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Quantifying antibiotic use in typhoid fever in India: a cross-sectional analysis of private sector medical audit data, 2013–2015

Shaffi Fazaludeen Koya ,[1] Habib Hasan Farooqui,[2] Aashna Mehta ,[3] Sakthivel Selvaraj ,[3] Sandro Galea[4]

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[1]Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA
[2]College of Medicine, Qatar University, Doha, Ad Dawhah, Qatar
[3]Health Economics, Financing and Policy Division, Public Health Foundation of India, New Delhi, India
[4]School of Public Health, Boston University, Boston, Massachusetts, USA

Correspondence to
Dr Shaffi Fazaludeen Koya; fmshaffi@bu.edu

ABSTRACT

Objectives To estimate the antibiotic prescription rates for typhoid in India.

Design Cross-sectional study.

Setting Private sector primary care clinicians in India.

Participants The data came from prescriptions of a panel of 4600 private sector primary care clinicians selected through a multistage stratified random sampling accounting for the region, specialty type and patient turnover. The data had 671 million prescriptions for antibiotics extracted from the IQVIA database for the years 2013, 2014 and 2015.

Primary and secondary outcome measures Mean annual antibiotic prescription rates; sex-specific and age-specific prescription rates; distribution of antibiotic class.

Results There were 8.98 million antibiotic prescriptions per year for typhoid, accounting for 714 prescriptions per 100 000 population. Children 10–19 years of age represented 18.6% of the total burden in the country in absolute numbers, 20–29 year age group had the highest age-specific rate, and males had a higher average rate (844/100 000) compared with females (627/100 000). Ten different antibiotics accounted for 72.4% of all prescriptions. Cefixime–ofloxacin combination was the preferred drug of choice for typhoid across all regions except the south. Combination antibiotics are the preferred choice of prescribers for adult patients, while cephalosporins are the preferred choice for children and young age. Quinolones were prescribed as monotherapy in 23.0% of cases.

Conclusions Nationally representative private sector antibiotic prescription data during 2013–2015 indicate a higher disease burden of typhoid in India than previously estimated. The total prescription rate shows a declining trend. Young adult patients account for close to one-third of the cases and children less than 10 years account for more than a million cases annually.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study provides the first age-specific typhoid antibiotic prescription estimates for India, using a large volume of geographically representative medical prescription audit data.
- ⇒ The study shows a high rate of antibiotic prescription (714/100 000 population) for typhoid indicating a higher disease burden than previously estimated, especially among young adults and children
- ⇒ The lack of laboratory confirmation of typhoid may lead to some degree of misclassification. However, this is reflective of the real-world setting, where laboratory confirmation is not the norm in India.

INTRODUCTION

Enteric fever, a systemic infection caused by Salmonella enterica serotypes *Salmonella typhi* and *Salmonella paratyphi,* remains an important public health problem. Globally, there was a 44% decline in typhoid and paratyphoid fever between 1990 and 2017,[1] but India remains one of the high burden countries. A systematic review in 2016 estimated an annual incidence of 377/100 000 (95% Confidence Interval (CI) 178 to 801) typhoid and 105/100 000 (95% CI 74 to 148) paratyphoid cases.[2] The global burden of diseases (GBD) 2017 estimates reported a higher incidence of 586.3 typhoid/paratyphoid cases per 100 000 population (95% Uncertainty Interval 515.7 to 661.8), though this is 60% lower compared with 1990 GDB estimates.[1]

Unfortunately, the reported incidences are based on data from a limited number of population-based studies and the disease surveillance system, which is largely limited to the public healthcare system in India while the reporting of typhoid from private sector that dominates outpatient care in the country is missing or incomplete.[3] Hence. these estimates are prone to the risk of either over estimation or under estimation due to non-uniformity in the definition and diagnostic methods adopted to detect typhoid disease and the limited sample size in the population-based studies. At the same time, the relatively easy availability of low-cost antibiotics without prescription leads to lower probability of diagnosis and reporting through the formal

Table 1 Antibiotic prescription for typhoid in India, for the years 2013, 2014 and 2015

	No of prescriptions in millions (%)		
Variable/year	2013	2014	2015
Total	9.9	9.1	7.9
Sex			
Male	5.7 (58.1)	5.2 (57.5)	4.4 (55.1)
Female	4.2 (41.9)	3.8 (42.5)	3.5 (44.9)
Age groups*			
0–4 years	0.61 (6.1)	0.56 (6.3)	0.52 (6.5)
5–9 years	1.5 (14.9)	1.3 (14.2)	1.0 (13.0)
10–19 years	2.0 (20.1)	1.8 (19.9)	1.6 (19.9)
20–29 years	1.3 (13.3)	1.2 (13.4)	1.1 (13.3)
30–39 years	0.79 (8.0)	0.71 (7.9)	0.63 (7.9)
40–49 years	0.67 (6.7)	0.58 (6.5)	0.50 (6.3)
50–59 years	0.43 (4.3)	0.38 (4.2)	0.33 (4.2)
60–64 years	0.14 (1.4)	0.13 (1.5)	0.12 (1.5)
65 and above	0.17 (1.7)	0.17 (1.8)	0.17 (2.2)
Geographical regions			
East	0.68 (6.8)	0.60 (6.7)	0.52 (6.6)
North	3.6 (36.2)	3.2 (35.6)	2.8 (35.2)
South	2.2 (22.4)	2.1 (23.0)	2.0 (25.2)
West	3.5 (34.7)	3.1 (34.7)	2.6 (33.1)
Urban location			
Metro cities	4.6 (46.4)	4.2 (46.9)	3.5 (44.6)
Class 1/1A towns	5.3 (53.6)	4.8 (53.1)	4.4 (55.4)

*The age groups include only those prescriptions with age data available, and therefore, will not add up to the total.

healthcare system, low rates of confirmatory diagnostic testing for typhoid, and low sensitivity of blood culture tests. These remain challenges for effective typhoid surveillance in India.[4]

Further, the emergence of antibiotic resistance among typhoid is also a growing concern.[5 6] Studies show that resistance to quinolones has increased in recent years and resistance to third-generation cephalosporins remains low, while resistance to ampicillin and trimethoprim–sulfamethoxazole resistance has decreased.[7] A recent mathematical modelling study showed that introducing typhoid conjugate vaccine (TCV) can avert 42.5 million cases of quinolone non-suspectable typhoid cases globally over 10 years and that includes 21.1 million cases in India.[8] Data on prescription and sales of antibiotics can be a useful proxy to understand the burden of disease and variations across age groups, sex and regions, besides understanding prescription patterns.[9–11] Therefore, in this study, we aimed to generate new evidence on annual antibiotic prescription rates and sex-specific and age-specific prescription rates for typhoid, and the distribution of antibiotic class in these prescriptions in India during 2013–2015 that can inform policy and practice.

METHODS

This is a cross-sectional analysis of secondary data on antibiotic prescription. We used data on systemic antibiotic (J01) prescription by private sector primary care physicians in India collected by IQVIA (formerly Intercontinental Medical Statistics (IMS) Health) for the years 2013, 2014 and 2015.[12] IQVIA collects data and provides information on medical practice, especially on the use of medicines, in over 100 countries around the world. The monthly prescription audit data in India pertains to prescriptions by a panel of 4600 clinicians who practice modern medicine selected through a multistage stratified random sampling accounting for the region specialty type and patient turnover. The sample includes general practitioners and specialist physicians from 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). IQVIA enumerates the providers in all metro locations and one-third towns every year and the final sample covers providers from 38% locations; including 100% metros, 98% class 1 towns and 24% class 1A towns. The data are then extrapolated using a proprietary algorithm to reflect the private sector prescription pattern.[12]

This database provides information on patient characteristics such as age group, sex, diagnosis and medicines prescribed, besides the geographical location categories (zone—east, west, north and south) and urban locality categories (Metropolitan cities or class 1/1A towns). IQVIA organises medicines according to the Anatomical Therapeutic Classification (ATC) of the European Pharmaceutical Market Research Association, but the authors used the ATC index provided by the WHO WHO collaborating centre to convert them to the WHO ATC classification.[13] The full list of formulations in IQVIA list and the equivalent WHO ATC codes are given in online supplemental table 1.

We extracted the information on the diagnosis reported on prescriptions and used the ICD codes A01.0 and A01.10 to identify typhoid and para typhoid cases, respectively. We used the aggregated, processed and extrapolated data to estimate the total antibiotic prescriptions for typhoid to understand the private sector antibiotic prescription practices for typhoid in the country. We further used India population data and the age structure of Indian population from the population pyramid to calculate sex-specific and age-specific rates of antibiotic prescriptions for typhoid.[14] For doing the age-specific analysis, we used only the prescriptions with age data. In addition, we also compared the prescription patterns with the available information on antibiotic resistance for typhoid for a selected classes of antibiotics for recent years. All data were extracted to Microsoft Excel and analysed using Excel and R. We compared the prescription

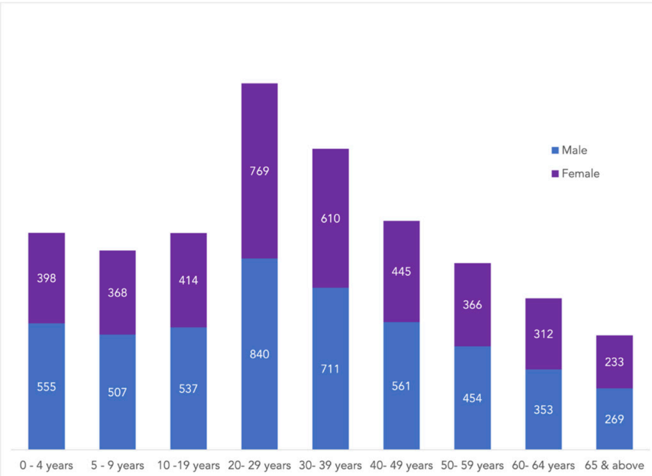

Figure 1 Sex-specific, 3-year average antibiotic prescription rates (2013–2015) for typhoid, across various age groups, per 100 000 population, India.

rates across years, sex, age groups, zones, locations and WHO ATC categories. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Considering that a prescription with a recorded typhoid diagnosis serves as a proxy for a case of typhoid, we can safely assume that the number of prescriptions roughly corresponds to the number of diagnosed cases of typhoid. However, individual patient behaviour may determine whether they complete the course of treatment or not. Further, the data do not capture the public sector prescriptions and therefore our analysis only reflects outpatient typhoid diagnosis and antibiotic prescription patterns in the private sector in the country.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

RESULTS

We analysed 671 million prescriptions for the 3-year period (2013–2015), of which 26.9 million (4.01%) antibiotic prescriptions were made for enteric fever (typhoid and paratyphoid cases), averaging 8.98 million per year in India. The average annual countrywide antibiotic prescription rate for typhoid was 714/100 000 population during the period 2013–2015. Table 1 shows the number of prescriptions across the 3 years. The antibiotic prescriptions for enteric fever (typhoid and paratyphoid cases) decreased by 9.5% between 2013 and 2014 (from 9.9 million in 2013 to 9.1 million in 2014) and further by 11.3% to 7.9 million in 2015. The data were scanty for paratyphoid fever (only 1163 total cases in 2013, 315 in 2014 and 124 in 2015), and therefore, the data largely represent typhoid fever in the country. North and west regions of the country had the highest reported cases, around 35% each in all the 3 years . The majority of cases were reported from metropolitan cities.

The prescription rate varied across age groups and gender. Over the 3-year period (2013–2015), the age groups 0–4 years and 10–19 years showed a similar average rate (479/100 000). However, the 10–19 years age group represented 18.6% of the total burden in the country in absolute numbers. On average, more than 35% of the cases were below 20 years of age. The overall prescription rate sharply increased in the age group 20–29 years (806/100 000). With more than a quarter (26.4%) of the total cases in the country, the 20–29 years age group also had the highest age-specific rate. The prescription rate decreased sharply after the age of 30.

Males had a higher average rate (844/100 000) compared with females (627/100 000) over the 3-year period. Figure 1 shows the distribution of sex-specific, 3-year average antibiotic prescription rates across age groups. There were clear differences in the number and rate of prescriptions between the sexes in all age groups, with males sharing a higher burden. The difference was maximum in the age group 0–4 years (28% higher for boys) while the age group 20–29 had the least difference (8%) (online supplemental table 2, online supplemental figure 1).

The overall prescription rate decreased from 792/100 000 in 2013 to 716/100 000 in 2014 and further to 635/100 000 population in 2015. Figure 2 shows the annual age-adjusted, sex-specific rates over the years. The rate decreased by 22% among males (947/100 000 in 2013 to 738/100 000 in 2015) and 17% among females (683/100 000 in 2013 to 570/100 000 in 2015) during the 3 years.

Antibiotic combinations (WHO antibiotic class J01R, 33.96%) and cephalosporins (WHO antibiotic class J01D, 32.96%) were the most prescribed antibiotics for typhoid during 2013–2015 (table 2).Combination antibiotics (J01R) were the preferred choice of prescribers for adult patients, while cephalosporins (J01D) were the preferred choice in children and young age (up to 20 years). However, quinolones were prescribed as monotherapy in 23% of cases. We did not observe any major changes in the prescription share for antibiotic classes over the 3-year period (online supplemental figure 2). On average, there were 108 different formulations of antibiotics prescribed for typhoid. The number of different formulations used varied across age groups, ranging from 47 for patients aged 60–64 years to 84 for patients in 20–29 age group (online supplemental figure 3). In general, young adults were treated with a wide range of formulations.

Ten different antibiotics accounted for three-quarter of all prescriptions (72.4%) (online supplemental figure 4). Cefixime–ofloxacin combination was the preferred drug of choice for typhoid across metro and class 1 cities and across regions except south India, where cefixime was the most prescribed antibiotic (online supplemental figures 5, 6). Ciprofloxacin is still widely used in west and south regions and in class 1/1A towns, whereas it was not among the top

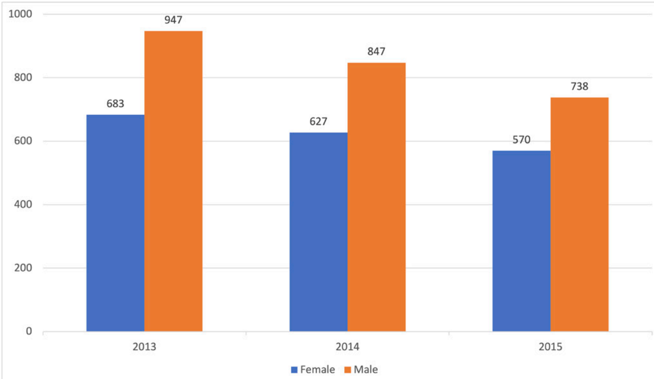

Figure 2 Annual age-adjusted, sex-specific rates (per 100 000 population) for typhoid antibiotic prescriptions, 2013–2015, India.

five preferred antibiotics in metro as well as north and east regions. Combinations of antibiotics (mostly a combination of cephalosporin and fluroquinolone) and cephalosporins are the most used antibiotic classes, both in metro cities and class 1/1A towns. The age group wise preference of antibiotic class is given in online supplemental figure 7.

DISCUSSION

To our knowledge, this is the first age-specific typhoid antibiotic prescription estimate for India, using geographically representative medical audit data. This study reports a typhoid related average antibiotic prescription rate of 714/100 000 population during the 3 years (2013–2015), which signals a higher estimate of typhoid burden in the country compared with some previous reports including a systematic review in 2016 which estimated an incidence of 377/100 000 and the GBD 2017 estimate of 586.3/100 000 population.[1 2 15] However, considering that our numerator includes only the population being seen by private practitioners and the denominator includes the whole population, this may be still an underestimate. Our study used data from private sector that caters for 70% of outpatient care services in India which represents the majority of the typhoid related prescription as only 6 out of every 1000 typhoid cases require hospitalisation.[16–19] 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 to improve sanitation facilities, namely the Swachh Bharat (clean India) mission, as a previous analysis showed.[20] Alternatively, it may also be due to shifting of patients from the private to the public sector, as suggested by other studies.[21]

Resistance to typhoid antibiotics is a global public health issue.[6 22 23] Antibiotic resistance in typhoid is a well-acknowledged problem in India as well.[24–26] Available data show that resistance to quinolones, the third most commonly used class of antibiotics for typhoid, has been consistently increasing in India, from 11% in 2008 to 68% in 2015 whereas resistance to cephalosporins, the second most commonly used class, remained low.[27] Resistance to the other classes of antibiotics ranges from 8% for penicillin to 12% for aminoglycosides and 23% for trimethoprim–sulfamethoxazole. A recent systematic review showed that the typhoid antibiotic resistance in India has moved from a multidrug resistance pattern to one primarily led by quinolone resistance.[24]

Our study showed similarities and differences in antibiotic prescription preferences among practitioners across the four regions of the country. Our analysis shows that a combination of cephalosporins and quinolones is the preferred antibiotic of choice by providers in India. However, a significant proportion of cases in India are still treated with quinolones alone (23%), and the top five antibiotics used in the south and west regions of the country include two quinolones, ciprofloxacin and ofloxacin. We found that ofloxacin is the third most common antibiotic used. Ciprofloxacin is widely used as monotherapy, at least in the west and south regions, even though the drug was known to have developed resistance for two decades.[28] WHO recommends ciprofloxacin as well as ofloxacin only for fully sensitive typhoid cases. In the absence of antibiotic sensitivity test results for most of the typhoid cases diagnosed, the use of these drugs as monotherapy needs attention, especially in high endemic regions of the country.

In India, the highest proportion of hospitalisation is still due to infections.[29] The cost of treating an episode of typhoid in outpatient care ranges from US$2.0 to US$2.6 (mean, US$2.3, 2010 US$), and from US$96 to US$132(mean US$113, 2010 US$) for hospitalised care.[30] If we can achieve a higher vaccination coverage across population at risk with the newly available prequalified TCV we can reduce the typhoid burden and demand for antibiotics and consequently the risk of resistance. Modelling-based studies and clinical trials have highlighted that the introduction of pathogen-specific vaccines reduces demand for antibiotics by reducing the force of transmission and incidence of diseases, which consequently can reduce antibiotic resistance.[31] Further, the vaccine is a cost effective preventive strategy for typhoid.[32] This was reiterated by the most recent mathematical modelling study which showed that with routine immunisation at 9 months of age with a catch-up campaign up to age 15 years we can avert 46%–74% of all typhoid fever cases in

Table 2 WHO ATC class of antibiotics prescribed for typhoid, 2013–2015

Antibiotic class	Prescriptions	Percentage
Combinations, J01R	6.9 million	33.96
Cephalosporins, J01D	6.7 million	32.96
Quinolones, J01M	4.8 million	23.12
Macrolides, J01F	768 317	3.77
Aminoglycosides, J01G	488 034	2.39
Amphenicols, J01B	469 381	2.30
Others*	305 007	1.50

*Includes penicillin (J01C), tetracyclines (J01A), others (J01X) and sulfonamide–trimethoprim (J01E).

73 countries eligible for the Global Alliance for Vaccines and Immunisation support.[8] Trials including those conducted in India have shown that the currently available conjugate vaccine is safe and highly immunogenic.[33 34]

The age-specific rates in our study corroborates with some recent studies from Vietnam, Bangladesh and Pakistan, besides Kolkata in India.[18 29 35–38] Contrary to earlier understanding,[2] our analysis shows that a higher proportion of young adults compared with children are treated every year for typhoid in India. This may be because of the atypical nature of the clinical presentation of typhoid in children, especially among less than 5 years, that might lead to reduced laboratory testing for typhoid among young age group and a subsequent smaller number of cases being diagnosed. However, our finding is in concurrence with a recent study using laboratory data, which showed that more than 50% of culture positive typhoid cases were among adults aged 18–49 years.[7] Even then, our analysis suggests that around two million prescriptions in the year 2013, 1.8 million in 2014, and 1.1 million prescriptions in 2015 were issued for children less than ten years of age. Well-designed prospective studies[19] and community-level surveillance systems across various regions can generate more real-world estimates to understand the true age-specific incidence in the Indian context.[39]

Limitations

The study has a few limitations. First, we used prescription data from a panel of private sector providers, and therefore, threats of validity due to social desirability or survey effects cannot be ruled out. Second, the data do not have information on the laboratory confirmation of typhoid and therefore some degree of misclassification can be expected. However, this is reflective of the real-world setting, where laboratory confirmation is not the norm. Third, low proportional distribution of private sector providers in our sample for eastern zone might have affected the reported number of prescriptions from the zone, and there may be cases of typhoid that may be treated by informal or less than formally qualified or unqualified providers across all zones that our data do not capture. Fourth, the prescription data pertain to private sector providers in small towns and urban areas. However, there is not much reason to believe that the prescription will be different in rural areas, although the prescription patterns may be different in the public sector. Finally, we excluded 20% prescriptions from age-specific analysis as they did not have data on age groups, which might have underestimated the age-specific rates in some age groups and overestimated in some others.

CONCLUSION

Using a large volume of private sector data, we found that typhoid antibiotic prescription in India decreased by two million between 2013 and 2015. Still, the country has a large burden of typhoid with 7.9 million prescriptions in 2015, corresponding to around 635 typhoid cases/million population. There is variation in antibiotic usage across ages and regions. Quinolones are still widely used in monotherapy, despite evidence of high resistance. Young patients account for close to one-third of the cases and children less than 10 years of age account for more than a million cases annually. Introduction of conjugate typhoid vaccine in immunisation programmes alongside improvement in water, hygiene and sanitation facilities can help to reduce the typhoid burden as well as demand for antibiotics.

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Contributors SFK, SS and HHF designed the study. The data were gathered by AM supported by SS. SFK and HHF were responsible for statistical analysis of the results. SFK wrote the first draft of the manuscript that was then critically reviewed and revised by all coauthors. SG critically reviewed the drafts of the paper. All authors approved the final version of the manuscript for submission. SFK, AM and HHF had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. SFK is the guarantor, and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; and that any discrepancies from the study as planned have been explained.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Individual-level data were not collected and there was no personal identifier in the dataset that we analysed. Therefore, we did not require ethical approval for our study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as online supplemental information. This study used proprietary data from the IQVIA India. IQVIA can be approached for data access through their website, https://www.iqvia.com/locations/india

ORCID iDs
Shaffi Fazaludeen Koya http://orcid.org/0000-0002-1220-5754
Aashna Mehta http://orcid.org/0000-0003-4099-9915
Sakthivel Selvaraj http://orcid.org/0000-0001-5940-1958

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