PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antibiotic use and bacterial complications following upper respiratory tract infections: a population based study
AUTHORS	Cars, Thomas; Eriksson, Irene; Granath, Anna; Wettermark, B; Hellman, Jenny; Norman, Christer; Ternhag, Anders

VERSION 1 – REVIEW

REVIEWER	Ann Hermansson ENT dept University Hospital Lund
REVIEW RETURNED	25-Mar-2017

GENERAL COMMENTS	This is a very good paper on an interesting subject. I only have some small comments. Generally the method of coding could be remarked on. In Introduction it is stated that stricter guidelines were implemented for example for pharyngotonsillitis and sinusitis. It would be better to state pharyngotonsillitis and AOM since the swedish guidelines for sinusitis would need an update while AOM are updated. I would also like a little more said about complications to sinusitis and why the deep throat and neck infections seem to be rising. It is stated that this might depend on for instance teeth problems. This should be further emphazised since it obscures the results. Otherwise tumbs up!

REVIEWER	Morten Lindbæk Antibiotic centre for primary care Department og general practice Institute for Health and society University of Oslo, Norway
REVIEW RETURNED	17-Apr-2017

GENERAL COMMENTS	During the last years there has been a lot of focus on reducing antibiotic use outside hospitals because of rising concern on AMR. Sweden has through Strama managed to make a large reduction in antibiotic use during the last 20 years. Thus it is important to study whether this reduction in use is safe, which has been mostly evaluated through number of complications and hospital use. Cars et al has done a considerable job to study this topic in their study of complications. They have had access to large data sets from primary care and hospital care which seem to be complete. The study gives important clues as to number of serious complications related to URTIs, and whether lack of antibiotic treatment may give more complications. I have however some important issues which should be considered:

	1. The main question is what is considered a complication. When comparing with other studies, I especially miss the number of pneumonia. This was the most frequent complication in Gullifords study and was about 10 times as frequent as peritonsillar abscess. The authors have not discussed this at all in the paper. They may argue that they only deal with URTIs and that pneumonia is not relevant. But a number of URTIs can give complications to lower respiratory tract, such as acute sinusitis with postnasal drip. Acute bronchitis is often regarded as a URTI which may definetely lead to pneumonia. In my opinion pneumonia is also a relevant complication to be evaluated in this study. 2. Anpther relevant question is whether septicemia in general should be considered to be a possible complication and not only related to streptococcus. I miss that this topic is discussed more in depth. 3. The paper has not included the most frequent complication in acute sinusitis: maxiallary empyema which occurs in 1-2 % of all patients (Lindbaek, van Buchem). 4. Furthermore have you included data from private ENT-specialists who may have handled a number of patients with sinus empyema, without being sent to hospitals? They may also have handled a number of cases with peritonsillitis 5. I also miss a more in depth discussion on problems with exact diagnosis in primary care, as registered in the computer systems . There are large variations on this, both between countries and between GPs. Although ICD 10 may be well defined in theory, diagnostic work in primary care is quite variable. There are a number of symptom diagnoses in ICPC which is used in most other European countries. I assume that J06 in ICD 10 is the unspecified group of URTI corresponding to R74/symptomdiagnoses in ICPC. It could be of interest to compare the numbers with those from Gjelstads JAC-paper.. 6. Cars et al have found a surprisingly high proportion of otitis media treated with antibiotics. The proportion of acute otitis media treated with antibiotics is hard to understand. This is both due to Swedish guidelines that recommend no antibiotics for uncomplicated otitis media. This is also in contrast to findings from Norway and the Netherlands where a much smaller proportion is treated. 7. It is apparent that the unspecified group of URTI/sinusitis is quite large, and may well have included cases with LRTIs. This is another argument why pneumonia should have been included among the complications. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ. 1996 Aug 10;313(7053):325-9 van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet. 1997 Mar 8;349(9053):683-7 Gjelstad S, Straand J, Dalen I, Fetveit A, Strøm H, Lindbæk M.Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections?J Antimicrob Chemother. 2011 Oct;66(10):2425-33.

REVIEWER	Nick Francis Cardiff University UK
REVIEW RETURNED	18-Apr-2017

GENERAL COMMENTS	This paper addresses and important topic and uses what sounds like an impressive database. My main concern is a lack of clarity around the objectives. The main objective described in the abstract, and at the end of the discussion paper, is to, "Set up a process for continuous monitoring of upper respiratory tract infections …". Setting up a process, however, is not a research question / objective in itself. The authors could have produced a paper that addresses questions about how to set up a system for continuous monitoring of URTIs, or the barriers and facilitators to setting up a system, but this paper does not do those things, and is actually primarily a paper describing two analyses looking at associations between URTI diagnoses and antibiotic prescribing. However, study questions are vague and it is not clear whether the aims are purely descriptive or if there are hypotheses that are being explored. This all needs to be clarified with specific objectives that then match with methods and results. There are a number of specific points that I would like to see addressed: The first study is described as an ecological study, and while I agree with this, I think it would be more informative to describe it as an ecological time-trend analysis, or just a time-trend analysis. I would like to see a bit more detail about the quality of the data. Does VAL include out of hours care? How well are infections coded in VAL? Has there been any validity work? Please be more specific about the aims of the ecological time trend study. Was it purely descriptive, or were there specific hypotheses that were under investigation (i.e. reduction in AB prescribing would not be associated with increase in complications). How would you have handled increase in some AB and decrease in others? It all feels a bit vague at the moment. The definition of cohort 4 (page 7, lines 41-42) is not clear to me. Does it include all patients in cohort 3 AND those with URTI? What is meant by, 'of multiple and unspecified sites'? I found the description (and figure) of the definitions around episode start and end date confusing. Is the end date the first of, 1) 30 days following the start of the episode, 2) the date that an antibiotic is dispensed (if dispensed within 3 days of a consultation), 3) the date of a complication? Outcomes – The term 'peritonsillitis' is not in common use in the UK and I had to look up a definition. I am not convinced that 'peritonsillitis' can be accurately classified distinctly from 'tonsillitis' or 'pharyngitis'. Is there evidence that this is a useful distinction? Does it really make sense to classify it as a complication? Analysis – The study aims are not entirely clear, but it would appear that one of the aims is to compare complication rates in those exposed and not exposed to antibiotics.

	Indeed, comparisons are described in the Discussion section. However, this is not mentioned in the analysis section and no statistical tests have been used to compare rates in exposed and unexposed groups. Why was this? There is no mention of any ethical or other approval for use of the data. Results There are some formatting issues around pages 9-11 and some of the text seems to be missing. The series of p values presented in the text of page 10 and in Figure 3 do not provide a very comprehensive, and could be quite misleading) description of the trends observed. There is no mention in methods of tests for trend. What is the hypothesis that is being tested? Some show considerable variation. How do you explain this variation? What is described as 'peritonsillitis' in the text seems to be referred to as peritonsillar abscess in Figure 3. Discussion What is described as simply, 'Selection bias' (page 12, lines 33-34) I think would more accurately be described as, 'Confounding by indication' or 'Indication bias'. On page 13 (lines 31-32) you state that you have demonstrated that routinely collected data, 'can be used in continuous monitoring of antibiotics use and related patient outcomes.' This would suggest to me that you have demonstrated the ability to do this in an ongoing (preferably real-time) way. However, it appears as though you have been able to do a 'one-off' retrospective analysis, and I don't think it is reasonable to describe this as, 'continuous monitoring'. There could be more discussion about the possible reasons for the results seen, as well as the implications.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Ann Hermansson
ENT dept University Hospital Lund

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a very good paper on an interesting subject. I only have some small comments.

Comment: Generally the method of coding could be remarked on. In Introduction it is stated that stricter guidelines were implemented for example for pharyngotonsillitis and sinusitis. It would be better to state pharyngotonsillitis and AOM since the swedish guidelines for sinusitis would need an update while AOM are updated. I would also like a little more said about complications to sinusitis and why the deep throat and neck infections seem to be rising.

It is stated that this might depend on for instance teeth problems. This should be further emphazised since it obscures the results. Otherwise tumbs up!

Response: Thank you for taking the time to review our manuscript. We are grateful for your comments and have done the following to address them:

1. Regarding the method of coding – we hope it is clear (though we appreciate that our description may be rather concise) that the following codes were used: ICD-10 for diagnoses and ATC for medicines. The exact codes used in all definitions are available in the supplementary materials. With regards to processes of data management and analyses, we used SAS 9.4 to handle and analyse the data.
2. Regarding the guidelines – we have changed as per your suggestion. This now reads “Most of this decline has been attributed to limiting the inappropriate antibiotic use in viral respiratory tract infections or mild self-healing bacterial infections(10) by the implementation of stricter guidelines, for example for pharyngotonsillitis and acute otitis media (11-13).”
3. We added more information on the bacterial complications to sinusitis in the discussion. It is unknown to us what the reasons for the increase is and it was outside of the scope of this study to investigate this in depth. We added the following sentence in the discussion: “Retro- and parapharyngeal abscesses are uncommon diseases and it was outside of scope of this study to investigate what may have contributed to the discreet increase in these complications observed during the study period. Risk factors for these heterogeneous infections are local trauma, immunosuppression, and dental infections.”

Reviewer: 2

Morten Lindbæk
Antibiotic centre for primary care, Department of general practice, Institute for Health and society, University of Oslo, Norway
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

General comments:
During the last years there has been a lot of focus on reducing antibiotic use outside hospitals because of rising concern on AMR. Sweden has through Strama managed to make a large reduction in antibiotic use during the last 20 years. Thus it is important to study whether this reduction in use is safe, which has been mostly evaluated through number of complications and hospital use. Cars et al has done a considerable job to study this topic in their study of complications. They have had access to large data sets from primary care and hospital care which seem to be complete. The study gives important clues as to number of serious complications related to URTIs, and whether lack of antibiotic treatment may give more complications.
I have however some important issues which should be considered:

Response:Thank you for taking the time to review our manuscript. We appreciate your comments which we address one by one.

Comment 1. The main question is what is considered a complication. When comparing with other studies, I especially miss the number of pneumonia. This was the most frequent complication in Gullifords study and was about 10 times as frequent as peritonsillar abscess. The authors have not discussed this at all in the paper. They may argue that they only deal with URTIs and that pneumonia is not relevant. But a number of URTIs can give complications to lower respiratory tract, such as acute sinusitis with postnasal drip.

Acute bronchitis is often regarded as a URTI which may definetely lead to pneumonia. In my opinion pneumonia is also a relevant complication to be evaluated in this study.

Response: While we agree that pneumonia could be considered for inclusion in such analyses we however made a decision at the point of the study design to not include pneumonia as complication following URTIs because

a) Common URTIs are not considered equally established risk factors for community acquired pneumonia as smoking, alcohol consumption, and co-morbidities especially chronic respiratory disease including COPD.
b) Acute bronchitis may proceed to pneumonia, but it is not recommended to use prophylactic antibiotics in these cases. We did not aim to study if prophylactic use of antibiotics may have a protective effect in these cases
c) Some of the patients with cough in the Gulliford study may have had a pneumonia that was not diagnosed properly. These patients should have been treated with antibiotics if they were correctly diagnosed initially, but now the pneumonia diagnosis was late due to doctor´s delay.

We also added the following sentence in the Methods->Outcomes section:

" We therefore included as outcomes in the study those bacterial complications that have an established or plausible association to various URTIs."

Comment 2. Anpther relevant question is whether septicemia in general should be considered to be a possible complication and not only related to streptococcus. I miss that this topic is discussed more in depth.

Response: Just like pneumonia, septicaemia could also be studied as a complication. We however decided not to include this because

a) It is mainly the risk for invasive group A streptococcal disease (GAS) associated with tonsillitis, and if delayed or no antibiotics could increase the risk for invasive disease that have been of concern from some experts. However, we did not find any association and believe that co-morbidities and skin lesions may be risk factors for invasive disease, but in many cases there are no risk factors reported (J Clin Microbiol 2008 Jul; 46(7): 2359). Why GAS in certain situations invade the oropharynx or skin tissue may have to do with specific virulence factors in certain strains (M protein, hyaluronidase, peptidase etc.) and HLA class II allelic variations.
b) We did not include invasive pneumococcal disease because pneumonia is the dominating infectious focus and not URTIs
c) Sepsis due to alfa streptococcus and S aureus are not complications to URTIs.

Comment: 3. The paper has not included the most frequent complication in acute sinusitis: maxiallary empyema which occurs in 1-2 % of all patients (Lindbaek, van Buchem).

Response: Maxillary empyema is pus and pathogenic bacteria in the sinus. In the van Buchen trial were patients with a history and findings at examination compatible with acute maxillary sinusitis referred to CT. Ca 55% of those had abnormal radiographs (and was randomized to amoxicillin or placebo). The absolute majority of those with abnormal CT-findings would have growth of bacteria if a sinus aspirate would have been done. That is, we consider CT verified acute maxillary sinusitis and maxillary empyema the same clinical entity. Of note, the included patients in this trial had all proven CT findings and most likely worse symptoms than the original group as a whole and also compared to unselected sinusitis patients at general practitioners (Lancet 1997 Mars 8;349:683-7).

Comment 4. Furthermore have you included data from private ENT-specialists who may have handled a number of patients with sinus empyema, without being sent to hospitals? They may also have handled a number of cases with peritonsillitis

Response: Based on our knowledge of the clinical practice in Stockholm County and our knowledge of the database used we expect that the patients with sinus empyema would have likely been diagnosed (ICD-10) at the time of first contact. Regardless of the provider being private or public the data would be reported to our databases thus taken into account in our analyses.

Comment 5. I also miss a more in depth discussion on problems with exact diagnosis in primary care, as registered in the computer systems. There are large variations on this, both between countries and between GPs. Although ICD 10 may be well defined in theory, diagnostic work in primary care is quite variable. There are a number of symptom diagnoses in ICPC which is used in most other European countries. I assume that J06 in ICD 10 is the unspecified group of URTI corresponding to R74/symptomdiagnoses in ICPC. It could be of interest to compare the numbers with those from Gjelstads JAC-paper.

Response: We used ICD-10 codes as this is the diagnosis classification used in Sweden. All healthcare settings here report data using ICD-10 codes. While there have been no comprehensive validation studies of diagnoses reported by GP done in our region we expect that the comprehensive algorithm used in our study should have helped interpret the recorded data. We also did note in the limitations that we rely on the accurate recording of these data in our databases.

We do not have experience of working with the ICPC codes and are not aware of any studies done to investigate the comparability of the codes for URTIs ICD-10 to the ICPC. It may be that the ICD-10 allows clinicians to document diagnoses with more precision (some studies were done to compare the accuracy of the disease codes in other therapeutic areas (see for example Valkhoff et al J Clin Epidemiol. 2014).

Comment 6. Cars et al have found a surprisingly high proportion of otitis media treated with antibiotics. The proportion of acute otitis media treated with antibiotics is hard to understand. This is both due to Swedish guidelines that recommend no antibiotics for uncomplicated otitis media. This is also in contrast to findings from Norway and the Netherlands where a much smaller proportion is treated.

Response: We agree that our proportion of otitis media treated with antibiotics compared to Norway is surprisingly high. However, we believe that this may be explained by use of different coding frameworks (ICD vs ICPC). This may also be explained by different methods to define a treated episode of otitis media where we classified an episode as treated if antibiotics was dispensed at any time during the episode.

Response: We have added the following sentence in the Discussion:

“Of interest also is that while the proportion of patients with tonsillitis, sinusitis and other URTI receiving antibiotics in our study was comparable with that of Norway(25) the doctors in Stockholm prescribed antibiotics to a larger proportion of AOM patients than the doctors in Norway did. This may possibly be explained by different frameworks for coding AOM (ICD-10 vs. ICPC) and different definitions for exposure to antibiotic. Our definition of the antibiotic-exposed group included patients receiving an antibiotic anytime during their URTI episode thus likely resulting in a more complete capture of patients treated with antibiotics.”

Comment 7. It is apparent that the unspecified group of URTI/sinusitis is quite large, and may well have included cases with LRTIs. This is another argument why pneumonia should have been included among the complications.

Response: See answer to Q1. There are of course patients with pneumonia with no lower RTI symptoms present initially who later develop cough or increased respiratory rate or chest pain. In a secondary data-based study like this one, we however cannot differentiate that group from the suggested hypothetical patient group with URTI/sinusitis who have a local spread of bacteria's from sinus/oropharynx to lung parenchyma.

The role of respiratory viruses in URTI in the pathogenesis of community acquired pneumonia is complex. They probably impair local immune defense and enables bacterial infections, or mixed infections (Clin Infect Dis. 2005 Aug 1;41(3):345-51). However, patients with acute bronchitis should not receive antibiotics regardless of viral or bacterial etiology (https://www.nice.org.uk/guidance/cg69 and Cochrane Database Syst Rev. 2014 Mar 1;(3):CD000245. doi: 10.1002/14651858.CD000245.pub3). We therefore decided not to include complications such as pneumonia in patients with URTI/sinusitis who may simultaneously at presentation have had acute bronchitis.

Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults.
BMJ. 1996 Aug 10;313(7053):325-9

van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis.
Lancet. 1997 Mar 8;349(9053):683-7

Gjelstad S, Straand J, Dalen I, Fetveit A, Strøm H, Lindbæk M.Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections?J Antimicrob Chemother. 2011 Oct;66(10):2425-33.

Reviewer: 3

Nick Francis
Cardiff University, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment: This paper addresses and important topic and uses what sounds like an impressive database.

Comment: My main concern is a lack of clarity around the objectives. The main objective described in the abstract, and at the end of the discussion paper, is to, "Set up a process for continuous monitoring of upper respiratory tract infections …". Setting up a process, however, is not a research question / objective in itself. The authors could have produced a paper that addresses questions about how to set up a system for continuous monitoring of URTIs, or the barriers and facilitators to setting up a system, but this paper does not do those things, and is actually primarily a paper describing two analyses looking at associations between URTI diagnoses and antibiotic prescribing. However, study questions are vague and it is not clear whether the aims are purely descriptive or if there are hypotheses that are being explored. This all needs to be clarified with specific objectives that then match with methods and results.

Response: Thank you for taking the time to review our manuscript. We appreciate your comments which we address one by one.

Comment: Regarding the objective – this work was indeed part of our work on setting up continuous monitoring of patients outcomes in view of the more restrictive antibiotic guidelines that we felt was necessary to reassure patients prescribers and decision-makers. We agree that this is not a research question in itself. The research question is whether or not the use (or non-use) of antibiotics is associated with bacterial complications following URTIs. We have now changed the objective to "To investigate if use of antibiotics was associated with bacterial complications following URTIs."

Response: We agree that the study ended up being very much descriptive in nature as when we analysed the data we saw that the bacterial complications were very rare. With so few events we were not able to reliably compare the antibiotic-exposed and non-exposed individuals. Moreover, our data indicated that the confounding by indication was obviously present in our study.

There are a number of specific points that I would like to see addressed:

Comment: The first study is described as an ecological study, and while I agree with this, I think it would be more informative to describe it as an ecological time-trend analysis, or just a time-trend analysis.

Response: Thank you, we have updated per your suggestion throughout the manuscript.

Comment: I would like to see a bit more detail about the quality of the data. Does VAL include out of hours care? How well are infections coded in VAL? Has there been any validity work?

Response: The VAL-database includes out of hours care. While there have been no comprehensive validation studies of diagnoses reported by GP done in our region we expect that the comprehensive algorithm used in our study should have helped interpret the recorded data. We also did note in the limitations that we rely on the accurate recording of these data in our databases. We as suggested by the reviewer added more information about the quality of the data in the discussion.

Comment: Please be more specific about the aims of the ecological time trend study. Was it purely descriptive, or were there specific hypotheses that were under investigation (i.e. reduction in AB prescribing would not be associated with increase in complications). How would you have handled increase in some AB and decrease in others? It all feels a bit vague at the moment.

Response: The ecological time trend study was descriptive but we also hypothesized if decrease in use of antibiotics on a population level was associated with bacterial complications following URTIs. This is now written more clearly as we clarified the objective of the study.

Comment: The definition of cohort 4 (page 7, lines 41-42) is not clear to me. Does it include all patients in cohort 3 AND those with URTI? What is meant by, 'of multiple and unspecified sites'?

Response: The cohort 4 comprises patients included in cohort 3 as well as those with URTI. The 'of multiple and unspecified sites' is part of the description of the ICD-10 diagnosis used (J06 Acute upper respiratory infections of multiple and unspecified sites).

Comment: I found the description (and figure) of the definitions around episode start and end date confusing. Is the end date the first of, 1) 30 days following the start of the episode, 2) the date that an antibiotic is dispensed (if dispensed within 3 days of a consultation), 3) the date of a complication?

Response: As in this study we used secondary data (our data are essentially reimbursement claims data recorded for the purposes of healthcare administration and reimbursement rather than research) we had to develop an algorithm that, based on our clinical knowledge and the knowledge of the processes leading to the data generation, would be able to reflect the routine clinical practice. We created episodes to combine recorded diagnoses attributed to the same URTI. The first recorded diagnoses in an episode was set to episode start date. To be classified as a new episode there must be at least 30 days free from recorded diagnosis before index. If only one diagnosis was recorded in the episode, then start and end date of that episode was the same date. Furthermore, this episode was then followed for 30 days after end date. If several diagnoses were recorded within the same episode (ie less than 30 days between recorded diagnoses) they were attributed to the same episode. In this situation, episode start was the date of the first recorded diagnoses and end of episode that date of the last recorded diagnosis in the episode. In this case, this episode was followed 30 days from the episode end date. To reflect the strategy of watchful waiting we also allowed a dispensation of antibiotics within 3 days after the last recorded diagnosis in an episode. In this situation, the date on dispensation constituted the episode end date.

Ccomment: Outcomes – The term ‘peritonsillitis’ is not in common use in the UK and I had to look up a definition. I am not convinced that ‘peritonsillitis’ can be accurately classified distinctly from ‘tonsillitis’ or ‘pharyngitis’. Is there evidence that this is a useful distinction? Does it really make sense to classify it as a complication?

Response: By peritonsillitis we mean a peritonsillar abscess (PTA) and have changed the term throughout the manuscript. It is in most cases easy to distinguish PTA from tonsillitis on examination. The infected tonsil is displaced, uvula deviated to the contralateral side, and often trismus. Bilateral peritonsillar abscesses is rare (Am J Otolaryngol 2006 Nov-Dec;27(6):443).

Comment: Analysis – The study aims are not entirely clear, but it would appear that one of the aims is to compare complication rates in those exposed and not exposed to antibiotics. Indeed, comparisons are described in the Discussion section. However, this is not mentioned in the analysis section and no statistical tests have been used to compare rates in exposed and unexposed groups. Why was this?

Response: We have clarified the objectives. We have not included relative risks or confidence intervals due to the very low number of bacterial complications. We agree that the study ended up being very much descriptive in nature as when we analysed the data we saw that the bacterial complications were very rare. With so few events we were not able to reliably compare the antibiotic-exposed and non-exposed individuals. Moreover, our data indicated that the confounding by indication was obviously present in our study.

Comment: There is no mention of any ethical or other approval for use of the data.

Response: This information is provided in the Methods section: Because this study used only anonymized administrative healthcare data, informed consent was not required. The study was approved by the regional ethics committee in Stockholm, Sweden (Ref. no. 2015/158-31).

Results
Comment: There are some formatting issues around pages 9-11 and some of the text seems to be missing.

Response: Thank you, we have now addressed.

Comment: The series of p values presented in the text of page 10 and in Figure 3 do not provide a very comprehensive, and could be quite misleading) description of the trends observed. There is no mention in methods of tests for trend. What is the hypothesis that is being tested? Some show considerable variation. How do you explain this variation?

Response: The series of p-values presented in the Results section and in Figure 3 is a test for trend between 2006 and 2015. For this we used negative binominal regression which is mentioned in the Statistical analysis part.

We have no explanation why the number of cases with pansinusitis (between 10 and 25 per year) and ethmoiditis (between 30-80 per year) show these fluctuations.

Comment: What is described as 'peritonsillitis' in the text seems to be referred to as peritonsillar abscess in Figure 3.

Response: By peritonsillitis we mean a peritonsillar abscess (PTA) and have changed the term throughout the manuscript.

Discussion
Comment: What is described as simply, 'Selection bias' (page 12, lines 33-34) I think would more accurately be described as, 'Confounding by indication' or 'Indication bias'.

Response: Thank you! We have changed per your suggestion.

Comment: On page 13 (lines 31-32) you state that you have demonstrated that routinely collected data, 'can be used in continuous monitoring of antibiotics use and related patient outcomes.' This would suggest to me that you have demonstrated the ability to do this in an ongoing (preferably real-time) way. However, it appears as though you have been able to do a 'one-off' retrospective analysis, and I don't think it is reasonable to describe this as, 'continuous monitoring'. There could be more discussion about the possible reasons for the results seen, as well as the implications.

Response: Thank you for pointing this out! As we mentioned earlier in our reply this work has indeed been part of our work on setting up continuous monitoring of patients outcomes in view of the more restrictive antibiotic guidelines that we felt was necessary to reassure patients prescribers and decision-makers. We agree that this is not a research question in itself. The research question is whether or not the use (or non-use) of antibiotics is associated with bacterial complications following URTIs. We have now addressed this.

Comment: We hope that the revised discussion addressing your comments as well as comments from the other reviewers now is more informative.

VERSION 2 – REVIEW

REVIEWER	Morten Lindbæk Antibiotic Centre for primary care University of Oslo
REVIEW RETURNED	18-Jun-2017

GENERAL COMMENTS	1. The main question is what is considered a complication. When comparing with other studies, I especially miss the number of pneumonia. This was the most frequent complication in Gullifords study and was about 10 times as frequent as peritonsillar abscess. The authors have not discussed this at all in the paper. They may argue that they only deal with URTIs and that pneumonia is not relevant. But a number of URTIs can give complications to lower respiratory tract, such as acute sinusitis with postnasal drip. Acute bronchitis is often regarded as a URTI which may definetely lead to pneumonia. In my opinion pneumonia is also a relevant complication to be evaluated in this study. While we agree that pneumonia could be considered for inclusion in such analyses we however made a decision at the point of the study design to not include pneumonia as complication following URTIs because a) Common URTIs are not considered equally established risk factors for community acquired pneumonia as smoking, alcohol consumption, and co-morbidities especially chronic respiratory disease including COPD. b) Acute bronchitis may proceed to pneumonia, but it is not recommended to use prophylactic antibiotics in these cases. We did not aim to study if prophylactic use of antibiotics may have a protective effect in these cases c) Some of the patients with cough in the Gulliford study may have had a pneumonia that was not diagnosed properly. These patients should have been treated with antibiotics if they were correctly diagnosed initially, but now the pneumonia diagnosis was late due to doctor´s delay. 2. Another relevant question is whether septicemia in general should be considered to be a possible complication and not only related to streptococcus. I miss that this topic is discussed more in depth. Just like pneumonia, septicaemia could also be studied as a complication. We however decided not to include this because a) It is mainly the risk for invasive group A streptococcal disease (GAS) associated with tonsillitis, and if delayed or no antibiotics could increase the risk for invasive disease that have been of concern from some experts. However, we did not find any association and believe that co-morbidities and skin lesions may be risk factors for invasive disease, but in many cases there are no risk factors reported (J Clin Microbiol 2008 Jul; 46(7): 2359). Why GAS in certain situations invade the oropharynx or skin tissue may have to do with specific virulence factors in certain strains (M protein, hyaluronidase, peptidase etc.) and HLA class II allelic variations.

	b) We did not include invasive pneumococcal disease because pneumonia is the dominating infectious focus and not URTIs c) Sepsis due to alfa streptococcus and S aureus are not complications to URTIs. 3. The paper has not included the most frequent complication in acute sinusitis: maxiallary empyema which occurs in 1-2 % of all patients (Lindbaek, van Buchem). 4. Furthermore have you included data from private ENT-specialists who may have handled a number of patients with sinus empyema, without being sent to hospitals? They may also have handled a number of cases with peritonsillitis 5. I also miss a more in depth discussion on problems with exact diagnosis in primary care, as registered in the computer systems. There are large variations on this, both between countries and between GPs. Although ICD 10 may be well defined in theory, diagnostic work in primary care is quite variable. There are a number of symptom diagnoses in ICPC which is used in most other European countries. I assume that J06 in ICD 10 is the unspecified group of URTI corresponding to R74/symptomdiagnoses in ICPC. It could be of interest to compare the numbers with those from Gjelstads JAC-paper. 6. Cars et al have found a surprisingly high proportion of otitis media treated with antibiotics. The proportion of acute otitis media treated with antibiotics is hard to understand. This is both due to Swedish guidelines that recommend no antibiotics for uncomplicated otitis media. This is also in contrast to findings from Norway and the Netherlands where a much smaller proportion is treated. 7. It is apparent that the unspecified group of URTI/sinusitis is quite large, and may well have included cases with LRTIs. This is another argument why pneumonia should have been included among the complications.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Morten Lindbæk
Antibiotic Centre for primary care, University of Oslo

Comment 1. The main question is what is considered a complication. When comparing with other studies, I especially miss the number of pneumonia. This was the most frequent complication in Gullifords study and was about 10 times as frequent as peritonsillar abscess. The authors have not discussed this at all in the paper. They may argue that they only deal with URTIs and that pneumonia is not relevant. But a number of URTIs can give complications to lower respiratory tract, such as acute sinusitis with postnasal drip. Acute bronchitis is often regarded as a URTI which may definetely lead to pneumonia. In my opinion pneumonia is also a relevant complication to be evaluated in this study.

Response: While we agree that pneumonia could be considered for inclusion in such analyses we however made a decision at the point of the study design to not include pneumonia as complication following URTIs because:

a) Common URTIs are not considered equally established risk factors for community acquired pneumonia as smoking, alcohol consumption, and co-morbidities especially chronic respiratory disease including COPD.
b) Acute bronchitis may proceed to pneumonia, but it is not recommended to use prophylactic antibiotics in these cases. We did not aim to study if prophylactic use of antibiotics may have a protective effect in these cases
c) Some of the patients with cough in the Gulliford study may have had a pneumonia that was not diagnosed properly. These patients should have been treated with antibiotics if they were correctly diagnosed initially, but now the pneumonia diagnosis was late due to doctor´s delay.

We also added the following sentence in the Methods->Outcomes section:

”We therefore included as outcomes in the study those bacterial complications that have an established or plausible association to various URTIs.”

REVIEWER: THANKS FOR YOUR RESPONSE. I STILL DON’T THINK YOU ARGUE WELL ENOUGH WHY PNEUMONIA SHOULD NOT BE INCLUDED AS A BACTERIAL COMPLICATION. THIS IS CLINICALLY COMPLEX, SUCH AS THE J06 GROUP, INFLUENZA-LIKE INFECTIONS. I LIKE YOUR ADDITION TO THE METHODS SECTION, BUT STILL I THINK THIS TOPIC SHOULD HAVE BEEN MENTIONED UNDER LIMITATIONS IN DISCUSSION, THAT YOUR CHOICE OF COMPLICATIONS ALSO IS BASED ON UNCERTAINTY.

Our response:
Thank you for your comment. As mentioned in our previous response we made the decision to not include pneumonia as a bacterial complication during the design of this study. It should, however, be very interesting to analyse pneumonia as a bacterial complication in a separate study. To include pneumonia as a bacterial complication would need a new ethical approval and new permissions from data holders which approximately would take one year and we believe that that is not feasible at this late stage of the manuscript.

As suggested, we have added the following sentence under limitations in the discussion section:

”We based our selection of bacterial complications on those that we perceived have an established association to various URTIs. There could be other bacterial complications such as pneumonia that we have missed by narrowing the number of complications we looked for.”

The Gulliford study differ from ours in several ways. One important difference is that Gulliford in their RTIs not only included URTIs, as we did, but also cough and acute bronchitis so their decision to include pneumonia among complications are more reasonable. Still one can argue that the clinical diagnoses of pneumonia without radiology in primary care is difficult, so all pneumonia complications in their study are probably not valid.

Comment 2. Anpther relevant question is whether septicemia in general should be considered to be a possible complication and not only related to streptococcus. I miss that this topic is discussed more in depth.

Just like pneumonia, septicaemia could also be studied as a complication. We however decided not to include this because

a) It is mainly the risk for invasive group A streptococcal disease (GAS) associated with tonsillitis, and if delayed or no antibiotics could increase the risk for invasive disease that have been of concern from some experts. However, we did not find any association and believe that co-morbidities and skin lesions may be risk factors for invasive disease, but in many cases there are no risk factors reported (J Clin Microbiol 2008 Jul; 46(7): 2359). Why GAS in certain situations invade the oropharynx or skin tissue may have to do with specific virulence factors in certain strains (M protein, hyaluronidase, peptidase etc.) and HLA class II allelic variations.
b) We did not include invasive pneumococcal disease because pneumonia is the dominating infectious focus and not URTIs
c) Sepsis due to alfa streptococcus and S aureus are not complications to URTIs.

REVIEWER: DON'T FULLY AGREE HERE. BOTH IN SINUSITIS AND OTITIS MEDIA PNEUMOCOCCI IS A MAJOR PATHOGEN WHICH MAY LEAD TO SEPTICAEMIA.

Our response:
Like our response to your previous comment we did not, at the design of this study, include septicaemia as a complication. We have added the following sentence in the discussion part:

"We based our selection of bacterial complications on those that we perceived have an established association to various URTIs. There could be other bacterial complications such as pneumonia that we have missed by narrowing the number of complications we looked for."

Comment 3. The paper has not included the most frequent complication in acute sinusitis: maxiallary empyema which occurs in 1-2 % of all patients (Lindbaek, van Buchem).

Our response: Maxillary empyema is pus and pathogenic bacteria in the sinus. In the van Buchen trial were patients with a history and findings at examination compatible with acute maxillary sinusitis referred to CT. Ca 55% of those had abnormal radiographs (and was randomized to amoxicillin or placebo). The absolute majority of those with abnormal CT-findings would have growth of bacteria if a sinus aspirate would have been done. That is, we consider CT verified acute maxillary sinusitis and maxillary empyema the same clinical entity. Of note, the included patients in this trial had all proven CT findings and most likely worse symptoms than the original group as a whole and also compared to unselected sinusitis patients at general practitioners (Lancet 1997 Mars 8;349:683-7).

REVIEWER: I DON'T SEE THAT THIS AN ARGUMENT AGAINST WHY SINUS EMPYEMA SHOULD HAVE BEEN INCLUDED AS A COMPLICATION. IF AN EMPYEMA IS ESTABLISHED, IT IS NECESSARY TO MAKE A PUNCTURE FOR DRAINING THE PUS. FURTHERMORE, YOUR DESCRIPTION OF THE REFERENCED STUDIES IS NOT PRECISE. VAN BUCHEM USED X-RAY WHILE WE USED CT AS REFERENCE STANDARD. AND IT IS NOT RIGHT THAT ANY FINDING ON SINUS CT (FOR EX MUCOSAL THICKENING) IS SYNONYMOUS WITH SINUS EMPYEMA. A VIRAL SINUSITIS CAN GIVE EXTENSIVE CT-FINDINGS.

Our response:
Thank you for your comment. We agree on your opinion on CT-findings and the difficulties to differ empyema from mucous membrane swelling. However, we don't have information on CT findings in this register-based study, and further, acute maxillary sinusitis and acute maxillary empyema are both coded J01 in ICD-10 and can not be used to distinguish the two from each other. Therefore, we are unable to include sinus empyema as a bacterial complication in this study.

Comment 4. Furthermore have you included data from private ENT-specialists who may have handled a number of patients with sinus empyema, without being sent to hospitals? They may also have handled a number of cases with peritonsillitis

Based on our knowledge of the clinical practice in Stockholm County and our knowledge of the database used we expect that the patients with sinus empyema would have likely been diagnosed (ICD-10) at the time of first contact. Regardless of the provider being private or public the data would be reported to our databases thus taken into account in our analyses.

REVIEWER: OK, FINE

Comment 5. I also miss a more in depth discussion on problems with exact diagnosis in primary care, as registered in the computer systems. There are large variations on this, both between countries and between GPs. Although ICD 10 may be well defined in theory, diagnostic work in primary care is quite variable. There are a number of symptom diagnoses in ICPC which is used in most other European countries. I assume that J06 in ICD 10 is the unspecified group of URTI corresponding to R74/symptomdiagnoses in ICPC. It could be of interest to compare the numbers with those from Gjelstads JAC-paper.

We used ICD-10 codes as this is the diagnosis classification used in Sweden. All healthcare settings here report data using ICD-10 codes. While there have been no comprehensive validation studies of diagnoses reported by GP done in our region we expect that the comprehensive algorithm used in our study should have helped interpret the recorded data. We also did note in the limitations that we rely on the accurate recording of these data in our databases.

We do not have experience of working with the ICPC codes and are not aware of any studies done to investigate the comparability of the codes for URTIs ICD-10 to the ICPC. It may be that the ICD-10 allows clinicians to document diagnoses with more precision (some studies were done to compare the accuracy of the disease codes in other therapeutic areas (see for example Valkhoff et al J Clin Epidemiol. 2014).

REVIEWER: OK, STILL I THINK THIS SHOULD HAVE BEEN MENTIONED IN THE LIMITATIONS PART.

Comment 6. Cars et al have found a surprisingly high proportion of otitis media treated with antibiotics. The proportion of acute otitis media treated with antibiotics is hard to understand. This is both due to Swedish guidelines that recommend no antibiotics for uncomplicated otitis media. This is also in contrast to findings from Norway and the Netherlands where a much smaller proportion is treated.

Response: We agree that our proportion of otitis media treated with antibiotics compared to Norway is surprisingly high. However, we believe that this may be explained by use of different coding frameworks (ICD vs ICPC). This may also be explained by different methods to define a treated episode of otitis media where we classified an episode as treated if antibiotics was dispensed at any time during the episode.

We have added the following sentence in the Discussion:

“Of interest also is that while the proportion of patients with tonsillitis, sinusitis and other URTI receiving antibiotics in our study was comparable with that of Norway(25) the doctors in Stockholm prescribed antibiotics to a larger proportion of AOM patients than the doctors in Norway did. This may possibly be explained by different frameworks for coding AOM (ICD-10 vs. ICPC) and different definitions for exposure to antibiotic. Our definition of the antibiotic-exposed group included patients receiving an antibiotic anytime during their URTI episode thus likely resulting in a more complete capture of patients treated with antibiotics.”

REVIEWER: OK FINE

Comment 7. It is apparent that the unspecified group of URTI/sinusitis is quite large, and may well have included cases with LRTIs. This is another argument why pneumonia should have been included among the complications.

Response: See answer to Q1. There are of course patients with pneumonia with no lower RTI symptoms present initially who later develop cough or increased respiratory rate or chest pain. In a secondary data-based study like this one, we however cannot differentiate that group from the suggested hypothetical patient group with URTI/sinusitis who have a local spread of bacteria’s from sinus/oropharynx to lung parenchyma.

The role of respiratory viruses in URTI in the pathogenesis of community acquired pneumonia is complex. They probably impair local immune defense and enables bacterial infections, or mixed infections (Clin Infect Dis. 2005 Aug 1;41(3):345-51). However, patients with acute bronchitis should not receive antibiotics regardless of viral or bacterial etiology (https://www.nice.org.uk/guidance/cg69 and Cochrane Database Syst Rev. 2014 Mar 1;(3):CD000245. doi: 10.1002/14651858.CD000245.pub3). We therefore decided not to include complications such as pneumonia in patients with URTI/sinusitis who may simultaneously at presentation have had acute bronchitis.

REVIEWER: I DON’T AGREE. THESE PATIENTS MAY NOT ONLY HAVE DEVELOPED AN ACUTE BRONCHITIS, BUT ALSO A PNEUMONIA AS A COMPLICATION TO THEIR ORIGINAL URTI.

Our response:
See our previous responses regarding inclusion of pneumonia as a complication.

VERSION 3 – REVIEW

REVIEWER	Morten Lindbæk Antibiotic Centre for primary care University of Oslo, NOrway
REVIEW RETURNED	02-Sep-2017

GENERAL COMMENTS	I still don't fully aggree With the Choice of complications in this paper, but I see that it is not feasible to make a New study based on New data. So I conclude that it should be accepted as is. I am happy With the New discussion