% was because the majority of male residents in rural areas had moved to cities for temporary jobs. This overrepresentation of females may raise concerns about selection biases. Fortunately our analysis did not reveal statistically significant differences between males and females in terms of all the symptoms and responses following RTIs except for taking leftover medicines. We have explained this in the first paragraph of the Results section (Page 5, line 37-39) and have discussed gender differences in the Discussion and Limitations sections of our revised manuscript. (Page 10, line 39-41)

Comment 9
Page 6: Figure 2: Generally I think there is to many variables that has its one diagram and with very little difference in results. Rhinorrhea with and without pus could be one variable, cough also.
Response: Thank you for this comment. We have now combined rhinorrhea with pus and rhinorrhea without pus into “rhinorrhea”; and dry cough and productive cough into “cough”. In addition, we removed “earache and/or tinnitus” from the figure. By doing this, Figure 2 has been reduced from 9 sub-figures into 6. (Figure 2)

Comment 10
Table 1: This table is too big with too many numbers, and no bold text or other marks. B is not explained and not Exp(B) (Odds Ratio). I think some variables should be added together, and use bold text for significant values, and remove some columns (B).
Response: We have removed columns (B) and have used bold text for significant values. Please note this is now Table 2 as we have provided an additional table showing associations between time since onset of infection and data collection. (Table 2)

Comment 11
Figure 4: What is the difference between getting medicines from the shop and getting antibiotics from the shops? Not clearly defined.
Response: In this analysis we treat ‘medicines’ as comprising all kinds of drugs used for treating illnesses, whereas antibiotics are one specific kind of medicines that are particularly important because of the problem of antimicrobial resistance. We have clarified this in the figure. (Figure 5 and Table 2)

Comment 12
Figure 4: The figure shows no demographic variables as the text in the article says. And gender was not significant associated with any difference so I think this figure is not interesting. Looking at the figure it seems like more than 90 % have got antibiotics at 7 days or more, totally? If that is correct it should have been mentioned in the article text.

Response: Thank you for pointing out this error. We have amended the sentence “Figure 4 displays the relationships between service-seeking and number of concurrent symptoms in total and by demographics” to “Figure 5 and appendices 5-6 display the relationships between service-seeking and number of concurrent symptoms in total and by demographic characteristics” and added two additional appendices showing the relationships between service-seeking and number of concurrent symptoms by age and education.
The figure was misleading. The numbers along the horizontal “X” axis stand for numbers of symptoms rather than days following the infection. We have added a note clarifying this below the figure. (Figure 5 and appendices 5-6)

Comment 13
Discussion
Page 7 First paragraph: My main objection to the article is that it claims to describe the course of respiratory infections using symptoms and that this is essential for clinicians and patients as it can provide information that is useful for predicting the course and explaining expectations. When more than 80% of the study population has used antibiotics, this will not be any longer interesting or correct. The majorities of respiratory infections are viral or mixed infections. It is becoming very weak to say that this is normal course of illness without specifying what treatment is given.

The one article referred to here is also only done on children (ref 6), while the study performed here is only adults. The conclusion must be reformed and include these assumptions.

It is less useful and transferable to populations with lower antibiotic use as described now.

Response: We appreciate these insightful comments which point out an important omission in our explanation of the data. We have added the following as the first point in the study limitations paragraph (page 9, lines 25-34): First, prior care may have affected the symptom trajectories reported in this paper. Given that over 80% of patients had used antibiotics, the curves of RTI symptoms derived in this study may differ from ’natural’ trajectories without any treatment and in western communities where antibiotics use is much lower. Unfortunately, we were unable to find similar trajectory data from western populations. However, although antibiotic use is much higher in China than in US, data about RTI duration from our populations seem to be close to that from US. [19,42].This suggests that the effect of antibiotics on RTI trajectory in the community may not be particularly important, since the majority of RTIs are caused by viruses rather than bacteria. (Page 10, lines 8-17) We have also clarified that the main purpose of our study was not to derive “natural” trajectories of symptoms of RTIs. This is not possible via a retrospective survey of the kind we had carried out. Rather, we have interpreted our data as providing insights into what people in the community perceive and recall as the course and duration of their symptoms and we have made this more explicit in the manuscript, by amending the first paragraph of our discussion section to read: ‘This study has uncovered useful data for better understanding the experience of RTIs among patients in the community and their relations with healthcare seeking and antibiotics use. Since the respondents’ reports of RTI symptoms are retrospective and relate to experiences of illness and its treatment occurring up to nine months previously, our data provide insights into their perceptions of symptom trajectories rather than actual trajectories. However, self-reported disease courses are of equal (if not greater) significance than actual ones in terms of healthcare-seeking. When faced with an RTI, a patient’s experiences and recollections of previous similar symptoms may affect his/her prediction of the current infection and thus inform decisions about whether or what type of healthcare to use; while perceptions leading to inappropriate treatment imply education and counseling needs.’ (Page 8, lines 2-12) We have also added a sentence in the Study Limitations section to explain that, ‘…our analysis treats these data as proxy evidence of patients’ typical perceptions of the course of infection rather than of the actual course of infection’, (Page 10, lines 33-35) and amended the Conclusions section of the Abstract and the bullet points.

We have also removed the reference to the article on children (ref 6) and kept only the article on adults (ref 31).

Comment 14
Page 9, 2 paragraph: Limitations: here it also should be mentioned the limitation that high rate of antibiotics give to the study.
Response: As mentioned in our response to the above comment 13, we have discussed the potential problems due to the high rate of antibiotics use.

Reviewer 2
Comment 1
Main concerns: The time interval between the last RTI and the data collection is not shown. Anyway, it is not likely that the patients can remember the appearance and duration of each symptom. The symptom peaks after 1, 3 and 7 days strongly indicate the influence of guessing. I would recommend to drop all the figures with symptom trajectories. Presence and number of symptoms are probably more reliable.

Response: We performed additional data analysis and have added a new table (Table 1) showing healthcare-seeking behaviors by subgroups with different time interval between onset of infection and data collection. We also added a couple of sentences briefing the key findings from additional data analysis. (Page 6, lines 4-8)
We strongly share the memory concerns raised by the reviewer here. However, our interpretation of the featured curves (a sharp increase and peak followed by a long tail) is that they reflect the joint effects of not only the pathology of RTIs, but also health service use, psycho-social factors, as well as memory/self-report biases. Bearing these in mind, comparison of such curves for different symptoms and from different populations may yield insights into how patients experience and recall symptom trajectories and how these perceptions affect both concurrent treatment-seeking and inform subsequent healthcare-seeking. Our study found that multiple peaks occurred only in the curves of days on which symptom recovered and that different symptoms peaked after different days rather than the same day. These phenomena may not be fully explained by guessing. The peaks on day 7 and 10 may be attributed more to “rough reporting” than to “wild guessing”. In China people are used to plan activities and measure time length in “Zhou (a week)” or “Xun (ten days)”. (Page 8, lines 22-32)More importantly, from the view point of healthcare-seeking, self-reported disease courses are of equal (if not greater) significance as actual ones. When faced with an RTI, a patient’s experiences (even guesses) from the previous similar infections may affect his/her prediction of the current infection and thus decisions about whether or not or what type of healthcare to use; while incorrect perceptions imply education and counseling needs. (Page 8, lines 8-12)
We have included the above explanation in the discussion section of our revised manuscript.

Comment 2
Page 4 lines 12-12. I dot understand how a yearly incidence of 84-121% is the same as 2-4 cases per person per year. And further, hjw can a country with less than 2 billion people have 16 billion cases a year? (Maybe I misunderstand, I am not sure about the meaning of “person-times”.

Response: We apologize for this error and are grateful to the reviewer for pointing it out. We have changed the sentence, “These translate into 2 to 4 times of RTIs per person per year and 16 billion person-times of RTIs annually in the whole country” into “These translate into 1.16 to 1.67 billion person-times of RTIs annually in the whole country”. (Page 3, lines 35-37)

Comment 3
Page 5, line 5. Medicine shops, is this the same as pharmacies, can you explain?

Response: Yes, by “medicine shops” in our manuscript we mean the same as “pharmacies” in western countries. In China, a pharmacy is generally referred to as an integral department within a hospital or clinic that provides medicines to its patients according to prescriptions by the clinicians working for the same hospital/clinic; while a medicine shop is usually referred to as an independent shop that sells medicines to customers with or without prescriptions by clinicians. The revenue of hospitals/ clinics depends heavily on their pharmacies but has nothing to do with the sales of any medicine shops.
In order to give readers better understanding of China’s health systems context, we have added the following at the ‘Questionnaire’ paragraph:
‘In China, a pharmacy generally refers to a department within a hospital or clinic that dispenses medicines to patients according to prescriptions by the clinicians working for the same hospital/clinic; while a medicine shop is an independent business that sells medicines to customers with or without prescriptions from clinicians’. (Page 4, lines 34-38)

Comment 4
Page 5, lines 53-55. It should be made clear that the 20.8% who did nothing was excluded before calculating the use of antibiotics.

Response: Yes, that is correct.

Comment 5
Page 9, limitations. The frequency of seeking help for RTI was high, is it possible that mild RTIs have been forgotten by the respondents?

Response: This is again an insightful comment. “Seeking help from clinics” in China is, to a large extent, equivalent to “seeking professional care” in the USA. In our study, the RTI patients who had sought help from clinics accounted for 55.7%; while as mentioned in the introduction section, a 2014 study of patients with cough and cold in the USA documented 55% utilization of “professional care”. Although over 80% of our RTI patients used antibiotics, this does not necessarily mean all of them had sought professional care, some had used antibiotics leftover from previous infections and others purchased antibiotics from medicines shops directly without help from any clinicians. In order to prevent potential misunderstandings, we have added the following sentences into the Methods section: ‘Seeking help from clinics’ refers to visiting a local health facility staffed by a qualified health professional and is thus largely equivalent to ’seeking professional care’ in western countries. Conversely, the use of antibiotics does not necessarily mean that professional care was sought. Antibiotics may be purchased from medicine shops directly without prescription or kept at home for subsequent use. Almost all medicine shops in China sell both OTC and non-OTC medicines, including antibiotics. Although they may be displayed in separate cabinets, in practice non-OTC medicines may be purchased directly without prescription and customers generally do not distinguish these two types of medicines. (Page 4, lines 38-41 and Page 5, lines 1-6)

Our findings do suggest some degree of recall recall/memory bias. However, this may not be as significant as expected. As shown in the newly added Table 1, no statistical difference was found among subgroups with different time interval between onset of infection and data collection for all the healthcare-seeking behaviors except for use of leftover medicines. We have added some sentences addressing this concern in the ’limitation’ section as well as in the Discussion.

In addition please note that:
We added a new Figure (Figure 4: distribution of healthcare-seeking by time difference between day on which patient sought healthcare and day on which symptom peaked) to show the relationships between healthcare-seeking behaviors and symptom trajectory.
We also changed the title of our manuscript slightly from “Symptoms of respiratory tract infections and healthcare-seeking and antibiotics use: a cross sectional survey in rural Anhui, China” into “How patients’ experiences of respiratory tract infections affect healthcare seeking and antibiotic use: Insights from a cross sectional survey in rural Anhui, China”, and make our hypothesis more explicit.

VERSION 2 – REVIEW

REVIEWER	Ingrid Keilegavlen Rebnord Uni Research Norway
REVIEW RETURNED	30-Nov-2017

GENERAL COMMENTS	The article is well-prepared according to the comments from the first review. I only have a few comments on typing errors/language: Page 4, line 8: suggest: This study aims to investigate ... Page 4, line 13: suggest: The study used a retrospective cross-sectional household survey design. And generally some very long sentences, fore example: page 8, line 8-12. I can not find a checklist

REVIEWER	Hasse Melbye UIT the Arctic University of Norway
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	My main concern with the manuscript was that the trajectories are unreliable and has to be taken out. They are not needed for the main analysis and omitting them will not change the main result. A description of the clinical course of symptoms during diseases has to be based on prospective registration. You have included a collague who has helped you with the language editing as a coauthor. As far as I know this is not in line with the ethical guidelnes for scientific publications.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Comment 1
Page 4, line 8: suggest: This study aims to investigate ...
Response: We changed the sentences as suggested. (Page 4, Line 7)

Comment 2
Page 4, line 13: suggest: The study used a retrospective cross-sectional household survey design.
Response: We changed the sentences as suggested. (Page 4, Line 12)

Comment 3
And generally some very long sentences, fore example: page 8, line 8-12.
Response: We removed the sentences in response to the second reviewer's comments.

Comment 4
I can not find a checklist
Response: We submitted the checklist via the online system and it may not be viewable to reviewers but only editors.

Reviewer: 2
Comment 1
My main concern with the manuscript was that the trajectories are unreliable and has to be taken out. They are not needed for the main analysis and omitting them will not change the main result. A description of the clinical course of symptoms during diseases has to be based on prospective registration.
Response: We removed the symptom trajectories.

Comment 2
You have included a collague who has helped you with the language editing as a coauthor. As far as I know this is not in line with the ethical guidelnes for scientific publications.
Response: The previous explanation why we added Professor Helen Lambert as a coauthor was too simplified. She is in fact one of the key collaborators of the second grant mentioned in the manuscript that had provided financial support to the current study. And as we had specified in our manuscript, "Helen Lambert contributed to the interpretation of data and revised and finalized the manuscript."

VERSION 3 – REVIEW

REVIEWER	Hasse Melbye UIT the Arctic University of Norway
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	Th e trjectory of symptomes i still in in aim of the abstract, and should be removed. likewise I would suggest to remove the info related to the trajectories from the method section as well.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
The trjectory of symptomes i still in in aim of the abstract, and should be removed. likewise I would suggest to remove the info related to the trajectories from the method section as well.

Response: We removed "symptom trajectories" from abstract and method sections.