PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study
AUTHORS	Landstedt, Kristoffer; Sharma, Ashish; Johansson, Fredrik; Lundborg, Cecilia; Sharma, Megha

VERSION 1 - REVIEW

REVIEWER	DR ABDUL GHAFUR APOLLO HOSPITAL,CHENNAI,INDIA
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS	The article is very promising and targets the serious issue of irrational antibiotic use. How ever I would like to make some comments and need a few clarifications 1. Have authors studied the case records of all patients in detail? What I understand from the paper is, the only available clinical data is from ICD code and not based on day-to-day progress details recorded by doctors. This is very important, as empirical antibiotic usage based on clinical judgment is rational as long there is a strong clinical suspicion of bacterial infection, substantiated by relevant history and clinical findings and doctors have discontinued antibiotics once infection is ruled out. I do not agree with the authors' argument that antibiotic usage without a confirmed infection is irrational. The two references quoted supporting this argument are insufficient. (Page 18, lines 3,4,5 references 15,16). Rates of irrational antibiotic usage in both study centres could be erroneously high due to the above concern. 2. Have authors analysed the reliability of ICD coding in the two centres? It is a well-known fact that junior doctors in India writing the patient discharge summary do not often include sub entities, unlike most western centres. For e.g. for a patient with Myocardial infarction, with a confirmed diagnosis of pneumonia or urinary infection, doctors may document only MI and may not even mention about UTI or pneumonia in the final diagnosis part of discharge summary. This is due to the inadequate discharge summary preparation practices in many Indian hospitals. For this reason, it is very important to study case records in detail. 3. Is there any data on Microbiology culture results of any of these patients, in groups documented as confirmed bacterial infection or patients with no documented bacterial infection? Starting antibiotics without sending cultures or not rationalizing antibiotics based on culture results are indicators of irrational prescribing. 4. I do agree that, it will be very difficult at this stage to go back to case records of 20 thousand patients for detailed clinical data, if not already collected. So please discuss the above mentioned pitfalls of

	the study in detail, unless authors have strong arguments not to do so.

REVIEWER	Mieke van Driel University of Queensland, Australia
REVIEW RETURNED	28-Jul-2016

GENERAL COMMENTS	This paper describes antibiotic prescribing for patients admitted to medicine wards in 2 Indian hospitals over a period of 3 years. Given the global impact of local antibiotic resistance, it is important to understand prescribing in high AB use countries such as India. Considerable work has been done in the area of antimicrobial stewardship in hospitals worldwide and this study can inform AMS in India. Although a worthwhile study, there are some issues with this paper that require attention. - In general this is interesting work, but the data collected is quite old (2008-2011). Why did it take so long to publish and how generalisable could this study be to the current date? AMS has moved ahead worldwide, and also in India but this is not at all discussed in the paper. The authors have not convinced me of the importance of the data they report and how this could inform AMS efforts in their hospitals, region and country in 2016. - Setting: what is the patient throughput in each of the hospitals? This would give a better idea of the volume of patient encounters. more so than just a bed capacity. - Methods: what happened to the incomplete records? How many records were incomplete and how could this have impacted on the results? - Methods: data collection was done by nurses, so after the doctor had finished filling in the record? Who did the coding and how was this checked for consistency? - Methods: the classification of the diseases that was used may cause bias, especially the group b and c. It is mostly impossible to distinguish viral from bacterial diseases clinically, so how was this distinction made? The whole analysis seems to be based on comparing the indications that don't require AB with the ones that justify AB use. Therefore this classification is crucial and needs to be described in much more detail. In a way this distinction adds to the complexity of the paper. The message about overall (high) prescribing and choices of AB is interesting and important in its own right. Trying to dig deeper and make judgments about the appropriateness of prescribing introduces a risk of missing the mark. The reason why I am worried about this classification is for instance the low incidence of pneumonia (0 in the TH and 1 case in the NTH over the entire study period!!! That does not make sense to me. Please explain and review. - Essential medicines list; results are discussed in the context of the list but it is stated on pg 6 that this list was not available at the time! So how relevant is this for now? - page 11: explain FDC - Results: is scripts per patient the correct unit? As far as I can tell data are not linked to individual patients but rather to patient episodes/presentations. This means that the same patient can contribute to AB scripts. - Results: how useful is comparison of generic vs trade names if the availability of AB is regulated in the TH?

	- Discussion needs some editorial review as the text flows much less than other sections of the paper. - Reference list needs to be checked for consistency.

VERSION 1 – AUTHOR RESPONSE

The article is very promising and targets the serious issue of irrational antibiotic use.
However I would like to make some comments and need a few clarifications:
Response: We thank the reviewer for the appreciation and encouraging words also for recognizing the significance of the problem focused in the manuscript.

1a. Have authors studied the case records of all patients in detail? What I understand from the paper is, the only available clinical data is from ICD code and not based on day today progress details recorded by doctors.

Response 1a: We connect with reviewer's concern and would like to explain the data collection procedure here in detail.
This was a prospective study and according to the study protocol all patients admitted in Medicine wards of two study hospitals were included in the study. The data collection form was updated on daily basis for all inpatients that were prescribed antibiotics. It was done based on day to day progress report as written by the treating consultant in the patient files.
All indications, diagnoses and/or symptoms present in the patient files were recorded in the data collection form and were included in the analysis. Diagnoses were recorded on the day of discharge to minimize the risk of missing diagnosis or indications written in the patient files on the discharge day.
The variables; such as ICD codes, ATC codes, DDDs were added during data entry process by trained data entry operators and not by the nurses. Both, the diagnoses and ICD-10 codes were used for categorization of patients in various diagnosis groups.
The forms and the patient files were randomly cross checked for consistency by the last author and persons designed by her.
We have now modified the text to make this point clear in METHODS section in Data sources and considerations: Page 8-9
The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes),[20,21] and the generic names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day ,[15].

1b. This is very important, as empirical antibiotic usage based on clinical judgment is rational as long there is a strong clinical suspicion of bacterial infection, substantiated by relevant history and clinical findings and doctors have discontinued antibiotics once infection is ruled out. I do not agree with the authors' argument that antibiotic usage without a confirmed infection is irrational. Rates of irrational antibiotic usage in both study centres could be erroneously high due to the above concern.

Response 1b: We partly agree to the comment made by the reviewer, that in view of strong clinical suspicion, empiric antibiotic prescribing is considered to be rational. However, in order to continue the therapy; supporting laboratory investigation reports are essential. We have modified the text.
We have added new text in DISCUSSION, Page : 18-19
Interestingly, more than 35% of inpatients in the 'cardiovascular group with no registered bacterial

infection' were prescribed antibiotics in both hospitals. As per the treatment guidelines and recommendations, only those patients who have confirmed infectious diagnosis are expected to receive an antibiotic prescription,[15, 16]. Nonetheless, empirical or presumptive antibiotic therapy is also accepted when based on a clinical diagnosis in presence of strong clinical suspicion of bacterial infection, substantiated by relevant history and clinical findings,[29].
We have added new text as per the suggestion made by the reviewer: STRENGTHS AND LIMITATIONS, Page 23
The results of the study were based on the notes included in the patient files. Extensive efforts were made to document all notes including diagnoses written in the patient files. However, the possibility of missing a few diagnoses and losing some data during the transition from the forms to the digital storage cannot be excluded.

1c. The two references quoted supporting this argument are insufficient. (Page 18, lines 3,4,5 references 15,16).
Response 1c: We have now added three relevant references in support of our argument.
29. National centre for disease Control India. India National Treatment Guidelines for Antimicrobial Use in Infectious Diseases. Vol. 0. New Dehli; 2016; p. 1–64.
http://www.ncdc.gov.in/writereaddata/linkimages/AMR_guideline7001495889.pdf

30. Bennet JE, Dolin R, Blaser MJ. Madell, Douglas and Bennet´s Principles and Practice of Infectious Diseases. 8th ed. Philadelphia: Saunders; 2014.

31. Davey P, Wilcox M, Irwing W, et al. Antimicrobial Chemotherapy. 7th ed. Oxford: Oxford University Press; 2015.

2a. Have authors analysed the reliability of ICD coding in the two centres?

Response 2a: As mentioned in response to comment 1a, the ICD codes were entered by two trained data entry persons during the data entry process and not by the nurses. Since fewer persons were involved in this step it increases the reliability.
Moreover, the entered ICD codes were checked for corresponding diagnoses by the first (KL) and last author (MS) at the time of analysis.
We have now modified the text to make this point clear in METHODS section in Data sources and considerations: Page 8-9
The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes),[20,21] and the generic names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day,[15].

2b. It is a well known fact that junior doctors in India writing the patient discharge summary do not often include sub entities, unlike most western centres. For e.g. for a patient with Myocardial infarction, with a confirmed diagnosis of pneumonia or urinary infection, doctors may document only MI and may not even mention about UTI or pneumonia in the final diagnosis part of discharge summary.

This is due to the inadequate discharge summary preparation practices in many Indian hospitals. For this reason, it is very important to study case records in detail.

Response 2b: Although this could be the case at some Indian healthcare facilities but we could not find any published article to quote the statement mentioned by the reviewer here. We hereby explain the data collection process and our response for the point 2b. If the reviewer still suggests to add the statement in the manuscript, we would be pleased to get the details of the references to include in our manuscript.
In our setting the prescription and diagnoses are primarily written by the treating consultants. In our study design, the data collection forms were updated mainly from the patient files and not only from the discharge summary. All indications, diagnoses and/or symptoms present in the patient files were transferred in the data collection forms. In most of the cases more than one diagnosis/ indications were present and recorded from the patient files. All possible efforts were done to minimize the missing of data. However, we cannot totally exclude the possibility of missing some diagnoses in a few cases. This has now been clarified on Page- 24 (please see below).
We could not find any published article to quote this statement as well. However as mentioned above, the data collection forms were updated mainly from the patient files and not only from the discharge summary. After reviewing the modifications made in the main text (below), if the reviewer still suggests to modify the statement in the manuscript, we would be pleased to get the details of the references to include in our manuscript.
We have now added text in STRENGTHS AND LIMITATIONS, Page 23
The results of the study were based on the notes included in the patient files. Extensive efforts were made to document all notes including diagnoses written in the patient files. However, the possibility of missing a few diagnoses and losing some data during the transition from the forms to the digital storage cannot be excluded.

3a. Is there any data on Microbiology culture results of any of these patients, in groups documented as confirmed bacterial infection or patients with no documented bacterial infection?

Response 3a: As mentioned in the manuscript, few samples from the patients suspected for malaria (non bacterial fever) in the diagnosis 'Group '(b)' on (Page 9) were sent to confirm different types of malaria. For the remaining diagnosis groups in general no samples were sent for bacterial culture and susceptibility testing thus confirmation of the diagnosis as bacterial or non bacterial infection was not possible. Therefore, going through each patient’s records will also not add any value.
We have now added text in METHODS on Page 9
Groups (a) and (b) were selected for detail study of the antibiotic prescribing for non-bacterial diagnoses as per the study aim. In 'Group (a)', hypertension, acute myocardial infarction and valvular heart disease were the most common diagnoses. In 'Group (b)' different types of malaria and cases of viral fever were included. These non-bacterial fevers were common in both study settings. It has previously been reported that antibiotics are prescribed to a high extent to patients having malaria or viral fever in malaria endemic countries like Uganda (Figure 1),[24]. Groups (a) and (b) comprised the largest homogenous patient groups in our study settings.

3b. Starting antibiotics without sending cultures or not rationalizing antibiotics based on culture results are indicators of irrational prescribing
Response 3b: The clinical diagnosis made and mentioned by the treating physician in the patient files were considered as final. [As mentioned by the reviewer in comment 1b: Presumed to be based on strong clinical suspicion of bacterial infection, substantiated by relevant history and clinical findings which might have led them to prescribe antibiotics]. Based on these diagnoses and the ICD-10 codes the patients were categorized in 3 main diagnoses groups. Patients were further categorized in 4 diagnoses sub-groups (infectious / non infectious) based on the (clinical) diagnoses made by treating consultants.
We completely agree with the reviewer that, "Starting antibiotics without sending cultures or not rationalizing antibiotics based on culture results are indicators of irrational prescribing."

We have now modified the text in DISCUSSION on Page - 19.
According to the WHO and the Indian National Treatment Guidelines for Antimicrobial Use; presumptive therapy is typically a one-time treatment given for clinically presumed infection while waiting for the culture report,[31,32]. In combination of clinical findings laboratory and radiological reports are considered to confirm the diagnosis and lead to the definitive therapy,[32].
Microbiology laboratories were highly under-utilized in both study hospitals. None of the patient records in the selected four sub-groups included notes about sending samples for culture and susceptibility testing. Therefore, the practice of prescribing antibiotics to the patient groups with no registered bacterial infection in absence of laboratory confirmation could not be considered to be rational. Among the COPD and RHD patients the aetiology of the current episode of hospitalization could potentially be expected to be non-bacterial (e.g. viral infection). However, this could not be confirmed due to the absence of laboratory investigations. It is worth mentioning here that prolonged empiric antibiotic treatment without a clear evidence of infection is one of the causes of the development of antibiotic resistance.

4. I do agree that, it will be very difficult at this stage to go back to case records of 20 thousand patients for detailed clinical data, if not already collected. So please discuss the above mentioned pitfalls of the study in detail, unless authors have strong arguments not to do so.
Response 4: All possible efforts were conducted to document complete notes from the patient files. The nurses were instructed to document all diagnosis/ indications that were registered in the patient files from the day of hospital admission till the day of discharge.
However, we agree with the reviewer and as per suggestion, we have now added the text in the manuscript in Strengths and limitation section.
We have modified text in DISCUSSION on Page: 23
The results of the study were based on the notes included in the patient files. Extensive efforts were made to document all notes including diagnoses written in the patient files. However, the possibility of missing a few diagnoses and losing some data during the transition from the forms to the digital storage cannot be excluded.

Reviewer 2: Mieke van Driel
This paper describes antibiotic prescribing for patients admitted to medicine wards in 2 Indian hospitals over a period of 3 years.

Given the global impact of local antibiotic resistance, it is important to understand prescribing in high AB use countries such as India. Considerable work has been done in the area of antimicrobial stewardship in hospitals worldwide and this study can inform AMS in India.
Response: We thank the reviewer for these encouraging comments.
A. Although a worthwhile study, there are some issues with this paper that require attention. In general this is interesting work, but the data collected is quite old (2008-2011).
Why did it take so long to publish and how generalizable could this study be to the current date?

Response A: We thank the reviewer for recognizing the importance of the results of the study conducted in semi urban settings of India.
As mentioned in the Method section; the two study hospitals are resource constrained hospitals and are run by a trust on "No Profit- No Loss" basis. The data collection and analysis process had several steps which could not be presented in detail in this manuscript due to word limitation but is explained at http://www.biomedcentral.com/1471-2334/12/155/abstract as mentioned on Page 8.
We would however, like to explain even more in detail here for you again.
The data collection form was developed locally and was pilot tested before main data collection. The data were collected manually by the nursing staff as the patient's records in both hospitals were not computerized. The nurses were trained before hand for recording the data and the training was conducted for the new recruited staff. The data collection form was attached to each patient files and

was updated on daily basis by trained nurses for all admitted patients who were prescribed antibiotics. All data related to prescribed antibiotics and all symptoms recorded in the patients' record were transferred to an individual patient data collection form.
One patient could have more than one diagnosis. All indications, diagnoses and/or symptoms present in the patient files were recorded in the data collection form and were included in the analysis. After completion, the forms were collected at least weekly by the last author or a person designed by her. There after the forms were checked manually and data was entered in EPI Info 3.1 software and Microsoft Excel data files. The data was then checked for incompleteness and the patient record archive was visited several times to check the original patient records and to complete the missing information, wherever seen. Additionally the forms and the patient files were randomly cross checked from the archive for the consistency and reliability of the data by the last author or persons designed by her. Best possible efforts were done to make the data complete. As per study protocol all incomplete records left after this step were not included in the analysis.
Antibiotics could be prescribed using Trade/ Brand or Generic names. The names (Trade or Generic names) as mentioned by the treating consultant in the patient files were transferred in the data collection forms and later in the soft data files. For antibiotics prescribed using trade names, respective generic names were introduced for the antibiotics by going through the contents in the formulation. Hospital and nearby pharmacies were visited several time by last author (MS) for this step. After this step the variables such as ICD codes (for diagnoses), ATC codes and DDDs (for prescribed antibiotics) were introduced and entered during data entry process by trained data entry operators (and not by the nurses) based WHOCC and CDC guidelines.

• http://www.whocc.no/atc_ddd_index/
• Ref: ICD-10: International Statistical Classification of diseases and Related Health Problems, 10th revision, Volume 3, Alphabetical Index, 2010 Edition, World Health Organization, ISBN: 9789241548342
• Ref: http://apps.who.int/classifications/icd10/browse/2010/en
• Ref: http://www.cdc.gov/nchs/icd/icd10cm.htm.

After completion of this step it was found that some of the fixed dose combinations were not given any ATC code by the WHO, therefore WHOCC Norway was consulted and after a multiple e-mail discussions we got permission to assign ATC codes for those new FDCs. (http://www.biomedcentral.com/1471-2334/12/155/abstract). This was also time consuming task. All efforts where done to ensure highest achievable correctness of the data. Since it was a prospective and detailed study with more than 21,000 data records and all the steps were done manually dealing with a large number of patients' records, the whole process was laborious and time consuming.
We have now modified the text to make this point clear in METHODS section in Data sources and considerations: Page 8-9
The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes),[20,21] and the generic names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day ,[15].

B. AMS has moved ahead worldwide, and also in India but this is not at all discussed in the paper. The authors have not convinced me of the importance of the data they report and how this could inform AMS efforts in their hospitals, region and country in 2016.

Response B: We agree with the reviewer that today AMS has moved ahead worldwide however, due

to lack of studies the existing policies, guidelines and programs developed are mainly based on the available results of few studies with empirical data.
The knowledge on antibiotic prescribing pattern is limited from many countries including the second most populated country in the world i.e. India. WHO Global action plan on Antibiotic Resistance has recognized the problem of misuse of antibiotics and non availability of baseline data in its statement; "Surveillance of antimicrobial use tracks how and why antimicrobials are being used and misused by patients and healthcare providers. Monitoring antimicrobial prescription and consumption behaviour provides insights and tools needed to inform therapy decisions, to assess the public health consequences of antimicrobial misuse, and to evaluate the impact resistance containment interventions." and thus encourage to conduct antibiotic surveillance studies.
This is the first study of its kind that presents antibiotic prescribing patterns at Medicine wards and relates the prescribing with diagnosis of the two tertiary care private sector hospitals from India and the region.
The situation and policy regulations at private sector hospitals in India including the study hospitals has not changed much since the study years till now; in terms of development and implementation of policies, prescribing guidelines and management and control on antibiotic prescribing. The result of our study gives an overview and highlights the problem of under or no use of laboratory services and over prescribing of antibiotics mostly irrational combinations of antibiotics to the patients present in non- bacterial infectious diagnosis group. This is a profound situation and need an immediate attention at local and national level.
The results of our study will serve as a baseline to understand the situation of antibiotic prescribing, to initiate Focus group discussions among the prescribers based on the results and to develop relevant antibiotic stewardship program for these hospitals. Once validated the program could be implemented at other similar settings in India.
In accordance to one of the WHO goals, our study -
1. Put forward a tested tool and method of data collection which could be used in other constrained settings worldwide.
2. Suggests to conduct and share similar long term surveillance studies in the settings where we have limited knowledge of antibiotic utilization and resistance patterns both in India and worldwide.
3. Recommends to encourage utilization of laboratory services
We have now included new text in DISCUSSION on Page 24
The data collection method used in the study is robust and reliable. In accordance with one of the WHO goals of "Global-action-plan" and in view of limited knowledge of antibiotic utilization and resistance patterns our study findings suggest that there is a need to conduct and share similar long term surveillance studies globally. The data collection method and tested tool used in the study could easily be adapted in other settings that lack computerized patient records. The management in the TH had a policy to control the purchase and supply of medicines. This control shows positive effects at the TH compared to the NTH; to minimize antibiotic prescribing, in better adherence to the NLEMI and in use of generic names. This control could be implemented and tested in other constrained settings. The recruitment of nursing staff for manual data collection who routinely work in the department would have helped to minimize the influence on the prescribers. High prescribing rates of antibiotics and use of FDCs among inpatients in these settings could broadly be considered as representative for similar health care settings in low-middle income countries. Lack of culture of sending cultures is another important issue raised by the study. The need to develop and implement local diagnosis specific prescribing guidelines in conjugation with continuous follow-up is also emphasized by our study. The physicians should be motivated to send samples for cultures before prescribing antibiotics. Improving hygiene practices is another recommendation to prevent spread of infection and to decrease in the 'prophylactic' use of antibiotics.

Setting:
C. what is the patient throughput in each of the hospitals? This would give a better idea of the volume of patient encounters. more so than just a bed capacity.

Response C: Thank you for this comment. The total patients admitted during study period in the study hospitals were: in the teaching hospital- 29026 and in the Non-teaching hospital-41561
We have now added following text on Page 8
Patient throughput in the TH and the NTH amounted to 29026 and 41561 patients respectively.

Methods:
D. What happened to the incomplete records? How many records were incomplete and how could this have impacted on the results?
Response D: All possible efforts were done to complete the records. As per study protocol all incomplete records which could not be completed were excluded from further analysis, however in present data set all records could be completed.
We have now included new text in the METHODS section mentioning about the incomplete records on Page 11 and in modified the Figure 1 as well (Please see Figure 1)
During the study period, totally 21557 patients were admitted to the two medicine departments, 7176 patients in the TH and 14381 in the NTH (Figure 1). Of the admitted patients records of 20 patients were incomplete, 949 (5%) stayed less than one night and 285 patients (1%) were aged <15 years. Therefore, as per the inclusion criteria 1254 patient records were excluded and 20303 (94%) records were included for further analysis (6961 at the TH and 13342 at the NTH, Figure 1).

Methods:
E. data collection was done by nurses, so after the doctor had finished filling in the record? Who did the coding and how was this checked for consistency?
Response E: The data collection form was updated on daily basis for all inpatients that were prescribed antibiotics. It was done based on day to day progress report as written by the treating consultant in the patient files.
The variables; such as ICD codes, ATC codes, DDDs were entered during data entry process by two specifically trained data entry operators and not by the nurses. Around 20% forms were cross checked with the patient files for consistency by the last author and persons designed by her.
The entered ICD codes were checked for the consistency with the corresponding diagnoses by the first and last author (MS). Similarly, the ATC codes and values of DDDs of prescribed antibiotics were also checked.
We have now modified the text to make this point clear under METHODS in Data sources and considerations: Page 8-9
The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes),[20,21] and the generic names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day ,[15].

Methods:
F. The classification of the diseases that was used may cause bias, especially the group b and c. It is mostly impossible to distinguish viral from bacterial diseases clinically, so how was this distinction made? The whole analysis seems to be based on comparing the indications that don't require AB with the ones that justify AB use. Therefore this classification is crucial and needs to be described in much more detail. In a way this distinction adds to the complexity of the paper.

Response F: Thank you for this comment.
We have considered all those diagnoses which clearly indicate the presence of the bacterial infection (clinically decided by the treating consultant) to categorize the diagnoses in three groups and further

into four sub-groups. We have now added text explaining the reason of selecting the diagnoses groups to study in detail.
In relation to clarify the categorisation of the diagnoses we have modified the text on Page 9, Para first
In order to exclude all clinically suspected cases of bacterial infection and following the aim of the study, best possible efforts were made to distinguish the patients who had any indications even for secondary antibiotic prophylaxis from those who did not,[22–24]. The patients were categorized into three main groups using the diagnoses registered in the patient files and the ICD-10 codes; Group (a) cardiovascular diseases, (b) non-bacterial fevers and (c) all diagnoses other than Group a and b including all types of bacterial infections. Sixty seven percent of patients in the TH and 75% in the NTH were included in Group (c). All cases of chronic obstructive pulmonary disease (COPD) were also included in Group c. Although aetiology of the disease was seldom specified in the records but these patients should receive less restricted antibiotic treatment.
Groups (a) and (b) were selected for detail study of the antibiotic prescribing for non-bacterial diagnoses as per the study aim. In 'Group (a)', hypertension, acute myocardial infarction and valvular heart disease were the most common diagnoses. In 'Group (b)' different types of malaria and cases of viral fever were included. These non-bacterial fevers were common in both study settings. It has previously been reported that antibiotics are prescribed to a high extent to patients having malaria or viral fever in malaria endemic countries like Uganda (Figure 1),[24]. Moreover, Groups (a) and (b) comprised the largest homogenous patient groups in our study settings.
These groups were further divided into four sub-groups to identify and analyse the patients exclusively having non-bacterial diagnoses corresponding to our study aim. The cardiovascular group (Group a) was divided in two sub-groups; 'cardiovascular diseases with no registered bacterial infection' (sub-group 1), 'cardiovascular diseases with suspected bacterial infection' (sub-group 2). Similarly, the non-infectious fever group (Group b) was divided 'malaria or viral fever with no registered bacterial infection' (sub-group 3) and 'malaria or viral fever with suspected bacterial infection' (sub-group 4, Figure 1).
As far as the complexity of distinguishing viral infections from bacterial infections is concern; the treating consultants were the deciding authorities for the type of infections present. They assessed, mostly clinically, and wrote the diagnosis in patient records during patient's hospital stay. We have analysed and presented the results based on the notes written in the patient records and following the study design (observational) we have not inferred any conclusion from these notes.
Additionally we also would like to mention that the decision made by the consultants during clinical assessment might not be correct every time, therefore sending bacterial culture samples for investigations before administration of first dose of antibiotic is important.
We have already stated in the text on Page 10, Ethics statement:
Being an observational study, the data collection did not interfere with the treatment or caused any extra risks for the patients.

G. The message about overall (high) prescribing and choices of AB is interesting and important in its own right. Trying to dig deeper and make judgments about the appropriateness of prescribing introduces a risk of missing the mark. The reason why I am worried about this classification is for instance the low incidence of pneumonia (0 in the TH and 1 case in the NTH over the entire study period!!! That does not make sense to me. Please explain and review.
Response G: Thank you for this comment.
The two study hospitals are tertiary care hospitals having a number of speciality departments. Some of the specialty departments are: Pediatrics, Obstetrics and Gynaecology, Surgery, Orthopaedics, Pulmonary Medicine, Intensive care unit, Neonatal Intensive care unit, Surgery Intensive care unit, burn unit and so on.
The patients presenting with specific complaints or symptoms are guided/ suggested from the registration counter or are redirected from other out-patient departments to visit the concerned

speciality. For example; patients presenting with the complaints related to lungs and chest (other than heart) are treated mainly in Pulmonary Medicine department. The Pulmonary Medicine department of the hospitals primarily evaluates and treats people with diseases of the lungs and the other organs of breathing, manages diseases in the chest other than the heart. This is the reason why there were none or few cases of pneumonia in the present data of Medicine departments at both the hospitals.
Taking the comment in account we have now added new text in the
We have now modified text under Study setting on Page 7
Both hospitals are tertiary care hospitals with a number of specialty departments such as; Pediatrics, Obstetrics and Gynaecology, Surgery, Orthopaedics, Pulmonary Medicine, and so on to treat specific patients. For example; patients presenting with complaints related to lungs and chest (other than heart) visit the Pulmonary Medicine department.

H. Essential medicines list; results are discussed in the context of the list but it is stated on pg 6 that this list was not available at the time! So how relevant is this for now?
Response H: We apologies for this confusion. We would like to draw your attention to the point that the essential medicine list was available in the TH but the local prescribing guidelines were not available in any of the hospitals. The results were thus compared for the National level Essential medicine list which is available and is expected to be known to all healthcare facilities and doctors.
We have now modified the text to make it clearer in the main text.
We have now modified text in METHODS: Page 6
Hospital level Essential medicine list was available in written form at the TH but no specific implementation activities were conducted during the study period. Local prescribing guidelines were not present in any of the hospitals.
We have now modified text in DISCUSSION: Page 20-21
A higher proportion of prescribed antibiotics at the TH (77%) were from the NLEMI compared with the NTH (60%, $p<0.001$). This could be attributed to the presence of a management policy to purchase and supply medicines at the TH. However, there is a need to improve adherence to the NLEMI at both hospitals.

I. page11: explain FDC

Response I: As normal practice abbreviations are explained at first place in the paper in this paper for FDC it is on Page 7 and after that it is used as abbreviations.
Fixed dose combinations of antibiotics (FDCs) that did not have an ATC code assigned by WHOCC were assigned the code 'J01RA*' according to Sharma et al,[17].

Results:
J. is scripts per patient the correct unit? As far as I can tell data are not linked to individual patients but rather to patient episodes/presentations. This means that the same patient can contribute to AB scripts.
Response J: In India, the citizens does not have any personal ID number so it is not possible to follow the patients for all visits made at a healthcare facility. Each admission in Medicine ward was considered as new patient.
The study was conducted for a comparatively long period (3 years) and hence there is a possibility that some persons might have visited more than once in the hospitals during the study period. We also agree that prescribers' choice can vary based on re-admission of a patient but this could not be controlled due to the non possibility to follow uniquely identified patients.
We have now added following text in Data sources and considerations on Page 8
Every admission in the department was considered as a new patient.

Results:
K. how useful is comparison of generic vs trade names if the availability of AB is regulated in the TH?

Response K: We have the same opinion as the reviewer that the medicines made available by the management in the TH might be one of the reasons for higher generic name prescribing in the TH than in the NTH. This indicates that if the supply of medicines is regulated by the management or a regulatory body the prescribing could be modified and rationalised (use of generic medicines or cost regulated medicines).
We have mentioned this point in the manuscript under GENERALISABILITY AND FUTURE IMPLICATIONS, Page 24. Please see.
The management in the TH had a policy to control the purchase and supply of medicines. This control shows positive effects at the TH compared to the NTH; to minimise antibiotic prescribing, in better adherence to the NLEMI and in use of generic names. The policy could be implemented and tested in other constrained settings.

Discussion
L. needs some editorial review as the text flows much less than other sections of the paper.
Response L: The manuscript is now edited according to the comments received from a native English speaking person

Reference
M. list needs to be checked for consistency.
Response M: The reference list has been checked and modified for consistency as suggested

VERSION 2 – REVIEW

REVIEWER	DR ABDUL GHAFUR CONSULTANT IN INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY, APOLLO HOSPITAL,CHENNAI
REVIEW RETURNED	01-Oct-2016

GENERAL COMMENTS	Authors have done all the necessary modifications. Good article

REVIEWER	Mieke van Driel University of Queensland, Australia
REVIEW RETURNED	25-Oct-2016

GENERAL COMMENTS	The authors have addressed many of the comments and concerns adequately, however, a few concerns still remain: A. the authors have not really answered my question why the data is so old; they address generalisability in the discussion but this does not explain why more recent data were not used. F. I still find the classification system very confusing. On page 10 group b is labeled "non-infectious fever" and then it is subsequently subdivided into "malaria or viral fever with no registered bacterial infection" and "malaria or viral fever with suspected bacterial infection". These are "infectious" conditions! I am unsure what 'viral fever' is? Is this how it was documented in the chart or your interpretation? If the former than you have a strong point of inappropriate AB use. In table 1 Rheumatic heart disease features in subgroup 4; should it not be in subgroup 2? J. As per your explanation (i.e that you data are not linked to individual patients) it is more correct to speak of patient-presentations or patient-episode as the unit of analysis.

VERSION 2 – AUTHOR RESPONSE

The authors have addressed many of the comments and concerns adequately, however, a few concerns still remain:
A. the authors have not really answered my question why the data is so old; they address generalisability in the discussion but this does not explain why more recent data were not used.

Response A: We are contented that the reviewer is convinced about the importance and generalizability present study, however we apologies for not being clear to the reviewer about the time taken by us to analyse and data and write up the manuscript. We are thankful to the reviewer for giving us another chance to explain our point.
At the healthcare facilities of low- middle income countries (LMICs), absence of computerized data recording systems is common and the healthcare facilities within the city or state are not linked with each other. Inhabitants of LMICs including India, do not have personal identification number therefore; a person could not be tracked for the visits made at various healthcare facilities and type of treatment advised.
It is an established fact that lack of computerized patient records makes long term drug utilization studies; cumbersome and intensive to the limit of non feasibility. This is one of the main reasons for the universal paucity of the surveillance studies, particularly from the LMICs.
The present study was conducted prospectively at medicine departments of two resource constrained tertiary healthcare settings of India. None of the study hospitals had computerized patient record systems. The patients' treatment records were kept in paper form as patient files. Thus manual data collection was the only option to conduct present study. Being a part of Indian private healthcare sector, as expected the patient thoughtput was high in the hospitals.
Lack of computerization, untrained staff and absence of computerized record system made present study, time consuming and onerous exercise but at the same time lead to relatively more accurate description of the prescribing patterns. Being first of its kind of study; vigilance and supervision for the data and data cleaning were the most challenging and time consuming tasks to maintain the reliability of the data.

The data collection and analysis had several steps, as explained below:
1. Establishment of manual data collection system and trainingthe nursing staff: The nursing staff were not involved in any scientific research before the present study was conductedat the settings. Therefore, regular and robust training; accompanied with continue monitoring and checking of the collected data at various stages was a pre requisite.
The nurses were trained for data collection and considering high turnover of the nursing staff, the training was repeated regularly for the newly recruited staff. Monthly meetings were held with the nurses to maintain the pace and interest for the data collection. The form, attached to each patient's file on the day of admission,was updated daily by the trained nurses until the patient was discharged or expired. All possible efforts were done to minimize the risk of missing data.
The filled forms were collected from the medicine wards at least weekly by the last author or a person designed by her. There after the forms were checked manually for completeness. In absence of social security number system in India, two persons were trained to assign unique codes to the patients and maintain full confidentiality.
The data was then entered in EPI Info 3.1 software and Microsoft Excel data files. The computer operators were trained for the data entry. The entered data was checked randomly by the first and last author for accuracy.
2. Checking for the data of incomplete forms from original patient records: Once the data was entered in the data files, it was checked for the completeness and archive was visited a number of times to check the original patient records (paper files) and to complete the missing information. For the consistency and reliability of the data the filled forms and the patient files from the archive were randomly cross checked by the first and last author or persons designed by her. Best possible efforts were done to make the data complete and to maintain reliability. As per study protocol all incomplete

records left after this step were excluded from the analysis.
3. Coding of the prescribed antibiotics:
In a healthcare setting, medicines including antibiotics could be prescribed using Trade/ Brand or Generic names. The names (Trade or Generic names) as mentioned by the treating consultant in the patient files were transferred in the data collection forms and later in the data files. Based on the WHOCCATC and DDD index, respective generic names were introduced for the antibiotics prescribed using trade names. Since the data was collected manually there were a number of spelling mistakes for the name of prescribed antibiotics. The hospital archive and nearby pharmacies were visited several times by last author (MS) to get the correct trade and generic name of theantibiotics.
The study was a part of lager project that was conducted between 2008- 2011. After the data collection was completed and checked for completeness at the study setting site, the ICD codes (for the diagnoses), ATC codes and DDDs were calculated for prescribed antibiotics for international comparison of the results. The variables were entered in the data files by the trained data entry operatorsbased WHOCC and CDC guidelines.The components were identified for the fixed dose combinations.

4. Assignment of ATC codes for new FDCs
After completion of assigning the generic names it was found that a number of the fixed dose combinations were not given any ATC code by the WHO.Therefore, efforts were made to establish communication with the authorities at the WHOCC Norway and the list of new FDCs were sent for appropriate guidance and suggestion. Elaborated and fruitful exchange of emails were done for long time period; thereafter we were given an authority to assign ATC codes to these non-listed FDCs prescribed in our settings (coded as J01RA*). These ATCs were used during analysis in present communication.
This step prolonged the data cleaning process. All possible efforts where done to ensure highest achievable correctness of the data. Since it was a prospective and detailed study with more than 21,000 data records and all the steps were done manually dealing with a large number of patients' records, the whole process was laborious and time consuming.
The analysis was conducted using final data sets, only after above mentioned steps including data checking were completed.
5. Funds
Article processing charges was another problem to get the present communication published in a peer reviewed journal. There is no need to mention that articles published in peer reviewed journals reaches maximum number of readers, researchers and policy makers and could be used as a baseline for future researches. We have now managed some funds for the publication and have therefore proceeded to publish these important results.
We would also like to draw your kind attention to the fact that the study not only presents the patterns of antibiotic prescribing during a particular time period but also describes crucial issues such as excessive use of new FDCs, variations from WHO recommended DDDs, use of non-recommended antibiotics for various diagnoses, use of antibiotics in unindicated situations and so on. In addition to these, there are several points of generalisability which were explained before in response and are also mentioned in the manuscript.
Although using manual data collection is laborious and extremely time consuming but is worth to initiate and establish a system in the resource constrain settings for future researches.

We have now added the text on Page 23, DISCUSSION section last paragraph:
Absence of computerized record systems in hospitals, absence of personal identification number, untrained staff and high staff turnover makes a detailed study like this, time consuming and onerous exercise and delays the analysis. We are aware that extensive manual checking and working with the data like adding the ICD codes and the ATCs for the new FDCs to the data has prolonged the analysis process and has delayed the presentation. However, use of man power is the only option to conduct such detailed studies at resource constrained settings but at the same time lead to relatively

more accurate description of the prescribing patterns.

F. I still find the classification system very confusing. On page 10 group b is labeled "non-infectious fever" and then it is subsequently subdivided into "malaria or viral fever with no registered bacterial infection" and "malaria or viral fever with suspected bacterial infection". These are "infectious" conditions! I am unsure what 'viral fever' is? Is this how it was documented in the chart or your interpretation? If the former than you have a strong point of inappropriate AB use.
Response F: Thank you for this point. As rightly pointed out by the reviewer; Group (b) is 'non-bacterial fevers' and not 'non-infectious fevers'. We missed to change 'non-infectious fevers' to 'non-bacterial fevers' at one place on Page 10, which might have created the confusion. We apologise this.

We have now changed the text on Page 10:
Similarly, the non-bacterial fever group (Group b) was divided 'malaria or viral fever with no registered bacterial infection' (sub-group 3) and 'malaria or viral fever with suspected bacterial infection' (sub-group 4, Figure 1).

Response: To categorise all patients at the diagnosis level, we have considered primary diagnosis, for this we preferred the most likely cause for the current episode of hospitalisation. For example, viral fever was preferred over hypertension, but not over myocardial infarction or COPD.
“Viral fever” was written as a diagnosis by the treating physicians in the patient records and was recorded in data files which represent the ICD-10 code B34.9.

We have now added the ICD code for viral fever in text at page 9:
In 'Group (b)' different types of malaria and cases of viral fever (ICD code- B34.9) were included.

In table 1 Rheumatic heart disease features in subgroup 4; should it not be in subgroup 2?
Response: Rheumatic fever is a chronic condition and Malaria is acute condition therefore, different types of Malaria were considered as the most plausible cause of current hospitalisation for the patients. To rule out all confounders for the presence of bacterial infections in subgroup 3, these patients were grouped in the sub-group 4: Malaria or viral fever with suspected bacterial infection. We have mentioned this on page 10 and have modified based on reviewer's comment.

We have now modified text in METHOD SECTION on page 10:
All patients with rheumatic heart disease (RHD) were categorized either in sub-group 2 or in sub-group 4 to rule out all possible bacterial infection as a confounder, since the WHO guidelines for secondary prevention after rheumatic fever sets the duration of preventive antibiotic treatment from five years up to life-long, depending on a number of factors e.g. time since the last episode of rheumatic fever and severity of valve engagement and supports an individual assessment of every case,[22,23].

J. As per your explanation (i.e that you data are not linked to individual patients) it is more correct to speak of patient-presentations or patient-episode as the unit of analysis.
Response J: The data was collected for individual inpatient and is linked per patient with the assigned unique code instead of; for example social security number. However, the analysis was conducted at group level to maintain confidentiality and not at individual level.
As written in the method section all inpatients were assigned a new unique number each time they were admitted in the hospitals, therefore it was not possible to link the multiple hospital stays for one patient.

We have now modified the text in Ethics statement on page 10 to make this point clear:
The data was collected at individual level for all inpatients and was linked per patient with the

assigned unique codes instead of; for example social security number. However, the analysis was conducted at group level to maintain the confidentiality.