BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062401
Article Type:	Original research
Date Submitted by the Author:	02-Mar-2022

Complete List of Authors:	Fazaludeen Koya, Shaffi; Boston University School of Public Health, Epidemiology Hasan Farooqui, Habib; Qatar University, College of Medicine Mehta, Aashna; Public Health Foundation of India, Health Economics, Financing and Policy Division Selvaraj, Sakthivel; Public Health Foundation of India, Health Economics, Financing and Policy Division Galea, Sandro; Boston University, School of Public Health

Keywords:	INFECTIOUS DISEASES, PUBLIC HEALTH, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™ Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Title page

a. Title:

Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

b. Corresponding author

Dr. Shaffi Fazaludeen Koya

Department of Epidemiology, Boston University School of Public Health,

715 Albany St, Boston, Massachusetts, USA 02118

fmshaffi@bu.edu

c. Name(s) of the author(s):

Shaffi Fazaludeen Koya[1] fmshaffi@bu.edu

Habib Hasan Farooqui[2] hfarooqui@qu.edu.qa

Aashna Mehta[3] aashna.mehta@phfi.org

Sakthivel Selvaraj[3] shakti@phfi.org

Sandro Galea[4] sgalea@bu.edu

Affiliation(s) of author(s)

[1] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

[2] College of Medicine, Qatar University, Doha, Qatar

[3] Health Economics, Financing and Policy Division, Public Health Foundation of India, New Delhi, Delhi, India

[4] Boston University, School of Public Health, Boston, MA, USA

d. Keywords: antibiotics, antibiotic resistance, drug prescription, typhoid, typhoid conjugate vaccine

e. Word count: 2,602

For peer review only

For peer review only

Abstract

Objective

India's typhoid burden estimates are based on a limited number of population-based studies and data from a grossly incomplete disease surveillance system. Further, growing antimicrobial resistance and multi-drug-resistant typhoid are emerging problems in the country. In this study, we estimated the total and sex-and age-specific antibiotic prescription rates for typhoid during a three-year period, 2013 – 2015, and described the antibiotics used to treat typhoid.

Methods

Data on systemic antibiotics (J01) prescription by private sector primary care physicians in India collected by IQVIA for the years 2013, 2014, and 2015 were used to estimate sex and age-specific rates of antibiotic prescriptions for typhoid. In addition, we categorized antibiotics using the WHO classification system and calculated the prescription rates for various classes of antibiotics.

Results

We analyzed 671 million prescriptions for the three-year period (2013-2015), of which an average of 8.98 million antibiotic prescriptions per year were for typhoid, accounting for 714 prescriptions per 100,000 population. Ten different antibiotics accounted for three-quarters of all prescriptions (72.4%). Cefixime-ofloxacin combination was the preferred drug of choice for typhoid across all regions except south India,

where cefixime was the most prescribed antibiotic. Combination antibiotics are the preferred choice of prescribers for adult patients, while cephalosporins are the preferred choice for children and young age.

Conclusion

Nationally representative private-sector antibiotic prescription data during 2013-15 indicate a higher disease burden of typhoid in India than previously estimated. Young patients account for close to one-third of the cases and children less than 10 years account for more than a million cases annually.

For peer review only

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.*

For peer review only

Key messages/summary box

What is already known on this topic

- The reported incidence of typhoid in India are based on data from limited number of population-based studies and the disease surveillance program which is largely limited to public healthcare system in India.
- The emergence of antibiotic resistance among typhoid is a growing concern.

What this study adds

- The first age-specific typhoid antibiotic prescription estimates for India, using a large volume of geographically representative medical prescription audit data 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
- Fluroquinolones are still widely used as monotherapy for the treatment of typhoid in India.

How this study might affect research, practice, or policy

- Better surveillance systems that capture private sector data are needed to understand the true age specific incidence in the Indian context
- India may consider conjugate typhoid vaccine in routine immunization programs to reduce the typhoid burden in young age group as well as to reduce antibiotic demand.

Introduction

Enteric Fever, a systemic infection caused by Salmonella enterica serotypes *S. typhi* and *S. para typhi,* remains an important public health problem. Globally, there was a 44% decline in typhoid and para-typhoid 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% CI: 178–801) typhoid and 105/100,000 (95% CI: 74–148) para-typhoid cases.[2] The global burden of diseases (GBD) 2017 estimates reported a higher incidence of 586.3 typhoid/para-typhoid cases per 100,000 population (95% UI: 515.7, 661.8), though this is 60% lower compared to 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 formal 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–

For peer review only

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.[9,10,11] Therefore, in this study, we aimed to generate new evidence on age and sex-specific rates of antibiotic prescriptions for typhoid in India during 2013-15 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 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, specialist physicians, and dentists, 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). The data is then extrapolated to reflect the private sector prescription pattern.

For peer review only

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, south) and urban locality categories (Metropolitan cities or class 1/1A towns). IQVIA organizes 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 World Health Organization WHO collaborating center 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 supplementary 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- 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 analyzed using Excel and R. We compared the prescription rates across years, sex, age-groups, zones, locations, and WHO ATC categories. Results are reported in accordance with the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.

For peer review only

In the private sector, antibiotics are usually prescribed for the entire duration of the course of treatment for a particular disease. In that sense, each prescription of an antibiotic corresponds to a diagnosed case of typhoid and therefore, it is a good proxy for measuring the prevalence of typhoid. However, 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.

Ethical approval

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

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 analyzed 671 million prescriptions for the three-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 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 three years. The antibiotic prescriptions for enteric fever (typhoid and paratyphoid cases) decreased by 9.5% between 2013 and

For peer review only

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 para-typhoid 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 three years . The majority of cases were reported from metropolitan cities.

The prescription rate varied across age groups and gender. Over the three-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-year 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 to females (627/ 100,000) over the three-year period. Figure 1 shows the distribution of sex-specific, three- 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%) [supplementary table 2, supplementary figure 1]

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

	Number of prescriptions in millions (%)		
Variable/Year	**2013**	**2014**	**2015**

For peer review only

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.

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 three 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

For peer review only

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% cases. We did not observe any major changes in the prescription share for antibiotic classes over the three-year period. [supplementary 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. [supplementary figure 3] In general, young adults were treated with a wide range of formulations.

Table 2: WHO ATC class of antibiotics prescribed for typhoid, 2013-15

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[1]	305,007	1.50

[1] *Includes Penicillin (J01C), Tetracyclines (J01A), Others (J01X), and Sulfonamide-Trimethoprim (J01E)*

Ten different antibiotics accounted for three-quarter of all prescriptions (72.4%). [supplementary 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. (supplementary 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 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 Supplement [supplementary figure 7].

For peer review only

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 three years (2013-2015), that signals a higher estimate of typhoid burden in the country compared to 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 in India.[19,16] Outpatient care records represent the majority of the typhoid related prescription as only six out of every 1000 typhoid cases require hospitalization.[17,18,19]

Resistance to typhoid antibiotics is a global public health issue.[6,20,21] Antibiotic resistance in typhoid is a well-acknowledged problem in India as well.[22,23,24] 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.[25] 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 multi-drug resistance pattern to one primarily led by quinolone resistance.[22]

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.[26] 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 hospitalization is still due to infections.[27] The cost of treating an episode of typhoid in outpatient care ranges from $2.0-$2.6 (mean, $2.3, 2010 US$), and from $96 to $132(mean $113, 2010 US$) for hospitalized care.[28] If we can achieve a higher vaccination coverage across population at risk with the newly available prequalified typhoid conjugate vaccine (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.[29] Further, the vaccine is a cost effective preventive strategy for typhoid.[30] This was reiterated by the most recent mathematical modeling study which showed that with routine immunization at nine months of age with a catch-up campaign up to age 15 years we can avert 46–74% of all typhoid fever cases in 73 countries eligible for the

For peer review only

Global Alliance for Vaccines and Immunization (GAVI) support.[8] Trials including those conducted in India have shown that the currently available conjugate vaccine is safe and highly immunogenic.[31,32]

The age-specific rates in our study corroborates with some recent studies from Vietnam, Bangladesh, and Pakistan, besides Kolkata in India.[18, 29,33–36] Contrary to earlier understanding,[2] our analysis shows that higher proportion of young adults than 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. 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 besides the cost and sequalae of the infection.[37]

Limitations

The study has a few limitations. The study used prescription data from a representative sample of private sector providers. The data does 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. The prescription data pertains 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,

For peer review only

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 account for more than a million cases annually. Introduction of conjugate typhoid vaccine in immunization programs alongside improvement in water, hygiene, and sanitation facilities can help to reduce the typhoid burden as well as demand for antibiotics.

For peer review only

Figure legends

Figure 1: Sex-specific, three-year average antibiotic prescription rates (2013-15) for typhoid, across various age groups, per 100,000 population, India

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

For peer review only

Contributor statement:

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 and HHF 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.

Competing interests:

None declared

Funding:

SFK is supported by The Rockefeller Foundation–Boston University 3-D Commission as a Research Fellow (2019 HTH 024)

Data sharing statement:

No data are available. This study used proprietary data from the IQVIA India (previously IMS Health). IQVIA can be approached for data access through their website (https://www.iqvia.com/locations/india).

For peer review only

Reference:

1. Stanaway JD, Reiner RC, Blacker BF, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. 2019;19(4):369-381. doi:10.1016/S1473-3099(18)30685-6

2. John J, Van Aart CJC, Grassly NC. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. Baker S, ed. *PLoS Negl Trop Dis*. 2016;10(4):e0004616. doi:10.1371/journal.pntd.0004616

3. Phalkey RK, Butsch C, Belesova K, et al. From habits of attrition to modes of inclusion: enhancing the role of private practitioners in routine disease surveillance. *BMC Health Serv Res*. 2017;17(1):1-15. doi:10.1186/s12913-017-2476-9

4. Pitzer VE, Meiring J, Martineau FP, et al. The Invisible Burden: Diagnosing and Combatting Typhoid Fever in Asia and Africa. *Clin Infect Dis*. 2019;69(Supplement_5):S395-S401. doi:10.1093/cid/ciz611

5. Gibani MM, Britto C, Pollard AJ. Typhoid and paratyphoid fever: a call to action. *Curr Opin Infect Dis*. 2018;31(5):440-448. doi:10.1097/QCO.0000000000000479

6. Dyson ZA, Klemm EJ, Palmer S, et al. Antibiotic Resistance and Typhoid. *Clin Infect Dis*. 2019;68(Supplement_2):S165-S170. doi:10.1093/cid/ciy1111

7. Gandra S, Mojica N, Klein EY, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. *Int J Infect Dis*. 2016;50:75-82. doi:10.1016/j.ijid.2016.08.002

8. Birger R, Antillón M, Bilcke J, et al. Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study. *Lancet Infect Dis*. 2022;0(0). doi:10.1016/S1473-3099(21)00627-7

9. Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis*. 2016;16(11):1255-1260. doi:10.1016/S1473-3099(16)30259-6

10. Arinaminpathy N, Batra D, Maheshwari N, et al. Tuberculosis treatment in the private healthcare sector in India: an analysis of recent trends and volumes using drug sales data. *BMC Infect Dis*. 2019;19. doi:10.1186/s12879-019-4169-y

11. Schwartz KL, Chen C, Langford BJ, et al. Validating a popular outpatient antibiotic database to reliably identify high prescribing physicians for patients 65 years of age and older. *PLOS ONE*. 2019;14(9):e0223097. doi:10.1371/journal.pone.0223097

12. IQVIA India. Accessed June 1, 2021. https://www.iqvia.com/locations/india

13. WHOCC - ATC/DDD Index. Accessed September 7, 2020. https://www.whocc.no/atc_ddd_index/

14. India population pyramid 2014. PopulationPyramid.net. Accessed September 7, 2020. https://www.populationpyramid.net/it/india/2014/

15. Marchello CS, Hong CY, Crump JA. Global Typhoid Fever Incidence: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2019;68(Supplement_2):S105-S116. doi:10.1093/cid/ciy1094

For peer review only

16. Patel V, Parikh R, Nandraj S, et al. Assuring health coverage for all in India. *The Lancet*. 2015;386(10011):2422-2435. doi:10.1016/S0140-6736(15)00955-1

17. Bahl R, Sinha A, Poulos C, et al. Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy. *J Health Popul Nutr*. 2004;22(3):304-310.

18. Sur D, von Seidlein L, Manna B, et al. The malaria and typhoid fever burden in the slums of Kolkata, India: data from a prospective community-based study. *Trans R Soc Trop Med Hyg*. 2006;100(8):725-733. doi:10.1016/j.trstmh.2005.10.019

19. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. *Lancet Lond Engl*. 1999;354(9180):734-737. doi:10.1016/S0140-6736(98)09001-1

20. Browne AJ, Kashef Hamadani BH, Kumaran EAP, et al. Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC Med*. 2020;18(1):1. doi:10.1186/s12916-019-1443-1

21. Anderson ES. The problem and implications of chloramphenicol resistance in the typhoid bacillus. *J Hyg (Lond)*. 1975;74(2):289-299. doi:10.1017/s0022172400024360

22. Britto CD, John J, Verghese VP, et al. A systematic review of antimicrobial resistance of typhoidal Salmonella in India. *Indian J Med Res*. 2019;149(2):151-163. doi:10.4103/ijmr.IJMR_830_18

23. Chandra R, Srinivasan S, Nalini P, et al. Multidrug resistant enteric fever. *J Trop Med Hyg*. 1992;95(4):284-287.

24. Balaji V, Kapil A, Shastri J, et al. Longitudinal Typhoid Fever Trends in India from 2000 to 2015. *Am J Trop Med Hyg*. 2018;99(3_Suppl):34-40. doi:10.4269/ajtmh.18-0139

25. Resistance Map - Antibiotic Resistance. Accessed September 7, 2020. https://resistancemap.cddep.org/

26. Mukhopadhyay B, Sur D, Gupta SS, et al. Typhoid fever: Control & challenges in India. *Indian J Med Res*. 2019;150(5):437-447. doi:10.4103/ijmr.IJMR_411_18

27. National Sample Survey Organization. India - Social Consumption - Health Survey: NSS 71st Round, 2014. Accessed June 2, 2021. http://www.icssrdataservice.in/datarepository/index.php/catalog/107

28. Bilcke J, Antillón M, Pieters Z, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infect Dis*. 2019;19(7):728-739. doi:10.1016/S1473-3099(18)30804-1

29. Rosini R, Nicchi S, Pizza M, et al. Vaccines Against Antimicrobial Resistance. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.01048

30. Cook J, Jeuland M, Whittington D, et al. The cost-effectiveness of typhoid Vi vaccination programs: Calculations for four urban sites in four Asian countries. *Vaccine*. 2008;26(50):6305-6316. doi:10.1016/j.vaccine.2008.09.040

For peer review only

31. Mohan VK, Varanasi V, Singh A, et al. Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin Infect Dis*. 2015;61(3):393-402. doi:10.1093/cid/civ295

32. Jin C, Gibani MM, Moore M, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet Lond Engl*. 2017;390(10111):2472-2480. doi:10.1016/S0140-6736(17)32149-9

33. Owais A, Sultana S, Zaman U, et al. Incidence of Typhoid Bacteremia in Infants and Young Children in Southern Coastal Pakistan. *Pediatr Infect Dis J*. 2010;29(11):1035-1039.

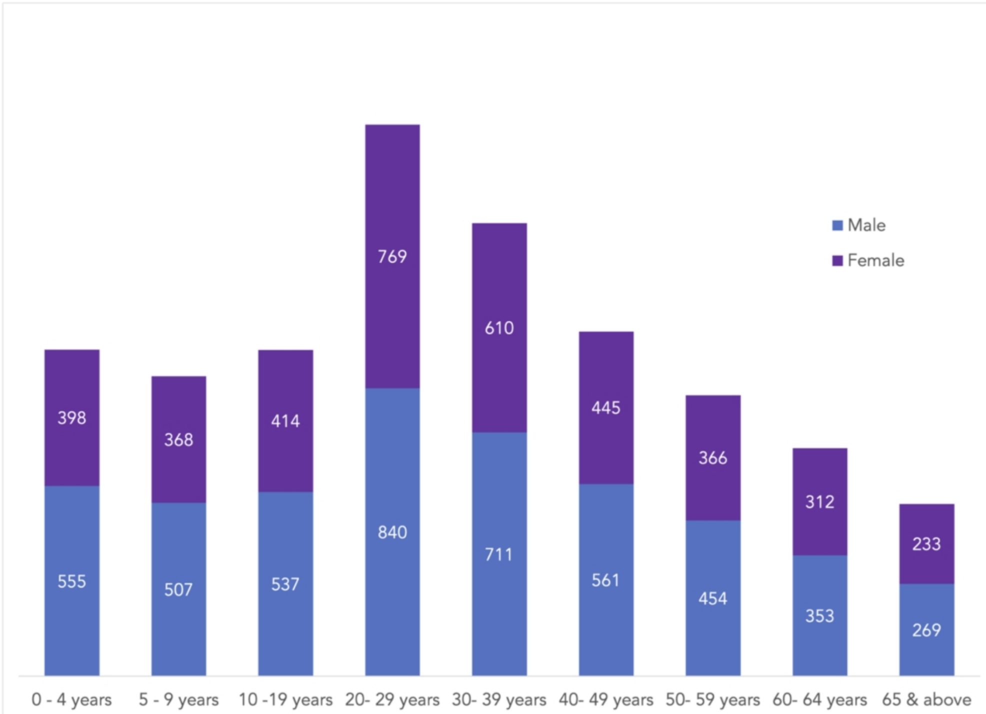
34. Rasul F, Sughra K, Mushtaq A, et al. Surveillance report on typhoid fever epidemiology and risk factor assessment in district Gujrat, Punjab, Pakistan. *Biomed Res*. 2017;28(16). Accessed June 2, 2021.

35. Saha S, Islam MS, Sajib MSI, et al. Epidemiology of Typhoid and Paratyphoid: Implications for Vaccine Policy. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2019;68(Suppl 2):S117-S123. doi:10.1093/cid/ciy1124

36. Nga TVT, Duy PT, Lan NPH, et al. The Control of Typhoid Fever in Vietnam. *Am J Trop Med Hyg*. 2018;99(3 Suppl):72-78. doi:10.4269/ajtmh.18-0035

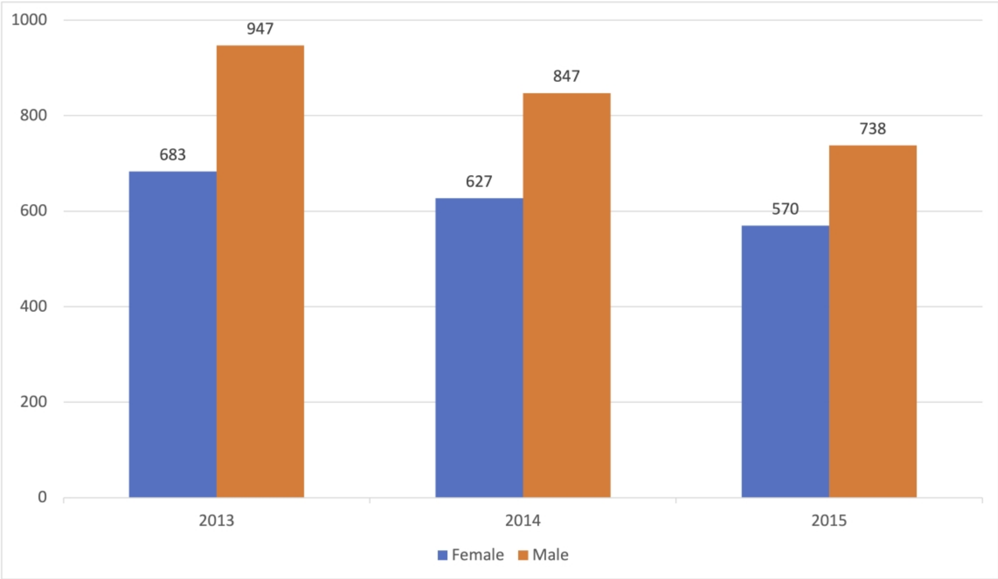
37. John J, Bavdekar A, Rongsen-Chandola T, et al. Estimating the incidence of enteric fever in children in India: a multi-site, active fever surveillance of pediatric cohorts. *BMC Public Health*. 2018;18. doi:10.1186/s12889-018-5498-2

For peer review only



Sex-specific, three-year average antibiotic prescription rates (2013-15) for typhoid, across various age groups, per 100,000 population, India

1300x940mm (72 x 72 DPI)



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

1655x962mm (72 x 72 DPI)

Supplementary file: Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

Supplementary table 1: Recoding of IQVIA ATC groups to WHO ATC groups

Antibiotic	IQVIA ATC	WHO ATC
Ambroxol+Roxithromycin	J01FG	J01F
Amikacin	J01K3	J01G
Amoxy + Cloxa. Solids	J01CD	J01R
Amoxy. & Clav. Inject.	J01CI	J01R
Amoxy. & Clav. Liquids	J01CH	J01R
Amoxy. & Clav. Solids	J01CG	J01R
Amoxy. & Clav. Solids	J01CG	J01R
Amoxy. +Clav. +Lactob.A.	J01CL	J01R
Amoxy. +Cloxa. +Lactob.A.	J01CK	J01R
Amoxy. +Lactob.A.	J01CJ	J01R
Amoxycillin Injectables	J01C6	J01C
Amoxycillin Oral Liquids	J01C5	J01C
Amoxycillin Oral Solids	J01C4	J01C
Ampicillin Injectables	J01C3	J01C
Ampicillin Oral Solids	J01C1	J01C
Azithromycin Injectables	J01F6	J01F
Azithromycin Oral Liquids	J01F5	J01F
Azithromycin Oral Solids	J01F4	J01F
Azithromycin+Levoflox.	J01LL	J01R
Balofloxacin	J01LW	J01M
Cefadroxil + Clavulanic A	J01DH	J01R
Cefadroxil Oral Liquids	J01D5	J01D
Cefadroxil Oral Solids	J01D4	J01D
Cefdinir Oral Sol.&Liq.	J01D7	J01D
Cefixime + Azithromycin	J01D8	J01R
Cefixime + Clav. Liquids	J01D6	J01R
Cefixime + Clav. Solids	J01D3	J01R
Cefixime + Linezolid	J01M2	J01R
Cefixime + Ofloxacin	J01DS	J01R
Cefixime Oral Liq.	J01DM	J01D
Cefixime Oral Sol.	J01DL	J01D
Cefixime+Cloxa. +Lactob.A.	J01DY	J01R
Cefixime+Lactob.A.	J01DX	J01R
Cefoperazone Injectables	J01DG	J01D
Cefoperazone+Sulbactum	J01DO	J01R
Cefotaxime Injectables	J01DD	J01D
Cefpod. + Clav. Liquids	J01DQ	J01R
Cefpodoxime Liquids	J01DW	J01D
Cefpodoxime Solids	J01DV	J01D

For peer review only

Antibiotic	IQVIA ATC	WHO ATC
Ceftazidime Injectables	J01DE	J01D
Ceftriaxone + Tazobactam	J01D9	J01R
Ceftriaxone Injectabls	J01DC	J01D
Ceftriaxone+Sulbactam	J01DZ	J01R
Cefuroxime Injectables	J01DF	J01D
Cefuroxime Oral Liquid	J01DK	J01D
Cefuroxime Oral Solids	J01DI	J01D
Cephalexin Oral Liquids	J01D2	J01D
Cephalexin Oral Solids	J01D1	J01D
Chloram. - Comb. Inject.	J01B3	J01B
Chloram. - Comb. Liquids	J01B2	J01B
Chloram. - Comb. Solids	J01B1	J01B
Ciprofloxacin Injectables	J01L3	J01M
Ciprofloxacin Oral Solids	J01L1	J01M
Clarithromycin Injectable	J01FC	J01F
Clarithromycin Oral Liqui	J01FB	J01F
Clarithromycin Oral Solid	J01FA	J01F
Clavulanic Acid+Cefuroxi	J01DP	J01R
Clindamycin	J01FD	J01F
Cloxa. & Ampi.Comb. Inject	J01CC	J01R
Cloxa. & Ampi.Comb. Solid	J01CA	J01R
Colistine Inj.	J01KD	JO1X
Doxycycline Oral Solids	J01A5	J01A
Doxycycline+Lactob A.	J01A8	J01R
Erythromycin Oral Liquids	J01F2	J01F
Erythromycin Oral Solids	J01F1	J01F
Faropenem	J01N2	J01D
Gatifloxacin	J01LG	J01M
Gemifloxacin	J01LI	J01M
Gentamycin	J01K1	J01G
Levofloxacin	J01LF	J01M
Lincomycin	J01FE	J01F
Linezolid	J01M1	J01X
Macrolides Combination So	J01FM	J01R
Meropenem	J01N1	J01D
Metronidazole Inj.	J01K2	J01X
Moxifloxacin	J01LH	J01M
Netilmicin	J01KH	J01G
Norfloxacin Oral Solids	J01L4	J01M
Ofloxacin Injectables	J01LE	J01M
Ofloxacin Oral Liquids	J01LD	J01M
Ofloxacin Oral Solids	J01LC	J01M
Ofloxacin+Cefpodoxime	J01LK	J01R
Oth. Amoxy. Comb. Sol.	J01CP	J01R

For peer review only

Antibiotic	IQVIA ATC	WHO ATC
Oth. Ampi. Comb. Inj.	J01CO	J01R
Oth. Ampi. Comb. Sol.	J01CM	J01R
Oth. Cephalo Liquids	J01DB	J01D
Oth. Cephalo. Inje	J01DT	J01D
Oth. Cephalo. Solids	J01DA	J01D
Oth.Cephalo.Comb.Inj.	J01DU	J01R
Oth.Cephalo.Comb.Sol&Liq.	J01DR	J01R
Other Antibiotics	J01K9	J01X
Other Penicillines-Inject	J01H2	J01C
Other Penicillines-Orals	J01H1	J01C
Other Quino.Injectables	J01LV	J01M
Other Quino.Oral Liquids	J01LU	J01M
Other Quino.Oral Solids	J01LT	J01M
Piperacillin+Tazobactam	J01K5	J01R
Prulifloxacin	J01LJ	J01M
Quino.Comb. Oral Solids	J01LX	J01R
Roxithromycin Oral Liquid	J01F8	J01F
Roxithromycin Oral Solids	J01F7	J01F
Sparfloxacin Oral Solids	J01LB	J01M
Streptomycines And Comb.	J01G1	J01G
Sulbactam+Cefotaxime	J01DJ	J01R
Tetra.Oral Solids	J01A1	J01A
Trimetho. & Simi. Liquids	J01E2	J01E
Trimetho. & Simi. Solids	J01E1	J01E

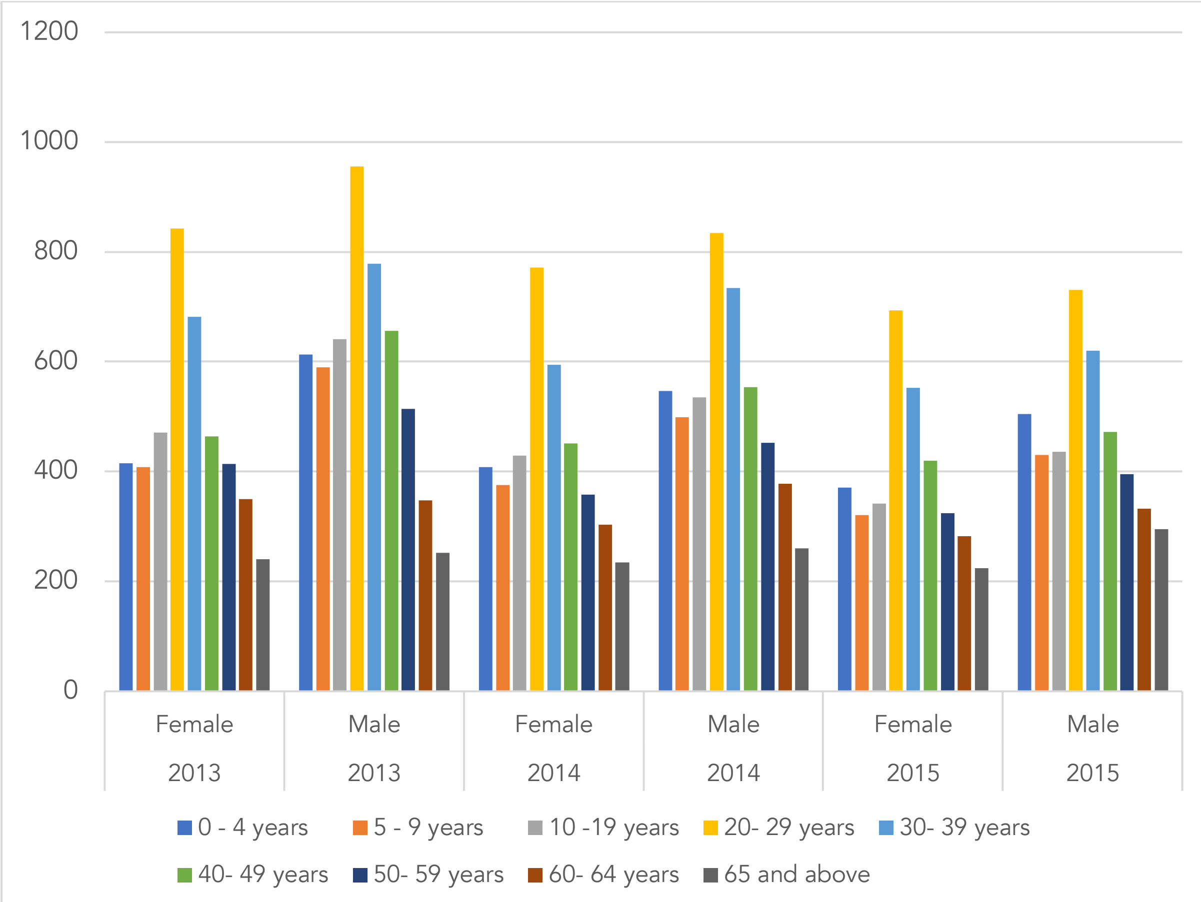
For peer review only

Supplementary table 2: Average rate of antibiotic prescriptions for typhoid across sexes (per 100,000 population), 2013-15

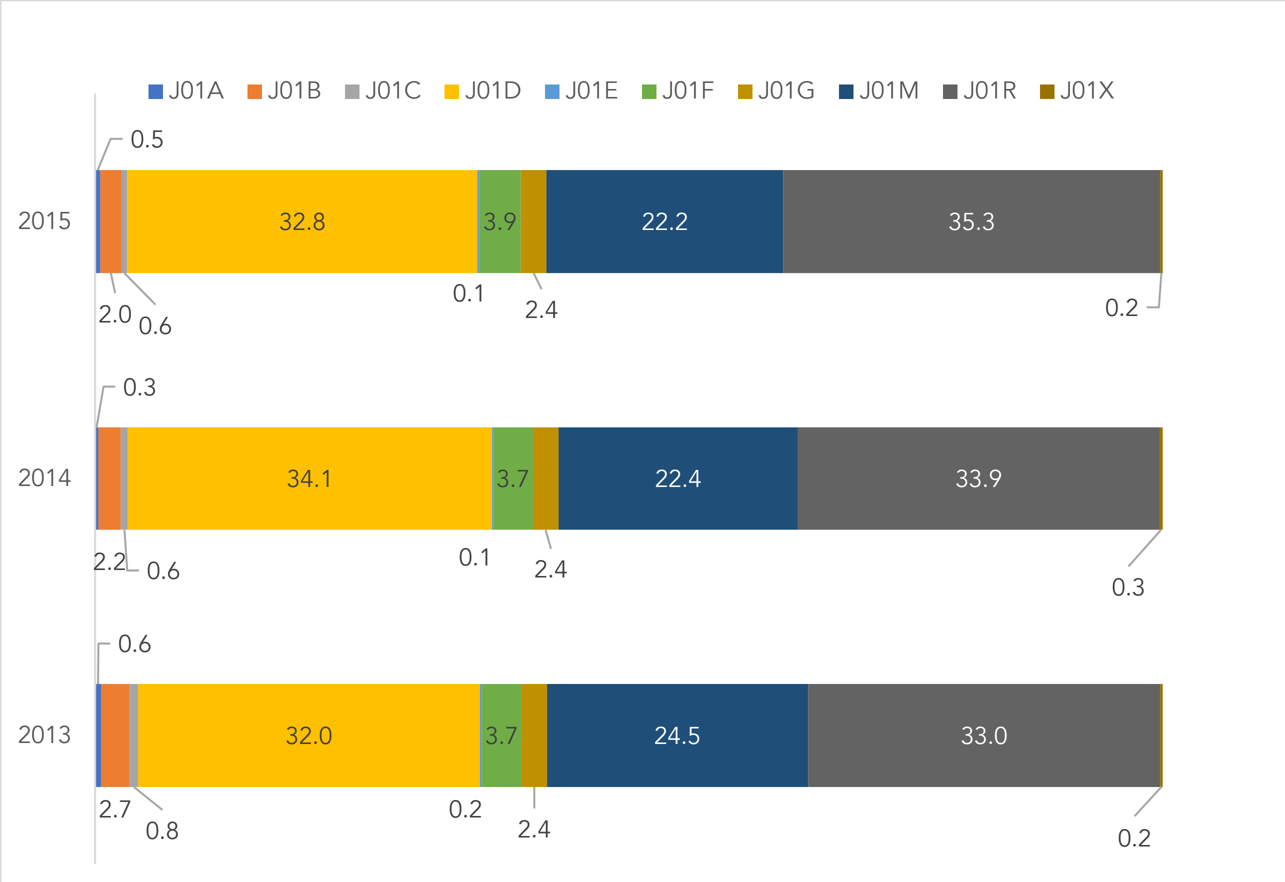
Age groups	Male	Female	Difference, %
0 - 4 years	555	398	28
5 - 9 years	507	368	27
10 -19 years	537	414	23
20- 29 years	840	769	8
30- 39 years	711	610	14
40- 49 years	561	445	21
50- 59 years	454	366	20
60- 64 years	353	312	12
65 & above	269	233	13

For peer review only

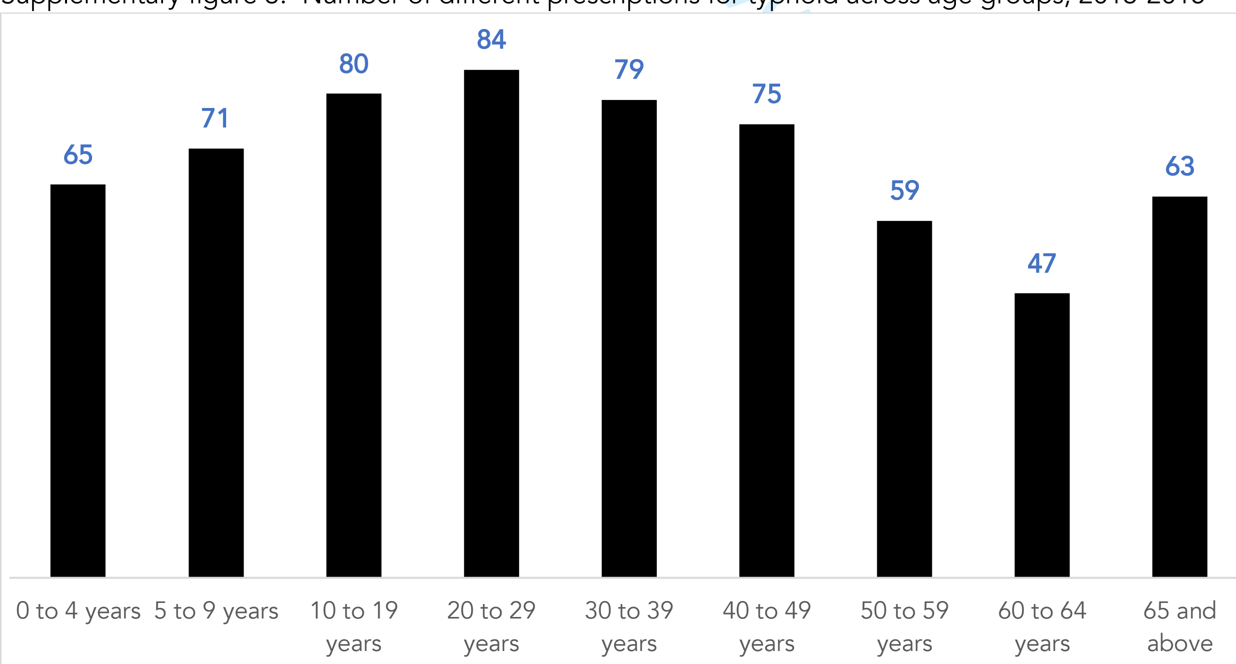
Supplementary figure 1: Age and sex specific prescription rates for typhoid (per 100,000 population) in 2013, 2014 and 2015



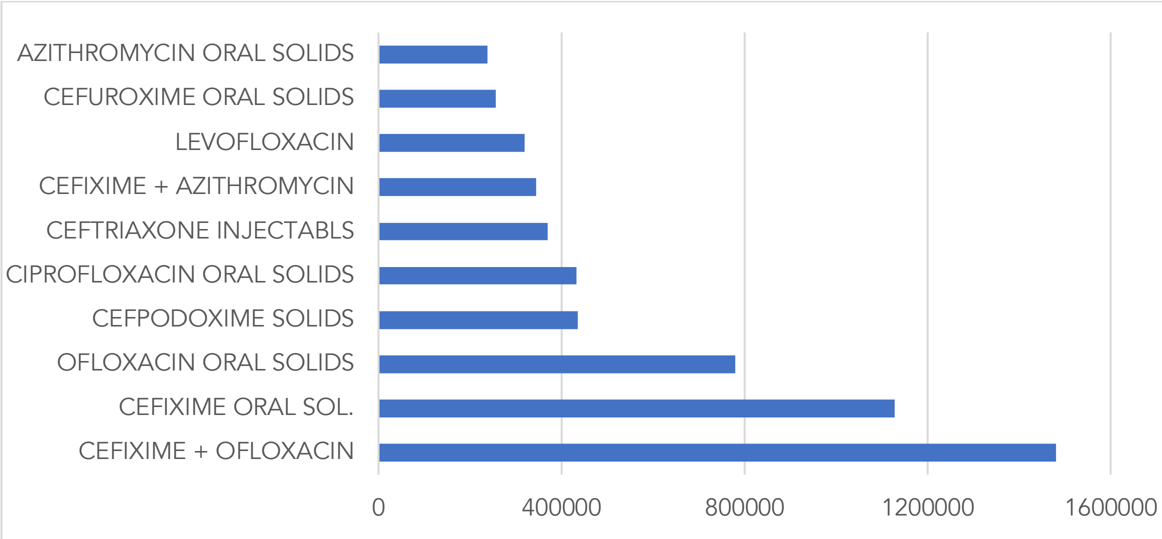
Supplementary figure 2: Share (in percentage) of various antibiotic classes for typhoid across years 2013 to 2015



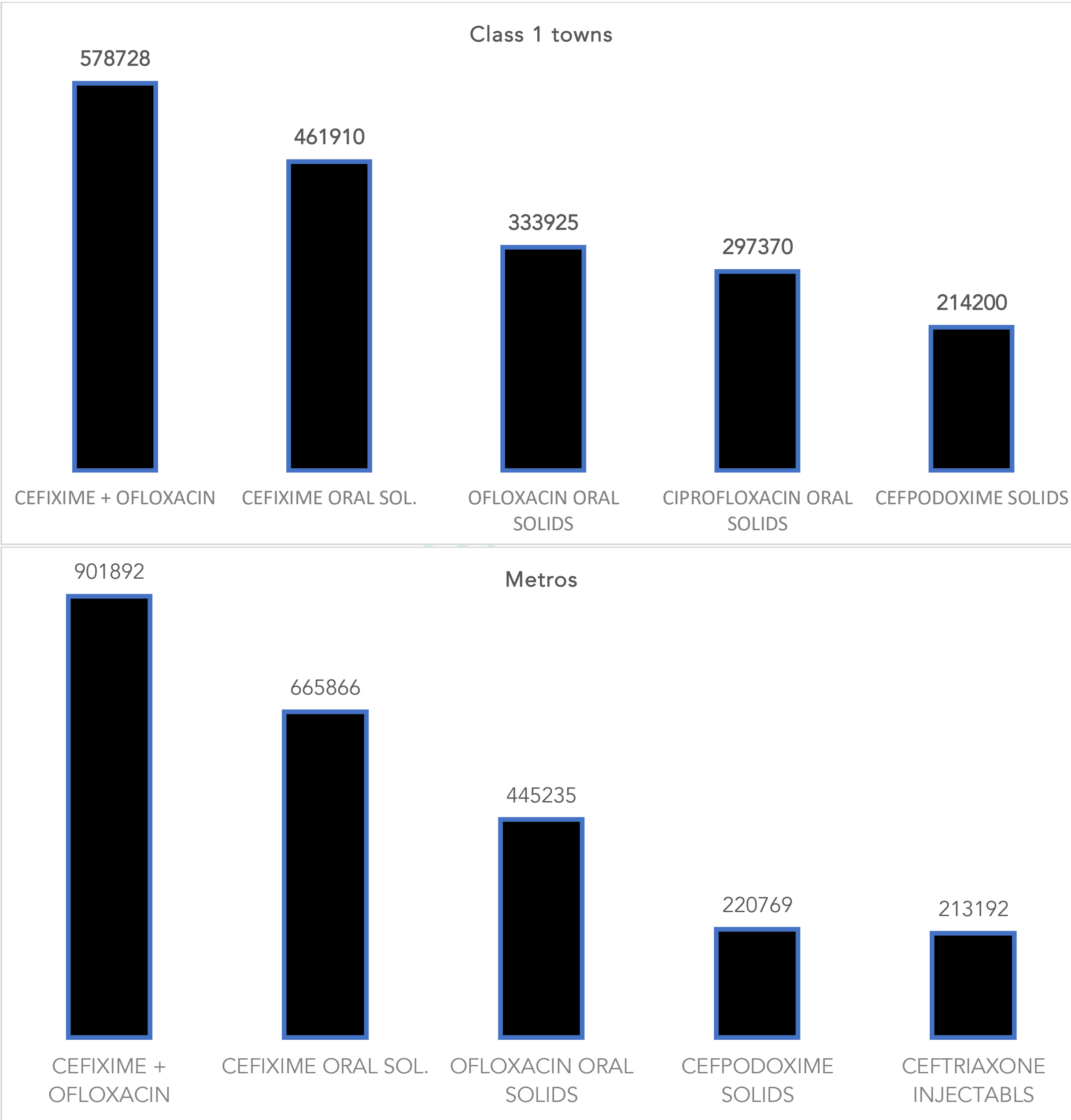
Supplementary figure 3: Number of different prescriptions for typhoid across age groups, 2013-2015



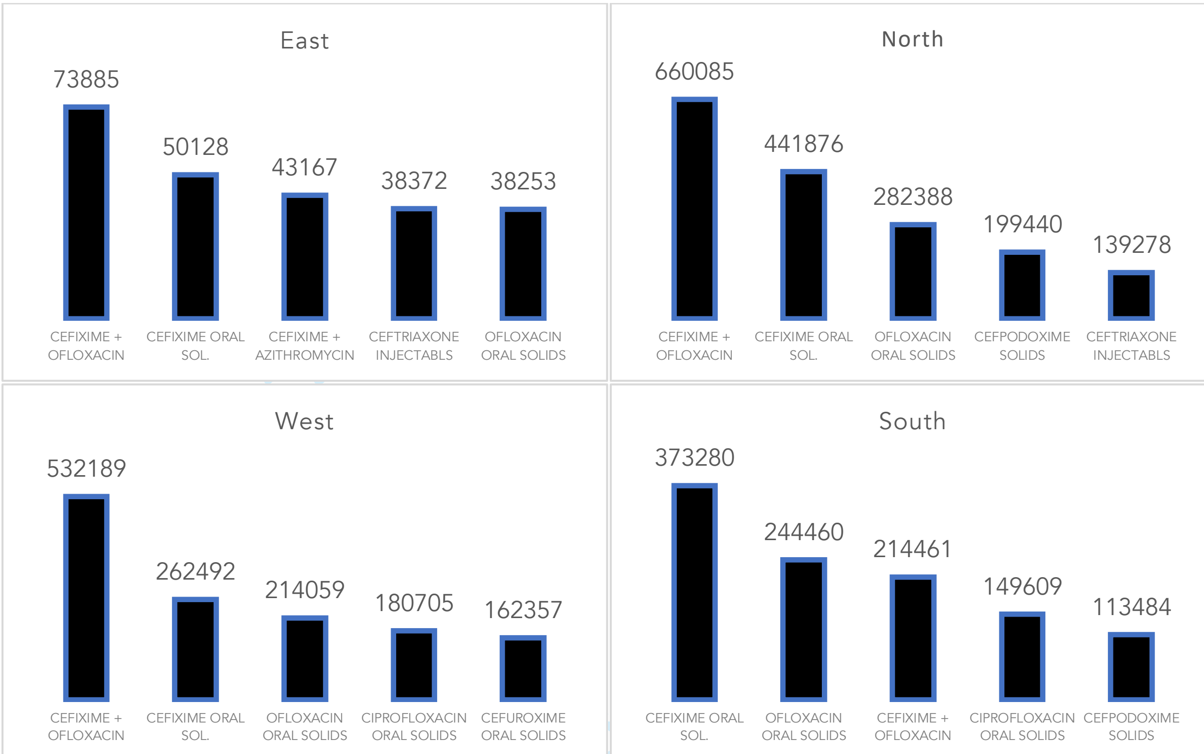
Supplementary figure 4. Top ten prescriptions (in numbers) for typhoid across India, 2015



Supplementary figure 5: Top five prescriptions (in numbers) for typhoid across cities and metros, 2015 (number)

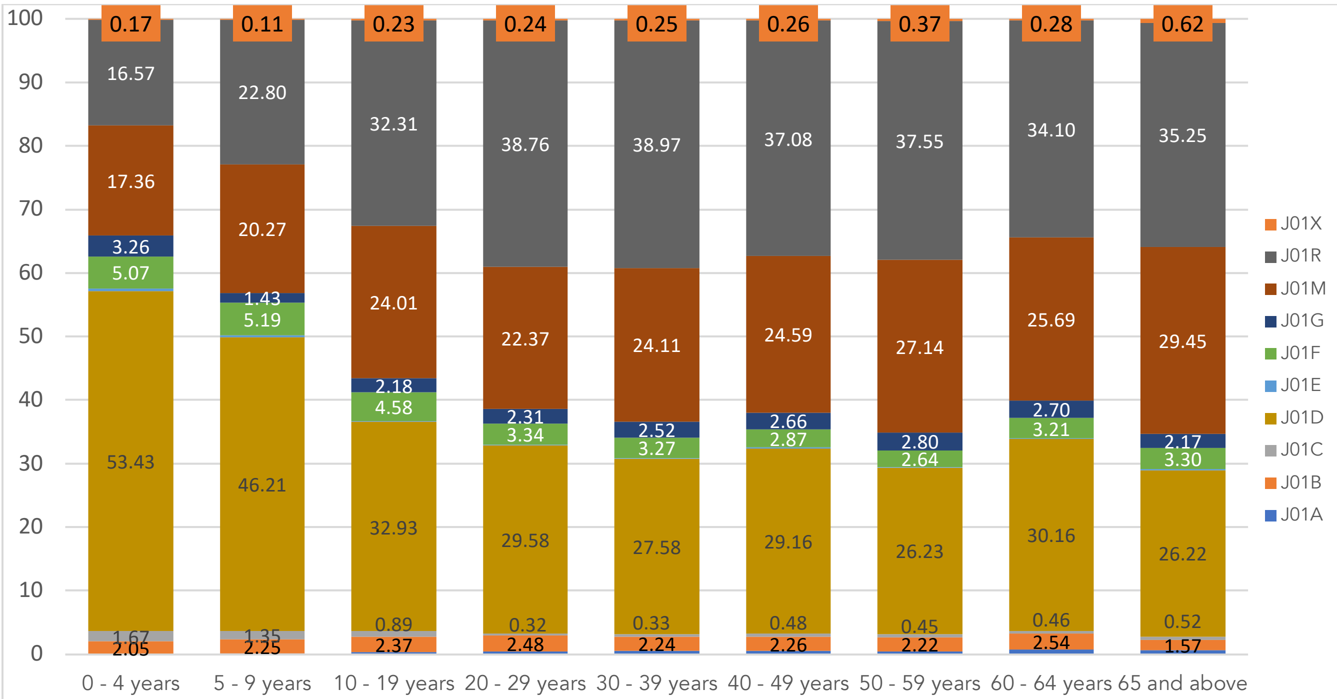


Supplementary figure 6: Top five prescriptions (in numbers) for typhoid across zones, 2015 (Numbers)



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Supplementary figure 7: Age- group wise average rate of prescription of typhoid antibiotics, 2013-15



BMJ Open

Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062401.R1
Article Type:	Original research
Date Submitted by the Author:	06-May-2022
Complete List of Authors:	Fazaludeen Koya, Shaffi; Boston University School of Public Health, Epidemiology Hasan Farooqui, Habib; Qatar University, College of Medicine Mehta, Aashna; Public Health Foundation of India, Health Economics, Financing and Policy Division Selvaraj, Sakthivel; Public Health Foundation of India, Health Economics, Financing and Policy Division Galea, Sandro; Boston University, School of Public Health
Primary Subject Heading:	Global health
Secondary Subject Heading:	Infectious diseases
Keywords:	INFECTIOUS DISEASES, PUBLIC HEALTH, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Title page

a. Title:

Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

b. Corresponding author

Dr. Shaffi Fazaludeen Koya

Department of Epidemiology, Boston University School of Public Health,

715 Albany St, Boston, Massachusetts, USA 02118

fmshaffi@bu.edu

c. Name(s) of the author(s):

Shaffi Fazaludeen Koya[1] fmshaffi@bu.edu

Habib Hasan Farooqui[2] hfarooqui@qu.edu.qa

Aashna Mehta[3] aashna.mehta@phfi.org

Sakthivel Selvaraj[3] shakti@phfi.org

Sandro Galea[4] sgalea@bu.edu

Affiliation(s) of author(s)

[1] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

[2] College of Medicine, Qatar University, Doha, Qatar

[3] Health Economics, Financing and Policy Division, Public Health Foundation of India, New Delhi, Delhi, India

[4] Boston University School of Public Health, Boston, MA, USA

d. Keywords: antibiotics, antibiotic resistance, drug prescription, typhoid, typhoid conjugate vaccine

e. Word count: 2,830

For peer review only

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 4,600 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- 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 to 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 2013-15 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

1 **Strengths and limitations of this study**

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

8

For peer review only

Introduction

Enteric Fever, a systemic infection caused by Salmonella enterica serotypes *S. typhi* and *S. para typhi,* remains an important public health problem. Globally, there was a 44% decline in typhoid and para-typhoid 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% CI: 178–801) typhoid and 105/100,000 (95% CI: 74–148) para-typhoid cases.[2] The global burden of diseases (GBD) 2017 estimates reported a higher incidence of 586.3 typhoid/para-typhoid cases per 100,000 population (95% UI: 515.7, 661.8), though this is 60% lower compared to 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 formal 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–

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.[9,10,11] Therefore, in this study, we aimed to generate new evidence on annual antibiotic prescription rates and sex- and age-specific prescription rates for typhoid, and the distribution of antibiotic class in these prescriptions in India during 2013-15 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 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

For peer review only

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, south) and urban locality categories (Metropolitan cities or class 1/1A towns). IQVIA organizes 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 World Health Organization WHO collaborating center 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 supplementary 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- 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 analyzed using Excel and R. We compared the prescription rates across years, sex,

For peer review only

age-groups, zones, locations, and WHO ATC categories. Results are reported in accordance with the STROBE (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 behavior 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.

Ethical approval

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

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

For peer review only

We analyzed 671 million prescriptions for the three-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 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 three 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 para-typhoid 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 three years . The majority of cases were reported from metropolitan cities.

For peer review only

The prescription rate varied across age groups and gender. Over the three-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-year 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 to females (627/ 100,000) over the three-year period. Figure 1 shows the distribution of sex-specific, three- year average antibiotic prescription rates across age-groups. There were clear differences in the number

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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%) [supplementary table 2, supplementary figure 1]

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

	Number 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.

For peer review only

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 three 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% cases. We did not observe any major changes in the prescription share for antibiotic classes over the three-year period. [supplementary 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. [supplementary figure 3] In general, young adults were treated with a wide range of formulations.

Table 2: WHO ATC class of antibiotics prescribed for typhoid, 2013-15

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[1]	305,007	1.50

[1] Includes Penicillin (J01C), Tetracyclines (J01A), Others (J01X), and Sulfonamide-Trimethoprim (J01E)

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ten different antibiotics accounted for three-quarter of all prescriptions (72.4%). [supplementary 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. (supplementary 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 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 Supplement [supplementary 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 three years (2013-2015), that signals a higher estimate of typhoid burden in the country compared to 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 six out of every 1000 typhoid cases require hospitalization.[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

For peer review only

facilities, namely the Swachh Bharat (clean India) mission, as a previous analysis showed.[20] Alternatively, it may be also due to shifting in 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 multi-drug 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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 hospitalization is still due to infections.[29] The cost of treating an episode of typhoid in outpatient care ranges from $2.0-$2.6 (mean, $2.3, 2010 US$), and from $96 to $132(mean $113, 2010 US$) for hospitalized care.[30] If we can achieve a higher vaccination coverage across population at risk with the newly available prequalified typhoid conjugate vaccine (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 modeling study which showed that with routine immunization at nine months of age with a catch-up campaign up to age 15 years we can avert 46–74% of all typhoid fever cases in 73 countries eligible for the Global Alliance for Vaccines and Immunization (GAVI) 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 to 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,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 18- to 49-year-old adults.[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-

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 immunization programs alongside improvement in water, hygiene, and sanitation facilities can help to reduce the typhoid burden as well as demand for antibiotics.

For peer review only

Figure legends

Figure 1: Sex-specific, three-year average antibiotic prescription rates (2013-15) for typhoid, across various age groups, per 100,000 population, India

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

For peer review only

Contributor statement:

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.

Competing interests:

None declared

Funding:

SFK is supported by The Rockefeller Foundation–Boston University 3-D Commission as a Research Fellow (2019 HTH 024). The funding agency did not have any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Data sharing statement:

This study used proprietary data from the IQVIA India (previously IMS Health). IQVIA can be approached for data access through their website, https://www.iqvia.com/locations/india

For peer review only

Reference:

1. Stanaway JD, Reiner RC, Blacker BF, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. 2019;19(4):369-381. doi:10.1016/S1473-3099(18)30685-6

2. John J, Van Aart CJC, Grassly NC. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. Baker S, ed. *PLoS Negl Trop Dis*. 2016;10(4):e0004616. doi:10.1371/journal.pntd.0004616

3. Phalkey RK, Butsch C, Belesova K, et al. From habits of attrition to modes of inclusion: enhancing the role of private practitioners in routine disease surveillance. *BMC Health Serv Res*. 2017;17(1):1-15. doi:10.1186/s12913-017-2476-9

4. Pitzer VE, Meiring J, Martineau FP, et al. The Invisible Burden: Diagnosing and Combatting Typhoid Fever in Asia and Africa. *Clin Infect Dis*. 2019;69(Supplement_5):S395-S401. doi:10.1093/cid/ciz611

5. Gibani MM, Britto C, Pollard AJ. Typhoid and paratyphoid fever: a call to action. *Curr Opin Infect Dis*. 2018;31(5):440-448. doi:10.1097/QCO.0000000000000479

6. Dyson ZA, Klemm EJ, Palmer S, et al. Antibiotic Resistance and Typhoid. *Clin Infect Dis*. 2019;68(Supplement_2):S165-S170. doi:10.1093/cid/ciy1111

7. Gandra S, Mojica N, Klein EY, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. *Int J Infect Dis*. 2016;50:75-82. doi:10.1016/j.ijid.2016.08.002

8. Birger R, Antillón M, Bilcke J, et al. Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study. *Lancet Infect Dis*. 2022;0(0). doi:10.1016/S1473-3099(21)00627-7

9. Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis*. 2016;16(11):1255-1260. doi:10.1016/S1473-3099(16)30259-6

10. Arinaminpathy N, Batra D, Maheshwari N, et al. Tuberculosis treatment in the private healthcare sector in India: an analysis of recent trends and volumes using drug sales data. *BMC Infect Dis*. 2019;19. doi:10.1186/s12879-019-4169-y

11. Schwartz KL, Chen C, Langford BJ, et al. Validating a popular outpatient antibiotic database to reliably identify high prescribing physicians for patients 65 years of age and older. *PLOS ONE*. 2019;14(9):e0223097. doi:10.1371/journal.pone.0223097

12. IQVIA India. Accessed June 1, 2021. https://www.iqvia.com/locations/india

13. WHOCC - ATC/DDD Index. Accessed September 7, 2020. https://www.whocc.no/atc_ddd_index/

14. India population pyramid 2014. PopulationPyramid.net. Accessed September 7, 2020. https://www.populationpyramid.net/it/india/2014/

15. Marchello CS, Hong CY, Crump JA. Global Typhoid Fever Incidence: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2019;68(Supplement_2):S105-S116. doi:10.1093/cid/ciy1094

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Patel V, Parikh R, Nandraj S, et al. Assuring health coverage for all in India. *The Lancet*. 2015;386(10011):2422-2435. doi:10.1016/S0140-6736(15)00955-1

17. Bahl R, Sinha A, Poulos C, et al. Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy. *J Health Popul Nutr*. 2004;22(3):304-310.

18. Sur D, von Seidlein L, Manna B, et al. The malaria and typhoid fever burden in the slums of Kolkata, India: data from a prospective community-based study. *Trans R Soc Trop Med Hyg*. 2006;100(8):725-733. doi:10.1016/j.trstmh.2005.10.019

19. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. *Lancet Lond Engl*. 1999;354(9180):734-737. doi:10.1016/S0140-6736(98)09001-1

20. Nandi A, Megiddo I, Ashok A, Verma A, Laxminarayan R. Reduced burden of childhood diarrheal diseases through increased access to water and sanitation in India: A modeling analysis. *Social Science & Medicine*. 2017;180:181-192. doi:10.1016/j.socscimed.2016.08.049

21. Selvaraj S, Karan AK, Mao W, et al. Did the poor gain from India's health policy interventions? Evidence from benefit-incidence analysis, 2004—2018. *International Journal for Equity in Health*. 2021;20(1). doi:10.1186/s12939-021-01489-0

22. Browne AJ, Kashef Hamadani BH, Kumaran EAP, et al. Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC Med*. 2020;18(1):1. doi:10.1186/s12916-019-1443-1

23. Anderson ES. The problem and implications of chloramphenicol resistance in the typhoid bacillus. *J Hyg (Lond)*. 1975;74(2):289-299. doi:10.1017/s0022172400024360

24. Britto CD, John J, Verghese VP, et al. A systematic review of antimicrobial resistance of typhoidal Salmonella in India. *Indian J Med Res*. 2019;149(2):151-163. doi:10.4103/ijmr.IJMR_830_18

25. Chandra R, Srinivasan S, Nalini P, et al. Multidrug resistant enteric fever. *J Trop Med Hyg*. 1992;95(4):284-287.

26. Balaji V, Kapil A, Shastri J, et al. Longitudinal Typhoid Fever Trends in India from 2000 to 2015. *Am J Trop Med Hyg*. 2018;99(3_Suppl):34-40. doi:10.4269/ajtmh.18-0139

27. Resistance Map - Antibiotic Resistance. Accessed September 7, 2020. https://resistancemap.cddep.org/

28. Mukhopadhyay B, Sur D, Gupta SS, et al. Typhoid fever: Control & challenges in India. *Indian J Med Res*. 2019;150(5):437-447. doi:10.4103/ijmr.IJMR_411_18

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

29. National Sample Survey Organization. India - Social Consumption - Health Survey: NSS 71st Round, 2014. Accessed June 2, 2021. http://www.icssrdataservice.in/datarepository/index.php/catalog/107

30. Bilcke J, Antillón M, Pieters Z, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infect Dis*. 2019;19(7):728-739. doi:10.1016/S1473-3099(18)30804-1

31. Rosini R, Nicchi S, Pizza M, et al. Vaccines Against Antimicrobial Resistance. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.01048

32. Cook J, Jeuland M, Whittington D, et al. The cost-effectiveness of typhoid Vi vaccination programs: Calculations for four urban sites in four Asian countries. *Vaccine*. 2008;26(50):6305-6316. doi:10.1016/j.vaccine.2008.09.040

33. Mohan VK, Varanasi V, Singh A, et al. Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin Infect Dis*. 2015;61(3):393-402. doi:10.1093/cid/civ295

34. Jin C, Gibani MM, Moore M, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet Lond Engl*. 2017;390(10111):2472-2480. doi:10.1016/S0140-6736(17)32149-9

35. Owais A, Sultana S, Zaman U, et al. Incidence of Typhoid Bacteremia in Infants and Young Children in Southern Coastal Pakistan. *Pediatr Infect Dis J*. 2010;29(11):1035-1039.

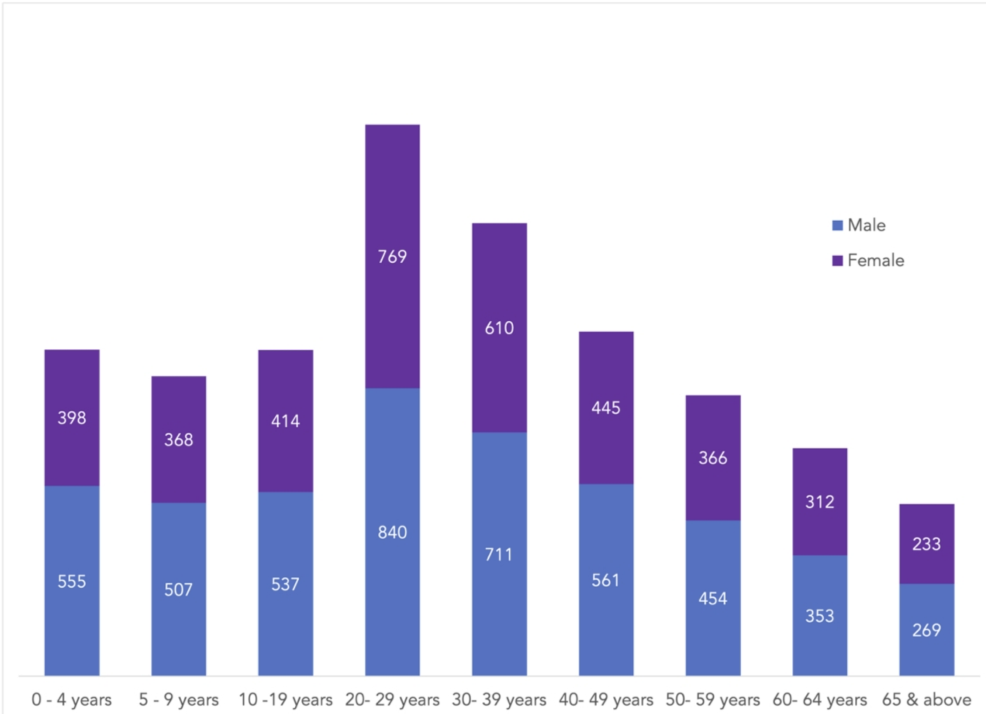
36. Rasul F, Sughra K, Mushtaq A, et al. Surveillance report on typhoid fever epidemiology and risk factor assessment in district Gujrat, Punjab, Pakistan. *Biomed Res*. 2017;28(16). Accessed June 2, 2021.

37. Saha S, Islam MS, Sajib MSI, et al. Epidemiology of Typhoid and Paratyphoid: Implications for Vaccine Policy. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2019;68(Suppl 2):S117-S123. doi:10.1093/cid/ciy1124

38. Nga TVT, Duy PT, Lan NPH, et al. The Control of Typhoid Fever in Vietnam. *Am J Trop Med Hyg*. 2018;99(3 Suppl):72-78. doi:10.4269/ajtmh.18-0035

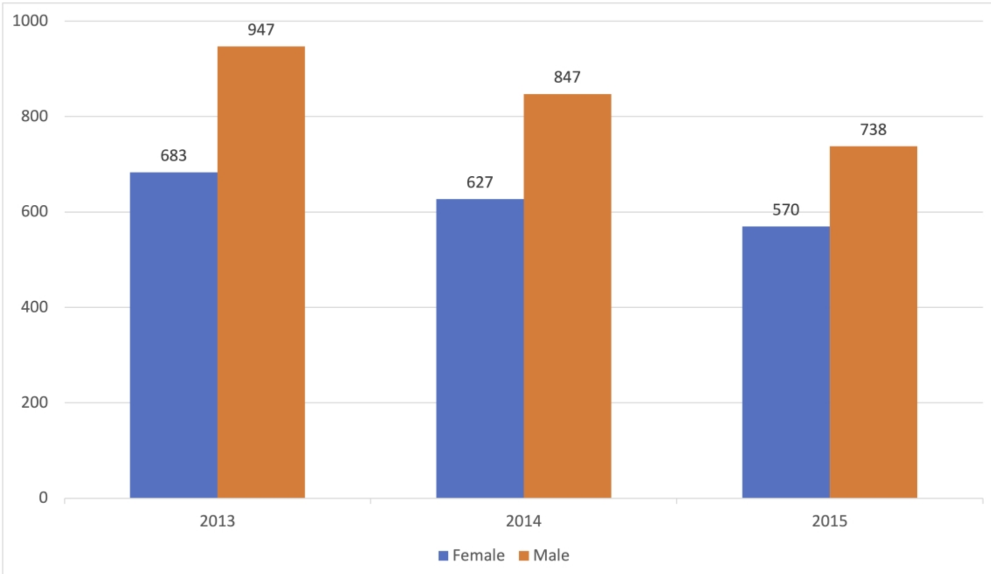
39. John J, Bavdekar A, Rongsen-Chandola T, et al. Estimating the incidence of enteric fever in children in India: a multi-site, active fever surveillance of pediatric cohorts. *BMC Public Health*. 2018;18. doi:10.1186/s12889-018-5498-2

For peer review only



Sex-specific, three-year average antibiotic prescription rates (2013-15) for typhoid, across various age groups, per 100,000 population, India

1300x940mm (72 x 72 DPI)



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

1655x962mm (72 x 72 DPI)

Supplementary file: Quantifying antibiotic use in typhoid fever in India: A cross-sectional analysis of private sector medical audit data, 2013-15

Supplementary table 1: Recoding of IQVIA ATC groups to WHO ATC groups

Antibiotic	IQVIA ATC	WHO ATC
Ambroxol+Roxithromycin	J01FG	J01F
Amikacin	J01K3	J01G
Amoxy + Cloxa. Solids	J01CD	J01R
Amoxy. & Clav. Inject.	J01CI	J01R
Amoxy. & Clav. Liquids	J01CH	J01R
Amoxy. & Clav. Solids	J01CG	J01R
Amoxy. & Clav. Solids	J01CG	J01R
Amoxy. +Clav. +Lactob.A.	J01CL	J01R
Amoxy. +Cloxa. +Lactob.A.	J01CK	J01R
Amoxy. +Lactob.A.	J01CJ	J01R
Amoxycillin Injectables	J01C6	J01C
Amoxycillin Oral Liquids	J01C5	J01C
Amoxycillin Oral Solids	J01C4	J01C
Ampicillin Injectables	J01C3	J01C
Ampicillin Oral Solids	J01C1	J01C
Azithromycin Injectables	J01F6	J01F
Azithromycin Oral Liquids	J01F5	J01F
Azithromycin Oral Solids	J01F4	J01F
Azithromycin+Levoflox.	J01LL	J01R
Balofloxacin	J01LW	J01M
Cefadroxil + Clavulanic A	J01DH	J01R
Cefadroxil Oral Liquids	J01D5	J01D
Cefadroxil Oral Solids	J01D4	J01D
Cefdinir Oral Sol.&Liq.	J01D7	J01D
Cefixime + Azithromycin	J01D8	J01R
Cefixime + Clav. Liquids	J01D6	J01R
Cefixime + Clav. Solids	J01D3	J01R
Cefixime + Linezolid	J01M2	J01R
Cefixime + Ofloxacin	J01DS	J01R
Cefixime Oral Liq.	J01DM	J01D
Cefixime Oral Sol.	J01DL	J01D
Cefixime+Cloxa. +Lactob.A.	J01DY	J01R
Cefixime+Lactob.A.	J01DX	J01R
Cefoperazone Injectables	J01DG	J01D
Cefoperazone+Sulbactum	J01DO	J01R
Cefotaxime Injectables	J01DD	J01D
Cefpod. + Clav. Liquids	J01DQ	J01R
Cefpodoxime Liquids	J01DW	J01D
Cefpodoxime Solids	J01DV	J01D

For peer review only

Antibiotic	IQVIA ATC	WHO ATC
Ceftazidime Injectables	J01DE	J01D
Ceftriaxone + Tazobactam	J01D9	J01R
Ceftriaxone Injectabls	J01DC	J01D
Ceftriaxone+Sulbactam	J01DZ	J01R
Cefuroxime Injectables	J01DF	J01D
Cefuroxime Oral Liquid	J01DK	J01D
Cefuroxime Oral Solids	J01DI	J01D
Cephalexin Oral Liquids	J01D2	J01D
Cephalexin Oral Solids	J01D1	J01D
Chloram. - Comb. Inject.	J01B3	J01B
Chloram. - Comb. Liquids	J01B2	J01B
Chloram. - Comb. Solids	J01B1	J01B
Ciprofloxacin Injectables	J01L3	J01M
Ciprofloxacin Oral Solids	J01L1	J01M
Clarithromycin Injectable	J01FC	J01F
Clarithromycin Oral Liqui	J01FB	J01F
Clarithromycin Oral Solid	J01FA	J01F
Clavulanic Acid+Cefuroxi	J01DP	J01R
Clindamycin	J01FD	J01F
Cloxa. & Ampi.Comb. Inject	J01CC	J01R
Cloxa. & Ampi.Comb. Solid	J01CA	J01R
Colistine Inj.	J01KD	JO1X
Doxycycline Oral Solids	J01A5	J01A
Doxycycline+Lactob A.	J01A8	J01R
Erythromycin Oral Liquids	J01F2	J01F
Erythromycin Oral Solids	J01F1	J01F
Faropenem	J01N2	J01D
Gatifloxacin	J01LG	J01M
Gemifloxacin	J01LI	J01M
Gentamycin	J01K1	J01G
Levofloxacin	J01LF	J01M
Lincomycin	J01FE	J01F
Linezolid	J01M1	J01X
Macrolides Combination So	J01FM	J01R
Meropenem	J01N1	J01D
Metronidazole Inj.	J01K2	J01X
Moxifloxacin	J01LH	J01M
Netilmicin	J01KH	J01G
Norfloxacin Oral Solids	J01L4	J01M
Ofloxacin Injectables	J01LE	J01M
Ofloxacin Oral Liquids	J01LD	J01M
Ofloxacin Oral Solids	J01LC	J01M
Ofloxacin+Cefpodoxime	J01LK	J01R
Oth. Amoxy. Comb. Sol.	J01CP	J01R

For peer review only

Antibiotic	IQVIA ATC	WHO ATC
Oth. Ampi. Comb. Inj.	J01CO	J01R
Oth. Ampi. Comb. Sol.	J01CM	J01R
Oth. Cephalo Liquids	J01DB	J01D
Oth. Cephalo. Inje	J01DT	J01D
Oth. Cephalo. Solids	J01DA	J01D
Oth.Cephalo.Comb.Inj.	J01DU	J01R
Oth.Cephalo.Comb.Sol&Liq.	J01DR	J01R
Other Antibiotics	J01K9	J01X
Other Penicillines-Inject	J01H2	J01C
Other Penicillines-Orals	J01H1	J01C
Other Quino.Injectables	J01LV	J01M
Other Quino.Oral Liquids	J01LU	J01M
Other Quino.Oral Solids	J01LT	J01M
Piperacillin+Tazobactam	J01K5	J01R
Prulifloxacin	J01LJ	J01M
Quino.Comb. Oral Solids	J01LX	J01R
Roxithromycin Oral Liquid	J01F8	J01F
Roxithromycin Oral Solids	J01F7	J01F
Sparfloxacin Oral Solids	J01LB	J01M
Streptomycines And Comb.	J01G1	J01G
Sulbactam+Cefotaxime	J01DJ	J01R
Tetra.Oral Solids	J01A1	J01A
Trimetho. & Simi. Liquids	J01E2	J01E
Trimetho. & Simi. Solids	J01E1	J01E

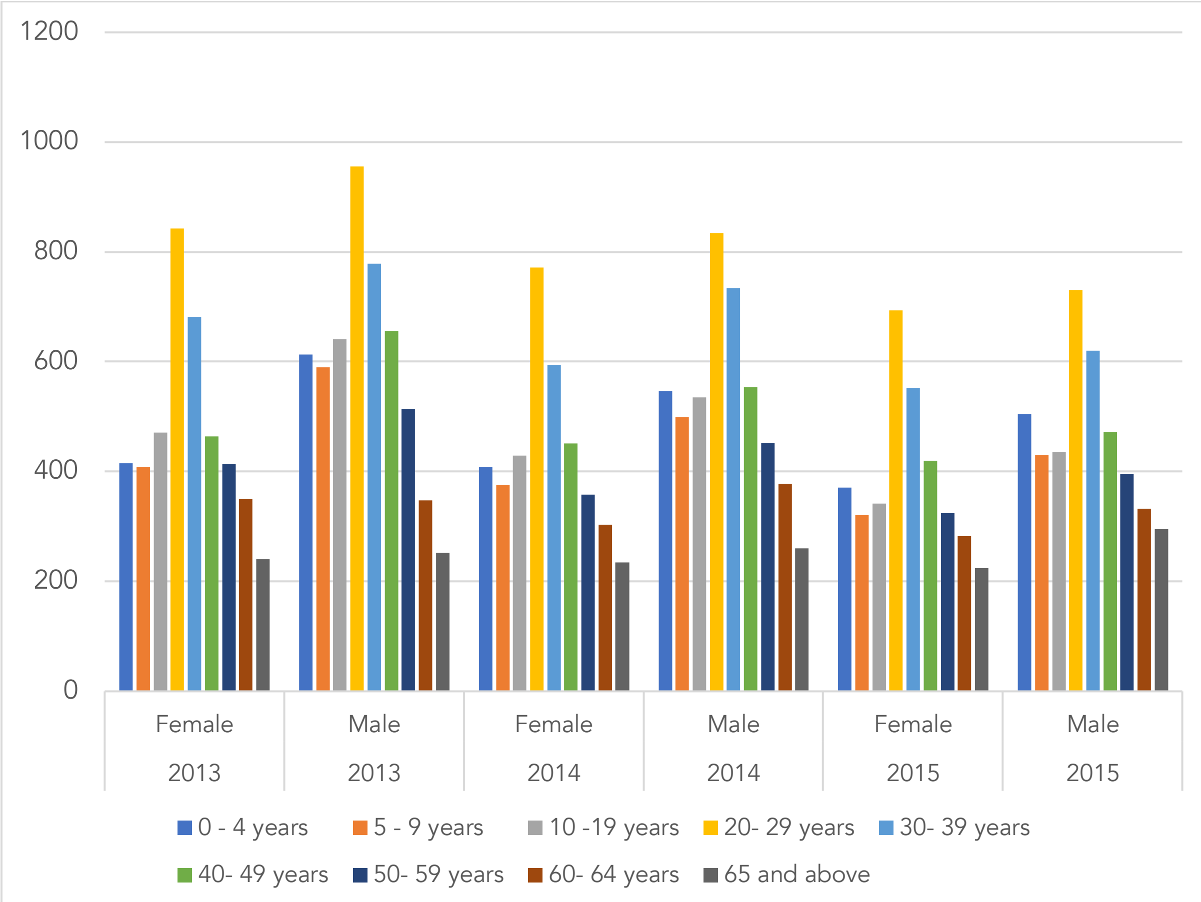
For peer review only

Supplementary table 2: Average rate of antibiotic prescriptions for typhoid across sexes (per 100,000 population), 2013-15

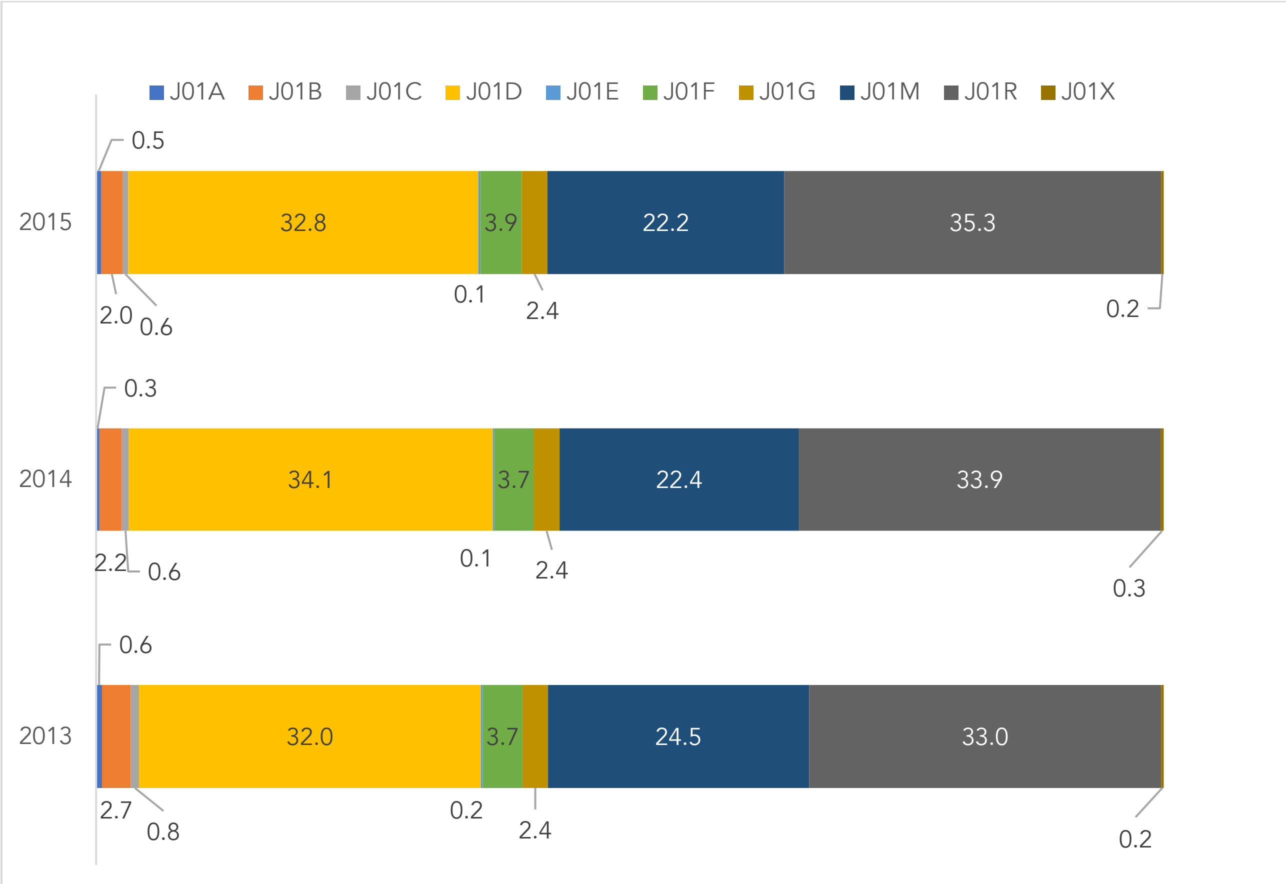
Age groups	Male	Female	Difference, %
0 - 4 years	555	398	28
5 - 9 years	507	368	27
10 -19 years	537	414	23
20- 29 years	840	769	8
30- 39 years	711	610	14
40- 49 years	561	445	21
50- 59 years	454	366	20
60- 64 years	353	312	12
65 & above	269	233	13

For peer review only

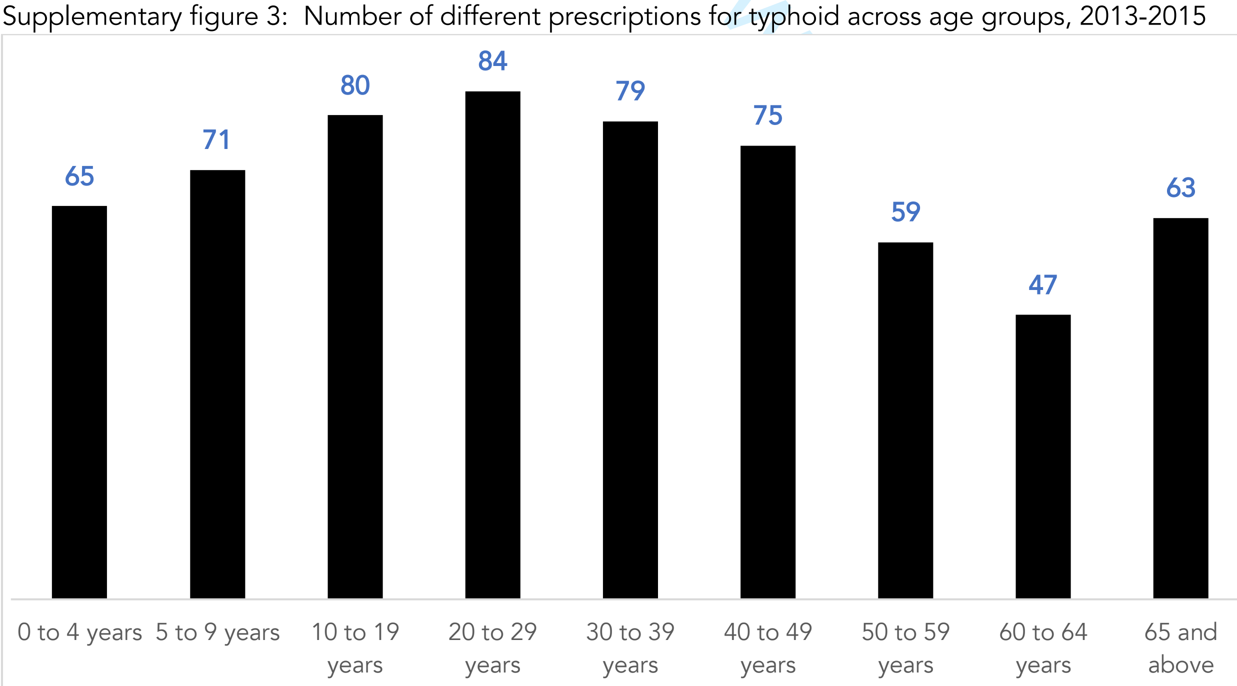
Supplementary figure 1: Age and sex specific prescription rates for typhoid (per 100,000 population) in 2013, 2014 and 2015



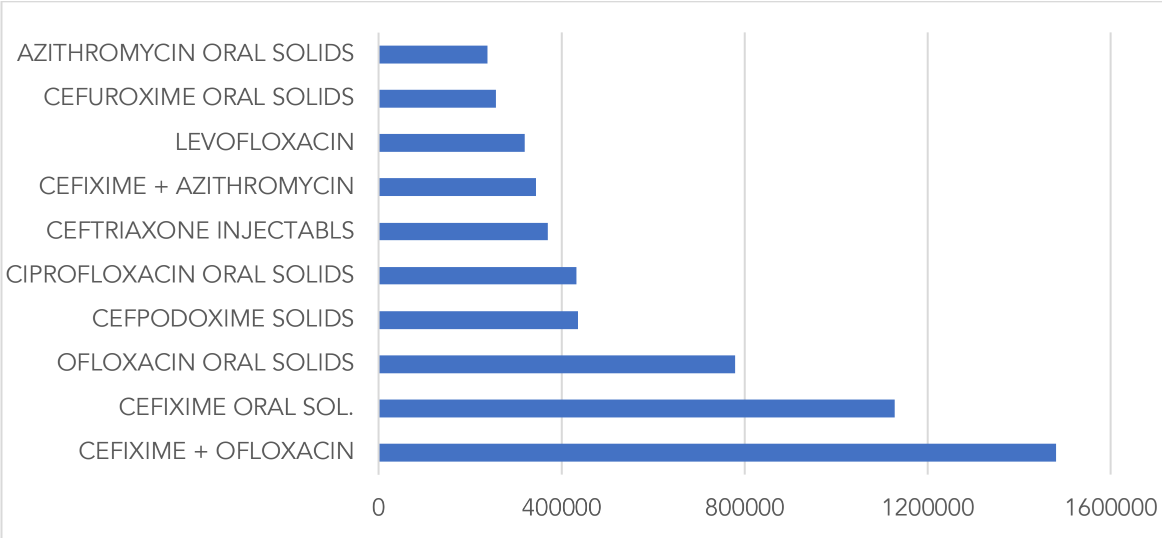
Supplementary figure 2: Share (in percentage) of various antibiotic classes for typhoid across years 2013 to 2015



Supplementary figure 3: Number of different prescriptions for typhoid across age groups, 2013-2015

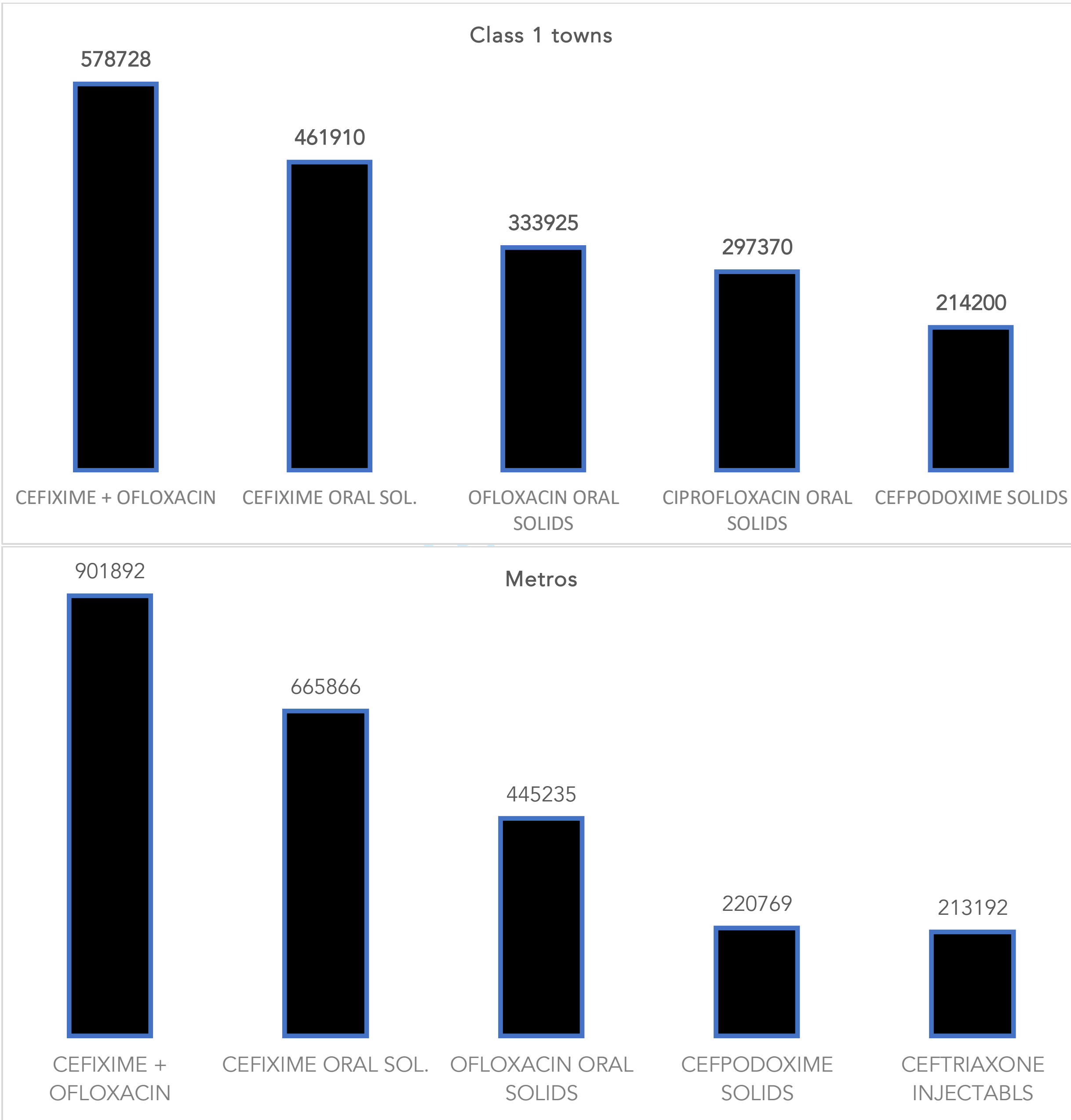


Supplementary figure 4. Top ten prescriptions (in numbers) for typhoid across India, 2015

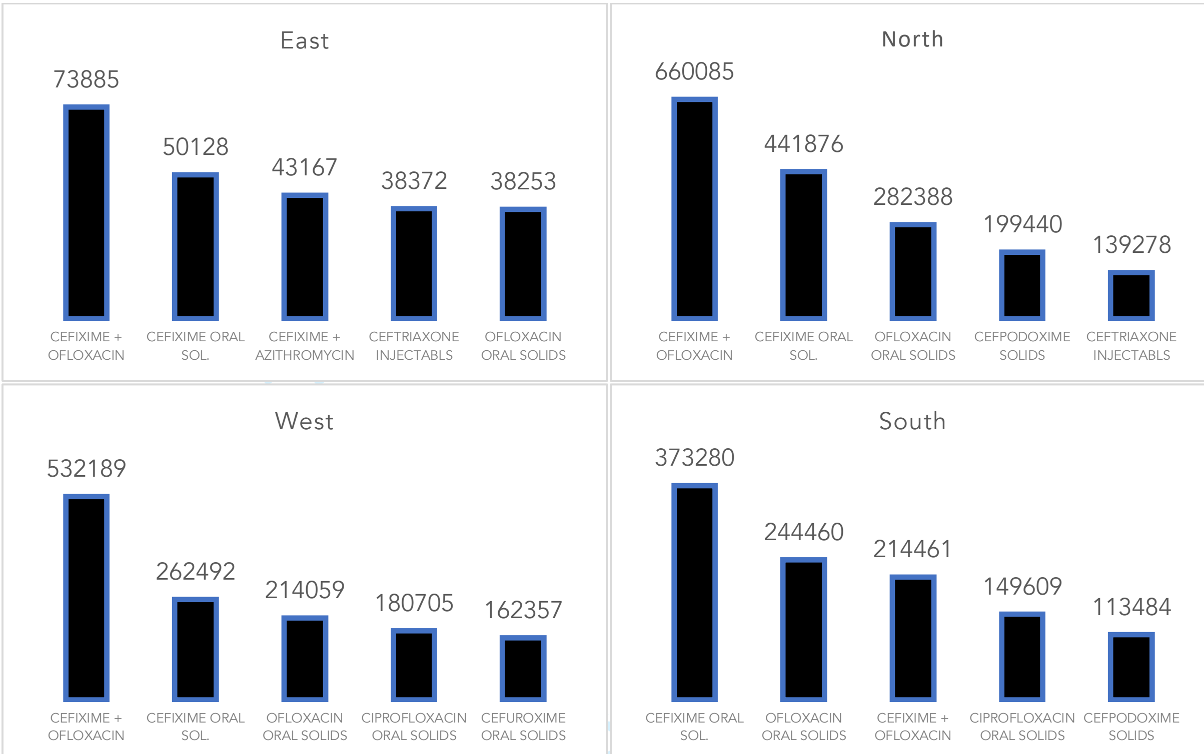


For peer review only

Supplementary figure 5: Top five prescriptions (in numbers) for typhoid across cities and metros, 2015 (number)

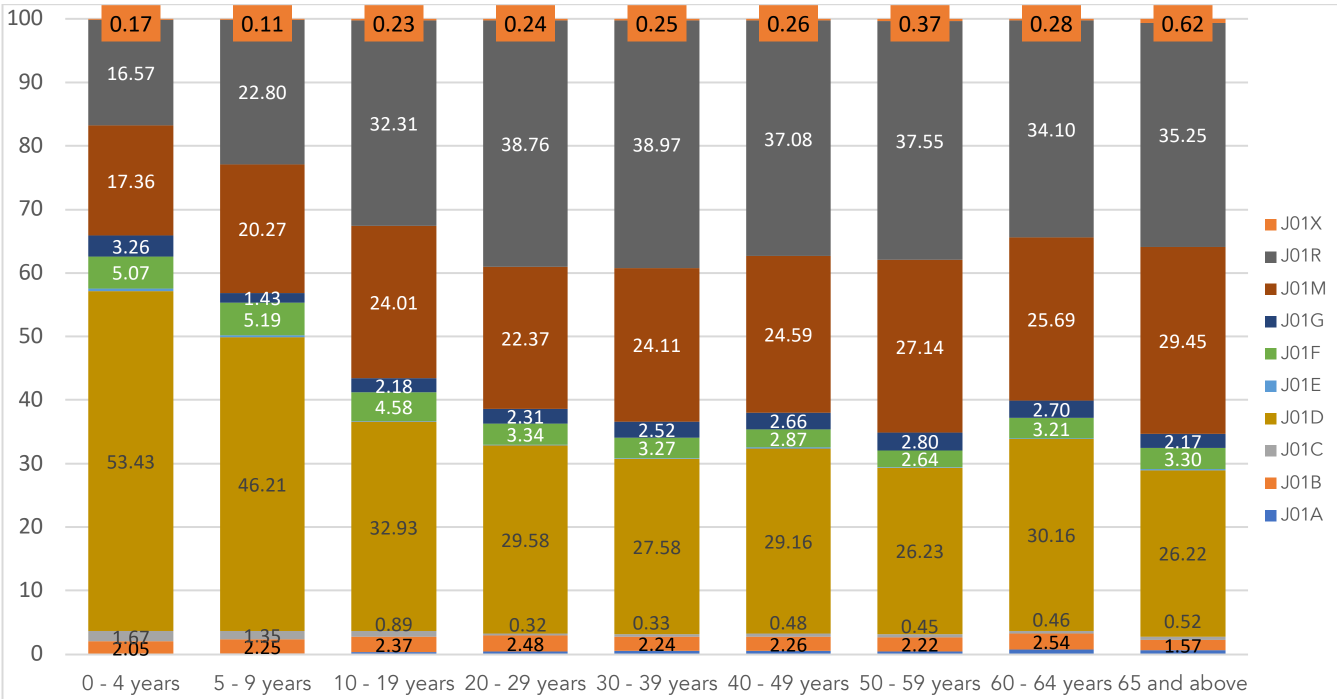


Supplementary figure 6: Top five prescriptions (in numbers) for typhoid across zones, 2015 (Numbers)



For peer review only

Supplementary figure 7: Age- group wise average rate of prescription of typhoid antibiotics, 2013-15



Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7

For peer review only

Bias	#9	Describe any efforts to address potential sources of bias	7-8
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8-10
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8-10
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	8-10

For peer review only

Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
Main results	#16b	Report category boundaries when continuous variables were categorized	8-10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12-15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 4 May 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

For peer review only