Antibiotic abuse in low- and middle-income countries

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i. Abstract

Antimicrobial resistance (AMR) is a major public health concern globally, and the inappropriate use of antibiotics plays a key role in its emergence and spread. Sales data suggest that antibiotic consumption has alarmingly increased over the past two decades, mostly driven by a considerable rise in low- and middle-income countries (LMICs), with a substantial proportion involving outpatient care settings. In this manuscript-based thesis, I assess the degree and patterns of antibiotic use in such contexts, with a particular focus on India, the largest antibiotic consumer in the world. I have published a systematic review of the literature (Sulis G et al, PLoS Med 2020), which suggests that approximately half of all patients seeking care for any reason across a range of primary healthcare settings in 27 LMICs are prescribed at least one antibiotic. Although some studies reported a high proportion of inappropriate use, the true extent remains challenging to assess particularly in outpatient care. Methods typically used to assess inappropriateness of antibiotic prescription, such as prescription audits, medical records and patient exit interviews, have several limitations. In contrast, standardized patients (SPs) offer a unique opportunity to explore prescribing practices and more accurately estimate over-prescription. As case presentations are fixed by design, comparisons can be made across settings and providers. I conducted and published secondary analyses of data from nine SP studies carried out in India, China and Kenya for a total of over 8,500 SP-provider interactions across a range of providers, with the aim to calculate an unbiased prevalence estimate of antibiotic over-prescription (Sulis G et al, BMJ Glob Health 2020). Of note, all SPs across these studies portrayed clinical conditions that do not require antibiotic treatment. About 30% of interactions in China and 50% of those performed in India and Kenya resulted in antibiotic overuse. The choice of antibiotics given to patients is concerning, as several agents with high potential for resistance selection are often inappropriately prescribed especially in India and China. As richer data were available from India, I utilized hierarchical Poisson models to investigate factors associated with antibiotic overuse in this country and found that adjusted prevalence ratios (aPR) were significantly lower in urban vs rural areas (aPR 0.70; 95% CI: 0.52-0.96), and higher

among qualified vs non-qualified providers (aPR 1.55; 95% CI: 1.42-1.70) as well as for presumptive TB cases vs other conditions (aPR 1.19; 95% CI: 1.07-1.33). The COVID-19 pandemic is posing additional threats in an already alarming scenario, further fostering the inappropriate antibiotic use. I have conducted interrupted time-series analyses to estimate the impact of the pandemic on national antibiotic and hydroxychloroquine (HCQ) sales volumes in India's private sector, which accounts for a substantial proportion of the overall consumption in the country. Sales data collected at monthly intervals from Jan 2018 to Sep 2020 were obtained from IQVIA. Segmented regression models were adjusted for the effect of lockdown as well as underlying seasonal and non-seasonal trends using fixed-effect terms, Fourier series and autocorrelation error terms. Among key findings, I estimated that, between Jun and Sep 2020, COVID-19 was likely responsible for substantial excess sales of non-pediatric formulations of total antibiotics (+225.2 million doses) and of azithromycin in particular (+39.0 million doses), with potentially deleterious consequences on resistance patterns. Overall, this body of work contributes to fill some knowledge gaps regarding why and how antibiotics are prescribed or dispensed by health professionals in LMICs and specifically in India, thus helping to design and implement tailored interventions aimed to promote the rational use of antibiotics at a time in which such measures are more needed than ever.

ii. Résumé

La résistance aux antimicrobiens (RAM) est un grave problème de santé publique mondial et l'utilisation inappropriée des antibiotiques joue un rôle clé dans son évolution. Depuis 20 ans, la consommation d'antibiotiques a crû de manière alarmante, due principalement à une forte augmentation dans les pays à revenu faible et intermédiaire (PRFI), où l'usage dans les soins en clinique externe est marqué. Dans cette thèse, j'évalue le degré et les profils d'utilisation des antibiotiques dans de tels contextes, avec une attention particulière sur l'Inde, le plus important consommateur d'antibiotiques. J'ai publié une revue systématique (Sulis G et al, PLoS Med 2020) indiquant que la moitié des patients utilisant différents services de santé primaire dans 27 PRFI se voient prescrire au moins un antibiotique. Bien que certaines études signalent une proportion élevée d'utilisation inappropriée, la portée réelle du phénomène reste difficile à déterminer, spécialement en clinique externe. Les méthodes généralement utilisées pour la pertinence de la prescription d'antibiotiques (vérification des ordonnances ou dossiers médicaux, enquêtes auprès des patients) présentent plusieurs limites. À l'inverse, les patients standardisés (PS) permettent d'explorer les pratiques et d'estimer plus rigoureusement la sur-prescription. Les présentations de cas étant préétablies, les comparaisons entre contextes et entre prescripteurs sont possibles. J'ai mené et publié des analyses secondaires des données provenant de neuf études, avec PS présentant des conditions cliniques ne nécessitant aucun antibiotique, réalisées en Inde, en Chine et au Kenya, pour un total de plus de 8 500 visites, dans le but de calculer une estimation non biaisée de la prévalence de la sur-prescription d'antibiotiques (Sulis G et al, BMJ Glob Health 2020). Une surutilisation d'antibiotiques a été observée dans environ 30% des visites en Chine et 50% en Inde et au Kenya. Le choix des antibiotiques administrés est préoccupant, car plusieurs agents à fort potentiel de sélection de RAM sont souvent prescrits, surtout en Inde et en Chine. Les données disponibles pour l'Inde étant plus riches, j'ai utilisé des modèles hiérarchiques de Poisson pour étudier les facteurs associés à la surutilisation des antibiotiques dans ce pays. Cette analyse a montré que le taux de prévalence ajusté était largement inférieur dans les zones urbaines vs rurales (0.70; 95% IC: 0.52-0.96), et

supérieur parmi les professionnels qualifiés vs non-qualifiés (1.55; 95% IC: 1.42-1.70), ainsi que pour les cas de TB présumée ou confirmée vs autres conditions cliniques (1.19; 95% IC: 1.07-1.33). En favorisant encore plus l'utilisation inappropriée des antibiotiques, la pandémie de COVID-19 pose des menaces supplémentaires. J'ai effectué des analyses de séries temporelles interrompues pour estimer l'impact de la pandémie sur les ventes d'antibiotiques et d'hydroxychloroquine (données mensuelles de jan. 2018 à sept. 2020 recueillies par IQVIA Inc.) dans le secteur privé en Inde, responsable d'une part substantielle de la consommation totale du pays. Les modèles ont été ajustés pour tenir compte de la phase de confinement ainsi que des tendances saisonnières et non-saisonnières, en utilisant des effets fixes, des séries de Fourier et des termes d'erreur d'autocorrélation. J'ai estimé qu'entre juin et sept. 2020 la COVID-19 a probablement été responsable de ventes excédentaires considérables des formulations non-pédiatriques d'antibiotiques en général (+225.2 M doses) et particulièrement d'azithromycine (+39.0 M doses), avec des conséquences potentiellement néfastes sur la RAM. Ce travail de recherche contribue à combler certaines lacunes au niveau des raisons et modalités de prescription d'antibiotiques dans les PRFI, aidant ainsi à planifier et mettre en œuvre des interventions adaptées promouvant l'utilisation rationnelle des antibiotiques dans une époque où de telles mesures sont plus que jamais nécessaires.

iii. Acknowledgements

Embarking on a tough PhD program after many years of academic and clinical training was not an easy choice, but one I would make over and over again. Having the opportunity to learn with and from exceptional students and faculty such as those of McGill EBOH Department was definitely worth the effort and investment. I would like to express my sincere gratitude to my supervisor, Dr. Madhu Pai, not only for guiding me throughout my doctoral training, but also for giving me the privilege to join his amazing team. It is thanks to my outstanding colleagues and their continuous support that the last three years have been so special.

My deepest thanks go to my committee members, Drs. Sumanth Gandra, Jishnu Das and Amrita Daftary, for constantly sharing their feedback and providing me with new and broader perspectives. I am particularly grateful to Sumanth who has played a key role in mentoring me and making my interrupted time series analysis possible.

I offer my profound appreciation to all my research collaborators and co-authors without whom this thesis would have never seen the light.

I am extremely grateful for receiving the Richard H. Tomlinson Doctoral Fellowship (2017-2020) and the David G. Guthrie Fellowship in Medicine (2020-2021), along with additional financial support from McGill Faculty of Medicine, McGill International TB Centre and McGill Global Health Programs.

Last but not least, I would like to extend my heartfelt thanks to my parents for encouraging and supporting me at each step from the other side of the ocean. And huge thanks to my new and old friends who have helped me get through this journey.

iv. Preface and contribution of authors

As first author on all manuscripts included in this thesis, with feedback from Dr. Pai, my committee and the other manuscript authors, I personally developed the protocols for all three objectives. I conducted all analyses and was responsible for the interpretation of the results and drafting of the manuscripts. The chapters in this thesis were written by me. Detailed author contributions for specific manuscripts are reported below.

Manuscript 1: Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis

I developed the study protocol and objectives with input from Dr. Madhu Pai, Dr. Jishnu Das, Dr. Sumanth Gandra and Dr. Amrita Daftary. I developed the search strategy with assistance from Ms. Genevieve Gore who executed the search and generated the library used for study screening and selection. I screened, extracted and adjudicated all included studies with assistance from Dr. Pierrick Adam and Ms. Vaidehi Nafade. I drafted the manuscript and all authors provided critical feedback.

Manuscript 2: Antibiotic overuse in the primary healthcare setting: a secondary data analysis of standardized patient studies from India, China and Kenya

I developed the study design and objectives with input from Dr. Madhu Pai, Dr. Jishnu Das and Mr. Benjamin Daniels. I performed the data cleaning and coding with supervising support from Mr. Benjamin Daniels. I designed and performed the analysis, interpreted the results and drafted the manuscript with input from Dr. Madhu Pai. All authors revised the draft and provided key feedback.

Manuscript 3: Impact of COVID-19 on antibiotics and hydroxychloroquine sales in India: an interrupted time series analysis

I developed the study design and objectives with input from Dr. Sumanth Gandra and Dr. Madhu Pai. I performed the data management, designed and conducted the analysis with

input from Dr. Brice Batomen. I interpreted the results and drafted the manuscript under the guidance of Dr. Sumanth Gandra; all authors provided critical feedback.

v. Statement of originality

The three manuscripts that form this thesis are all original scholarship and provide contributions to knowledge. My systematic review (Chapter 2, Manuscript 1) is the first to synthesize the extent of antibiotic use across a range of primary healthcare settings in low- and middle-income countries (LMICs) and highlight the difficulties of accurately measuring inappropriate use of these drugs.

As pointed out in my systematic review, antibiotics are largely prescribed in outpatient care regardless of patients' age and reason for seeking care. However, the extent and pattern of inappropriate antibiotic use remains challenging to assess, particularly in LMICs. My Chapter 3 (Manuscript 2) is a large secondary analysis of nine standardized patient (SP) studies conducted in three LMICs (India, China and Kenya) and originally conceived to assess overall quality of care. This study makes use of the SP methodology to generate more accurate and less biased estimates of antibiotic overuse for a set of clinical conditions that do not require antibiotic treatment and are frequently encountered in primary care across LMICs. Hence, this is a significant improvement over commonly employed methodologies such as prescription audits, patient exit interviews and direct observation of patient-provider visits. This work also sets the stage for the use of SPs in future research investigating antibiotic prescribing practices more in depth.

My interrupted time series analysis (Chapter 4, Manuscript 3) is the first nationwide assessment of the impact of the COVID-19 pandemic on antibiotic sales in a lower-middle income country. This study provides robust estimates of COVID-attributable excess sales of total antibiotics, azithromycin and hydroxychloroquine in India, accounting for the effect of the lockdown period as well as for seasonal and non-seasonal cycles. The implications of this work are very important not only for India, which is the largest consumer of antibiotics in the world and among the hardest hit countries in this pandemic, but also for other LMICs.

vi. List of abbreviations

AMR	Antimicrobial resistance
aPR	Adjusted prevalence ratio
ATC	Anatomical, Therapeutic, Chemical
AWaRe	Access, Watch, Reserve
BL	Beta-lactam
BLI	Beta-lactamase inhibitor
BRIC	Brazil, Russia, India, China
CAF	Child-appropriate formulation
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics and Policy
CI	Confidence interval
CICU	Coronary intensive care unit
COVID-19	Coronavirus disease 2019
CQ	Chloroquine
DOT	Days of therapy
DP	Days present
DRI	Drug Resistance Index
ES	Effect size
ESBL	Extended-spectrum beta-lactamase
FDC	Fixed-dose combination
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HCQ	Hydroxychloroquine
HICs	High-income countries
ICMR	Indian Council of Medical Research
IQR	Interquartile range
IM	Internal medicine

ITS	Interrupted time series
LICs	Low-income countries
LMICs	Low- and middle-income countries
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MICU	Medical intensive care unit
MRSA	Methicillin-resistant *S. aureus*
OR	Odds ratio
OTC	Over the counter
PICU	Pediatric intensive care unit
PM	Progressive medicine
PNG	Papua New Guinea
PR	Prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SP	Standardized patient
SU	Standard Unit
TB	Tuberculosis
UMICs	Upper-middle income countries
URI	Upper respiratory illness
WHO	World Health Organization

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Chapter 1: Introduction

Since their introduction in the first half of the twentieth century, antimicrobials have dramatically revolutionized medical practice and significantly improved individual and population health. Inevitably, the growing use of these drugs has acted as a selective pressure on microorganisms, thus leading to the rapid development and spread of antimicrobial resistance (AMR) (Figure 1-1).[1,2]

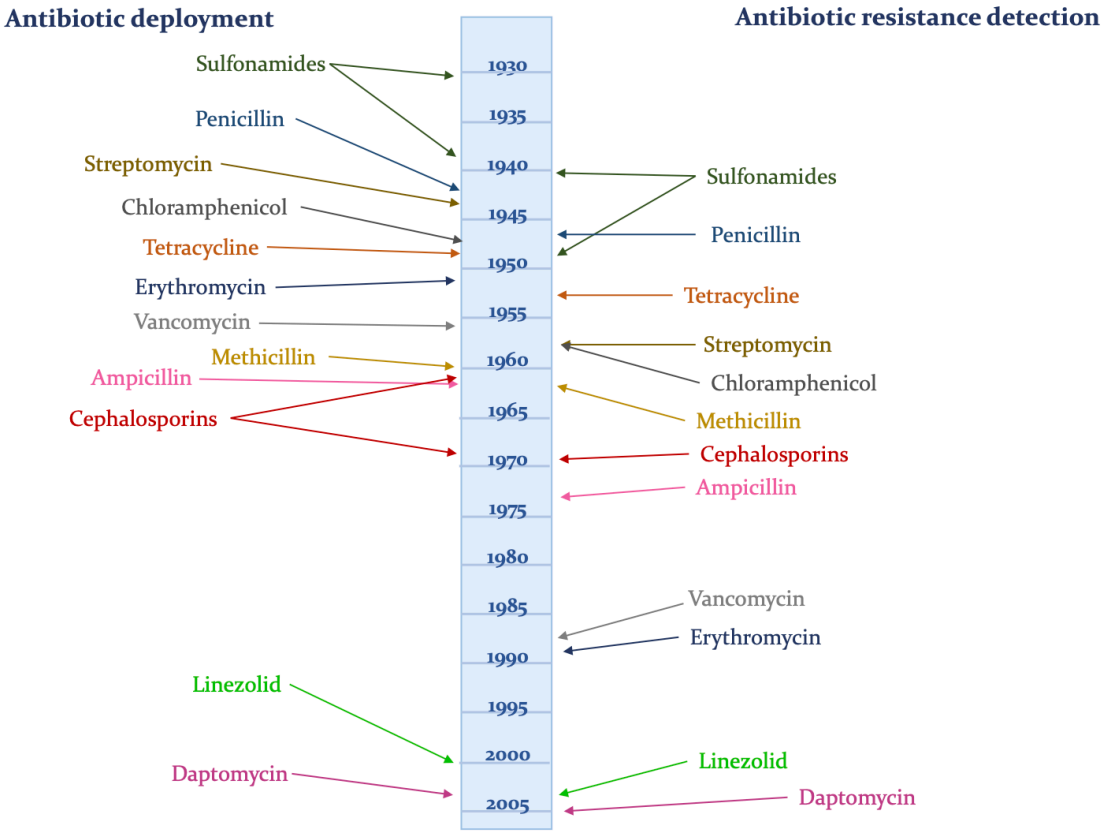

Figure 1-1 Years of deployment and first resistance detection for selected antibiotics (adapted from Clotworthy A.E. et al, Nat Chem Biol, 2007)

AMR is defined as the ability of a microorganism (including bacteria, viruses, fungi, protozoa and helminths) to stop an antimicrobial from acting against it. As a consequence, antimicrobial treatment (based on the use of antibiotics, antivirals, antimycotics or antiparasitics depending on the type of pathogen involved) becomes ineffective, thus hindering cure and favoring the further spread of the infection where a transmission potential exists.

Resistance mechanisms have evolved over the years and across microbial species, resulting in a diverse range of sophisticated strategies that have jeopardized the efficacy of available antimicrobials and posed important challenges to the development of new molecules.[3] This is particularly important for bacteria and their response to antibiotics. Genetic mutations occurring spontaneously or resulting from some sort of selective pressure may confer resistance to one or more antibiotics; such mutations can involve the main bacterial chromosome and/or in plasmids and can thus be transmitted both vertically and horizontally particularly in the presence of survival advantage. Traditionally, antibiotic resistance is detected by culturing bacteria from the site of infection and exposing them to a given antibiotic in vitro.[5] Several methods, all based on standardized protocols, can be adopted to measure susceptibility, such as disk diffusion, broth microdilution, agar dilution, etc. Antibiotic resistance is typically reported as a binary measure, where the "resistant" status for a given pathogen/antibiotic combination is determined according to the minimum inhibitory concentration (MIC), that is the lowest concentration of an antibiotic that will inhibit the visible growth of a microorganism after incubation. The range of tested antibiotic concentrations and the reference threshold are predefined for each pathogen/antibiotic combination and cannot be based on the evaluation of absolute values per se. Generally speaking, the lower the MIC value observed as compared to the threshold, the larger the susceptibility of that particular microorganism to a given antibiotic.[5] More recently, a variety of genome-based techniques have evolved, allowing to assess resistance patterns more rapidly, although their implementation in resource-limited settings remains difficult because of the greater requirements in terms of laboratory infrastructures and personnel training.

While the global burden of infectious diseases substantially declined as compared to the pre-antibiotic era, AMR is now among the biggest public health concerns and could seriously undermine our ability to fight against a range of multidrug-resistant (MDR) pathogens. In such a scenario, even the most common and easily treatable infections can turn into hard-to-treat potentially life-threatening conditions in the absence of effective drugs.[6] As estimated in 2015 by O'Neill and colleagues, AMR is expected to cause 10 million annual deaths and economic losses for over 100 trillion dollars by 2050 (Figure 1-2).[7]

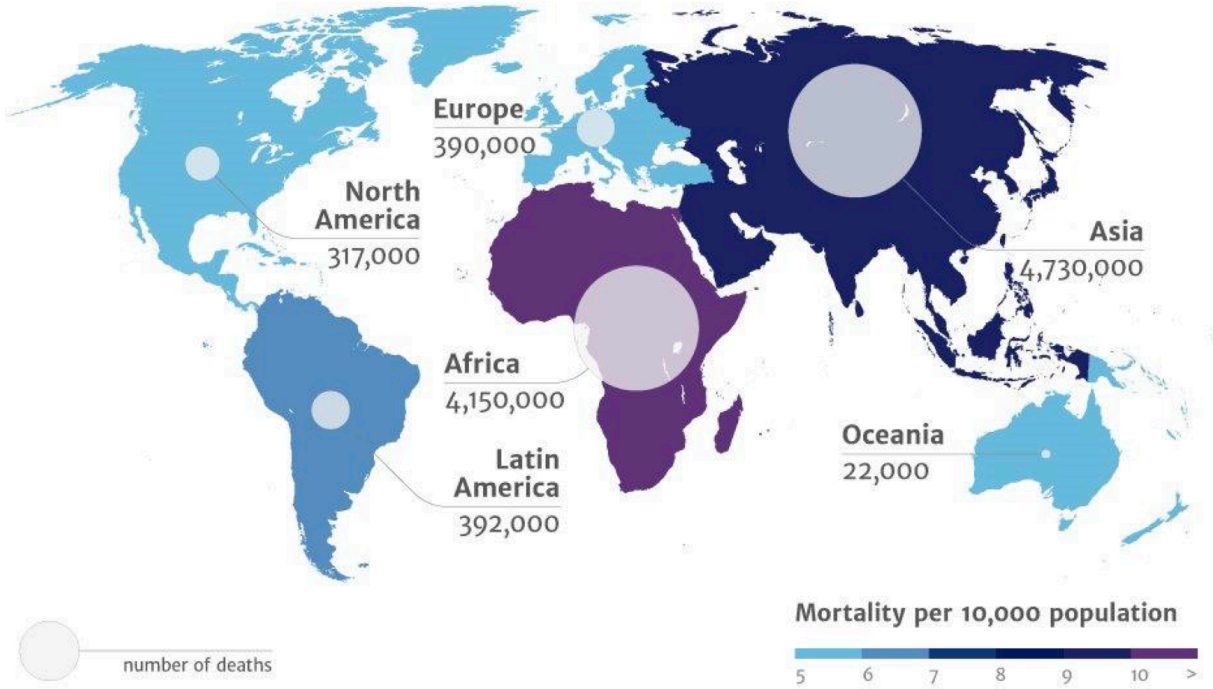

Figure 1-2 Projected mortality due to resistant infections in different regions (Source: "Review on Antimicrobial Resistance", O'Neill Report (2015); https://amr-review.org/infographics.html).

In our interconnected world, AMR knows no boundaries and affects all areas and populations with critical consequences everywhere and even more so in low- and middle-income countries (LMICs).[8,9]

1.1 Epidemiology of AMR in LMICs

About 85% of the world's population lives in LMICs, and approximately 40% is concentrated in the BRIC countries (Brazil, Russia, India and China). Densely populated areas where hygiene and sanitation are often problematic, access to quality healthcare is limited and antibiotic use in humans, animals and crops is indiscriminate and largely unregulated, constitute the ideal environment for AMR to thrive and spread rapidly. Based on available data, the rates of drug-resistant infections in humans are estimated to be higher in LMICs than in high-income countries (HICs), with India, Ecuador, Thailand and Venezuela showing the highest rates.[6] However, the exact quantification of AMR remains challenging and hard to monitor. As of July 2019, only 34 LMICs had started providing information on their surveillance systems and reporting AMR data in the context of the Global Antimicrobial Resistance and Use Surveillance System (GLASS) project, first launched by the WHO in 2015 (Table 1-1).[10] However, in many countries the number of surveillance sites participating in the global surveillance system is still very low and far from representative. For instance, only 130 sites (including 65 hospitals and 65 outpatient facilities) are currently involved in AMR surveillance in India, a country of nearly 1.4 billion people.[10] New sites are enrolled once the first sentinel sites achieve an acceptable standard in core functions, but this process depends on a number of factors such as the availability of laboratory infrastructures, the quality control systems in place, the existence of a national action plan including allocation of targeted funds, and so forth.[10,11] GLASS covers a group of pathogens that are deemed particularly important for AMR surveillance (*Acinetobacter* spp., *E. coli*, *K. pneumoniae*, *N. gonorrhoeae*, *Salmonella* spp., *Shigella* spp., *S. aureus* and *S. pneumoniae*), and data are collected in a standardized manner through a case-finding surveillance system.[10]

Because efforts to set up or improve surveillance systems in line with GLASS requirements began quite recently, accurate estimates of country-level antibiotic resistance rates are not yet available, particularly for LMICs.

Table 1-1 List of LMICs currently reporting AMR data and information on national surveillance systems in the context of the GLASS project (adapted from GLASS Report 2020, WHO).

	Country income level		
	Low	**Lower-middle**	**Upper-middle**
Countries reporting AMR data and information on national surveillance systems	Afghanistan	Bangladesh	Bosnia and Erzegovina
	Ethiopia	Cambodia	Brazil
	Madagascar	Egypt	Georgia
	Mali	India	Iran (Islamic Republic of)
	Nepal	Indonesia	Iraq
	Syrian Arab Republic	Jordan	Lebanon
	Uganda	Lao People's Democratic Republic	Malaysia
		Mozambique	Maldives
		Myanmar	Russian Federation
		Nigeria	South Africa
		Pakistan	Thailand
		Philippines	North Macedonia
		Sri Lanka	
		Sudan	
		Tunisia	

Tables 1-2 and 1-3 summarize the estimated proportions of resistant isolates for selected critical and high-priority pathogens identified in seven LMICs.[3,12] These data are regularly put together by the Center for Disease Dynamics, Economics and Policy (CDDEP) based on what reported by existing national surveillance systems,[12] most of which have not yet achieved the GLASS requirements and thus are not contributing to the global surveillance project. Of note, only blood and cerebrospinal fluid samples are considered in this assessment. As shown in the tables, denominators are generally quite small and specimen collection is likely affected by a substantial amount of selection bias, thus imposing caution in interpreting current estimates. Yet, it is worth highlighting that data from India reflect fairly well the high levels of antibiotic consumption, which are fueling the emergence of AMR. For instance, resistance to carbapenems among a range of Gram-negative bacteria is quite common, posing serious challenges in terms of clinical management and patient outcomes. About 10% of *S. aureus* isolates from blood and CSF in 2015 were methicillin-resistant (MRSA),[12] but the prevalence of MRSA is rising at a

rapid pace. According to the 2020 annual report on AMR compiled by the Indian Council of Medical Research (ICMR), the overall proportion of MRSA throughout the country had reached an alarming 42.1% in 2019, with a nearly 10% increase compared to the previous year.[13]

Table 1-2 Percent resistant among total isolates of selected Gram-negative pathogens from blood and cerebrospinal fluid in 7 LMICs. Most recent data are shown for each pathogen and country. (Source: Centers for Disease Dynamics, Economics and Policy [CDDEP], ResistanceMap)

Country	Gram-negative pathogens							
	Carbapenem-resistant *A. baumannii*		Carbapenem-resistant *P. aeruginosa*		Carbapenem-resistant *E. coli*		Carbapenem-resistant *K. pneumoniae*	
	Isolates tested	Percent resistant (95% CI)	Isolates tested	Percent resistant (95% CI)	Isolates tested	Percent resistant (95% CI)	Isolates tested	Percent resistant (95% CI)
Ecuador	38	55 (39-70)	46	22 (12-35)	374	1 (0-2)	251	33 (27-39)
China	1,563	82 (80-84)	1,010	25 (22-28)	6,520	3 (3 – 3)	4,826	36 (35-37)
India	503	77 (73-81)	496	30 (26-34)	1,619	18 (16-20)	1,497	59 (56-61)
Pakistan	95	63 (53-72)	NA	NA	814	10 (8-12)	181	43 (36-50)
Thailand	164	46 (39-54)	784	18 (15-21)	414	1 (0-2)	202	13 (9-18)
South Africa	2,904	73 (71-75)	2,012	30 (28-32)	6,489	0 (0-0)	7,499	7 (6-8)
Venezuela	177	79 (73-84)	50	22 (12-35)	141	1 (0-4)	39	8 (2-20)

Table 1-3 Percent resistant among total isolates tested, reported for selected Gram-positive pathogens in 7 LMICs. Most recent data are shown for each pathogen and country. (Source: Centers for Disease Dynamics, Economics and Policy [CDDEP], ResistanceMap)

Country	Gram-positive pathogens					
	Vancomycin-resistant *E. faecium*		Methicillin-resistant *S. aureus*		Vancomycin-resistant *S. aureus*	
	Isolates tested	Percent resistant (95% CI)	Isolates tested	Percent resistant (95% CI)	Isolates tested	Percent resistant (95% CI)
Ecuador	30	40 (24-58)	208	41 (34-48)	208	0 (0-2)
China	1,398	3 (2-4)	2,385	38 (36-40)	2,385	0 (0-0)
India	314	27 (22-32)	922	39 (36-42)	1,040	1 (1-2)
Pakistan	NA	NA	193	63 (56-70)	64	0 (0-5)
Thailand	252	4 (2-7)	204	17 (12-23)	133	0 (0-2)
South Africa	1,945	5 (4-6)	6,396	27 (26-28)	3,354	0 (0-0)
Venezuela	123	51 (42-60)	70	54 (42-65)	76	4 (1-10)

In 2011, the Center for Disease Dynamics, Economics and Policy (CDDEP) and other institutions involved in AMR research developed an intuitive approach to combine resistance data with antibiotic use data, resulting in a global measure of the relative

efficacy of antibiotic treatment in different countries, called Drug Resistance Index (DRI).[14]

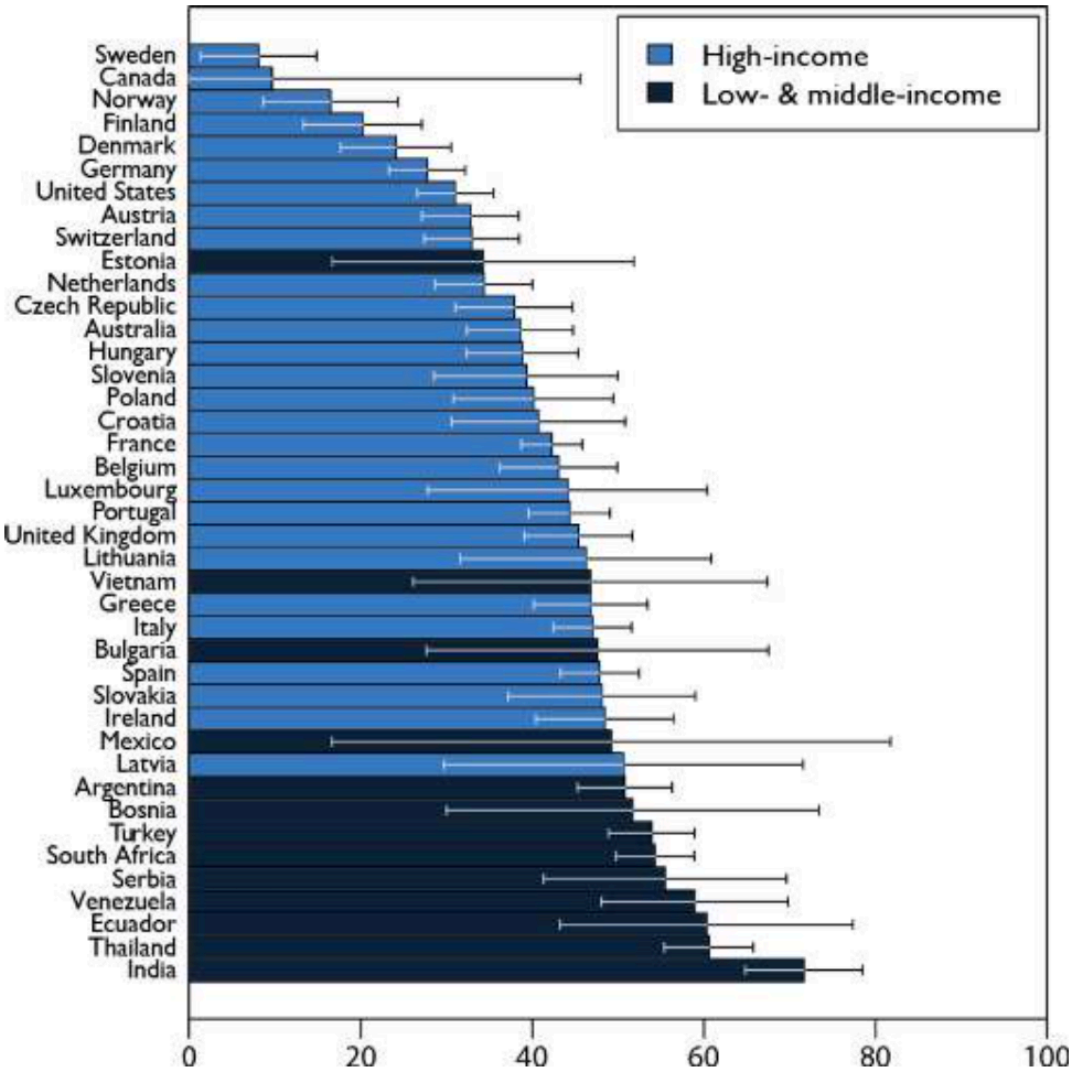

Figure 1-3 Drug Resistance Index (DRI) across 41 countries. Each bar reports the DRI for countries reporting antibiotic resistance for 5 or more pathogens and for 15 or more pathogen–antibiotic combinations for at least 1 year between 2012 and 2015. Data for the most recent year are shown. All countries included had resistance data for all seven antibiotic classes except Vietnam, which did not have resistance data for glycopeptides. Country income classifications were based on World Bank analytical classifications for fiscal year 2015. (Source: Klein EY et al, BMJ Glob Health 2019; reuse permitted under the terms of the Creative Commons CC BY 4.0).

The DRI is computed for pre-specified pathogen-antibiotic combinations and takes values from 0 to 100%, where 0 corresponds to full susceptibility and 100 represents 100% resistance. This method was first employed in the United States, where richer and

accurate data are collected.[14] More recently, the DRI was calculated for 41 countries, including some LMICs, providing a very useful indicator to monitor antibiotic effectiveness. This work suggests that resistance rates for priority pathogens are generally higher in LMICs, with India showing an overall DRI > 70% (Figure 1-3).[6]

It should be noted, however, that the DRI is as accurate as the data used to calculate it. While data on antibiotic use were obtained from IQVIA Inc. and thus can be considered reasonably accurate and nationally representative, resistance data have major limitations for the reasons explained above. As better AMR data become available, more accurate estimates of the DRI will be generated.

1.2 Role of antibiotics in the development and spread of AMR

Several factors fuel AMR (Figure 1-4), with inappropriate use of antibiotics being one of its most important drivers.[15] The large and often unjustified use of antibiotics in livestock and agriculture is a well-known problem and represents an important source of resistance with widespread consequences; however, this thesis will only focus on the use of antibiotics in human medicine because very scanty and poorly reliable data are currently available regarding the use of antibiotics in other sectors across LMICs, thus making any attempt to estimate the size of the problem particularly challenging. Gathering data about antibiotic use and resistance is one of the top five priorities of the 2015 Global Action Plan by the World Health Organization (WHO) to tackle AMR.[16] According to a recent analysis of drug sales data in 76 countries, global antibiotic consumption increased by 65% between 2000 and 2015.[17] The greatest rise was observed in LMICs (+114% over the study period), with broad-spectrum penicillins, cephalosporins, quinolones, and macrolides being the predominant classes. This is in sharp contrast to the only 6% rise in antibiotic use observed in high-income countries (HICs), mostly driven by an increased consumption of new-generation molecules.[17] The high level of antibiotic consumption observed in LMICs originates from a range of contributing factors such as the high

burden of infectious diseases, lack of regulations concerning drug prescription (or lack of enforcement) leading to over-the-counter (OTC) sale of antibiotics, inadequate training of healthcare professionals, and the limited availability of essential diagnostics that ultimately favours large-scale empirical use of antibiotics.[18-20]

Figure 1-4 Causes of antibiotic resistance (Source: WHO)

1.3 Research gaps addressed by this thesis

Until recently, most studies investigating antibiotic use in human medicine have focused on HICs, particularly in hospital settings.[21-23] This has left a number of unanswered questions about current practices at the primary care level, particularly in LMICs.

Furthermore, a thorough assessment of inappropriate antibiotic use in LMICs remains challenging. No standardized tool exists for this purpose, and methods typically used in HICs are often difficult to implement in resource-limited settings.[24,25] In these contexts, prescription audits, medical records abstraction, patient exit interviews and direct observation of patient-provider encounters often fail to provide a clear picture of the amount of inappropriate antibiotic use and its underlying determinants. On the other hand, the standardized patient (SP) methodology allows to overcome many of the typical issues that affect conventional methods and is considered the gold standard approach to assess quality of care.[25] The typical structure of an SP study is graphically shown in Figure 1-5. This approach could have interesting applications to more accurately evaluate antibiotic prescribing practices.

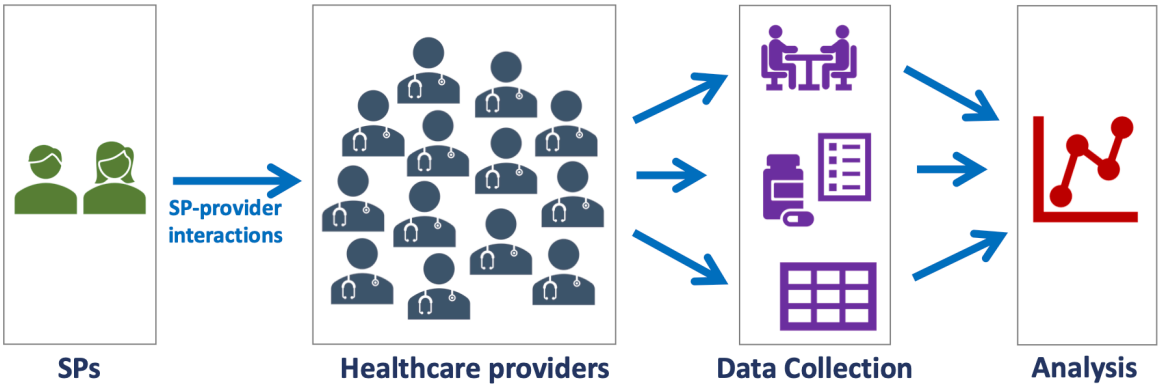

Figure 1-5 Standardized patient (SP) study flow.

The ongoing coronavirus disease 2019 (COVID-19) pandemic is posing additional threats, likely increasing the overall use of antibiotics, most often inappropriately.[26] Besides the

large empirical use of antibiotics in the clinical management of COVID-19 cases,[27-29] many drugs including hydroxychloroquine (HCQ) and certain antibiotics (e.g. azithromycin) have been repurposed for the prevention and treatment of COVID-19 despite evidence of no benefit from randomized control trials.[30-35] This is of particular concern for countries with already high levels of antibiotic use along with a high number of COVID-19 cases, such as India. However, no assessments of this phenomenon have been attempted in LMICs.

This work will summarize the currently available evidence on the prevalence of antibiotic prescribing across a range of primary healthcare settings in LMICs. Using data from previously conducted standardized patient (SP) studies from India, China and Kenya, I will then estimate a more accurate and unbiased prevalence of antibiotic overuse for selected clinical conditions not requiring antibiotic treatment that are commonly encountered in primary care. Factors associated with antibiotic overuse in India will also be investigated. Finally, I will estimate the impact of COVID-19 pandemic on antibiotic and HCQ sales in India through an interrupted time series design.

1.4 Objectives

In this manuscript-based thesis, I will address three objectives:

1) Systematically review and meta-analyze the literature on the prevalence of antibiotic prescribing across primary healthcare settings in LMICs.

2) Estimate the prevalence of antibiotic overuse for selected clinical conditions in a range of primary healthcare settings in India, China and Kenya.

3) Estimate the impact of COVID-19 pandemic on antibiotics and hydroxychloroquine (HCQ) sales in India.

1.5 References

1. Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol. 2007;3(9):541-8. Epub 2007/08/22. doi: 10.1038/nchembio.2007.24.
2. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-87. Epub 2015/11/26. doi: 10.1016/s0140-6736(15)00473-0.
3. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-27. Epub 2017/12/26. doi: 10.1016/s1473-3099(17)30753-3.
4. Patel J, Richter S. Mechanisms of Resistance to Antibacterial Agents*, p 1212-1245. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, Eleventh Edition*. ASM Press, Washington, DC. 2015. doi: 10.1128/9781555817381.ch69.
5. Turnidge J. Susceptibility Test Methods: General Considerations, p 1246-1252. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, Eleventh Edition*. ASM Press, Washington, DC. 2015. doi: 10.1128/9781555817381.ch70.
6. Klein EY, Tseng KK, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. BMJ Glob Health. 2019;4(2):e001315. Epub 2019/05/30. doi: 10.1136/bmjgh-2018-001315.
7. O'Neill J. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. HM Government and Welcome Trust, UK, 2016.
8. Laxminarayan R, Van Boeckel T, Frost I, Kariuki S, Khan EA, Limmathurotsakul D, et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. Lancet Infect Dis. 2020;20(4):e51-e60. Epub 2020/02/16. doi: 10.1016/s1473-3099(20)30003-7.

9. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057-98. Epub 2013/11/21. doi: 10.1016/s1473-3099(13)70318-9.
10. World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2016–2017. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1.
11. Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR Surveillance in low and middle-income settings - A roadmap for participation in the Global Antimicrobial Surveillance System (GLASS). Wellcome Open Res. 2017;2:92. Epub 2017/10/25. doi: 10.12688/wellcomeopenres.12527.1.
12. Center for Disease Dynamics, Economics and Policy (CDDEP). ResistanceMap: Antibiotic resistance. 2021; available at: https://resistancemap.cddep.org/AntibioticResistance.php (last accessed January 6, 2021).
13. Indian Council of Medical Research (ICMR). Annual Report: Antimicrobial Resistance Surveillance and Research Network. January 2019 to December 2019. New Delhi, India; 2020. Available at: http://iamrsn.icmr.org.in/index.php/resources/amr-icmr-data.
14. Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. BMJ Open. 2011;1(2):e000135. doi: 10.1136/bmjopen-2011-000135.
15. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis. 2018;18(12):e368-e78. Epub 2018/09/03. doi: 10.1016/S1473-3099(18)30296-2.
16. World Health Organization. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.

17. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-E70. Epub 2018/03/28. doi: 10.1073/pnas.1717295115.
18. Center for Disease Dynamics, Economics and Policy, Global Antibiotic Resistance Partnership. The state of the world's antibiotics 2015. Washington (DC): Center for Disease Dynamics, Economics and Policy; 2015 [cited 2020 May 13]. Available from: https://www.cddep.org/wp-content/uploads/2017/06/swa_executive_summary_edits_2016.pdf.
19. World Health Organization. Antimicrobial resistance and primary health care. Geneva: World Health Organization; 2018 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/326454/WHO-HIS-SDS-2018.56-eng.pdf.
20. Auta A, Hadi MA, Oga E, Adewuyi EO, Abdu-Aguye SN, Adeloye D, et al. Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. Journal of Infection. 2019;78(1):8-18. doi:10.1016/j.jinf.2018.07.001.
21. Machowska A, Stalsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. Int J Environ Res Public Health. 2018;16(1). Epub 2018/12/26. doi: 10.3390/ijerph16010027.
22. Chua KP, Fischer MA, Linder JA. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. BMJ. 2019;364:k5092. Epub 2019/01/18. doi: 10.1136/bmj.k5092.
23. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619-e29. Epub 2018/04/24. doi: 10.1016/S2214-109X(18)30186-4.

24. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis. 2016;63(12):1639-44. Epub 2016/09/30. doi: 10.1093/cid/ciw658.
25. Kwan A, Bergkvist S, Daniels B, Das J, Das V, Pai M. Using standardized patients to measure health care quality: a manual and toolkit for projects in low- and middle-income countries. 2019.
26. Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH. Tackling antimicrobial resistance in the COVID-19 pandemic. Bull World Health Organ. 2020;98(7):442-a. Epub 2020/08/04. doi: 10.2471/blt.20.268573.
27. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. Epub 2020/04/30. doi: 10.1016/j.cmi.2020.04.024.
28. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020. Epub 2020/07/28. doi: 10.1016/j.cmi.2020.07.016.
29. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Epub 2020/05/31. doi: 10.1016/j.jinf.2020.05.046.
30. Kotwani A, Gandra S. Potential pharmacological agents for COVID-19. Indian J Public Health. 2020;64(Supplement):S112-s6. Epub 2020/06/05. doi: 10.4103/ijph.IJPH_456_20.
31. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med. 2020. Epub 2020/07/17. doi: 10.7326/m20-4207. www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-4207.
32. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020;383(6):517-25. Epub 2020/06/04. doi: 10.1056/NEJMoa2016638.

33. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2019014.
34. Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet. 2020;396(10256):959-67. Epub 2020/09/09. doi: 10.1016/s0140-6736(20)31862-6.
35. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2021801.

Chapter 2: Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis

2.1 Preface

Measuring the proportion of patients seeking care who receive antibiotics is a key step to develop targeted and effective antibiotic stewardship interventions. This systematic review is the first to collate the available literature evidence regarding the prevalence of antibiotic prescribing across a range of outpatient primary care settings in LMICs. Since antibiotic consumption in LMICs is on the rise and primary care facilities contribute for a substantial proportion to the overall amount, this work contributes to fill an important gap. It also highlights the limitations of studies conducted so far to assess the extent and patterns of inappropriate antibiotic use in these contexts.

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2.2 Title page

Antibiotic prescription practices in primary care in low- and middle-income countries : A Systematic Review and Meta-Analysis

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2.3 Abstract

Background: The widespread use of antibiotics plays a major role in the development and spread of antimicrobial resistance. However, important knowledge gaps still exist regarding the extent of their use in low- and middle-income countries (LMICs), particularly at the primary care level. We performed a systematic review and meta-analysis of studies conducted in primary care in LMICs to estimate the prevalence of antibiotic prescriptions as well as the proportion of such prescriptions that are inappropriate.

Methods and findings: We searched PubMed, Embase, Global Health, and CENTRAL for articles published between 1 January 2010 and 4 April 2019 without language restrictions. We subsequently updated our search on PubMed only to capture publications up to 11 March 2020. Studies conducted in LMICs (defined as per the World Bank criteria) reporting data on medicine use in primary care were included. Three reviewers independently screened citations by title and abstract, whereas the full-text evaluation of all selected records was performed by 2 reviewers, who also conducted data extraction and quality assessment. A modified version of a tool developed by Hoy and colleagues was utilized to evaluate the risk of bias of each included study. Meta-analyses using random-effects models were performed to identify the proportion of patients receiving antibiotics. The WHO Access, Watch, and Reserve (AWaRe) framework was used to classify prescribed antibiotics. We identified 48 studies from 27 LMICs, mostly conducted in the public sector and in urban areas, and predominantly based on medical records abstraction and/or drug prescription audits. The pooled prevalence proportion of antibiotic prescribing was 52% (95% CI: 51%–53%), with a prediction interval of 44%–60%. Individual studies' estimates were consistent across settings. Only 9 studies assessed rationality, and the proportion of inappropriate prescription among patients with various conditions ranged from 8% to 100%. Among 16 studies in 15 countries that reported details on prescribed antibiotics, Access-group antibiotics accounted for more than 60% of the total in 12 countries. The interpretation of pooled estimates is limited by the considerable between-study heterogeneity. Also, most of the available studies suffer from

methodological issues and report insufficient details to assess appropriateness of prescription.

Conclusions: Antibiotics are highly prescribed in primary care across LMICs. Although a subset of studies reported a high proportion of inappropriate use, the true extent could not be assessed due to methodological limitations. Yet, our findings highlight the need for urgent action to improve prescription practices, starting from the integration of WHO treatment recommendations and the AWaRe classification into national guidelines.

Registration: PROSPERO CRD42019123269.

2.4 Author summary

Why was this study done?

- Inappropriate use of antibiotics, both in terms of incorrect regimens and prescription without clinical indication, is a major driver of antibiotic resistance.
- Global drug sales data indicate a substantial increase in antibiotic use in low- and middle-income countries (LMICs) over the past 2 decades.
- An accurate quantification of antibiotic prescribing in primary care across LMICs is not available.

What did the researchers do and find?

- We conducted a systematic review and meta-analysis to estimate the proportion of antibiotic prescribing across primary care settings in LMICs.
- Our study showed that, on average, approximately half of patients attending primary care facilities in LMICs received at least 1 antibiotic.
- Very few included studies made an attempt to assess the extent of inappropriate prescriptions and indicate potential misuse.
- Among studies that provided information on the types of antibiotics used, we found that, in 12/16 studies, 60% of prescriptions were for antibiotics with low potential for resistance selection as defined by the World Health Organization (WHO).

What do these findings mean?

- Our study highlights that antibiotics are highly prescribed in outpatient primary care settings.
- Better quality data are necessary to dig deeper into the patterns of inappropriate use according to local epidemiologic scenarios.
- Adapting WHO treatment recommendations and incorporating the WHO Access, Watch, and Reserve (AWaRe) classification of antibiotics into national guidelines will be a first key step to improve prescription practices.

2.5 Introduction

Antimicrobial resistance (AMR) is a major health threat globally.[1] Growing morbidity and mortality rates due to resistant infections in humans are expected worldwide, along with a substantial economic impact in terms of productivity losses and healthcare expenditures.[2,3]

Several factors are known to play a role in the development and spread of AMR, with inappropriate use of antibiotics being one of its most important drivers.[4] Gathering data about resistance as well as antibiotic use is 1 of the top 5 priorities of the Global Action Plan on Antimicrobial Resistance by the World Health Organization (WHO).[5]

A multinational survey conducted across 76 countries to determine the magnitude of antibiotic consumption and its trend over time revealed a dramatic increase between 2000 and 2015 (+65% globally), mostly driven by a sharp rise in low- and middle-income countries (LMICs) (+114%), where the levels of antibiotic consumption are high and rapidly approaching those observed in high-income countries (HICs).[6] However, this analysis was based on drug sales data, thus providing limited information regarding providers' prescription habits.

The high level of antibiotic consumption in LMICs is because of multiple factors, including the high burden of infectious diseases, lack of regulations (or weak enforcement) to prevent over-the-counter sale of antibiotics, inadequate training of healthcare professionals, and the limited availability of essential diagnostics, which favors empirical use of antibiotics.[1,7,8] Besides misuse (i.e., prescription without clinical indication), another huge concern is the inappropriate use of antibiotics in terms of choice of a suitable molecule, dosage, and duration of treatment according to the site of infection and patient's characteristics.

Most studies investigating the magnitude and determinants of antibiotic use have focused on HICs, and those from LMICs have been carried out predominantly in hospital settings,[9-12] leaving a number of unanswered questions about current practices at the primary healthcare level, where the bulk of antibiotic use takes place.

Of note, there is a paucity of information regarding the degree and pattern of antibiotic use in outpatient primary healthcare facilities, i.e., any service (other than pharmacies) providing care for people making an initial contact with a health professional. Having this information will be helpful to design and implement effective stewardship interventions and policies in LMICs.

We conducted a systematic review of the literature to assess the extent and patterns of antibiotic prescription and their determinants at the primary healthcare level in LMICs, as well as the proportion of such prescriptions deemed to be inappropriate.

2.6 Methods

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (identifier: CRD42019123269) and followed the PRISMA guidelines.[13] The PRISMA checklist and PROSPERO protocol are provided as S2-1 PRISMA Checklist and S2-1 PROSPERO Protocol.

Search strategy and selection criteria

We performed a systematic review of cross-sectional studies that were conducted in primary care in LMICs and reported the proportion of individuals receiving any antibiotic or the proportion of drug prescriptions that included an antibiotic. We also examined randomized and non-randomized trials as well as other observational studies to determine whether potentially relevant information (e.g., results from preliminary field assessments including cross-sectional drug prescription data) was provided. Conference proceedings and abstracts, commentaries, editorials, reviews, mathematical modeling studies, economic analyses, qualitative studies, and studies published in predatory journals as defined by Beall were excluded.[14] Studies conducted solely in an inpatient setting, those that focused on veterinary use of antibiotics, and those that only enrolled patients belonging to special cohorts (e.g., patients with cystic fibrosis or neutropenia or

other underlying conditions that may justify an increased empirical use of antibiotics, or patients receiving antibiotics as part of prophylactic regimens) were also ineligible. No restrictions were applied with regards to the population characteristics in terms of age, sex, pregnancy status, or HIV status.

For the purpose of the study, we considered as "primary care" any care provided by any health professional (other than pharmacists) with whom patients have their initial contact, in the public or private sector, including primary care delivered in hospital settings wherever appropriate. In cases of uncertainty, we contacted the study authors for clarification. Antibiotics were defined as any agents included in the J01 group of the ATC (Anatomical Therapeutic Chemical) classification system.[15] Inappropriate prescriptions were reported when such assessment was performed in the original studies. Countries were classified as low, lower-middle, upper-middle, or high income following the World Bank categorization based on gross national income per capita (GNI) of the study start year.[16] GNI thresholds for the definition of such categories, which have changed slightly over time, are provided in S2-1 Table. Given that there is no international standard definition of "urban" and "rural" areas, we classified the study settings in accordance with the authors' statements. If not explicitly stated by the investigators, we categorized as "urban" any site with a minimum population of 2,000 inhabitants, i.e., the most frequently used cutoff.[17]

The search strategy was built in collaboration with a medical librarian (GG), using key terms for "antibiotic," "primary healthcare," "prescribing," and "LMICs" (both as a group and as individual countries, adopting a filter that was developed according to the World Bank categories). Medline (PubMed), Embase (Ovid), Global Health (Ovid), and CENTRAL (Cochrane Library) were systematically searched from 1 January 2010 until 4 April 2019. We also reran our search on 11 March 2020 using PubMed only; for feasibility reasons, the update could not be conducted through all data sources used in the initial search. Studies conducted before 1 January 2010 were excluded. The start date of our search was established after the conduction of an exploratory review of the literature showing that only a small number of studies were performed before 2010 in relevant

settings, in the face of the exponentially higher number of total records identified through our search strategy, which would have posed substantial feasibility issues with very little benefit. Additionally, as patterns of antibiotic prescribing have changed substantially over time, including older studies would have been of limited value for understanding the current situation. No language restrictions were applied. The full search strategies for each database are presented in S2-1 Text.

Study screening and data extraction

Search results were imported into a citation manager (EndNote X9, Clarivate Analytics), and duplicates were removed. Three authors (GS, PA, and VN) independently screened citations by title and abstract against predefined eligibility criteria. The full-text review of all selected records was performed by 2 authors (GS and PA). An electronic data extraction form was piloted on 5 randomly selected papers and then used by 2 reviewers (GS and PA) to extract information from all eligible publications. At each stage of the screening and data extraction process, disagreements were resolved through discussion, and, if necessary, a third author (SG) was consulted to reach consensus. Study authors were contacted to request clarifications or additional data if needed. A detailed description of the screening and data extraction process is provided in S2-2 Text along with interrater agreement statistics.

Assessment of study quality and publication bias

A modified version of a tool developed by Hoy and colleagues was utilized to evaluate the risk of bias of each included study (S2-2 Table).[18] Our checklist included 8 methodological items (rated as low or high risk of bias), plus a summary item on the overall risk of study bias (rated as low, moderate, or high); no numeric scores were applied. All findings from this assessment were recorded in the data extraction form by the same independent reviewers. As a sensitivity analysis, we excluded studies with a high overall risk of bias.

No formal assessment of publication bias could be performed since traditional approaches such as funnel plots and tests for asymmetry are considered unsuitable for prevalence studies.[19]

Statistical analysis

Depending on the type of data available from individual studies, we calculated either the proportion of patients evaluated in a given health facility or by a certain provider who received antibiotics or the proportion of all drug prescriptions containing any antibiotics, along with their Clopper–Pearson (or exact) 95% confidence intervals (CIs).[20] The 2019 WHO Access, Watch, and Reserve (AWaRe) framework was used to classify antibiotics according to their potential for selecting resistance.[21] Access-group antibiotics are first-line and narrow-spectrum agents such as penicillin, amoxicillin, and trimethoprim-sulfamethoxazole. Watch-group antibiotics are broad-spectrum agents with higher resistance selection such as second- and third-generation cephalosporins, and fluoroquinolones. Reserve-group antibiotics include last-resort antibiotics such as colistin. Fixed-dose combinations of antibiotics (e.g., ciprofloxacin/ornidazole) were classified as "discouraged" antibiotics, in line with WHO recommendations.

Random-effects meta-analyses were performed to estimate pooled proportions after Freeman–Tukey transformation to normalize the outcome.[22] To assess the between-study heterogeneity, we used the I^2 statistic and calculated prediction intervals (i.e., a type of confidence interval that provides the 95% range of true values to be expected in similar studies).[23,24] Random-effects meta-regression with Knapp–Hartung adjustment (aimed to accommodate high degrees of heterogeneity) was employed to investigate the sources of heterogeneity. Categorical predictors for facility location (urban/rural), healthcare sector (public/private), age group (adults/children/all), type of patients (i.e., patients seeking care for any reason or individuals with a specific condition, e.g., diarrhea), and source of prescription information were considered for building the model. If collinearity issues were observed, variables with the lowest number of missing values were prioritized and included in the model.

Subgroup analyses were conducted to investigate potential differences across levels of country income and types of patients involved (with a focus on studies where all patients attending 1 or more facilities were considered without placing restrictions based on their clinical presentation).

Sensitivity analyses were done by repeating analyses without studies that (i) were conducted in Iran as they were all based on administrative data from national registers; (ii) did not report details on the population and/or health facility location; (iii) were conducted in low-income countries; (iv) were based on the standardized patient methodology, in which antibiotics were deemed inappropriate by indication; (v) were deemed to be low quality (i.e., overall risk of study bias scored as "high").

All analyses were conducted in Stata (version 14; StataCorp).[25,26]

2.7 Results

Our initial search yielded 9,604 unique citations, and an additional 590 were retrieved through our search update. A total of 48 studies (all cross-sectional) were finally included in the analyses (Figure 2-1).[27-74]. All included publications were in English language, except for 1 that was in Spanish. A summary of the main study characteristics is presented in Table 2-1, and the full dataset used for analyses is provided as S2-1 Data. Most studies were conducted in lower-middle- or upper-middle-income countries (22 and 19, respectively), while only 6 were in a low-income country. Additionally, 1 study was carried out in 3 countries (1 low income and 2 lower-middle income).[70] Both public and private healthcare services were involved in 10 of the 48 (20.8%) included studies, whereas 26 (54.2%) studies were focused on the public sector, 4 (8.3%) were focused on the private sector, and 8 (16.7%) did not provide this information; none of the studies mentioned any involvement of informal practitioners. Facilities located in urban areas were more represented than those located in rural areas (17/48 studies [35.4%; 95% CI: 22.2%–50.5%] versus 10/48 studies [20.8%; 95% CI: 10.5%–35.0%]), with 13 (27.1%) studies involving both settings and 8 (16.7%) not reporting sufficient details. While 9 (18.8%) studies only

included individuals presenting with 1 prespecified condition (i.e., acute respiratory illness, diarrhea, or fever), the other studies did not apply restrictions on the reason for seeking care and/or the final diagnosis (if any) and likely included patients with various conditions. None of the studies focused solely on dental care; although it is possible that patients seeking dental care were included in some studies, this group likely represented a negligible proportion of the total sample. Of note, no clinical information was reported in most studies.

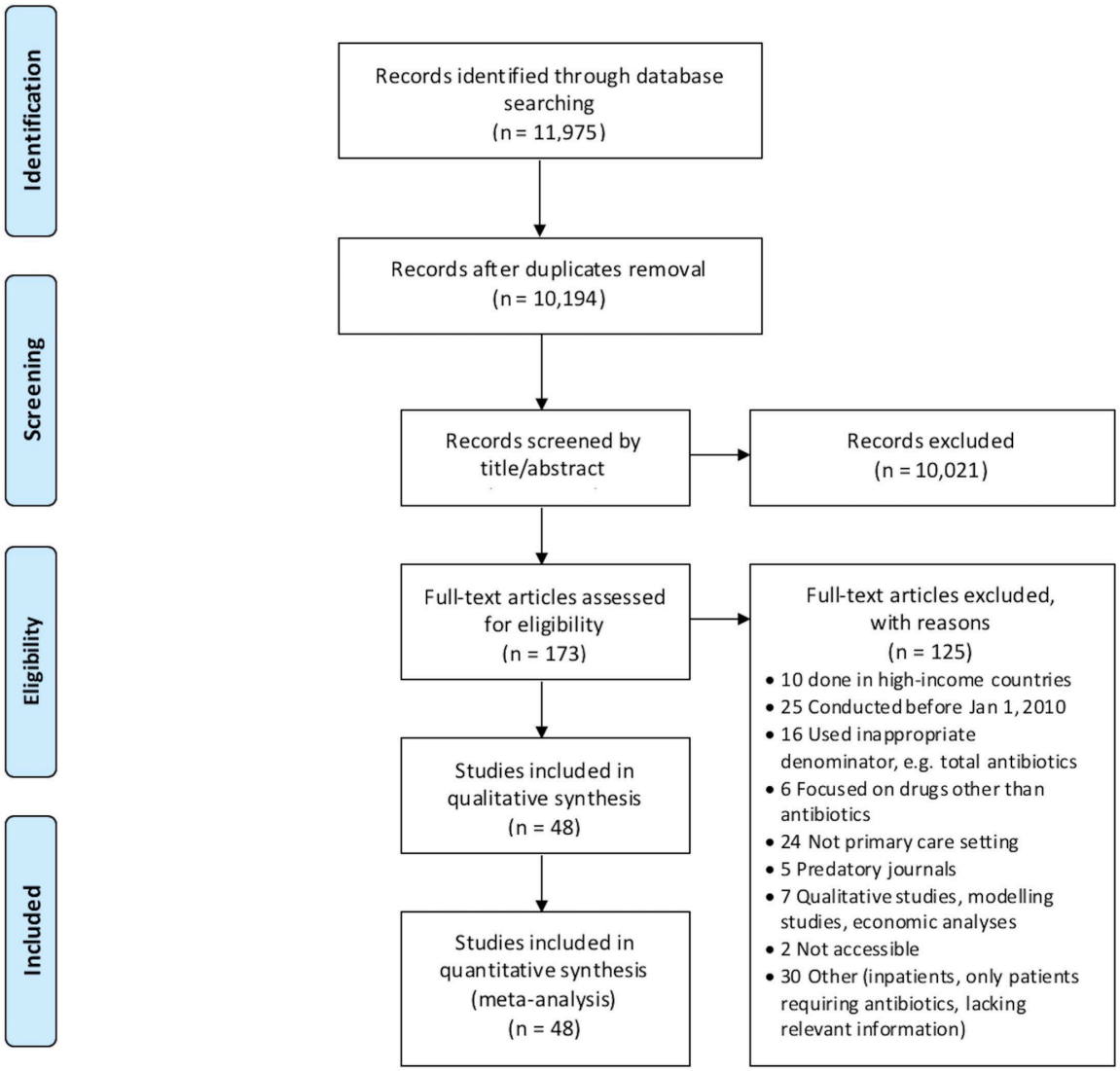


Figure 2-1 PRISMA diagram

Table 2-1 Characteristics of studies identified through systematic review.

Income level	Study [reference]	Country	Health sector	Facility location	Number of facilities involved	Data source	Age group	Denominator*
Low	Baltzell 2019 [68]	Malawi	Private	Rural	NA	Medical records	NA	9,924 (P)
	Mukonzo 2013 [27]	Uganda	Both	Both	1	Medical records, prescription audit	All	173 (P)
	Nepal 2020 [73]	Nepal	Public	Urban	NA	Prescription audit	All	950 (P)
	Savadogo 2014 [28]	Burkina Faso	Public	Urban	2	Medical records	Children	376 (P)
	Worku 2018 [29]	Ethiopia	Public	Urban	6	Medical records, prescription audit	All	898 (D)
	Yebyo 2016 [30]	Ethiopia	Public	Rural	4	Medical records	Adults	414 (P)
Lower-middle	Abdulah 2019 [31]	Indonesia	Public	NA	25	Prescription audit	Adults	10,118 (D)
	Adisa 2015 [32]	Nigeria	Public	Urban	8	Prescription audit	Adults	400 (P)
	Ahiabu 2016 [33]	Ghana	Both	Both	4	Medical records	All	1,600 (D)
	Akl 2014 [34]	Egypt	Public	Urban	10	Medical records	NA	1,000 (D)
	Atif 2016 [35]	Pakistan	NA	Urban	10	Prescription audit	NA	1,000 (D)
	Beri 2013 [36]	India	Private	Urban	20§	Provider interview	All	400 (P)
	Chem 2018 [37]	Cameroon	Both	Both	26	Medical records	All	30,096 (D)
	El Mahalli 2011 [38]	Egypt	Public	Urban	2	Medical records	Children	300 (P)
	Graham 2016 [39]	Zambia	NA	NA	90§	Provider interview	Children	537 (P)
	Jose 2016 [40]	India	Public	Rural	1	Prescription audit	Children	552 (D)
	Kasabi 2015 [41]	India	Public	NA	20	Medical records	NA	600 (P)
	Mekuria 2019 [72]	Kenya	Private	Urban	4	Prescription audit	All	17,382 (P)
	Ndhlovu 2015 [42]	Zambia	Both	Both	148	Patient interview, medical records	All	872 (P)
	Omole 2018 [43]	Nigeria	Both	Rural	NA	Prescription audit	NA	4,255 (D)
	Oyeyemi 2013 [44]	Nigeria	Public	Urban	4	Medical records	All	600 (D)
	Raza 2014 [45]	Pakistan	Both	Urban	NA	Prescription audit	NA	1,097 (D)
	Sarwar 2018 [46]	Pakistan	Public	Both	32	Prescription audit	NA	6,400 (D)
	Saurabh 2011 [47]	India	NA	Rural	4	Prescription audit	NA	600 (D)
	Saweri 2017 [48]	PNG	Public	Both	7	Ad hoc form	All	6,008 (P)
	Sudarsan 2016 [49]	India	Public	Urban	1	Prescription audit	NA	360 (D)
	Yousif 2016 [50]	Sudan	Both	NA	220§	Prescription audit	NA	19,690 (D)
	Yuniar 2017 [51]	Indonesia	Both	NA	56	Prescription audit	NA	1,657 (D)
Upper-middle	Ahmadi 2017 [52]	Iran	Public	Rural	103	Prescription audit	NA	352,399 (D)
	Alabid 2014 [53]	Malaysia	Private	Urban	70	Patient interview	Adults	140 (P)
	Bielsa-Fernandez 2016 [54]	Mexico	NA	Urban	109§	Provider interview	All	1,840 (P)
	Gasson 2018 [55]	South Africa	Public	Urban	8	Medical records	All	654 (P)
	Greer 2018 [56]	Thailand	Public	Both	32	Medical records	All	83,661 (P)

Income level	Study [reference]	Country	Health sector	Facility location	Number of facilities involved	Data source	Age group	Denominator*
	Lima 2017 [57]	Brazil	NA	NA	20	Prescription audit	NA	399 (D)
	Liu 2019 [71]	China	Public	Both	65	Prescription audit	All	428,475 (D)
	Mashalla 2017 [58]	Botswana	Public	Urban	19	Prescription audit	All	550 (D)
	Ab Rahman 2016 [59]	Malaysia	Both	Both	545	Medical records	All	27,587 (P)
	Sadeghian 2013 [60]	Iran	NA	NA	NA	Prescription audit	NA	4,940,767 (D)
	Safaeian 2015 [61]	Iran	NA	Both	3,772[§]	Prescription audit	NA	7,439,709 (D)
	Sánchez Choez 2018 [62]	Ecuador	Public	Both	1	Prescription audit	All	1,393 (P)
	Sun 2015 [63]	China	Public	Both	24	Prescription audit	All	1,468 (D)
	Wang 2014 [64]	China	Public	Both	48	Medical records	All	7,311 (D)
	Xue 2019 [65]	China	Public	Rural	NA	SP exit interview	All	526 (P)
	Yin 2015 [66]	China	Both	Urban	2,501	Prescription audit	NA	42,200 (D)
	Yin 2019 [74]	China	Public	Rural	8	Prescription audit	All	14,526 (D)
	Zhan 2019 [69]	China	Public	Rural	17	Prescription audit	All	1,720 (D)
	Zhang 2017 [67]	China	Public	Rural	20	Prescription audit	Children	9,340 (D)
Multiple	Kjærgaard 2019 [70]	Kyrgyzstan, Uganda, Vietnam	NA	NA	NA	Medical records, provider interview	Children	699 (P)

Abbreviations: NA, not available; PNG, Papua New Guinea; SP, standardized patient.

*Denominator used to calculate the outcome (i.e., total number of patients evaluated [P] or total number of drug prescriptions [D]).

[§] Number of healthcare workers involved.

Importantly, almost all the studies identified through our systematic review only assessed drug prescription and did not account for direct dispensing of unlabeled medicines, which is likely a common practice.[75] This may underestimate the true antibiotic prescribing proportion.

Study quality

Figure 2-2 displays the summary of the risk of bias assessment, while the individual studies' quality assessment results are presented in S2-3 Table. The overall risk of study bias was scored as high for 21/48 studies (43.8%), moderate for 11 (22.9%), and low for 16 (33.3%). The proportion of studies assigned to the high-risk group was higher among those conducted in low- and lower-middle-income countries (14/28; 50%) and lower among those performed in upper-middle-income countries (7/19; 36.8%).

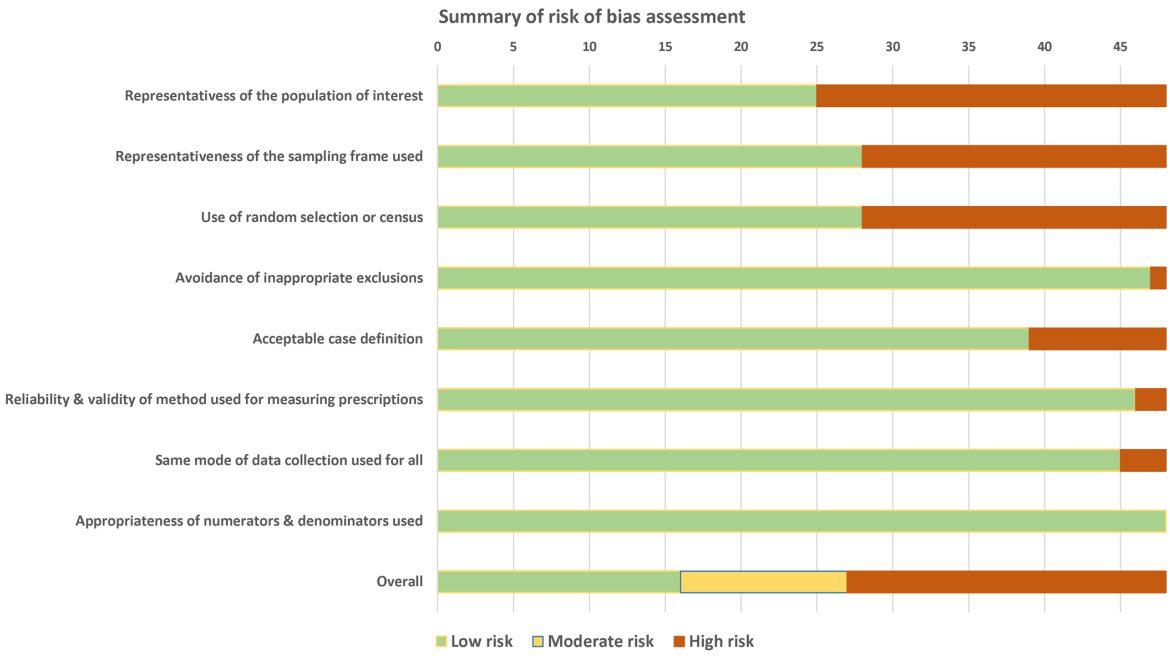


Figure 2-2 Summary of study risk of bias assessment.

No major changes were observed in terms of overall study quality over time, although this could be due to the limited number of studies. In general, the biggest issues were observed with regards to external validity: some form of random sampling or a census was seldom performed, and the study population was rarely representative of the target, mostly due to the fact that prescriptions were often selected from one or a few facilities in circumscribed areas. The case definition was considered inadequate for studies that did not record clinical details about patients receiving prescriptions. The risk of bias concerning the data collection method was deemed to be low for studies that used medical records or similar sources to retrieve prescription information. This choice was made based on the fact that medical records and drug prescription audits constitute good sources to estimate the proportion of antibiotic prescribing, although they are generally poorly suited for an accurate evaluation of appropriateness of prescription. On the other hand, studies using patient or provider questionnaires were considered at high risk of bias given the potential for recall bias and Hawthorne effect.[76,77]

Prevalence of antibiotic prescription

Among the 21 studies that reported the total number of patients attending a certain facility at the time of data collection,[27,28,30,32,36,38,39,41,42,48,53–56,59,62,65,68,70,72,73] the average proportion of individuals receiving an antibiotic prescription ranged widely, from 19.6% (95% CI: 14.0%–26.4%) to 90.8% (95% CI: 89.3%–92.0%).[27,54] Among the 27 studies in which the denominator was the total number of drug prescriptions,[29,31,33–35,37,40,43–47,49–52,57,58, 60,61,63,64,66,67,69,71,74] the proportion of prescriptions containing antibiotics varied between 17.8% (95% CI: 14.2%–21.9%) and 79.2% (95% CI: 74.4%–82.7%).[46,57] We could not identify any specific pattern in the distribution of antibiotic prescription rates across levels of country income, partly due to small sample sizes. As very few studies were conducted solely in the private health sector, no comparisons could be made against public facilities. Similar considerations apply to the health service location (i.e., urban versus rural areas). Furthermore, we did not observe any specific variation over time in

the proportion of patients receiving antibiotics, either overall or after stratifying by country income level.

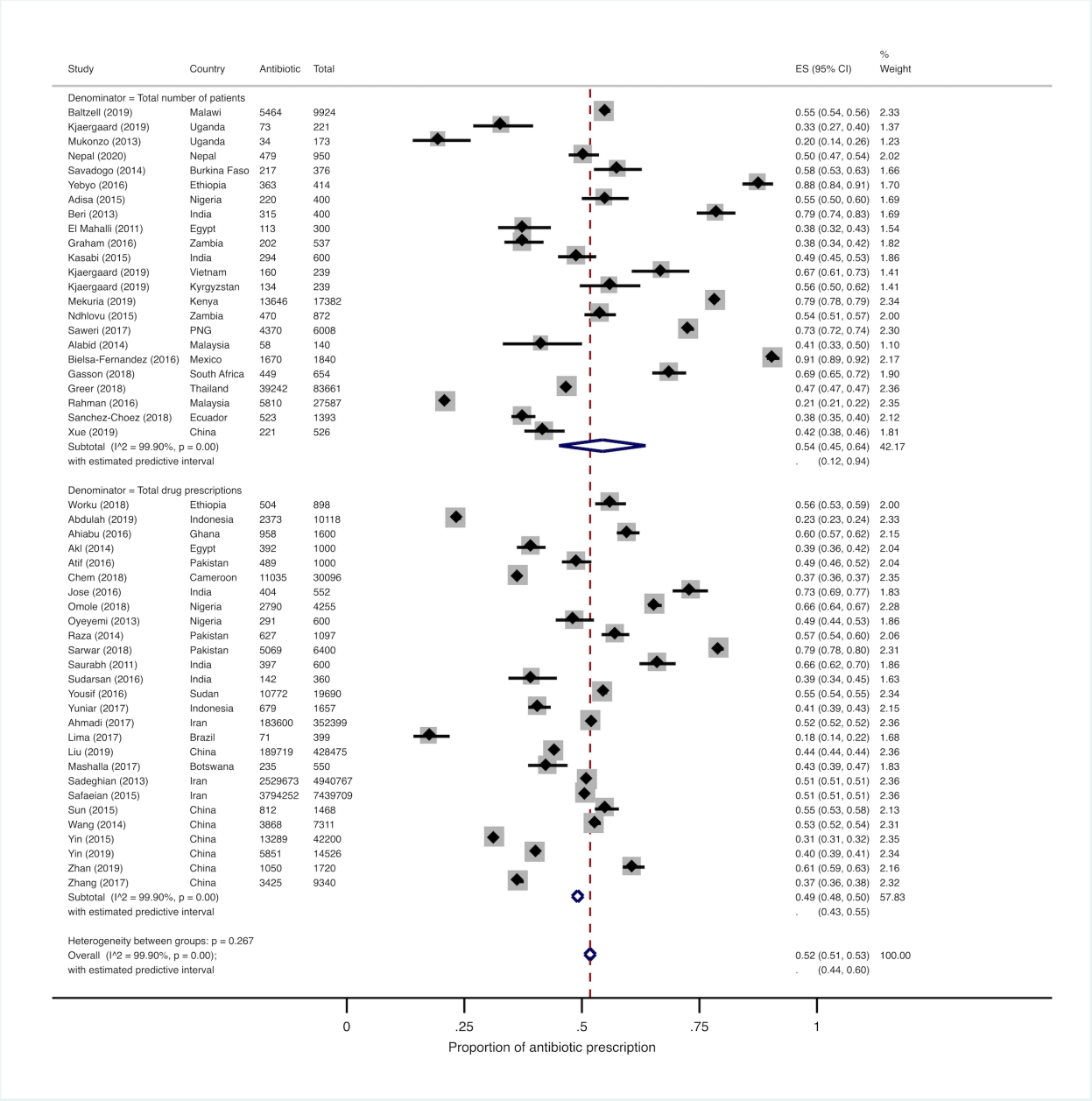


Figure 2-3 Forest plot of antibiotic prescription prevalence across all studies stratified by type of denominator used (i.e., either total number of patients or total number of drug prescriptions).

CI, confidence interval; ES, effect size; PNG, Papua New Guinea.

Since almost all patient–provider encounters included in studies using patients as the denominator resulted in a treatment prescription, prevalence estimates can be considered

comparable to those derived from the 27 studies using drug prescriptions as the denominator. The pooled proportion of patients who received antibiotics resulting from a meta-analysis of all studies was 52% (95% CI: 51%–53%), and both stratum-specific pooled proportions for studies using one or the other type of denominator were reasonably close to the overall estimate (Figure 2-3). As expected, very high levels of between-study heterogeneity were observed (I^2 values were above 98% overall, in subgroup analyses, and in sensitivity analyses), thus limiting the reliability of our pooled estimates.

However, the 95% prediction interval calculated in the primary analysis was quite narrow, ranging from 44% to 60%, indicating that a new potential observation in a similar setting would likely yield a proportion of patients receiving antibiotics close to 50%. The prediction interval is wider than the conventional confidence interval owing to the fact that it accounts for uncertainty about both the population mean and the distribution of values.

Subgroup analyses (e.g., after stratification by country income level, type of denominator, or type of patients examined) and sensitivity analyses yielded similar point estimates, but confidence and prediction intervals became much wider (S2-1 – S2-4 Figures). Unsurprisingly, given the results of subgroup meta-analyses, the overall model could only explain a negligible proportion of the observed heterogeneity (S2-4 Table).

Inappropriate antibiotic prescription

As previously mentioned, we recorded the proportion of inappropriate prescriptions when available in individual studies. In most cases, the authors made their judgment based on national and/or international guidelines for treatment of key conditions. Among the 9 studies that assessed the rationality of antibiotic prescriptions,[36,39,46,53,55,62,64,65,67] the proportion judged inappropriate ranged widely, reflecting the significant differences in study designs as well as in the sets of criteria that were adopted to determine the outcome (Table 2-2). The lowest level of inappropriate prescription (7.9%; 95% CI: 4.6%–12.5%) was reported in a study conducted in Zambia that included 537 children aged <5

years presenting with an acute respiratory syndrome, of whom 37.6% (95% CI: 33.5%–41.9%) were given antibiotics.[39] All antibiotic prescriptions were classified as inappropriate in 3 studies: 2 of them employed standardized patients portraying conditions that did not require antibiotics such as common cold, watery diarrhea, presumptive tuberculosis, and chest pain indicative of angina, with an overall antibiotic prescription prevalence of about 41%–42%;[53,65] the other study was performed in China and included 9,340 drug prescriptions issued for children with acute respiratory tract infection of likely viral etiology, 36.6% (95% CI: 35.7%–37.6%) of whom received an antibiotic.[67] The proportion of inappropriate antibiotic prescriptions exceeded 50% in the remaining 5 studies.

Information regarding individual antibiotics was available from 16 studies in 15 countries. Of note, 11 of these studies included patients seeking care for any reason, while the remaining 5 studies focused on a specific condition (i.e., respiratory tract infection [4 studies] or diarrhea [1 study]) (Table 2-3). Access-group antibiotics accounted for the majority of prescriptions (more than 60%) in 13 studies from 12 countries, whereas Watch-group antibiotics accounted for high proportions of prescriptions among studies from Mexico (90.3%; 95% CI: 88.8%–91.7%), China (78.4%; 95% CI: 75.7%–81.0%), and Pakistan (47.8%; 95% CI: 46.5%–49.1%) (Table 2-3).[46,54,63]

Table 2-2 Main findings of studies that assessed inappropriate antibiotic prescription.

Study [reference]	Country	Country income	Healthcare sector	Sample size	Type of patients	Antibiotic prescriptions *n* (%; 95% CI)	Inappropriate antibiotic prescriptions *n* (%; 95% CI)
Beri (2013) [36]	India	Lower-middle	Private	400	Patients of all ages with any clinical presentation	315 (78.8; 74.4–82.7)	179 (56.8; 51.2–62.4)
Graham (2016) [39]	Zambia	Lower-middle	Not reported	537	Children under age 5 years with acute respiratory illness	202 (37.6; 33.5–41.9)	16 (7.9; 4.6–12.5)
Sarwar (2018) [46]	Pakistan	Lower-middle	Public	6,400	Patients with any clinical presentation	5,069 (79.2; 78.2–80.2)	4,238 (83.6; 82.6–84.6)
Gasson (2018) [55]	South Africa	Upper-middle	Public	654	Patients with any clinical presentation	449 (68.7; 64.9–72.2)	305 (67.9; 63.4–72.2)
Sánchez Choez (2018) [62]	Ecuador	Upper-middle	Public	1,393	Patients of all ages with upper respiratory tract infection	523 (37.5; 35.0–40.1)	472 (90.2; 87.4–92.7)
Wang (2014) [64]	China	Upper-middle	Public	7,311	Patients of all ages with any clinical presentation	3,868 (52.9; 51.8–54.1)	2,344 (60.6; 59.0–62.1)
Alabid (2014) [53]	Malaysia	Upper-middle	Private	140	Adult SPs with common cold	58 (41.4; 33.2–50.1)	58 (100)
Xue (2019) [65]	China	Upper-middle	Public	526	Adult and child SPs with 1 of the following: diarrhea (viral gastroenteritis), chest pain (suspicious for angina), fever and cough (presumptive TB)	221 (42.0; 37.8–46.4)	221 (100)
Zhang (2017) [67]	China	Upper-middle	Public	9,340	Children with upper respiratory tract infection	3,425 (36.7; 35.7–37.7)	3,425 (100)

Abbreviations: CI, confidence interval; SP, standardized patient; TB, tuberculosis.

Table 2-3 AWaRe classification of antibiotic prescriptions in a subset of studies included in analysis.

Study [reference], total number (*n*) of antibiotics prescribed or dispensed	**Country**	**Patients' clinical presentation**	**Access-group antibiotics (%)**	**Watch-group antibiotics (%)**	**Reserve-group antibiotics (%)**	**Discouraged antibiotics (%)**
Abdulah (2019) [31], *n* = 2,389	Indonesia	Any	1,667 (69.8)	287 (12.0)	NA	NA
Sarwar (2018) [46], *n* = 5,853	Pakistan	Any	3,055 (52.2)	2,798 (47.8)	0	0
Sánchez Choez (2018) [62], *n* = 553	Ecuador	Acute respiratory syndrome	463 (83.7)	90 (16.3)	0	0
Worku (2018) [29], *n* = 553	Ethiopia	Any	431 (77.9)	122 (22.1)	0	0
Gasson (2018) [55], *n* = 519	South Africa	Any	361 (69.6)	158 (30.4)	0	0
Chem (2018) [37], *n* = 12,350	Cameroon	Any	11,109 (90.0)	1,241 (10.0)	0	0
Mashalla (2017) [58], *n* = 289	Botswana	Any	240 (83.0)	49 (17.0)	0	0
Ab Rahman (2016) [59], *n* = 6,009	Malaysia	Any	3,879 (64.6)	2,073 (34.5)	NA	NA
Adisa (2015) [32], *n* = 303	Nigeria	Any	224 (73.9)	61 (20.1)	0	18 (5.9)
Yebyo (2016) [30], *n* = 373	Ethiopia	Acute respiratory syndrome	312 (83.6)	61 (16.4)	0	0
Ndhlovu (2015) [42], *n* = 561	Zambia	Any	490 (87.3)	42 (7.5)	0	0
Sun (2015) [63], *n* = 978	China	Acute respiratory syndrome	174 (17.8)	767 (78.4)	NA	NA
Bielsa-Fernandez (2016) [54], *n* = 1,718	Mexico	Diarrhea	166 (9.7)	1,551 (90.3)	1 (0.06)	0
Mukonzo (2013) [27], *n* = 9,683	Uganda	Any	7,735 (79.9)	1,908 (19.7)	NA	NA
Nepal (2020) [73], *n* = 479	Nepal	Any	299 (62.4)	165 (34.4)	NA	NA
Mekuria (2019) [72], *n* = 13,646	Kenya	Acute respiratory syndrome	8,461 (62.0)	4,880 (35.7)	NA	278 (2.0)

Note: Denominator for percentage calculations is the total number of antibiotics dispensed/prescribed. Access-group antibiotics are first-line and narrow-spectrum agents such as penicillin, amoxicillin, and trimethoprim-sulfamethoxazole. Watch-group antibiotics are broad-spectrum agents with higher resistance selection such as second- and third-generation cephalosporins, and fluoroquinolones. Reserve-group antibiotics include last-resort antibiotics such as colistin. Discouraged antibiotics are fixed-dose combinations such as ciprofloxacin/ornidazole.

Abbreviations: NA, not available.

2.8 Discussion

To our knowledge, this is the first comprehensive analysis of antibiotic prescriptions in primary care in LMICs. We found that the proportion of patients seeking care for any reason who were prescribed antibiotics in this context often exceeded 50%. Although the interpretation of our pooled estimates is limited by the considerable between-study heterogeneity, values were quite consistent across settings. Available studies from LMICs often suffer from several methodological issues and report scanty details concerning patients' clinical features that would help accurately judge the appropriateness of prescription. The number of health facilities involved in individual studies is often very small, particularly in low-income countries (a total of 13 facilities across 4 studies that reported this information), indicating major discrepancies in the quality of information among geographic areas. Although all included studies examined prescription data in primary care facilities, we recognize that primary care entails a wide range of facility types, each with its own peculiarities and challenges. This variegated scenario prevented us from conducting specific subgroup analyses that could inform targeted antibiotic stewardship strategies. Two studies, both conducted in an Iranian province, had a very large sample size because prescription details were captured through an electronic data collection system that is available nationwide. However, clinical information on patients receiving each prescription is much more challenging to obtain from this system, thus hindering a thorough assessment of inappropriate drug use.

WHO recommends that the proportion of patients receiving antibiotics in an outpatient setting should be less than 30%.[78] However, this threshold was established somewhat arbitrarily more than 2 decades ago, due to a lack of evidence on prescription practices and actual needs according to patients' clinical features. If accurate and nationally representative prescribing data were available for individual countries, these could be used as a benchmark to define condition-specific ideal prescribing proportions that account for context-related variables.

High infectious disease burden in LMICs could potentially explain the high prevalence of antibiotic use; however, our results raise concerns about potential misuse of antibiotics based on a subset of studies that assessed the rationality of antibiotic prescriptions. For example, high levels of antibiotic prescriptions (41%–42%) were reported in 2 standardized patient studies in Malaysia and China, where nobody should have received antibiotics, by design.[53,65] In a study conducted in Mexico, 69% of patients had had watery diarrhea for less than 48 hours, but almost everybody received antibiotics instead of rehydration alone.[54] Similarly, in a nationwide health facility survey in Zambia, 72.2% of patients met the criteria for suspected malaria, for which antibiotics are not appropriate treatment, but nonetheless more than half were given antibiotics.[42] Studies focused on individuals with upper respiratory symptoms such as common cold or pharyngitis reported unacceptably high antibiotic prescribing proportions, ranging from 36.7% to 55.3%.[39,62,63,67]

To promote the optimal use of antibiotics and assist antibiotic stewardship efforts, WHO introduced the AWaRe classification in 2017.[21] The classification underlines that, where appropriate, narrow-spectrum antibiotics included in the Access group should be preferred over broad-spectrum antibiotics from Watch and Reserve groups in order to limit the selection and spread of antibiotic resistance. Accordingly, WHO recommends that Access-group antibiotics should constitute at least 60% of overall antibiotic use.[21] Only 16 of the 48 studies identified through our systematic review reported detailed information on individual antibiotic drugs, and all but 3 had at least 60% of antibiotics being from the Access group.[21] Three studies with a high proportion of Watch-group antibiotics were from Mexico, China, and Pakistan; however, we cannot generalize these estimates to overall antibiotic consumption in these countries based on only 1 study in each country. Interestingly, a recent study that analyzed pediatric antibiotic sales data using AWaRe categories in 70 countries showed a high proportion of Watch-group antibiotics in China, Pakistan, and Mexico.[79]

A recently published umbrella review on antibiotic use for adults in primary care (though focused on dental care) identified several factors that appear to affect prescribing

behaviors in HICs, such as socio-cultural context, financial incentives, personal beliefs, patients' attitudes, and AMR awareness.[80] Similar considerations likely apply to prescription practices in LMICs, although a deeper understanding of underlying determinants remains challenging. Among the biggest issues is the poor documentation of clinical reasons leading to antibiotic prescription, as observed in other settings.[81] Reaching a definitive diagnosis is often a huge challenge in resource-constrained areas, where point-of-care diagnostic tests for the most common conditions observed in primary care are frequently lacking.[82]

Along with potential antibiotic misuse, therapeutic schemes may be inappropriate because of inadequate choice of antibiotic or incorrect dose or duration. However, a thorough assessment of prescription practices that includes such considerations is made particularly difficult by the variability in national treatment guidelines regarding antibiotic regimens.[83] In an attempt to foster the harmonization of such guidelines and minimize differences across countries, WHO recently released antibiotic treatment guidelines for 26 common infectious syndromes encountered in primary care and inpatient settings.[84] These guidelines currently indicate when and what antibiotics should be prescribed, and further work on harmonizing dose, duration, and formulation is ongoing.[21]

In summary, the pooled estimate of antibiotic prescription in primary care settings across LMICs was 52%, but there was significant between-study heterogeneity. Further, the true extent of misuse was hard to discern, given the lack of data on appropriateness and the low quality of studies included. Future studies should use methodologies such as standardized patients, where the diagnosis is fixed by design, or include thorough laboratory testing to match diagnoses with antibiotic use. Accurate prescription audit tools are difficult to implement in most LMICs owing to the limited availability of electronic records. Also, the paucity of clinical details that can be captured through medical records (paper-based or not) makes it even harder to determine the appropriateness of prescription.[85]

There is a need for better quality data to accurately measure the magnitude of antibiotic prescribing and dispensing by healthcare professionals at the primary care level accounting for local epidemiologic patterns. Global burden of disease data combined with nationally representative AMR surveillance data could be utilized to estimate the amount and type of antibiotics needed in a country, which could then be compared with existing national antibiotic consumption databases.[6,86,87] Meanwhile, LMICs should adapt the WHO infection treatment guidelines and incorporate the AWaRe categorization into their national antibiotic treatment guidelines to improve antibiotic prescribing. This will help countries to prioritize surveillance and stewardship efforts aimed at curbing the spread of AMR and preserving the efficacy of currently available antibiotics.

2.9 References

1. World Health Organization. Antimicrobial resistance and primary health care. Geneva: World Health Organization; 2018 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/326454/WHO-HIS-SDS-2018.56-eng.pdf.
2. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. London: Review on Antimicrobial Resistance; 2016 [cited 2020 May 13]. Available from: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.
3. de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Med. 2016;13(11):e1002184. doi: 10.1371/journal.pmed.1002184
4. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis. 2018;18(12):e368–78. doi: 10.1016/S1473-3099(18)30296-2
5. World Health Organization. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.
6. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463–70. doi: 10.1073/pnas.1717295115
7. Center for Disease Dynamics, Economics and Policy, Global Antibiotic Resistance Partnership. The state of the world's antibiotics 2015. Washington (DC): Center for Disease Dynamics, Economics and Policy; 2015 [cited 2020 May 13]. Available from: https://www.cddep.org/wp-content/uploads/2017/06/swa_executive_summary_edits_2016.pdf.

8. Auta A, Hadi MA, Oga E, Adewuyi EO, Abdu-Aguye SN, Adeloye D, et al. Global access to antibiotics without prescription in community pharmacies: a systematic review and meta-analysis. J Infect. 2019;78(1):8–18. doi: 10.1016/j.jinf.2018.07.001
9. Machowska A, Stalsby Lundborg C. Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health. 2018;16(1):27. doi: 10.3390/ijerph16010027
10. Chua KP, Fischer MA, Linder JA. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. BMJ. 2019;364:k5092. doi: 10.1136/bmj.k5092
11. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619–29. doi: 10.1016/S2214-109X(18)30186-4
12. Kardas P, Devine S, Golembesky A, Roberts C. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. Int J Antimicrob Agents. 2005;26(2):106–13. doi: 10.1016/j.ijantimicag.2005.04.017
13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. doi: 10.1186/2046-4053-4-1
14. Beall's list of potential predatory journals and publishers: Potential predatory scholarly open-access journals. beallslist.net; 2019 [cited 2020 May 13] Available from: https://beallslist.net/standalone-journals/.
15. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system 2019. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2019.
16. World Bank. World Bank country and lending groups. Washington (DC): World Bank; 2020 [cited 2020 May 13]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

17. Uchida H, Nelson A. Agglomeration index: towards a new measure of urban concentration. Working Paper No. 2010/29. Helsinki: World Institute for Development Economics Research; 2010 [cited 2020 May 13]. Available from: https://www.wider.unu.edu/sites/default/files/wp2010-29.pdf.
18. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934–9. doi: 10.1016/j.jclinepi.2011.11.014
19. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol. 2014;67(8):897–903. doi: 10.1016/j.jclinepi.2014.03.003
20. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404–13. doi: 10.1093/biomet/26.4.404
21. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278–80. doi: 10.1016/S1473-3099(19)30532-8
22. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013;67(11):974–8. doi: 10.1136/jech-2013-203104
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. doi: 10.1136/bmj.327.7414.557
24. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016;6(7):e010247. doi: 10.1136/bmjopen-2015-010247
25. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39. doi: 10.1186/2049-3258-72-39
26. Harbord RM, Higgins JPT. Meta-regression in Stata. Stata J. 2008;8(4):493–519. doi: 10.1177/1536867x0800800403

27. Mukonzo JK, Namuwenge PM, Okure G, Mwesige B, Namusisi OK, Mukanga D. Over-the-counter suboptimal dispensing of antibiotics in Uganda. J Multidiscip Healthc. 2013;6:303–10. doi: 10.2147/JMDH.S49075
28. Savadogo LGB, Ilboudo B, Kinda M, Boubacar N, Hennart P, Dramaix M, et al. Antibiotics prescribed to febrile under-five children outpatients in urban public health services in Burkina Faso. Health. 2014;6(2):165–70. doi: 10.4236/health.2014.62026
29. Worku F, Tewahido D. Retrospective assessment of antibiotics prescribing at public primary healthcare facilities in Addis Ababa, Ethiopia. Interdiscip Perspect Infect Dis. 2018;2018:4323769. doi: 10.1155/2018/4323769
30. Yebyo H, Medhanyie AA, Spigt M, Hopstaken R. C-reactive protein point-of-care testing and antibiotic prescribing for acute respiratory tract infections in rural primary health centres of North Ethiopia: a cross-sectional study. NPJ Prim Care Respir Med. 2016;26:15076. doi: 10.1038/npjpcrm.2015.76
31. Abdulah R, Insani WN, Putri NE, Purba HP, Destiani DP, Barliana MI. Pattern of medication use in geriatric patients at primary health care facilities in Karawang, Indonesia. Drug Healthc Patient Saf. 2019;11:1–5. doi: 10.2147/dhps.S187829
32. Adisa R, Fakeye TO, Aindero VO. Evaluation of prescription pattern and patients' opinion on healthcare practices in selected primary healthcare facilities in Ibadan, South-Western Nigeria. Afr Health Sci. 2015;15(4):1318–29. doi: 10.4314/ahs.v15i4.35
33. Ahiabu MA, Tersbol BP, Biritwum R, Bygbjerg IC, Magnussen P. A retrospective audit of antibiotic prescriptions in primary health-care facilities in Eastern Region, Ghana. Health Policy Plan. 2016;31(2):250–8. doi: 10.1093/heapol/czv048
34. Akl OA, El Mahalli AA, Elkahky AA, Salem AM. WHO/INRUD drug use indicators at primary healthcare centers in Alexandria, Egypt. J Taibah Univ Med Sci. 2014;9(1):54–64. doi: 10.1016/j.jtumed.2013.06.002
35. Atif M, Sarwar MR, Azeem M, Naz M, Amir S, Nazir K. Assessment of core drug use indicators using WHO/INRUD methodology at primary healthcare centers in Bahawalpur, Pakistan. BMC Health Serv Res. 2016;16(1):684. doi: 10.1186/s12913-016-1932-2

36. Beri SG, Pandit VA, Khade KS, Sarda KD. The pattern of drug use in acute fever by general practitioners (GPs) in Pune City, India. J Clin Diagn Res. 2013;7(3):467–72. doi: 10.7860/jcdr/2013/4719.2800
37. Chem ED, Anong DN, Akoachere JKT. Prescribing patterns and associated factors of antibiotic prescription in primary health care facilities of Kumbo East and Kumbo West Health Districts, North West Cameroon. PLoS ONE. 2018;13(3):e0193353. doi: 10.1371/journal.pone.0193353
38. El Mahalli AA, Akl OA. Effect of adopting integrated management of childhood illness guidelines on drug use at a primary health care center: a case study from Egypt. J Family Community Med. 2011;18(3):118–23. doi: 10.4103/2230-8229.90010
39. Graham K, Sinyangwe C, Nicholas S, King R, Mukupa S, Kallander K, et al. Rational use of antibiotics by community health workers and caregivers for children with suspected pneumonia in Zambia: a cross-sectional mixed methods study. BMC Public Health. 2016;16:897. doi: 10.1186/s12889-016-3541-8
40. Jose J, Devassykutty D. Paediatric prescription analysis in a primary health care institution. J Clin Diagn Res. 2016;10(11):FC05–8. doi: 10.7860/jcdr/2016/22350.8797
41. Kasabi GS, Thilakavathi S, Allam RR, Grace CA, Shivanna R, Murhekar MV. Prescription practices & use of essential medicines in the primary health care system, Shimoga district, Karnataka, India. Indian J Med Res. 2015;142(2):216–9. doi: 10.4103/0971-5916.164261
42. Ndhlovu M, Nkhama E, Miller JM, Hamer DH. Antibiotic prescribing practices for patients with fever in the transition from presumptive treatment of malaria to 'confirm and treat' in Zambia: a cross-sectional study. Trop Med Int Health. 2015;20(12):1696–706. doi: 10.1111/tmi.12591
43. Omole VN, Joshua IA, Muhammad-Idris ZK, Usman NO, Ahmad IA. Use of injections and antibiotics and profile of health workers in rural primary health care facilities in north-western Nigeria. Int J Med Health Dev. 2018;23(1):183–8. doi: 10.4314/jcm.v23i1.3

44. Oyeyemi AS, Ogunleye OA. Rational use of medicines: assessing progress using primary health centres in Shomolu local government area of Lagos, Nigeria. West Afr J Med. 2013;32(2):121–5.
45. Raza UA, Khursheed T, Irfan M, Abbas M, Irfan UM. Prescription patterns of general practitioners in Peshawar, Pakistan. Pak J Med Sci. 2014;30(3):462–5. doi: 10.12669/pjms.303.4931
46. Sarwar MR, Saqib A, Iftikhar S, Sadiq T. Antimicrobial use by WHO methodology at primary health care centers: a cross sectional study in Punjab, Pakistan. BMC Infect Dis. 2018;18(1):492. doi: 10.1186/s12879-018-3407-z
47. Saurabh MK, Biswas NK, Yadav AK, Singhai A, Saurabh A. Study of prescribing habits and assessment of rational use of drugs among doctors of primary health care facilities. Asian J Pharm Clin Res. 2011;4(4):102–5.
48. Saweri OPM, Hetzel MW, Mueller I, Siba PM, Pulford J. The treatment of non-malarial febrile illness in Papua New Guinea: findings from cross sectional and longitudinal studies of health worker practice. BMC Health Serv Res. 2017;17(1):10. doi: 10.1186/s12913-016-1965-6
49. Sudarsan M, Sitikantha B, Aparajita D. Audit and quality assessment of prescriptions in an urban health centre of Kolkata. Int J Med Public Health. 2016;6(3):136–9. doi: 10.5530/ijmedph.2016.3.8
50. Yousif BM, Supakankunti S. General practitioners' prescribing patterns at primary healthcare centers in national health insurance, Gezira, Sudan. Drugs Real World Outcomes. 2016;3(3):327–32. doi: 10.1007/s40801-016-0087-0
51. Yuniar CT, Anggadiredja K, Islamiyah AN. Evaluation of rational drug use for acute pharyngitis associated with the incidence and prevalence of the disease at two community health centers in Indonesia. Sci Pharm. 2017;85(2):22. doi: 10.3390/scipharm85020022
52. Ahmadi F, Zarei E. Prescribing patterns of rural family physicians: a study in Kermanshah Province, Iran. BMC Public Health. 2017;17(1):908. doi: 10.1186/s12889-017-4932-1

53. Alabid AH, Ibrahim MI, Hassali MA. Antibiotics dispensing for urtis by community pharmacists (CPs) and general medical practitioners in Penang, Malaysia: a comparative study using simulated patients (SPs). J Clin Diagn Res. 2014;8(1):119–23. doi: 10.7860/jcdr/2014/6199.3923
54. Bielsa-Fernandez MV, Frati-Munari AC, Ariza-Andraca R. Treatment to patients with acute diarrhea: survey to a group of general practitioners from Mexico. Atencion Familiar. 2016;23(4):119–24. doi: 10.1016/j.af.2016.10.002
55. Gasson J, Blockman M, Willems B. Antibiotic prescribing practice and adherence to guidelines in primary care in the Cape Town Metro District, South Africa. S Afr Med J. 2018;108(4):304–10. doi: 10.7196/SAMJ.2017.v108i4.12564
56. Greer RC, Intralawan D, Mukaka M, Wannapinij P, Day NPJ, Nedsuwan S, et al. Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open. 2018;8(7):e022250. doi: 10.1136/bmjopen-2018-022250
57. Lima MG, Dutra KR, Martins UCM. Prescribing indicators in primary health care in Belo Horizonte, Brazil: associated factors. Int J Clin Pharm. 2017;39(4):913–8. doi: 10.1007/s11096-017-0501-z
58. Mashalla Y, Setlhare V, Massele A, Sepako E, Tiroyakgosi C, Kgatlwane J, et al. Assessment of prescribing practices at the primary healthcare facilities in Botswana with an emphasis on antibiotics: findings and implications. Int J Clin Pract. 2017;71(12). doi: 10.1111/ijcp.13042
59. Ab Rahman N, Teng CL, Sivasampu S. Antibiotic prescribing in public and private practice: a cross-sectional study in primary care clinics in Malaysia. BMC Infect Dis. 2016;16:208. doi: 10.1186/s12879-016-1530-2
60. Sadeghian GH, Safaeian L, Mahdanian AR, Salami S, Kebriaee-Zadeh J. Prescribing quality in medical specialists in Isfahan, Iran. Iran J Pharm Res. 2013;12(1):235–41.
61. Safaeian L, Mahdanian AR, Salami S, Pakmehr F, Mansourian M. Seasonality and physician-related factors associated with antibiotic prescribing: a cross-sectional study in Isfahan, Iran. Int J Prev Med. 2015;6:1. doi: 10.4103/2008-7802.151431

62. Sánchez Choez X, Armijos Acurio ML, Jimbo Sotomayor RE. Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador. BMC Pharmacol Toxicol. 2018;19(1):46. doi: 10.1186/s40360-018-0237-y
63. Sun Q, Dyar OJ, Zhao L, Tomson G, Nilsson LE, Grape M, et al. Overuse of antibiotics for the common cold—attitudes and behaviors among doctors in rural areas of Shandong Province, China. BMC Pharmacol Toxicol. 2015;16:6. doi: 10.1186/s40360-015-0009-x
64. Wang J, Wang P, Wang X, Zheng Y, Xiao Y. Use and prescription of antibiotics in primary health care settings in China. JAMA Intern Med. 2014;174(12):1914–20. doi: 10.1001/jamainternmed.2014.5214
65. Xue H, Shi Y, Huang L, Yi H, Zhou H, Zhou C, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. J Antimicrob Chemother. 2019;74(1):256–63. doi: 10.1093/jac/dky390
66. Yin X, Gong Y, Yang C, Tu X, Liu W, Cao S, et al. A comparison of quality of community health services between public and private community health centers in urban China. Med Care. 2015;53(10):888–93. doi: 10.1097/mlr.0000000000000414
67. Zhang Z, Hu Y, Zou G, Lin M, Zeng J, Deng S, et al. Antibiotic prescribing for upper respiratory infections among children in rural China: a cross-sectional study of outpatient prescriptions. Glob Health Action. 2017;10(1):1287334. doi: 10.1080/16549716.2017.1287334
68. Baltzell K, Kortz TB, Scarr E, Blair A, Mguntha A, Bandawe G, et al. 'Not all fevers are malaria': a mixed methods study of non-malarial fever management in rural southern Malawi. Rural Remote Health. 2019;19(2):4818. doi: 10.22605/RRH4818
69. Zhan Q, Wang YL, Chen X. Evaluation of antibacterial use in outpatients of township and community primary medical institutions in a district of Sichuan Province, China. J Glob Antimicrob Resist. 2019;19:201–6. doi: 10.1016/j.jgar.2019.04.021

70. Kjærgaard J, Anastasaki M, Stubbe Østergaard M, Isaeva E, Akylbekov A, Nguyen NQ, et al. Diagnosis and treatment of acute respiratory illness in children under five in primary care in low-, middle-, and high-income countries: a descriptive FRESH AIR study. PLoS ONE. 2019;14(11):e0221389. doi: 10.1371/journal.pone.0221389
71. Liu C, Wang D, Zhang X. Intrinsic and external determinants of antibiotic prescribing: a multi-level path analysis of primary care prescriptions in Hubei, China. Antimicrob Resist Infect Control. 2019;8:132. doi: 10.1186/s13756-019-0592-5
72. Mekuria LA, de Wit TF, Spieker N, Koech R, Nyarango R, Ndwiga S, et al. Analyzing data from the digital healthcare exchange platform for surveillance of antibiotic prescriptions in primary care in urban Kenya: a mixed-methods study. PLoS ONE. 2019;14(9):e0222651. doi: 10.1371/journal.pone.0222651
73. Nepal A, Hendrie D, Robinson S, Selvey LA. Analysis of patterns of antibiotic prescribing in public health facilities in Nepal. J Infect Dev Ctries. 2020;14(1):18–27. doi: 10.3855/jidc.11817
74. Yin J, Dyar OJ, Yang P, Yang D, Marrone G, Sun M, et al. Pattern of antibiotic prescribing and factors associated with it in eight village clinics in rural Shandong Province, China: a descriptive study. Trans R Soc Trop Med Hyg. 2019;113(11):714–21. doi: 10.1093/trstmh/trz058
75. Kwan A, Daniels B, Saria V, Satyanarayana S, Subbaraman R, McDowell A, et al. Variations in the quality of tuberculosis care in urban India: a cross-sectional, standardized patient study in two cities. PLoS Med. 2018;15(9):e1002653. doi: 10.1371/journal.pmed.1002653
76. Leonard K, Masatu MC. Outpatient process quality evaluation and the Hawthorne effect. Soc Sci Med. 2006;63(9):2330–40. doi: 10.1016/j.socscimed.2006.06.003
77. Leonard KL, Masatu MC. The use of direct clinician observation and vignettes for health services quality evaluation in developing countries. Soc Sci Med. 2005;61(9):1944–51. doi: 10.1016/j.socscimed.2005.03.043
78. Using indicators to measure country pharmaceutical situations. Fact book on WHO Level I and Level II monitoring indicators. Geneva: World Health Organization; 2006

[cited 2020 May 13]. Available from: https://www.who.int/medicines/publications/WHOTCM2006.2A.pdf.

79. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. Lancet Infect Dis. 2019;19(1):67–75. doi: 10.1016/S1473-3099(18)30547-4
80. Thompson W, Tonkin-Crine S, Pavitt SH, McEachan RRC, Douglas GVA, Aggarwal VR, et al. Factors associated with antibiotic prescribing for adults with acute conditions: an umbrella review across primary care and a systematic review focusing on primary dental care. J Antimicrob Chemother. 2019;74(8):2139–52. doi: 10.1093/jac/dkz152
81. Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother. 2018;73(Suppl. 2):ii2–10. doi: 10.1093/jac/dkx504
82. Kohli M, Sen P, Pai M. Improving access to essential tests for infectious diseases. Microbes Infect. 2019;21(1):1–3. doi: 10.1016/j.micinf.2018.08.003
83. Pulcini C, ESGAP AMOXDOSE working group. Amoxicillin dosing recommendations are very different in European countries: a cross-sectional survey. Clin Microbiol Infect. 2017;23(6):414–5. doi: 10.1016/j.cmi.2016.11.013
84. World Health Organization. Executive summary: the selection and use of essential medicines 2019. Report of the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines. Geneva: World Health Organization; 2019 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?sequence=1&isAllowed=y.
85. Spivak ES, Cosgrove SE, Srinivasan A. Measuring appropriate antimicrobial use: attempts at opening the black box. Clin Infect Dis. 2016;63(12):1639–44. doi: 10.1093/cid/ciw658

86. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789–858. doi: 10.1016/S0140-6736(18)32279-7
87. World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2016–2017. Geneva: World Health Organization; 2017 [cited 2020 May 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1.

S2-1 PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction section, paragraphs 1-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction section, paragraph 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods section, paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods section, sub-section 1, paragraph 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods section, sub-section 1, paragraph 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Text
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods section, sub-section 2,

			paragraph 1, S2 Text
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods section, sub-section 2, paragraph 1, S2 Text
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	S2 Text
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Method section, sub-section 3, paragraph 1, Table S3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods section, sub-section 4, paragraph 1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Method section, sub-section 4, paragraphs 1-2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Method section, sub-section 3, paragraph 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Method section, sub-section 4, paragraph 3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results section, paragraph 1, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results section, paragraph 1, Table 1

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results section, sub-section 1, Fig. 2, S4 Table
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results section – paragraph 1; Results section – sub-section 3; Tables 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results section, sub-section 2; Fig. 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results section, sub-section 2; Figg. S1-S4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion section – paragraphs 1-2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion section – paragraphs 2-3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion section – paragraphs 3-7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

S2-1 PROSPERO Protocol

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title
Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Antibiotic prescription practices at the primary healthcare level in low- and middle-income countries: a systematic review

2. Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3.* Anticipated or actual start date.
Give the date when the systematic review commenced, or is expected to commence:
24/01/2019

4.* Anticipated completion date.
Give the date by which the review is expected to be completed.
30/09/2019

5.* Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified. This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

Review stage

Preliminary searches	Started
Piloting of the study selection process	Not started
Formal screening of search results against eligibility criteria	Not started
Data extraction	Not started
Risk of bias (quality) assessment	Not started

Data analysis Not started

6.* Named contact.
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Dr. Giorgia Sulis

7.* Named contact email.
Give the electronic mail address of the named contact.
giorgia.sulis@mail.mcgill.ca

8. Named contact address
Give the full postal address for the named contact
McGill University, Department of Epidemiology, Biostatistics and Occupational Health, 1020 Pine Avenue W, H3A 1A2 Montreal, QC, Canada

9. Named contact phone number.
Give the telephone number for the named contact, including international dialling code

10.* Organisational affiliation of the review
Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
McGill University

11.* Review team members and their organisational affiliations
Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr. Giorgia Sulis, McGill University
Vaidehi Nafade, McGill University
Dr. Sumanth Gandra, Washington University School of Medicine in St. Louis
Benjamin Daniels, World Bank
Dr. Jishnu Das, World Bank
Dr. Madhukar Pai, McGill University

12.* Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None.

13.* Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15.* Review question

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The questions this systematic review aims to answer are:
1) What proportion of patients receives an antibiotic prescription at the primary healthcare level in low- and middle-income countries?
and
2) What proportion of such prescriptions is deemed to be appropriate?

The objectives of this study are to:
Estimate the overall proportion of patients who received any antibiotic prescription, and, if reported, the overall proportion of antibiotic use that was deemed to be unnecessary or incorrect.
Estimate the proportion of patients who received an antibiotic prescription stratified by antibiotic class.
Estimate the proportion of patients who received any antibiotic prescription stratified by health condition.

16.* Searches

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The search will be performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We will work with a medical librarian to systematically search the following electronic databases: PubMed/MEDLINE, EMBASE, Cochrane Library, Global Health and the International Pharmaceutical Abstracts.
The search terms will be based on key terms such as; “antimicrobial” or “antibiotic” or “anti-infective agent” and “primary care”, and it will include relevant studies published from January 1, 2010 through present, without any language restriction.

17. URL to search strategy

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.
NA
Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.
NA
Do not make this file publicly available until the review is complete

18.* Condition or domain being studied.
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Antimicrobial resistance (AMR) is a major public health concern globally. The inappropriate use of antibiotics plays a key role in the development and spread of AMR, and the optimization of antimicrobial use in humans and animals is among the top-five priorities of the Global Action Plan launched by the WHO in 2015 to tackle AMR. According to a recent analysis of drug sales data in 76 countries, global antibiotic consumption increased by 65% between 2000 and 2015. In LMICs, high burden of infectious diseases, the lack of regulations concerning drug prescription and over-the-counter sale of antibiotics, the inadequate training of healthcare professionals on rationale use of medicines, and the limited availability of essential diagnostics that leads to large-scale empirical use of antibiotics are all important factors contributing to the level of antibiotic use. However, limited information is available on the degree and type of antibiotic use in outpatient primary healthcare facilities in such contexts, thus making any intervention to promote the rational use of antibiotics particularly challenging.

19.* Participants/population.
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
This study will include all individuals, regardless of age, sex or pregnancy status, for which information on antibiotic prescription is available. We have defined adults to be persons 15 years of age or older, and children as those who are less than 15 years old.

20.* Intervention(s), exposure(s).
Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
Antibiotic prescription to patients attending outpatient services at the primary healthcare level in LMICs.

21.* Comparator(s)/control.
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Not applicable.

22.* Types of study to be included.
Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies conducted in LMICs that report the proportion of subjects receiving any antibiotic prescription at the primary healthcare level. Studies eligible for inclusion will be cross-sectional studies, prospective and retrospective cohort studies, randomized controlled trials, reports on programmatic evaluations and time-series analyses. No restriction will be placed on age, sex, or pregnancy status of the study participants. We will exclude qualitative studies, economic analyses, mathematical modelling studies, commentaries and editorials. Reports of

antibiotic sales and those concerning direct dispensing of antibiotics by pharmacies without reference to a physician's prescription will not be considered. Studies conducted solely in an inpatient setting, those that focused on veterinary use of antibiotics, and those focused on special cohorts (e.g. patients with cystic fibrosis or neutropenia or other underlying conditions that may justify an increased empirical use of antibiotics, or patients receiving antibiotics as part of prophylactic regimens), will also be excluded.

23. Context.
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24.* Main outcome(s).
Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Antibiotic use will be estimated as the ratio of the number of individuals receiving at least one antibiotic prescription to the number of persons attending a given outpatient clinic within a specified time period.

25. * Additional outcome(s).
List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

26.* Data extraction (selection and coding).
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Search results will be imported into a reference management database, and duplicate citations will be removed. Two reviewers will independently review the title and abstract of all studies identified by the search. To determine whether each study meets inclusion and exclusion criteria as described above, the same two reviewers will independently review the full text of all selected studies. Any queries or disagreements will be resolved with a third reviewer, after which a final list of articles and literature will be produced as a consensus of all three reviewers.
An electronic data extraction form will be created and pilot-tested on five randomly selected studies. Once the form has been finalized, two independent reviewers will extract data on study methodology, quality and predefined outcomes from the final list of included studies. Disagreements or queries will be resolved between the review authors; if no agreement can be reached, a third author will mediate and decide on the issue. In the case that data are not reported at the level required for each analysis, we will contact authors directly by email.
The following main data items will be collected (this is a non-exhaustive list):
- Study location
- Outcome(s) definition
- Source of information concerning antibiotic prescription (e.g. patients' records, exit interviews, clinic database, registers, prescription audits)
- Types of healthcare providers involved (i.e. physicians, nurses, others)

- Healthcare sector (i.e. private or public facility or informal sector)
- Types of antibiotics used (if available)
- Patients' characteristics (age, sex, medical conditions for which they were seeking care)
- Number of subjects who attended the facility over the study period
- Number of subjects who were prescribed a medication
- Number of subjects who were prescribed one or more antibiotics.
- Percentage of antibiotics that were deemed to be unnecessary or incorrect and methodology used to make this judgement.

27.* Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The two reviewers responsible for data extraction will independently evaluate the risk of bias and internal validity of each included study, using an adapted version of a tool developed by Hoy D. and colleagues for prevalence studies. Reviewers will evaluate each study to ensure that its design and conduct did not compromise the integrity of the results, irrespective of the specific study design utilized. As with study selection, any disagreements or queries with regards to methodological quality will be resolved by a third reviewer. Findings from this assessment will be recorded within the data extraction form.

28.* Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Utilizing the data collected through the systematic review, meta-analyses will be conducted if heterogeneity is not a concern. For each study, we will report the proportion (and 95% confidence interval) of patients receiving at least one antibiotic prescription, as described above. Heterogeneity will be assessed using the I^2 statistic. As we anticipate substantial between-studies heterogeneity, the proportions of antibiotic prescriptions will be pooled using random effects meta-analysis, and subgroup analyses will be used to identify sources of heterogeneity.

29.* Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co- morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised). Random-effects weighted proportions will be assessed for the following subgroups: major health conditions (e.g. febrile illness, respiratory syndrome, gastrointestinal syndrome, genitourinary syndrome, etc), age (adults vs. children), males vs. females, empirical vs. diagnosis-driven prescription, provider-type (physician vs. non-physician), healthcare sector (public vs. private).

30.* Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Systematic review

Health area of the review:
Infections and infestations
Public health (including social determinants of health)
Service delivery

31. Language.
Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

32. Country.
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
Canada

33. Other registration details.
Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

NA

34. Reference and/or URL for published protocol.
Give the citation and link for the published protocol, if there is one Give the link to the published protocol. Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.
Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.
NA

35. Dissemination plans.
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Results from this review will be submitted for publication to a peer-reviewed journal and will also be included in a PhD thesis at McGill University (GS).

36. Keywords.
Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

NA

37. Details of any existing review of the same topic by the same authors.
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

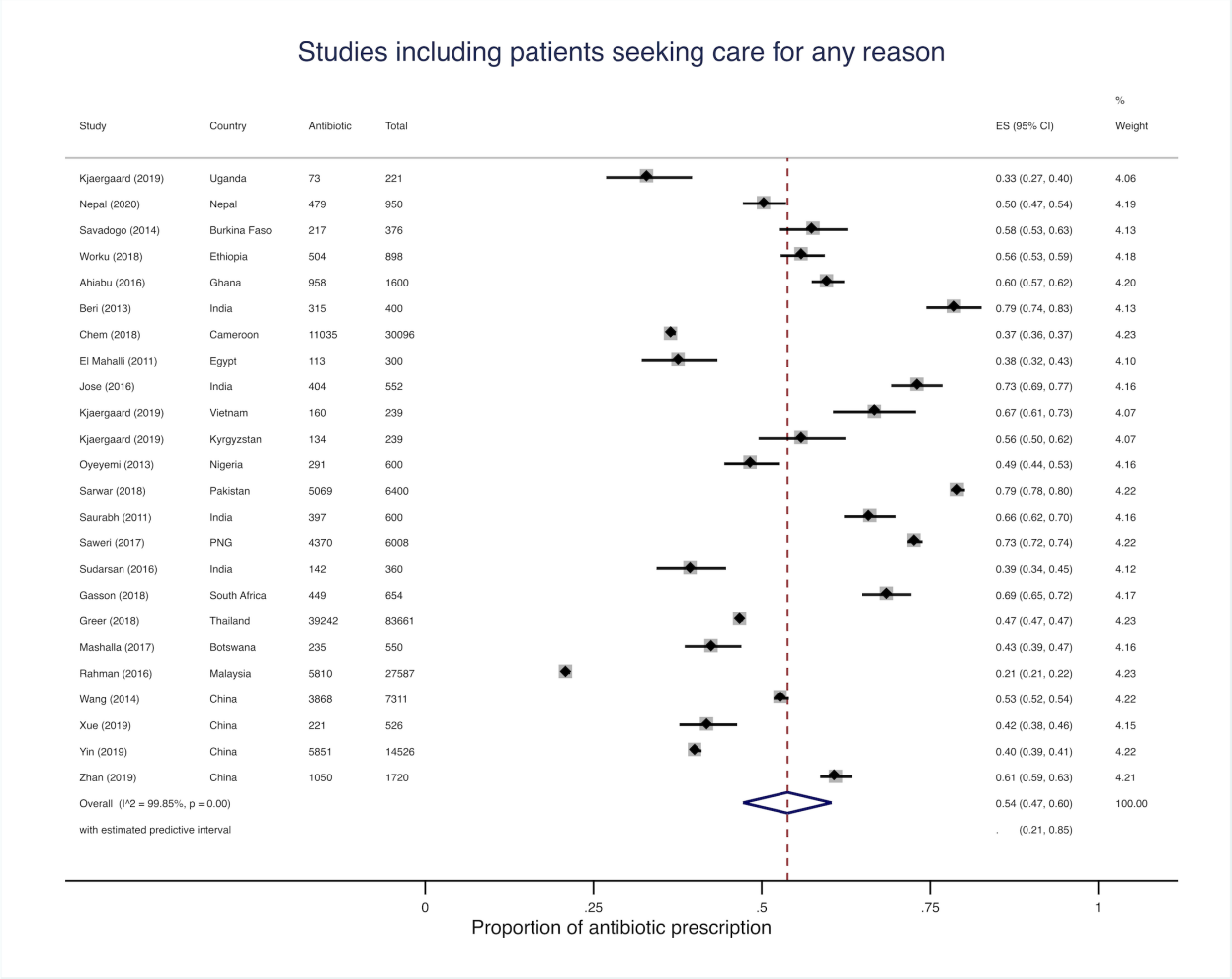
NA

38.* Current review status.
Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing. Please provide anticipated publication date

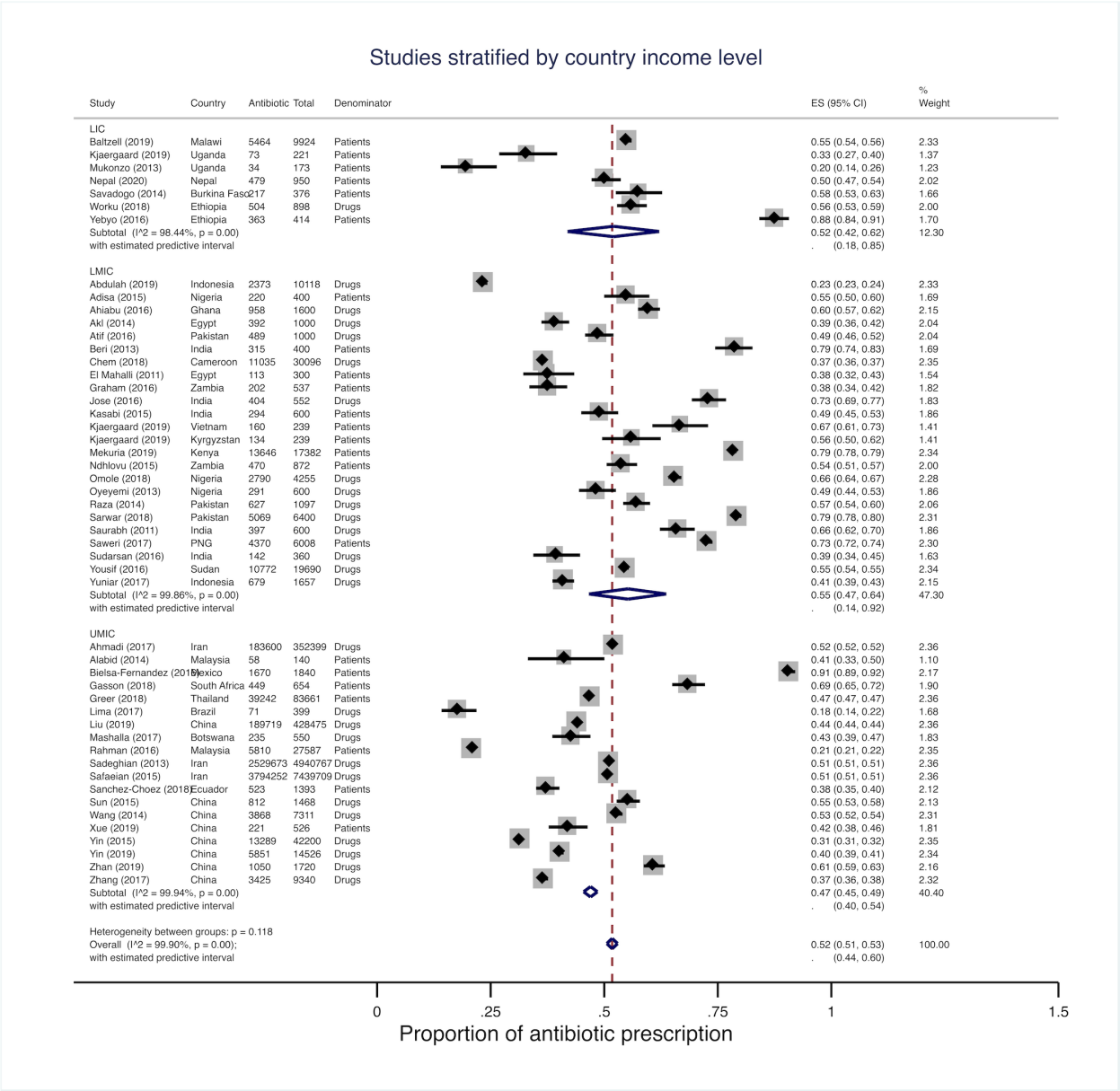
Review Ongoing

39. Any additional information
Provide any other information the review team feel is relevant to the registration of the review.
NA

S2-1 Figure: Forest plot of proportion of patients receiving antibiotics, restricted to studies including patients seeking care for any reason.

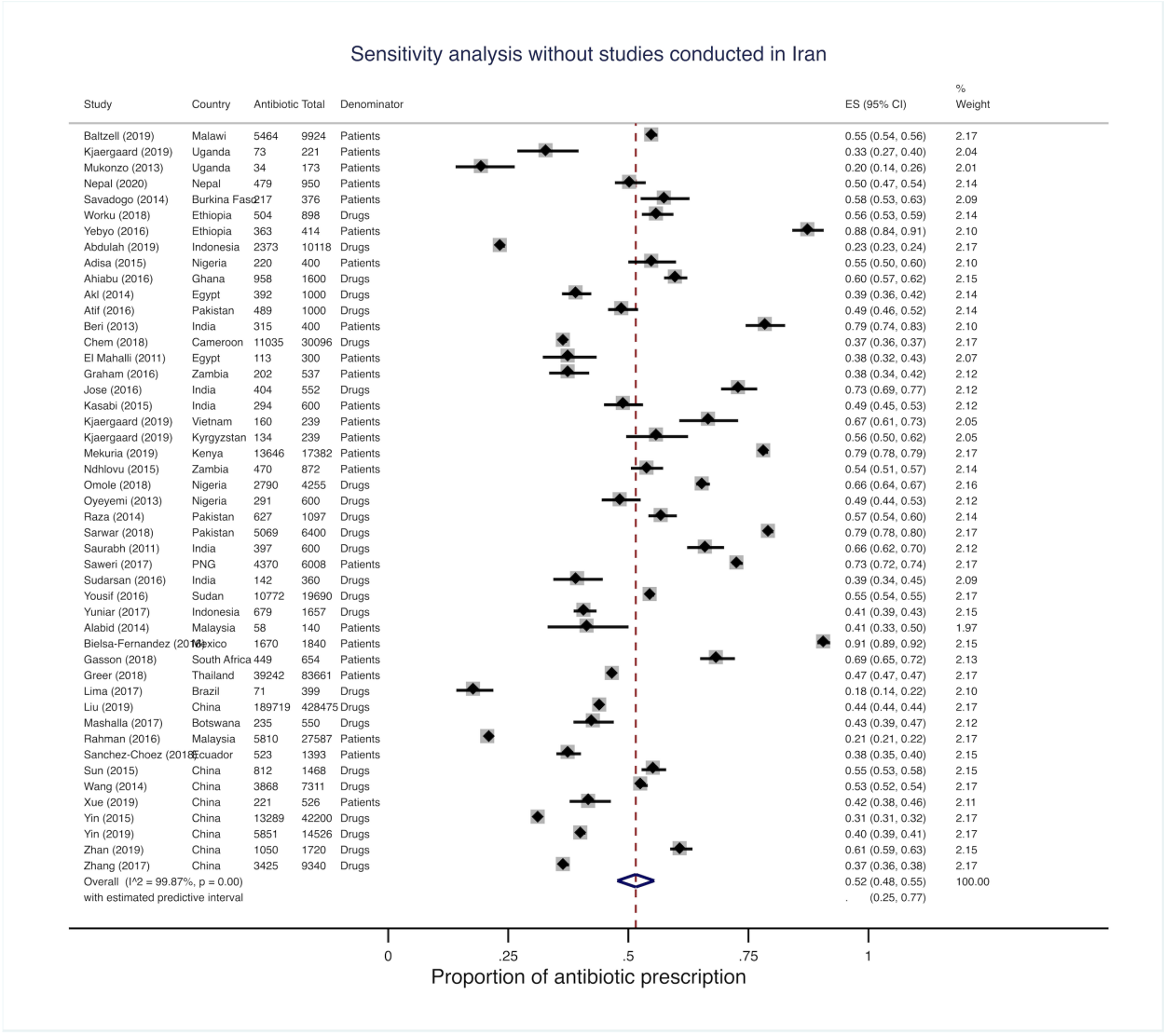


S2-2 Figure: Forest plot of proportion of patients receiving antibiotics stratified by country income level

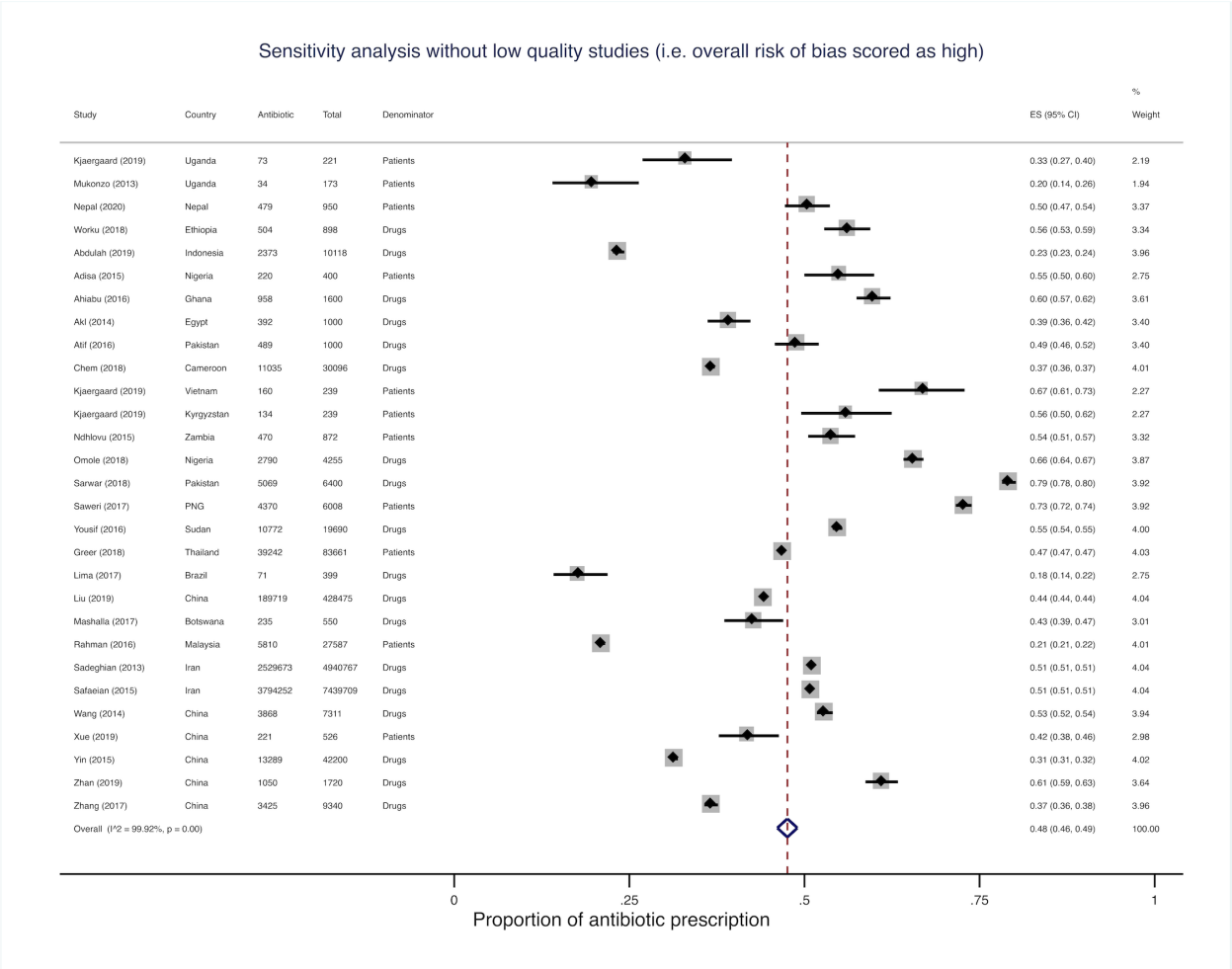


Abbreviations: LIC = low-income country; LMIC = lower-middle-income country; UMIC = upper-middle-income country.

S2-3 Figure: Forest plot of proportion of patients receiving antibiotics, including all studies except those conducted in Iran.



S2-4 Figure: Forest plot of proportion of patients receiving antibiotics, excluding studies whose overall risk of bias was scored as "high."



S2-1 Table: World Bank criteria for the definition of countries' income level 2010–2018.

Country income	2010	2011	2012	2013	2014	2015	2016	2017	2018
Low	<= 1,005	<= 1,025	<= 1,035	<= 1,045	<= 1,045	<= 1,025	<= 1,005	<= 995	<= 1,025
Lower-middle	1,006-3,975	1,026-4,035	1,036-4,085	1,046-4,125	1,046-4,125	1,026-4,035	1,006-3,955	996-3,895	1,026-3,995
Upper-middle	3,976-12,275	4,036-12,475	4,086-12,615	4,126-12,745	4,126-12,735	4,036-12,475	3,956-12,235	3,896-12,055	3,996-12,375
High	> 12,275	> 12,475	> 12,615	> 12,745	> 12,735	> 12,475	> 12,235	> 12,055	> 12,375

Note: Country income categories are defined as gross national income (GNI) per capita in US dollars in accordance to World Bank criteria for each fiscal year (available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups).

S2-2 Table: Risk of bias assessment tool (adapted from Hoy et al.).

Risk of bias item	Criteria for answers
External validity	
1. Was the study's target population **a close representation** of the population of interest in relation to relevant variables, e.g. age, sex, occupation, health status or other?	• **Yes (LOW RISK):** The study's target population was a close representation of the national population. • **No (HIGH RISK):** The study's target population was clearly NOT representative of the national population.
2. Was the sampling frame a **true or close representation** of the target population?	• **Yes (LOW RISK):** The sampling frame was a true or close representation of the target population. • **No (HIGH RISK):** The sampling frame was NOT a true or close representation of the target population.
3. Was some form of **random selection** used to select the sample, OR, was a census undertaken?	• **Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • **No (HIGH RISK):** A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.
4. Did the study avoid inappropriate exclusions?	• **No (LOW RISK)** • **Yes (HIGH RISK)**
Internal validity	
5. Was an acceptable case definition used in the study?	• **Yes (LOW RISK):** An acceptable case definition was used. • **No (HIGH RISK):** An acceptable case definition was NOT used.
6. Is the study method for measuring drug prescription shown to have **reliability and validity (if necessary)**? i.e. is there an opportunity for misclassification	• **Yes (LOW RISK):** The method is shown to have minimal misclassification potential • **No (HIGH RISK):** The method is NOT shown to have minimal misclassification potential
7. Was the **same mode of data collection** used for all subjects?	• **Yes (LOW RISK):** The same mode of data collection was used for all subjects. • **No (HIGH RISK):** The same mode of data collection was NOT used for all subjects.
8. Were the **numerator(s) and denominator(s)** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest. • **No (HIGH RISK):** The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.
Summary item on the overall risk of study bias	
• **LOW RISK OF BIAS:** Further research is very unlikely to change our confidence in the estimate. • **MODERATE RISK OF BIAS:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. • **HIGH RISK OF BIAS:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.	

S2-3 Table: Risk of bias assessment of all studies included in final synthesis.

Study	Representative of the target population	Appropriate sampling frame used	Random selection or census used	Avoidance of inappropriate	Appropriate case definition	Reliability & validity of data collection method	Same mode of data collection for all	Appropriate numerators and	Overall risk of bias
Abdulah et al, Drug Healthc Patient Saf (2019)	HR	LR	LR	LR	HR	LR	LR	LR	**MODERATE**
Xue et, J Antimicrob Chemother (2019)	LR	LR	HR	LR	LR	LR	LR	LR	**MODERATE**
Sarwar et al, BMC Infect Dis (2018)	LR	LR	LR	LR	HR	LR	LR	LR	**MODERATE**
Greer et al, BMJ Open (2018)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Sanchez-Choez et al, BMC Pharmacol Toxicol (2018)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Worku et al, Interdiscip Prospect Infect Dis (2018)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Gasson et al, S Afr Med J (2018)	HR	HR	LR	HR	LR	LR	LR	LR	**HIGH**
Chem et al, PLoS ONE (2018)	HR	LR	LR	LR	LR	LR	LR	LR	**MODERATE**
Ahmadi et al, BMC Public Health (2017)	HR	LR	HR	LR	HR	LR	LR	LR	**HIGH**
Mashalla et al, Int J Clin Pract (2017)	HR	LR	LR	LR	LR	LR	LR	LR	**MODERATE**
Lima et al, Int J Clin Pharm (2017)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Zhang et al, Glob Health Action (2017)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Jose et al, J Clin Diagn Res (2016)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Atif et al, BMC Health Serv Res (2016)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Yousif et al, Drugs Real World Outcomes (2016)	LR	LR	LR	LR	HR	LR	LR	LR	**MODERATE**
Graham et al, BMC Public Health (2016)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Rahman et al, BMC Infect Dis (2016)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Adisa et al, Afr Health Sci (2015)	LR	LR	HR	LR	LR	LR	LR	LR	**MODERATE**
Yebyo et al, NPJ Prim Care Resp Med (2016)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Yin et al, Med Care (2015)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Ndhlovu et al, Trop Med Int Health (2015)	LR	LR	LR	LR	LR	LR	HR	LR	**LOW**
Ahiabu et al, Health Policy Plan (2016)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Sun et al, BMC Pharmacol Toxicol (2015)	LR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Safaeian, et al, Int J Prev Med (2015)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Wang et al, JAMA Intern Med (2014)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**

Study	Representative of the target population	Appropriate sampling frame used	Random selection or census used	Avoidance of inappropriate	Appropriate case definition	Reliability & validity of data collection method	Same mode of data collection for all	Appropriate numerators and	Overall risk of bias
Raza et al, Pak J Med Sci (2014)	HR	HR	HR	LR	HR	LR	LR	LR	**HIGH**
Alabid et al, J Clin Diagn Res (2014)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Sadeghian et al, Iran J Pharm Res (2013)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Oyeyemi et al, West Afr J Med (2013)	HR	HR	LR	LR	LR	LR	LR	LR	**HIGH**
Beri et al, J Clin Diagn Res (2013)	HR	HR	HR	LR	LR	HR	LR	LR	**HIGH**
El Mahalli et al, J Fam Community Med (2011)	HR	HR	LR	LR	LR	LR	LR	LR	**HIGH**
Kasabi et al, Indian J Med Res (2015)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Omole et al, Int J Med Health Dev (2018)	LR	LR	LR	LR	HR	LR	LR	LR	**MODERATE**
Savadogo et al, Health (2014)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Saweri et al, BMC Health Serv Res (2017)	LR	LR	LR	LR	LR	LR	HR	LR	**LOW**
Sudarsan et al, Int J Med Public Health (2016)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Akl et al, J Taibah Univ Med Sci (2014)	LR	LR	LR	LR	HR	LR	LR	LR	**MODERATE**
Bielsa-Fernandez et al, Atención Familiar (2016)	HR	HR	HR	LR	LR	HR	LR	LR	**HIGH**
Mukonzo et al, J Multidiscip Healthc (2013)	LR	LR	LR	LR	HR	LR	HR	LR	**MODERATE**
Saurabh et al, Asian J Pharmacy Clin Res (2011)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Yuniar et al, Jurnal Kefarmasian Indonesia (2017)	HR	HR	HR	LR	HR	LR	LR	LR	**HIGH**
Baltzell et al, Rural Remote Health (2019)	LR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Kjaergaard et al, PloS One (2019)	HR	LR	LR	LR	LR	LR	LR	LR	**MODERATE**
Liu et al, Antimicrob Resist Infect Control (2019)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Mekuria et al, PloS One (2019)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Nepal et al, J Infect Dev Ctries (2020)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**
Yin et al, Trans R Soc Trop Med Hyg (2019)	HR	HR	HR	LR	LR	LR	LR	LR	**HIGH**
Zhan et al, J Glob Antimicrob Resist (2019)	LR	LR	LR	LR	LR	LR	LR	LR	**LOW**

Abbreviations: HR = high risk; LR = low risk

S2-4 Table: Results of meta-regression analysis.

Predictor	OR	95% CI
LMIC	**1.06**	**0.91 – 1.24**
UMIC	**0.92**	**0.78 – 1.07**
Urban areas only	**0.91**	**0.79 – 1.04**
Both urban and rural areas	**0.92**	**0.80 – 1.06**
Public sector	**0.88**	**0.73 – 1.07**
Source of data	**1.03**	**0.85 – 1.24**

Notes: The inclusion of calendar time (i.e. study start year) had no effect on the model's performance. Similar considerations apply to overall risk-of-bias scores.
Abbreviations: CI = Confidence interval; LMIC = Lower-middle income country; OR = Odds ratio; UMIC = Upper-middle income country.

S2-1 Text: Search strategies employed.

1a: Search strategy used for PubMed

(("primary health care"[mesh] OR primary care[tw] OR primary health*[tw] OR community health*[tw] OR community care[tw] OR community worker*[tw] OR clinic[tw] OR clinics[tw] OR “general practitioners”[mesh] OR general practi*[tw] OR family medicine[tw] OR family practi*[tw] OR “physicians, family”[mesh] OR family physician*[tw] OR family doctor*[tw] OR "physicians, primary care"[mesh]))

AND

(("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR "anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR antibiotic*[tw] OR antimicrobial*[tw] OR antibacterial*[tw] OR anti bacterial*[tw] OR anti-infective*[tw]))

AND

("therapeutic use"[sh] OR "drug prescriptions"[mesh] OR "drug utilization"[mesh] OR “inappropriate prescribing”[mesh] OR “drug utilization review”[mesh] OR "practice patterns, physicians'"[mesh] OR use[tiab] OR user*[tiab] OR used[tiab] OR overuse*[tiab] OR underuse*[tiab] OR misuse*[tiab] OR utiliz*[tiab] OR overutili*[tiab] OR underutili*[tiab] OR prescri*[tw] OR overprescri*[tiab] OR underprescri*[tiab])

AND

((Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Albania[Mesh:noexp] OR Algeria[Mesh:noexp] OR American Samoa[Mesh:noexp] OR Angola[Mesh:noexp] OR "Antigua and Barbuda"[Mesh:noexp] OR Argentina[Mesh:noexp] OR Armenia[Mesh:noexp] OR Azerbaijan[Mesh:noexp] OR Bahrain[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Barbados[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR Belize[Mesh:noexp] OR Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Bosnia-Herzegovina[Mesh:noexp] OR Botswana[Mesh:noexp] OR Brazil[Mesh:noexp] OR Bulgaria[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Chile[Mesh:noexp] OR China[Mesh:noexp] OR Colombia[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Costa Rica[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Croatia[Mesh:noexp] OR Cuba[Mesh:noexp] OR Cyprus[Mesh:noexp] OR Czechoslovakia[Mesh:noexp] OR Czech Republic[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR Dominica[Mesh:noexp] OR Dominican Republic[Mesh:noexp] OR East Timor[Mesh:noexp] OR Ecuador[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Estonia[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Fiji[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR Greece[Mesh:noexp] OR Grenada[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Guam[Mesh:noexp] OR Guyana[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR Hungary[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Iran[Mesh:noexp] OR Iraq[Mesh:noexp] OR Jamaica[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kazakhstan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Korea[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Latvia[Mesh:noexp] OR Lebanon[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Libya[Mesh:noexp] OR Lithuania[Mesh:noexp] OR Macedonia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR

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Grenadines"[Mesh:noexp] OR Samoa[Mesh:noexp] OR Saudi Arabia[Mesh:noexp] OR Senegal[Mesh:noexp] OR Serbia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Slovenia[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Thailand[Mesh:noexp] OR Togo[Mesh:noexp] OR Tonga[Mesh:noexp] OR "Trinidad and Tobago"[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Turkey[Mesh:noexp] OR Turkmenistan[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp] OR Uruguay[Mesh:noexp] OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Venezuela[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]) OR (Macedonia[ot] OR Madagascar[ot] OR Malagasy Republic[ot] OR Malaysia[ot] OR Malaya[ot] OR Malay[ot] OR 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Filter: Publication date from 2010/01/01

The LMIC filter was obtained from the following source: Cochrane Effective Practice and Organisation of Care. LMIC filters. https://epoc.cochrane.org/lmic-filters

1b: Search strategy used for Embase <1996 to 2019 Week 13>

((exp primary health care/ or general practitioner/) OR (community care/ or health auxiliary/) OR ((primary care or primary health* or community care or community health* or general practi* or family medicine or family practi* or family physician* or family doctor*).mp,jw) OR ((clinic or clinics or private practice* or ambulatory or outpatient* or out patient*).mp))

AND

((exp antibiotic therapy/ or exp *antibiotic agent/) OR (antimicrobial therapy/ or *antiinfective agent/) OR ((antibiotic* or antimicrobial* or antibacterial* or anti bacterial* or anti-infective* or antiinfective*).tw))

AND

((exp "drug use"/) OR (exp inappropriate prescribing/ or drug indication/) OR (exp "drug utilization review"/) OR ("use" or user* or used or overuse* or underuse* or misuse* or utiliz* or overutili* or underutili* or prescri* or deprescri* or overprescri* or underprescri* or practice pattern*).mp)

AND

(Developing Country.sh.) OR ((Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,ti,ab,cp) OR ((Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or

Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,ti,ab,cp) OR (((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab) OR (((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab) OR ((low* adj (gdp or gnp or gross domestic or gross national)).ti,ab) OR ((low adj3 middle adj3 countr*).ti,ab) OR ((lmic or lmics or third world or lami countr*).ti,ab) OR (transitional countr*.ti,ab)
Filter: Publication year from 2010 to 2019

1c: Search strategy used for CENTRAL (Cochrane Library)

((primary next care OR primary next health* OR community next health* OR community next care OR community next worker* OR clinic OR clinics OR general next practi* OR family next medicine OR family next practi* OR family next physician* OR family next doctor* or ambulatory or outpatient* or out next patient* or private next practice*):ti,ab,kw)

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((antibiotic* OR anti next biotic* OR antimicrobial* OR anti next microbial* OR antibacterial* OR anti next bacterial* OR anti next infective* OR antiinfective*):ti,ab,kw)

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((use OR user* OR used OR overuse* OR underuse* OR misuse* OR utiliz* OR overutili* OR underutili* OR prescri* OR deprescri* OR overprescri* OR underprescri*):ti,ab,kw)

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(Africa or Asia or Caribbean or "West Indies" or "South America" or "Latin America" or "Central America") OR ((Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic"):ti,ab,kw) OR ((Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or

Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania):ti,ab,kw) OR ((Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico"):ti,ab,kw) OR ((Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or "New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia):ti,ab,kw) OR ((developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income or underserved or "under served" or deprived or poor*) NEXT (countr* or nation* or population* or world):ti,ab,kw) OR ((developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income) NEXT (economy or economies):ti,ab,kw) OR (low* NEXT (gdp or gnp or "gross domestic" or "gross national"):ti,ab,kw) OR ((low NEAR/3 middle NEAR/3 countr*):ti,ab,kw) OR ((lmic or lmics or "third world" or "lami country" or "lami countries"):ti,ab,kw) OR ("transitional country" or "transitional countries"):ti,ab,kw

Filter: Publication year from 2010 to 2019

1d: Search strategy for Global Health <1973 to 2019 Week 12>

((primary health care/ or community care/ or community health/ or general practitioners/) OR ((primary care or primary health* or community care or community health* or general practi* or family medicine or family practi* or family physician* or family doctor*).mp,jx) OR ((clinic or clinics or private practice* or ambulatory or outpatient* or out patient*).mp))

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((exp antibiotics/ or antibacterial agents/ or antiinfective agents/) OR ((antibiotic* or antimicrobial* or antibacterial* or anti bacterial* or anti-infective* or antiinfective*).mp))

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((prescriptions/) OR (("use" or user* or used or overuse* or underuse* or misuse* or utiliz* or overutili* or underutili* or prescri* or deprescri* or overprescri* or underprescri* or practice pattern*).mp))

Filter: Publication year from 2010 to 2019

S2-2 Text: Selection process and data extraction.

The study screening was performed through a three-step process. First, three authors (GS, PA and VN) conducted a title-based screening, assessing one third of all citations each. At this stage, we adopted a highly conservative approach, only excluding records whose title clearly referred to high-income settings, hospitals providing services other than primary care, animal studies, conditions or approaches that were totally unrelated to our study question (e.g. non-communicable diseases, HIV, diagnostic accuracy studies). All records that were discarded by one of the three reviewers were double-checked by another reviewer and retained for further assessment in the event of disagreement. The interrater agreement during this phase of the screening process was excellent (>95%).
Second, the same three authors as above screened all abstracts that were selected during step 1. The following exclusion criteria were considered to make a decision:

- Conference proceedings and abstracts;
- Commentaries or editorials;
- Reviews;
- Mathematical modelling studies;
- Economic analyses;
- Qualitative studies;
- Studies conducted only in an inpatient setting;
- Studies focused on veterinary or agricultural use of antibiotics;
- Studies focused exclusively on specials cohorts such as (i) patients with cystic fibrosis or neutropenia or other underlying conditions that may justify an increased empirical use of antibiotics, or (ii) patients receiving antibiotics as part of prophylactic regimens (e.g. cotrimoxazole preventive therapy provided to HIV-infected individuals).

If any of the aforementioned criteria could not be ruled out from the abstract only, the publication was retained for full-text evaluation. All abstracts that were selected by each reviewer were jointly discussed to reach consensus about inclusion or exclusion.

Third, two authors (GS and PA) applied the same criteria as above to perform the full-text screening. Publications from predatory journals defined in accordance with Beall's list (https://beallslist.net/standalone-journals/) were excluded. To validate exclusion/inclusion based on the Beall's list, we also used the item checklist suggested in the Think-Check tool (https://thinkchecksubmit.org/check/). At this stage of the screening process, the reviewers also devoted attention to the level of care involved in the studies being examined and only those conducted in primary care were selected. In case of uncertainties regarding the level of care, or if multiple tiers of the health system were evaluated, the study authors were contacted for clarifications and/or to request additional information including disaggregated data where available.

The overall percent agreement between reviewers regarding allocation of full-text publications to one of three categories ("included", "excluded", "authors to be contacted") was 69.5%. The Randolph's free-marginal kappa statistic was 54%, suggesting an intermediate to good interrater agreement.

Any discrepancies were discussed until consensus was reached. A senior authors (SG) was consulted to finalize the decisions on inclusion and exclusion of individual studies into final analyses.

Data extracted from each study included in final synthesis:

1. Bibliographic information
2. Study information:
    - Study design;
    - Study period;
    - Study site: geographic region as per WHO classification, country, income level as per World Bank classification, healthcare sector, type of health facility and providers, facility location (urban or rural area);
    - Sampling strategy;

- Source of data (e.g. medical records, drug prescription audits, patient exit interviews, provider questionnaires, direct observation, other);
- Methods used to assess the appropriateness of antibiotic prescriptions (if any).

3. Population details:
    - Age and sex demographics;
    - HIV status;
    - Reason for seeking care;
4. Antibiotic prescription information:
    - Number of patients evaluated;
    - Number of patients receiving a drug prescription;
    - If available, overall as well as by healthcare sector (public/private), health facility location (urban/rural), age group (adults/children), sex (males/females) and clinical condition (acute respiratory illness, diarrhea/gastroenteritis, genitourinary syndrome, fever):
        i. Number of patients receiving one or more antibiotics;
        ii. Number of inappropriate antibiotic prescriptions;
        iii. Number of antibiotics prescriptions belonging to each of the three categories of the WHO AWaRe classification (https://adoptaware.org).

Chapter 3: Antibiotic overuse in the primary healthcare setting: a secondary data analysis of standardized patient studies from India, China and Kenya

3.1 Preface

My systematic review in Chapter 2 indicated that approximately 50% of patients seeking care in outpatient primary healthcare facilities across LMICs receive antibiotics. This proportion can be higher depending on presenting symptoms, patients' age and setting. However, very few studies made an attempt to evaluate the appropriateness of prescription and, when this was done, a range of limitations were observed both in terms of sample size and approach. The standardized patients (SP) methodology allows to overcome many of the issues that are typically encountered with conventional methods like prescription audits, medical records abstraction, patient exit interviews and clinical vignettes. Moreover, it is considered the gold standard to assess quality of care. SP studies have been conducted in various countries with the primary aim of determining whether patients with predefined (tracer) clinical conditions were correctly managed by a range of different healthcare providers. Information on drug prescribing and dispensing has been collected in these studies, although it has never been analyzed in depth.

In this manuscript, I report the results of a large secondary analysis of 9 SP studies carried out across a range of primary healthcare settings in India, China and Kenya and provide a more accurate estimate of the prevalence of antibiotic overuse for selected common clinical conditions. I also investigate on factors associated to this practice in India, using hierarchical Poisson models with a random intercept to account for between-study variance.

This work was published in September 2020 in *BMJ Global Health*.

3.2 Title Page

Antibiotic overuse in the primary healthcare setting: a secondary data analysis of standardized patient studies from India, China and Kenya

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** Contributed equally as senior authors*

3.3 Abstract

Introduction: Determining whether antibiotic prescriptions are inappropriate requires knowledge of patients' underlying conditions. In low and middle-income countries (LMICs), where misdiagnoses are frequent, this is challenging. Additionally, such details are often unavailable for prescription audits. Recent studies using standardized patients (SPs) offer a unique opportunity to generate unbiased prevalence estimates of antibiotic overuse, as the research design involves patients with predefined conditions.

Methods: Secondary analyses of data from nine SP studies were performed to estimate the proportion of SP-provider interactions resulting in inappropriate antibiotic prescribing across primary care settings in three LMICs (China, India, Kenya). In all studies, SPs portrayed conditions for which antibiotics are unnecessary (watery diarrhea, presumptive tuberculosis (TB), angina, asthma). We conducted descriptive analyses reporting overall prevalence of antibiotic overprescribing by healthcare sector, location, provider qualification and case. The WHO Access-Watch-Reserve (AWaRe) framework was used to categorize antibiotics based on their potential for selecting resistance. As richer data were available from India, we examined factors associated with antibiotic overuse in that country through hierarchical Poisson models.

Results: Across health facilities, antibiotics were given inappropriately in 2392/4798 (49.9%; 95% CI: 40.8-54.5) interactions in India, 83/166 (50.0%; 95% CI: 42.2-57.8) in Kenya, and 259/899 (28.8%; 95% CI: 17.8-50.8) in China. Prevalence ratios of antibiotic overuse in India were significantly lower in urban versus rural areas (adjusted prevalence ratio (aPR) 0.70; 95% CI: 0.52-0.96), and higher for qualified versus non-qualified providers (aPR 1.55; 95% CI: 1.42-1.70), and for presumptive TB cases versus other conditions (aPR 1.19; 95% CI: 1.07-1.33). Access antibiotics were predominantly used in Kenya (85%), but Watch antibiotics (mainly quinolones and cephalosporins) were highly prescribed in India (47.6%) and China (32.9%).

Conclusion: Good-quality SP data indicate alarmingly high levels of antibiotic over-prescription for key conditions across primary care settings in India, China and Kenya, with broad-spectrum agents being excessively used in India and China.

3.4 Key questions

What is already known?

- A recent systematic review and meta-analysis showed that, across 48 studies from 27 low- and middle-income countries including China, India, and Kenya, approximately half of all patients evaluated in outpatient primary care received an antibiotic prescription.
- Methods used to assess inappropriateness of antibiotic prescription, such as prescription audits, medical records, and patient exit interviews, have multiple limitations.
- Standardized patients (SPs) offer a unique opportunity to explore prescribing practices and accurately estimate over-prescription because case presentations are fixed by design, thus allowing comparisons across settings and providers.

What are the new findings?

- In this secondary analysis of data from nine SP studies carried out in India, Kenya and China, we provide a more unbiased prevalence estimate of antibiotic over-prescription for selected clinical conditions (asthma, angina, watery diarrhea, presumptive or confirmed tuberculosis (TB)) across a range of primary healthcare providers.
- About 30% of SP-provider interactions in China and 50% of those performed in India and Kenya resulted in inappropriate antibiotic prescription.
- Watch-antibiotics (i.e. broad-spectrum agents with higher potential for selecting resistance) were very commonly prescribed in India (about 50%) and China (over 32%), and some patients (0.8%) even received last-resort antibiotics belonging to the "Reserve" group.
- In India, the average prevalence of antibiotic prescribing was 30% lower in urban versus rural areas, 55% higher among qualified providers compared to non-qualified ones, and 19% higher for patients presenting with presumptive TB versus other conditions.

What do the new findings imply?

- Our findings indicate alarming levels of antibiotic over-prescription for conditions that are frequently encountered in primary care, potentially leading to toxic effects and diagnostic delays.
- The choice of antibiotics given to patients is concerning, as several agents with high potential for resistance selection are often inappropriately prescribed.
- The SP methodology could prove useful to further investigate antibiotic prescribing practices and its underlying determinants, using other case presentations across a range of different contexts.

3.5 Introduction

Antibiotic stewardship is critical for tackling antimicrobial resistance (AMR), especially in the context of the ongoing COVID-19 pandemic.[1] In a recent systematic review on antibiotic prescription practices in primary care settings across low-income and middle-income countries (LMICs), we showed that approximately 50% of patients of any age seeking care for any reason received at least one antibiotic.[2]

However, determining inappropriate prescription in LMICs is a challenge, and a standardized tool for its assessment is currently unavailable. Inappropriate antibiotic prescribing can derive from a range of failings: 1) prescription in the absence of clinical indication (i.e. "over-prescription"), which not only produces zero benefit to the patient but can also be harmful (e.g. drug toxicities or costs for patients); 2) failure to prescribe antibiotics when necessary (i.e. "under-prescription"); 3) suboptimal antibiotic choice with respect to etiology (confirmed or presumptive), site, severity of infection, and patient characteristics (e.g. age, comorbidities, pregnancy status, etc.); 4) prescription of wrong dosage and/or duration of antibiotic treatment as compared with national and international guidelines.[3,4]

Methods used to assess inappropriateness, such as prescription audits, medical records, and patient exit interviews, have multiple limitations.[3,5] Electronic records are seldom available in LMICs, particularly in primary care, thus making accurate prescription audit tools difficult to implement. Also, the paucity and variation of clinical details that can be captured through medical records (paper-based or not), if they even exist, makes it even harder to determine the appropriateness of prescription.[3] Patient exit interviews are commonly used alternatives but come with several major drawbacks that can result in poor and inaccurate estimates that are incomparable. Data collected in this manner are subject to recall bias, poor recall and limited clinical expertise among patients. Further, not only are clinical presentations highly heterogeneous but also the difficulty in actually determining what patients have makes comparisons very challenging for research.

A less biased method is the use of standardized patients (SPs), also known as "simulated" or "mystery" patients, that is, healthy individuals recruited from local communities and extensively trained to portray a standardized clinical condition to a healthcare provider.[5] Since their clinical presentations are fixed by design, SPs offer an important opportunity to overcome the methodological limitations typical of other studies, thus making the assessment of inappropriateness of antibiotic use less biased and more accurate.[5] Because the underlying illness is pre-specified, the SP methodology allows to accurately assess if an antibiotic is inappropriately prescribed. The SP approach is not affected by poor recall, recall bias, or the Hawthorne effect, that are commonly observed in patient exit interviews and direct observations of patient-provider encounters.[5]

Considering the aforementioned advantages, we performed a secondary analysis of prescription data from previously conducted SP studies in three LMICs (India, China, and Kenya) with two objectives: i) to estimate the overall proportion of SP-provider interactions (separately for pharmacy-based and health facility-based studies) that resulted in prescription or dispensing of at least one antibiotic in the absence of clinical indication (i.e. over-prescription), and ii) to identify factors associated with antibiotic overprescribing in health facilities.

3.6 Methods

Study design and data sources

Data on SP-provider interactions (i.e. completed SP visits with a provider at a health facility or a pharmacy) from studies conducted by members of our team (India, Kenya) or had used SP cases developed by our team or obtained from publicly accessible sources (China) were gathered to compile a pooled dataset for secondary analyses.[6-15] The methods used are described in our published manual and toolkit on how to conduct SP studies.[5]

Among studies carried out in India, four involved primary health facilities across five sites (Delhi, Mumbai, Patna, three districts in the State of Madhya Pradesh, and Birbhum

district in the State of West Bengal),[6-9] while two were performed in pharmacies located in four different areas (Mumbai, Patna, Delhi, and Udupi district of Karnataka).[10,11] We also examined data from a pilot study carried out in Nairobi (Kenya) and two studies completed in rural areas of China (Shaanxi, Sichuan, and Anhui provinces), all involving only primary healthcare providers.[12-15]

Information regarding medications prescribed by healthcare providers were reported in these published SP studies but were not analysed in depth, especially with regards to inappropriate use. This is because, in most instances, the primary publications focused on overall quality of care, rather than the specific components of care.

Provider selection in original studies

Sampling approaches adopted in each primary study from which our data were drawn are summarized in Table 3-1. For the two pharmacy-based studies, a random sample of pharmacies was selected from a comprehensive list of all those eligible obtained from relevant authorities.[10,11] In six of the other eight studies, healthcare providers were randomly sampled after performing a census or street-by-street mapping in the study areas.[7-9, 13-15] A convenience sample of practitioners was selected in two pilot studies respectively performed in Delhi and Nairobi.[6, 12] A waiver of provider consent was obtained in four out of nine studies, all carried out in India, two of which involved pharmacies.[7, 9-11] In all the others, verbal or written informed consent was sought at least six weeks prior to the commencement of SP-provider interactions in order to reduce the risk of SP detection. Yet, participation rates were very high (85-100%) among eligible health practitioners, and non-participation was usually due to logistical issues on the day of the visits rather than active refusal to be involved in the project. Hence, it is reasonable to expect negligible differences between participants and non-participants, making non-response bias a minor concern. In all studies, SPs were randomly assigned to providers, and completion rates of SP-provider interactions were always very high.

Table 3-1 Main features of SP studies included in our analysis

Study site (year)	SP-provider interactions	Tracer conditions	Healthcare sector	Facility location	Provider selection approach	Provider consent	Provider participation*
China (2013)	600	Angina, Child diarrhea	public	rural	Census of all clinics designated under the New Cooperative Medical Scheme (i.e. the major public health insurance program in rural areas), followed by random selection of providers.	Yes	100%
China (2015)	299	Presumptive TB	public	rural	Census of all public providers followed by random sampling from 1 prefecture in each of 3 provinces out of a total of 47 prefectures, chosen to be representative of rural health systems.	Yes	274/274 (100%)
Kenya (2014)	166	Angina, Asthma, Child diarrhea, Presumptive TB	public & private	urban	Non-random convenience sample designed to include low-income, middle-income and high-income neighbourhoods in various Nairobi areas.	Yes	46/49 (93·9%)
Madhya Pradesh – India (2010-2011)	1,123	Angina, Asthma, Child diarrhea	public & private	rural	Census of all medical care providers working in 60 villages randomly sampled in 3 districts in Madhya Pradesh. All public providers and qualified private providers were automatically sampled. For each public provider, the closest private practitioner was also sampled.	No	Not applicable
Delhi – India (2014)	250	Presumptive and confirmed TB, Presumptive MDR-TB	private	urban	Convenience sample (pilot study).	Yes	Not available
Mumbai & Patna – India (2014-2015)	2,602	Presumptive and confirmed TB, Presumptive MDR-TB	private	urban	Street-by-street mapping of private providers who were known to see adult outpatients with respiratory symptoms, followed by random sampling stratified by provider qualification and PPIA (Private Provider Interface Agency) registration status.	No	Not applicable

Study site (year)	SP-provider interactions	Tracer conditions	Healthcare sector	Facility location	Provider selection approach	Provider consent	Provider participation*
Birbhum district, West Bengal – India (2012-2014)	823	Angina, Respiratory distress, Child diarrhea	private	rural	Census of private health providers who had been practicing for at least 3 years in 203 villages across Birbhum district.	Yes	304/360 (84·4%)
Mumbai, Patna & Delhi – India (2014-2015)	1,200	Presumptive TB, Confirmed TB	pharmacies	urban	Convenience sample of 54 pharmacies from 28 low-income localities in Delhi (pilot phase). Random sampling of pharmacies in Mumbai and Patna from a list of all pharmacies registered in the two cities.	No	Not applicable
Udupi district, Karnataka – India (2018)	1,522	For both adults and children: Upper resp tract infection, Diarrhea, Presumptive malaria	pharmacies	urban & rural	Of the 350 pharmacies registered in the district as per the local pharmacy association, 279 were considered eligible for the study after excluding those operating inside hospitals (47), those permanently closed or under renovations (10), those that could not be identified by the field team (4), those for veterinarian purposes only (1), and those used for SP training (10).	No	Not applicable

* For studies in which provider consent was not required.

Tracer conditions

Tracer conditions (i.e. SP case presentations) were defined similarly across SP studies, thus allowing comparisons across settings. Cases ranged from presumptive or confirmed tuberculosis (TB) (which requires specific anti-TB treatment as per WHO recommendations) to self-limiting infections, such as watery diarrhea or upper respiratory tract illness (which only need support treatment, e.g. rehydration therapy for diarrhea), to non-communicable diseases like asthma or chest pain indicative of angina (these should be referred to a higher level of care). Importantly, none of such conditions requires antibiotics, which means that any antibiotic prescribed to SPs is deemed inappropriate by indication (i.e. over-prescription).

Outcome assessment

Raw data from original studies were harmonized and recoded as needed. We used the available information on medications that were prescribed or dispensed during each SP-provider interaction to categorise individual drugs. Antibacterial agents were further classified using both the ATC (Anatomical – Therapeutic – Chemical) Index and the WHO Access-Watch-Reserve (AWaRe) framework.[16,17] Fixed-dose combinations (FDCs) of antibiotics (e.g. ciprofloxacin/ornidazole) were classified as "discouraged" antibiotics as per WHO recommendations.

The primary outcome measure was expressed as the proportion of SP-provider interactions that resulted in antibiotic prescription or dispensing. Secondary outcomes were proportions of specific groups of antibiotics that were prescribed or dispensed both overall and across strata of key variables of interest. These proportions provide a direct measure of antibiotic overuse.

Statistical analyses

For studies carried out in health facilities, we conducted country-level descriptive analyses and reported the crude proportion of SP-provider interactions that resulted in antibiotic prescription or dispensing. The overall proportion of prescribed or dispensed antibiotics along with ATC-class and AWaRe group-specific proportions were calculated across strata defined by key variables of interest such as healthcare sector (public/private), facility location (urban/rural), provider qualification (qualified/non-qualified, defined based on whether they had at least a bachelor's degree in medicine), and tracer conditions. For all prevalence proportions we computed 95% CIs using bootstrapping in order to account for clustering at the study level.[18]

In order to examine the factors associated with antibiotic prescribing in health facilities in India, we fit a hierarchical Poisson regression model that allows to directly estimate adjusted prevalence ratios (aPRs) even if the outcome is common as in this case. Our model included a random intercept for studies and dummy variables for facility location,

healthcare sector, provider qualification, and tracer conditions as predictors.[19] As we anticipated a fair amount of between-study heterogeneity, we decided to opt for a mixed model that could better account for it as compared with including the study or study site as a covariate. Among tracer conditions, only angina, asthma and presumptive TB could be included in order to avoid sparse data problems (i.e. violations of the positivity assumption). The effect of all predictors was expected to be similar across studies, and therefore only fixed slopes were considered. These analyses were restricted to India because we had diverse and more data. We also considered alternative models and examined the pros and cons of each. A full description of our analyses is provided in S3-1 File.

Data from pharmacies were not pooled because contexts and tracer conditions were highly heterogeneous in the two available studies. Therefore, we only calculated prevalence proportions and 95% CIs of dispensed antibiotics, both overall and in stratified analyses.

All analyses were performed using Stata 16.

Patient and Public involvement

It was not possible to involve patients or the public in design, or conduct, or reporting, or dissemination plans of our research because this is a secondary analysis of previously conducted studies.

3.7 Results

The main features of SP studies that were included in our analyses are summarized in Table 3-1. A total of 4,798 SP-provider interactions were completed in health facilities across urban and rural India, predominantly in the private sector. Both private and public healthcare providers were involved in the pilot study carried out in Nairobi (166 interactions), whereas studies from rural China only targeted the public sector (899

interactions). For these health facility-based studies, we first present summary statistics and then report results from our models.

Antibiotic overuse across settings

In India, 2,392 of 4,798 (49.9%; 95% CI: 40.8–54.5) SP-provider interactions resulted in at least one antibiotic prescription (Table 3-2). Similar proportions were observed in Nairobi (83 of 166; 50.0% [95% CI: 42.2–57.8]), while a lower percentage was found in the China studies (259 of 899; 28.8% [95% CI: 17.8–50.8]). However, in the latter case, the confidence interval was substantially wide, reflecting the considerable between-study variance due to differences in tracer conditions evaluated.

In most instances, only one antibiotic was given during an individual SP-provider interaction; less than 5% of interactions across all settings resulted in two or more antibiotics prescriptions. Crude analyses of data from India indicate that antibiotic over-prescription was more common among healthcare providers in urban areas, among those working in the private sector and among qualified professionals. Furthermore, antibiotics were largely overprescribed to patients presenting with a diverse range of clinical conditions in all countries (Figure 3-1). In India, the percentage of subjects receiving antibiotics was close to 50% for most case types, with a peak of 59.4% (95% CI: 50.5-75.0) among child diarrhea cases. However, for angina cases it was 19.2% (95% CI: 16.8–21.1). About half of the visits for presumptive TB in China received antibiotics inappropriately, as opposed to 9.2% (95% CI: 5.9–12.4) of visits for suspicious angina and 27.4% (95% CI: 21.8–32.5) for child diarrhea. Case-specific estimates from Nairobi are highly imprecise due to the small sample size.

Table 3-2 Number, proportion and bootstrapped 95% CIs (based on study-level clusters) of SP-provider interactions in health facilities that resulted in prescription or dispensing of antibiotics across strata of key variables.

Variable	Country							
	All		India		China		Kenya	
	n/N	Proportion (95% CI)	n/N	Proportion (95% CI)	n/N	Proportion (95% CI)	n/N	Proportion (95% CI)
At least one antibiotic	2734/5863	46.6 (33.4; 53.9)	2392/4798	49.9 (40.8; 54.5)	259/899	28.8 (17.8; 50.8)	83/166	50.0 (42.2; 57.8)
No. antibiotics								
0	3129/5863	53.4 (46.1; 66.6)	2406/4798	50.1 (45.4; 57.9)	640/899	71.2 (49.2; 71.2)	83/166	50.0 (42.2; 57.8)
1	2,465/5863	42.0 (31.4; 47.4)	2159/4798	45.0 (39.8; 48.2)	229/899	25.5 (25.5; 42.8)	77/166	46.4 (39.2; 54.2)
2	260/5863	4.4 (1.6; 6.5)	225/4798	4.7 (1.4; 6.6)	29/899	3.2 (3.2; 7.7)	6/166	3.6 (1.2; 6.6)
3	9/5863	0.2 (0.02; 0.3)	8/4798	0.2 (0.03; 0.3)	1/899	0.1 (0.1; 0.3)	0/166	0
Health facility location								
Urban	1653/3018	54.8 (50.0; 55.2)	1570/2852	55.0 (53.0; 55.2)	-	-	83/166	50.0 (42.8; 57.8)
Rural	1081/2845	38.0 (26.6; 48.1)	822/1946	42.2 (39.0; 46.7)	259/899	28.8 (17.8; 50.8)	-	-
Healthcare sector								
Public	443/1321	33.5 (20.6; 50.8)	156/367	42.5 (37.6; 47.7)	259/899	28.8 (17.8; 50.8)	28/55	50.9 (38.2; 63.6)
Private	2291/4542	50.4 (40.8; 54.5)	2236/4431	50.5 (50.2; 54.5)	-	-	55/111	49.5 (40.1; 51.6)
Provider qualification								
Qualified	1186/1906	62.2 (45.4; 71.3)	1115/1768	63.1 (44.6; 71.8)	71/138	51.4 (42.8; 59.4)	NA	NA
Non-qualified	1358/3191	42.6 (38.7; 48.6)	1277/3030	42.1 (37.8; 47.9)	81/161	50.3 (42.9; 57.8)	NA	NA
Clinical presentation								
Angina	169/955	17.7 (12.2; 28.3)	115/598	19.2 (16.8; 21.1)	29/315	9.2 (5.9; 12.4)	25/42	59.5 (45.2; 73.8)
Asthma	330/718	46.0 (44.0; 50.2)	308/676	45.6 (43.5; 49.0)	-	-	22/42	52.4 (38.1; 66.7)
Child diarrhea	490/997	49.1 (33.4; 67.9)	399/672	59.4 (50.5; 75.0)	78/285	27.4 (21.8; 32.5)	13/40	32.5 (17.5; 45.5)
Presumptive TB	1293/2253	57.4 (51.3; 58.6)	1118/1912	58.5 (58.4; 59.3)	152/299	50.8 (44.8; 56.2)	23/42	54.8 (39.3; 69.0)
Confirmed TB	194/404	48.0 (47.7; 50.0)	194/404	48.0 (47.7; 50.0)	-	-	-	-
Presumptive MDR-TB	258/536	48.1 (48.0; 48.1)	258/536	48.1 (48.0; 48.1)	-	-	-	-
Patient referred for further evaluation*								
Yes	101/767	13.2 (9.4; 20.4)	65/498	13.1 (9.7; 17.4)	33/263	12.5 (7.3; 31.6)	3/6	50.0 (16.7; 83.3)
No	2163/4384	50.7 (35.6; 57.5)	1928/3628	53.1 (38.4; 58.0)	226/636	35.5 (23.3; 55.4)	67/120	55.8 (47.5; 64.2)

* All child diarrhea cases from India and Kenya (n = 712) were excluded from this analysis because children were not directly assessed by the provider.

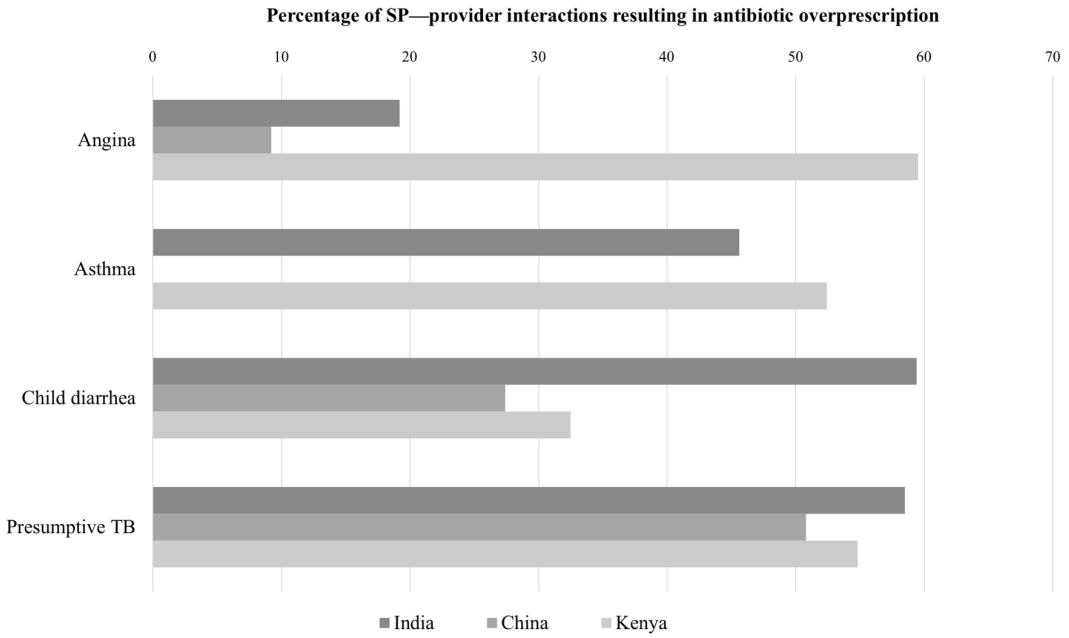

Figure 3-1 Crude percentage of SP-provider interactions resulting in antibiotic prescription/dispensing, by country and selected conditions (pharmacy-based studies are not included).

Type of antibiotics used

Across studies performed in India, 2,768 antibiotics were given to 2,392 patients. The top ten most prescribed antibiotics across SP-provider interactions in India were: azithromycin (381; 13.8%), amoxicillin+beta-lactamase inhibitor (344; 12.4%), amoxicillin (264; 9.5%), levofloxacin (202; 7.3%), cefixime (198; 7.2%), ofloxacin (165; 6.0%), ofloxacin+ornidazole (150; 5.4%), norfloxacin+tinidazole (136; 4·9%), ciprofloxacin (102; 3.7%), and cefpodoxime (88; 3.2%). Broad-spectrum agents with higher potential for selecting resistance (Watch antibiotics) were disproportionately represented (47.6%; 95% CI: 26.8–54.0), and even more so in urban areas (54.9%; 95% CI: 54.9–55.4) (Table 3-3). This reflects the heavy use of quinolones, cephalosporins and macrolides that respectively accounted for 18.8% (95% CI: 16.6–24.2), 13.0% (95% CI: 8.2–14.6), and 15.4% (95% CI: 4.1–19.3) of all antibiotics prescribed in India.

Table 3-3 Frequency of antibiotics prescribed/dispensed in health facilities across study countries, overall and according to both the AWaRe (Access – Watch – Reserve) and ATC (Anatomical – Therapeutic – Chemical) classifications.

Drug type	INDIA						CHINA	
	All settings		Urban India		Rural India			
	N	Proportion (95% CI)	N	Proportion (95% CI)	N	Proportion (95% CI)	N	Proportion (95% CI)
Any antibiotic	2,768	-	1,896	-	872	-	301	-
AWaRe Classification								
Access	876	31.6 (30.0; 38.9)	584	30.8 (29.8; 30.8)	292	33.5 (29.9; 37.1)	126	41.9 (36.2; 47.2)
Watch	1,317	47.6 (26.8; 54.0)	1,041	54.9 (54.9; 55.4)	276	31.7 (21.2; 40.3)	99	32.9 (27.6; 37.9)
Reserve	23	0.8 (0.5; 1.8)	8	0.4 (0.4; 0.5)	15	1.7 (1.0; 2.1)	1	0.3 (0.3; 1.3)
Discouraged	334	12.1 (4.3; 36.3)	50	2.6 (2.6; 2.8)	284	32.6 (25.1; 44.8)	1	0.3 (0.3; 1.3)
Not available*	218	7.9 (5.4; 10.8)	213	11.2 (11.2; 11.5)	5	0.57 (0.3; 1.0)	74	24.6 (19.9; 29.2)
ATC Classification								
Penicillin	711	25.7 (18.8; 27.0)	535	28.2 (27.7; 28.2)	176	20.2 (17.6; 21.7)	68	22.6 (17.6; 27.2)
Cephalosporin	361	13.0 (8.2; 14.6)	294	15.0 (14.9; 15.0)	76	8.7 (7.8; 10.7)	75	24.9 (20.9; 29.2)
First generation	21	0.8 (0.6; 1.8)	9	0.5 (0.47; 0.51)	12	1.4 (1.1; 2.1)	0	0
Second generation	22	0.8 (0.2; 1.1)	20	1.1 (1.1; 1.2)	2	0.2 (0.2; 0.4)	7	2.3 (0.7; 4.0)
Third generation	318	11.5 (7.1; 12.9)	256	13.5 (13.3; 13.5)	62	7.1 (6.4; 8.1)	1	0.3 (0.3; 1.0)
Not available*	0	0	0	0	0	0	67	22.3 (18.3; 26.6)
Macrolide	425	15.4 (4.1; 19.3)	389	20.5 (20.4; 21.3)	36	4.1 (4.1; 4.3)	60	19.9 (15.6; 24.3)
Quinolone	520	18.8 (16.6; 24.2)	354	18.7 (18.5; 18.7)	166	19.0 (18.5; 26.8)	37	12.3 (9.0; 15.9)
Tetracycline	67	2.4 (1.7; 4.6)	34	1.8 (1.4; 1.8)	33	3.8 (3.0; 4.1)	0	0
Imidazole†	61	2.2 (0.8; 7.1)	1	0.05 (0.05; 0.06)	60	6.9 (6.3; 7.5)	1	0.3 (0.3; 1.3)
Sulfonamide§	18	0.7 (0.2; 1.9)	3	0.16 (0.16; 0.17)	15	1.7 (0.9; 2.1)	9	3.0 (1.3; 5.0)
Aminoglycoside	6	0.2 (0.1; 1.0)	0	0	6	0.7 (0.7; 1.3)	45	15.0 (11.3; 18.6)
Combinations#	289	12.1 (5.1; 34.2)	50	2.6 (2.6; 2.8)	284	32.6 (25.1; 34.2)	1	0.3 (0.3; 1.3)
Antimycobacterial	229	8.3 (0.3; 10.9)	226	11.9 (11.9; 12.2)	3	0.3 (0.2; 0.5)	1	0.3 (0.3; 1.3)
Other antibiotics	36	1.3 (1.0; 2.4)	19	1.0 (0.1; 1.0)	17	1.9 (1.8; 2.6)	4	1.3 (0.3; 2.7)

Note: The unit of analysis is the individual drug, NOT the SP-provider interaction.

* For these drugs, only the antibiotic class (e.g. cephalosporin) was available.

† Only metronidazole was prescribed/dispensed.

§ Only trimethoprim-sulfamethoxazole (TMP-SMX) was prescribed/dispensed.

This category does not include combinations of anti-mycobacterial drugs.

Nearly 80% of Watch-antibiotics were given to SPs portraying a TB case (1,086/1,362). Three different last-resort or 'Reserve' antibiotics (colistin, linezolid and faropenem) were prescribed in a total of 23 SP-provider interactions in India, mainly for child diarrhea (14/23).

"Discouraged" antibiotics, that is, FDCs other than anti-mycobacterial drugs (such as norfloxacin+tinidazole or ofloxacin+ornidazole) accounted for 12.1%, of which all but one were given for child diarrhea. Anti-TB medications represented 8.3% of antibiotics in India, almost all of them were given by healthcare providers in urban areas, and none could be considered appropriate based on the expected correct management of such cases.

About one-quarter of drugs prescribed in studies from China could not be categorized based on the AWaRe framework because only the drug class was reported. These were mainly cephalosporins, most likely second or higher generation, and therefore the overall proportion of Watch-group antibiotics is expected to be greater than 32.9% (Table 3-3). Undefined cephalosporins were by far the most prescribed antibiotics in China (76/301; 25.2%), followed by gentamicin (45/301; 15.0%), amoxicillin (37/301; 12.3%), erythromycin (26/301; 8.6%), and levofloxacin (18/301; 6.0%).

Subgroup analyses of antibiotic prescriptions patterns among SP-provider interactions that took place in Nairobi were limited by the small sample size. However, 85.4% (76/89) of all antibiotics prescribed were first-line and narrow-spectrum agents from the 'Access' group, while the remaining belonged to the 'Watch' group.

Factors associated with antibiotic overuse in India

Prevalence ratios of antibiotic overuse and their 95% CIs estimated through mixed-effects Poisson regression analysis are reported in Figure 3-2. The adjusted prevalence of antibiotic prescribing was lower in urban versus rural areas (aPR = 0.70; 95% CI: 0.52–0.96), for subjects presenting with suspicious angina (aPR = 0.33; 95% CI: 0.27–0.40), and asthma (aPR = 0.77; 95% CI: 0.66–0.89). Patients with presumptive TB were more likely to

receive inappropriate antibiotics (aPR = 1.19; 95% CI: 1.07–1.33) as compared to individuals with other clinical conditions. Qualified practitioners were more likely to prescribe antibiotics than non-qualified ones (aPR 1.55; 95% CI: 1.42–1.70).

The hierarchical Poisson model did not show any significant difference between public and private providers, but this is in contrast with what emerged from alternative models as described in S3-1 File.

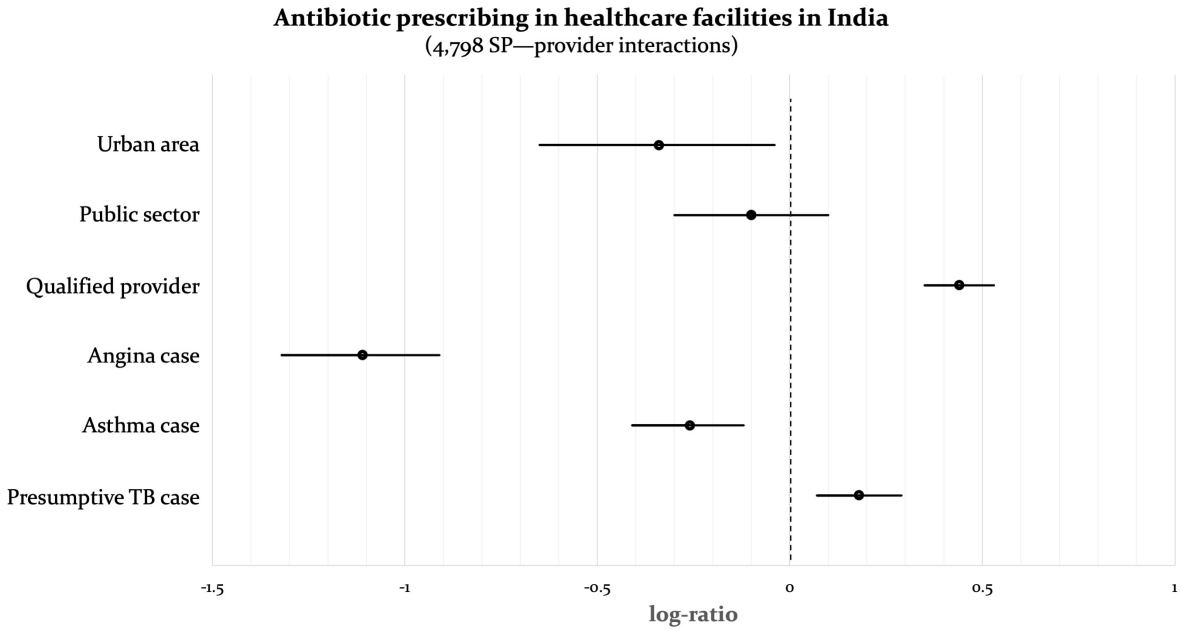

Figure 3-2 Factors associated with antibiotic prescribing/dispensing in health facilities in India. Covariate-adjusted prevalence ratios and their 95% CIs estimated from a hierarchical Poisson model are reported on the logarithmic scale.

Antibiotic dispensing in pharmacies

Our secondary analysis of data from two pharmacy-based SP studies showed that over-the-counter antibiotic dispensing is also a common problem in various parts of India (Table 3-4).

In Udupi district (Karnataka state) the proportion of SP-pharmacist interactions that resulted in antibiotic dispensing was 3.6% (95% CI: 2.6–4.6), with a similar pattern in both urban and rural areas. In contrast, at least one antibiotic was dispensed in 319/1,200

interactions performed across Delhi, Mumbai and Patna, corresponding to 26.6% (95% CI: 24.2–29.2) of the total. However, a direct comparison between these two studies is not possible owing to the very different contexts involved and particularly to the different types of cases that were examined. As observed in studies from healthcare facilities, subjects presenting to pharmacies with symptoms suggestive of TB were generally more likely to receive an antibiotic as compared to other conditions.

Table 3-4 Antibiotic dispensing in Indian pharmacies

Variable	Study setting			
	Udupi district, Karnataka (n = 1,522)		Mumbai, Delhi and Patna (n = 1,200)	
	n/N	Proportion (95% CI)	n/N	Proportion (95% CI)
Number of antibiotics				
1	55/1,522	3.6 (2.6; 4.6)	294/1,200	24.5 (22.2; 27.0)
2	0	0	25/1,200	2.1 (1.3; 2.9)
Pharmacy location				
Urban	25/744	3.3 (2.2; 4.7)	319/1,200	26.6 (24.2; 29.2)
Rural	30/778	3.9 (2.7; 5.2)	-	-
Clinical presentation				
Adult with URI	11/250	4.4 (2.0; 7.2)	-	-
Adult with diarrhea	12/259	4.6 (2.3; 7.1)	-	-
Adult with fever (malaria suspect)	10/252	4.0 (1.6, 6.3)	-	-
Child with URI	0/252	0	-	-
Child with diarrhea	20/250	8.0 (4.8; 11.2)	-	-
Child with fever (malaria suspect)	2/259	0.8 (0.4; 1.9)	-	-
Adult with presumptive TB	-	-	221/599	36.9 (33.1; 40.7)
Adult with confirmed TB	-	-	98/601	16.3 (13.5; 19.3)
Patient referred to health provider				
Yes	15/710	2.1 (1.1; 3.1)	41/497	8.2 (5.8; 10.9)
No	40/812	4.9 (3.6; 6.4)	278/703	39.5 (36.1; 43.2)

Abbreviations: TB = tuberculosis; URI = upper respiratory illness.

The average proportion of Watch-antibiotics (predominantly quinolones and cephalosporins) dispensed across the three cities was 49.4% (95% CI: 43.9–54.4), ranging from 24.0% (95% CI: 15.0–32.0) in Mumbai to 60.9% (95% CI: 55.1–67.1) in Patna. A deeper evaluation of antibiotic dispensing in Udupi district is limited by the small sample size. Only 55 antibiotics were dispensed across 1,522 interactions, thus making subgroup analyses less meaningful. Yet, it is worth highlighting that nearly half of these antibiotics were discouraged FDCs of two antibiotics, whereas the remaining were almost equally

distributed among Access- and Watch-groups. More details regarding the types of antibiotics dispensed across pharmacies in both studies are presented in S3-2 File.

3.8 Discussion

Our analysis of past SP studies involving 4,798 SP-provider interactions in India showed that healthcare providers in primary care settings prescribed antibiotics to about half (49.9%) of patients presenting with clinical conditions that do not require antibiotics. Antibiotic overprescribing was found to be similar (50% of SP-provider interactions) in a small SP study carried out in Nairobi, Kenya. Pooled data from two studies conducted in China showed lower levels of antibiotic overuse (28.8%), but it should be noted that percentages differed substantially across individual studies, likely reflecting the different type of cases being involved. In fact, SP-provider interactions involving presumptive TB cases were more likely to result in antibiotic prescription as compared to other clinical conditions. Among the two pharmacy-based SP studies done in India,[10,11] the proportion of antibiotic dispensing was 26.6% and 3.6%, respectively.

Although our focus was on LMICs, the overuse of antibiotics is not confined to LMICs. Large population-based cohort data have shown that antibiotic overuse in ambulatory settings across the United States was 30% among children and 17% among adults with certain respiratory tract illnesses for which antibiotics are not indicated (e.g. asthma, allergies, acute bronchitis or bronchiolitis, etc.).[20] An analysis of antibiotic prescription practices based on administrative data from Ontario, Canada, recently reported an overall rate of unnecessary antibiotic prescribing in primary care of 15.4%, though much higher percentages were observed for some respiratory conditions such as acute bronchitis (52.6%).[21] However, a direct comparison with higher income countries cannot be done due to differences in study methodologies and local epidemiology.

Nearly 50% of all antibiotics prescribed in the context of India SP studies belonged to the 'Watch' list, with a peak of 80% among patients presenting with symptoms suggestive of TB, which is consistent with national antibiotic sales.[22] Watch-antibiotics accounted for

almost 33% of all antibiotics across China SP studies, but this is likely underestimated because nearly one quarter of all antibiotics could not be classified due to insufficient information. Of note, we observed a large use of cephalosporins (presumably second or third generation ones), which is in line with previous findings from drug sales analyses and prescription audits conducted in various parts of China.[2,23,24] In contrast, the small SP study conducted in Nairobi revealed that over 85% of prescribed antibiotics were from the 'Access' group, and half of these were either trimethoprim/sulfamethoxazole or amoxicillin. This is in line with what observed in another SP study carried out in urban public primary healthcare facilities in South Africa, where 10/119 (8.4%) interactions for presumptive TB resulted in antibiotic prescriptions, all of which belonged to the "Access" group.[25] As with the Nairobi study, however, the small sample size does not allow to draw meaningful conclusions on antibiotic prescribing patterns in the area.

Discouraged FDCs of antibiotics were commonly given in India but not in other settings, accounting for 10.4% of the total. FDCs were finally banned in India in September 2018, thus leaving hope for a change in the near future.

Alarmingly, we observed the use of some 'Reserve' antibiotics in primary care settings. In India, oral colistin was prescribed for pediatric diarrhea, and faropenem was given to one patient with presumptive TB. This is very concerning as parenteral colistin is the last resort drug for treatment of extremely drug-resistant Gram-negative infections,[26] and using the oral formulation could drive resistance in the community. Similarly, faropenem is an oral penem antibiotic which has been shown to cause cross-resistance to intravenous carbapenems.[27] In China SP studies, one presumptive TB case received aztreonam, indicated for treatment of serious infections due to drug-resistant Gram-negative bacteria.

According to our findings from India, antibiotic overuse was particularly common in rural areas, among qualified providers and for patients presenting with presumptive TB. Besides leading to potentially dangerous diagnostic delays,[28,29] the unnecessary use of

antibiotics causes harms to the patient in terms of drug-associated adverse events and increased out-of-pocket costs.

While normative boundaries may partly explain why qualified providers prescribed more antibiotics than non-qualified ones as observed in our analyses for India, the widespread overuse of antibiotics suggests that important training gaps likely exist. However, prescribing behaviours among healthcare providers also depend on a number of other factors, including financial incentives from pharmaceutical companies, patient expectations and requests, or just old habits that are hard to die.[8,30,31]

The biggest strength of our study lies in the nature and quality of the data used to investigate the extent and patterns of antibiotic overprescribing. Although previous research had already highlighted that Watch-group antibiotics are highly prescribed across India and China, such studies could not provide a clear picture of inappropriate antibiotic use owing to the limited amount of clinical information available from prescription audits and evaluations of drug sales data.[32-34] Among the main advantages of using SPs to evaluate prescription practices is the fact that tracer conditions are standardized.[5] In all studies included in our analyses, such conditions were very common illnesses that are frequently encountered in primary care and that require a well-defined diagnostic and therapeutic management that does not involve antibiotic use.

Furthermore, representative samples of healthcare providers from public and/or private sectors were selected in all SP studies conducted in India, with the only exception of one relatively small pilot study in Delhi. In this pooled dataset, private practitioners were much more represented than public providers, but we lacked statistical power to make appropriate comparisons between the two groups. Yet, this distribution well reflects the fact that about 75% of outpatient visits in India take place in the private sector, with nearly 70% of primary care in the country being delivered by informal providers.[35,36]

Of note, available data originated from a range of geographical areas with different socio-cultural and economic profiles and could be generalizable to similar contexts in India. For all these reasons, the representativeness of our findings is very good, and selection bias is

likely negligible due to the robust mapping and sampling approach used across all SP studies.

There are limitations in our study. First, the SP study data from China and Kenya were limited and lacked generalizability. Second, our analyses were restricted to over-prescription and to a limited number of clinical scenarios. Third, we could not investigate other important forms of inappropriate antibiotic use, such as the choice of the incorrect drug and dosage to treat a given infection. This is an intrinsic limitation that arises from the type of tracer conditions used across SP studies so far. Although the SP methodology was initially implemented to assess overall quality of care in LMICs and to evaluate educational/behavioural programs in high-income countries, this approach is being increasingly adopted to gain insight into medication use, and especially drug dispensing practices among pharmacists. Data recording systems in SP studies are therefore improving in order to facilitate the collection of key details regarding medications that were harder to capture from studies whose main objective was not related to drug use.

In conclusion, the prevalence of antibiotic overprescribing estimated from SP studies ranged from 29% in China to 50% in India and Kenya, and 'Watch' antibiotics accounted for a large proportion of antibiotics prescribed in both India and China. Combining the SP methodology with new tracer conditions would allow overcoming many of the typical limitations of most studies aimed at evaluating inappropriate antibiotic use in greater detail. SPs represent a unique opportunity to further explore prescription practices among healthcare providers, including the management of common infectious diseases such as pneumonia or urinary tract infections that contribute substantially to the overall antibiotic use in primary care. Future studies also need to focus on untangling the channels for antibiotic over-prescription and better understand the determinants of such practice among public and private healthcare providers in various contexts.

The extent of antibiotic overuse in primary care across LMICs is a serious concern and requires targeted antimicrobial stewardship interventions aimed at improving rational and locally adapted prescribing practices. An active involvement of private providers in

all such interventions would be essential to ensure uptake, particularly in countries where the private sector plays a major role in healthcare. Greater efforts are also necessary to develop and scale up accurate point-of-care tests that could guide therapeutic choices where resources are scarce. Additional research is also required to evaluate whether antibiotic use (especially use of drugs such as azithromycin and hydroxychloroquine) will dramatically increase as a consequence of the COVID-19 pandemic, and concerns have already been raised about the implications for AMR.[37]

Competing interests

M. Pai is on the editorial boards of BMJ Global Health. All other authors declare that they have no conflicts of interest.

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Ethics approval

Each study had been conducted after ethics approval. Our study was approved by the McGill Faculty of Medicine Institutional Review Board (IRB review number: A04-B19-20B (20-04-053)), and all primary studies we included had their own independent ethics approvals.

3.9 References

1. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. Epub 2020/04/30. doi: 10.1016/j.cmi.2020.04.024.
2. Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med. 2020;17(6):e1003139. doi: 10.1371/journal.pmed.1003139.
3. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis. 2016;63(12):1639-44. Epub 2016/09/30. doi: 10.1093/cid/ciw658.
4. Smieszek T, Pouwels KB, Dolk FCK, Smith DRM, Hopkins S, Sharland M, et al. Potential for reducing inappropriate antibiotic prescribing in English primary care. The Journal of antimicrobial chemotherapy. 2018;73(Suppl. 2):ii36-ii43. doi: http://dx.doi.org/10.1093/jac/dkx500.
5. Kwan A, Bergkvist S, Daniels B, Das J, Das V, Pai M. Using standardized patients to measure health care quality: a manual and toolkit for projects in low- and middle-income countries. 2019.
6. Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. Lancet Infect Dis. 2015;15(11):1305-13. Epub 2015/08/14. doi: 10.1016/S1473-3099(15)00077-8.
7. Kwan A, Daniels B, Saria V, Satyanarayana S, Subbaraman R, McDowell A, et al. Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. PLoS Med. 2018;15(9):e1002653. Epub 2018/09/27. doi: 10.1371/journal.pmed.1002653.
8. Das J, Chowdhury A, Hussam R, Banerjee AV. The impact of training informal health care providers in India: A randomized controlled trial. Science (New York, NY). 2016;354(6308). Epub 2016/11/16. doi: 10.1126/science.aaf7384.

9. Das J, Holla A, Das V, Mohanan M, Tabak D, Chan B. In urban and rural India, a standardized patient study showed low levels of provider training and huge quality gaps. Health Aff (Millwood). 2012;31(12):2774-84. Epub 2012/12/06. doi: 10.1377/hlthaff.2011.1356.
10. Satyanarayana S, Kwan A, Daniels B, Subbaraman R, McDowell A, Bergkvist S, et al. Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. Lancet Infect Dis. 2016;16(11):1261-8. Epub 2016/10/30. doi: 10.1016/S1473-3099(16)30215-8.
11. Nafade V, Huddart S, Sulis G, Daftary A, Miraj SS, Saravu K, et al. Over-the-counter antibiotic dispensing by pharmacies: a standardised patient study in Udupi district, India. BMJ Glob Health. 2019;4(6):e001869. Epub 2019/12/05. doi: 10.1136/bmjgh-2019-001869.
12. Daniels B, Dolinger A, Bedoya G, Rogo K, Goicoechea A, Coarasa J, et al. Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. BMJ Glob Health. 2017;2(2):e000333. Epub 2017/12/12. doi: 10.1136/bmjgh-2017-000333. P
13. Sylvia S, Shi Y, Xue H, Tian X, Wang H, Liu Q, et al. Survey using incognito standardized patients shows poor quality care in China's rural clinics. Health policy and planning. 2015;30(3):322-33. Epub 2014/03/22. doi: 10.1093/heapol/czu014.
14. Sylvia S, Xue H, Zhou C, Shi Y, Yi H, Zhou H, et al. Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. PLoS Med. 2017;14(10):e1002405. Epub 2017/10/19. doi: 10.1371/journal.pmed.1002405.
15. Xue H, Shi Y, Huang L, Yi H, Zhou H, Zhou C, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. The Journal of antimicrobial chemotherapy. 2019;74(1):256-63. Epub 2018/10/05. doi: 10.1093/jac/dky390. P
16. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential

Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278-80. Epub 2019/11/30. doi: 10.1016/S1473-3099(19)30532-8.

17. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system 2020. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2020.
18. DiCiccio TJ, Efron B. Bootstrap Confidence intervals. Stat Sci. 1996;11(3):189-228.
19. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PloS one. 2012;7(10):e46042. Epub 2012/10/03. doi: 10.1371/journal.pone.0046042.
20. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr., et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA, Journal of the American Medical Association. 2016;315(17):1864-73. doi: 10.1001/jama.2016.4151.
21. Schwartz KL, Langford BJ, Daneman N, Chen B, Brown KA, McIsaac W, et al. Unnecessary antibiotic prescribing in a Canadian primary care setting: a descriptive analysis using routinely collected electronic medical record data. CMAJ Open. 2020;8(2):E360-E9. Epub 2020/05/07. doi: 10.9778/cmajo.20190175.
22. Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO Antibiotic Consumption and Access Targets: 2000-2015. Lancet Infectious Diseases. 2020; in press.
23. Wushouer H, Tian Y, Guan XD, Han S, Shi LW. Trends and patterns of antibiotic consumption in China's tertiary hospitals: Based on a 5 year surveillance with sales records, 2011-2015. PloS one. 2017;12(12):e0190314. Epub 2017/12/27. doi: 10.1371/journal.pone.0190314.
24. Lin H, Dyar OJ, Rosales-Klintz S, Zhang J, Tomson G, Hao M, et al. Trends and patterns of antibiotic consumption in Shanghai municipality, China: a 6 year surveillance with sales records, 2009-14. The Journal of antimicrobial chemotherapy. 2016;71(6):1723-9. Epub 2016/02/17. doi: 10.1093/jac/dkw013.

25. Christian CS, Gerdtham UG, Hompashe D, Smith A, Burger R. Measuring Quality Gaps in TB Screening in South Africa Using Standardised Patient Analysis. Int J Environ Res Public Health. 2018;15(4). Epub 2018/04/12. doi: 10.3390/ijerph15040729.
26. Bergen PJ, Smith NM, Bedard TB, Bulman ZP, Cha R, Tsuji BT. Rational Combinations of Polymyxins with Other Antibiotics. Adv Exp Med Biol. 2019;1145:251-88. doi: 10.1007/978-3-030-16373-0_16.
27. Gandra S, Choi J, McElvania E, Green SJ, Harazin M, Thomson RB, et al. Faropenem resistance causes in vitro cross-resistance to carbapenems in ESBL-producing Escherichia coli. Int J Antimicrob Agents. 2020;55(3):105902. Epub 2020/01/17. doi: 10.1016/j.ijantimicag.2020.105902.
28. Getnet F, Demissie M, Assefa N, Mengistie B, Worku A. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. BMC Pulm Med. 2017;17(1):202. Epub 2017/12/13. doi: 10.1186/s12890-017-0551-y.
29. Robson J, Ayerbe L, Mathur R, Addo J, Wragg A. Clinical value of chest pain presentation and prodromes on the assessment of cardiovascular disease: a cohort study. BMJ Open. 2015;5(4):e007251. Epub 2015/04/15. doi: 10.1136/bmjopen-2014-007251.
30. Currie J, Lin W, Meng J. Addressing Antibiotic Abuse in China: An Experimental Audit Study. J Dev Econ. 2014;110:39-51. doi: 10.1016/j.jdeveco.2014.05.006.
31. Fitzpatrick A, editor Do Informed Consumers Reduce the Price and Prevalence of Counterfeit Drugs ? Evidence from the Antimalarial Market2015.
32. Kotwani A, Holloway K. Antibiotic prescribing practice for acute, uncomplicated respiratory tract infections in primary care settings in New Delhi, India. Tropical medicine & international health : TM & IH. 2014;19(7):761-8. Epub 2014/04/23. doi: 10.1111/tmi.12327.
33. Chandy SJ, Thomas K, Mathai E, Antonisamy B, Holloway KA, Stalsby Lundborg C. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore,

South India. The Journal of antimicrobial chemotherapy. 2013;68(1):229-36. Epub 2012/09/05. doi: 10.1093/jac/dks355.

34. Farooqui HH, Mehta A, Selvaraj S. Outpatient antibiotic prescription rate and pattern in the private sector in India: Evidence from medical audit data. PloS one. 2019;14(11):e0224848. Epub 2019/11/14. doi: 10.1371/journal.pone.0224848.
35. Mackintosh M, Channon A, Karan A, Selvaraj S, Cavagnero E, Zhao H. What is the private sector? Understanding private provision in the health systems of low-income and middle-income countries. Lancet. 2016;388(10044):596-605. Epub 2016/07/01. doi: 10.1016/S0140-6736(16)00342-1.
36. Treatment Guidelines for Antimicrobial Use in Common Syndromes. New Delhi, India: Indian Council of Medical Research (ICMR), 2019.
37. Press release: Record number of countries contribute data revealing disturbing rates of antimicrobial resistance. [Internet]. Geneva, Switzerland: World Health Organization (WHO); 2020. Available from: https://www.who.int/news-room/detail/01-06-2020-record-number-of-countries-contribute-data-revealing-disturbing-rates-of-antimicrobial-resistance.

S3-1 File: Evaluation of factors associated with antibiotic prescribing in India – description of all analyses

To examine the factors associated with antibiotic prescribing or dispensing in India, we conducted univariate and multivariate analyses, where the outcome of interest was a binary variable for antibiotic prescription. Four different models were utilized to directly estimate prevalence ratios (PRs) and results were compared to evaluate consistency and identify the most appropriate analytical approach.[1-4]

We first fitted a Poisson regression model with dummy variables for facility location, healthcare sector, provider qualification, and tracer condition as predictors (Model 1). Because the high frequency of the outcome generates issues of under-dispersion, robust variance estimates were obtained. This model was expected to perform fairly well in this context because the sample size is large.[4,5] Among tracer conditions, only angina, asthma and presumptive TB could be included in order to avoid positivity violations.

Secondly, we used log-binomial regression including the same predictors as before, with cluster-based robust variance estimator (Model 2). Thirdly, a hierarchical Poisson regression model with a random intercept for studies was utilized (Model 3).

Lastly, a hierarchical logistic regression model, also including a random intercept for studies, was fitted (Model 4). In Models 3 and 4, the effect of predictors was expected to be similar across studies, and therefore only fixed slopes were considered. Exponentiated estimates from simpler versions of the models described above, including up to two predictor variables, were checked against Mantel-Haenszel-adjusted PRs to evaluate the models' performance.[4]

Prevalence ratios of antibiotic overuse and their 95% CIs estimated through univariable and multivariable analyses for Models 1-4 are reported in S3-1 Table. All models were concordant in showing that the adjusted prevalence of antibiotic prescribing/dispensing was lower in urban versus rural areas, for subjects presenting with suspicious angina, and

for those presenting with asthma. Adjusted prevalence ratios were consistently greater than one for patients with presumptive TB, suggesting that this condition more often leads providers to inappropriately prescribe antibiotics. Qualified practitioners also appear to be more likely to prescribe antibiotics than non-qualified ones.

Our results are inconclusive with regards to the healthcare sector (public versus private). It should be noted that the distribution of private and public providers in the sample population was substantially uneven, leading to insufficient statistical power to detect meaningful differences between the two groups. In fact, private practitioners constitute the largest majority of all providers involved across studies. The results of a subgroup analysis of antibiotic prescribing among private practitioners are presented in S3-2 Table.

Furthermore, a head-to-head comparison of public versus private sector was only undertaken in rural Madhya Pradesh, where SPs only presented cases of angina, asthma and child diarrhea. Hence, we conducted subgroup analyses restricted to this study. Both log-binomial and robust Poisson did not identify any statistically significant differences between public and private practitioners in the selected area.

As expected, the hierarchical logistic regression model substantially overestimated the prevalence ratios owing to the high frequency of the outcome under investigation.[6] Estimates from simpler versions of all models except for the hierarchical logistic one, were perfectly aligned with those obtained with Mantel-Haenszel method. However, we observed lack of convergence with the full log-binomial regression model, as is often the case with this approach.[3] Robust Poisson and hierarchical Poisson with a random intercept for studies yielded pretty similar estimates. Unsurprisingly, the hierarchical model produced larger standard errors because it accounts for both between- and within-study variance.[1]

References

1. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and

recommendations for practice. PloS one. 2012;7(10):e46042. Epub 2012/10/03. doi: 10.1371/journal.pone.0046042.

2. Skov T, Deddens J, Petersen MR, Endahl L. Prevalence proportion ratios: estimation and hypothesis testing. Int J Epidemiol. 1998;27(1):91-5. doi: 10.1093/ije/27.1.91.
3. Petersen MR, Deddens JA. A comparison of two methods for estimating prevalence ratios. BMC Med Res Methodol. 2008;8:9. Epub 2008/02/28. doi: 10.1186/1471-2288-8-9.
4. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003;3:21. Epub 2003/10/20. doi: 10.1186/1471-2288-3-21.
5. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. doi: 10.1093/aje/kwh090.
6. Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occup Environ Med. 1998;55(4):272-7. doi: 10.1136/oem.55.4.272.

S3-1 Table Factors associated with antibiotic prescribing/dispensing in India: results of univariate and multivariate analyses using four different models based on 4,798 SP-provider interactions.

Predictor	**Model 1** (Poisson with robust variance estimates)		**Model 2** (Log-binomial with clustering)		**Model 3** (Poisson with random intercept)		**Model 4** (Logistic with random intercept)	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
	PR (95% CI)	*PR (95% CI)*	*PR (95% CI)*	*PR (95% CI)*	*PR (95% CI)*	*PR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Urban areas	1.30 (1.23 – 1.39)	0.74 (0.67 – 0.81)	1.30 (1.16 – 1.47)	0.53 (0.53 – 0.54)	1.30 (1.20 – 1.42)	0.70 (0.52 – 0.96)	1.61 (1.29 – 2.00)	0.47 (0.26 – 0.86)
Public sector	0.84 (0.75 – 0.95)	0.77 (0.68 – 0.89)	0.84 (0.72 – 0.98)	0.62 (0.62 – 0.63)	1.09 (0.90 – 1.33)	0.90 (0.74 – 1.10)	1.20 (0.93 – 1.55)	0.77 (0.58 – 1.02)
Qualified provider	1.50 (1.42 – 1.58)	1.47 (1.39 – 1.55)	1.50 (1.17 – 1.91)	1.18 (indeterminate)	1.57 (1.44 – 1.72)	1.55 (1.42 – 1.70)	2.66 (2.33 – 3.03)	2.71 (2.36 – 3.11)
Conditions								
Angina	0.35 (0.30 – 0.42)	0.33 (0.28 – 0.40)	0.35 (0.32 – 0.40)	0.23 (0.21 – 0.25)	0.36 (0.30 – 0.44)	0.33 (0.27 – 0.40)	0.21 (0.17 – 0.26)	0.16 (0.12 – 0.21)
Asthma	0.90 (0.83 – 0.98)	0.77 (0.69 – 0.85)	0.90 (0.78 – 1.04)	0.54 (0.51 – 0.57)	1.10 (0.95 – 1.27)	0.77 (0.66 – 0.89)	1.21 (1.00 – 1.47)	0.56 (0.45 – 0.70)
Presum. TB	1.32 (1.25 – 1.40)	1.19 (1.11 – 1.29)	1.32 (1.18 – 1.49)	1.21 (1.20 – 1.22)	1.26 (1.13 – 1.40)	1.19 (1.07 – 1.33)	1.58 (1.35 – 1.84)	1.50 (1.27 – 1.76)

Abbreviations: CI, confidence interval; OR, odds ratio; PR, prevalence ratio; TB, tuberculosis

S3-2 Table: Factors associated with antibiotic prescribing/dispensing among private providers in India: results of univariate and multivariate subgroup analyses using hierarchical Poisson models based on 4,431 SP-provider interactions.

Predictor	Univariable analysis	Multivariable analysis
	PR (95% CI)	*PR (95% CI)*
Urban areas	1.29 (1.14 – 1.47)	0.67 (0.50 – 0.91)
Qualified provider	1.58 (1.44 – 1.73)	1.54 (1.41 – 1.69)
Conditions		
Angina	0.33 (0.27 – 0.43)	0.29 (0.23 – 0.36)
Asthma	1.03 (0.88 – 1.21)	0.70 (0.59 – 0.83)
Presumptive TB	1.25 (1.12 – 1.39)	1.19 (0.50 – 0.74)

Abbreviations: CI, confidence interval, PR, prevalence ratio; TB, tuberculosis

S3-2 File: Frequency of antibiotics dispensed in pharmacies, overall and according to both the AWaRe (Access – Watch – Reserve) and ATC (Anatomical – Therapeutic – Chemical) classifications.

Drug type	Udupi district, Karnataka		Mumbai, Delhi and Patna	
	N	Proportion (95% CI)	N	Proportion (95% CI)
Any antibiotic	55	-	344	-
AWaRe Classification				
Access	16	29.1 (16.4; 40.0)	172	50.0 (45.1; 55.2)
Watch	12	21.8 (12.7; 32.7)	170	49.4 (43.9; 54.4)
Reserve	0	-	0	-
Discouraged	25	45.5 (32.7; 58.2)	2	0.6 (0.3; 1.5)
Other*	2	3.6 (1.8; 9.1)	0	-
ATC Classification				
Penicillin	11	20.0 (9.1; 30.9)	163	47.4 (41.9; 52.3)
Cephalosporin	5	9.1 (3.6; 16.4)	38	11.0 (7.8; 14.5)
Macrolide	1	1.8 (1.8; 7.3)	57	16.6 (12.5; 20.6)
Quinolone	6	10.9 (3.6; 20.0)	81	23.5 (18.6; 28.2)
Tetracycline	0	-	2	0.6 (0.3; 1.5)
Imidazole†	5	9.1 (1.8; 18.2)	0	-
Combinations#	25	45.5 (32.7; 58.2)	2	0.6 (0.3; 1.5)
Other antibiotics§	2	3.6 (1.8; 9.1)	1	0.3 (0.29; 0.9)

Note: The unit of analysis is the individual drug, not the SP-provider interaction.
* In the Udupi study, antibiotics classified as "other" were all quiniodochlor.
† Only metronidazole was dispensed.
# This category does not include combinations of anti-mycobacterial drugs.
§ Quiniodochlor in the Udupi study and chloramphenicol in the other study.

Chapter 4: Impact of COVID-19 on antibiotics and hydroxychloroquine sales in India: an interrupted time series analysis

4.1 Preface

As reported in Chapter 3, antibiotics are often prescribed or dispensed in the absence of clinical indication, i.e. for conditions not requiring antibiotic treatment. COVID-19 is among such conditions because it is of viral etiology and bacterial coinfections are only observed in a small proportion of patients with severe disease, thus not justifying the routine empirical use of antibiotics in the management of COVID-19 cases. Additionally, various drugs such as hydroxychloroquine (HCQ) and certain antibiotics (e.g. azithromycin) have been repurposed for use in COVID-19 management, even though a growing number of studies shows no clinical benefit. India is the largest consumer of antibiotics in the world, and the private sector is responsible for a substantial proportion of such consumption. India is also being heavily affected by the pandemic, generating serious concerns regarding the widespread inappropriate use of antibiotics in an already alarming scenario.

Here, I present the results of an interrupted time series analysis aimed at assessing the impact of COVID-19 pandemic on national antibiotic and HCQ sales in India, using pharmaceutical data from the private sector obtained from IQVIA Inc.

This work was submitted to a peer-reviewed journal and is currently under review.

4.2 Title Page

Impact of COVID-19 on antibiotics and hydroxychloroquine sales in India: an interrupted time series analysis

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4.3 Abstract

Background: We assessed the impact of COVID-19 pandemic in India on the national consumption of antibiotics and hydroxychloroquine (HCQ) in 2020 compared to the expected level of use had the pandemic not occurred.

Methods: We performed interrupted time-series analyses (ITS) of sales volumes reported in standard units (i.e. doses), collected at regular monthly intervals from January 2018 to September 2020 and obtained from IQVIA Inc., India. As children are less prone to develop symptomatic coronavirus disease 2019 (COVID-19), we hypothesized a predominant increase in non-child appropriate formulations (non-CAF). COVID-19-attributable changes in level and trend of the monthly sales of total antibiotics, azithromycin and HCQ were estimated, accounting for seasonality and lockdown period where appropriate.

Findings: A total of 12039.56 million doses of antibiotics were sold in India between January and September 2020, which is slightly less than the amount of the same period of 2018 and 2019. However, the proportion of non-CAF antibiotics increased from 72.6% (95%CI: 71.9%; 73.4%) in 2019 to 76.2% (95%CI: 75.9; 77.4) in 2020. Our ITS analyses estimated that COVID-19 likely contributed to 225.2 million (95%CI: 65.6; 384.6) excess doses of non-CAF antibiotics and 39.0 million excess doses (95%CI: 26.8; 51.3) of non-CAF azithromycin (equivalent to a minimum of 6.3 million azithromycin treatment courses) between June and September 2020. In March 2020, we estimated a COVID-attributable change in level of +10.8 million doses (95%CI: 9.2; 12.4) for HCQ sales, whereas a weak negative change in monthly trend was found for this drug.

Interpretation: A significant increase in antibiotics sales occurred during COVID-19 pandemic in India indicating the need for urgent antibiotic stewardship measures.

Funding: Funds for data purchase received from the Division of Infectious Diseases, Washington University School of Medicine in St. Louis, MO, USA.

4.4 Author summary

Why was this study done?

- There are concerns that the widespread and often inappropriate use of antibiotics has been aggravated by the COVID-19 pandemic, but little is known regarding the true impact of the pandemic on antibiotic use, particularly in low- and middle-income countries (LMICs).
- India is the largest antibiotic user in the world and among countries that are most severely affected by the pandemic.
- A substantial proportion of inpatient and outpatient care in India is private, and this unregulated and fragmented private sector accounts for the vast majority of antibiotic consumption, raising major concerns on the potential effects of COVID-19 on prescribing practices.

What did the researchers do and find?

- Using an interrupted time-series (ITS) design, we examined national sales volumes of total antibiotics, azithromycin alone, and hydroxychloroquine (HCQ) in India's private sector from January 2018 to September 2020.
- Focusing on non-pediatric formulations and adjusting for underlying seasonal and non-seasonal trends and accounting for the effect of lockdown, we estimated the impact of the pandemic on monthly sales.
- Based on our models, COVID-19 likely contributed to about 225 million excess doses of total antibiotics and 39.0 million excess doses (95%CI: 26.8; 51.3) of azithromycin between June and September 2020 (i.e. after the lockdown).
- HCQ sales peaked in March 2020, reflecting the widespread use of this drug for both prophylaxis and treatment of COVID-19 (+10.8 million doses [95% CI: 9.2; 12.4]), followed by a slow decline afterwards.

What do these findings mean?

- Our findings indicate a significant increase in antibiotics sales, particularly azithromycin, during COVID-19 pandemic in India.
- Similar trends are likely observable in other LMICs where antibiotics are often overused.
- The medium- and long-term consequences on bacterial resistance patterns are highly concerning, highlighting the need for urgent antibiotic stewardship measures.

4.5 Introduction

India is the largest consumer of antibiotics in the world.[1,2] Broad spectrum antibiotics such as second/third generation cephalosporins, macrolides and quinolones are overused for acute respiratory tract infections in India.[3] There is a concern that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection designated as coronavirus disease 2019 (COVID-19) could lead to a substantial increase in antibiotic consumption (often inappropriately), thus promoting antibiotic resistance.[4]

In many countries, azithromycin and hydroxychloroquine (HCQ) are reportedly being used off label in prophylactic and therapeutic regimens either alone or in combination, although an increasing number of studies observed no beneficial effects and raised safety concerns.[5-8]

A growing number of observational studies from multiple countries consistently indicate that only a small proportion of hospitalized COVID-19 patients develop secondary bacterial infections, with higher rates observed in intensive care units.[9,10] The risk of developing bacterial co-infections remains presumably very low in non-hospitalized patients with mild disease, who represent the majority of individuals with symptomatic SARS-CoV-2 infection.

These observations point against the routine empiric use of antibiotics in the treatment of COVID-19 cases unless there is evidence of bacterial infection as recommended by the WHO and Indian Ministry of Health guidelines.[11,12] To date, a few before-and-after studies have been conducted to determine the impact of COVID-19 on antibiotic use, but these were all done in high-income countries (United States or Spain) and were mostly focused on selected hospital settings (see S4-1 Text and S4-1 – S4-2 Tables).[13-20]

With about 9.7 million COVID-19 cases reported as of 7th December 2020, India is among the hardest hit countries in the world.[21] In this study, we assessed the impact of COVID-19 pandemic on the national consumption of antibiotics and HCQ in 2020 in India.

4.6 Methods

Study design

We conducted interrupted time-series analyses (ITS) using total antibiotics, azithromycin and HCQ sales volumes as our continuous outcome, and COVID-19 pandemic as the exposure of interest.[22] Our counterfactual (i.e. sales volumes had the pandemic not occurred) was thus the extrapolation of the pre-pandemic period.

Temporal data on COVID-19 in India

The first imported case of SARS-CoV-2 infection in India was identified on January 30th, 2020. Until late March 2020 the number of cases detected across the country remained very low (about 0.1 per 100,000), although this might be explained by the limited number of tests being performed. In order to examine associations between drug sales volumes and COVID-19 cases, national and state-wise data regarding the monthly number of new cases detected in India were obtained from the publicly accessible online repository compiled by the Indian non-profit organization PRS Legislative Research, based on data from the Ministry of Health and Family Welfare, Government of India.[21] The monthly number of tests performed in the country was obtained from Our World in Data;[23] however, this information is not available for individual states. Projected population estimates as determined by the National Commission on Population, Ministry of Health and Family Welfare were utilized to calculate monthly rates of new cases and tests per 100,000.[24]

For the purpose of our regression analyses, the exposure was treated as a binary variable (pre-pandemic phase coded 0 versus pandemic phase coded 1) as detailed below.

Antibiotic and HCQ sales data

The main outcomes of interest for this study was the sales volume of antibiotics and HCQ in India, using data obtained from IQVIA Inc., which is a reliable source of drug sales data.[1,25] IQVIA is a company which collects over the counter (OTC) and prescription-based sales data through a representative panel of drug stockists and offers an overall 95%

coverage of the total pharmaceutical market combining the retail sector, hospitals and dispensing doctors. In India, all antibiotics are included in Schedule H or H1. Schedule H is a class of prescription drugs which cannot be purchased without the prescription of a qualified doctor. For Schedule H1 drugs, in addition to having a prescription, the dispenser should record the prescriber and patient details, the drug and the quantity dispensed and maintain the record for three years and be open for inspection by regulatory officials. However, OTC dispensing of antibiotics is common in India.[26] Regular monthly data points from January 2018 to September 2020 were available for the purpose of our analyses. Sales volumes were reported in standard units (SU), and 1 SU (i.e. 1 dose) was defined as a single tablet, capsule, ampoule, vial, or a 5 mL liquid preparation for oral consumption as reported previously.[25] Information on formulation type with regard to the route of administration (oral, parenteral, topical) was also available. We further classified oral drugs as child-appropriate formulations (CAF) or non-CAF based on the description of the package content (the list of formulation types considered for this purpose is reported in S4-3 Table), as reported previously.[25] Antibiotics were categorized according to the Anatomical - Therapeutic - Chemical (ATC) Index 2020 and the WHO Access - Watch - Reserve (AWaRe) framework 2019.[27,28] The full list of drugs (intended as active molecule) included in our dataset is available in S4-4 Table.

Data analysis

We performed descriptive analyses of antibiotics and HCQ sales data throughout the observation period, reporting the absolute number of doses sold along with crude percentages of each drug class relative to the total. Medians and interquartile ranges (IQR) were also used to describe overall and stratum-specific monthly sales volumes. The correlation between sales volume and new COVID-19 cases detected monthly was investigated using Pearson's coefficient. Descriptive analyses were also performed to explore trends in selected states/territories reporting either a very high number of cases

(Andhra Pradesh, Delhi, Karnataka, Maharashtra, Tamil Nadu) or a very low number of cases (Bihar, Gujarat, Madhya Pradesh, Rajasthan, West Bengal).

Secondly, we conducted segmented regression analyses of time series data to assess how much the pandemic onset affected monthly sales volumes of 1) all antibiotics (including azithromycin), 2) azithromycin only, and 3) HCQ.[22,29] We decided a priori to exclude CAF from these assessments as we anticipated an increase in antibiotic sales mainly among adult patients. Children constitute a small proportion of reported COVID-19 cases and are much less likely to develop symptomatic SARS-CoV-2 infection.[30,31] Furthermore, social distancing measures and school closure are still underway in most Indian states. As also documented in the United States,[20,32] such a scenario likely plays a role in reducing the transmission of many respiratory infections that typically spread among children, leading to a lower antibiotic use.

Our models for total non-CAF antibiotics (Equation 4.1) and azithromycin (Equation 4.2) estimated the following measures: 1) pre-pandemic trend (January 2018 to March 2020), 2) average level change in the mean monthly sales during the preventive lockdown, and 3) the slope (trend) change in the outcome after the lockdown phase (i.e. from June to September 2020). This approach allowed us to account for the effect of the nationwide lockdown enforced by the Government of India between March 24th and May 31st, 2020 which could have negatively affected antibiotic sales. A fixed effect term for rainy season (July to October) was included in the model for antibiotics to adjust for seasonality. As this approach did not perform equally well for azithromycin sales, for this outcome we used harmonic seasonal model to better account for seasonal changes,[33] along with further adjustments for non-seasonal autocorrelation.

Equation 4.1: $$Y_m = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 XT + \beta_4 Z + \varepsilon$$

Equation 4.2: $$Y_m = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 XT + sin1 + cos1 + sin2 + cos2 + R_m$$

where Y_m is the continuous outcome, T is time in months, X is the pandemic (coded 1 from April 2020 onwards), XT is a scaled interaction term with time (coded 0 until the

end of lockdown and increasing by one unit each month afterwards), ε and R_m are error terms (the latter of which includes autocorrelated errors).

Given the initial recommendation for HCQ-based prophylaxis,[34] we expected a weaker effect of lockdown on HCQ sales and did not account for it in the model (Equation 4.3). We thus estimated the average change in level and the slope change in the outcome assuming the start of the COVID-19 pandemic in March 2020. Autocorrelated errors were also included to correct for the remaining serial correlation in the data, whereas no adjustments for seasonality were deemed necessary. HCQ is not recommended for malaria treatment according to Indian guidelines, so no major seasonal changes are expected to occur in its use.

Equation 4.1: $$Y_m = \beta_0 + \beta_1 T + \beta_2 W + \beta_3 WT + R_m$$

where Y_m is the continuous outcome, T is time in months, W is the pandemic (coded 1 from March 2020 onwards), WT is a scaled interaction term with time (coded 0 until March 2020 and increasing by one unit each month afterwards), R_m is an error term which includes autocorrelated errors.

A detailed description of model specification and diagnostics is provided in the Supplementary appendix (S4-2 Text, S4-1 – S4-2 Figures).

Descriptive analyses were performed in STATA version 16.1 (StataCorp LLC, College Station, TX, USA), and regression analyses were conducted in R (version 4.0.3).

Ethics considerations

The Institutional Review Boards of Washington University in St. Louis and McGill University exempted this study from ethics review as no identifiable information about living individuals were obtained (i.e. secondary use of anonymous information).

Role of the funding source

No external funding sources were involved in this study. Data were purchased from IQVIA Inc. using funds from the Division of Infectious Diseases, Washington University School of Medicine in St. Louis, MO, USA.

4.7 Results

The absolute cumulative volume of antibiotics sold between January and September 2020 was 12039.56 million doses, which is slightly lower than the 13597.33 million doses and 13519.82 million doses sold in the same period of 2019 and 2018, respectively (Table 4-1). The CAF sales volume from January to September amounted to 2815.01 million doses in 2020 as opposed to 3719.18 million doses in 2019 and 3752.80 million doses in 2018. Between January and September, the proportion of non-CAF sales among total antibiotics, likely prescribed to adolescents and adults (although pediatric and non-pediatric use are indistinguishable for injectables), increased from 72.6% (95% CI: 71.9; 73.4) in 2019 to 76.2% (95% CI: 75.9; 77.4) in 2020 (Figure 4-1).

The distribution of AWaRe categories remained almost stable over time except for a slight decline in the use of 'Discouraged' fixed dose antibiotic combinations (FDCs), that could be ascribed to the policy change introduced in September 2018 and was accompanied by a joint increase in use of 'Access' antibiotics (Table 4-1, S4-3 -S4-4 Figures). The median (interquartile range, IQR) percentages of the different AWaRe groups relative to the total non-CAF antibiotics sold monthly throughout the entire study period (January 2018 to September 2020) were as follows: 42.9% (42.1-44.3) 'Access', 36.8% (35.4-37.5) 'Watch', 0.8% (0.7-0.9) 'Reserve', and 18.9% (17.7-19.7) 'Discouraged'.

The distribution of antibiotics by ATC class remained stable except for a noteworthy increase in non-CAF macrolides (J01F) sales, jumping from 690.61 million doses in January-September 2018 to 826.55 million doses during the same period of 2020 (Table 4-1, S4-5 Figure). After the end of lockdown, between June and September 2020,

azithromycin (J01FA10) sales were 34.4% higher than observed in the corresponding months of the previous year (Figure 4-1).

Table 4-1 Cumulative sales volume in January-September of each year (2018-2020), and distribution by AWaRe category and ATC class for formulations other than child-appropriate ones (non-CAF).

Category	Cumulative sales volume in million standard units					
	Jan-Sep 2018		Jan-Sep 2019		Jan-Sep 2020	
	N	%	N	%	N	%
All antibacterial drugs	13519.82	100.00	13597.33	100.00	12039.56	100.00
Non-child-appropriate formulations*	9767.02	72.24	9877.45	72.64	9224.55	76.62
Child-appropriate formulations*	3752.80	27.76	3719.88	27.36	2815.01	23.38
AWaRe groups (non-CAF)**						
Access	4106.93	42.05	4247.40	43.00	4146.95	44.96
Watch	3559.11	36.44	3582.24	36.27	3351.77	36.36
Reserve	62.20	0.64	83.32	0.84	81.51	0.88
Discouraged	1957.93	20.05	1890.01	19.13	1588.22	17.22
Not included in AWaRe	80.84	0.83	74.47	0.75	56.10	0.61
ATC groups (non-CAF)**						
Aminoglycosides	181.43	1.86	182.21	1.84	135.86	1.47
BL-BLI	891.17	9.12	1013.96	10.27	954.47	10.35
Carbapenems***	28.63	0.29	33.49	0.34	33.35	0.36
Cephalosporin-BLI	309.97	3.17	350.15	3.54	294.47	3.19
Cephalosporins (1st)	292.82	3.00	294.14	2.98	273.85	2.97
Cephalosporins (2nd)	169.99	1.74	184.27	1.87	157.78	1.71
Cephalosporins (3rd)	1051.74	10.77	1218.83	12.34	1089.75	11.81
Cephalosporins (4th+)	1.63	0.02	1.60	0.02	1.01	0.01
Combinations	1691.56	17.32	1575.76	15.95	1322.05	14.33
Glycopeptides	2.52	0.03	2.72	0.03	2.21	0.02
Imidazoles	1114.25	11.41	1164.92	11.79	1101.05	11.94
Macrolides	690.61	7.07	729.87	7.39	826.55	8.96
Penicillins	820.91	8.40	848.07	8.59	869.28	9.42
Polymyxins	1.39	0.01	1.37	0.01	0.99	0.01
Quinolones	1289.17	13.20	1251.23	12.67	1154.64	12.52
Sulfonamides	251.46	2.57	151.74	1.54	243.14	2.64

Category	Cumulative sales volume in million standard units					
	Jan-Sep 2018		Jan-Sep 2019		Jan-Sep 2020	
	N	%	N	%	N	%
Tetracyclines	646.48	6.62	510.89	5.17	420.63	4.56
Other antibiotics	331.25	3.39	362.14	3.67	343.44	3.72

Abbreviations: BL, beta-lactam; BLI, beta-lactamase inhibitor; CAF, child-appropriate formulation.
* Percentages are calculated relative to all antibacterial drugs.
** Percentages are calculated relative to non-child-appropriate formulations of antibacterial drugs.
*** Including combinations of carbapenems and BLI

Monthly doxycycline (J01AA02) sales did not change much until September 2020, when a considerable peak was observed (+25.9% compared to September 2019). Faropenem (J01DI03) use has been rising constantly over the years, but a 23.4% increase was registered in September 2020 versus the year before (Figure 4-1). No major changes were observed in the sales volumes of other broad-spectrum antibiotic classes, such as second/third generation cephalosporins and quinolones. Similarly, monthly sales of selected parenteral antibiotics that are typically used in inpatient care such as carbapenems, glycopeptides, third generation cephalosporins and polymyxins, has remained almost stable (S4-4 – S4-6 Figure).

Furthermore, the cumulative HCQ sales (only available as non-CAF) increased by approximately 45.5% between 2019 and 2020 (from 202.46 million doses in January-September 2019 to 294.52 million doses in the same period of 2020) (Figure 4-1).

Crude monthly sales of non-CAF antibiotics increased with the number of new COVID-19 cases per 100,000 population (Pearson's coefficient = 0.93), a trend that is clearly observable both nationally (Figure 4-2) and in selected Indian states with different epidemic curves (Figure 4-3, S4-7 – s4-8 Figures).

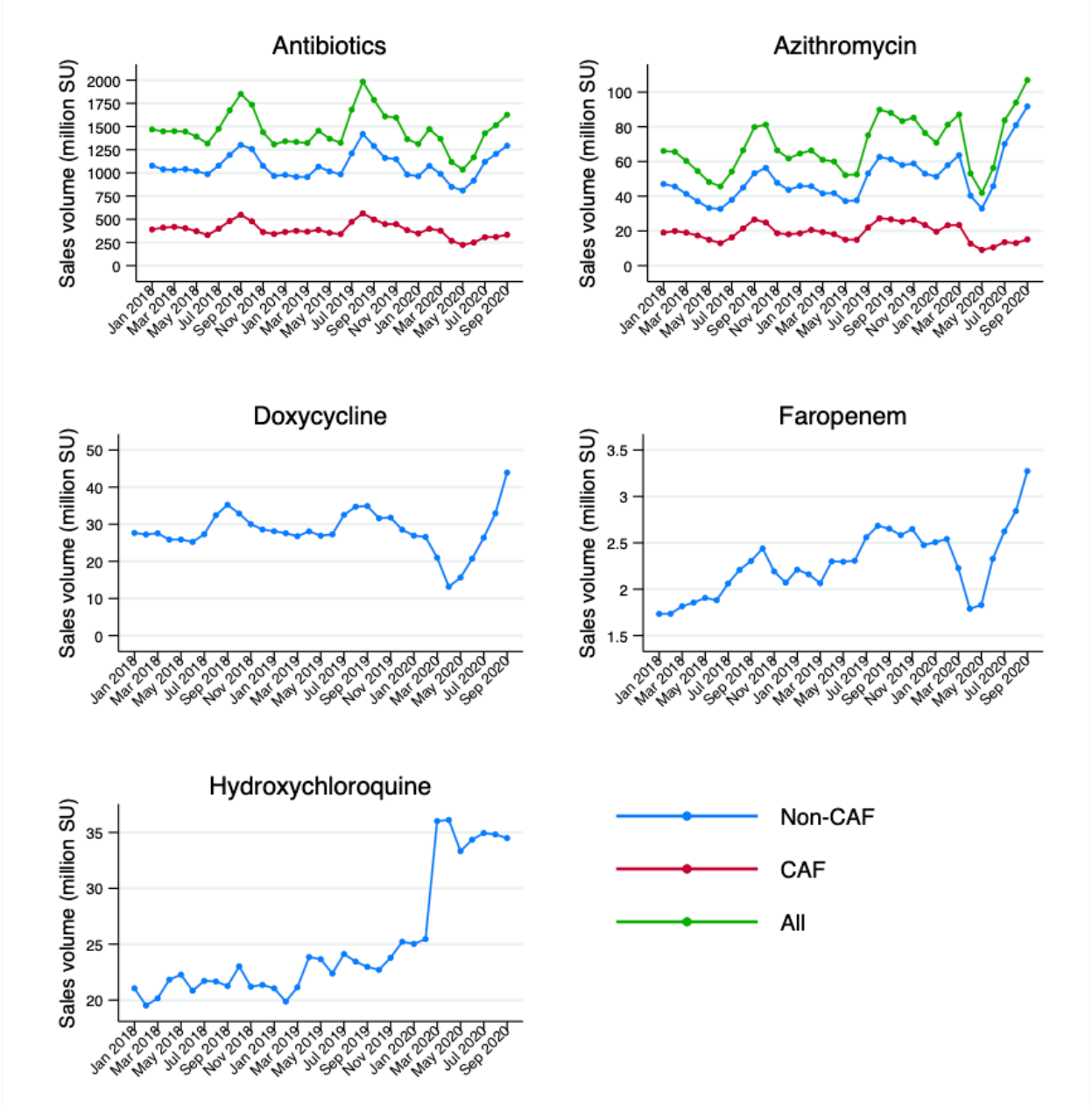

Figure 4-1 Trend in sales volumes of total antibiotics, azithromycin, doxycycline, faropenem and hydroxychloroquine (HCQ) in India from January 2018 to September 2020. Child-appropriate formulations (CAF), non-CAF and total are presented in the graphs as relevant.

Notes: Data on antibiotics are inclusive of azithromycin. HCQ and faropenem are only shown as non-CAF only because CAF are not available for these drugs. As only a very small proportion of doxycycline is sold as CAF, this is omitted in the graph.

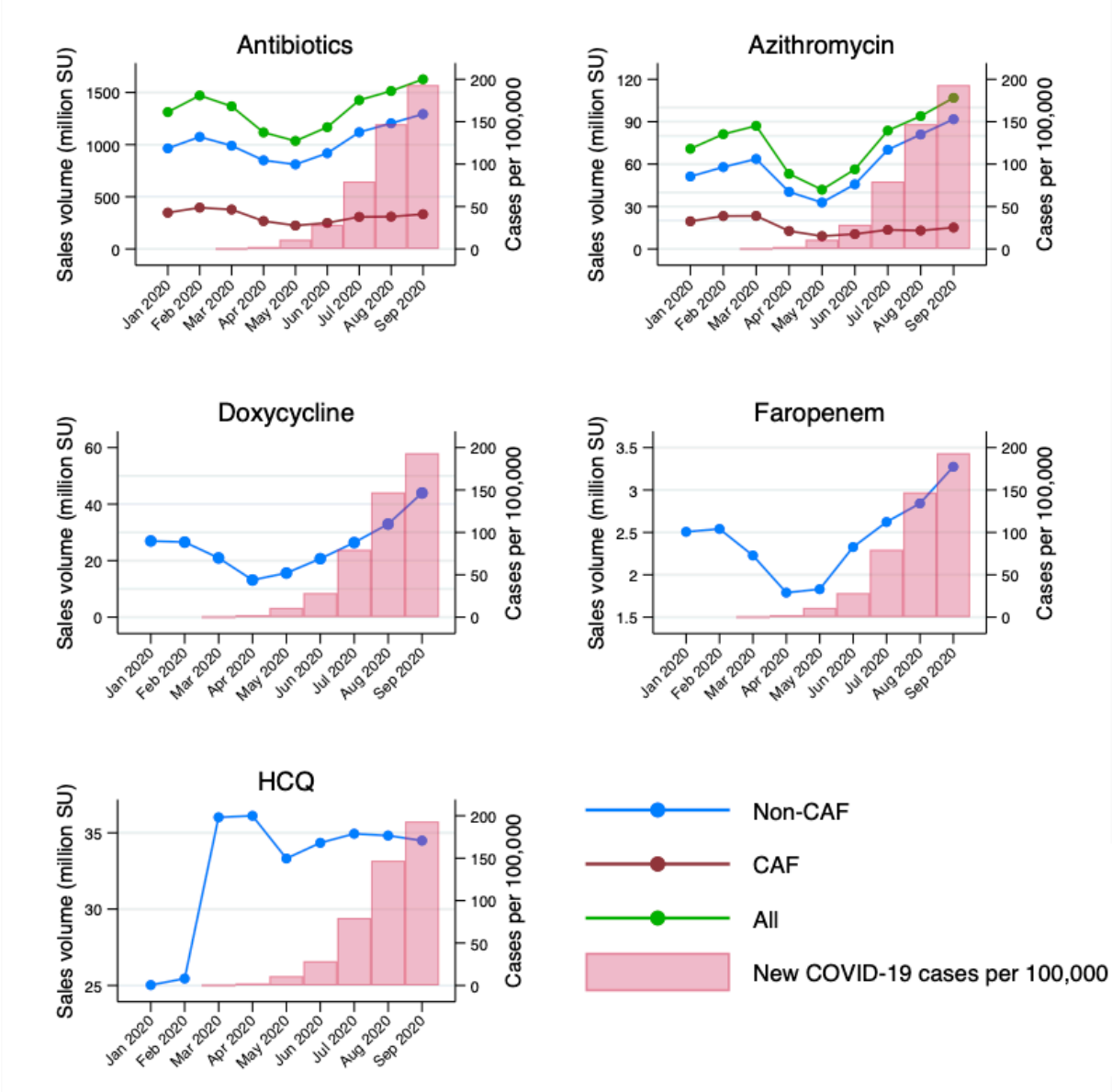

Figure 4-2 Relationship between new COVID-19 cases per 100,000 and national sales volumes of antibiotics, azithromycin, doxycycline, faropenem and hydroxychloroquine (HCQ) per month from January to September 2020. Child-appropriate formulations (CAF), non-CAF and totals are reported.

Notes: Data on antibiotics are inclusive of azithromycin. HCQ and faropenem are only shown as non-CAF only because CAF are not available for these drugs. As only a very small proportion of doxycycline is sold as CAF, this is omitted in the graph.
Abbreviations: CAF, child appropriate formulations; HCQ, hydroxychloroquine, SU, standard unit.

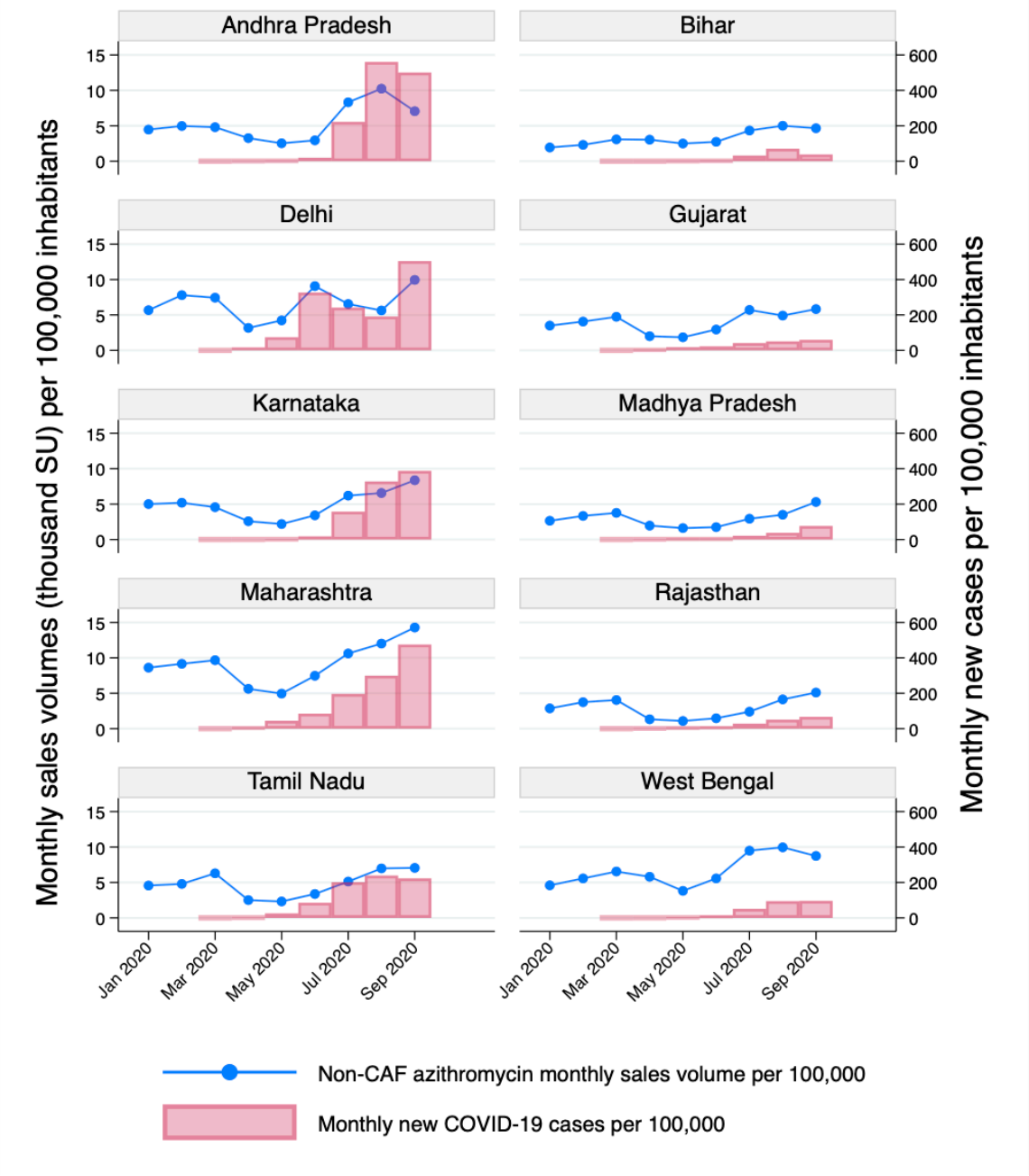

Figure 4-3 Relationship between monthly new COVID-19 cases per 100,000 and azithromycin sales volumes per 100,000 (only non-child appropriate formulations, non-CAF) in 10 states of India from January to September 2020.

Note: States with the highest rates of detected COVID-19 cases are shown on the left side of the graph, whereas states with the lowest rates of detected COVID-19 cases are on the right.

Rising trends are evident both in states with a high number of reported cases and in those with lower incidence. The reported number of COVID-19 cases in India remained quite

low until June, reflecting the difficulties in testing scale-up across the country particularly during the first semester of 2020 (S4-9 Figure).

Antibiotic sales volumes declined in April and May 2020, likely due to the very limited mobility allowed during the lockdown phase. As estimated through segmented regression analyses (Table 4-2, Figure 4-4), non-CAF antibiotics and azithromycin sales in April 2020 decreased on average by 198.24 million doses (95% CI: -297.36; -99.12; P<0.001) and 15.22 million doses (95% CI: -23.78; -6.66; P<0.001), respectively. Moreover, we observed a monthly increase in trend after the lockdown period for both non-CAF antibiotics (+56.31 million doses [95% CI: 16.46; 96.16]; P=0.010), and for non-CAF azithromycin (+9.75 million doses [95% CI: 6.69; 12.83]; P<0.001), likely attributable to the pandemic surge.

Table 4-2 Estimated change in monthly sales volume (expressed in million standard units) according to adjusted segmented regression models for total antibiotics, azithromycin and hydroxychloroquine (HCQ). Only non-child appropriate formulations were considered for these analyses.

Predictors	Outcomes (ES [95% CI])		
	Antibiotics*	**Azithromycin****	**HCQ*****
Baseline level (Jan 2018)	1012.39 (958.11; 1066.67)	39.01 (34.09; 43.93)	19.88 (18.99; 20.77)
Pre-pandemic trend (monthly change from Jan 2018 to Mar 2020)	0.57 (-2.70; 3.84)	**0.68 (0.41; 0.95)**	**0.17 (0.12; 0.24)**
Average change in level during lockdown (Apr-May 2020) versus the pre-pandemic period	**-198.24 (-297.36; -99.12)**	**-15.22 (-23.78; -6.66)**	**10.20 (9.20; 12.40)**
Change in trend after lockdown (from Jun 2020 to September 2020)	**56.31 (16.46; 96.16)**	**9.75 (6.69; 12.83)**	**-0.41 (-0.80; -0.02)**

Abbreviations: CI, confidence interval; ES, estimate; HCQ, hydroxychloroquine.
* Model adjusted for seasonality using a fixed effect term indicating the rainy season.
** Harmonic seasonal model to adjust for seasonality and autocorrelated errors to account for the remaining serial correlation in the data.
*** The change in trend started in April 2020 and we adjusted for non-seasonal autocorrelation.

Cumulative excess antibiotics sales from June to September 2020 amounted to 225.24 million doses (95% CI: 65.84; 384.64) for non-CAF antibiotics and 39.0 million doses (95% CI: 26.76; 51.32) of non-CAF azithromycin. The latter is equivalent to about 6.32 million

azithromycin treatment courses for respiratory tract infection, considering 500 mg daily for 5 days (S4-2 Text).

We also estimated a +10.20 million doses (95% CI: 9.20; 12.40; P<0.001) level change in HCQ sales in March 2020. After this peak, sales began declining slowly, as confirmed by the weak negative change in trend suggested by our model (-0.41 million doses [95% CI: -0.80; 0.02]; P=0.041).

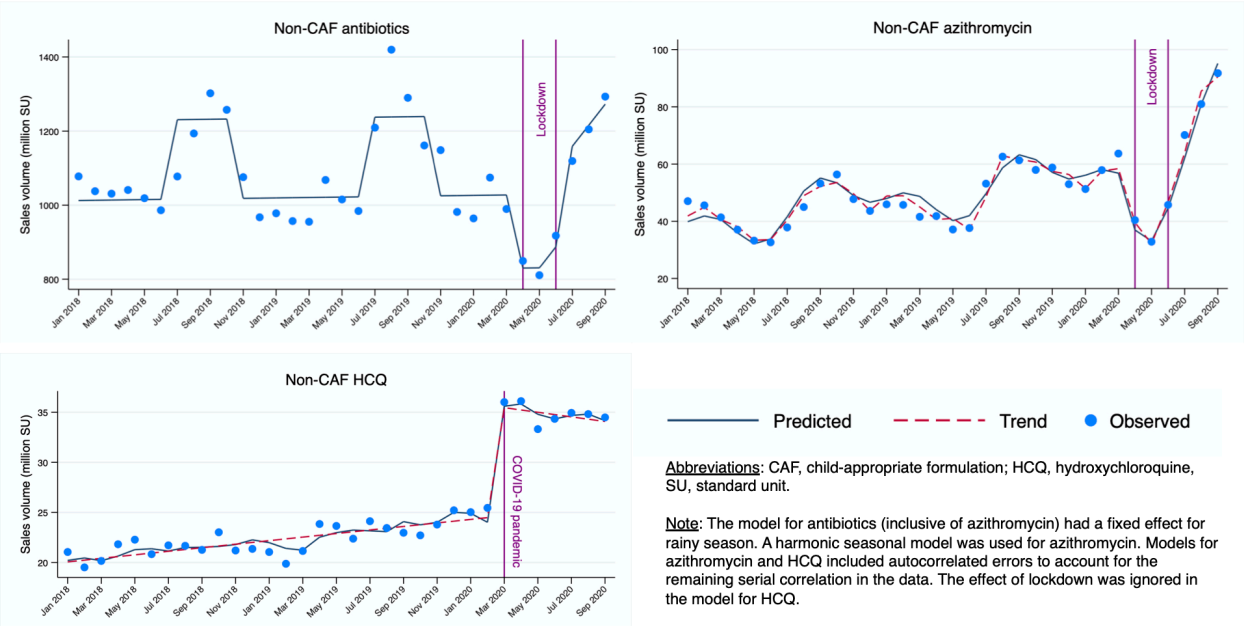

Figure 4-4 Results of segmented regression analysis for monthly sales volumes of non-CAF antibiotics, azithromycin and hydroxychloroquine (HCQ) between January 2018 and September 2020.

4.8 Discussion

We estimate that between June and September 2020, COVID-19 likely contributed to excess sales of 225.24 million doses of non-CAF antibiotics and 39.0 million doses of non-CAF azithromycin. The excess antibiotic sales likely resulted from the sudden surge in the number of patients seeking medical care for presumptive or confirmed COVID-19 both in the community and in the hospitals, as suggested by the abrupt increase in use of azithromycin, often prescribed for this condition. Assuming perfect adherence to the

recommended dosage and duration of azithromycin treatment for respiratory tract infections as per Indian national guidelines (i.e.: 500 mg daily for 5 days), 39 million excess doses from June to September 2020 correspond to about 6.32 million treatment courses. This is consistent with the 6 million new COVID-19 cases reported in India during the same period.[21] However, azithromycin is often prescribed for shorter duration (e.g. 500 mg per day for 3 days),[35] potentially suggesting that more people could have been treated empirically without diagnostic confirmation of SARS-CoV-2 infection. To support this, in states like Bihar, Gujarat and West Bengal where the number of cases is reportedly low and tests are not widely available nor accessible, azithromycin consumption has risen considerably. It should also be noted that healthcare seeking behaviours have changed substantially during the pandemic period, with fewer people presenting to healthcare facilities for conditions other than acute respiratory infections (i.e. COVID-19 suspicion). Therefore, we expect antibiotics to be less commonly prescribed for other types of illness as compared to the previous years, suggesting that the COVID-attributable excess sales indicated by our models might be an underestimation. On the other hand, we observed a notable reduction in CAF sales, suggesting that antibiotic use among children declined since the start of the pandemic which is in line with our hypotheses.[20,30,32]

Notably, the massive increase in azithromycin use raises several serious concerns. First, a recent randomized control study investigating the effects of mass distribution of azithromycin in Nigerian children has demonstrated an increase not only in macrolide resistance determinants but also non-macrolide resistance in the gut flora such as resistance to beta-lactams.[36] Multi-drug resistant *Enterobacterales* including extended spectrum beta-lactamase (ESBL)-producing strains are highly prevalent among healthy adults in the community and could be further aggravated with this unexpected increase in azithromycin use.[37] Second, the sudden ongoing mass consumption of azithromycin has the potential to further exacerbate the selection of azithromycin-resistant typhoidal and non-typhoidal *Salmonella* strains.[38] This is of particular concern for India, where enteric fever is highly endemic with an estimated annual incidence of 377 cases per

100,000 population and azithromycin has been increasingly chosen for empiric treatment.[39] The recent emergence of azithromycin-resistant *S.* Typhi strains in India sounds as a further alarm bell.[40] Another threat coming from this unexpected increase in azithromycin use is the possible selection of pan-oral drug resistant *S.* Typhi, requiring hospitalization for parenteral treatment administration.[38] Furthermore, azithromycin is currently recommended by the Centers for Disease Control and Prevention (CDC) for travelers' diarrhea in South Asia and South-East Asia due to increasing fluoroquinolone-resistant strains among common bacterial diarrheal pathogens such as *Salmonella*, *Shigella* and *Campylobacter spp*.[41] The growing use of azithromycin could further jeopardize the available therapeutic choices for this condition. Finally, the empiric use of azithromycin for presumptive COVID-19 could lead to a progressive substitution of beta-lactam antibiotics (J01C) for any acute respiratory tract illness, aggravating the concerns regarding resistance selection.

Among other oral agents commonly used for respiratory tract infections, doxycycline and faropenem sales peaked in September 2020. Faropenem is an oral "penem" drug that has been approved in India for several clinical indications including community-acquired respiratory tract infections.[42] A recent in vitro study demonstrated cross-resistance to carbapenems among ESBL-producing *E. coli* isolates.[42] The unnecessary use of faropenem could promote intestinal colonization of carbapenem-resistant *Enterobacterales* in a context like India where there is a high community burden of ESBL positivity. Regarding HCQ, the sudden increase in consumption registered in March 2020 could be attributed to prophylaxis for healthcare workers as initially recommended by the Ministry of Health.[34] The national guidelines were subsequently revised on June 27th, limiting the prescription of HCQ for moderate to severe COVID-19 cases and for patients with mild disease if immunocompromised or under 5 years old.[43] This change in recommendations is reflected in the slowly declining trend observed after the initial peak. Moreover, HCQ is unlikely to be prescribed for mild cases evaluated by primary care physicians or informal healthcare providers who often recommend/dispense antibiotics like azithromycin but have less experience in handling HCQ-based treatment. Additionally, in March 2020, the

Indian government issued an emergency order imposing stronger restrictions on HCQ sales by including it in Schedule H1.[44]

There are some limitations in our study. First, IQVIA data only cover the private healthcare sector thus potentially underestimating the excess use of antibiotics and HCQ due to COVID-19. Yet, India's largely unregulated and fragmented private sector contributes to 75% of outpatient visits and 62% of inpatient visits thus accounting for majority of antibiotic consumption in the country.[45] Second, our data could not distinguish between inpatient and outpatient use of antibiotics, but the latter is known to be largely predominant. Third, while we applied the most appropriate techniques to adjust for seasonal variations in the outcome, the suboptimal number of pre- and post-pandemic data points available for our analyses remains a limitation in that sense. Nonetheless, our models were quite robust and fitted the data reasonably well as the residuals of each model were behaving as a white noise. Fourth, we did not account for the time-varying under-ascertainment of COVID-19 cases because the number of cases reported monthly was not directly utilized in our segmented regression models. The timing of the exposure was defined based on the shape of the epidemic curve, which is assumed to be a good representation of the true scenario, in spite of the limited testing capacity. While it is possible that estimated excess sales volumes do not accurately reflect the impact of the pandemic on pharmaceutical consumption, we do expect the direction of the effect to be fairly well captured. Finally, ivermectin is also used off-label for COVID-19 treatment in India, but ivermectin sales data were not available for this study.[46]

Our findings have important implications for antimicrobial resistance globally and even more so for low and middle-income countries (LMICs). Like in India, the overuse of antibiotics is common in other LMICs,[2,47] where similar prescribing patterns among presumptive or confirmed COVID-19 cases likely exist. The situation could be even worse in other countries like Pakistan where azithromycin is the only treatment option for *S.* Typhi infections, and an outbreak of extremely drug-resistant strains recently occurred.[48]

Policy makers in India and other LMICs should recognize this substantial overuse of antibiotics induced by COVID-19. Considering the ongoing pandemic trends, the likelihood of a second wave as happening in Western countries and the amount of time necessary to eventually vaccinate the entire population, immediate action is needed to reduce the overuse of antibiotics for COVID-19. India will need to greatly increase COVID-19 testing access to reduce empirical treatments. Issuing further restrictions on azithromycin prescription by moving it from Schedule H to H1 as done with HCQ could potentially help limit the widespread use of this important antibiotic. Similar restrictions on azithromycin use should also be considered in other LMICs. Antimicrobial stewardship interventions have never been so critical, and mass media awareness campaigns targeting prescribers and the general public to discourage the routine use of antibiotics for COVID-19 need to be rapidly implemented in India and other LMICs.

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Conflicts of interest

All authors declare they have no conflicts of interest.

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4.9 References

1. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-E70. Epub 2018/03/28. doi: 10.1073/pnas.1717295115.
2. Sulis G, Daniels B, Kwan A, Gandra S, Daftary A, Das J, et al. Antibiotic overuse in the primary health care setting: a secondary data analysis of standardised patient studies from India, China and Kenya. BMJ Glob Health. 2020;5(9). Epub 2020/09/18. doi: 10.1136/bmjgh-2020-003393.
3. Farooqui HH, Mehta A, Selvaraj S. Outpatient antibiotic prescription rate and pattern in the private sector in India: Evidence from medical audit data. PloS one. 2019;14(11):e0224848. Epub 2019/11/14. doi: 10.1371/journal.pone.0224848.
4. Nieuwlaat R, Mbuagbaw L, Mertz D, Burrows L, Bowdish DME, Moja L, et al. COVID-19 and Antimicrobial Resistance: Parallel and Interacting Health Emergencies. Clin Infect Dis. 2020. Epub 2020/06/17. doi: 10.1093/cid/ciaa773.
5. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020;383(6):517-25. Epub 2020/06/04. doi: 10.1056/NEJMoa2016638.
6. Rodríguez-Molinero A, Pérez-López C, Gálvez-Barrón C, Miñarro A, Macho O, López GF, et al. Observational study of azithromycin in hospitalized patients with COVID-19. PloS one. 2020;15(9):e0238681. Epub 2020/09/04. doi: 10.1371/journal.pone.0238681.
7. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030-40. Epub 2020/10/09. doi: 10.1056/NEJMoa2022926.
8. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2021801.

9. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Epub 2020/05/31. doi: 10.1016/j.jinf.2020.05.046.
10. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020. Epub 2020/07/28. doi: 10.1016/j.cmi.2020.07.016.
11. Clinical management of COVID-19. Interim guidance - 27 May 2020. Geneva, Switzerland: World Health Organization (WHO); 2020. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
12. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.: COVID-19 Treatment Guidelines Panel. National Institutes of Health (NIH); 2020. Available from: https://www.covid19treatmentguidelines.nih.gov/.
13. Abelenda-Alonso G, Padullés A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, et al. Antibiotic prescription during the COVID-19 pandemic: A biphasic pattern. Infect Control Hosp Epidemiol. 2020;41(11):1371-2. Epub 2020/07/31. doi: 10.1017/ice.2020.381.
14. Buehrle DJ, Decker BK, Wagener MM, Adalja A, Singh N, McEllistrem MC, et al. Antibiotic Consumption and Stewardship at a Hospital outside of an Early Coronavirus Disease 2019 Epicenter. Antimicrob Agents Chemother. 2020;64(11). Epub 2020/08/21. doi: 10.1128/aac.01011-20.
15. Dieringer TD, Furukawa D, Graber CJ, Stevens VW, Jones MM, Rubin MA, et al. Inpatient antibiotic utilization in the Veterans' Health Administration during the coronavirus disease 2019 (COVID-19) pandemic. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/10/21. doi: 10.1017/ice.2020.1277.
16. Gonzalez-Zorn B. Antibiotic use in the COVID-19 crisis in Spain. Clin Microbiol Infect. 2020. Epub 2020/11/30. doi: 10.1016/j.cmi.2020.09.055.
17. Nestler MJ, Godbout E, Lee K, Kim J, Noda AJ, Taylor P, et al. Impact of COVID-19 on pneumonia-focused antibiotic use at an academic medical center. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/07/24. doi: 10.1017/ice.2020.362.

18. Staub MB, Beaulieu RM, Graves J, Nelson GE. Changes in Antimicrobial Utilization During the COVID-19 Pandemic after Implementation of a Multispecialty Clinical Guidance Team. Infect Control Hosp Epidemiol. 2020:1-28. Epub 2020/10/27. doi: 10.1017/ice.2020.1291.
19. Velasco-Arnaiz E, López-Ramos MG, Simó-Nebot S, Jordan I, Ríos-Barnés M, Urrea-Ayala M, et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/06/25. doi: 10.1017/ice.2020.312.
20. Katz SE, Spencer H, Zhang M, Banerjee R. Impact of the COVID-19 Pandemic on Infectious Diagnoses and Antibiotic Use in Pediatric Ambulatory Practices. Journal of the Pediatric Infectious Diseases Society. 2020. doi: 10.1093/jpids/piaa124.
21. COVID-19: Details on cases. New Delhi, India: PRS Legislative Research 2020.
22. Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. J Clin Epidemiol. 2018;103:82-91. Epub 2018/06/10. doi: 10.1016/j.jclinepi.2018.05.026.
23. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19). Our World in Data. 2020.
24. Census of India 2011. Population projections for India and States, 2011-2036: Report of the Technical Group on population projections. Nirman Bhawan, New Delhi, India: National Commission on Population, Ministry of Health and Family Welfare, Government of India, 2019.
25. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. Lancet Infect Dis. 2019;19(1):67-75. Epub 2018/12/14. doi: 10.1016/S1473-3099(18)30547-4.
26. Nafade V, Huddart S, Sulis G, Daftary A, Miraj SS, Saravu K, et al. Over-the-counter antibiotic dispensing by pharmacies: a standardised patient study in Udupi district, India. BMJ Glob Health. 2019;4(6):e001869. Epub 2019/12/05. doi: 10.1136/bmjgh-2019-001869.

27. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system 2019. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2019.

28. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278-80. Epub 2019/11/30. doi: 10.1016/S1473-3099(19)30532-8.

29. Xiao H, Augusto O, Wagenaar BH. Reflection on modern methods: a common error in the segmented regression parameterization of interrupted time-series analyses. Int J Epidemiol. 2020. Epub 2020/10/25. doi: 10.1093/ije/dyaa148.

30. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Pearson CAB, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nature Medicine. 2020;26(8):1205-11. doi: 10.1038/s41591-020-0962-9.

31. CDC COVID Data Tracker Atlanta, Georgia: Centers for Disease Control and Prevention (CDC); 2020 [cited 2020 Dec 5, 2020]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics.

32. Hatoun J, Correa ET, Donahue SMA, Vernacchio L. Social Distancing for COVID-19 and Diagnoses of Other Infectious Diseases in Children. Pediatrics. 2020;146(4). Epub 2020/09/04. doi: 10.1542/peds.2020-006460.

33. Jebb AT, Tay L, Wang W, Huang Q. Time series analysis for psychological research: examining and forecasting change. Frontiers in Psychology. 2015;6(727). doi: 10.3389/fpsyg.2015.00727.

34. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for COVID-19 infection [issued on 25th May, 2020 in supersession of previous advisory dated 23rd March, 2020]. New Delhi, India: Ministry of Health and Family Welfare, Government of India; 2020.

35. Donde S, Mishra A, Kochhar P. Azithromycin in acute bacterial upper respiratory tract infections: an Indian non-interventional study. Indian J Otolaryngol Head Neck Surg. 2014;66(Suppl 1):225-30. Epub 2014/02/18. doi: 10.1007/s12070-011-0437-x.

36. Doan T, Worden L, Hinterwirth A, Arzika AM, Maliki R, Abdou A, et al. Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution. N Engl J Med. 2020;383(20):1941-50. Epub 2020/11/12. doi: 10.1056/NEJMoa2002606.
37. Babu R, Kumar A, Karim S, Warrier S, Nair SG, Singh SK, et al. Faecal carriage rate of extended-spectrum β-lactamase-producing Enterobacteriaceae in hospitalised patients and healthy asymptomatic individuals coming for health check-up. J Glob Antimicrob Resist. 2016;6:150-3. Epub 2016/08/18. doi: 10.1016/j.jgar.2016.05.007.
38. Hooda Y, Tanmoy AM, Sajib MSI, Saha S. Mass azithromycin administration: considerations in an increasingly resistant world. BMJ Glob Health. 2020;5(6). Epub 2020/06/12. doi: 10.1136/bmjgh-2020-002446.
39. John J, Van Aart CJ, Grassly NC. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. PLoS Negl Trop Dis. 2016;10(4):e0004616. Epub 2016/04/16. doi: 10.1371/journal.pntd.0004616.
40. Carey ME, Jain R, Yousuf M, Maes M, Dyson ZA, Thu TNH, et al. Spontaneous emergence of azithromycin resistance in independent lineages of Salmonella Typhi in Northern India. bioRxiv. 2020:2020.10.23.351957. doi: 10.1101/2020.10.23.351957.
41. Connor BA. Preparing International Travelers: Travelers' diarrhea. 2020. In: CDC Yellow Book 2020: Health Information for International Travel [Internet]. New York, NY, USA: Oxford University Press. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2020/preparing-international-travelers/travelers-diarrhea.
42. Gandra S, Choi J, McElvania E, Green SJ, Harazin M, Thomson RB, et al. Faropenem resistance causes in vitro cross-resistance to carbapenems in ESBL-producing Escherichia coli. Int J Antimicrob Agents. 2020;55(3):105902. Epub 2020/01/17. doi: 10.1016/j.ijantimicag.2020.105902.
43. Clinical management protocol: COVID-19. New Delhi, India: Directorate General of Health Services (EMR Division), Ministry of Health and Family Welfare, Government of India; 2020. Available from:

https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf.

44. Gazette Notification (26th March, 2020), (2020).
45. Mackintosh M, Channon A, Karan A, Selvaraj S, Cavagnero E, Zhao H. What is the private sector? Understanding private provision in the health systems of low-income and middle-income countries. Lancet. 2016;388(10044):596-605. Epub 2016/07/01. doi: 10.1016/S0140-6736(16)00342-1.
46. Vora A, Arora VK, Behera D, Tripathy SK. White paper on Ivermectin as a potential therapy for COVID-19. Indian J Tuberc. 2020;67(3):448-51. doi: 10.1016/j.ijtb.2020.07.031.
47. Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med. 2020;17(6):e1003139. doi: 10.1371/journal.pmed.1003139.
48. Qamar FN, Yousafzai MT, Khalid M, Kazi AM, Lohana H, Karim S, et al. Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. Lancet Infect Dis. 2018;18(12):1368-76. Epub 2018/12/07. doi: 10.1016/s1473-3099(18)30483-3.

S4-1 Text: Summary of the evidence regarding the impact of COVID-19 pandemic on antibiotic use.

Objective

We conducted a rapid systematic review to collate the available evidence on the impact of COVID-19 on antimicrobial utilization.

Methods

We searched PubMed for potentially relevant studies published from December 31st to present, using a combination of terms related to the concepts of "COVID-19" and "antibiotic" (S4-1 Table). No restrictions were placed with regards to language, geographic area or population. The screening process was performed in two steps (title/abstract screening followed by full-text screening) in order to select studies that had evaluated antibiotic consumption trends prior to and during the pandemic. Studies aimed at assessing the efficacy or effectiveness of specific therapeutic regimens for COVID-19 cases and those solely reporting on the proportion of COVID-19 patients receiving antimicrobials without any sort of comparison against the pre-pandemic period were considered ineligible. Qualitative studies that reported on prescribing behaviours among practitioners were also excluded, unless quantitative data on actual antibiotic use were also collected.

Key findings

A total of 3,553 unique citations were identified as of December 2nd, 2020. After title and abstract screening, 52 publications were deemed potentially relevant and were thus selected for full-text evaluation. We excluded:

- 22 studies that only reported on the proportion of bacterial coinfections among COVID-19 cases and/or the proportion of these patients receiving antimicrobial treatment without attempting any kind of comparison with the pre-pandemic phase;[1–22]
- 15 commentaries or perspective pieces;[23–37]

- 7 reviews (including two systematic reviews on the incidence of bacterial co-infections in COVID-19 cases).[38-44]

We found 8 ecologic studies aimed at assessing the impact of the pandemic on antibiotic use, conducted either in Spain (3/8) or in the United States (5/8) (S4-2 Table).[45-51] All but one were hospital-based studies, the exception being a study based on IQVIA data from Spain which did not distinguish between inpatient and outpatient care. Most of these studies (6/8) utilized a difference-in-difference analysis technique to compare antibiotic use levels between two or more periods before and during the pandemic, and one study used an interrupted time series analysis to examine the trends in consumption over time and evaluate the impact of COVID-19 from March 2020 onwards.[46] The study based on IQVIA data only provided a descriptive analysis of time series data from 2017 to March 2020.[51] Although populations and settings varied substantially across studies, a consistent increase in antibiotic use in inpatient adult care was observed particularly in March and April 2020. This increase was mostly attributable to a greater use of selected antibiotics such as azithromycin and, in certain settings, ceftriaxone. In contrast, antibiotic use was reported to be lower in pediatric care settings, possibly reflecting the lower number of visits occurred during the pandemic period as compared to the pre-pandemic phase, both overall and for infectious conditions. It should be noticed, however, that most of these studies suffered from a very short observation period and often failed to properly account for seasonality.

References

1. Bogossian EG, Taccone FS, Izzi A, Yin N, Garufi A, Hublet S, et al. The Acquisition of Multidrug-Resistant Bacteria in Patients Admitted to COVID-19 Intensive Care Units: A Monocentric Retrospective Case Control Study. Microorganisms. 2020;8(11). Epub 2020/11/25. doi: 10.3390/microorganisms8111821.

2. Castaldi S, Luconi E, Marano G, Auxilia F, Maraschini A, Bono P, et al. Hospital Acquired Infections in COVID-19 patients in sub intensive care unit. Acta Biomed. 2020;91(3):e2020017. Epub 2020/09/15. doi: 10.23750/abm.v91i3.10376.
3. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care. 2020;10(1):119. Epub 2020/09/08. doi: 10.1186/s13613-020-00736-x.
4. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalised patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2020. Epub 2020/08/04. doi: 10.1016/j.cmi.2020.07.041.
5. Gomez-Simmonds A, Annavajhala MK, McConville TH, Dietz DE, Shoucri SM, Laracy JC, et al. Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/11/18. doi: 10.1093/jac/dkaa466.
6. Li J, Wang J, Yang Y, Cai P, Cao J, Cai X, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrob Resist Infect Control. 2020;9(1):153. Epub 2020/09/24. doi: 10.1186/s13756-020-00819-1.
7. Luyt CE, Sahnoun T, Gautier M, Vidal P, Burrel S, Pineton de Chambrun M, et al. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care. 2020;10(1):158. Epub 2020/11/25. doi: 10.1186/s13613-020-00775-4.
8. Montrucchio G, Corcione S, Sales G, Curtoni A, De Rosa FG, Brazzi L. Carbapenem resistant Klebsiella pneumoniae in ICU-admitted COVID-19 Patients: Keep an eye on the ball. J Glob Antimicrob Resist. 2020;23:398-400. Epub 2020/11/27. doi: 10.1016/j.jgar.2020.11.004.
9. Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City

pandemic surge. Infect Control Hosp Epidemiol. 2020:1-5. Epub 2020/07/25. doi: 10.1017/ice.2020.368.

10. Para O, Caruso L, Ronchetti M, Finocchi M, Guidi S, Spinicci M. Superinfection with difficult-to-treat bacteria in COVID-19 patients: a call for compliance with diagnostic and antimicrobial stewardship. Intern Emerg Med. 2020:1-3. Epub 2020/11/23. doi: 10.1007/s11739-020-02537-3.
11. Tiri B, Sensi E, Marsiliani V, Cantarini M, Priante G, Vernelli C, et al. Antimicrobial Stewardship Program, COVID-19, and Infection Control: Spread of Carbapenem-Resistant Klebsiella Pneumoniae Colonization in ICU COVID-19 Patients. What Did Not Work? J Clin Med. 2020;9(9). Epub 2020/08/29. doi: 10.3390/jcm9092744.
12. Yu D, Ininbergs K, Hedman K, Giske CG, Strålin K, Özenci V. Low prevalence of bloodstream infection and high blood culture contamination rates in patients with COVID-19. PLoS One. 2020;15(11):e0242533. Epub 2020/11/24. doi: 10.1371/journal.pone.0242533.
13. Goncalves Mendes Neto A, Lo KB, Wattoo A, Salacup G, Pelayo J, DeJoy R, 3rd, et al. Bacterial Infections and Patterns of Antibiotic Use in Patients with COVID-19. J Med Virol. 2020. Epub 2020/08/19. doi: 10.1002/jmv.26441
14. Karami Z, Knoop BT, Dofferhoff ASM, Blaauw MJT, Janssen NA, van Apeldoorn M, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. Infect Dis (Lond). 2020:1-9. Epub 2020/10/27. doi: 10.1080/23744235.2020.1839672.
15. Liu H, Gao J, Wang Y, Jie J, Luo J, Xu Y, et al. Epidemiological and clinical characteristics of 2019 novel coronavirus disease (COVID-19) in Jilin, China: A descriptive study. Medicine (Baltimore). 2020;99(47):e23407. Epub 2020/11/22. doi: 10.1097/md.0000000000023407.
16. Rothe K, Feihl S, Schneider J, Wallnöfer F, Wurst M, Lukas M, et al. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study

in light of antibiotic stewardship. Eur J Clin Microbiol Infect Dis. 2020. Epub 2020/11/04. doi: 10.1007/s10096-020-04063-8.

17. Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S, et al. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect. 2020. Epub 2020/09/29. doi: 10.1016/j.jinf.2020.09.024.
18. Shin DH, Kang M, Song KH, Jung J, Kim ES, Kim HB. A Call for Antimicrobial Stewardship in Patients with COVID-19: A Nationwide Cohort Study in Korea. Clin Microbiol Infect. 2020. Epub 2020/11/03. doi: 10.1016/j.cmi.2020.10.024.
19. Stevens RW, Jensen K, O'Horo JC, Shah A. Antimicrobial prescribing practices at a tertiary-care center in patients diagnosed with COVID-19 across the continuum of care. Infect Control Hosp Epidemiol. 2020:1-4. Epub 2020/07/25. doi: 10.1017/ice.2020.370.
20. Townsend L, Hughes G, Kerr C, Kelly M, O'Connor R, Sweeney E, et al. Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. JAC Antimicrob Resist. 2020;2(3):dlaa071. Epub 2020/08/31. doi: 10.1093/jacamr/dlaa071.
21. Vaughn VM, Gandhi T, Petty LA, Patel PK, Prescott HC, Malani AN, et al. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study. Clin Infect Dis. 2020. Epub 2020/08/22. doi: 10.1093/cid/ciaa1239.
22. Wang L, Amin AK, Khanna P, Aali A, McGregor A, Bassett P, et al. An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/11/14. doi: 10.1093/jac/dkaa475.
23. Abena PM, Decloedt EH, Bottieau E, Suleman F, Adejumo P, Sam-Agudu NA, et al. Chloroquine and Hydroxychloroquine for the Prevention or Treatment of COVID-19 in Africa: Caution for Inappropriate Off-label Use in Healthcare Settings. Am J Trop Med Hyg. 2020;102(6):1184-8. Epub 2020/04/24. doi: 10.4269/ajtmh.20-0290.

24. Arshad M, Mahmood SF, Khan M, Hasan R. Covid -19, misinformation, and antimicrobial resistance. Bmj. 2020;371:m4501. Epub 2020/11/26. doi: 10.1136/bmj.m4501.
25. Comber SDW, Upton M, Lewin S, Powell N, Hutchinson TH. COVID-19, antibiotics and One Health: a UK environmental risk assessment. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/08/14. doi: 10.1093/jac/dkaa338.
26. DeJong C, Wachter RM. The Risks of Prescribing Hydroxychloroquine for Treatment of COVID-19-First, Do No Harm. JAMA internal medicine. 2020;180(8):1118-9. Epub 2020/04/30. doi: 10.1001/jamainternmed.2020.1853.
27. Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH. Tackling antimicrobial resistance in the COVID-19 pandemic. Bull World Health Organ. 2020;98(7):442-a. Epub 2020/08/04. doi: 10.2471/blt.20.268573.
28. Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. Lancet Glob Health. 2020. Epub 2020/11/15. doi: 10.1016/s2214-109x(20)30444-7.
29. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. Epub 2020/04/30. doi: 10.1016/j.cmi.2020.04.024.
30. Miranda C, Silva V, Capita R, Alonso-Calleja C, Igrejas G, Poeta P. Implications of antibiotics use during the COVID-19 pandemic: present and future. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/08/25. doi: 10.1093/jac/dkaa350.
31. Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? Euro Surveill. 2020;25(45). Epub 2020/11/14. doi: 10.2807/1560-7917.Es.2020.25.45.2001886.
32. Nieuwlaat R, Mbuagbaw L, Mertz D, Burrows L, Bowdish DME, Moja L, et al. COVID-19 and Antimicrobial Resistance: Parallel and Interacting Health Emergencies. Clin Infect Dis. 2020. Epub 2020/06/17. doi: 10.1093/cid/ciaa773.

33. Pulia MS, Wolf I, Schulz LT, Pop-Vicas A, Schwei RJ, Lindenauer PK. COVID-19: An Emerging Threat to Antibiotic Stewardship in the Emergency Department. West J Emerg Med. 2020;21(5):1283-6. Epub 2020/09/25. doi: 10.5811/westjem.2020.7.48848.
34. Rawson TM, Ming D, Ahmad R, Moore LSP, Holmes AH. Antimicrobial use, drug-resistant infections and COVID-19. Nat Rev Microbiol. 2020;18(8):409-10. Epub 2020/06/04. doi: 10.1038/s41579-020-0395-y.
35. Rawson TM, Moore LSP, Castro-Sanchez E, Charani E, Davies F, Satta G, et al. COVID-19 and the potential long-term impact on antimicrobial resistance. J Antimicrob Chemother. 2020;75(7):1681-4. Epub 2020/05/21. doi: 10.1093/jac/dkaa194.
36. Vaillancourt M, Jorth P. The Unrecognized Threat of Secondary Bacterial Infections with COVID-19. mBio. 2020;11(4). Epub 2020/08/10. doi: 10.1128/mBio.01806-20.
37. Youngs J, Wyncoll D, Hopkins P, Arnold A, Ball J, Bicanic T. Improving antibiotic stewardship in COVID-19: Bacterial co-infection is less common than with influenza. J Infect. 2020;81(3):e55-e7. Epub 2020/07/01. doi: 10.1016/j.jinf.2020.06.056.
38. Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: What can we expect? Clin Infect Dis. 2020. Epub 2020/05/04. doi: 10.1093/cid/ciaa524.
39. Fattorini L, Creti R, Palma C, Pantosti A. Bacterial coinfections in COVID-19: an underestimated adversary. Ann Ist Super Sanita. 2020;56(3):359-64. Epub 2020/09/23. doi: 10.4415/ann_20_03_14.
40. Kotwani A, Gandra S. Potential pharmacological agents for COVID-19. Indian J Public Health. 2020;64(Supplement):S112-s6. Epub 2020/06/05. doi: 10.4103/ijph.IJPH_456_20.
41. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020. Epub 2020/07/28. doi: 10.1016/j.cmi.2020.07.016.
42. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Epub 2020/05/31. doi: 10.1016/j.jinf.2020.05.046.

43. Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi HAA, Jeda AS, et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020. Epub 2020/08/10. doi: 10.1002/iub.2356.
44. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020. Epub 2020/05/03. doi: 10.1093/cid/ciaa530.
45. Abelenda-Alonso G, Padullés A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, et al. Antibiotic prescription during the COVID-19 pandemic: A biphasic pattern. Infect Control Hosp Epidemiol. 2020;41(11):1371-2. Epub 2020/07/31. doi: 10.1017/ice.2020.381.
46. Buehrle DJ, Decker BK, Wagener MM, Adalja A, Singh N, McEllistrem MC, et al. Antibiotic Consumption and Stewardship at a Hospital outside of an Early Coronavirus Disease 2019 Epicenter. Antimicrob Agents Chemother. 2020;64(11). Epub 2020/08/21. doi: 10.1128/aac.01011-20.
47. Dieringer TD, Furukawa D, Graber CJ, Stevens VW, Jones MM, Rubin M, et al. Inpatient antibiotic utilization in the Veterans Administration during the COVID-19 pandemic. Infect Control Hosp Epidemiol. 2020:1-9. Epub 2020/10/21. doi: 10.1017/ice.2020.1277.
48. Nestler M, Godbout E, Lee K, Kim J, Noda AJ, Taylor P, et al. Impact of COVID-19 on Pneumonia-Focused Antibiotic Use at an Academic Medical Center. Infect Control Hosp Epidemiol. 2020:1-9. Epub 2020/07/24. doi: 10.1017/ice.2020.362.
49. Staub MB, Beaulieu RM, Graves J, Nelson GE. Changes in Antimicrobial Utilization During the COVID-19 Pandemic after Implementation of a Multispecialty Clinical Guidance Team. Infect Control Hosp Epidemiol. 2020:1-28. Epub 2020/10/27. doi: 10.1017/ice.2020.1291.
50. Velasco-Arnaiz E, López-Ramos MG, Simó-Nebot S, Jordan I, Ríos-Barnés M, Urrea-Ayala M, et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/06/25. doi: 10.1017/ice.2020.312.
51. Gonzalez-Zorn B. Antibiotic use in the COVID-19 crisis in Spain. Clin Microbiol Infect.

2020. Epub 2020/11/30. doi: 10.1016/j.cmi.2020.09.055.

S4-1 Table: Search strategy used in the rapid systematic review regarding the impact of COVID-19 pandemic on antibiotic use.

Concept	Search terms
COVID-19	(("Severe acute respiratory syndrome coronavirus 2"[nm] OR "COVID-19"[nm] OR 2019-nCoV[tiab] OR 2019nCoV[tiab] OR COVID-19[tiab] OR COVID19[tiab] OR SARS-CoV-2[tiab] OR SARS COV2[tiab] OR SARSCOV2[tiab] OR SARSCOV 2[tiab] OR (((wuhan[all fields] AND coronavirus*[tiab]) OR new coronavirus[tiab] OR novel coronavirus[tiab]))
AND	
Antibiotic	(("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR "anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR antibiotic*[tw] OR antimicrobial*[tw] OR antibacterial*[tw] OR anti bacterial*[tw] OR anti-infective*[tw]))

S4-2 Table: Features and findings of studies that evaluated the impact of COVID-19 on antibiotic use.

Study reference	Country	Design	Population and setting	Main findings
Abelenda-Alonso et al, *Infect Contr Hosp Epidemiol* (2020)	Spain	Before-and-after cross-sectional study comparing antibiotic dispensing in Jan-Apr 2019 versus Jan-Apr 2020.	All patients admitted to Bellvitge University Hospital (Barcelona).	▪ Similar levels of antibiotic use in Jan-Feb 2019 versus 2020. ▪ Significant increase in dispensing in Mar-Apr 2020 compared to 2019 (p<0.001). ▪ Rapid increase in use of amoxicillin/clavulanate in Mar 2020, followed by an increase in broad-spectrum agents in April.
Buehrle et al, *Antimicrob Agents Chemother* (2020)	United States	Interrupted time series analysis of selected antibiotic use between Jan 2018 and June 2020, comparing pre-pandemic period versus pandemic period (from March 2020).	All patients admitted at VA Pittsburgh hospital.	▪ 6.5% (95% CI: 3.0-10.1) monthly reduction in antibiotic use in Mar-Jun 2020 versus Jan 2018 – Feb 2020. ▪ 1.3% (95% CI: 0.7-4.8) monthly increase in antibiotic DOT per 1.000 patient bed days of care in Mar-Jun 2020. ▪ Significant increases in use of non-antipseudomonal penicillins and macrolides, with decrease in use of antipseudomonal penicillins, non-antipseudomonal cephalosporins and quinolones.
Dieringer et al, *Infect Control Hosp Epidemiol* (2020)	United States	Before-and-after study comparing antibiotic use in Jan-May 2020 versus the same period of 2015-2019.	All patients admitted to acute inpatient care in 84 facilities of Veterans' Health Administration.	▪ In Jan-May of each year during 2015-2019, antibiotic use decreased from 638 to 602 DOT per 1,000 DP (mean decrease, 9.1 DOT per 1,000 DP per year). ▪ Antibiotic use increased from 602 to 628 DOT per 1,000 DP in Jan-May 2020. ▪ Greatest increase in broad-spectrum agents used to treat community-acquired and hospital-acquired infections.
Gonzalez-Zorn, *Clin Microbiol Infect* (2020)	Spain	Descriptive study of antibiotic use in Spain based on time series data from IQVIA comparing March 2020 against the period Jan 2017-Feb 2020.	National antibiotic sales data, presumably in the private sector only.	▪ Azithromycin use in March 2020 was 400% the use in February 2020 and 320% that of January 2019. ▪ Other antibiotics increased in consumption in March 2020 as compared to February 2020 (e.g. ceftaroline, ceftolozane/tazobactam, cefditoren, ceftriaxone, colistin, doxycycline and linezolid). ▪ No impact evaluation and no adjustment for seasonality were performed.
Katz et al, *J Ped Infect Dis Soc* (2020)	United States	Before-and-after study comparing ambulatory pediatric antibiotic prescription rates and diagnoses in Mar-May 2020 versus Mar-May 2019.	Prescription data from 4 ambulatory settings affiliated with Vanderbilt University Medical Center (i.e. emergency department, urgent care clinics, primary care clinics, and retail health clinics).	▪ The number of visits and the proportion of visits for infectious conditions declined in 2020 (4267/7010 [60.8%] vs 11 412/16 671 [68.5%] in 2019; P < 0.001). ▪ The percent of visits with an antibiotic prescription was lower in 2020 vs 2019 both overall (2240/7010 [32%] vs 6373/16 671 [38.2%], P < 0.001) and among visits for infectious diseases (1324/2943 [45%] vs 3941/7471 [52.8%], P < 0.001).
Nestler et al, *Infect Contr Hosp Epidemiol* (2020)	United States	Before-and-after study comparing selected antibiotic use in Apr 2019 – Mar 2020 versus Apr-May 2020.	Pneumonia patients admitted to MICU, CICU or PM unit at Virginia Commonwealth University (VCU)	▪ Significant increase in ceftriaxone (+131, +138 and +193 DOT per 1,000 patient-days respectively in CICU, PM and MICU) and azithromycin (+103 and +109 DOT per 1,000 patient-days respectively in PM and MICU) use in Apr 2020.

Study reference	Country	Design	Population and setting	Main findings
			Health System, an 865-bed urban academic medical center.	▪ Significant decrease in levofloxacin use in May 2020 (-14 and -24 DOT per 1,000 patient-days respectively in CICU and MICU).
Staub et al, *Infect Contr Hosp Epidemiol* (2020)	United States	Before-and-after study comparing antibiotic use across three periods: Dec 2019 – Feb 2020, Mar 2020 and Apr-May 2020.	Patients admitted to either IM or MICU at Vanderbilt University Medical Center.	▪ Increase in weekly antibiotic use in the first COVID-19 period versus pre-COVID-19, both in IM (+145.3 DOT/1,000 days) and MICU (+204 DOT/1,000 days). ▪ Significant decrease in weekly azithromycin use (-58.2 DOT/1,000 days) during the second COVID-19 period in IM (no change in MICU).
Velasco-Arnaiz et al, *Infect Contr Hosp Epidemiol* (2020)	Spain	Before-and after study comparing antibiotic use in Feb-Apr 2020 versus the same period of 2019.	Patients admitted to PICU and non-PICU areas at San Joan de Deu Hospital, Barcelona.	▪ Increase in total antibiotic use in Mar 2020 versus Mar 2019 (+1.6 DOT/100 DP, mainly in non-PICU) and in Apr 2020 versus Apr 2019 (+35.5 DOT/100 DP, mainly in PICU). ▪ Increase in azithromycin use in 2020 versus 2019, mostly associated with hydroxychloroquine, particularly in PICU.

Abbreviations: CICU, coronary intensive care unit; DOT, days of therapy; DP, days present; IM, internal medicine; MICU, medical intensive care unit; PICU, pediatric intensive care unit; PM, progressive medicine.

S4-3 Table: List of oral formulations considered as child-appropriate

Type	Formulation
Solid	Chewable tablets
	Dispersible tablets
	"Kid" tablets*
	"Paediatric" tablets*
Liquid	Drops
	Dry suspensions
	Ordinary liquids
	Soluble powders
	Syrups

* According to the package label

S4-4 Table: List of all antimicrobials included in our dataset, along with AWaRe (2019) and ATC categories (2020).

Molecule	AWaRe category	ATC group
Amikacin	Access	Aminoglycosides
Amikacin/Cefepime	Discouraged	Combinations
Amoxicillin	Access	Penicillins
Amoxicillin/Clavulanate	Access	BL-BLI
Amoxicillin/Cloxacillin	Discouraged	Combinations
Amoxicillin/Dicloxacillin	Discouraged	Combinations
Amoxicillin/Flucloxacillin	Discouraged	Combinations
Amoxicillin/Sulbactam	Discouraged	BL-BLI
Amoxicillin/Tinidazole	Not included	Combinations
Ampicillin	Access	Penicillins
Ampicillin/Cloxacillin	Discouraged	Combinations
Ampicillin/Dicloxacillin	Discouraged	Combinations
Ampicillin/Flucloxacillin	Discouraged	Combinations
Ampicillin/Sulbactam	Access	BL-BLI
Arbekacin	Watch	Aminoglycosides
Azithromycin	Watch	Macrolides
Azithromycin/Cefixime	Discouraged	Combinations
Azithromycin/Cefpodoxime	Discouraged	Combinations
Azithromycin/Fluconazole/Ornidazole	Not included	Combinations
Azithromycin/Levofloxacin	Discouraged	Combinations
Azithromycin/Ofloxacin	Discouraged	Combinations
Aztreonam	Reserve	Other antibiotics
Balofloxacin	Watch	Quinolones
Cefaclor	Watch	Cephalosporins - 2nd
Cefadroxil	Access	Cephalosporins - 1st
Cefadroxil/Clavulanate	Discouraged	Cephalosporin - BLI
Cefalexin	Access	Cephalosporins - 1st
Cefalexin/Clavulanate	Discouraged	Cephalosporin - BLI
Cefazolin	Access	Cephalosporins - 1st
Cefdinir	Watch	Cephalosporins - 3rd
Cefditoren	Watch	Cephalosporins - 3rd
Cefepime	Watch	Cephalosporins - 4th & higher
Cefepime/Sulbactam	Discouraged	Cephalosporin - BLI
Cefepime/Tazobactam	Discouraged	Cephalosporin - BLI
Cefetamet	Watch	Cephalosporins - 3rd

Molecule	AWaRe category	ATC group
Cefixime	Watch	Cephalosporins - 3rd
Cefixime/Cefpodoxime	Discouraged	Combinations
Cefixime/Clavulanate	Discouraged	Cephalosporin - BLI
Cefixime/Cloxacillin	Discouraged	Combinations
Cefixime/Dicloxacillin	Discouraged	Combinations
Cefixime/Levofloxacin	Discouraged	Combinations
Cefixime/Linezolid	Discouraged	Combinations
Cefixime/Moxifloxacin	Discouraged	Combinations
Cefixime/Ofloxacin	Discouraged	Combinations
Cefixime/Ornidazole	Discouraged	Combinations
Cefixime/Sulbactam	Discouraged	Cephalosporin - BLI
Cefoperazone	Watch	Cephalosporins - 3rd
Cefoperazone/Sulbactam	Discouraged	Cephalosporin - BLI
Cefoperazone/Tazobactam	Discouraged	Cephalosporin - BLI
Cefotaxime	Watch	Cephalosporins - 3rd
Cefotaxime/Sulbactam	Discouraged	Cephalosporin - BLI
Cefpirome	Reserve	Cephalosporins - 4th & higher
Cefpirome/Sulbactam	Discouraged	Cephalosporin - BLI
Cefpodoxime	Watch	Cephalosporins - 3rd
Cefpodoxime/Clavulanate	Discouraged	Cephalosporin - BLI
Cefpodoxime/Cloxacillin	Discouraged	Combinations
Cefpodoxime/Dicloxacillin	Discouraged	Combinations
Cefpodoxime/Levofloxacin	Discouraged	Combinations
Cefpodoxime/Ofloxacin	Discouraged	Combinations
Cefpodoxime/Sulbactam	Discouraged	Cephalosporin - BLI
Cefprozil	Watch	Cephalosporins - 2nd
Ceftaroline	Reserve	Cephalosporins - 4th & higher
Ceftazidime	Watch	Cephalosporins - 3rd
Ceftazidime/Avibactam	Reserve	Cephalosporin - BLI
Ceftazidime/Sulbactam	Discouraged	Cephalosporin - BLI
Ceftazidime/Tazobactam	Discouraged	Cephalosporin - BLI
Ceftazidime/Tobramycin	Discouraged	Combinations
Ceftizoxime	Watch	Cephalosporins - 3rd
Ceftizoxime/Sulbactam	Discouraged	Cephalosporin - BLI
Ceftizoxime/Tazobactam	Discouraged	Cephalosporin - BLI
Ceftriaxone	Watch	Cephalosporins - 3rd
Ceftriaxone/Sulbactam	Discouraged	Cephalosporin - BLI
Ceftriaxone/Tazobactam	Discouraged	Cephalosporin - BLI

Molecule	AWaRe category	ATC group
Ceftriaxone/Vancomycin	Discouraged	Combinations
Cefuroxime	Watch	Cephalosporins - 2nd
Cefuroxime/Clavulanate	Discouraged	Cephalosporin - BLI
Cefuroxime/Linezolid	Discouraged	Combinations
Cefuroxime/Ornidazole	Not included	Combinations
Cefuroxime/Sulbactam	Discouraged	Cephalosporin - BLI
Chloramphenicol	Access	Other antibiotics
Ciprofloxacin	Watch	Quinolones
Ciprofloxacin/Metronidazole	Discouraged	Combinations
Ciprofloxacin/Ornidazole	Discouraged	Combinations
Ciprofloxacin/Tinidazole	Discouraged	Combinations
Clarithromycin	Watch	Macrolides
Clarithromycin/Tinidazole	Not included	Combinations
Clindamycin	Access	Other antibiotics
Cloxacillin	Access	Penicillins
Colistin	Reserve	Polymyxins
Daptomycin	Reserve	Other antibiotics
Dicloxacillin	Access	Penicillins
Diloxanide/Metronidazole	Not included	Combinations
Diloxanide/Tinidazole	Not included	Combinations
Doripenem	Watch	Carbapenems
Doxycycline	Access	Tetracyclines
Doxycycline/Ornidazole	Not included	Combinations
Doxycycline/Tinidazole	Discouraged	Combinations
Ertapenem	Watch	Carbapenems
Erythromycin	Watch	Macrolides
Faropenem	Reserve	Carbapenems
Flucloxacillin	Access	Penicillins
Fluconazole/Ornidazole	Not included	Combinations
Fluconazole/Tinidazole	Not included	Combinations
Fosfomycin (O)	Watch	Other antibiotics
Fosfomycin (P)	Reserve	Other antibiotics
Furazolidone/Metronidazole	Not included	Combinations
Garenoxacin	Watch	Quinolones
Gatifloxacin	Watch	Quinolones
Gatifloxacin/Ornidazole	Discouraged	Combinations
Gemifloxacin	Watch	Quinolones
Gentamicin	Access	Aminoglycosides

Molecule	AWaRe category	ATC group
Imipenem/Cilastatin	Watch	Carbapenems
Isepamicin	Watch	Aminoglycosides
Kanamycin	Watch	Aminoglycosides
Levofloxacin	Watch	Quinolones
Levofloxacin/Metronidazole	Discouraged	Combinations
Levofloxacin/Ornidazole	Discouraged	Combinations
Lincomycin	Watch	Other antibiotics
Linezolid	Reserve	Other antibiotics
Lomefloxacin	Watch	Quinolones
Lymecycline	Watch	Tetracyclines
Meropenem	Watch	Carbapenems
Meropenem/Sulbactam	Discouraged	Carbapenem - BLI
Meropenem/Tazobactam	Discouraged	Carbapenem - BLI
Metronidazole	Access	Imidazoles
Metronidazole/Nalidixic Acid	Not included	Combinations
Minocycline (O)	Watch	Tetracyclines
Minocycline (P)	Reserve	Tetracyclines
Moxifloxacin	Watch	Quinolones
Nalidixic acid	Watch	Quinolones
Netilmicin	Watch	Aminoglycosides
Nimorazole/Ofloxacin	Discouraged	Combinations
Nitrofurantoin	Access	Other antibiotics
Norfloxacin	Watch	Quinolones
Norfloxacin/Metronidazole	Discouraged	Combinations
Norfloxacin/Tinidazole	Discouraged	Combinations
Ofloxacin	Watch	Quinolones
Ofloxacin/Metronidazole	Not included	Combinations
Ofloxacin/Ornidazole	Discouraged	Combinations
Ofloxacin/Tinidazole	Discouraged	Combinations
Ornidazole	Not included	Imidazoles
Oxytetracycline	Watch	Tetracyclines
Pazufloxacin	Watch	Quinolones
Penicillin G	Access	Penicillins
Penicillin G/Streptomycin	Discouraged	Combinations
Penicillin V	Access	Penicillins
Piperacillin/Tazobactam	Watch	BL-BLI
Polymyxin B	Reserve	Polymyxins
Prulifloxacin	Watch	Quinolones

Molecule	AWaRe category	ATC group
Roxithromycin	Watch	Macrolides
Sparfloxacin	Watch	Quinolones
Spiramycin	Watch	Macrolides
Streptomycin	Watch	Aminoglycosides
Sulbactam	Not included	BLI
Sultamicillin	Access	Penicillins
Teicoplanin	Watch	Glycopeptides
Tetracycline	Access	Tetracyclines
Tetracycline/Tinidazole	Not included	Combinations
Ticarcillin/Clavulanate	Discouraged	BL-BLI
Tigecycline	Reserve	Other antibiotics
Tinidazole	Not included	Imidazoles
Tobramycin	Watch	Aminoglycosides
Trimethoprim	Access	Sulfonamides
Trimethoprim/Sulfamethoxazole	Access	Sulfonamides
Vancomycin	Watch	Glycopeptides

Abbreviations: ATC, Anatomical Therapeutic Chemical; AWaRe, Access Watch Reserve; BL, beta-lactam; BLI, beta-lactamase inhibitor; CQ, chloroquine; HCQ, hydroxychloroquine.

S4-2 Text: Detailed methods

1. Interrupted time series analysis

We conducted segmented regression analyses of time series data to assess how much the spread of SARS-CoV-2 infection affected monthly sales volumes of the following drug groups, excluding child-appropriate formulations (CAF): 1) total antibiotics (including azithromycin), 2) azithromycin alone, and 3) hydroxychloroquine (HCQ).[1-5]

1.1 Robustness of sequential measures

Both pre-pandemic and pandemic-time data points were collected at regular monthly intervals, and no major concerns exist with respect to possible changes in the collection method over the study period. A total of 27 data points before the start of the pandemic were available for our analyses. On the one hand, this might not be enough to properly identify underlying seasonal trends. On the other hand, demographic, environmental and epidemiologic characteristics can be considered reasonably stable throughout the relatively short study period, the only exception being the spread of SARS-CoV-2 infection. Therefore, underlying historical trends were considered to be minimal and very unlikely to affect our estimates.[2] The effects of the ban on irrational fixed-dose combinations (FDCs) issued in September 2018, likely observable from 2019 onwards, were expected to be more qualitative (type of antibiotics being prescribed and sold) rather than quantitative, thus producing minor changes to the overall volume of antibiotic sales. Owing to the very limited number of data points available before this policy change, we could not adequately evaluate the potential changes it produced as compared to the previous period, but this is very unlikely to affect our estimates.

1.2 Model specification and checking

1.2.1 Impact of COVID-19 on non-CAF antibiotic sales

First, we used generalized linear models with least-squares estimation to predict the effect of the pandemic on sales volumes, without correcting for seasonality:

Model 1 $$Y_m = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 XT + \varepsilon$$

where:

- Y_m is the outcome, representing monthly sales volume expressed in Standard Units (SU);
- T is the time unit, expressed in months (from January 2018 to September 2020);
- X is a dummy variable representing the pre-pandemic period (up to March 2020, X = 0) and the pandemic period (from April 2020 onwards, X = 1);
- XT is a scaled interaction term with time that takes value 0 before the pandemic and until the end of the lockdown period (i.e. May 2020 inclusive), and subsequently increases by one-unit each month;
- β_0 is the intercept, interpreted as the outcome value at the beginning of the observation period (January 2018);
- β_1 is the pre-pandemic trend;
- β_2 is the average change in level for the initial phase of the pandemic (i.e. during the preventive lockdown period);
- β_3 is the slope or trend change in the outcome after the lockdown phase;
- ε is the error term.

However, Model 1 above did not account for autocorrelation, thus failing to accurately estimate both level and slope changes due to the pandemic.[1,2,6]

The outcome (sales volume of all antibacterial drugs) was found to follow a fairly normal distribution, but the visual inspection of correlograms suggested the presence of autocorrelation likely attributable to seasonality. Partial autocorrelation (i.e. correlation between non-consecutive values) was also observed, and a similar pattern could be identified in the distribution of residuals after fitting Model 1 without seasonal correction (S4-1 Figure).

In order to account for seasonality, we modified Model 1 and included a fixed effect term Z for the rainy season (July to October),[5,7] during which antimicrobial use seems to peak substantially as compared to the rest of the year:

Model 2 $$Y_m = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 XT + \beta_4 Z + \varepsilon$$

where β_4 represents the average change in level of Y for the rainy months compared to the other months.

The inclusion of a single dummy variable for the rainy season rather than several dummies for each month of the year or for quarters allowed to properly correct for seasonality without incurring in over-parameterization.[7,8]

The distribution of residuals improved substantially as compared to the previous model. Furthermore, the Durbin-Watson test statistic was not indicative of autocorrelation (DW = 2.0024), and the Ljung-Box test showed no evidence of lack of fit (P = 0.72).[6] We therefore chose Model 2 to estimate the impact of COVID-19 pandemic on monthly sales volume of antibacterial drugs.

1.2.2 Impact of COVID-19 on azithromycin sales

In order to examine the effect of the pandemic on azithromycin sales volumes, we followed the same steps described above for antibacterial drug sales. The outcome variable was found to follow an approximately normal distribution, similarly to what observed with the previous one. However, in the case of azithromycin sales, Model 2 (segmented regression with a fixed effect term for the rainy season) failed to properly account for the underlying seasonal and non-seasonal trends. For this reason, we opted for an alternative approach to seasonality adjustment, replacing the fixed effect term for rainy season with sine and cosine functions of time (harmonic seasonal model or Fourier terms).[5,7,9] Only those found to be statistically significant (P < 0.05) were retained in the model. Yet, we still found evidence

of residual serial correlation and further modified the model by including autocorrelated errors up to lag 4 as follows:

Model 3 $Y_m = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 XT + \beta_4 Z + sin1 + cos1 + sin2 + cos2 + R_m$

where *sin1*, *cos1*, *sin2* and *cos2* are the Fourier terms and R_m is the error term inclusive of autocorrelated errors ($R_m = \phi_1 + \phi_2 + \phi_3 + \phi_4 + \varepsilon$).

The model's goodness-of-fit substantially improved, as suggested by the Durbin-Watson test (DW = 2.0404), the Ljung-Box test (P = 0.55), the distribution of residuals and the visual inspection of the autocorrelation and partial autocorrelation function (S4-2 Figure). Model 3 was therefore selected to assess the impact of the pandemic on azithromycin sales volumes.

1.2.3 Impact of COVID-19 on HCQ sales

Contrary to the two outcomes examined previously, the distribution of monthly sales volume of HCQ was clearly skewed, particularly during the pandemic period. Because the stationary assumption was not satisfied and we lacked sufficient data points to use ARIMA models, we performed an exploratory analysis as detailed below. We first fitted Model 1 using an alternative definition of *X* and *XT*, such that COVID-19 pandemic was set to start in March 2020 and the effect of lockdown was ignored. Our choice was motivated by the visual inspection of crude time trends of HCQ sales showing an unexpected peak in March 2020, along with multiple reports from the field indicating a massive use of HCQ especially in prophylactic regimens. Hence, we fitted our model as follows:

Model 4 $Y_m = \beta_0 + \beta_1 T + \beta_2 W + \beta_3 WT + \varepsilon$

where:

- Y_m is the outcome, representing monthly sales volume expressed in Standard Units (SU);

- T is the time unit, expressed in months (from January 2018 to September 2020);
- W is a dummy variable representing the pre-pandemic period (up to February 2020, W = 0) and the pandemic period (from March 2020 onwards, W = 1);
- WT is a scaled interaction term with time that takes value 0 before the pandemic (i.e. March 2020 inclusive), and subsequently increases by one-unit each month;
- β_0 is the intercept, interpreted as the outcome value at the beginning of the observation period (January 2018);
- β_1 is the pre-pandemic trend;
- β_2 is the average change in level at the start of the pandemic;
- β_3 is the slope or trend change in the outcome from March 2020 onwards;
- ε is the error term.

Since HCQ is predominantly used as an immunomodulator and most commonly for non-infectious conditions, adjustment for seasonality was deemed unnecessary, and the model did not improve after adding a fixed effect for the rainy season or using alternative approaches for seasonality adjustment as done with total antibiotic sales and azithromycin sales. In order to account for the remaining serial correlation in the data, we corrected the model through the inclusion of an autocorrelated error term for lag 1:

Model 5 $$Y_m = \beta_0 + \beta_1 T + \beta_2 W + \beta_3 WT + R_m$$

where $R_m = \phi_1 + \phi_{10} + \varepsilon$.

The Durbin-Watson statistic (DW = 1.745) and Ljung-Box test (P = 0.59) were indicative of an acceptable goodness-of-fit for Model 5, and the autocorrelation function plot was also comforting. Yet, some degree of deviation from normality was observed in the distribution of residuals. These considerations along with the known violation of the stationary assumption impose caution in interpreting the results of this model.

1.3 Anticipated challenges and mitigation strategies

Although interrupted time-series (ITS) analysis was considered as the best approach for this study, this method does have limitations that were carefully evaluated and addressed. First, the correct specification of the underlying trend and seasonality is key to build the most appropriate model but, as mentioned previously, it is limited by the amount of available data points in the time series. A visual inspection of the series of each outcome seemed to suggest that the underlying trend was fairly linear after accounting for seasonal cycles. Furthermore, a range of approaches were explored to ensure the best possible adjustment for seasonality. In particular, a single fixed effect term for the rainy season was found to perform reasonably well in the model for non-CAF antibiotic sales. Attempts were also made with Fourier terms and spline functions of time, but the model with the fixed effect term resulted to be the best. In contrast, sine and cosine functions of time were successfully included in the model for azithromycin sales as this approach showed a better performance as compared to the alternatives. In addition, to capture non-seasonal trends, further adjustments were necessary to account for the remaining serial correlation in the data. We thus included autocorrelated errors until optimization of the autocorrelation and partial autocorrelation functions. With regards to the model for HCQ sales, autocorrelated errors were also used, but no seasonal adjustment was required given the different pattern of use of this drug.

For the selected models, residuals were found to behave as white noise, suggesting that the models might be correctly specified.[10]

Second, the likelihood of co-occurring events that could have acted as confounding factors was considered negligible. As discussed in section 1.1, no significant historical changes were anticipated.

Third, one of the assumptions of ITS analysis is that no major changes occurred in the way outcomes were recorded over the study period. Although the exact data collection method utilized by IQVIA Inc. has never been publicly released, their datasets have been used in several studies so far and are generally considered of very good quality. No significant

modifications have been introduced in the collection approach over the last 3 years, thus making us confident that the aforementioned assumption is satisfied.

2. Estimation of excess treatment courses from sales data

The IQVIA dataset available for our study includes dosage information for each formulation. While it is not possible to provide a reasonable and reliable estimate of the excess treatment courses from total antibiotics sales considered as a whole, we did so for azithromycin alone.

From our model, we found that, for the 4-month period from June to September 2020, over 99.5% of the formulations were either 500 mg (62%) or 250 mg (38%). According to the Indian national guidelines for antimicrobial use,[11] a single treatment course of azithromycin for respiratory tract infections is 500 mg once a day for 5 days.

Hence, we computed the number excess treatment courses as follows:

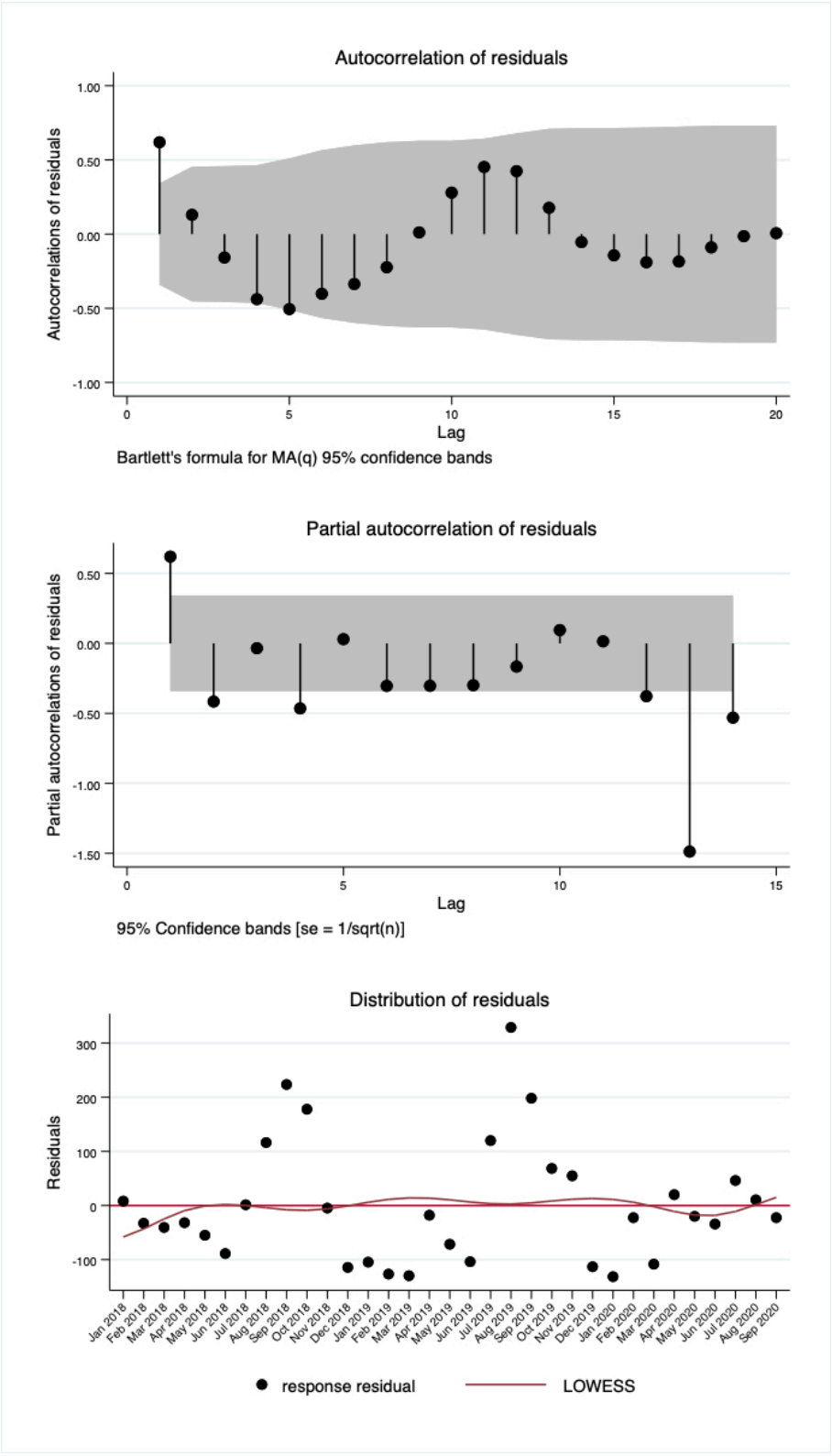
$$0.62 * \frac{39.0\ million\ doses\ sold}{5\ days} + 0.38 * \frac{\left(\frac{39.0\ million\ doses\ sold}{5\ days}\right)}{2} = 6.32 \text{ million treatment courses.}$$

References

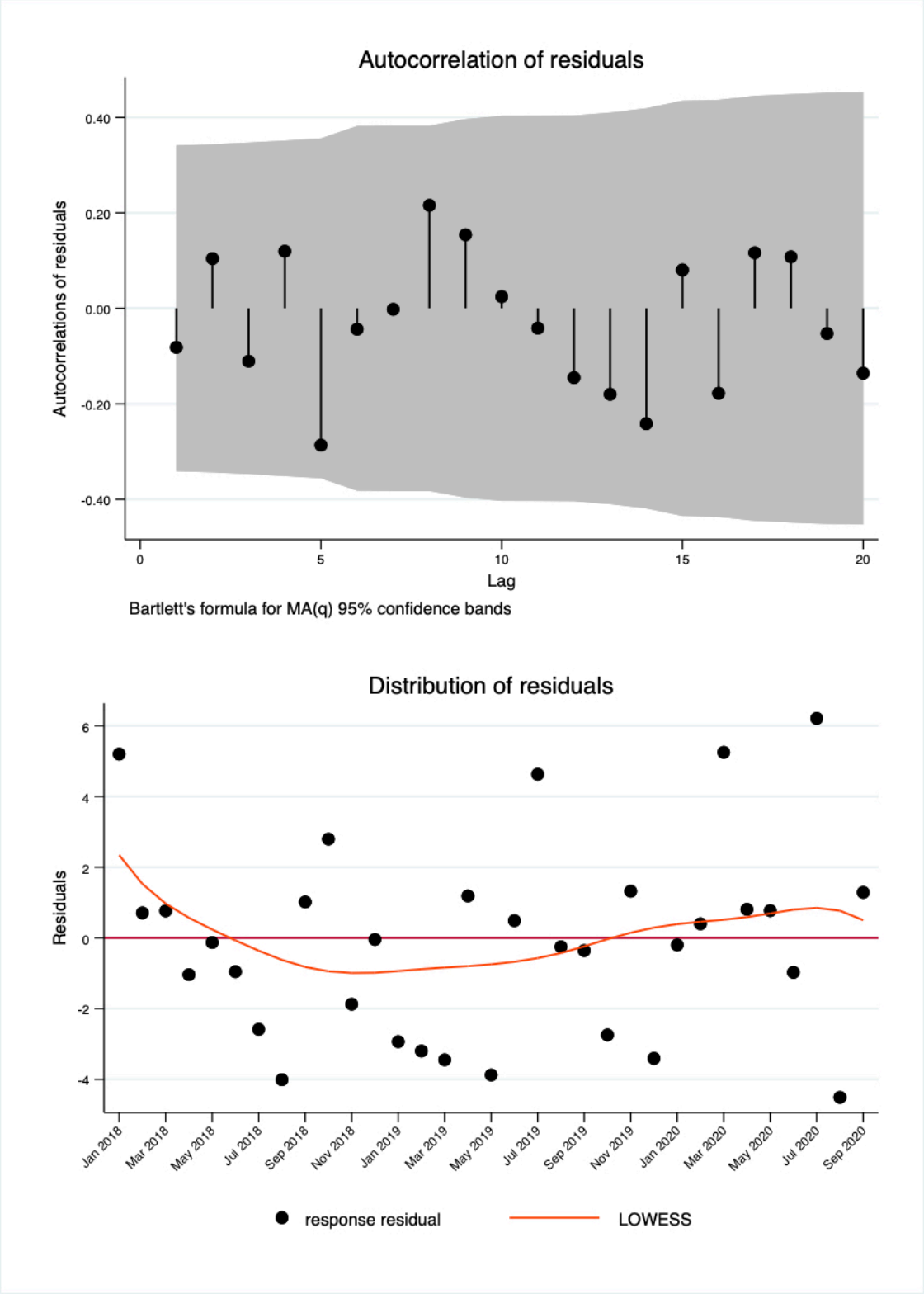
3. Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. J Clin Epidemiol. 2018;103:82-91. Epub 2018/06/10. doi: 10.1016/j.jclinepi.2018.05.026. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348-55. Epub 2016/06/11. doi: 10.1093/ije/dyw098.
4. Xiao H, Augusto O, Wagenaar BH. Reflection on modern methods: a common error in the segmented regression parameterization of interrupted time-series analyses. Int J Epidemiol. 2020. Epub 2020/10/25. doi: 10.1093/ije/dyaa148.

5. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309. Epub 2002/08/14. doi: 10.1046/j.1365-2710.2002.00430.x.
6. Shumway RH, Stoffer DS. Time series analysis and its applications : with R examples. 2017.
7. Linden A. Conducting Interrupted Time-series Analysis for Single- and Multiple-group Comparisons. The Stata Journal. 2015;15(2):480-500. doi: 10.1177/1536867X1501500208.
8. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. Int J Epidemiol. 2013;42(4):1187-95. Epub 2013/06/14. doi: 10.1093/ije/dyt092.
9. Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol. 2009;62(2):143-8. Epub 2008/11/18. doi: 10.1016/j.jclinepi.2008.08.007.
10. Jebb AT, Tay L, Wang W, Huang Q. Time series analysis for psychological research: examining and forecasting change. Frontiers in Psychology. 2015;6(727). doi: 10.3389/fpsyg.2015.00727.
11. Woodward WA, Gray HL, Elliott AC. Model identification. Applied time series analysis with R. 2nd ed: CRC Press; 2017.
12. National Standard Treatment Guidelines for Antimicrobial Use in Infectious Diseases. New Delhi, India: National Centre for Disease Control, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, 2016.

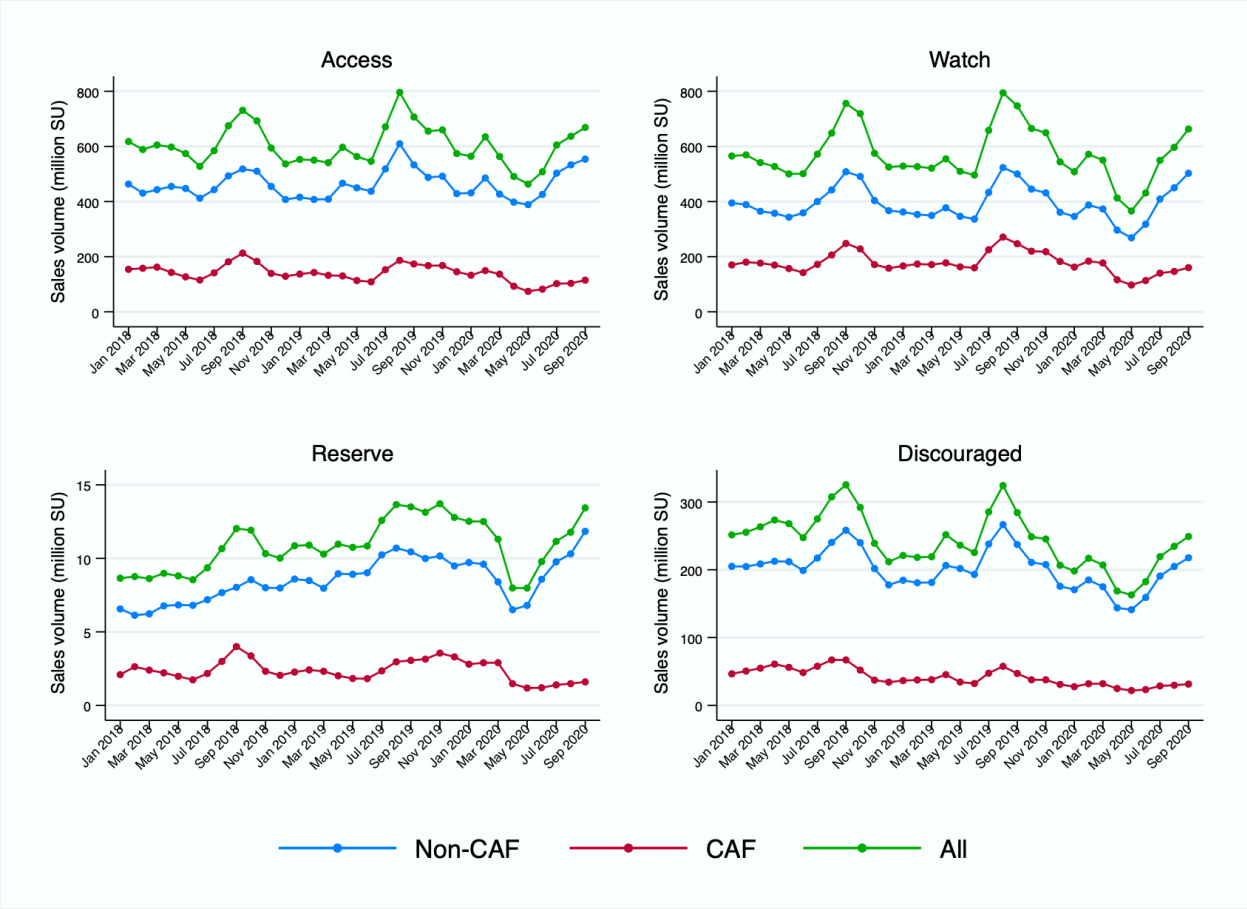
S4-1 Figure: Autocorrelation, partial autocorrelation and distribution of residuals from Model 1 for total antibiotics.



S4-2 Figure: Autocorrelation function and distribution of residuals from Model 3 for azithromycin.

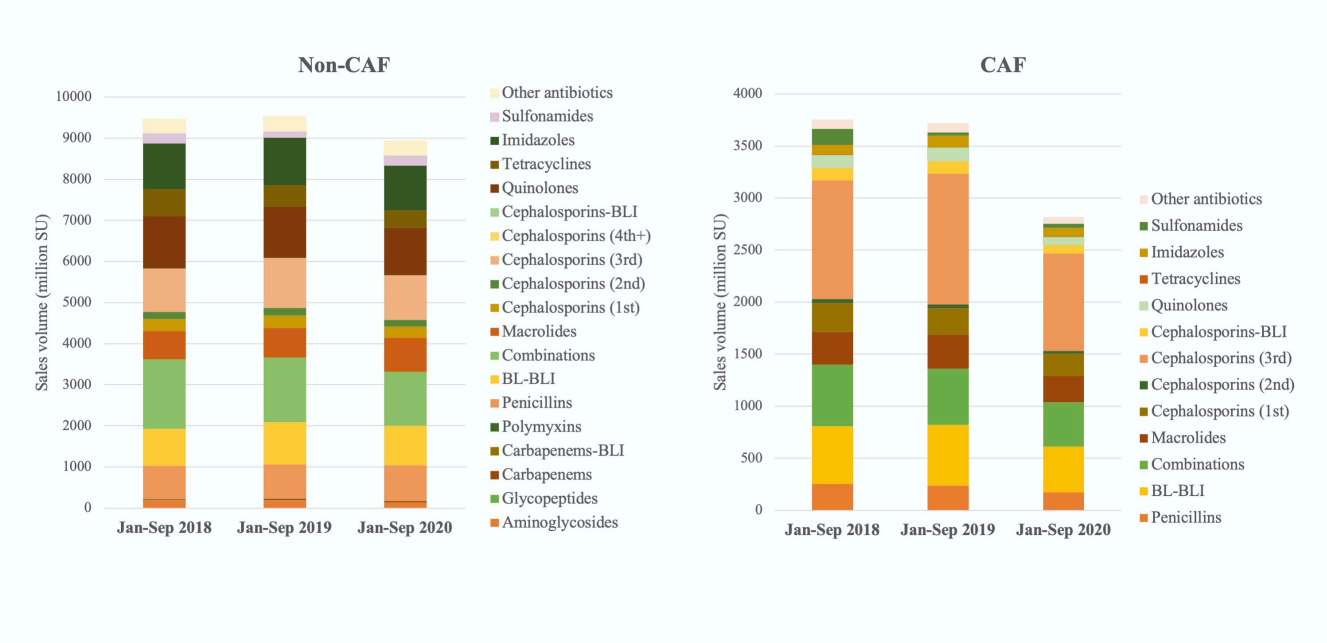


S4-3 Figure: Monthly sales volume of each AWaRe category in India between January 2018 and September 2020, separated for child-appropriate formulations (CAF) and non-CAF

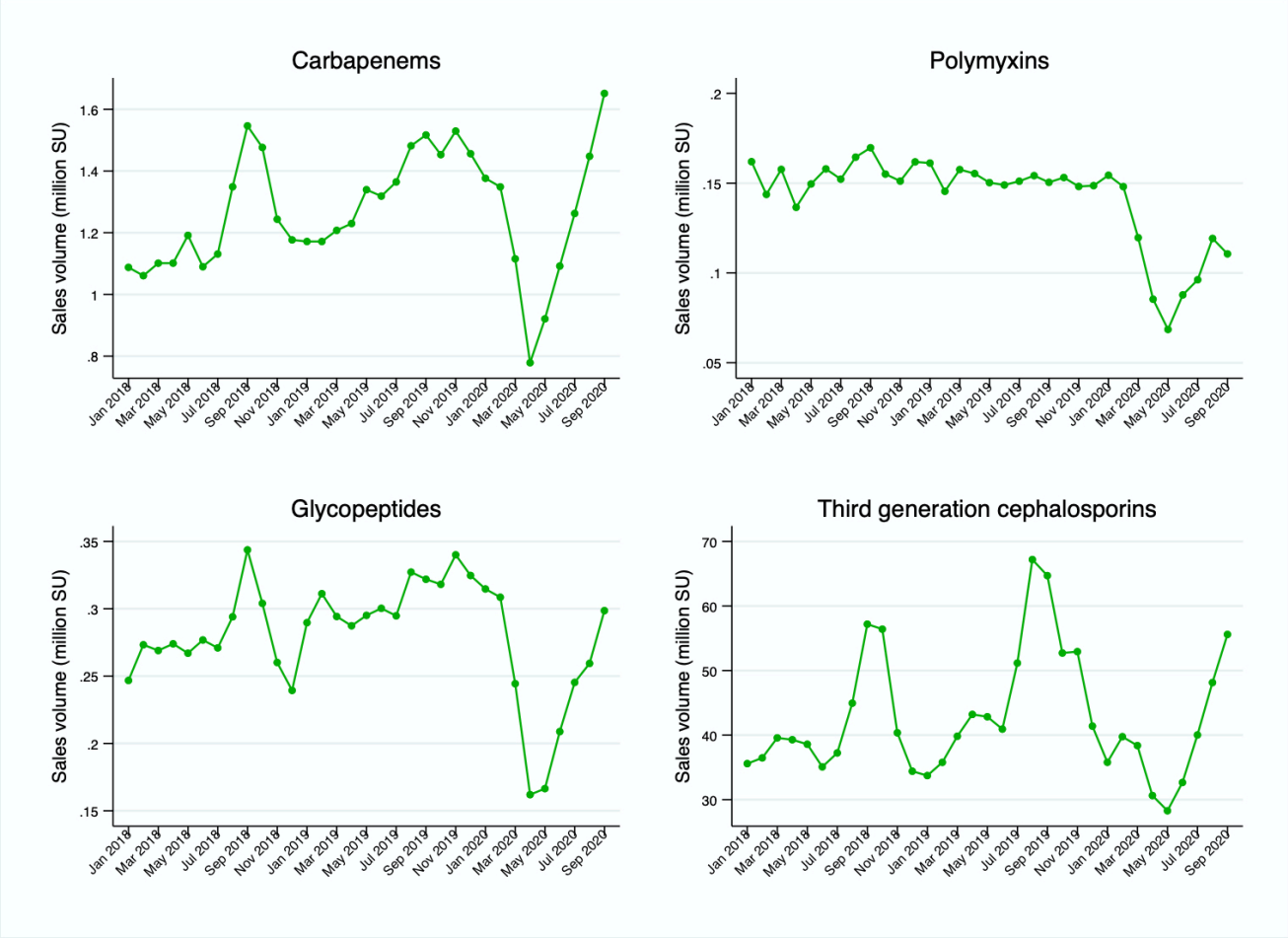


S4-4 Figure: Cumulative volume of antibiotics sold between January and September of each year 2018-2020, stratified by AWaRe category, presented separately for child-appropriate formulations (CAF) and non-CAF.

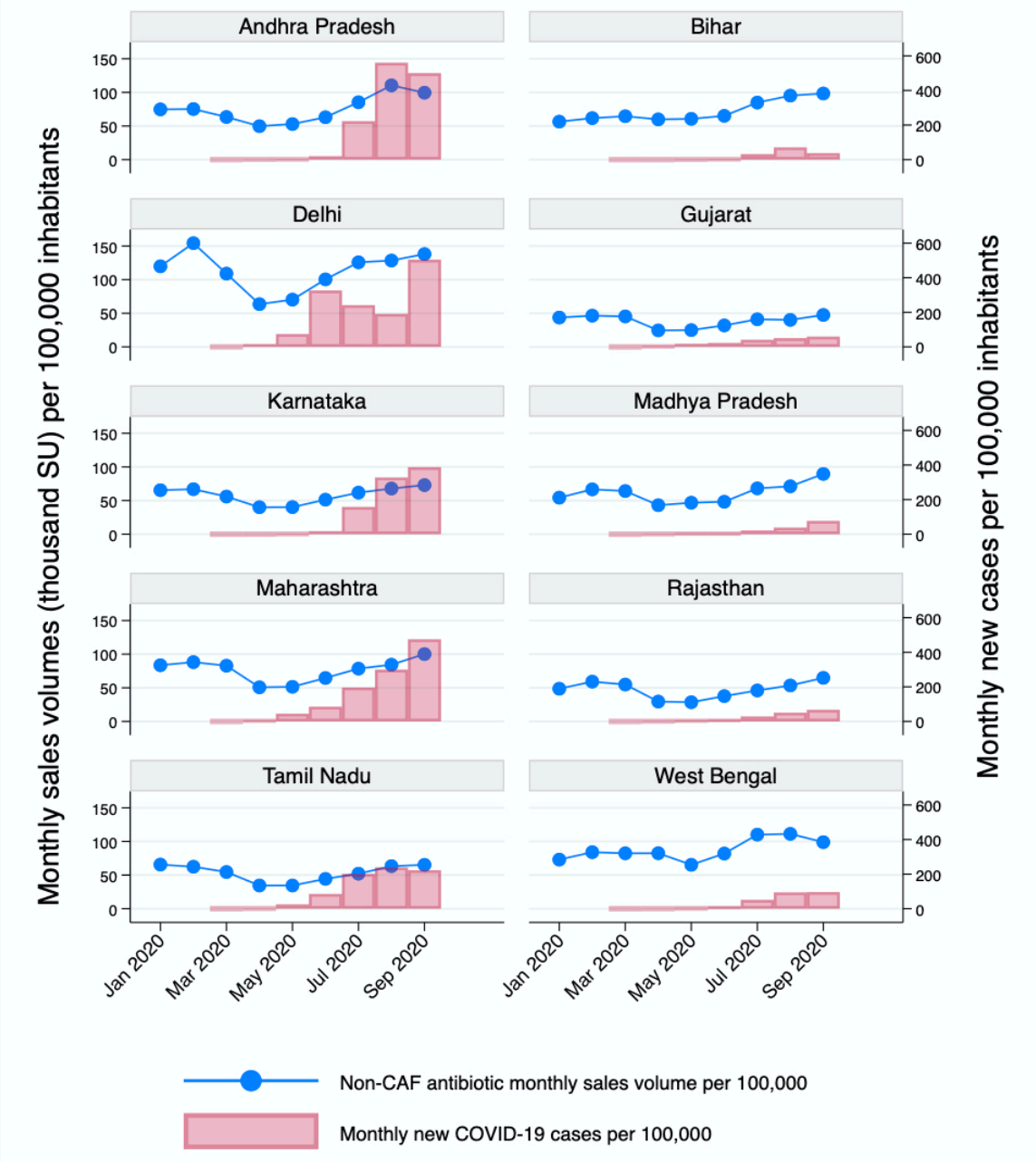
S4-5 Figure: Cumulative volume of antibiotics sold between January and September of each year 2018-2020, stratified by ATC class, presented separately for child-appropriate formulations and non-CAF.



S4-6 Figure: Monthly national sales volumes between January 2018 and September 2020 for selected antibiotic classes: parenteral carbapenems, glycopeptides, polymyxins and parenteral third generation cephalosporins (including those associated with a beta-lactamase inhibitor, BLI).

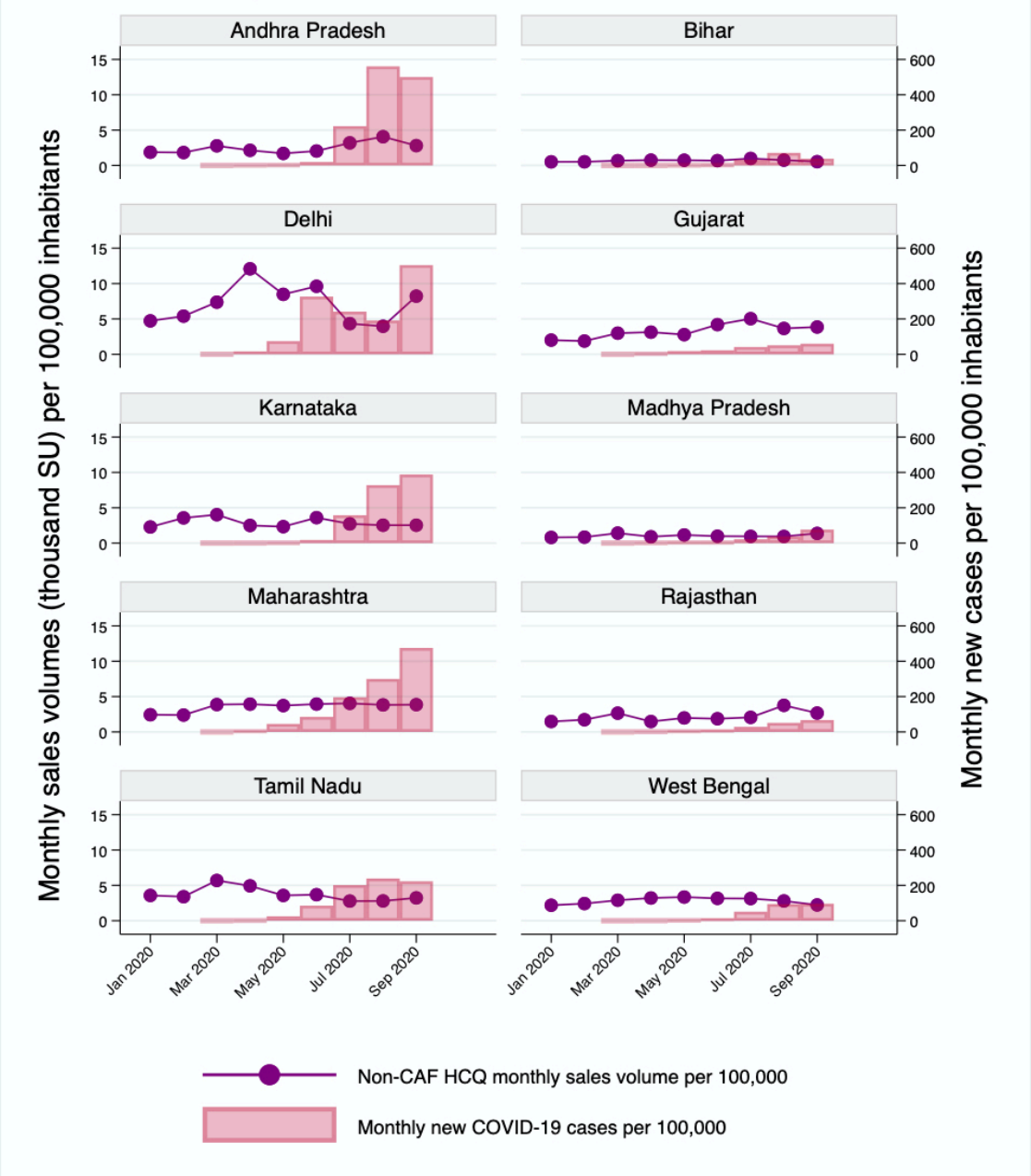


S4-7 Figure: Relationship between monthly new COVID-19 cases per 100,000 and antibiotic sales volumes per 100,000 (only non-child appropriate formulations, non-CAF) in 10 states of India from January to September 2020.



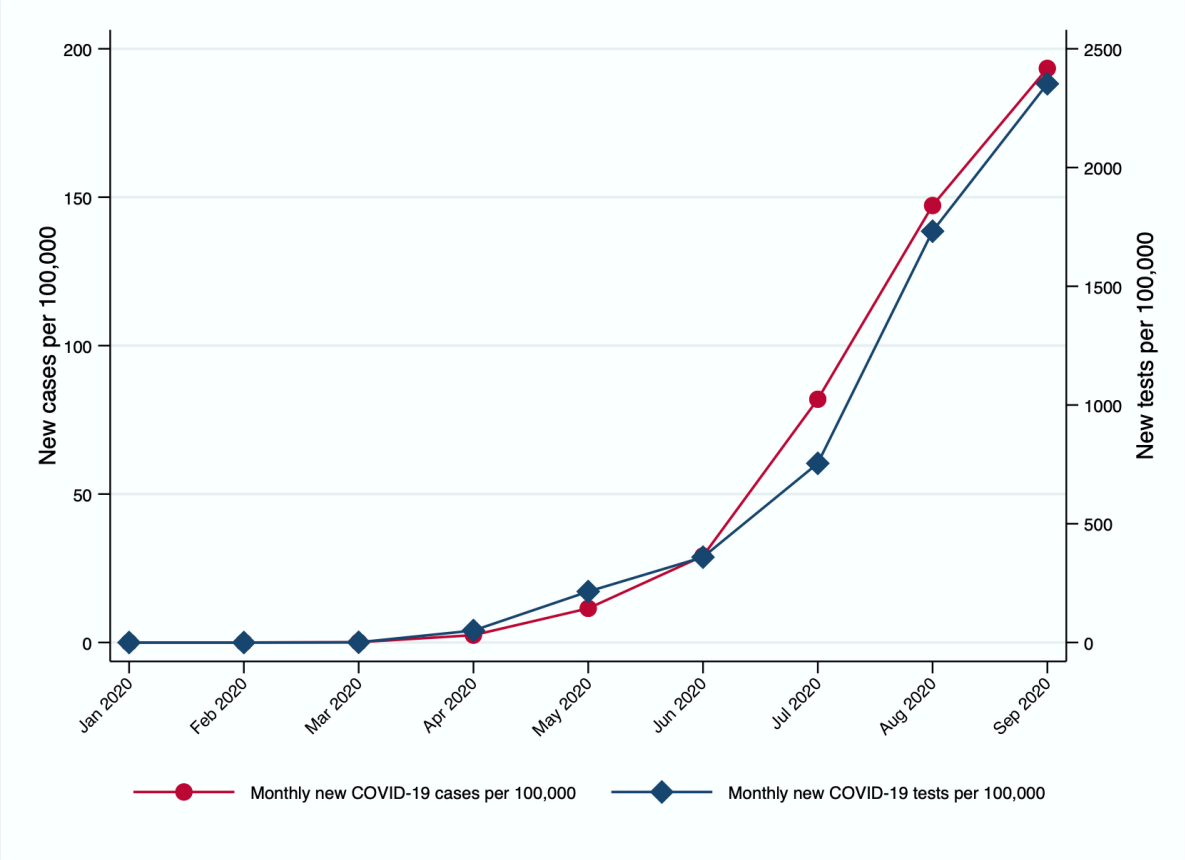
Note: States with the highest rates of detected COVID-19 cases are shown on the left side of the graph, whereas states with the lowest rates of detected COVID-19 cases are on the right.

S4-8 Figure: Relationship between monthly new COVID-19 cases per 100,000 and hydroxychloroquine (HCQ) sales volumes per 100,000 (only non-child appropriate formulations, non-CAF) in 10 states of India from January to September 2020.



Note: States with the highest rates of detected COVID-19 cases are shown on the left side of the graph, whereas states with the lowest rates of detected COVID-19 cases are on the right.

S4-9 Figure: Number of SARS-CoV-2 tests performed and new COVID-19 cases detected each month in India per 100,000 inhabitants between January and September 2020.



Chapter 5: Summary and conclusions

5.1 Summary of results

My systematic review (Chapter 2) indicates that an average 50% of patients seeking care in outpatient primary care facilities across LMICs receive antibiotics. However, very few studies have been conducted so far to estimate the proportion of antibiotic use that is inappropriate either because of lack of indication (overuse) or due to suboptimal drug choice. More specifically, I identified only nine studies that made an attempt to evaluate the rationality of antibiotic prescription. However, substantial between-study heterogeneity in terms of design, methodologies employed to assess prescribing practices and populations being considered prevented pooling and comparisons. The proportion on inappropriate prescriptions ranged from 7.9% (95% CI: 4.6-12.5) in a study from Zambia including only children under age five presenting with acute respiratory syndrome, to 100% in three studies carried out in China (n=2) and Malaysia (n=1) that were restricted to conditions not requiring antibiotics (acute watery diarrhea, presumptive tuberculosis [TB], angina, acute upper respiratory tract infections of likely viral etiology). Furthermore, across a subset of studies (16 in total) that examined in greater detail the types of antibiotics being prescribed, I found that broad-spectrum agents with a higher potential for selecting resistance ('Watch' antibiotics) represented an alarming 60% of all prescriptions in some contexts, whereas 'Access' antibiotics accounted for the majority of prescriptions (> 60%) in 13 studies from 12 countries. Yet, given the heterogeneity of settings and conditions being examined, it is difficult to depict a clear and comprehensive picture of how much and how well antibiotics are prescribed in the primary healthcare sector across LMICs in general. This work highlighted the need for better quality data to understand context-specific patterns of antibiotic use and accurately measure the proportion of inappropriate prescriptions.

As discussed in the previous chapters, I conducted secondary analyses of standardized patient (SP) studies carried out in India, China and Kenya to determine the extent of

antibiotic overuse (Chapter 3), thus overcoming many of the methodological issues typical of approaches typically used for the assessment of prescribing practices. In this work, I found that about 30% of SP-provider encounters conducted in China and 50% of those performed in India resulted in inappropriate prescribing or dispensing of antibiotics. Broad-spectrum agents were largely given to patients presenting with conditions not requiring antibiotic treatment (e.g. presumptive or confirmed TB, watery diarrhea, asthma, etc.) raising even greater concerns. This was observed particularly in India and China, where respectively 47.6% (95% CI: 26.8-54.0) and 32.9% (95% CI: 27.6-37.9) of all antibiotics belonged to the 'Watch' group. The proportion of 'Watch' antibiotics was likely higher in China: about 25% of antibiotics could not be categorized due to insufficient details, but many of these medications were cephalosporins, presumably second or third generation ones which belong to the 'Watch' group. As richer data were available from India, I also examined the factors associated with antibiotic prescribing in this country. Using a hierarchical Poisson model with a random intercept to account for between-study variance, I found that healthcare providers operating in urban areas were 30% less likely to prescribe antibiotics as compared to those active in rural areas (aPR 0.70; 95% CI: 0.52 – 0.96). Additionally, antibiotic prescribing resulted to be more common among qualified providers versus non-qualified ones (aPR 1.55; 95% CI: 1.42 – 1.70), and for patients presenting with presumptive TB as opposed to other clinical conditions (aPR 1.19; 95% CI: 1.07 – 1.33).

Finally, I discussed how the COVID-19 pandemic is exacerbating the issue of antibiotic overuse in the non-pediatric population (Chapter 4). As estimated in my interrupted time series analysis of India's national sales data from January 2018 to September 2020, about 225.2 million (95% CI: 65.6; 384.6) excess doses of antibiotics sold between June and September 2020 were likely attributable to the pandemic. These include as many as 39 million excess doses (95% CI: 26.8; 51.3) of azithromycin, a broad-spectrum antibiotic that is being widely prescribed to presumptive and confirmed COVID-19 patients despite no evidence of clinical benefit from clinical trials. I also found that hydroxychloroquine (HCQ) sales peaked in March 2020 (+10.8 million doses [95% CI: 9.2; 12.4]), likely

reflecting the large use of this drug in prophylactic and therapeutic regimens particularly in the initial phase of the pandemic.

5.2 Strengths and Limitations

My systematic review was the first to collate the available evidence on antibiotic prescribing practices across primary healthcare settings in LMICs, building on a highly sensitive search strategy and a rigorous study screening and selection process. However, this work reflects the intrinsic limitations of primary studies identified in the review. In fact, the overall risk of study bias was considered to be high for 21/48 studies included in final synthesis, moderate for 11 and low for 16. The greatest concerns were related to selection bias issues. Although data collection methods were generally deemed acceptable to determine the prevalence of antibiotic prescription, the most common approaches (i.e. medical records abstraction and prescription audit) were far from ideal to examine the appropriateness of prescription. For this reason and because of the substantial between-study heterogeneity, pooled estimates must be interpreted with caution. Overall, this work highlighted significant gaps in the literature and the need for better quality and context-specific data on antibiotic use and its appropriateness.

As compared to conventional methods that are typically employed to evaluate prescribing practices, my work with data from SP studies allowed to provide a more unbiased prevalence estimate of antibiotic overuse for a set of key clinical conditions often handled by primary healthcare providers across LMICs. This approach is not affected by major sources of bias such as poor or differential recall, Hawthorne effect, inadequate reporting and/or availability of proper medical records, etc.[1] Moreover, SPs allow for comparisons across providers and settings thanks to the use of standardized tracer conditions, which would not be possible with any other method. Selection bias in the identification of healthcare providers can be considered a minor concern when the SP methodology is applied rigorously.[1] Most studies included in my analysis utilized random sampling strategies to select providers from a pool of eligible practitioners in the area of interest.

Informed consent, by making providers aware about the research and thus potentially affecting their willingness to participate or even their behaviour during the visits, was requested in a subset of studies, but participation rates were always very high. Also, post-study surveys and other assessments were usually done to determine whether SPs were detected by providers, indicating that less than 5% of SPs were suspected to be fake patients, and this often happened after the visit. For all these reasons, data generated from SP studies offer very interesting opportunities to evaluate prescribing practices while accounting for key factors that cannot be adequately captured through other approaches. However, it is important to note the limitations of this study. First, the assessment of antibiotic overuse was restricted to a small range of conditions; although these have a high prevalence and thus represent a substantial proportion of patients seeking care in the outpatient primary healthcare setting, many others could not be taken into account. As none of the conditions under investigation requires antibiotic treatment, I decided to focus on one specific type of inappropriate antibiotic use, that is over-prescription. Second, factors associated with prescribing could be investigated only for India because data from other countries were insufficient. Nonetheless, it should be noted that prescribing practices observed in India are considered to reflect fairly well what happens in other LMICs (especially in South and South-East Asia). Third, public healthcare providers were underrepresented in the India's subsample, thus hindering an accurate comparison with private providers. It is possible that factors associated with antibiotic prescribing differ between public and private practitioners, but it is worth highlighting that the private sector contributes to 75% of outpatient visits in the country.[2] Fourth, while the SP methodology is an excellent way to make comparisons across settings, providers and clinical conditions, it does not allow to estimate the population average of antibiotic overprescribing. In fact, it is very difficult to determine the patient shares across providers, and thus we cannot know how many patients are typically evaluated by providers with different prescribing profiles. Yet, the fact that providers are usually selected in order to be representative of providers practicing in the study area may suggest that the SP methodology is still good to capture the average prescribing rates

for providers. Lastly, despite thorough training, there is no guarantee that SPs will act exactly as real patients. For instance, an individual that is not febrile at the time of the consultation or does not look sick enough, may lead the healthcare provider to handle the case differently. In such a scenario, it is likely that antibiotic prescribing estimates would be biased downward, leading to an underestimation of the actual prevalence of antibiotic overuse.

My interrupted time series analysis was the first of its kind to estimate the impact of the COVID-19 pandemic on antibiotic and HCQ sales. Although some before-and-after studies, mostly focused on one or few hospitals, have been conducted over short time periods in the United States and Spain, no such investigations have been carried out to date in LMICs. Besides conducting descriptive analyses to examine the extent and pattern of antibiotic use in India during the observation period, robust segmented regression models were built to estimate the effect of the pandemic on monthly sales. These models accounted for the lockdown phase when appropriate and were adjusted for seasonal trends to the best extent possible given the number of available data points. Additional time-varying confounders were not considered because no major historical changes were expected to have occurred throughout the relatively short observation period in terms of epidemiologic, environmental and socio-demographic features of the country population, other than what is directly attributable to the COVID-19 pandemic. The actual variation in the number of COVID-19 cases detected in India since the beginning of the pandemic was not directly accounted for in my segmented regression analyses, but information on the evolution of the epidemic curve was utilized to define the timing of the exposure. While the limited testing capacity certainly led to underestimate the true number of cases occurred in the country, I do not expect this to significantly affect the shape of the epidemic curve and thus my model estimates. The pharmaceutical data used in this work covered only the private sector, thus potentially leading to underestimate the excess use of antibiotics and HCQ due to the pandemic. However, as previously mentioned, most of the outpatient and inpatient care in India is delivered by private providers, who also contribute for a substantial proportion to the national antibiotic sales volume.[2] Although

the methods used by IQVIA to collect data from stockists across the country are not known in detail, this data source is regularly utilized for a range of scientific and policy investigations conducted by major public health agencies and research institutions.[3-5] In India, IQVIA covers as much as 95% of the total pharmaceutical market, encompassing the retail sector, hospitals and dispensing doctors. Furthermore, the data collection process is fully automatized and is unlikely to have experienced significant disruptions during the lockdown period. Nonetheless, while the data available for this study included both over-the-counter sales and prescription-based purchases, it is not possible to link such data with patients' demographics and clinical features or with providers' characteristics. Given the ecological nature of the data, no individual-level inferences can reasonably be made. Yet, I was able to generate quantitative evidence of the significant impact of the pandemic on national antibiotic consumption, that could have major policy implications.

Finally, one key limitation is intrinsic to the nature of the data used in all the studies the constitute this thesis: there is no ideal measure of antibiotic usage. While proportions of healthcare providers prescribing antibiotics, proportions of pharmacies dispensing them over the counter and pharmaceutical sales volumes do provide very useful information, none of them directly reflect actual consumption among patients. Prescribing and dispensing rates, however, do provide a good measure of provider-level practices that can specifically targeted in stewardship interventions. Pharmaceutical sales have the advantage of capturing both prescription-based and over the counter sales, that otherwise would be much harder to capture through conventional methods based on medical records or prescription audits. Patient-level behaviours, including adherence to treatment, cannot be captured and are often difficult to estimate and generalize. Furthermore, it is important to acknowledge that a substantial proportion of all medicines in the market across LMICs are counterfeit or substandard. Although this aspect could not be investigated further in this thesis, poor-quality antibiotics pose significant threats to the emergence of resistance, e.g. by favoring underdosage.

5.3 Implications and directions for future research

Generating more and higher quality data on antibiotic use and its appropriateness is essential to design and implement effective stewardship interventions, a key component of the fight against AMR. In many LMICs like India, where the private sector plays a major role in healthcare delivery, it is important to gather specific data on prescribing practices among private practitioners and actively involve them in targeted programs aimed at promoting the rational use of antibiotics.

The SP methodology offers interesting opportunities to further explore prescribing practices beyond the prevalence of antibiotic overuse reported in Chapter 3. For instance, new SP tracer conditions representing common infections such as community-acquired pneumonia or urinary tract infections could be developed and used in future research to better evaluate the adherence of national and international guidelines and determine the appropriateness of therapeutic choices. This was part of the original plans for the present doctoral thesis but could not be implemented owing to the COVID-19 pandemic. Once the global situation will make it possible, useful data can be generated through SP studies in a range of different settings. This approach could also prove to be valuable in assessing the impact of tailored antibiotic stewardship interventions. Fostering the transition from paper-based to electronic documentation and establishing minimum quality standards for prescription records in both private and public sectors would be key to conduct more accurate and nationally representative periodic evaluations of prescribing patterns. Because antibiotic use is closely intertwined with the emergence of resistance strains,[6] improving our knowledge on the amount of antibiotics used in human medicine and other sectors along with their underlying determinants remains a global priority.

Meanwhile, urgent action is needed to rapidly diminish the indiscriminate use of antibiotics for presumptive and confirmed COVID-19 cases, that is likely contributing to substantial overuse across the globe since early 2020.[7] Measuring the impact of the pandemic on antibiotic prescribing and calling for urgent actions to limit inappropriate use as I did for India could be a helpful starting point. National and local guidelines for

the management of COVID-19 cases have been developed in many countries, and the WHO recommendation against the routine use of antibiotics in such cases has been incorporated in most of these documents. However, adherence to guidelines is not immediately achieved and requires proper training and awareness that could be even more challenging to put in place in an emergency situation as the one we are going through. The considerable impact of the pandemic estimated in my study on antibiotic sales in India suggests that a substantial proportion of this consumption occurs in outpatient care, where mild cases are typically handled. Growing scientific evidence indicates that these patients have a very low probability of developing concomitant bacterial infections that could justify the prescription of antibiotics,[8] but - in the absence of targeted treatments for COVID-19 - many healthcare providers feel powerless and end up prescribing antibiotics even if not recommended. Patients' expectations, perceived or openly declared, could also play a role in inducing unnecessary antibiotic prescriptions, a phenomenon that is likely to be even stronger in the private sector. COVID-19 is thus exacerbating pre-existing issues that cannot be overlooked and postponed while waiting for the pandemic to resolve.

As stated in the introduction, the continuous emergence of multidrug- and extremely drug-resistant strains across the globe is compromising our ability to treat infections and the time to develop new effective antibiotics is running out.[9] Even in the midst of an unprecedented pandemic that is putting a strain on health systems worldwide, antibiotic stewardship needs to be systematically integrated in routine activities. While efforts are certainly needed to optimize the management of confirmed COVID-19 cases in line with the scientific evidence, another huge challenge comes from all those presumptive cases who do not get tested and cannot be confirmed as COVID-19 cases. Empiric antibiotic prescribing is likely even higher among these individuals who present with non-specific respiratory symptoms and do not have a definite diagnosis. Even before the ongoing pandemic, febrile illnesses were among the most common reasons for seeking care across LMICs (3-7 episodes per person per year in children under 5 years of age and 1-4 episodes per person per year in individuals older than 5),[10] and acute respiratory infections and

gastrointestinal infections represented the main causes of localized non-malarial fever in tropical and subtropical areas, predominantly of viral etiology and self-limiting without the need of antibiotic treatment.[11-19] However, as shown in Chapters 2 and 3, antibiotics are often empirically prescribed or dispensed, a phenomenon that is likely favored by an insufficient diagnostic capacity. Generic markers of inflammation, such as C-reactive protein (CRP), can help distinguish bacterial infections from other conditions and limit the inappropriate use of antibiotics, but the actual benefit of their use as point-of-care (POC) tests varies widely across contexts.[20,21] Nevertheless, CRP testing alone is generally not enough to guide the diagnostic and therapeutic process and needs to be supplemented with other tools such as pathogen-specific rapid diagnostic tests (RDTs), that are either non-existent or poorly accurate.[22] Hence, research needs to be carried out to develop and implement new diagnostic tools that are accurate, affordable and suitable for use at the primary care level in limited-resource areas as part of the global response against AMR.

The incorporation of the WHO AWaRe classification of antibiotics into national and local guidelines, as suggested in Chapter 2, could be helpful to improve prescribing practices and possibly reduce the widespread use of antibiotics that should be reserved for treatment of selected infections. The AWaRe framework could be utilized to shape normative boundaries more rationally, for example by imposing restrictions on the prescription and sale of 'Watch' and 'Reserve' antibiotics. However, as many studies have shown, no single action is able to generate a meaningful impact given the complexity of the problem. In order to achieve significant changes in prescribing and dispensing behaviours, a multipronged approach is required in any given setting that takes into account the peculiarities of specific areas, populations and categories of healthcare providers. While the general rules of antibiotic stewardship are theoretically universally applicable, these need to be adapted locally and implemented along with a whole range of other resources, starting from an improved diagnostic capacity.

5.4 Conclusion

This work contributes to fill some knowledge gaps regarding antibiotic prescribing practices in LMICs and particularly in India, where the highest levels of antibiotic consumption are registered. More efforts need to be undertaken to generate new accurate data and take action accordingly. AMR is a huge public health concern worldwide, and primary research on how antibiotics are used/abused could have great policy relevance across countries. Like the ongoing COVID-19 pandemic, AMR is a global problem that will require global solutions through international collaboration.

5.5 References

1. Kwan A, Bergkvist S, Daniels B, Das J, Das V, Pai M. Using standardized patients to measure health care quality: a manual and toolkit for projects in low- and middle-income countries. 2019.
2. Mackintosh M, Channon A, Karan A, Selvaraj S, Cavagnero E, Zhao H. What is the private sector? Understanding private provision in the health systems of low-income and middle-income countries. Lancet. 2016;388(10044):596-605. Epub 2016/07/01. doi: 10.1016/S0140-6736(16)00342-1.
3. Klein EY, Tseng KK, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. BMJ Glob Health. 2019;4(2):e001315. Epub 2019/05/30. doi: 10.1136/bmjgh-2018-001315.
4. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-E70. Epub 2018/03/28. doi: 10.1073/pnas.1717295115.
5. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income

and high-income countries. Lancet Infect Dis. 2019;19(1):67–75. doi: 10.1016/S1473-3099(18)30547-4

6. Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol. 2007;3(9):541-8. Epub 2007/08/22. doi: 10.1038/nchembio.2007.24.
7. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. Epub 2020/04/30. doi: 10.1016/j.cmi.2020.04.024.
8. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Epub 2020/05/31. doi: 10.1016/j.jinf.2020.05.046.
9. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-27. Epub 2017/12/26. doi: 10.1016/s1473-3099(17)30753-3.
10. World Health Organization. WHO informal consultation on fever management in peripheral health care settings: A global review of evidence and practice. Geneva, Switzerland; 2013. Available at: https://apps.who.int/iris/bitstream/handle/10665/95116/9789241506489_eng.pdf?sequence=1.
11. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, et al. Beyond malaria--causes of fever in outpatient Tanzanian children. N Engl J Med. 2014;370(9):809-17. Epub 2014/02/28. doi: 10.1056/NEJMoa1214482.
12. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis. 2013;7(7):e2324. Epub 2013/07/23. doi: 10.1371/journal.pntd.0002324.

13. Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Pérès A, Paris DH, Phetsouvanh R, et al. Causes of non-malarial fever in Laos: a prospective study. Lancet Glob Health. 2013;1(1):e46-54. Epub 2014/04/22. doi: 10.1016/s2214-109x(13)70008-1.
14. Acestor N, Cooksey R, Newton PN, Ménard D, Guerin PJ, Nakagawa J, et al. Mapping the aetiology of non-malarial febrile illness in Southeast Asia through a systematic review--terra incognita impairing treatment policies. PloS one. 2012;7(9):e44269. Epub 2012/09/13. doi: 10.1371/journal.pone.0044269.
15. Mørch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, et al. Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. BMC infectious diseases. 2017;17(1):665. Epub 2017/10/06. doi: 10.1186/s12879-017-2764-3.
16. Maze MJ, Bassat Q, Feasey NA, Mandomando I, Musicha P, Crump JA. The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management. Clin Microbiol Infect. 2018;24(8):808-14. Epub 2018/02/20. doi: 10.1016/j.cmi.2018.02.011.
17. Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. Clin Microbiol Infect. 2018;24(8):827-35. Epub 2018/05/20. doi: 10.1016/j.cmi.2018.05.001.
18. Shimelis T, Tadesse BT, F WG, Crump JA, Schierhout G, Dittrich S, et al. Aetiology of acute febrile illness among children attending a tertiary hospital in southern Ethiopia. BMC infectious diseases. 2020;20(1):903. Epub 2020/12/02. doi: 10.1186/s12879-020-05635-x.
19. Bhargava A, Ralph R, Chatterjee B, Bottieau E. Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions. Bmj. 2018;363:k4766. Epub 2018/12/01. doi: 10.1136/bmj.k4766.
20. Aabenhus R, Jensen JU, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014;(11):Cd010130. Epub 2014/11/07. doi: 10.1002/14651858.CD010130.pub2.

21. Kapasi AJ, Dittrich S, González IJ, Rodwell TC. Host Biomarkers for Distinguishing Bacterial from Non-Bacterial Causes of Acute Febrile Illness: A Comprehensive Review. PloS one. 2016;11(8):e0160278. Epub 2016/08/04. doi: 10.1371/journal.pone.0160278.
22. Kohli M, Sen P, Pai M. Improving access to essential tests for infectious diseases. Microbes Infect. 2019;21(1):1–3. doi: 10.1016/j.micinf.2018.08.003.

A. Complete reference list

Aabenhus R, Jensen JU, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014;(11):Cd010130. Epub 2014/11/07. doi: 10.1002/14651858.CD010130.pub2.

Ab Rahman N, Teng CL, Sivasampu S. Antibiotic prescribing in public and private practice: a cross-sectional study in primary care clinics in Malaysia. BMC Infect Dis. 2016;16:208. doi: 10.1186/s12879-016-1530-2

Abdulah R, Insani WN, Putri NE, Purba HP, Destiani DP, Barliana MI. Pattern of medication use in geriatric patients at primary health care facilities in Karawang, Indonesia. Drug Healthc Patient Saf. 2019;11:1–5. doi: 10.2147/dhps.S187829

Abelenda-Alonso G, Padullés A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, et al. Antibiotic prescription during the COVID-19 pandemic: A biphasic pattern. Infect Control Hosp Epidemiol. 2020;41(11):1371-2. Epub 2020/07/31. doi: 10.1017/ice.2020.381.

Abena PM, Decloedt EH, Bottieau E, Suleman F, Adejumo P, Sam-Agudu NA, et al. Chloroquine and Hydroxychloroquine for the Prevention or Treatment of COVID-19 in Africa: Caution for Inappropriate Off-label Use in Healthcare Settings. Am J Trop Med Hyg. 2020;102(6):1184-8. Epub 2020/04/24. doi: 10.4269/ajtmh.20-0290.

Acestor N, Cooksey R, Newton PN, Ménard D, Guerin PJ, Nakagawa J, et al. Mapping the aetiology of non-malarial febrile illness in Southeast Asia through a systematic review--terra incognita impairing treatment policies. PloS one. 2012;7(9):e44269. Epub 2012/09/13. doi: 10.1371/journal.pone.0044269.

Adisa R, Fakeye TO, Aindero VO. Evaluation of prescription pattern and patients' opinion on healthcare practices in selected primary healthcare facilities in Ibadan, South-Western Nigeria. Afr Health Sci. 2015;15(4):1318–29. doi: 10.4314/ahs.v15i4.35

Ahiabu MA, Tersbol BP, Biritwum R, Bygbjerg IC, Magnussen P. A retrospective audit of antibiotic prescriptions in primary health-care facilities in Eastern Region, Ghana. Health Policy Plan. 2016;31(2):250–8. doi: 10.1093/heapol/czv048

Ahmadi F, Zarei E. Prescribing patterns of rural family physicians: a study in Kermanshah Province, Iran. BMC Public Health. 2017;17(1):908. doi: 10.1186/s12889-017-4932-1

Akl OA, El Mahalli AA, Elkahky AA, Salem AM. WHO/INRUD drug use indicators at primary healthcare centers in Alexandria, Egypt. J Taibah Univ Med Sci. 2014;9(1):54–64. doi: 10.1016/j.jtumed.2013.06.002

Alabid AH, Ibrahim MI, Hassali MA. Antibiotics dispensing for urtis by community pharmacists (CPs) and general medical practitioners in Penang, Malaysia: a comparative study using simulated patients (SPs). J Clin Diagn Res. 2014;8(1):119–23. doi: 10.7860/jcdr/2014/6199.3923

Arshad M, Mahmood SF, Khan M, Hasan R. Covid -19, misinformation, and antimicrobial resistance. Bmj. 2020;371:m4501. Epub 2020/11/26. doi: 10.1136/bmj.m4501.

Atif M, Sarwar MR, Azeem M, Naz M, Amir S, Nazir K. Assessment of core drug use indicators using WHO/INRUD methodology at primary healthcare centers in Bahawalpur, Pakistan. BMC Health Serv Res. 2016;16(1):684. doi: 10.1186/s12913-016-1932-2

Auta A, Hadi MA, Oga E, Adewuyi EO, Abdu-Aguye SN, Adeloye D, et al. Global access to antibiotics without prescription in community pharmacies: a systematic review and meta-analysis. J Infect. 2019;78(1):8–18. doi: 10.1016/j.jinf.2018.07.001

Babu R, Kumar A, Karim S, Warrier S, Nair SG, Singh SK, et al. Faecal carriage rate of extended-spectrum β-lactamase-producing Enterobacteriaceae in hospitalised patients and healthy asymptomatic individuals coming for health check-up. J Glob Antimicrob Resist. 2016;6:150-3. Epub 2016/08/18. doi: 10.1016/j.jgar.2016.05.007.

Baltzell K, Kortz TB, Scarr E, Blair A, Mguntha A, Bandawe G, et al. 'Not all fevers are malaria': a mixed methods study of non-malarial fever management in rural southern Malawi. Rural Remote Health. 2019;19(2):4818. doi: 10.22605/RRH4818

Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013;67(11):974–8. doi: 10.1136/jech-2013-203104

Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003;3:21. Epub 2003/10/20. doi: 10.1186/1471-2288-3-21.

Beall's list of potential predatory journals and publishers: Potential predatory scholarly open-access journals. beallslist.net; 2019 [cited 2020 May 13] Available from: https://beallslist.net/standalone-journals/.

Bergen PJ, Smith NM, Bedard TB, Bulman ZP, Cha R, Tsuji BT. Rational Combinations of Polymyxins with Other Antibiotics. Adv Exp Med Biol. 2019;1145:251-88. doi: 10.1007/978-3-030-16373-0_16.

Beri SG, Pandit VA, Khade KS, Sarda KD. The pattern of drug use in acute fever by general practitioners (GPs) in Pune City, India. J Clin Diagn Res. 2013;7(3):467–72. doi: 10.7860/jcdr/2013/4719.2800.

Bhargava A, Ralph R, Chatterjee B, Bottieau E. Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions. Bmj. 2018;363:k4766. Epub 2018/12/01. doi: 10.1136/bmj.k4766.

Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. Int J Epidemiol. 2013;42(4):1187-95. Epub 2013/06/14. doi: 10.1093/ije/dyt092.

Bielsa-Fernandez MV, Frati-Munari AC, Ariza-Andraca R. Treatment to patients with acute diarrhea: survey to a group of general practitioners from Mexico. Atencion Familiar. 2016;23(4):119–24. doi: 10.1016/j.af.2016.10.002

Bogossian EG, Taccone FS, Izzi A, Yin N, Garufi A, Hublet S, et al. The Acquisition of Multidrug-Resistant Bacteria in Patients Admitted to COVID-19 Intensive Care Units: A Monocentric Retrospective Case Control Study. Microorganisms. 2020;8(11). Epub 2020/11/25. doi: 10.3390/microorganisms8111821.

Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020;383(6):517-25. Epub 2020/06/04. doi: 10.1056/NEJMoa2016638.

Buehrle DJ, Decker BK, Wagener MM, Adalja A, Singh N, McEllistrem MC, et al. Antibiotic Consumption and Stewardship at a Hospital outside of an Early Coronavirus Disease 2019 Epicenter. Antimicrob Agents Chemother. 2020;64(11). Epub 2020/08/21. doi: 10.1128/aac.01011-20.

Carey ME, Jain R, Yousuf M, Maes M, Dyson ZA, Thu TNH, et al. Spontaneous emergence of azithromycin resistance in independent lineages of Salmonella Typhi in Northern India. bioRxiv. 2020:2020.10.23.351957. doi: 10.1101/2020.10.23.351957.

Castaldi S, Luconi E, Marano G, Auxilia F, Maraschini A, Bono P, et al. Hospital Acquired Infections in COVID-19 patients in sub intensive care unit. Acta Biomed. 2020;91(3):e2020017. Epub 2020/09/15. doi: 10.23750/abm.v91i3.10376. PubMed PMID: 32921713.

Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2019014.

CDC COVID Data Tracker Atlanta, Georgia: Centers for Disease Control and Prevention (CDC); 2020 [cited 2020 Dec 5, 2020]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics.

Census of India 2011. Population projections for India and States, 2011-2036: Report of the Technical Group on population projections. Nirman Bhawan, New Delhi, India: National Commission on Population, Ministry of Health and Family Welfare, Government of India, 2019.

Center for Disease Dynamics, Economics and Policy, Global Antibiotic Resistance Partnership. The state of the world's antibiotics 2015. Washington (DC): Center for Disease Dynamics, Economics and Policy; 2015 [cited 2020 May 13]. Available from: https://www.cddep.org/wp-content/uploads/2017/06/swa_executive_summary_edits_2016.pdf.

Center for Disease Dynamics, Economics and Policy (CDDEP). ResistanceMap: Antibiotic resistance. 2021. Available from: https://resistancemap.cddep.org/AntibioticResistance.php (last accessed January 6, 2021).

Chandy SJ, Thomas K, Mathai E, Antonisamy B, Holloway KA, Stalsby Lundborg C. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-

income country setting: a repeated cross-sectional study in Vellore, South India. The Journal of antimicrobial chemotherapy. 2013;68(1):229-36. Epub 2012/09/05. doi: 10.1093/jac/dks355.

Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis. 2018;18(12):e368-e78. Epub 2018/09/03. doi: 10.1016/S1473-3099(18)30296-2.

Chem ED, Anong DN, Akoachere JKT. Prescribing patterns and associated factors of antibiotic prescription in primary health care facilities of Kumbo East and Kumbo West Health Districts, North West Cameroon. PLoS ONE. 2018;13(3):e0193353. doi: 10.1371/journal.pone.0193353

Christian CS, Gerdtham UG, Hompashe D, Smith A, Burger R. Measuring Quality Gaps in TB Screening in South Africa Using Standardised Patient Analysis. Int J Environ Res Public Health. 2018;15(4). Epub 2018/04/12. doi: 10.3390/ijerph15040729.

Chua KP, Fischer MA, Linder JA. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. BMJ. 2019;364:k5092. Epub 2019/01/18. doi: 10.1136/bmj.k5092.

Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: What can we expect? Clin Infect Dis. 2020. Epub 2020/05/04. doi: 10.1093/cid/ciaa524.

Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol. 2007;3(9):541-8. Epub 2007/08/22. doi: 10.1038/nchembio.2007.24.

Clinical management of COVID-19. Interim guidance - 27 May 2020. Geneva, Switzerland: World Health Organization (WHO); 2020. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19.

Clinical management protocol: COVID-19. New Delhi, India: Directorate General of Health Services (EMR Division), Ministry of Health and Family Welfare, Government of India; 2020. Available from: https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404–13. doi: 10.1093/biomet/26.4.404

Comber SDW, Upton M, Lewin S, Powell N, Hutchinson TH. COVID-19, antibiotics and One Health: a UK environmental risk assessment. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/08/14. doi: 10.1093/jac/dkaa338.

Connor BA. Preparing International Travelers: Travelers' diarrhea. 2020. In: CDC Yellow Book 2020: Health Information for International Travel [Internet]. New York, NY, USA: Oxford University Press. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2020/preparing-international-travelers/travelers-diarrhea.

Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care. 2020;10(1):119. Epub 2020/09/08. doi: 10.1186/s13613-020-00736-x.

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.: COVID-19 Treatment Guidelines Panel. National Institutes of Health (NIH); 2020. Available from: https://www.covid19treatmentguidelines.nih.gov/.

COVID-19: Details on cases. New Delhi, India: PRS Legislative Research 2020.

Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis. 2013;7(7):e2324. Epub 2013/07/23. doi: 10.1371/journal.pntd.0002324.

Currie J, Lin W, Meng J. Addressing Antibiotic Abuse in China: An Experimental Audit Study. J Dev Econ. 2014;110:39-51. doi: 10.1016/j.jdeveco.2014.05.006.

D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, et al. Beyond malaria--causes of fever in outpatient Tanzanian children. N Engl J Med. 2014;370(9):809-17. Epub 2014/02/28. doi: 10.1056/NEJMoa1214482.

Daniels B, Dolinger A, Bedoya G, Rogo K, Goicoechea A, Coarasa J, et al. Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. BMJ Glob Health. 2017;2(2):e000333. Epub 2017/12/12. doi: 10.1136/bmjgh-2017-000333.

Das J, Chowdhury A, Hussam R, Banerjee AV. The impact of training informal health care providers in India: A randomized controlled trial. Science (New York, NY). 2016;354(6308). Epub 2016/11/16. doi: 10.1126/science.aaf7384.

Das J, Holla A, Das V, Mohanan M, Tabak D, Chan B. In urban and rural India, a standardized patient study showed low levels of provider training and huge quality gaps. Health Aff (Millwood). 2012;31(12):2774-84. Epub 2012/12/06. doi: 10.1377/hlthaff.2011.1356. PubMed PMID: 23213162; PubMed Central PMCID: PMCPMC3730274.

Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. Lancet Infect Dis. 2015;15(11):1305-13. Epub 2015/08/14. doi: 10.1016/S1473-3099(15)00077-8.

Davies NG, Klepac P, Liu Y, Prem K, Jit M, Pearson CAB, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nature Medicine. 2020;26(8):1205-11. doi: 10.1038/s41591-020-0962-9.

de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Med. 2016;13(11):e1002184. doi: 10.1371/journal.pmed.1002184

DeJong C, Wachter RM. The Risks of Prescribing Hydroxychloroquine for Treatment of COVID-19-First, Do No Harm. JAMA internal medicine. 2020;180(8):1118-9. Epub 2020/04/30. doi: 10.1001/jamainternmed.2020.1853.

DiCiccio TJ, Efron B. Bootstrap Confidence intervals. Stat Sci. 1996;11(3):189-228.

Dieringer TD, Furukawa D, Graber CJ, Stevens VW, Jones MM, Rubin MA, et al. Inpatient antibiotic utilization in the Veterans' Health Administration during the coronavirus disease 2019 (COVID-19) pandemic. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/10/21. doi: 10.1017/ice.2020.1277.

Doan T, Worden L, Hinterwirth A, Arzika AM, Maliki R, Abdou A, et al. Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution. N Engl J Med. 2020;383(20):1941-50. Epub 2020/11/12. doi: 10.1056/NEJMoa2002606.

Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother. 2018;73(Suppl. 2):ii2–10. doi: 10.1093/jac/dkx504

Donde S, Mishra A, Kochhar P. Azithromycin in acute bacterial upper respiratory tract infections: an Indian non-interventional study. Indian J Otolaryngol Head Neck Surg. 2014;66(Suppl 1):225-30. Epub 2014/02/18. doi: 10.1007/s12070-011-0437-x.

El Mahalli AA, Akl OA. Effect of adopting integrated management of childhood illness guidelines on drug use at a primary health care center: a case study from Egypt. J Family Community Med. 2011;18(3):118–23. doi: 10.4103/2230-8229.90010

Farooqui HH, Mehta A, Selvaraj S. Outpatient antibiotic prescription rate and pattern in the private sector in India: Evidence from medical audit data. PloS one. 2019;14(11):e0224848. Epub 2019/11/14. doi: 10.1371/journal.pone.0224848.

Fattorini L, Creti R, Palma C, Pantosti A. Bacterial coinfections in COVID-19: an underestimated adversary. Ann Ist Super Sanita. 2020;56(3):359-64. Epub 2020/09/23. doi: 10.4415/ann_20_03_14.

Fitzpatrick A, editor Do Informed Consumers Reduce the Price and Prevalence of Counterfeit Drugs ? Evidence from the Antimalarial Market2015.

Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr., et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA, Journal of the American Medical Association. 2016;315(17):1864-73. doi: http://dx.doi.org/10.1001/jama.2016.4151.

Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet. 2020;396(10256):959-67. Epub 2020/09/09. doi: 10.1016/s0140-6736(20)31862-6.

Gandra S, Choi J, McElvania E, Green SJ, Harazin M, Thomson RB, et al. Faropenem resistance causes in vitro cross-resistance to carbapenems in ESBL-producing Escherichia coli. Int J Antimicrob Agents. 2020;55(3):105902. Epub 2020/01/17. doi: 10.1016/j.ijantimicag.2020.105902.

Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalised patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2020. Epub 2020/08/04. doi: 10.1016/j.cmi.2020.07.041.

Gasson J, Blockman M, Willems B. Antibiotic prescribing practice and adherence to guidelines in primary care in the Cape Town Metro District, South Africa. S Afr Med J. 2018;108(4):304–10. doi: 10.7196/SAMJ.2017.v108i4.12564

Gazette Notification (26th March, 2020), (2020).

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789–858. doi: 10.1016/S0140-6736(18)32279-7

Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH. Tackling antimicrobial resistance in the COVID-19 pandemic. Bull World Health Organ. 2020;98(7):442-a. Epub 2020/08/04. doi: 10.2471/blt.20.268573.

Getnet F, Demissie M, Assefa N, Mengistie B, Worku A. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. BMC Pulm Med. 2017;17(1):202. Epub 2017/12/13. doi: 10.1186/s12890-017-0551-y.

Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. Lancet Glob Health. 2020. Epub 2020/11/15. doi: 10.1016/s2214-109x(20)30444-7.

Global Action Plan on Antimicrobial Resistance. Geneva, Switzerland: World Health Organization (WHO), 2015.

Gomez-Simmonds A, Annavajhala MK, McConville TH, Dietz DE, Shoucri SM, Laracy JC, et al. Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/11/18. doi: 10.1093/jac/dkaa466.

Goncalves Mendes Neto A, Lo KB, Wattoo A, Salacup G, Pelayo J, DeJoy R, 3rd, et al. Bacterial Infections and Patterns of Antibiotic Use in Patients with COVID-19. J Med Virol. 2020. Epub 2020/08/19. doi: 10.1002/jmv.26441.

Gonzalez-Zorn B. Antibiotic use in the COVID-19 crisis in Spain. Clin Microbiol Infect. 2020. Epub 2020/11/30. doi: 10.1016/j.cmi.2020.09.055.

Graham K, Sinyangwe C, Nicholas S, King R, Mukupa S, Kallander K, et al. Rational use of antibiotics by community health workers and caregivers for children with suspected pneumonia in Zambia: a cross-sectional mixed methods study. BMC Public Health. 2016;16:897. doi: 10.1186/s12889-016-3541-8

Greer RC, Intralawan D, Mukaka M, Wannapinij P, Day NPJ, Nedsuwan S, et al. Retrospective review of the management of acute infections and the indications for antibiotic prescription in primary care in northern Thailand. BMJ Open. 2018;8(7):e022250. doi: 10.1136/bmjopen-2018-022250

Harbord RM, Higgins JPT. Meta-regression in Stata. Stata J. 2008;8(4):493–519. doi: 10.1177/1536867x0800800403

Hatoun J, Correa ET, Donahue SMA, Vernacchio L. Social Distancing for COVID-19 and Diagnoses of Other Infectious Diseases in Children. Pediatrics. 2020;146(4). Epub 2020/09/04. doi: 10.1542/peds.2020-006460. PubMed PMID: 32879032.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. doi: 10.1136/bmj.327.7414.557

Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-87. Epub 2015/11/26. doi: 10.1016/s0140-6736(15)00473-0.

Hooda Y, Tanmoy AM, Sajib MSI, Saha S. Mass azithromycin administration: considerations in an increasingly resistant world. BMJ Glob Health. 2020;5(6). Epub 2020/06/12. doi: 10.1136/bmjgh-2020-002446.

Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030-40. Epub 2020/10/09. doi: 10.1056/NEJMoa2022926.

Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934–9. doi: 10.1016/j.jclinepi.2011.11.014

Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. Lancet Infect Dis. 2019;19(1):67–75. doi: 10.1016/S1473-3099(18)30547-4

Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol. 2014;67(8):897–903. doi: 10.1016/j.jclinepi.2014.03.003

Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. Epub 2020/04/30. doi: 10.1016/j.cmi.2020.04.024.

Indian Council of Medical Research (ICMR). Annual Report: Antimicrobial Resistance Surveillance and Research Network. January 2019 to December 2019. New Delhi, India; 2020. Available at: http://iamrsn.icmr.org.in/index.php/resources/amr-icmr-data.

IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016;6(7):e010247. doi: 10.1136/bmjopen-2015-010247

Jebb AT, Tay L, Wang W, Huang Q. Time series analysis for psychological research: examining and forecasting change. Frontiers in Psychology. 2015;6(727). doi: 10.3389/fpsyg.2015.00727.

John J, Van Aart CJ, Grassly NC. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. PLoS Negl Trop Dis. 2016;10(4):e0004616. Epub 2016/04/16. doi: 10.1371/journal.pntd.0004616.

Jose J, Devassykutty D. Paediatric prescription analysis in a primary health care institution. J Clin Diagn Res. 2016;10(11):FC05–8. doi: 10.7860/jcdr/2016/22350.8797.

Kapasi AJ, Dittrich S, González IJ, Rodwell TC. Host Biomarkers for Distinguishing Bacterial from Non-Bacterial Causes of Acute Febrile Illness: A Comprehensive Review. PloS one. 2016;11(8):e0160278. Epub 2016/08/04. doi: 10.1371/journal.pone.0160278.

Karami Z, Knoop BT, Dofferhoff ASM, Blaauw MJT, Janssen NA, van Apeldoorn M, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. Infect Dis (Lond). 2020:1-9. Epub 2020/10/27. doi: 10.1080/23744235.2020.1839672.

Kardas P, Devine S, Golembesky A, Roberts C. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. Int J Antimicrob Agents. 2005;26(2):106–13. doi: 10.1016/j.ijantimicag.2005.04.017

Kasabi GS, Thilakavathi S, Allam RR, Grace CA, Shivanna R, Murhekar MV. Prescription practices & use of essential medicines in the primary health care system, Shimoga district, Karnataka, India. Indian J Med Res. 2015;142(2):216–9. doi: 10.4103/0971-5916.164261

Katz SE, Spencer H, Zhang M, Banerjee R. Impact of the COVID-19 Pandemic on Infectious Diagnoses and Antibiotic Use in Pediatric Ambulatory Practices. Journal of the Pediatric Infectious Diseases Society. 2020. doi: 10.1093/jpids/piaa124.

Kjærgaard J, Anastasaki M, Stubbe Østergaard M, Isaeva E, Akylbekov A, Nguyen NQ, et al. Diagnosis and treatment of acute respiratory illness in children under five in primary care in low-, middle-, and high-income countries: a descriptive FRESH AIR study. PLoS ONE. 2019;14(11):e0221389. doi: 10.1371/journal.pone.0221389

Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO Antibiotic Consumption and Access Targets: 2000-2015. Lancet Infectious Diseases. 2020;In press.

Klein EY, Tseng KK, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. BMJ Glob Health. 2019;4(2):e001315. Epub 2019/05/30. doi: 10.1136/bmjgh-2018-001315.

Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-E70. Epub 2018/03/28. doi: 10.1073/pnas.1717295115.

Kohli M, Sen P, Pai M. Improving access to essential tests for infectious diseases. Microbes Infect. 2019;21(1):1–3. doi: 10.1016/j.micinf.2018.08.003

Kotwani A, Gandra S. Potential pharmacological agents for COVID-19. Indian J Public Health. 2020;64(Supplement):S112-s6. Epub 2020/06/05. doi: 10.4103/ijph.IJPH_456_20.

Kotwani A, Holloway K. Antibiotic prescribing practice for acute, uncomplicated respiratory tract infections in primary care settings in New Delhi, India. Tropical medicine & international health : TM & IH. 2014;19(7):761-8. Epub 2014/04/23. doi: 10.1111/tmi.12327.

Kwan A, Bergkvist S, Daniels B, Das J, Das V, Pai M. Using standardized patients to measure health care quality: a manual and toolkit for projects in low- and middle-income countries. 2019.

Kwan A, Daniels B, Saria V, Satyanarayana S, Subbaraman R, McDowell A, et al. Variations in the quality of tuberculosis care in urban India: a cross-sectional, standardized patient study in two cities. PLoS Med. 2018;15(9):e1002653. doi: 10.1371/journal.pmed.1002653

Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020. Epub 2020/07/28. doi: 10.1016/j.cmi.2020.07.016.

Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75. Epub 2020/05/31. doi: 10.1016/j.jinf.2020.05.046.

Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057-98. Epub 2013/11/21. doi: 10.1016/s1473-3099(13)70318-9.

Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. BMJ Open. 2011;1(2):e000135. doi: 10.1136/bmjopen-2011-000135.

Laxminarayan R, Van Boeckel T, Frost I, Kariuki S, Khan EA, Limmathurotsakul D, et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. Lancet Infect Dis. 2020;20(4):e51-e60. Epub 2020/02/16. doi: 10.1016/s1473-3099(20)30003-7.

Leonard K, Masatu MC. Outpatient process quality evaluation and the Hawthorne effect. Soc Sci Med. 2006;63(9):2330–40. doi: 10.1016/j.socscimed.2006.06.003

Leonard KL, Masatu MC. The use of direct clinician observation and vignettes for health services quality evaluation in developing countries. Soc Sci Med. 2005;61(9):1944–51. doi: 10.1016/j.socscimed.2005.03.043

Li J, Wang J, Yang Y, Cai P, Cao J, Cai X, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrob Resist Infect Control. 2020;9(1):153. Epub 2020/09/24. doi: 10.1186/s13756-020-00819-1.

Lima MG, Dutra KR, Martins UCM. Prescribing indicators in primary health care in Belo Horizonte, Brazil: associated factors. Int J Clin Pharm. 2017;39(4):913–8. doi: 10.1007/s11096-017-0501-z

Lin H, Dyar OJ, Rosales-Klintz S, Zhang J, Tomson G, Hao M, et al. Trends and patterns of antibiotic consumption in Shanghai municipality, China: a 6 year surveillance with sales records, 2009-14. The Journal of antimicrobial chemotherapy. 2016;71(6):1723-9. Epub 2016/02/17. doi: 10.1093/jac/dkw013.

Linden A. Conducting Interrupted Time-series Analysis for Single- and Multiple-group Comparisons. The Stata Journal. 2015;15(2):480-500. doi: 10.1177/1536867X1501500208.

Liu C, Wang D, Zhang X. Intrinsic and external determinants of antibiotic prescribing: a multi-level path analysis of primary care prescriptions in Hubei, China. Antimicrob Resist Infect Control. 2019;8:132. doi: 10.1186/s13756-019-0592-5

Liu H, Gao J, Wang Y, Jie J, Luo J, Xu Y, et al. Epidemiological and clinical characteristics of 2019 novel coronavirus disease (COVID-19) in Jilin, China: A descriptive study. Medicine (Baltimore). 2020;99(47):e23407. Epub 2020/11/22. doi: 10.1097/md.0000000000023407.

Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348-55. Epub 2016/06/11. doi: 10.1093/ije/dyw098.

Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. J Clin Epidemiol. 2018;103:82-91. Epub 2018/06/10. doi: 10.1016/j.jclinepi.2018.05.026.

Luyt CE, Sahnoun T, Gautier M, Vidal P, Burrel S, Pineton de Chambrun M, et al. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care. 2020;10(1):158. Epub 2020/11/25. doi: 10.1186/s13613-020-00775-4.

Machowska A, Stalsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. Int J Environ Res Public Health. 2018;16(1). Epub 2018/12/26. doi: 10.3390/ijerph16010027.

Mackintosh M, Channon A, Karan A, Selvaraj S, Cavagnero E, Zhao H. What is the private sector? Understanding private provision in the health systems of low-income and middle-income countries. Lancet. 2016;388(10044):596-605. Epub 2016/07/01. doi: 10.1016/S0140-6736(16)00342-1.

Mashalla Y, Setlhare V, Massele A, Sepako E, Tiroyakgosi C, Kgatlwane J, et al. Assessment of prescribing practices at the primary healthcare facilities in Botswana with an emphasis on antibiotics: findings and implications. Int J Clin Pract. 2017;71(12). doi: 10.1111/ijcp.13042

Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Pérès A, Paris DH, Phetsouvanh R, et al. Causes of non-malarial fever in Laos: a prospective study. Lancet Glob Health. 2013;1(1):e46-54. Epub 2014/04/22. doi: 10.1016/s2214-109x(13)70008-1.

Maze MJ, Bassat Q, Feasey NA, Mandomando I, Musicha P, Crump JA. The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management. Clin Microbiol Infect. 2018;24(8):808-14. Epub 2018/02/20. doi: 10.1016/j.cmi.2018.02.011.

Mekuria LA, de Wit TF, Spieker N, Koech R, Nyarango R, Ndwiga S, et al. Analyzing data from the digital healthcare exchange platform for surveillance of antibiotic prescriptions in primary care in urban Kenya: a mixed-methods study. PLoS ONE. 2019;14(9):e0222651. doi: 10.1371/journal.pone.0222651

Miranda C, Silva V, Capita R, Alonso-Calleja C, Igrejas G, Poeta P. Implications of antibiotics use during the COVID-19 pandemic: present and future. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/08/25. doi: 10.1093/jac/dkaa350.

Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi HAA, Jeda AS, et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020. Epub 2020/08/10. doi: 10.1002/iub.2356.

Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. New England Journal of Medicine. 2020. doi: 10.1056/NEJMoa2021801.

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. doi: 10.1186/2046-4053-4-1

Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? Euro Surveill. 2020;25(45). Epub 2020/11/14. doi: 10.2807/1560-7917.Es.2020.25.45.2001886.

Montrucchio G, Corcione S, Sales G, Curtoni A, De Rosa FG, Brazzi L. Carbapenem resistant Klebsiella pneumoniae in ICU-admitted COVID-19 Patients: Keep an eye on the ball. J Glob Antimicrob Resist. 2020;23:398-400. Epub 2020/11/27. doi: 10.1016/j.jgar.2020.11.004.

Mørch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, et al. Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. BMC infectious diseases. 2017;17(1):665. Epub 2017/10/06. doi: 10.1186/s12879-017-2764-3.

Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. Clin Microbiol Infect. 2018;24(8):827-35. Epub 2018/05/20. doi: 10.1016/j.cmi.2018.05.001.

Mukonzo JK, Namuwenge PM, Okure G, Mwesige B, Namusisi OK, Mukanga D. Over-the-counter suboptimal dispensing of antibiotics in Uganda. J Multidiscip Healthc. 2013;6:303–10. doi: 10.2147/JMDH.S49075

Nafade V, Huddart S, Sulis G, Daftary A, Miraj SS, Saravu K, et al. Over-the-counter antibiotic dispensing by pharmacies: a standardised patient study in Udupi district, India. BMJ Glob Health. 2019;4(6):e001869. Epub 2019/12/05. doi: 10.1136/bmjgh-2019-001869.

National Standard Treatment Guidelines for Antimicrobial Use in Infectious Diseases. New Delhi, India: National Centre for Disease Control, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, 2016.

Ndhlovu M, Nkhama E, Miller JM, Hamer DH. Antibiotic prescribing practices for patients with fever in the transition from presumptive treatment of malaria to 'confirm and treat' in Zambia: a cross-sectional study. Trop Med Int Health. 2015;20(12):1696–706. doi: 10.1111/tmi.12591

Nepal A, Hendrie D, Robinson S, Selvey LA. Analysis of patterns of antibiotic prescribing in public health facilities in Nepal. J Infect Dev Ctries. 2020;14(1):18–27. doi: 10.3855/jidc.11817

Nestler M, Godbout E, Lee K, Kim J, Noda AJ, Taylor P, et al. Impact of COVID-19 on Pneumonia-Focused Antibiotic Use at an Academic Medical Center. Infect Control Hosp Epidemiol. 2020:1-9. Epub 2020/07/24. doi: 10.1017/ice.2020.362.

Nieuwlaat R, Mbuagbaw L, Mertz D, Burrows L, Bowdish DME, Moja L, et al. COVID-19 and Antimicrobial Resistance: Parallel and Interacting Health Emergencies. Clin Infect Dis. 2020. Epub 2020/06/17. doi: 10.1093/cid/ciaa773.

Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol. 2020:1-5. Epub 2020/07/25. doi: 10.1017/ice.2020.368.

Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39. doi: 10.1186/2049-3258-72-39

O'Neill J. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. HM Government and Welcome Trust, UK, 2016.

Omole VN, Joshua IA, Muhammad-Idris ZK, Usman NO, Ahmad IA. Use of injections and antibiotics and profile of health workers in rural primary health care facilities in north-western Nigeria. Int J Med Health Dev. 2018;23(1):183–8. doi: 10.4314/jcm.v23i1.3

Oyeyemi AS, Ogunleye OA. Rational use of medicines: assessing progress using primary health centres in Shomolu local government area of Lagos, Nigeria. West Afr J Med. 2013;32(2):121–5.

Para O, Caruso L, Ronchetti M, Finocchi M, Guidi S, Spinicci M. Superinfection with difficult-to-treat bacteria in COVID-19 patients: a call for compliance with diagnostic and antimicrobial stewardship. Intern Emerg Med. 2020:1-3. Epub 2020/11/23. doi: 10.1007/s11739-020-02537-3.

Patel J, Richter S. Mechanisms of Resistance to Antibacterial Agents*, p 1212-1245. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, Eleventh Edition*. ASM Press, Washington, DC. 2015. doi: 10.1128/9781555817381.ch69.

Petersen MR, Deddens JA. A comparison of two methods for estimating prevalence ratios. BMC Med Res Methodol. 2008;8:9. Epub 2008/02/28. doi: 10.1186/1471-2288-8-9.

Press release: Record number of countries contribute data revealing disturbing rates of antimicrobial resistance. [Internet]. Geneva, Switzerland: World Health Organization (WHO); 2020. Available from: https://www.who.int/news-room/detail/01-06-2020-record-number-of-countries-contribute-data-revealing-disturbing-rates-of-antimicrobial-resistance

Pulcini C, ESGAP AMOXDOSE working group. Amoxicillin dosing recommendations are very different in European countries: a cross-sectional survey. Clin Microbiol Infect. 2017;23(6):414–5. doi: 10.1016/j.cmi.2016.11.013

Pulia MS, Wolf I, Schulz LT, Pop-Vicas A, Schwei RJ, Lindenauer PK. COVID-19: An Emerging Threat to Antibiotic Stewardship in the Emergency Department. West J Emerg Med. 2020;21(5):1283-6. Epub 2020/09/25. doi: 10.5811/westjem.2020.7.48848.

Qamar FN, Yousafzai MT, Khalid M, Kazi AM, Lohana H, Karim S, et al. Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. Lancet Infect Dis. 2018;18(12):1368-76. Epub 2018/12/07. doi: 10.1016/s1473-3099(18)30483-3.

Rawson TM, Ming D, Ahmad R, Moore LSP, Holmes AH. Antimicrobial use, drug-resistant infections and COVID-19. Nat Rev Microbiol. 2020;18(8):409-10. Epub 2020/06/04. doi: 10.1038/s41579-020-0395-y.

Rawson TM, Moore LSP, Castro-Sanchez E, Charani E, Davies F, Satta G, et al. COVID-19 and the potential long-term impact on antimicrobial resistance. J Antimicrob Chemother. 2020;75(7):1681-4. Epub 2020/05/21. doi: 10.1093/jac/dkaa194.

Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020. Epub 2020/05/03. doi: 10.1093/cid/ciaa530.

Raza UA, Khursheed T, Irfan M, Abbas M, Irfan UM. Prescription patterns of general practitioners in Peshawar, Pakistan. Pak J Med Sci. 2014;30(3):462–5. doi: 10.12669/pjms.303.4931.

Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for COVID-19 infection [issued on 25th May, 2020 in supersession of previous advisory dated 23rd March, 2020]. New Delhi, India: Ministry of Health and Family Welfare, Government of India; 2020.

Robson J, Ayerbe L, Mathur R, Addo J, Wragg A. Clinical value of chest pain presentation and prodromes on the assessment of cardiovascular disease: a cohort study. BMJ Open. 2015;5(4):e007251. Epub 2015/04/15. doi: 10.1136/bmjopen-2014-007251.

Rodríguez-Molinero A, Pérez-López C, Gálvez-Barrón C, Miñarro A, Macho O, López GF, et al. Observational study of azithromycin in hospitalized patients with COVID-19. PloS one. 2020;15(9):e0238681. Epub 2020/09/04. doi: 10.1371/journal.pone.0238681.

Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19). Our World in Data. 2020.

Rothe K, Feihl S, Schneider J, Wallnöfer F, Wurst M, Lukas M, et al. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. Eur J Clin Microbiol Infect Dis. 2020. Epub 2020/11/04. doi: 10.1007/s10096-020-04063-8.

Sadeghian GH, Safaeian L, Mahdanian AR, Salami S, Kebriaee-Zadeh J. Prescribing quality in medical specialists in Isfahan, Iran. Iran J Pharm Res. 2013;12(1):235–41.

Safaeian L, Mahdanian AR, Salami S, Pakmehr F, Mansourian M. Seasonality and physician-related factors associated with antibiotic prescribing: a cross-sectional study in Isfahan, Iran. Int J Prev Med. 2015;6:1. doi: 10.4103/2008-7802.151431

Sánchez Choez X, Armijos Acurio ML, Jimbo Sotomayor RE. Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador. BMC Pharmacol Toxicol. 2018;19(1):46. doi: 10.1186/s40360-018-0237-y

Sarwar MR, Saqib A, Iftikhar S, Sadiq T. Antimicrobial use by WHO methodology at primary health care centers: a cross sectional study in Punjab, Pakistan. BMC Infect Dis. 2018;18(1):492. doi: 10.1186/s12879-018-3407-z

Satyanarayana S, Kwan A, Daniels B, Subbaraman R, McDowell A, Bergkvist S, et al. Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. Lancet Infect Dis. 2016;16(11):1261-8. Epub 2016/10/30. doi: 10.1016/S1473-3099(16)30215-8.

Saurabh MK, Biswas NK, Yadav AK, Singhai A, Saurabh A. Study of prescribing habits and assessment of rational use of drugs among doctors of primary health care facilities. Asian J Pharm Clin Res. 2011;4(4):102–5.

Savadogo LGB, Ilboudo B, Kinda M, Boubacar N, Hennart P, Dramaix M, et al. Antibiotics prescribed to febrile under-five children outpatients in urban public health services in Burkina Faso. Health. 2014;6(2):165–70. doi: 10.4236/health.2014.62026

Saweri OPM, Hetzel MW, Mueller I, Siba PM, Pulford J. The treatment of non-malarial febrile illness in Papua New Guinea: findings from cross sectional and longitudinal studies of health worker practice. BMC Health Serv Res. 2017;17(1):10. doi: 10.1186/s12913-016-1965-6.

Schwartz KL, Langford BJ, Daneman N, Chen B, Brown KA, McIsaac W, et al. Unnecessary antibiotic prescribing in a Canadian primary care setting: a descriptive analysis using routinely collected electronic medical record data. CMAJ Open. 2020;8(2):E360-E9. Epub 2020/05/07. doi: 10.9778/cmajo.20190175.

Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR Surveillance in low and middle-income settings - A roadmap for participation in the Global Antimicrobial Surveillance System (GLASS). Wellcome Open Res. 2017;2:92. Epub 2017/10/25. doi: 10.12688/wellcomeopenres.12527.1.

Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S, et al. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect. 2020. Epub 2020/09/29. doi: 10.1016/j.jinf.2020.09.024.

Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global

antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278–80. doi: 10.1016/S1473-3099(19)30532-8.

Shimelis T, Tadesse BT, F WG, Crump JA, Schierhout G, Dittrich S, et al. Aetiology of acute febrile illness among children attending a tertiary hospital in southern Ethiopia. BMC infectious diseases. 2020;20(1):903. Epub 2020/12/02. doi: 10.1186/s12879-020-05635-x.

Shin DH, Kang M, Song KH, Jung J, Kim ES, Kim HB. A Call for Antimicrobial Stewardship in Patients with COVID-19: A Nationwide Cohort Study in Korea. Clin Microbiol Infect. 2020. Epub 2020/11/03. doi: 10.1016/j.cmi.2020.10.024.

Shumway RH, Stoffer DS. Time series analysis and its applications : with R examples. 2017.

Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med. 2020. Epub 2020/07/17. doi: 10.7326/m20-4207. www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-4207.

Skov T, Deddens J, Petersen MR, Endahl L. Prevalence proportion ratios: estimation and hypothesis testing. Int J Epidemiol. 1998;27(1):91-5. doi: 10.1093/ije/27.1.91.

Smieszek T, Pouwels KB, Dolk FCK, Smith DRM, Hopkins S, Sharland M, et al. Potential for reducing inappropriate antibiotic prescribing in English primary care. The Journal of antimicrobial chemotherapy. 2018;73(Suppl. 2):ii36-ii43. doi: http://dx.doi.org/10.1093/jac/dkx500.

Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis. 2016;63(12):1639-44. Epub 2016/09/30. doi: 10.1093/cid/ciw658.

Staub MB, Beaulieu RM, Graves J, Nelson GE. Changes in Antimicrobial Utilization During the COVID-19 Pandemic after Implementation of a Multispecialty Clinical Guidance Team. Infect Control Hosp Epidemiol. 2020:1-28. Epub 2020/10/27. doi: 10.1017/ice.2020.1291.

Stevens RW, Jensen K, O'Horo JC, Shah A. Antimicrobial prescribing practices at a tertiary-care center in patients diagnosed with COVID-19 across the continuum of care. Infect Control Hosp Epidemiol. 2020:1-4. Epub 2020/07/25. doi: 10.1017/ice.2020.370.

Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PloS one. 2012;7(10):e46042. Epub 2012/10/03. doi: 10.1371/journal.pone.0046042.

Sudarsan M, Sitikantha B, Aparajita D. Audit and quality assessment of prescriptions in an urban health centre of Kolkata. Int J Med Public Health. 2016;6(3):136–9. doi: 10.5530/ijmedph.2016.3.8

Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med. 2020;17(6):e1003139. doi: 10.1371/journal.pmed.1003139.

Sulis G, Daniels B, Kwan A, Gandra S, Daftary A, Das J, et al. Antibiotic overuse in the primary health care setting: a secondary data analysis of standardised patient studies from India, China and Kenya. BMJ Glob Health. 2020;5(9). Epub 2020/09/18. doi: 10.1136/bmjgh-2020-003393.

Sun Q, Dyar OJ, Zhao L, Tomson G, Nilsson LE, Grape M, et al. Overuse of antibiotics for the common cold—attitudes and behaviors among doctors in rural areas of Shandong Province, China. BMC Pharmacol Toxicol. 2015;16:6. doi: 10.1186/s40360-015-0009-x

Sylvia S, Shi Y, Xue H, Tian X, Wang H, Liu Q, et al. Survey using incognito standardized patients shows poor quality care in China's rural clinics. Health policy and planning. 2015;30(3):322-33. Epub 2014/03/22. doi: 10.1093/heapol/czu014.

Sylvia S, Xue H, Zhou C, Shi Y, Yi H, Zhou H, et al. Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. PLoS Med. 2017;14(10):e1002405. Epub 2017/10/19. doi: 10.1371/journal.pmed.1002405.

Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-27. Epub 2017/12/26. doi: 10.1016/s1473-3099(17)30753-3.

Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occup Environ Med. 1998;55(4):272-7. doi: 10.1136/oem.55.4.272.

Thompson W, Tonkin-Crine S, Pavitt SH, McEachan RRC, Douglas GVA, Aggarwal VR, et al. Factors associated with antibiotic prescribing for adults with acute conditions: an umbrella review across primary care and a systematic review focusing on primary dental care. J Antimicrob Chemother. 2019;74(8):2139–52. doi: 10.1093/jac/dkz152

Tiri B, Sensi E, Marsiliani V, Cantarini M, Priante G, Vernelli C, et al. Antimicrobial Stewardship Program, COVID-19, and Infection Control: Spread of Carbapenem-Resistant Klebsiella Pneumoniae Colonization in ICU COVID-19 Patients. What Did Not Work? J Clin Med. 2020;9(9). Epub 2020/08/29. doi: 10.3390/jcm9092744.

Townsend L, Hughes G, Kerr C, Kelly M, O'Connor R, Sweeney E, et al. Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. JAC Antimicrob Resist. 2020;2(3):dlaa071. Epub 2020/08/31. doi: 10.1093/jacamr/dlaa071.

Treatment Guidelines for Antimicrobial Use in Common Syndromes. New Delhi, India: Indian Council of Medical Research (ICMR), 2019.

Turnidge J. Susceptibility Test Methods: General Considerations, p 1246-1252. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, Eleventh Edition*. ASM Press, Washington, DC. 2015. doi: 10.1128/9781555817381.ch70.

Uchida H, Nelson A. Agglomeration index: towards a new measure of urban concentration. Working Paper No. 2010/29. Helsinki: World Institute for Development Economics Research; 2010 [cited 2020 May 13]. Available from: https://www.wider.unu.edu/sites/default/files/wp2010-29.pdf.

Vaillancourt M, Jorth P. The Unrecognized Threat of Secondary Bacterial Infections with COVID-19. mBio. 2020;11(4). Epub 2020/08/10. doi: 10.1128/mBio.01806-20.

Vaughn VM, Gandhi T, Petty LA, Patel PK, Prescott HC, Malani AN, et al. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study. Clin Infect Dis. 2020. Epub 2020/08/22. doi: 10.1093/cid/ciaa1239.

Velasco-Arnaiz E, López-Ramos MG, Simó-Nebot S, Jordan I, Ríos-Barnés M, Urrea-Ayala M, et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. Infect Control Hosp Epidemiol. 2020:1-3. Epub 2020/06/25. doi: 10.1017/ice.2020.312.

Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619-e29. Epub 2018/04/24. doi: 10.1016/S2214-109X(18)30186-4.

Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619–29. doi: 10.1016/S2214-109X(18)30186-4

Vora A, Arora VK, Behera D, Tripathy SK. White paper on Ivermectin as a potential therapy for COVID-19. Indian J Tuberc. 2020;67(3):448-51. doi: 10.1016/j.ijtb.2020.07.031. PubMed PMID: 32825892.

Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309. Epub 2002/08/14. doi: 10.1046/j.1365-2710.2002.00430.x.

Wang J, Wang P, Wang X, Zheng Y, Xiao Y. Use and prescription of antibiotics in primary health care settings in China. JAMA Intern Med. 2014;174(12):1914–20. doi: 10.1001/jamainternmed.2014.5214

Wang L, Amin AK, Khanna P, Aali A, McGregor A, Bassett P, et al. An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. The Journal of antimicrobial chemotherapy. 2020. Epub 2020/11/14. doi: 10.1093/jac/dkaa475.

WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system 2019. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2019.

Woodward WA, Gray HL, Elliott AC. Model identification. Applied time series analysis with R. 2nd ed: CRC Press; 2017.

Worku F, Tewahido D. Retrospective assessment of antibiotics prescribing at public primary healthcare facilities in Addis Ababa, Ethiopia. Interdiscip Perspect Infect Dis. 2018;2018:4323769. doi: 10.1155/2018/4323769

World Bank. World Bank country and lending groups. Washington (DC): World Bank; 2020. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

World Health Organization. Antimicrobial resistance and primary health care. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/326454/WHO-HIS-SDS-2018.56-eng.pdf.

World Health Organization. Executive summary: the selection and use of essential medicines 2019. Report of the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?sequence=1&isAllowed=y.

World Health Organization. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.

World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2016–2017. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1.

World Health Organization. Using indicators to measure country pharmaceutical situations. Fact book on WHO Level I and Level II monitoring indicators. Geneva: World Health Organization; 2006. Available from: https://www.who.int/medicines/publications/WHOTCM2006.2A.pdf.

World Health Organization. WHO informal consultation on fever management in peripheral health care settings: A global review of evidence and practice. Geneva, Switzerland; 2013. Available at: https://apps.who.int/iris/bitstream/handle/10665/95116/9789241506489_eng.pdf?sequence=1.

Wushouer H, Tian Y, Guan XD, Han S, Shi LW. Trends and patterns of antibiotic consumption in China's tertiary hospitals: Based on a 5 year surveillance with sales records, 2011-2015. PloS one. 2017;12(12):e0190314. Epub 2017/12/27. doi: 10.1371/journal.pone.0190314.

Xiao H, Augusto O, Wagenaar BH. Reflection on modern methods: a common error in the segmented regression parameterization of interrupted time-series analyses. Int J Epidemiol. 2020. Epub 2020/10/25. doi: 10.1093/ije/dyaa148.

Xue H, Shi Y, Huang L, Yi H, Zhou H, Zhou C, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. J Antimicrob Chemother. 2019;74(1):256–63. doi: 10.1093/jac/dky390

Yebyo H, Medhanyie AA, Spigt M, Hopstaken R. C-reactive protein point-of-care testing and antibiotic prescribing for acute respiratory tract infections in rural primary health centres of North Ethiopia: a cross-sectional study. NPJ Prim Care Respir Med. 2016;26:15076. doi: 10.1038/npjpcrm.2015.76

Yin J, Dyar OJ, Yang P, Yang D, Marrone G, Sun M, et al. Pattern of antibiotic prescribing and factors associated with it in eight village clinics in rural Shandong Province, China: a descriptive study. Trans R Soc Trop Med Hyg. 2019;113(11):714–21. doi: 10.1093/trstmh/trz058

Yin X, Gong Y, Yang C, Tu X, Liu W, Cao S, et al. A comparison of quality of community health services between public and private community health centers in urban China. Med Care. 2015;53(10):888–93. doi: 10.1097/mlr.0000000000000414

Youngs J, Wyncoll D, Hopkins P, Arnold A, Ball J, Bicanic T. Improving antibiotic stewardship in COVID-19: Bacterial co-infection is less common than with influenza. J Infect. 2020;81(3):e55-e7. Epub 2020/07/01. doi: 10.1016/j.jinf.2020.06.056.

Yousif BM, Supakankunti S. General practitioners' prescribing patterns at primary healthcare centers in national health insurance, Gezira, Sudan. Drugs Real World Outcomes. 2016;3(3):327–32. doi: 10.1007/s40801-016-0087-0

Yu D, Ininbergs K, Hedman K, Giske CG, Strålin K, Özenci V. Low prevalence of bloodstream infection and high blood culture contamination rates in patients with COVID-19. PLoS One. 2020;15(11):e0242533. Epub 2020/11/24. doi: 10.1371/journal.pone.0242533.

Yuniar CT, Anggadiredja K, Islamiyah AN. Evaluation of rational drug use for acute pharyngitis associated with the incidence and prevalence of the disease at two community health centers in Indonesia. Sci Pharm. 2017;85(2):22. doi: 10.3390/scipharm85020022

Zhan Q, Wang YL, Chen X. Evaluation of antibacterial use in outpatients of township and community primary medical institutions in a district of Sichuan Province, China. J Glob Antimicrob Resist. 2019;19:201–6. doi: 10.1016/j.jgar.2019.04.021

Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol. 2009;62(2):143-8. Epub 2008/11/18. doi: 10.1016/j.jclinepi.2008.08.007.

Zhang Z, Hu Y, Zou G, Lin M, Zeng J, Deng S, et al. Antibiotic prescribing for upper respiratory infections among children in rural China: a cross-sectional study of outpatient prescriptions. Glob Health Action. 2017;10(1):1287334. doi: 10.1080/16549716.2017.1287334

Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. doi: 10.1093/aje/kwh090.

B. Doctoral training publication list

*indicates authors contributed equally

Under Review

Sulis G, Batomen B, Kotwani A, Pai M, Gandra S. Impact of COVID-19 on antibiotics and hydroxychloroquine sales in India: an interrupted time series analysis. (2021).

Sulis G, Pradhan R, Kotwani A, Gandra S. India's ban on antimicrobial fixed dose combinations: winning the battle, losing the war? (2021).

In preparation

Sulis G, Sayood S, Gandra S. Antimicrobial resistance in low- and middle-income countries: current status and future directions. *Expert Rev Anti Infect Ther*. In preparation.

Kwan A, **Sulis G**, Gertler P. How much can patient demand drive over-dispensing of inappropriate medicines in private sectors? A cross-sectional study using standardized patient method in Kenya. In preparation.

Salomon A, *et al*. Private sector prescribing practices when presented with TB symptoms: a cross-sectional standardized patient study in two urban regions of South Africa. In preparation.

2021

Sulis G, Gandra S. Access to antibiotics: not a problem in some LMICs. *Lancet Glob Health*. 2021 Mar 10: S2214-109x(21)00085-1. doi: 10.1016/S2214-109X(21)00085-1.

2020

Svadzian A,* **Sulis G**,* Gore G, Pai M, Denkinger C.M. Differential yield of universal versus selective drug-susceptibility testing of tuberculosis patients in high burden countries: a systematic review and meta-analysis. *BMJ Glob Health* 2020; 5:e003438. doi: 10.1136/bmjgh-2020-003438.

Sulis G, Daniels B, Kwan A, Gandra S, Daftary A, Das J,* Pai M.* Antibiotic overuse in the primary health care setting: a secondary data analysis of standardized patient studies from India, China and Kenya. *BMJ Glob Health* 2020; 5:e003393. doi:10.1136/bmjgh-2020-003393.

Campbell J, Uppal A, Oxlade O, Fregonese F, Bastos M, Lan Z, Law S, Russell WA, **Sulis G**, Winters N, Yanes Lane M, Brisson M, Laszlo S, Evans T, Menzies D. Active testing of groups at increased risk of acquiring SARS-CoV-2 in Canada: costs and human resource needs. *Can Med Assoc J*. 2020 Sep 9; cmaj.201128; doi: 10.1503/cmaj.201128.

Kouanda S, Ouedraogo HG, Cisse K, Compaoré TR, **Sulis G**, Diagbouga S, Roggi A, Tarnagda G, Villani P, Sangare L, Simporé J, Regazzi M, Matteelli A. Pharmacokinetic study of two different rifabutin doses co-administered with lopinavir/ritonavir in African HIV and tuberculosis co-infected adult patients. *BMC Infect Dis*. 2020; 20: 449. doi: 10.1186/s12879-020-05169-2.

Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, Das J, Gandra S,* Pai M.* Antibiotic prescription practices in primary care in low- and middle-income countries: a systematic review and meta-analysis. *Plos Med*. 2020 Jun 16; 17(6): e1003139. doi: 10.1371/journal.pmed.1003139.

Boffa J, Mhlaba T, **Sulis G**, Moyo S, Sifumba Z, Pai M, Daftary A. COVID-19 and tuberculosis in South Africa: a dangerous combination. S Afr Med J. 2020; 110 (5). doi: 10.7196/SAMJ.2020.v110i5.14747.

Sulis G, Pai M. Isoniazid-resistant tuberculosis: a problem we can no longer ignore. *Plos Med*. 2020 Jan 21; 17(1): e1003023. doi: 10.1371/journal.pmed.1003023.

Ouedraogo HG, Matteelli A, **Sulis G**, Compaore RT, Diagbouga S, Tiendrebeogo S, Roggi A, Cisse K, Giorgetti PF, Villani P, Sangare L, Simpore J, Regazzi M, Kouanda S. Pharmacokinetics of plasma lopinavir and ritonavir in tuberculosis-HIV co-infected African adult patients also

receiving rifabutin 150 or 300 mg three times per week. *Ann Clin Microbiol Antimicrob*. 2020; 19(1):3. doi: 10.1186/s12941-020-0345-6.

2019

Nafade V, Huddart S, **Sulis G,** Daftary A, Miraj SS, Saravu K, Pai M. Over-the-counter antibiotic dispensing by pharmacies: a standardised patient study in Udupi district, India. *BMJ Glob Health*. 2019 Nov 1; 4(6); e001869. doi: 10.1136/bmjgh-2019-001869.

MacLean E, **Sulis G,** Denkinger CM, Johnston JC, Pai M, Ahmad-Khan F. Diagnostic accuracy of stool Xpert MTB/Rif for detection of pulmonary tuberculosis in children: a systematic review and meta-analysis. *J Clin Microbiol.* 2019 May 24; 57(6). pii: e02057-18. doi: 10.1128/JCM.02057-18.

2018

Sulis G, Pai M. Tuberculosis in pregnancy: a treacherous yet neglected issue. *J Obstet Gynaecol Can.* 2018 Aug; 40(8):1003-1005.

Sulis G, Combary A, Getahun H, Gnanou S, Giorgetti PF, Konseimbo A, Capone S, Hamada Y, Baddeley A, Matteelli A. Implementation of tuberculosis prevention for exposed children, Burkina Faso. *Bull World Health Organ.* 2018 Jun 1; 96(6): 386-392. Epub 2018 Apr 20.

Kama Z, Ren X, Sen P, **Sulis G**, White A, Zhang E. Ethiopia's Health Extension Workers and maternal healthcare improvements. *McGill J Glob Health (The Prognosis).* 2018; 7(1).

Sulis G, Agliati A, Pinsi G, Bozzola G, Foccoli P, Gulletta M, Caligaris S, Tomasoni L, El Hamad I, Matteelli A. Xpert MTB/RIF as add-on test to microscopy in a low tuberculosis incidence setting. *Eur Respir J.* 2018 Mar 22; 51(3).

Sulis G, Carvalho ACC, Capone S, Hamada Y, Giorgetti PF, da Silva Martins P, Getahun H, Matteelli A. Policies and practices on the programmatic management of LTBI: a survey in the African Region. *Int J Tuberc Lung Dis*. 2018 Feb 1;22(2): 158-164.