

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15
AUTHORS	Fazaludeen Koya, Shaffi; Hasan Farooqui, Habib; Mehta, Aashna; Selvaraj, Sakthivel; Galea, Sandro

VERSION 1 – REVIEW

REVIEWER	Stephen Obaro University of Nebraska Medical Center College of Medicine, Pediatrics
REVIEW RETURNED	06-Apr-2022

GENERAL COMMENTS	<p>Koya and colleagues in this report provide an interesting perspective on the dispensing of antibiotics for typhoid fever from pharmacies in India. In a setting where typhoid fever is highly prevalent and access to diagnostic service is a challenge for many, and antibiotics are readily available, the approach here is pragmatic and likely reflects the situation across several LMIC settings.</p> <p>Minor comments</p> <ol style="list-style-type: none">1. The difference in prescription rate by age group, with the highest rates in adults as compared to children appears contrary to published literature on typhoid from India. While this observation is curious, there is possibility that the pattern of infection may be changing in the population. Are the authors able to access data from regional laboratories from the location of this study that have confirmed cases of typhoid fever by blood culture?2. How representative of the pharmacists/chemists that were used for this survey of the general population? Are there other dispensing locations that may not have a formal recording system and perhaps easier to access by the poor?
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REVIEWER	Megha Sharma Karolinska Institutet, Department of Global Public Health
REVIEW RETURNED	14-Apr-2022

GENERAL COMMENTS	<p>Thank you for sharing this interesting manuscript titled, Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15. The manuscript presents the data of prescriptions from selected private healthcare sector clinicians (4600) for typhoid fever during 3 consecutive years in India. The data was obtained from IQVIA and WHO ATC classification was used for the analysis.</p> <p>Please find below some comments- Method:</p>
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	<p>1. Page 10, lines 25-48: 'This is a cross-sectional analysis of secondary data ... Consideration of non- 23 metropolitan areas (population more than 1 million), 128 class 1 towns (population 100,000- 1 million) and 1A towns (population less than 100,000)'. Although 4600 clinicians and these many study points are big number in itself, however, considering the geographical area, population healthcare system of India, these seems to be few. The generalizability must be stated with caution.</p> <p>2. How were the 4600 clinicians selected for collecting data?</p> <p>3. How many were dentists and what is the point of including the dentists in the study aimed to study prescriptions for typhoid. The link seems to be missing here. Please explain the justification of including dentists.</p> <p>4. Page 11, line 4: 'In the private sector, antibiotics are usually prescribed for the entire duration of the course of treatment for a particular disease.' This seems to be unclear. Please explain the basis for this statement.</p> <p>5. Table 1: The number of prescriptions are too few from the East zone. Explain this. It will be important to mention how many clinicians were included from each zone.</p> <p>6. Figure 2 : What are the speculations for the decrease in overall prescription rate? Discuss</p> <p>7. In Supplementary table 1: what is the need of including the IQVIA ATC?</p> <p>8. It will be of interest to discuss the approval status of prescribed medicines by the Central Drugs Standard Control Organization (CDSCO) and what is the status of the presence of prescribed fixed dose combinations in the essential medicines lists both national and WHO.</p> <p>9. The WHO DDDs could also be calculated to analyse the amount prescribed during the years.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Stephen Obaro, University of Nebraska Medical Center College of Medicine

Comments to the Author:

Koya and colleagues in this report provide an interesting perspective on the dispensing of antibiotics for typhoid fever from pharmacies in India. in a setting where typhoid fever is highly prevalent and access to diagnostic service is a challenge for many, and antibiotics are readily available, the approach here is pragmatic and likely reflects the situation across several LMIC settings.

Thank you, Dr. Obaro, for your kind feedback and for the helpful comments.

Minor comments

1. The difference in prescription rate by age group, with the highest rates in adults as compared to children, appears contrary to published literature on typhoid from India. While this observation is curious, there is the possibility that the pattern of infection may be changing in the population. Are the authors able to access data from regional laboratories from the location of this study that has confirmed cases of typhoid fever by blood culture?

Thanks, we agree this is a very interesting way to look at the changes in the pattern of infection. Our findings are consistent with recent studies which used laboratory data that showed more young adults are found to be culture-positive than children. We have included this in our discussion section, now (p 14, line 7-9). Thanks.

2. How representative of the pharmacists/chemists that were used for this survey of the general population? Are there other dispensing locations that may not have a formal recording system and are perhaps easier to access by the poor?

Our analysis is based on the prescription written by the clinicians in the private sector, and not based on dispensing data. Yes, we agree that there are informal- less than fully qualified or unqualified- providers and dispensing locations without a recording system, but we can't expect a clinical/recorded diagnosis from those providers whether the case is typhoid or not. However, as mentioned, the providers in this database are representative of the large formal network of clinical providers (they are prescribers and not pharmacists) in the private sector in these locations. We have included this as a limitation now (p 15, lines 1-3)

Reviewer: 2

Dr. Megha Sharma, Karolinska Institutet, RD Gardi Medical College

Comments to the Author:

Thank you for sharing this interesting manuscript titled, Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private-sector medical audit data, 2013-15. The manuscript presents the data of prescriptions from selected private healthcare sector clinicians (4600) for typhoid fever for 3 consecutive years in India, The data was obtained from IQVIA, and WHO ATC classification was used for the analysis.

We thank the reviewer for the helpful feedback.

Please find below some comments-

Method:

1. Page 10, lines 25-48: 'This is a cross-sectional analysis of secondary data ... Consideration of non-23 metropolitan areas (population more than 1 million), 128 class 1 towns (population 100,000- 1 million) and 1A towns (population less than 100,000)'. Although 4600 clinicians and these many study points are big number in itself, however, considering the geographical area, population healthcare system of India, these seems to be few. The generalizability must be stated with caution.

Thanks, the point regarding generalizability is very pertinent. Our analysis included 671 million prescriptions of antibiotics including 8.98 million with a diagnosis of typhoid. It may also be noted that IQVIA collects the primary data and then extrapolates this primary data from 4600 clinicians using a proprietary extrapolation algorithm to reflect the prescription pattern of doctors having private practices in these locations across the country. We have included this detail now (page 5, line 21-) This is a substantial sample, but we agree that may not be fully generalizable. We have included this in our limitation section. (page 14, line 20-)

2. How were the 4600 clinicians selected for collecting data?

The sample (4600) was selected by IQVIA through a multistage stratified random sampling of all private practitioners of modern medicine, accounting for the region and patient turnover. We have included this in methods (page 5, lines 21-) . IQVIA enumerates the providers in all urban locations and in 1/3rd of other locations every year and updates the sample. The final sample covers 38% of all types of locations; including 100% of metros, 98% of class 1 towns and 24% of class 1A towns.

3. How many were dentists and what is the point of including the dentists in the study aimed to study prescriptions for typhoid. The link seems to be missing here. Please explain the justification of including dentists.

This was written when we described the overall general nature of the prescription database that we relied on in our analysis- which included prescription of all drugs including antibiotics. However, the prescription that we analyzed include only cases with a diagnosis of 'typhoid', and therefore these prescriptions do not come from dentists. We have edited it to avoid confusion.(p 6, line 1-6)

4. Page 11, line 4: 'In the private sector, antibiotics are usually prescribed for the entire duration of the course of treatment for a particular disease.' This seems to be unclear. Please explain the basis for this statement.

Thanks for pointing this out. We have appropriately edited it for clarity (p7, lines 10-13). We considered a prescription with a recorded typhoid diagnosis as a proxy for a case of typhoid. So, we can safely assume that the number of prescriptions roughly corresponds to the number of diagnosed cases of typhoid. However, individual patient behavior may determine whether they complete the course of treatment or not.

5. Table 1: The number of prescriptions is too few from the East zone. Explain this. It will be important to mention how many clinicians were included from each zone.

Yes, the number of prescriptions is few in the East probably due to the low proportional distribution of private sector providers in our sample for this zone. The number of sampling health provider units included in the IQVIA data is decided based on a multistage stratified random sampling accounting for the region and patient turnover. We have included this in limitation, page 15, lines 2-4

6. Figure 2 : What are the speculations for the decrease in overall prescription rate? Discuss

The role of the Swachh Bharat (clean India) mission that started during this period and the shift of patients to the public sector need to be studied. We have added these in the discussion section.

Further, our study shows a decline in prescriptions from 9.9 million in 2013 to 7.9 in 2015 largely due to the decline in the north and west regions. This may be examined further in the context of intense public health interventions during this period to improve sanitation facilities namely the Swachh Bharat (clean India) mission as some analyses have pointed out.²⁰ Alternatively, it may be also due to shifting in patients from the private to the public sector as suggested by other studies.²¹ (page 12, line 3-)

7. In Supplementary table 1: what is the need of including the IQVIA ATC?

As we included in the methods (p 6, line 10-13), IQVIA uses the anatomical therapeutic classification (ATC) of the European Pharmaceutical Market Research Association. But we used the ATC index provided by the World Health Organization WHO collaborating center to convert them to the WHO ATC classification. We thought it will help other researchers in their studies if we included this list in the supplement.

8. It will be of interest to discuss the approval status of prescribed medicines by the Central Drugs Standard Control Organization (CDSCO) and what is the status of the presence of prescribed fixed dose combinations in the essential medicines lists both national and WHO.

Thank you for this excellent suggestion. But as you would appreciate, this was beyond the scope of this paper. We are already working on a larger analysis which includes an analysis of antibiotics using the CDSCO approval status, essential medicines list, and FDCs/single formulations.

9. The WHO DDDs could also be calculated to analyze the amount prescribed during the years.

We agree that DDD is also useful to quantify antibiotic use. However, since the objective of our study was to estimate the total, and age and sex-specific rates of antibiotic prescriptions as a proxy for the burden of diseases and not really the amount of antibiotics used, we used the number of prescriptions as the unit of analysis.

VERSION 2 – REVIEW

REVIEWER	Megha Sharma Karolinska Institutet, Department of Global Public Health
REVIEW RETURNED	13-May-2022
GENERAL COMMENTS	I appreciate modifying the manuscript according to the comments.