Over-the-counter antibiotic dispensing in South India: a standardised patient study

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Abstract

Background. Antimicrobial resistance is a global health emergency, and one of the contributing factors is overuse and misuse of antibiotics. India is one of the world's largest consumers of antibiotics, and inappropriate use is potentially widespread, particularly in private pharmacies. This study aimed to use standardised patients (SPs) to measure over-the-counter antibiotic dispensing in one region.

Methods. Three adults from the local community in Udupi, India, were recruited and trained as SPs. Three conditions were considered: diarrhoea, upper respiratory tract infection (URI), and acute fever suggestive of malaria. For each condition, there was a paediatric case and an adult case, giving a total of six SP case presentations. Adult SPs were used as proxies for the paediatric cases. Each individual recruited as an SP visited 279 of 350 pharmacies in the district during July to October 2018, seeking care for a sick child at home with one of the conditions. Upon the completion of this interaction, the SP additionally asked for help for their own symptoms of one of the other conditions. A model using generalised estimating equations with a logit link was fit to determine if the following factors affected antibiotic dispensing: urban vs. rural pharmacy, presence of other customers, referral to another provider, questions asked by the pharmacy staff, and length of the SP-pharmacy interaction.

Results. A total of 1522 SP interactions were successfully completed. The proportion of SP interactions resulting in the provision of an antibiotic was 4.31% [95% CI: 3.04%, 6.08%] for adult SPs and 2.88% [95% CI: 1.86%, 4.4%] for child SPs. In the model, three covariates showed a significant association with the outcome of antibiotic dispensing. Referral to another provider was associated with an odds ratio of 0.38 [95% CI: 0.18 – 0.79], number of questions asked was associated with an odds ratio of 1.54 [95% CI: 1.30 – 1.84], and a SP-pharmacist interaction lasting longer than three minutes was associated with an odds ratio of 3.03 [95% CI: 1.11 – 8.27] as compared to an interaction lasting less than one minute. The difference between the proportion of antibiotic dispensing for the adult and paediatric cases was non-significant ($p = 0.1$), but in a model examining antibiotic dispensing for paediatric diarrhoea, dispensing for adult SPs was associated with an increase in the odds of the child SPs receiving an antibiotic.

Conclusion. Over-the-counter antibiotic dispensing rate was low in Udupi district and substantially lower than previously published SP studies in other regions of India. Dispensing was lowest when pharmacies referred to a doctor, and higher when pharmacies asked more questions or spent more time with clients.

Résumé

Introduction. La résistance aux antibiotiques est une menace pour la santé des êtres humains. L'une des causes principales est l'abus d'antibiotique, à savoir la surutilisation ou la mauvaise utilisation des antibiotiques. L'Inde en est l'un des plus grands consommateurs, et leur usage inapproprié y est répandu, particulièrement dans le secteur privé. Cette étude vise à utiliser des patients simulés (PS) pour mesurer la distribution d'antibiotiques sans prescription dans une région.

Méthode. Trois adultes de la communauté locale de Udupi en Inde ont été embauchés et entrainés comme patients simulés. Trois maladies ont été utilisées : diarrhée, infection des voies respiratoires supérieures, et une fièvre aiguë qui suggère le paludisme. Il y avait un cas simulé adulte et un cas simulé pédiatrique pour chacune d'entre elles, donnant un total de six cas simulés. Chaque adulte entrainé comme PS a visité 279 des 350 pharmacies de Udupi entre juillet et octobre 2018. Le PS commençait par demander de l'aide pour un enfant chez lui avec une des maladies choisies. Ensuite, il demandait de l'aide pour ses propres symptômes d'une autre maladie. En utilisant une régression logistique ajustée avec des équations d'estimation généralisées, nous avons essayé d'identifier si les caractéristiques de la visite affectaient la distribution d'antibiotiques. Nous avons considéré comme caractéristiques de la visite : l'emplacement de la pharmacie (urbaine ou rurale), la présence d'autres clients au moment de la visite, la référence médicale, le nombre de questions posées au PS par la pharmacie, et la durée de la visite.

Résultat. Un total de 1522 interactions PS-pharmacie ont été complétées avec succès. La proportion d'interactions qui ont mené à la distribution d'un antibiotique était de 4.31% [95% IC: 3.04%, 6.08%] pour les PS adultes et de 2.88% [95% IC: 1.86%, 4.4%] pour les PS enfants.

Dans ce modèle, trois covariables ont montré une association significative avec la variable de distribution d'antibiotiques. Pour la variable "référence médicale", le rapport des cotes était de 0.38 [95% IC: 0.18 – 0.79] et pour la variable "nombre de questions posées", il était de 1.54 [95% IC: 1.30 – 1.84]. Comparativement à une interaction durant moins d'une minute, une interaction qui durait plus de trois minutes avait 3.03 [95% CI: 1.11 – 8.27] fois plus de chances de se conclure par la distribution d'un antibiotique. Il n'y avait pas une différence statistiquement significative entre les proportions d'adultes et d'enfants qui ont reçu un antibiotique ($p = 0.1$). Cependant, dans un modèle pour la diarrhée pédiatrique, si le PS adulte recevait un antibiotique, le PS enfant avait plus de chances de recevoir un antibiotique.

Conclusion. La distribution d'antibiotiques sans prescription était faible à Udupi, particulièrement si nous comparons les résultats aux autres études de patients simulés qui ont pu être effectuées dans d'autres régions en Inde. La distribution était la plus faible lorsque les pharmacies dirigeaient les patients vers un médecin et plus élevée lorsque les pharmacies posaient plus de questions ou passaient plus de temps avec les patients.

Front matter

Preface

In India, pharmacies in the private sector have been known to provide antibiotics to patients without a prescription, though Indian laws require a valid prescription for all antibiotics. This is a major concern considering the high rates antibiotic use in India and the high burden of antimicrobial resistance as well. To study this behaviour in one region of India, we designed and carried out a standardised patient study in collaboration with our collaborators at the Manipal Academy of Higher Education in India. In chapter four of this thesis I present the results of this study in the form of a manuscript:

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The appendix to the manuscript is included at the end of the chapter, and provides more detailed information on our methodology, including the training of standardised patients and the statistical methods used.

Ahead of manuscript submission, the results have previously been presented:

Infectious Diseases and Immunity in Global Health (IDIGH) Research Day, April 2019. McGill University, Montreal, Canada. Oral presentation.

McGill Global Health Night, November 2018. McGill University, Montreal, Canada. Poster presentation.

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Author contributions

The study in this thesis (Chapter 4) was conceptualised by MP, KS, and VN. The protocol was written by VN with input from MP, KS, SS, and AD. Research assistants and SPs were recruited by KS, and training was carried out with staff from ISERDD India. VN supervised SP visits and data collection along with local field staff. All data cleaning and analysis was performed by VN with support from SH. The manuscript was written by VN with comments from all co-authors, SH, GS, AD, SS, KS, MP.

All other sections of this thesis were written by VN and edited by MP.

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List of key abbreviations

AMR	Antimicrobial resistance
BRICS	Brazil, Russia, India, China, South Africa
CI	Confidence interval
FDC	Fixed-dose combinations
GEE	Generalised estimating equations
GLMM	Generalised linear mixed model
HAI	Healthcare-associated infection
LMIC	Low- and middle- income country
MDR	Multi-drug resistant
OR	Odds ratio
OTC	Over-the-counter
SP	Standardised patient
WHO	World Health Organisation
URI	Upper respiratory tract infection
XDR	Extensively-drug resistant

List of tables and figures

Chapter 1. Introduction

Antimicrobial resistance (AMR) is a global health emergency, and the emergence of resistance in bacteria is linked to the use of antibiotics.[1] Antibiotic consumption has increased globally over the past two decades, and this has been led by low and middle income countries (LMICs); in particular, the rate of consumption has increased the most in India, with India now having the greatest total consumption of any country .[2] India also has a very high prevalence of antibiotic-resistant bacteria, and untreatable 'superbug' strains are emerging as well.[3] However, it is difficult to limit antibiotic use overall in India when many Indians lack access to antibiotics and there are still a substantial number of deaths due to infectious diseases.[4] It is thus important to promote the appropriate use of antibiotics and curb inappropriate practices such as over-the-counter (OTC) dispensing of these drugs without a prescription. Indeed, retail pharmacies in the private sector have been shown to be a source of non-prescription antibiotics, often in inappropriate doses and for clients who do not need antibiotics.[5] Many Indians, especially in rural areas, rely heavily on these community pharmacies for care.[6] The scope of this practice and the factors that affect OTC provision of antibiotics are not yet fully understood, particularly because pharmacies are poorly regulated, and there are generally no records of patient-pharmacy interactions.

Chapter 2. Literature review

2.1. Overview of antimicrobial resistance

Antimicrobial resistance, the emergence of micro-organisms – bacteria, parasites, viruses, and fungi – that are resistant to the antimicrobial drugs used against them, presents a grave risk to human health.[7] Though the exact burden of AMR is difficult to quantify,[8] data from research studies and surveillance programs shows that the number of resistant infections is increasing globally, and this has implications for a growing mortality burden, as well as increased costs to healthcare systems and national economies.[9] Moreover, organisms are increasingly resistant to more than one antibiotic; multi-drug resistance (MDR), generally defined as resistance to at least one drug in each of three classes of antibiotics, and extensive drug resistance (XDR), defined as resistance to all classes of antibiotics except one or two categories, has been observed in different bacterial species.[10]

In 2016, the Review on Antimicrobial Resistance, supported by the U.K. government and Wellcome Trust, was released, providing a comprehensive review of the problem of AMR and possible solutions.[11] At the time of its writing, it was estimated that AMR caused at minimum 700,000 deaths globally every year, and this number could rise to 10 million by 2050 if action was not taken.

AMR is a concern in regard to healthcare-associated infections (HAIs), which often occur among surgical patients and immunosuppressed individuals. Among HAIs, the majority are caused by the ESKAPE pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species.[12] Drug resistance among these species, such as methicillin-resistant *Streptococcus aureus* (MRSA), has been well-documented for over a decade now.[13] Increasingly multidrug-resistant species have been emerging, and the prevalence of these infections appears to be increasing, while treatment options remain limited due to the slow rate of antimicrobial discovery in recent years.[14,15]

The majority of the data on HAIs has come from Europe and the US, but these infections are also relevant for developing countries, particularly among hospitalised neonates.[16] A 2017 systematic review on the burden of AMR in developing countries concluded that of all drug-resistant pathogens, the ESKAPE pathogens were associated with the highest risk of mortality.[17] However, in many developing countries, community-acquired infections are also a leading cause of mortality and morbidity.[18] As such, other drug-resistant pathogens are of particular concern in these settings. Among bacterial infections, drug resistance and multidrug-resistance has now been observed among pathogens such as *Salmonella typhi* and *paratyphi*, *Vibrio cholerae*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*, the main causative agents of typhoid fever, cholera, pneumonia, and tuberculosis respectively.[19] Drug resistance has also been long established among parasites such as *Plasmodium falciparum*[20] and viruses such as the human immunodeficiency virus (HIV).[21]

Overall, resistance to antibiotics has been documented to virtually every antibiotic known, and resistant strains emerge soon after the introduction of new antibiotics.[22] Several factors contribute to the development of antibiotic resistance, some of which are highlighted in Figure 1. Broadly speaking, antibiotic resistance has been driven by the overuse and misuse of antibiotics, their extensive use in the agricultural industry, and the lack of new antibiotics which arises from a sluggish research and development (R&D) pipeline and the difficulty in obtaining regulatory approval for new antibiotics.[22]

In the Global Action Plan on Antimicrobial Resistance, the World Health Organization (WHO) stresses that antimicrobial use must be optimised and sustainable investment in R&D must be encouraged to combat AMR.[23] The Review on AMR outlines several areas that countries must focus on: public awareness, improving sanitation and reducing pollution, global surveillance, introducing and improving diagnostics and vaccines, and encouraging market investment.[11] Ultimately, antibiotics must be used responsibly and sustainably in order to limit the emergence of resistance, and this can be promoted by reducing demand, ensuring that these drugs are used only when necessary, and ensuring that antibiotics effective against resistant strains are available.

Figure 1. Causes of antibiotic resistance, from the World Health Organization.

2.2 The association between resistance and antibiotic use

Antibiotic resistance arises in bacteria through multiple molecular mechanisms, including mutations that affect bacterial structure, modifications to the bacterial target structure, or even modification of the antibiotic.[24] From an epidemiological perspective, both overall antibiotic use and antibiotic misuse – generally referring to use when antibiotics are not indicated or the use of an inappropriate antibiotic or inappropriate dose – are linked to resistance.

At the individual level, the mutant selection window hypothesis posits that if the concentration of an antibiotic is inadequate, naturally occurring mutants may be able to proliferate, or resistance may develop among other bacteria present in the physiological mileu.[25,26] The modern antibiotic course, and the long-standing instruction to always complete it, is thought to be based off this theory, with the idea that antibiotic courses should be long enough to prevent selection of mutant bacteria. However, it has been argued that there is little evidence to justify the current length of antibiotic courses.[27] A 2010 systematic review concluded that exposure to an antibiotic was associated with development of resistance in the individual exposed, but there was not enough data to comprehensively examine the effect of dose or adherence.[28] However, antibiotic pressure also occurs in a population, and the effects can be different at the group level compared to the individual level.[29]

There appears to be an association between overall antibiotic consumption and rates of resistance. Using data from 1994 to 2000 for 20 countries in Europe and North America, Albrich and colleagues reported in 2004 that countries that had greater overall antibiotic use also reported a higher proportion of penicillin-resistant *S pneumoniae*.[30] Since then, many more studies have been published reporting this association. A systematic review published in 2014 including both individual and ecologic studies concluded that there was enough evidence to support a positive association between antibiotic consumption and the emergence of resistance, at both the individual and community level.[1]

2.3 Global antibiotic use: quantity and quality

Globally, antibiotic use is expressed in defined daily doses (DDDs) per a population unit.[31] Global antibiotic consumption has been estimated by the IQVIA MIDAS® platform, which develops estimates of total consumption per drug by using national surveys of antibiotic sales.[32] National-level data on antibiotic consumption is available in many high-income countries (HICs), from large representative surveys, private prescribing databases such as the IQVIA Xponent® database in the United States,[33] and well as surveillance programs such as the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).[34]

Surveillance of antibiotic use in resource-constrained settings where national surveillance programs may not exist remains a challenge. In health facilities, patient exit interviews may be used to capture prescriptions and track use over time.[35] While antibiotic sales in North America and most of Europe are largely limited to patients with a valid prescription, antibiotics can be accessed without a prescription in most other countries, and this use will not be captured with prescription audits.[36] As such, many community surveys have been published, and a 2011 systematic review of these studies found that 58% of reported antibiotic use in Asia was non-prescription.[36] However, the included studies were highly variable, and the source of antimicrobials was poorly reported in the studies. A further issue with patient surveys is that this study method often does not allow for quantifying the appropriateness of antibiotic use; this is also an issue with prescription audits, as prescriptions generally do not include diagnoses.

Current estimates of global antibiotic use show that antibiotic consumption across the globe has been increasing across the last two decades, with the global rate, measured in the DDDs per 1000 inhabitants, increasing 39% between 2000 and 2015.[2] This was driven by LMICs, where the rate increased by 77%, while there was a 4% decrease among HICs. Among LMICs, the BRICS countries (Brazil, Russia, India, China, South Africa) appear to have had the greatest increase, as they account for 76% of the increase in global consumption from 2000 to 2010.[37] In particular, use of broad-spectrum penicillins, cephalosporins, and quinolones has increased in LMICs, while remaining relatively stable or even declining in HICs.[2] These global estimates were derived from the IQVIA MIDAS® database, which contained data for approximately 80 countries; the study authors used World Bank indicators to extrapolate use for other countries, and as a result direct comparisons between all LMICs is not feasible.[2]

In addition to quantifying antibiotic consumption, it is necessary to evaluate the appropriateness of the use of these drugs. Several measures have been proposed to measure quality of antibiotic use. The ESAC group has proposed disease-specific indicators,[38] and systematic reviews of other proposed quality indicators for both the outpatient[39] and hospitalised[40] population have been published.

Several studies have been published evaluating the quality of antibiotic use, though these are largely limited to HICs as the use of most quality indicators requires data on both prescription and diagnosis. In 2011 it was estimated that only 70% of antibiotic prescriptions in the US outpatient setting were necessary.[41] More recently, a large database study of prescribing in the English primary care setting resulted in estimates that approximately 9 – 23% of antibiotic prescriptions were inappropriate.[42] The quality of antibiotic prescribing has been shown to vary greatly according to the condition in question as well as the country.[43,44] Due to variations in methodology it is difficult to draw comparisons across studies, but collectively these studies suggest that inappropriate prescribing is prevalent in the outpatient setting in Europe and North America. In Western and Northern Europe, non-prescription antimicrobial use appears to be low, accounting for less than 5% of use; non-prescription use appears to be more prevalent in Eastern and Southern Europe, with estimates that it accounts for 20-30% of antimicrobial use.[36]

2.4 Antimicrobial resistance in India

In 2011, the Indian government released the National Policy for Containment of Antimicrobial resistance,[45] which included a strategy for AMR surveillance at the national level. The Indian Council of Medical Research has published surveillance data; for the 2017 year, 45,930 isolates were tested from hospitalised patients and outpatients.[46] The data from this report, and a large study that analysed 135,268 blood cultures from Indian laboratories,[47] demonstrate that the prevalence of drug-resistant infections is high in India. Overall, resistance among the Gram-negative ESKAPE pathogens – *K pneumoniae*, *A baumannii*, *P aeruginosa* – was above 50% for the first-line antibiotics fluoroquinolones and third-generation cephalosporins, as well as the carbapenem class of antibiotics, which is widely considered a last-resort option. In addition, both studies reported the proportion of MRSA to be above 40%. Similar rates of resistance were reported among causative agents of cholera (*V cholerae*), shigellosis (*Shigella* sp), pneumonia (*S pneumoniae*), and tuberculosis (*M tuberculosis*).[48] Further, the prevalence of MDR and XDR organisms appears to be increasing. MDR and XDR strains of the ESKAPE pathogens have been documented, and it has been shown that these strains are associated with a greater risk of mortality.[3]

The apparent high prevalence of AMR in India is particularly concerning considering the burden of infectious disease in the country. Diarrhoeal disease and lower respiratory tract infections are among the top five causes of morbidity and mortality in India (measured in disability-adjusted life years, DALYs).[49] Neonatal mortality is still high, and one of the causes is neonatal sepsis.[50] A prospective study of 13 530 neonates born between 2011 and 2014 in tertiary care centres in

Delhi found that the incidence of sepsis was 14.3% in total and 6.2% for culture-confirmed cases, and the ESKAPE pathogens were the main causative agents; this study also reported high rates of multidrug resistance among these organisms.[51] Approximately 56,524 neonatal deaths in India are directly attributable to antibiotic resistance each year.[4]

India also has a high burden of other community-acquired drug resistant infections. In particular, India has the highest TB burden of any country, with an estimated 2.7 million new cases in 2017, and accounts for 24% of all MDR-TB cases; cases of XDR-TB have also been documented.[52]

Recognising the burden of AMR in the country, the Indian government developed a National Action Plan on AMR (NAP-AMR) in collaboration with the WHO in 2017.[53] In addition to the priority areas in the WHO Global Action Plan,[23] the NAP-AMR stresses the importance of strengthening India's leadership role in the field.

2.5 Antibiotic use in India

India is now the largest consumer of antibiotics among all LMICs, and the antibiotic consumption rate increased by 63% between 2000 and 2015.[2] Figure 2 illustrates the trends in antibiotic use over this time period. In 2013 anti-infectives constituted 16.8% of the Indian pharmaceutical market.[54] The high overall consumption in India is likely attributable at least in part to the large population and infectious disease burden. Though India has the greatest total consumption of antibiotics, consumption per capita is on par with many LMICs according to data from the IQVIA database; in 2015, LMICs had an average rate of 13.5 DDDs per 1,000 inhabitants, as compared to 13.6 DDDs per 1,000 in India.[2]

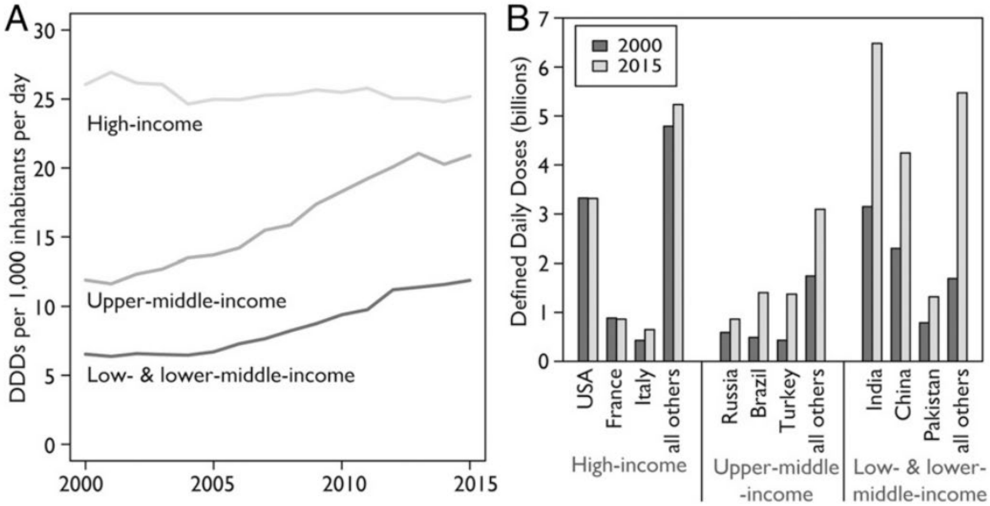

Figure 2. Trends in global antibiotic consumption between 2000 and 2015, illustrating in particular the increase in consumption in LMICs and India. (A) demonstrates the antibiotic consumption rate for countries grouped by income, and (B) demonstrates the total consumption for selected countries, including India. Figure reproduced from Klein et al. PNAS 2018.[2]

The use of certain antibiotics is a potential contributor to the increasing prevalence of drug resistant bacterial strains in India. In particular, the use of fixed-dose combinations (FDCs) and broad-spectrum antibiotics is highly prevalent. FDCs, which are products that contain two or more medicinal ingredients in a fixed ratio, are widely used in India,[55] and as of 2016, 118 antibiotic FDCs were available.[56] The efficacy of many FDCs is unclear, and they may pose a potential risk for increased antibiotic resistance.[57,58] Broad-spectrum antibiotics are those that are effective against a wide variety of bacteria, in contrast to narrow-spectrum antibiotics. Examples are cephalosporins and broad-spectrum penicillins, and the consumption of both of these have increased in India over the past two decades.[2] This is concerning as the unnecessary use of broad-spectrum antibiotics has been linked to the emergence of MDR bacterial strains.[59] Another broad-spectrum antibiotic that is being used more in India is faropenem. The consumption of faropenem has increased 154% since 2010, and this has the potential to result in cross-resistance to carbapenems, a class of antibiotics often used when certain bacterial species are resistant to other antibiotics.[60]

The increase in antibiotic consumption may reflect better treatment of bacterial disease. From 1990 to 2016 the deaths and DALYs due to communicable illnesses such as diarrhoeal disease and respiratory infection decreased.[49] However, the majority of diarrhoeal cases are self-limiting and require only oral rehydration salts (ORS) and zinc in children.[61] In 2003, about 88% of childhood deaths due to diarrhoeal disease globally were due to unsafe water and poor sanitation practices.[62] Meanwhile, pneumonia in children should be treated with antibiotics,[63] but globally only 39% of children receive this treatment.[64] In the absence of detailed data on the settings and appropriateness of antibiotic use in India, it is not possible to determine whether the increase in antibiotic use reflects an increase in appropriate use specifically.

Inappropriate use of antibiotics is a major concern in India, particularly the widespread use of antibiotics for conditions where they are not indicated, such as the common cold or diarrhoea.[65] In India, lack of knowledge, training, and the influence of pharmaceutical representatives is associated with practitioners' inappropriate antibiotic use.[66] Self-medication by patients – using leftover antibiotics or antibiotics provided to a family member – has also been documented.[67-69] However, while antibiotics are overused in some settings, there are still many Indians who lack access to certain classes of antibiotics, particularly in the public sector.[70] For example, it has been estimated that nearly 170,000 deaths among Indian children could be averted if timely access to antibiotics was improved.[4]

2.6 Pharmacies and antibiotic use

In many LMICs, care is delivered through both the private and public sectors, and patients' first point of contact with the healthcare system may not be a physician. Informal providers, including traditional healers, un- or under-qualified providers, and informal drug sellers are widely utilised because they are more convenient and affordable.[71] Community, or retail, pharmacies are another common point of contact. Pharmacies are often greater in number than primary health clinics and are easily accessed without appointment; in some communities, patients rely almost exclusively on pharmacists for care, especially if they are unable to afford a medical consultation.[6]

For these reasons, pharmacies are well-placed in the community to engage patients, provide counselling, and to refer individuals to other providers when necessary.[72] However, in most LMICs pharmacies are poorly regulated, and exist primarily as commercial entities.[6] There is often a lack of legislation regarding the sale of certain pharmaceutical agents, and even when legislation exists, enforcement may be poor, resulting in the sale of unregulated or prescription-only medications, including antibiotics.[73] The provision of prescription-only medications is not the only concern; patient management at retail pharmacies has been shown to be poor overall, with inadequate history-taking and counselling, lack of referrals, and inappropriate dosing.[5]

In India, over 750,000 private retail pharmacies provide care.[74] The decision to visit a community pharmacy rather than a physician is motivated by both the accessibility and affordability of local pharmacies.[75] Many pharmacies are owned by non-pharmacists, and often pharmacists are not present in the store, leaving staff or even family members to interact with patients.[76] One survey in Madhya Pradesh state reported that only 12% of staff in pharmacies had a formal qualification in pharmacy.[77] With no dispensing fee, pharmacies primarily make profit from the drugs sold, providing a strong financial incentive for the provision of prescription-only medications.[76] Pharmacies in India are preferentially used by individuals who cannot access a physician, either due to a lack of doctors in the area or the costs associated with visiting a physician, costs which are usually paid out-of-pocket.[75]

The Drugs and Cosmetics Rules from the Indian Ministry of Health and Welfare[78] details which drugs cannot be sold without a prescription in these pharmacies. Under this act, all antibiotics are designated as prescription-only. Specifically, prescription-only medications fall under three 'schedules': H, H1, and X. Schedule H medications can only be dispensed with a valid prescription; this is the largest schedule and includes a variety of drugs, including antibiotics. Schedule H1, introduced in 2013 in part to curb OTC dispensing of antibiotics, includes newer antibiotics and anti-tuberculosis drugs. Pharmacies must maintain a register of all schedule H1 drugs dispensed, with the dose and patient details. Schedule X drugs, which include narcotics and sedatives, are prescription-only and pharmacies must keep the original prescription for two years. Thus, clear legislative guidelines exist, but enforcement remains a challenge. As in other LMICs,[5,6] antibiotics appear to be widely dispensed in Indian pharmacies, often irrationally, with pharmacies providing antibiotics for common conditions where they are not indicated.[79]

The Indian government's NAP-AMR acknowledges the rampant misuse of antibiotics in the country, and describes strategies aimed at limiting OTC use of antibiotics, and also calls for the standardisation of guidelines for antibiotic use and ongoing surveillance in primary care settings.[53] In addition, the strategy calls for improved regulation in this sector, with registration of all manufacturers. In 2016, the Indian health ministry also launched the Medicines with a Red Line campaign; the goal was to have a red line on the packaging of all prescription-only antibiotics, and to educate the public on what this line means and the importance of antimicrobial stewardship.[80]

2.7 The standardised patient approach

A standardised patient (SP) – also known as a simulated patient, simulated client, mystery shopper, or pseudo patient, among other names – is an individual trained to visit a healthcare provider and present a scripted medical scenario. Generally, the provider is not aware that the SP is not a real patient.

The first widespread use of SPs was by medical schools and licensing bodies in North America, as an assessment tool for prospective physicians; since then, the methodology has been used to evaluate actual medical practice, often in primary care settings.[81] If there is reason to believe that healthcare providers behave differently when observed, unannounced SPs are an ideal method to measure actual practice. Other advantages of the SP methodology are shown in Table 1.

Measure of Quality	**Measures Knowledge**	**Measures Practice**	**Accounts for Case-Mix**	**Accounts for Patient-Mix**	**Hawthorne Effects***	**Illnesses Covered**
Vignettes	Yes	No	Yes	Yes	Yes	All
Clinical observation	No	Yes	No	No	Yes	Limited. “Serious” illnesses like unstable angina will show up on a sporadic basis. Also, the observer never knows the patients’ true condition, and doctors frequently make incorrect diagnoses.
Chart abstraction (health records)	No	Yes	No	No	No	Similar to clinical observation, but providers rarely keep records. Charts may be incomplete and don’t accurately reflect patient-provider interactions.
Standardised patients	No	Yes	Yes	Yes	No	Limited to i) adults with non-critical illness only; ii) conditions that don’t have

						obvious findings on physical exam as these cannot be mimicked, and iii) conditions that don't require invasive exams. Initial costs are high.

Table 1. Comparison of methods to measure quality of care. *Hawthorne effects refers to the phenomenon where individuals alter their behaviour when they are aware of observation.

In addition to evaluating physician practice, SPs have been widely used to study pharmacy practice,[82] including the provision of non-prescription medicines in pharmacies in LMICs.[83] There are generally no records of the sale of prescription-only drugs in retail pharmacies, so prescription or document audits cannot capture this dispensing.[84]

In India, SPs have been used to assess quality of care for a variety of conditions. In a study of general provider practice in primary care, SPs with common conditions – angina, asthma, and dysentery – were used, and the results demonstrated that many providers were underqualified and treatment often did not adhere to national guidelines.[85] In addition, the SP method has been validated and used to study quality of care for tuberculosis in the private sector

Several SP studies have been conducted in Indian pharmacies, assessing a variety of medical conditions. Table 2 summarises these studies. OTC antibiotic dispensing for paediatric diarrhoea has been high in SP studies conducted to date, though antibiotics are not indicated for this condition. Diwan and colleagues conducted a study visiting 164 pharmacies in a city in Madhya Pradesh state, and found that 40% of pharmacies provided an antibiotic.[86] Across 146 pharmacies in Bangalore, Karnataka, Shet and colleagues reported that 57% provided antibiotics without being asked.[87] Miller and Goodman report a SP study of 333 pharmacies in Bangalore and here, over 30% of paediatric diarrhoea cases received antibiotics.[88] All three studies additionally reported poor history-taking and the sale of antimotility drugs.

Respiratory tract infection in an adult was assessed by Shet et al., and across 115 pharmacies, 54% provided an antibiotic; an additional 17% provided an antibiotic when the SP then requested stronger medication.[87] Satyanaryana and colleagues assessed pharmacy management of adult tuberculosis in the cities of Mumbai and Patna, and reported that 36% of pharmacies provided antibiotics to a patient with symptoms of tuberculosis, while 16% provided antibiotics to a patient with symptoms and a confirmed laboratory report of tuberculosis, though anti-tuberculosis drugs were not dispensed.[89] Suspected adult tuberculosis was also assessed by Miller and Goodman; approximately 16% of SPs received antibiotics.[88]

Study	Location	Conditions	Number of pharmacies	Pharmacies providing antibiotics
Diwan et al. 2015[86]	Ujjain	Paediatric diarrhoea	164	40%
Shet et al. 2015[87]	Bangalore	Adult URI	115	54%
		Paediatric diarrhoea	145	57%
Satyanaryana et al. 2016[89]	Mumbai and Patna	Adult suspected TB	548	36%
		Adult confirmed TB	548	16%
Miller and Goodman 2017[88]	Bangalore	Adult suspected TB	333	16%
		Paediatric diarrhoea	333	39%

Table 2. Summary of SP studies conducted in Indian pharmacies

Chapter 3. Research context

3.1 Study objectives

The primary objective of this work was to use the standardised patient methodology assess non-prescription antibiotic dispensing by retail pharmacists in the district of Udupi for common medical syndromes, in both adults and children: URI, diarrhoea, and fever.

We also aimed to assess overall case management of these conditions, and how this differed between adults and children, specifically:

- Proportion of cases managed correctly according to available guidelines
- Proportion of interactions resulting in the provision of other drugs: any medication overall, schedule H, H1, and X medications, and potentially harmful medications
- History-taking by the pharmacy, measured by number of questions asked by pharmacy staff during the interaction

A further objective was to determine whether certain factors of the SP-pharmacy interaction affected the likelihood of the SP receiving an antibiotic. Specifically, we considered:

- Client volume, measured by the approximate number of other clients present at the pharmacy at the time of the interaction
- Visit length, the approximate number of minutes the SP spent interacting with the pharmacy staff
- Referral, whether the SP was referred to another provider (physician or hospital, in the public or private sector)
- Urbanicity, whether the pharmacy was in an area designated as ‘urban’ or ‘rural’
- History-taking, measured by the number of questions asked by pharmacy staff

3.2. Choice of standardised patient scenarios

The choice of SP case scenarios was motivated by three major considerations: i) it is reasonable to expect that individuals are more likely to visit pharmacies for common, non-severe symptoms; ii) in order to draw comparisons between the management of adults and children, all conditions must plausibly occur in both populations; and iii) none of the conditions should warrant the use of antibiotics.

Data for the incidence of these conditions among Indian children is available from the Indian government's National Family Health Survey.[90] In the two weeks preceding the survey, 5.1% of children under age five had diarrhoea, and 5.3% had symptoms of an acute respiratory infection in Udupi, suggesting that these are not uncommon symptoms.

According to guidelines from WHO, antibiotics are not indicated for children with cough and cold, diarrhoea, or fever; all three can be treated with certain symptomatic medications that are available over-the-counter.[61,91,92] In the case of a cough or diarrhoea, referral is not necessary in the absence of other symptoms, such as symptoms of pneumonia[63] or blood and mucus in the stool, which could indicate a more serious infection such as dystentery.[61] WHO also recommends that any patient with unexplained fever be referred for malaria testing in malaria-endemic regions.[92,93] Thus, providing non-prescription antibiotics would be inappropriate for any of the SP case scenarios in our study.

With these conditions, we were also able to assess other dimensions of patient management at the pharmacy: provision of the appropriate symptomatic treatment where applicable (e.g., oral rehydration salts and zinc for diarrhoea), history-taking, and suspicion of malaria in the case of the fever scenario.

To assess history-taking, SPs were taught scripted responses to any questions that pharmacy staff may ask. For the URI and diarrhoea condition, the answers were designed to help staff rule out the possibility of severe illness such as pneumonia or dysentery. For example, if asked, an SP presenting the diarrhoea scenario would respond that there is no blood or mucus in the stool, and the patient is still eating and drinking normally. In this case, pharmacists should adhere to the international guidelines for acute uncomplicated diarrhoea, which clearly indicate that antibiotics should not be used. For the fever scenario, the answers were meant to rule out common fever-causing illnesses such as a respiratory tract infection; upon questioning, pharmacists would find that there is no apparent cause for the fever, indicating that a malaria test should be done.

3.3 Study setting

The study was carried out in Udupi district, a southern coastal district in the state of Karnataka; Figure 1 illustrates the location and organisation of the district. The district is further subdivided into three taluks, Kundapura, Udupi, and Karkal.

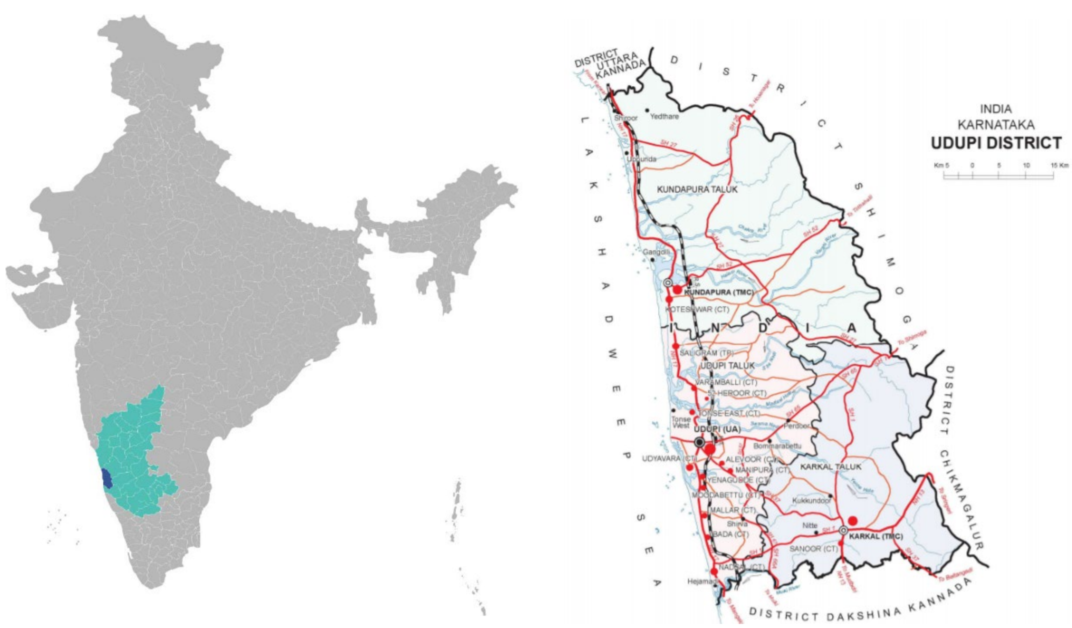

Figure 1. On the right, a map of India with Karnataka state highlighted in green and Udupi district in blue; on the right, the census map of Udupi district from the Indian Directorate of Census Operations.[94]

McGill University has an active research collaboration with the Manipal Academy of Higher Education (MAHE), located in the city of Manipal in Udupi, the Manipal-McGill Centre for Infectious Diseases (MAC ID). Udupi has an approximate population of 1.2 million, and the largest city is Udupi with a population of approximately 165,000.[94] It is a relatively well developed district, with good access to medical care strong health indicators relative to the rest of the state and the country, some of which are presented in Table 1. Data are from the Indian National Family Health Survey in 2015-2016.[90]

Indicator	**Udupi**	**Karnataka**	**India**
Population (female) aged 6 years and above who ever attended school (%)	80.1	70.7	68.8
Women who are literate (%)	86.0	71.7	68.4
Men who are literate (%)	88.1	85.1	85.7
Households with any usual member covered by a health scheme (%)	45.4	28.1	28.7
Households using an improved sanitation facility (%)	89.1	57.8	48.4
Institutional births (%)	97.9	94.0	78.9
Children age 12-23 months who are fully immunised (%)	64.6	62.6	62.0
Children under age 5 who are stunted (%)	21.1	36.2	38.4
Children under age 5 who are wasted (%)	20.9	26.1	21.0

Table 1. Key and health indicators from the National Family Health Survey 4, for Udupi district, Karnataka state, and India.

At the time of the study, 350 pharmacies were known to be registered and active in the district, including pharmacies associated with hospitals. Pharmacies within hospitals were not included in our study, as they are generally only accessed by patients of the health facility. We sampled 279 private retail pharmacies, and Figure 1 provides an example of the pharmacies in the district.

Figure 1. Pharmacies in Manipal, Udupi district. Radha Medicals (left) is a chain pharmacy with multiple locations in the region.

4. Manuscript: Over-the-counter antibiotic dispensing by pharmacies in South India: a standardised patient study

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4.1 Introduction

Antimicrobial resistance (AMR) is a global health emergency, and poor antimicrobial stewardship, which includes both overuse and misuse of these drugs, is a contributing factor.[1] Estimates suggest that 20-50% of global antibiotic use is inappropriate,[2] but it is difficult to measure this in resource-constrained settings where surveillance is a challenge.[3]

India is a leading consumer of antibiotics globally. Between 2000 and 2015, antibiotic consumption in India increased from 3.2 to 6.5 billion defined daily doses (103%) making India the highest-consuming low- and middle-income country (LMIC).[4] However, India also has a high infectious disease burden,[5] and a high burden of mortality due to drug-resistant pathogens.[6] India has a highly privatised medical system with a large informal sector where antibiotic use is common. Also, many patients access antibiotics over-the-counter (OTC) via over 750,000 retail pharmacies across the country.[7]

According to India's Drugs and Cosmetics Rules Act from the Ministry of health and Family Welfare,[8] all antibiotics are designated as Schedule H, which means that pharmacies cannot dispense these medications without a prescription from a qualified medical practitioner. In 2013, in an effort to regulate use of certain antibiotics such as newer cephalosporins and fluoroquinolones, carbapenems, and anti-tuberculosis drugs, the Indian government introduced a second schedule, H1. In addition to requiring a prescription, pharmacies must maintain a register of all Schedule H1 drugs dispensed, recording the name and quantity of the drug as well as patient details.[9] A further schedule of drugs, schedule X, requires pharmacists to also keep the original prescription on hand for two years; this schedule includes restricted drugs such as narcotics and sedatives.

Since these regulations are poorly enforced, it is not unusual for pharmacists to dispense antibiotics without a prescription, often inappropriately in terms of both indication and dosing.[10,11] This practice is particularly alarming in India, where a considerable number of people, especially the poor, first seek care at pharmacies.[12]

Over-the-counter dispensing of antibiotics is concerning both from a population perspective, as overall consumption in countries has been linked to a higher prevalence of antibiotic resistance,[13] and the individual perspective, as the use of antibiotics in the individual is also linked with the subsequent emergence of antibiotic-resistant bacteria in the body.[14] Thus, the practice providing antibiotics to individuals without a clear diagnosis may be unnecessarily promoting the development of resistance.

In the absence of a national surveillance strategy and audits of pharmacies, standardised (or simulated) patients (SPs) have been used to study pharmacy practices in India and other LMICs.[15,16] The SP methodology is considered the gold standard method to assess provider practice (as opposed to knowledge).[17,18] Specifically in India, this methodology has been successfully applied to provide insight on how pharmacists manage cases of presumptive or confirmed tuberculosis for adult patients[19,20] and paediatric diarrhoea.[20,21] These SP studies conducted in Indian pharmacies have consistently found that 15% to upwards of 40% of SP visits involved the provision of an unnecessary antibiotic without a prescription.

Accurately identifying conditions for which antibiotics are dispensed in Indian pharmacies, and the factors that affect this behaviour, can help inform antibiotic stewardship interventions. We report here the results of a cross-sectional SP study conducted in private pharmacies in Karnataka, India. This study builds on previous SP studies by our team[18,19] by extending the number of case scenarios to three common conditions: upper respiratory tract infection (URI), diarrhoea, and fever suggestive of malaria.

4.2 Methods

Objectives

This study was conducted in the district of Udupi, Karnataka, in South India. The primary objective was to assess overall non-prescription, OTC antibiotic dispensing by private, community retail pharmacies for adults and children for upper respiratory tract infection (URI), acute, uncomplicated diarrhoea, and a fever suggestive of malaria. Secondary objectives were to examine how this outcome differed between adults and children, and to determine which factors of the SP visit – history-taking by the pharmacy, client volume at the time of visit, whether the SP was referred to another provider, approximate time spent at the pharmacy, and pharmacy location (urban or rural) – were associated with antibiotic dispensing. We also assessed the provision of other medications designated as schedule H or schedule H1.

Standardised patients

Standardised patients (SPs) are people who are recruited locally, trained to make identically scripted clinical presentations, deployed incognito to visit health care providers, and debriefed using a structured reporting instrument. Table 1 summarises the three SP case scenarios. We chose conditions that fit the following criteria: 1) symptoms must be relatively common in both adults and children; 2) symptoms must be associated with both bacterial and non-bacterial illnesses. Treatment for each condition was benchmarked against available guidelines as described below, and antibiotics are not indicated in any case. Thus, any antibiotic dispensing in this study would be an example of irrational antibiotic use.

There is a lack of clear international guidelines on the management of URI, especially in pharmacies. URI is a common condition that is generally of viral aetiology, and for the symptoms of the common cold – runny nose, sore throat, cough, nasal congestion – only symptomatic treatment is recommended by the American Centers for Disease Control (CDC).[22] Symptomatic treatment includes the use antihistamines, decongestants, cough suppressants, and non-steroidal anti-inflammatory drugs (NSAIDs), so these drugs were considered 'acceptable' for adults in our study.[22] For children under age five with a cough and cold, the World Health Organization (WHO) primarily recommends oral rehydration therapy and paracetamol in the case of a fever, and discourages the use of combination drugs.[23] For this reason, combination cough syrups and antihistamines were considered 'unacceptable' for the paediatric case, though not 'harmful'. 'Harmful' drugs were antibiotics or other prescription-only medications that posed an unnecessary risk of side effects, such as bronchodilators.

Guidelines for the treatment of diarrhoea have been published by the WHO in the case of acute, uncomplicated diarrhoea, the recommended treatment is oral rehydration salts (ORS) and zinc supplementation in the case of children; the benefits of zinc in adults is yet unclear.[24] Anti-motility drugs such as loperamide may be effective in adults but are not recommended by the WHO for use in children as they appear to be less effective and are potentially associated with adverse effects in the paediatric population.[24] For this reason, we considered loperamide to be a harmful medication for children only. Prescription antiemetics and antacids such as H2 blockers or proton pump inhibitors were considered harmful for adult and paediatric SPs.

The WHO does not have published guidelines on fever specifically for pharmacies, and the initial symptoms of malaria are generally non-specific. However, in the guidelines for community health workers, children with fever in the last seven days living in a malaria endemic region should receive a malaria diagnostic test.[25] Further, the WHO guidelines on malaria recommend that in endemic areas, malaria should be suspected in any patient with a fever >37.5C.[27] Karnataka is a state with a relatively high burden of malaria,[26] with greatest incidence observed during the monsoon season when our study is carried out. We thus consider it reasonable to expect that pharmacists recognise the potential risk and refer the patient for malaria testing. Antibiotics (i.e. anti-malarials) or other prescription-only medications that posed an unnecessary risk of side effects were considered as ‘harmful’.

Three adults were recruited from the local community and trained as SPs. For the paediatric scenarios, adults were used as proxy SPs – no children were recruited. Each SP was responsible for presenting one adult scenario and one paediatric scenario. The SPs were instructed to visit the pharmacy and first request medication for a sick two-year-old child at home; upon the conclusion of this interaction, the SPs then requested medication for their own illness. Thus, both cases were presented in a single visit. In order to avoid priming the pharmacy staff for a particular condition, the SP never presented the same condition twice in a visit. For ease of implementation and to minimise variation in pharmacy behaviour according to the presenting SP’s individual characteristics, the following pairing of paediatric and adult case scenarios were used: paediatric diarrhoea and adult URI, paediatric fever and adult diarrhoea, and paediatric URI and adult fever. To reduce any variation in pharmacy staff’s behaviour due to patient demographic characteristics, all three recruited SPs were of similar age, presented as the same gender (male), and spoke Kannada, the local language. In order to avoid detection, all SPs were trained to be able to respond to basic questions regarding their symptoms or even their personal background. SPs were additionally trained to avoid any invasive interventions such as injections.

Selection of pharmacies and SP visits

The district of Udupi has a population of approximately 1.2 million people, and, according to a list provided by the local pharmacists' association, 350 private pharmacies were active in the area at the time of the study. Of these, 47 (13.43%) were associated with hospitals or clinics and were excluded as these pharmacies generally serve hospital or poly-clinic patients and are not reflective of the typical retail pharmacy that an individual might spontaneously approach for medical advice. A further 10 pharmacies (2.85%) were either permanently closed or undergoing renovations, and 4 pharmacies (1.14%) could not be identified by field staff at the listed address. One listed pharmacy was for veterinarian purposes only. SPs then visited 10 pharmacies for training purposes, leaving 279 pharmacies eligible to visit for the study. At the 95% confidence level and with a margin of error of 5%, 184 pharmacies would have been needed if 50% of pharmacies dispensed antibiotics. As the rate of dispensing was not known beforehand, 50% was used to obtain the largest possible sample size. This sample size also ensured that the study is powered to detect a subgroup difference (e.g., urban vs. rural) in antibiotic use rate of 10% with a power >80%.

Pharmacies were categorised as 'urban' or 'rural' according to governmental census guidelines, which are based on amenities and assets;[27] the sample included 155 rural pharmacies and 124 urban pharmacies. Between 23 July 18 and 6 October 2018, each SP was instructed to visit each pharmacy and present their respective adult and paediatric cases, resulting in a total of 780 potential visits and 1,560 potential interactions. No pharmacy received more than one SP visit in one day. Pharmacy visits were planned by field staff on a daily basis. If the pharmacy was temporarily closed or unavailable on the first attempt, the visit was scheduled for another day. If the pharmacy was closed again, that particular visit was considered incomplete. All of the pharmacies were successfully visited by at least one individual.

At each pharmacy, SPs were instructed to purchase any medications provided and place them in labeled envelopes. SPs filled out a structured questionnaire using the Epicollect 5 software on their mobile phones within half an hour of the interaction. The questionnaire allowed SPs to record: the approximate length of the interaction, the location of the pharmacy, the number of other clients present at the time of interaction (as a proxy for client volume), whether they were referred to another provider such as a hospital or medical practitioner, all questions asked by pharmacy staff, tests recommended, diagnoses mentioned, and total cost. The length of the interaction was measured by checking a watch or smartphone upon entry and exit, and was reported as an interval, e.g. approximately 3-5 minutes. In the case of the fever scenario, SPs reported whether a malaria test was recommended. Medications were then identified and classified as Schedule H or H1 by a trained research assistant. An infectious disease physician (GS) identified, coded, and classified all antibiotics and medicines.

Ethics

Approval for the study was obtained from the ethics committees of the Manipal Academy of Higher Education in Manipal, India, and McGill University in Montreal, Canada. Both committees approved a waiver of informed consent for the pharmacists. Our team has received such waivers of informed consent for SP studies conducted in India in the past,[18,19,28] and an ethical analysis on the use of SPs commissioned by the U.S. Department of Health and Human Services in 2012 concluded that such a waiver is justifiable if the study posed minimal risk to all participants and could generate socially valuable results.[29] The waiver was approved because informed consent posed a threat to the scientific validity of this study, as it would increase the risk of SP detection and providers may potentially alter their behaviour if they are aware of observation. The study posed minimal to no risk to pharmacies and their staff, as all information was kept strictly confidential and no personal information was collected at the pharmacy. There was also minimal risk to individuals recruited as SPs as they were trained to avoid detection and potentially invasive examinations.

Statistical analysis

The main outcome considered was the proportion of SP-pharmacy interactions resulting in the provision of an antibiotic. Secondary outcomes were the proportion of all interactions with acceptable case management (defined *a priori*) and the proportion of interactions resulting in the provision of any medication, a schedule H medication, a schedule H1 medication, or other medications of clinical relevance to that case. The proportions were compared for adults and children using McNemar's test for paired proportions. The adult and paediatric cases were considered paired for this because a single SP would present both in one interaction.

To evaluate factors associated with antibiotic dispensing, we fit a model using generalised estimating equations with a logit link to account for clustering by pharmacy. Adult and paediatric interactions were pooled for this analysis. The outcome was a binary variable (yes/no) indicating whether an antibiotic was dispensed in that particular SP-pharmacy interaction. Among the covariates evaluated, number of questions asked by pharmacy staff was the sole continuous variable. The dichotomous variables included were pharmacy location (urban vs. rural) and referral (SP referred to another provider vs. not referred). The categorical variables included were length of interaction (less than one minute, one to three minutes, or more than three minutes) and client volume at the time of interaction (no customers, one to three customers, or more than three customers). In order to account for variations in antibiotic dispensing according to SP scenarios, age of SP (adult vs. child) and case (URI, diarrhoea, and fever) were included as dummy variables in the model. All covariates were checked for collinearity prior to inclusion in the model and no issues were found.

To examine how antibiotic dispensing practices for adults and children were correlated, we fit a second logistic generalised estimating equation with antibiotic dispensing for the paediatric SP-pharmacy interactions as the binary outcome variable (yes/no). The covariate of interest was whether an antibiotic was dispensed for the corresponding adult interaction, i.e. the adult SP with the same condition at the same pharmacy, and this was binary (yes/no). Due to extremely low rates of antibiotic dispensing for some cases, only the paediatric diarrhoea case could be considered in this model. As such, dummy variables for case and age were not necessary. All the pharmacy variables included in the pooled model were included here as well, however length of interaction and number of customers were dichotomised. This was done because with fewer observations relative to the pooled model, there were very few observations in the “more than three minutes” and “more than three customers”, respectively.

Data were collected using Epicollect 5 and Excel (version 1901) and analysed using R (version 3.4.1).

4.3 Results

SPs visited a total of 279 pharmacies, with 155 urban pharmacies and 124 rural pharmacies. Of the 837 planned visits, 761 (91%) were successfully completed, resulting in a total of 1522 interactions including both adult and child cases. The average cost per visit was 38 Indian rupees (interquartile range 15 – 50 rupees) [$0.22 - $0.72 USD], with a maximum cost of 158 rupees

[$2.28 USD]. Of the 761 visits, there were no customers other than the SP present for 440 (58%). Visits were relatively short; 601 (79%) lasted less than one minute. Pharmacy staff asked an average of 1.18 questions per interaction and dispensed an average of 0.79 drugs per interaction. In total, 1218 medications were dispensed, of which 22 (1.8%) could not be identified as the tablet strip had been cut and the name could not be read. No loose, unlabelled pills were dispensed. To our knowledge, SPs were not detected in any visit, and no pharmacy staff attempted to perform any examinations on-site nor give any injections.

History taking

Recommended questions were pre-defined for each scenario and SPs reported on any questions asked by the pharmacy for each interaction. Adults were asked a mean of 1.04 (SD, standard deviation ± 0.87) and a median of 1.0 questions, and paediatric cases elicited a mean of 1.31 (SD ± 0.82) and a median of 1.0 questions.

Overall, history taking was highly variable according to case. Table 2 lists all recommended questions and how often they were asked, separated by SP case. Across all interactions, 86.5% [95% CI: 84.7%, 88.2%] of pharmacies asked at least one question. This percentage was 74.6% [95% CI: 71.3%, 77.6%] for adult scenarios, and 98.4% [97.2%, 99.1%] for paediatric scenarios. The case with the fewest questions asked was adult diarrhoea, with only 35.9% [95% CI: 30.1%, 42.1%] of pharmacies asking a question, and the case with the most questions was adult URI, with 100% [95% CI: 98.1%, 100%]. Across all paediatric scenarios, the most commonly asked question was the age of the child (97.9% of 764 interactions, [95% CI: 96.5%, 98.8%]), and only 22.4% [95% CI: 19.5%, 25.5%] of pharmacies asked some recommended question other than age. Overall, adult SPs were asked significantly more recommended questions than paediatric SPs.

Case management and medications dispensed

Table 3 shows the number and percentage of interactions for the primary and secondary outcomes and case management, overall and separated by SP case. The proportion of SP interactions resulting in the provision of any medication was 87.2% [95% CI: 84.5%, 89.4%] for adult SPs and 55.5% [95% CI: 51.9%, 59%] for child SPs. Antibiotics were provided in 33 adult interactions (4.31% of 761 interactions, [95% CI: 3.04%, 6.08%]) and 22 paediatric interactions (2.88% of 761 interactions, [95% CI: 1.86%, 4.4%]).

Case management, including medication dispensing, for adults vs. children is illustrated in Figure 1. Overall, case management was worst for the diarrhea condition, with not a single pharmacy managing this case correctly. This is because ORS were never offered to adults, and while ORS was provided in 13.4% [95% CI: 9.61%, 18.4%] of paediatric diarrhoea interactions, zinc was never dispensed. Fever was only managed correctly for 1.19% [0.31%, 3.73%] of adult SPs and 3.86% [1.97%, 7.2%] of child SPs as these were the only interactions where the SP was referred for a malaria test.

The majority (71.6% [95% CI: 69%, 73.6%]) of interactions resulted in the provision of some medication. All medications provided are listed in Figure 2, by active drug ingredient and separated by SP case scenario. Nearly half of SPs received schedule H medications. No schedule X medications were dispensed, and only five interactions resulted in the provision of a schedule H1 medication; all five were the antibiotic cefixime, a third-generation cephalosporin. The most common medications were paracetamol, loperamide for the diarrhoea, and cough and cold remedies including anti-histamines and bronchodilators for the URI and fever conditions.

Of the 1218 medications provided, 55 (4.5%) were products containing antibiotics. Of these, 25 were combinations of two antibiotics. Overall, diarrhoea was the condition resulting in the most antibiotic dispensing, accounting for 36.3% [95% CI: 21%, 54.9%] of antibiotics given to adults and 90.9% [95% CI: 69.4%, 98.4%] among children. As antibiotics were not indicated for any SP case by design, all antibiotic provision in this study was deemed inappropriate. Almost all antibiotics given for diarrhoea were fixed-dose quinolone and nitroimidazole combinations, such as ofloxacin and ornidazole, particularly for children. Among adults, dosing of antibiotics was variable. A total of 14 adults received the antibiotic amoxicillin, either for URI or fever, and they frequently received a few tablets from a strip that had been cut. Total individual doses ranged from one 250mg tablet to six 500mg tablets for a total dose of 3000mg.

Factors associated with antibiotic dispensing

The results of the pooled model are displayed in Table 4. The number of customers present at the time of the interaction and whether the pharmacy was urban or rural were both non-significant. Referral to another provider was associated with an odds ratio of 0.38 [95% CI: 0.18 – 0.79], indicating that pharmacy staff referring the SP to another provider was associated with lower odds of dispensing antibiotics. Increasing number of questions asked was associated with an odds ratio of 1.54 [95% CI: 1.30 – 1.84], indicating that as pharmacy staff asked more questions, the odds of dispensing an antibiotic increased. Finally, a SP-pharmacist interaction lasting longer than 3 minutes was associated with an odds ratio of 3.03 [95% CI: 1.11 – 8.27]; compared to an interaction lasting less than one minute, an interaction of this length was associated with increased odds of antibiotic dispensing. The odds ratio for interactions lasting one to three minutes, as compared to those lasting less than one minute, was non-significant.

Relationships between adult and paediatric outcomes

The difference between the proportion of adults (4.3%) and children (2.9%) SP interactions resulting in an antibiotic was non-significant ($p = 0.1$). However, adults received significantly more medications overall (87.4% of adult interactions vs. 55.7% of child interactions) and significantly more schedule H medications (76.7% of interactions vs. 18.3%), with $p < 0.001$ for both.

To further investigate how adult and paediatric outcomes were related, we fit a second model to see if the treatment of the adult predicted the treatment of the child. The results of the model are shown in Table 5. Dispensing of antibiotics for the corresponding adult SP interaction was associated with an odds ratio of 6.34 [1.69 – 23.82] for pediatric dispensing**.**

4.4 Discussion

To our knowledge, this is the first SP study to examine OTC antibiotic dispensing by pharmacies in the Indian private sector for multiple medical conditions, in both adults and children (by proxy). For both adults and children, antibiotics were provided without a prescription and in scenarios where they were not indicated, along with other schedule H medications such as anti-diarrhoeals and bronchodilators. Overall, antibiotics were dispensed in 4.31% of adult interactions and 2.88% of paediatric interactions, and diarrhoea was the condition resulting in the most antibiotic dispensing. Adults received significantly more medications overall, but the difference in the proportion of interactions resulting in the provision of an antibiotic was not statistically significant between adults and children. Our results also provide moderate evidence that adult and child outcomes are correlated. For the case of paediatric diarrhoea, whether the adult SP with diarrhoea also received an antibiotic was a significant predictor, suggesting that pharmacies that provided adults with antibiotics were more likely to do the same for children.

Given the results of previous SP studies[19-21,30] and qualitative data demonstrating that retail pharmacists are willing to provide antibiotics for common ailments such as diarrhoea, cough and cold, or mild fever,[31] it is not surprising that antibiotics were dispensed without prescription. The rate of antibiotic dispensing in our study, however, is considerably lower than that seen in other Indian studies, including those that presented a similar SP case; for example, two previous SP studies reported that over 30% of pharmacies provided antibiotics for paediatric diarrhoea.[20,21]

Regions within India are not only culturally different to some extent, but also vary in their degree of development, enforcement of regulations, and awareness about antimicrobial stewardship. It is thus plausible that pharmacy practice varies geographically. For example, a SP study conducted by Satyanaryana and colleagues in pharmacies in Patna and Mumbai, two major cities located in very different Indian states, found that approximately 15% of interactions in Mumbai resulted in the provision of an antibiotic, compared to approximately 39% in Patna.[19] Mumbai and Patna are very different demographically; Patna is the capital city of Bihar, the least developed state in India according to the human development index,[32] and has a literacy rate of 70.68%, compared to 89.73% in Mumbai.[33]

The district of Udupi, where our study was conducted, is well-developed. The literacy rate is 86.24%, 10% above the state average.[33] In 2013-2014, Udupi had the third greatest per capita income of any district in the state, had a comparatively high proportion of habitations with suitable drinking water, and less than 1% of the population lived in slums.[34] The district also performs well on many health indicators: for example, the percentage of deliveries that are institutional births is 19% above the national average and the prevalence of stunting in children under age five is 17% lower than the national average.[35] This may reflect better healthcare coverage and better access to doctors, in which case patients may rely less on pharmacists for medical care; as a result, pharmacists may not be as motivated to step into the role of a de facto medical care provider. As a result, Udupi is not reflective of the rest of the state or country. However, these are only anecdotal observations. As studies to date have only included one or two cities, further study would be required to determine if, and to what extent, demographic and geographic characteristics, such as development index, population density, enforcement of regulatory standards, or cultural factors such as religion, affect OTC antibiotic dispensing.

We present a direct comparison of our results and those from the Bengaluru study published by Miller and colleagues[20] as both studies used a proxy child SP and the case of a two-year-old with a one-day history of uncomplicated diarrhoea. Miller and colleagues reported a much higher rate of antibiotic dispensing, with over 30% of SPs receiving an antibiotic, compared to 8% for our paediatric diarrhoea case. History-taking was slightly better in our study but still poor overall, with 19% of pharmacies asking about duration of illness or the presence of other symptoms, compared to less than 10% in Bengaluru; and pharmacies also provided fewer schedule H medications, with a proportion of 20.6% here compared to 37% in chain pharmacies and 49% in independent pharmacies in Bengaluru.[20] There were not enough chain pharmacies in Udupi to compare chain and urban pharmacies in our study. However, no pharmacies correctly managed this case in either study, as zinc and ORS were never provided together. This may suggest that the factors that drive OTC antibiotic dispensing are partly different from those that affect other behaviours such as history-taking.

In the case of diarrhoea, both history-taking and case management were overall poor. However, improved history-taking does not necessarily result in better case management, as 100% of adults were asked at least one question for the fever condition but only 1% were referred for a malaria test. Further, bronchodilators and anti-allergy medications were frequently provided for this condition, although the SP case presentation did not involve any symptoms of respiratory illness. The poor case management for fever is concerning, as a study in the city of Mangaluru, a district adjacent to our study site, found that upwards of 30% of surveyed patients with a malaria diagnosis first visited a pharmacist.[36]

In contrast to diarrhoea and fever, the rate of correct case management for URI was very high – over 80% – for both adults and children, although only 28% of children were asked a recommended question. This level of questioning would not be enough to differentiate a common cold from a potentially serious respiratory condition such as pneumonia. Additionally, schedule H medications were still widely dispensed, especially for adults. The provision of unnecessary medications is concerning not only from a medical standpoint; it also reflects unnecessary financial costs to the individual patient. This is particularly unfortunate given that Indians in rural areas and with low income commonly rely on pharmacists, partly in an effort to save costs associated with visiting private providers.[37]

Despite the frequent provision of schedule H medications, it is good that very few schedule H1, and no schedule X, medications were dispensed. Similarly, the relatively low rate of antibiotic provision is encouraging, but the variation in dose is a potential cause for concern. Inadequate dosing has been documented in pharmacies across Asia for a variety of medications, and this is potentially more common when the medication is provided without a prescription.[10] Incomplete courses of antibiotics have long been considered a risk factor for the emergence of resistance, and the rhetoric surrounding this issue has often focused on patients choosing to stop treatment early.[38] While there has been recent evidence that modern antibiotic courses are unnecessarily long,[39] SPs in this study received extremely low doses of amoxicillin unlikely to have any therapeutic benefit. There is some evidence to suggest that patients in India and other LMICs request low-dose antibiotics, and this has been justified by the fact that patients only pay a few rupees for some tablets and then feel better after.[40] SPs in our study did not request low doses, but meeting perceived patient demand is a major factor in providers' behaviour in LMICs.[41] Additionally, private pharmacies, which are primarily driven by financial incentives, may provide lower doses of drug because this is more affordable and might prompt patients to return.[42]

Pharmacist knowledge is also a factor in pharmacists' behaviour and antibiotic dispensing.[10,41] Knowledge was not specifically evaluated in our study, but referral, a potential indicator of better pharmacist practice, was associated with lower provision of OTC antibiotics. However, history-taking had the opposite effect: as pharmacists asked more questions, the odds of dispensing antibiotics increased. This is unexpected as the scripted responses to potential questions were designed to rule out the possibility of more severe illness for the SPs, thus discouraging the provision of antibiotics. A potential explanation for this could be a situation of reverse causality: it is possible that pharmacy staff first decided to dispense antibiotics, and then asked more questions to determine the type of antibiotic to give or the dosing.

We also included the length of the SP-pharmacy interaction in our model. We found that particularly long interactions were associated with greater odds of antibiotic dispensing. This is also unexpected; similar to history-taking, it is plausible that pharmacy staff who spend more time with an SP would be more likely to identify that the SP's symptoms are not severe and do not warrant the use of antibiotics. However, the number of questions asked was not highly correlated with length of interaction, indicating that long interactions were not necessarily because of increased history-taking by the pharmacy. The direction of these effects may indicate that the decision to dispense antibiotics is not necessarily motivated by a perception of the drug's necessity. As discussed above, patient demand – real or perceived – and financial incentives drive pharmacies to provide antibiotics even when they do not suspect bacterial illness.[41,43]

We expected to find difference in antibiotic prescribing behaviour between urban and rural areas,[43] but this variable was non-significant in the logistic regression model. Studies examining the prescribing behaviour of physicians have suggested that feeling rushed or having already seen many patients contributes to over-prescribing.[44,45] For this reason, we also evaluated the effect of client volume, using the number of customers present at the time of the interaction as a proxy for this variable, but this variable was also non-significant.

Some key strengths of our study are worth mentioning. Using SPs is an ideal method for studying OTC antibiotic dispensing, as it measures actual pharmacy practice rather than what they know (i.e. knowledge) or say they would do (i.e. self-reported practices). Our study had a limited risk of poor recall, as very few questions were asked, and SPs filled out a questionnaire within half an hour of completing their interaction with the pharmacy. Standardising cases across individuals ensures that specific patient characteristics are unlikely to influence provider behaviour. We build on the results generated from previous SP studies by extending the number of medical conditions assessed and by providing a direct comparison between adults and children. We additionally report how various factors of the SP visit affect antibiotic dispensing to better understand sources of variation. Lastly, our study covered 80% of all pharmacies in the district.

However, this study has some limitations. It was conducted at a single site, meaning that the results are not generalisable to the rest of the country or even the state. Second, only male SPs were used in this study, and there is some evidence to suggest that patient gender affects providers' prescribing behaviour, though these results are inconsistent and come from studies of physicians.[43] However, our choice was motivated by practical safety considerations, as some pharmacies were located in isolated areas and all SPs were always unaccompanied during their visits. Third, our study was based on a single SP visit from an individual that has not visited the pharmacy before, and we cannot evaluate how an existing relationship or familiarity with a patient affects pharmacies' behaviour. We also cannot be sure that the staff member the SP interacted with was the licensed pharmacist; a review of community pharmacy practice in India found that medications were often by non-qualified employees such as assistants or even relatives of the pharmacist.[46] We cannot attribute pharmacy practices to individual characteristics of the dispensing pharmacist. We also note that a single adult SP presented both an adult and a paediatric case in the same interaction; this has been done before,[20] and we do not believe that this would have a significant effect, particularly as all cases involved very common symptoms and SPs did not present the same condition twice in one visit. However, we cannot rule out the possibility that the results would be slightly different if the cases were presented separately or with the adult case presented first.

Ultimately, pharmacies are well-placed in the community to provide support to patients due to their accessibility. Still, in many LMICs their primary role is that of a retail outlet,[47] despite some evidence that suggests that even their non-dispensing practices such as patient counselling may improve patient health outcomes.[48] As pharmacies are often the first point of contact with the healthcare system, they are also well-placed to manage common syndromes such as the common cold or diarrhoea with the provision of appropriate symptomatic treatment or advice. The results of our study are an example of this missed opportunity. For example, ORS and zinc have been shown to reduce the severity and duration of diarrhoea in children,[49] which remains a leading cause of mortality in India,[5] but were never provided together here. The provision of non-prescription antibiotics not only promotes the development of antibiotic resistance unnecessarily but exposes patients to risks and costs, as patients receive an unneeded antibiotic while potentially not receiving beneficial symptomatic treatment. Interventions to reduce antibiotic use in pharmacies can also promote better adherence to clinical guidelines to improve overall patient management.

4.5 Conclusion

Our study showed that non-prescription antibiotic dispensing by pharmacies in Udupi district was low, although prescription-only schedule H medications were frequently provided. However, even when antibiotics were not dispensed, overall case management was poor, with a lack of adequate history-taking and referrals, and the dispensing of other unnecessary medications. Both dispensing and case management varies according to symptoms and the age of the patient. Additional research is required to better understand the low rates of antibiotic dispensing by pharmacies in this area and use the knowledge to inform antibiotic stewardship interventions in other areas of the country.

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Competing interests

None of the authors have any conflicts of interest.

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4.6 References to manuscript

1. World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva: WHO, 2015.

2. World Health Organization. The World Medicines Situation: 2011. Geneva: WHO; 2011.

3. World Health Organization. Community-based surveillance of antimicrobial use and resistance in resource-constrained settings. Report on five pilot projects. Geneva, Switzerland: WHO; 2009.

4. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463.

5. India State-Level Disease Burden Initiative C. Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. *Lancet (London, England)* 2017; **390**(10111): 2437-60.

6. Gandra S, Tseng KK, Laxminarayan R, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. 2018.

7. All India Organisation of Chemists & Druggists. All India Organisation of Chemists & Druggists history. 2018. http://www.aiocd.net/ (accessed September 15 2018).

8. Ministry of Health and Family Welfare Government of India. The Drugs and Cosmetics Rules, 1945. 2013. https://mohfw.gov.in/sites/default/files/638332522.pdf (accessed January 4 2019).

9. Government of India Ministry of Health and Family Welfare. Notification G.S.R. 588(E). Health Do, ed New Delhi: The Gazette of India Extraordinary. 2013.

10. Goodman C, Miller R. Performance of retail pharmacies in low- and middle-income Asian settings: a systematic review. *Health Policy and Planning* 2016; **31**(7): 940-53.

11. Smith F. The quality of private pharmacy services in low and middle-income countries: A systematic review. *Pharmacy World & Science* 2009; **31**(3): 351-61.

12. Kotwani A, Holloway K. Access to antibiotics in New Delhi, India: implications for antibiotic policy. *Journal of Pharmaceutical Policy and Practice* 2013; **6**(1): 6.

13. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infectious Diseases* 2014; **14**(1): 13.

14. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340**: c2096.

15. Xu T, de Almeida Neto Abilio C, Moles Rebekah J. A systematic review of simulated-patient methods used in community pharmacy to assess the provision of non-prescription medicines. *International Journal of Pharmacy Practice* 2012; **20**(5): 307-19.

16. Watson MC, Norris P, Granas AG. A systematic review of the use of simulated patients and pharmacy practice research. *International Journal of Pharmacy Practice* 2006; **14**(2): 83-93.

17. Rethans J-J, Gorter S, Bokken L, Morrison L. Unannounced standardised patients in real practice: a systematic literature review. *Medical Education* 2007; **41**(6): 537-49.

18. Das J, Kwan A, Daniels B, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. *The Lancet Infectious Diseases* 2015; **15**(11): 1305-13.

19. Satyanarayana S, Kwan A, Daniels B, 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.

20. Miller R, Goodman C. Do chain pharmacies perform better than independent pharmacies? Evidence from a standardised patient study of the management of childhood diarrhoea and suspected tuberculosis in urban India. *BMJ Global Health* 2017; **2**(3).

21. Diwan V, Sabde Y, Bystrom E, De Costa A. Treatment of pediatric diarrhea: a simulated client study at private pharmacies of Ujjain, Madhya Pradesh, India. *The Journal of Infection in Developing Countries* 2015; **9**(1972-2680 (Electronic)): 505-11.

22. Centers for Disease Control and Prevention. Appropriate Antibiotic Use: Adult Treatment Recommendations. 2017. https://www.cdc.gov/antibiotic-use/community/for-hcp/outpatient-hcp/adult-treatment-rec.html (accessed January 4 2019).

23. World Health Organization. Cough and cold remedies for the treatment of acute respiratory infections in young children. Geneva: WHO, 2001.

24. World Health Organization. The treatment of diarrhoea: a manual for physicians and other senior health workers. Geneva: WHO, 2005.

25. World Health Organization. Caring for the sick child in the community. Geneva: WHO, 2011.

26. Kumar A, Valecha N, Jain T, Dash AP. Burden of Malaria in India: Retrospective and Prospective View. In: Breman J, Alilo M, White N, editors. Defining and Defeating the Intolerable Burden of Malaria III: Progress and Perspectives: Supplement to Volume 77(6) of American Journal of Tropical Medicine and Hygiene. Northbrook, IL: American Society of Tropical Medicine and Hygiene; 2007.

27. Directorate of Census Operations. Census of India 2011, District Census Handbook Udupi. 2011. http://censusindia.gov.in/2011census/dchb/2915_PART_B_DCHB_UDUPI.pdf (accessed January 4 2019).

28. Kwan A, Daniels B, Saria V, et al. Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *PLoS medicine* 2018; **15**(9): e1002653.

29. Rhodes KV, Miller FG. Simulated Patient Studies: An Ethical Analysis. *The Milbank Quarterly* 2012; **90**(4): 706-24.

30. Shet A, Sundaresan S, Forsberg BC. Pharmacy-based dispensing of antimicrobial agents without prescription in India: appropriateness and cost burden in the private sector. *Antimicrobial resistance and infection control* 2015; **4**: 55-.

31. Kotwani A, Wattal C, Katewa S, Joshi PC, Holloway K. Irrational use of antibiotics and role of pharmacists: an insight from a qualitative study in New Delhi, India. *Journal of Clinical Pharmacy Therapeutics June* 2012; **37**.

32. Global Data Lab. Subnational Human Development Index. 2019. https://globaldatalab.org/shdi/shdi/ (accessed March 11 2019).

33. Census Population 2011 2015. https://www.census2011.co.in/ (accessed March 11 2019).

34. Department of Planning Programme Monitoring & Statistics. Economic survey of Karnataka - 2015-2016. 2016. http://des.kar.nic.in/docs/Economic%20Survey%202015-16_English%20Final.pdf (accessed March 11 2019).

35. International Institute for Population Sciences. National Family Health Survey 4. 2016. http://rchiips.org/nfhs/about.shtml (accessed March 11 2019).

36. Dayanand KK, Punnath K, Chandrashekar V, et al. Malaria prevalence in Mangaluru city area in the southwestern coastal region of India. *Malaria journal* 2017; **16**(1): 492-.

37. Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. Social determinants of antibiotic misuse: a qualitative study of community members in Haryana, India. *BMC Public Health* 2017; **17**(1).

38. World Health Organization. Antibiotic resistance: Multi-country public awareness survey. Geneva: WHO, 2015.

39. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. *BMJ* 2017; **358**: j3418.

40. Dua V, Kunin CM, VanArsdale White L. The use of antimicrobial drugs in Nagpur, India. A window on medical care in a developing country. *Social Science & Medicine* 1994; **38**(5): 717-24.

41. Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med* 2003; **57**.

42. Daftary A, Jha N, Pai M. Enhancing the role of pharmacists in the cascade of tuberculosis care. *Journal of Epidemiology and Global Health* 2017; **7**(1): 1-4.

43. McKay R, Mah A, Law MR, McGrail K, Patrick DM. Systematic Review of Factors Associated with Antibiotic Prescribing for Respiratory Tract Infections. *Antimicrobial Agents and Chemotherapy* 2016; **60**(7): 4106.

44. Gidengil CA, Mehrotra A, Beach S, Setodji C, Hunter G, Linder JA. What Drives Variation in Antibiotic Prescribing for Acute Respiratory Infections? *Journal of general internal medicine* 2016; **31**(8): 918-24.

45. Linder JA, Doctor JN, Friedberg MW, et al. Time of day and the decision to prescribe antibiotics. *JAMA Intern Med* 2014; **174**(12): 2029-31.

46. Basak SC, van Mil JWF, Sathyanarayana D. The changing roles of pharmacists in community pharmacies: perception of reality in India. *Pharmacy World & Science* 2009; **31**(6): 612-8.

47. Sakeena MHF, Bennett AA, McLachlan AJ. Enhancing pharmacists' role in developing countries to overcome the challenge of antimicrobial resistance: a narrative review. *Antimicrobial Resistance & Infection Control* 2018; **7**(1): 63.

48. Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2013; (2).

49. Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2016; (12).

4.7 Tables and figures

Description of the case scenario	Symptoms	Opening statement by the SP upon entering the pharmacy	Expected management
Upper respiratory tract infection, likely of viral aetiology	Individual with a 2-day history of acute onset low-grade fever, with runny nose, and non-productive cough; does not look sick. Family members have similar symptoms.	Child with URI: “Sir/Ma’am, my niece at home has fever and cough. Can you give me some medicine for her?”	Acceptable: not dispensing antibiotics, with or without referral to a doctor; dispensing symptomatic treatments according to current guidelines
		Adult with URI: “Since two days I have cough and fever. Can you help me?”	Unacceptable: Dispensing antibiotics and/or steroids
Uncomplicated, acute diarrhoea	Individual with 1-day history of acute onset, watery diarrhoea; no blood in the stool. No fever. Appears well hydrated.	Child with diarrhoea: “Sir/Ma’am, my niece at home has diarrhoea. Can you give me some medicine for her?”	Acceptable: Dispensing oral rehydration salts (ORS), not dispensing antibiotics, with or without referral to a doctor. For paediatric SPs, zinc should be given with ORS
		Adult with diarrhoea: “I have diarrhoea. Can you help me?”	Unacceptable: Dispensing antibiotics and restricted anti-motility drugs such as loperamide
Acute febrile illness suggestive of malaria	Individual with a 4-day history of high fever with shivering/chills, every other day; no cough or any other symptoms. No headache, fits, or altered consciousness.	Child with fever: “Sir/Ma’am, since four days my niece has fever and chills. Can you give me some medicine for him?”	Acceptable: Referral for malaria blood test without dispensing anti-malarials or antibiotics

		Adult with fever: "I have fever since a few days that is not going away. I also get chills."	Unacceptable: Dispensing anti-malarials, other antibiotics, or steroids

Table 1. Standardised patient case scenarios for both adults and children, with expected management.

		Percentage of interactions (95% CI)	
		Adult	Paediatric
URI	Age (child only)	NA	98.4% (95.7%, 99.4%)
	Degree of fever	29.6% (24.2%, 35.7%)	16.3% (12.1%, 21.5%)
	Cough containing sputum	61.4% (54.9%, 67.2%)	1.2% (0.31%, 3.73%)
	Cough containing blood	0.79% (0.14%, 3.1%)	1.2% (0.31%, 3.73%)
	Presence of runny nose	31.2% (25.6%, 37.4%)	4.8% (2.6%, 8.4%)
	Difficulty breathing or wheezing	0 (0, 1.9%)	0 (0, 1.9%)
	Any pain (child only)	NA	0 (0, 1.9%)
	Throat or ear pain (adult only)	0.79% (0.14%, 3.1%)	NA
	Chest pain (adult only)	5.9% (3.5%, 9.9%)	NA
	Sick household members	0 (0, 1.9%)	0 (0, 1.9%)
	Any question (excluding age)	88.9% (84.2%, 92.4%)	28.2% (22.8%, 34.2%)
Diarrhoea	Age (child only)	NA	97.6% (94.7%, 99.0%)
	Duration of diarrhoea	29.7% (24.3%, 35.8%)	14.6% (10.6%, 19.7%)
	Number of stools per day	13.9% (10%, 18.9%)	12.% (8.6%, 17.1%)
	Blood or mucus in the stool	0.77% (0.13%, 3.1%)	0.79% (0.14%, 3.1%)
	Vomiting in the past 8 hours	0.39% (0.02%, 2.5%)	4.7% (2.6%, 8.3%)
	Presence of a fever	1.9% (0.71%, 4.7%)	3.6% (1.7%, 6.9%)
	Any problems urinating	0 (0, 1.8%)	0 (0, 1.9%)
	Feeding practices while sick	0 (0, 1.8%)	6.3% (3.8%, 10.3%)
	Medication taken while sick	0 (0, 1.8%)	3.6% (1.7%, 6.9%)
	Any question (excluding age)	35.9% (30.1%, 42.1%)	19.4% (14.8%, 24.9%)

Fever	Age (child only)	NA	97.7% (94.8%, 99.1%)
	Duration of symptoms	88.5% (83.7%, 92%)	7.3% (4.6%, 11.4%)
	Presence of cough	21.4% (16.6%, 27.1%)	16.6% (12.4%, 21.8%)
	Any pain (child only)	NA	0.39% (0.02%, 2.5%)
	Throat or ear pain (adult only)	0 (0, 1.9%)	NA
	Headache (adult only)	22.2% (17.3%, 28%)	NA
	Occurrence of fits or fainting	0 (0, 1.9%)	0 (0, 1.8%)
	Regular feeding and bowel movements	0 (0, 1.9%)	0 (0, 1.8%)
	Any question (excluding age)	100% (98.1%, 100%)	19.7% (15.1%, 25.2%)

Table 2. History taking by pharmacies, separated by SP case. Percentages refer to percentage of interactions where the pharmacist posed this question. Values do not sum to 100% as some pharmacies posed multiple questions.

	Adult (percentage, [95% CI])			Paediatric (percentage, [95% CI])			Total (percentage, [95% CI])
	URI	Diarrhoea	Fever	URI	Diarrhoea	Fever	
Number of SP interactions	250	259	252	252	250	259	1528
Any medication	85% [79.8%, 89%]	91.1% [86.8%, 94.2%]	85.3% [80.2%, 89.3%]	51.6% [45.2%, 57.9%]	32.4% [26.8%, 38.6%]	81.9% [76.5%, 86.2%]	71.3% [69%, 73.6%]
Mean number of medicines dispensed (range)	0.89 (0 – 2)	1.1 (0 – 3)	1 (0 – 3)	0.59 (0 – 2)	1.15 (0 – 3)	0.85 (0 – 2)	0.79 (0 – 3)
Any antibiotic	4.35% [2.3%, 7.86%]	4.63% [2.53%, 8.16%]	3.97% [2.03%, 7.4%]	0 [0, 1.87%]	7.91% [5.02%, 12.1%]	0.77% [0.14%, 3.06%]	3.6% [2.75%, 4.69%]
Schedule H drug	78.7% [73%, 83.4%]	89.2% [84.6%, 92.6%]	61.1% [54.8%, 67.1%]	26.6% [21.3%, 32.6%]	20.6% [15.9%, 26.2%]	7.72% [4.9%, 11.9%]	47.3% [44.8%, 45%]
Schedule H1 drug	1.19% [0.31%, 3.71%]	0 [0, 1.82%]	0 [0, 1.87%]	0 [0, 1.87%]	0 [0, 1.87%]	0.77% [0.13%, 3.06%]	0.33% [0.12%, 0.81%]
% of interactions with acceptable management	85% [79.8%, 89%]	0 [0, 1.82%]	1.19% [0.31%, 3.73%]	75.4% [69.5%, 80.5%]	0 [0, 1.87%]	3.86% [1.97%, 7.2%]	33.3% [30.1%, 35.7%]

Table 3. Number of interactions, proportion, and 95% confidence interval for primary and secondary outcomes, by SP case.

Variable	Odds ratio* [95% confidence interval]
History taking	
Number of questions asked	1.54 [1.30 – 1.84]
Pharmacy location	
Urban pharmacy	Reference
Rural pharmacy	0.94 [0.52 – 1.68]
Referral	
Patient not referred	Reference
Patient referred to another provider	0.38 [0.18 – 0.79]
Client volume at the pharmacy	
No customers present	Reference
One to three customers	0.97 [0.48 – 1.97]
More than three customers	1.18 [0.39 – 3.59]
Length of interaction	
Less than one minute	Reference
One to three minutes	0.93 [0.41 – 2.08]
More than three minutes	3.03 [1.11 – 8.27]
Case	
URI	Reference
Diarrhoea	2.83 [1.47 – 5.45]
Fever	0.83 [0.37 – 1.83]
Patient age	
Child	Reference
Adult	1.65 [0.92 – 2.96]

Table 4. Results of model fit using generalised estimating equations with a logit link for all interactions (n = 1522). Odds ratios are for the outcome of antibiotic dispensing by the pharmacy. *All odds ratios are adjusted for case and age of SP (adult/child).

Variable	Odds ratio [95% confidence interval]
History taking	
Number of questions asked	1.34 [0.94 – 1.93]
Pharmacy location	
Urban pharmacy	Reference
Rural pharmacy	2.54 [0.90 – 7.20]
Referral	
Patient not referred	Reference
Patient referred to another provider	0.07 [0.02 – 0.25]
Client volume at the pharmacy	
No customers present	Reference
Customers present	1.23 [0.41 – 3.70]
Length of interaction	
Less than one minute	Reference
One to three minutes	1.37 [0.42 – 4.48]
Antibiotic dispensed for adult	
Not dispensed	Reference
Dispensed	6.34 [1.69 – 23.82]

Table 5. Results of model fit using generalised estimating equations with a logit link with antibiotics dispensed for paediatric SPs with diarrhoea as the outcome (n = 233). 'Antibiotic dispensed for adult' refers to dispensing for an adult SP with diarrhoea at the same pharmacy.

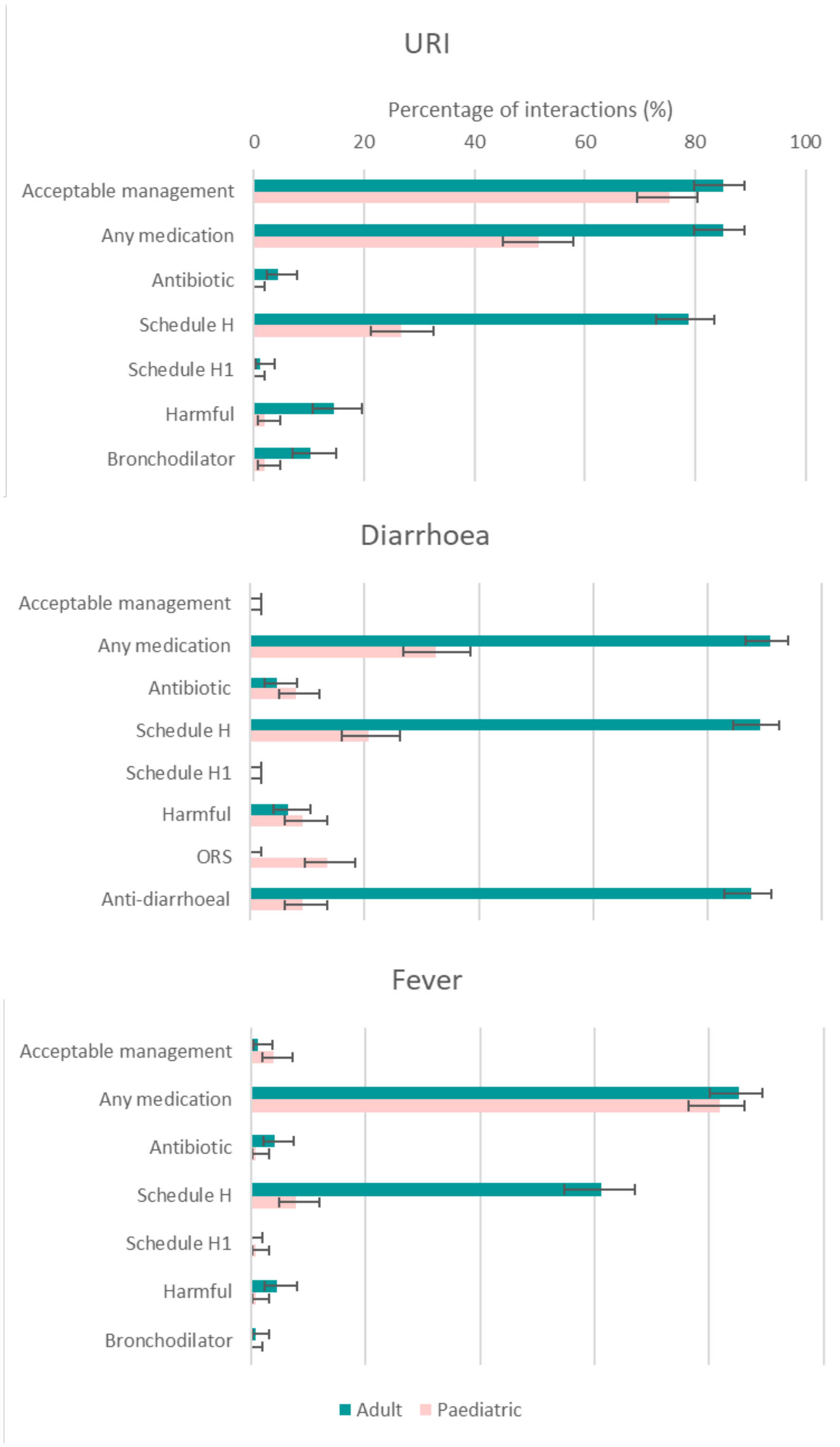

Figure 1. Management of SP cases, by condition, for adults and children. Error bars indicate 95% confidence interval.

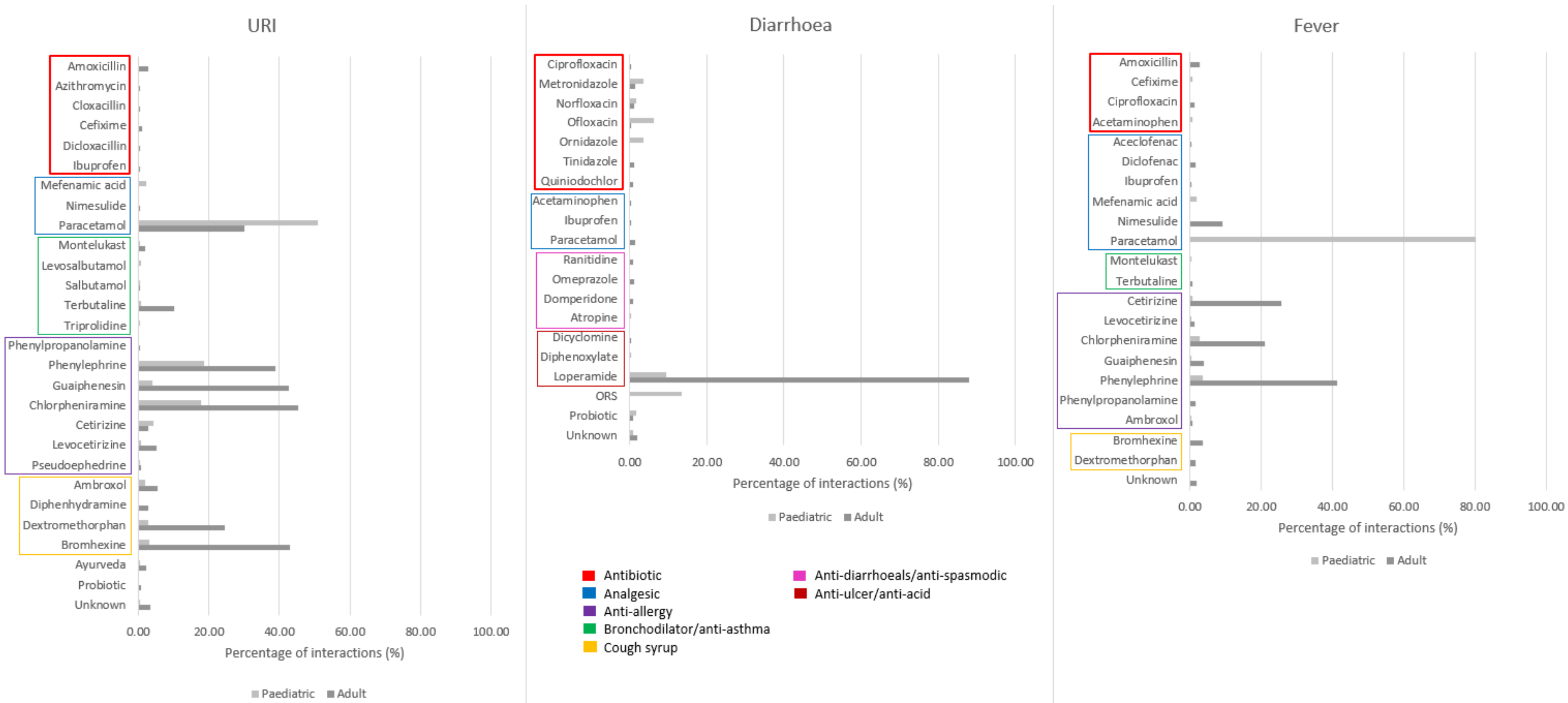

Figure 2. Active drug ingredients in medications provided to SPs by SP case, for adults and children. Percentages do not sum to 100% as one medication may have contained more than one active drug ingredient.

4.8 Appendix to manuscript

4.9.1. Rationale for the approval of a waiver of informed consent

A waiver of informed consent for the pharmacies visited was approved by the IRBs of both McGill University and Manipal Academy of Higher Education. We provide below the rationale for requesting and receiving such a waiver. Principally, we believe that if pharmacies were aware that they were part of our study, it would not have been possible to obtain scientifically valid estimates of antibiotic dispensing.

We cite a report by Rhodes et al. (2012) on the ethical aspects of standardised patient studies.[1] This report, commissioned by the US Department of Health and Human Services, concluded that "As long as adequate protections of confidentiality of research data are in place, minimally intrusive simulated patient research that gathers policy-relevant data on the health system without the consent of individuals working in that system can be ethically justified when the risks and burdens to research subjects are minimal and the research has the potential to generate socially valuable knowledge."

SPs have routinely been used in low- and middle- income countries for assessing pharmacist practice.[2] Members of our research team have validated the SP approach in India for assessing quality of care for tuberculosis (TB) patients,[3] and this was successfully extended to assess the management of TB in pharmacies.[4] The pilot study demonstrated that the methodology presents minimal to no risk for participants and providers, while being highly effective at measuring quality of care.

Regarding the objectives of the current study, it is difficult to estimate current practice in pharmacies. Prescription audits fail to measure off-prescription drug use, and the direct observation approach has several limitations. Notably, direct observation is limited by the

Hawthorne effect, which suggests that individuals have a natural propensity to alter their behaviour when they are aware that they are being observed. If pharmacists are aware that they are in a study and the customer in front of them is an SP, they may be more or less likely to prescribe certain medications. In that case, the results in our study would not have reflected the actual practice in the pharmacies studied, and antibiotic prescribing rates would not have been accurately measured, compromising our study validity.

The lack of provider consent was unlikely to have an adverse effect on the pharmacists in our study. No financial losses were incurred, as SPs purchased any medications provided to them by the pharmacist as a regular customer would. Other customers were at most inconvenienced by the few minutes the SP interaction requires. Further, all information collected was kept strictly confidential by our team. The identities of the pharmacists and any identifying information on their store will not be released to the public or published in any format.

The study also poses minimal to no risk to individuals recruited to be SPs. No harm to SPs was documented in our previous pharmacy SP study in India, and the quality of care pilot study demonstrated that there is little to no risk of SPs being detected by health care providers. All SPs in our study presented with relatively common and non-severe symptoms, so there was no reason to expect extreme or unusual responses from pharmacy staff. Importantly, SPs were subject to any therapeutic or diagnostic interventions. They purchased medications prescribed by the pharmacist but were instructed not to take any of the medications. Pharmacists may provide referrals to a physician or for further testing, but SPs did not visit any other health care providers or consent to any invasive or non-invasive medical procedures.

4.9.2. Case development and SP training

Cases and ideal case management were defined prior to SP recruitment. After conceptualising the symptoms of the three cases, clinicians developed a list of potentially relevant questions that pharmacies may ask. Answers for each question were prepared with the intent of developing SP case scenarios that do not warrant the use of antibiotics.

SPs were recruited by advertising at the Manipal Academy of Higher Education and the local community. Ultimately, three individuals, all male, were hired as SPs. All were of a similar age (in their 20s) and from the local area, meaning they were familiar with the district geography and spoke the local language of Kannada, as well as at least basic English. Each SP was responsible for one paediatric and one adult case as follows:

- SP1 – paediatric diarrhoea + adult URI
- SP2 – paediatric fever + adult diarrhoea
- SP3 – paediatric URI + adult fever

For each set of two cases, a script was developed. The SP was instructed to first present the paediatric case and upon the completion of that interaction, present the adult case. The adult case was presented regardless of the outcome of the paediatric case. The script included some basic information about the background of each SP, such as their living situation and some behaviours that would be relevant to their health (e.g. consumption of alcohol and/or tobacco). Scripts were developed in conjunction with the research team including local field staff, a local clinician, and the individuals recruited as SPs. We first prepared the scripts in English and then translated them into Kannada, again with SP participation. SP input was extremely helpful for this stage as they were able to provide examples of the vocabulary used in the community.

For SP training, the research team worked with a member of the Institute of Socio-Economic Research on Development and Democracy (ISERDD), an organisation based in Delhi, India, that has assisted our team with SP training in the past. Training began with a discussion regarding the relevance of the developed cases for the local community, followed by the development of the scripts as described above and a discussion regarding the relevance of the developed cases. Once the scripts were developed, SPs were trained to learn all aspects of the script. When supervisors felt that SPs had adequately learnt the script, we completed supervised dry runs at local pharmacies, where the supervisor would be present in the pharmacy under the pretense of purchasing something while the SP completed the interaction. This was followed by unsupervised practice visits. We aimed to ensure that 1) SPs correctly recalled all aspects of case presentation; 2) SPs correctly recalled all aspects of the interaction; 3) SPs successfully avoided detection.

SPs were trained to avoid detection by engaging in a discussion of potential questions pharmacy staff may ask, and role-playing exercises to help the SP internalise the details of their case and represent it more accurately. Mock interviews with both scripted and unscripted questions were used to aid with this as well as script recall. In addition, it was essential to train SPs to avoid any uncomfortable situations. SPs together with supervisors discussed potentially difficult situations that may arise, such as a pharmacist attempting to perform examination or insisting that the SP bring in the sick child for examination. Subsequently, SPs were trained on risk mitigation strategies in case such a situation arose. SPs were also instructed to immediately contact local field staff if they encountered any dangerous situations during field visits, though this did not ultimately occur.

4.9.3. Post-visit questionnaire

Upon completion of each visit, SPs were instructed to fill out a post-visit questionnaire using the Epicollect5 mobile application on their smartphones (iPhone/Android). SPs practiced using the applicating during piloting to ensure that there would be no errors. The questionnaire was available even if the phone was not connected to a data network; multiple entries can be saved offline and uploaded when a network is available. SPs were instructed not to fill out the questionnaire directly in front of the pharmacy, but rather walk or drive a short distance away before completing it in order to avoid drawing attention to themselves at the pharmacy. Epicollect5 was chosen as a data collection method as all uploaded entries are automatically saved on the server. Additionally, the smartphone application automatically records date, time, and GPS location of the user at the time the questionnaire is accessed. This enabled study supervisors to verify that the correct pharmacy was visited. The data was only available to the investigators and local research assistant. With this method, data was immediately digitised, minimising the risk of transcription errors. We also believed that using a smartphone would be less conspicuous than stopping to fill out a paper form, additionally helping to protect SPs from being detected. Each completed questionnaire was verified for missing data at the end of the day by a trained research assistant.

4.9.4. Sample size calculation

The following formula was used to calculate sample size per SP case:

$$\mathbf{n = [Np(1\text{-}p)]/\ [(d^2/Z^2*(N\text{-}1)+p*(1\text{-}p)]}$$

Where:

n = Number of pharmacies required
N = Number of pharmacies in sampling frame
p = Hypothesised outcome proportion
d^2 = Absolute confidence limits (%)
Z^2 = Z-score for confidence level

This is appropriate for a binary outcome, and our primary outcome was antibiotic dispensing (coded as yes/no). Sample size was calculated for outcome proportions from 0.1 to 0.5. The computation is symmetric around 0.5, so the sample size calculated for a proportion of 0.3 is the same as that needed for an outcome proportion of 0.7.

Required sample size	**100**	**145**	**169**	**180**	**184**
Pharmacies in sampling frame	350	350	350	350	350
Hypothesised outcome proportion	0.1	0.2	0.3	0.4	0.5
Width of confidence interval	+/- 5%	+/- 5%	+/- 5%	+/- 5%	+/- 5%
Confidence level	95%	95%	95%	95%	95%

Table A1. Required sample size for differing outcome proportions. The sample size represents the number of pharmacies needed per SP case.

4.9.5. Statistical analysis

The outcome of interest in our analyses was antibiotic dispensing for a given SP-pharmacy interaction, which was coded as follows: 1 = antibiotic dispensed, 0 = no antibiotic dispensed. For a binary outcome, logit models best account for the error structure.

Model 1: pooled model

The purpose of the pooled model was to determine which factors of the SP-pharmacy interaction were associated with antibiotic dispensing in the study. The pharmacy variables of interest were:

Variable	Type of variable	Coded as
Referred to another provider	Dichotomous	1 = yes 0 = no
Urban vs. rural pharmacy	Dichotomous	1 = urban 0 = rural
Length of visit	Categorical	<1 minute (reference) 1-3 minutes 3+ minutes
Number of customers present at the time of the interaction	Categorical	No customers (reference) 1-3 customers 3+ customers
Questions asked by pharmacy	Continuous	Minimum: 0 Maximum: 7

Table A2. Variables of interest in pooled model.

To obtain efficient and accurate estimates of these effects, our final model should also account for other factors that affect antibiotic dispensing. It is likely that not all SP case scenarios will result in the same proportion of antibiotic dispensing. This was ultimately observed in the data, with diarrhoea being the condition for which antibiotics were provided more frequently. Further, we assumed that our observations are not independent due to clustering by pharmacy.

Four logit models were fit to the full dataset comprised of 1,522 SP-pharmacy interactions, and the coefficient estimates from all for are shown in Figure S1 as the difference in log odds. Odds ratios can be obtained by exponentiating these coefficients. We began by fitting a generalised linear model (GLM) with a logit link, or a logistic regression model, with only the pharmacy variables as covariates (model 1). For model 2, we added one dummy variable for age (as this variable has two levels, adult and child), and two dummy variables for case (this variable has the levels URI, diarrhoea, and fever) to account for all six SP case scenarios. We can show that model 2 provides a better fit for the data by using the likelihood ratio test to compare the log likelihoods of the two models. The log likelihood of model 1 is -226 while the log likelihood of model 2 is -216, and the Chi-square test results a significant result ($p<0.001$).

Model 2 accounts for SP case scenario but does not take into consideration potential clustering by pharmacy ($n = 279$). We considered two different models that can account for this clustering. First, we fit a generalised linear mixed model (GLMM) with a logit link, where we included random intercepts for all pharmacies in the dataset (model 3). The second method was to model the data using generalised estimating equations (GEE) with a logit link (model 4).

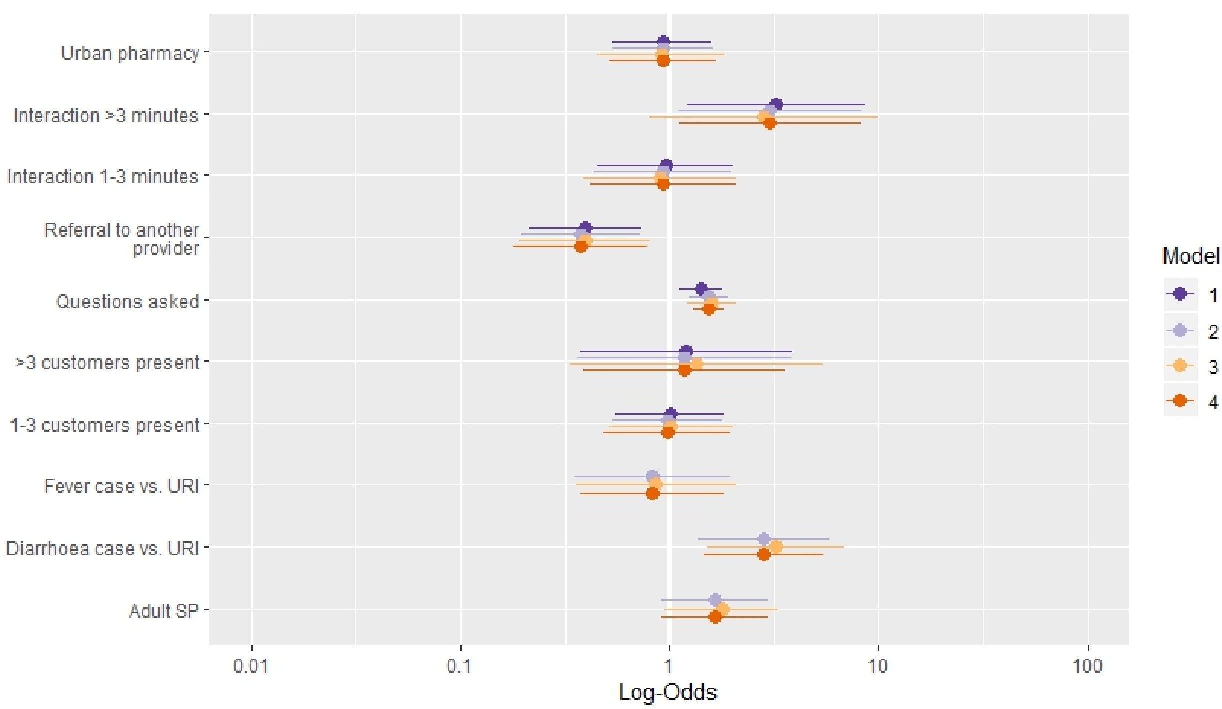

Figure A1. Comparison of logit models for pooled model (n = 1,522). Model 1: logistic regression with no fixed or random effects; model 2: logistic regression with case and age dummy variables; model 3: GLMM with logit link with case and age dummy variables, and random intercepts by pharmacy; model 4: GEE with logit link with case and age dummy variables, and clustering by pharmacy.

Both models 3 and 4 also include dummy variables for case and age; thus, both account for variation by SP case scenario and by pharmacy visited. However, the interpretation of the coefficients for the pharmacy variables (variables of interest) are different. GLMM estimates conditional effects, where a coefficient represents the effect of that variable, while holding the value of all other variables constant. Meanwhile, GEE estimates marginal effects, where the coefficient represents the population average effect of the variable.

Figure A1 demonstrates that coefficient estimates were very similar between GLMM and GEE. The major difference is that the confidence interval estimated for the "Interaction >3 minutes" crosses the null in model 3, but not in model 4. However, the comparatively large standard errors may be due to a loss of efficiency with GLMM with random effects when the number of clusters is large (n = 279 in this case), as a random intercept must be fit for each cluster.

We report results from the GEE analysis in the main paper for the reasons described above:

- Marginal effect estimates may be more conventionally interpretable.
- The number of clusters is large, potentially reducing the efficiency of GLMM.
- GEE does not require any distributional assumptions and the determination of standard errors is robust to misspecification of the correlation structure.

Theoretically, it is possible that SP characteristics such as sex, age, height, or weight, could affect pharmacists' behaviour. However, as each SP case scenario was only portrayed by one individual in this study, any potential variation here will be accounted for with the case fixed effect, and SP characteristics were never included as an additional covariate in the models.

Model 2: predicting paediatric antibiotic dispensing

To examine whether dispensing for adults and children was correlated, we chose to fit a second logit model where the outcome was antibiotic dispensing for the paediatric SP-pharmacy interactions (coded as 1 = yes and 0 = no). Due to the lower rates of antibiotic dispensing for the URI and fever conditions, this analysis was restricted to diarrhoea only. The variable of interest was antibiotic dispensing for the corresponding adult interaction, i.e., the adult SP with diarrhoea at the same pharmacy (again coded as 1 = yes and 0 = no). Thus, the model would hypothetically include 250 observations, the number of paediatric diarrhoea SP-pharmacy interactions. However, as not all visits were successfully completed and the number of interactions is not perfectly equal between adults and children, 17 paediatric diarrhoea interactions do not have a corresponding adult interaction, and these were excluded.

For this analysis, length of interaction and number of customers present were dichotomised and included as less than one minute vs. more than one minute, and no customers vs. customers present, respectively. This was done as there were very few observations in the categories "visit length more than three minutes" and "more than three customers present" when only a subset of all the visits were considered.

The coefficient estimates from the logit models fit to this data are displayed in Figure A2. As with the pooled model, we first fit a logistic regression model including only the pharmacy variables in addition to our new covariate of interest, antibiotic dispensing for the adult (model

1). Models 2 and 3 correspond to the GLMM and GEE models described above. As the outcome was restricted to diarrhoea interactions, dummy variables for case and age were not included. Again, coefficient estimates are very similar between the two models, and we report the results from model 3 in the main paper for the reasons described above.

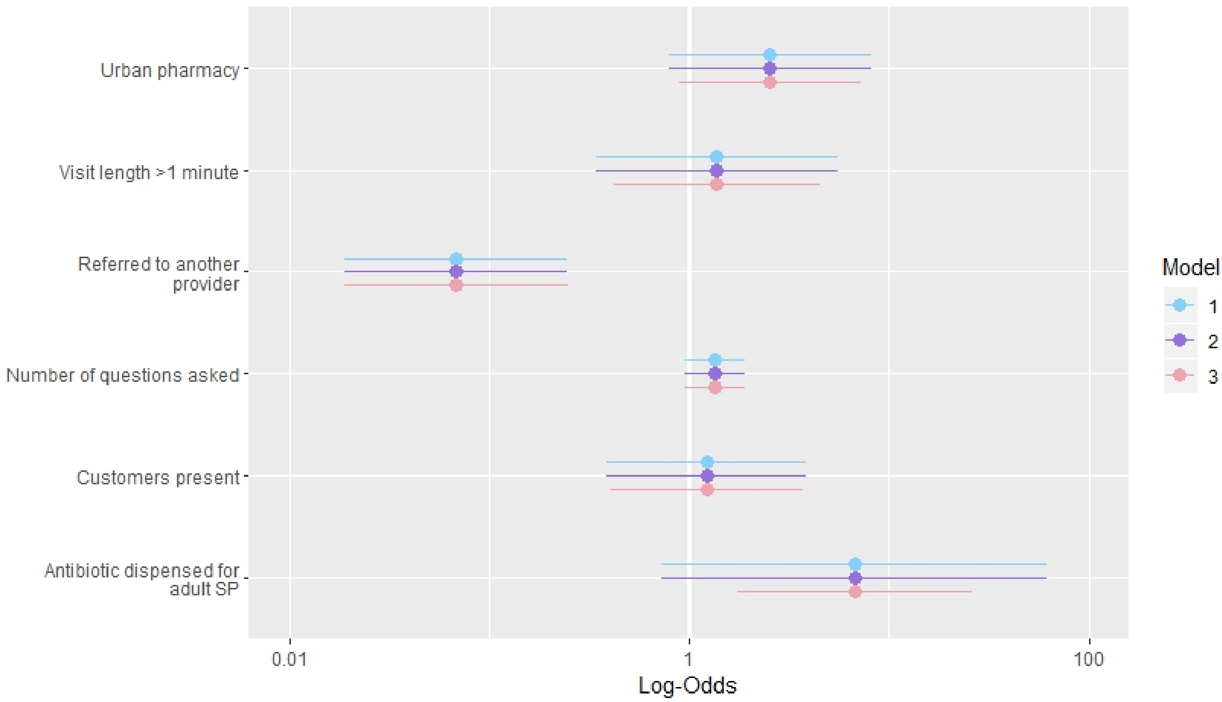

Figure A2. Comparison of logit models for paediatric diarrhoea antibiotic dispensing model with adult and child outcomes paired based on condition (n = 233). ‘Antibiotic dispensed for adult SP’ refers to whether the adult SP with diarrhoea received an antibiotic at the same pharmacy. Model 1: logistic regression with no fixed or random effects; model 2: GLMM with logit link with random intercepts by pharmacy; model 3: GEE with logit link accounting for clustering by pharmacy.

We additionally fit a second model using antibiotic dispensing for paediatric diarrhoea as the outcome, but the corresponding adult interaction was defined as the adult SP case scenario presented in the same visit. With our experimental design, paediatric diarrhoea was presented alongside adult URI. Figure A3 presents the logit models fit using this definition. Antibiotic dispensing for the adult was also a significant predictor here. We present the results of the model comparing children and adults with diarrhoea in the main paper as that better takes into consideration the differing frequency of antibiotic dispensing according to condition.

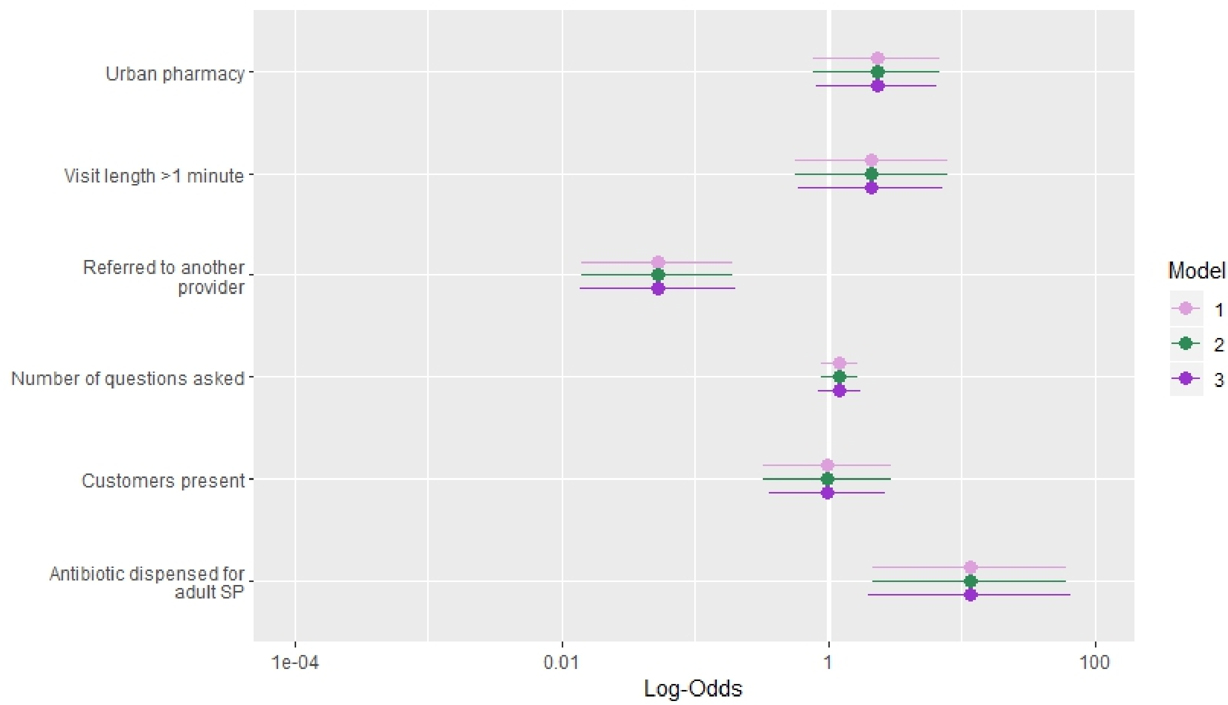

Figure A3. Comparison of logit models for paediatric diarrhoea antibiotic dispensing model with adult and child outcomes paired based on SP visit (n = 250). 'Antibiotic dispensed for adult SP' refers to whether the adult SP case presented during the same visit as the paediatric case received an antibiotic. Model 1: logistic regression with no fixed or random effects; model 2: GLMM with logit link with random intercepts by pharmacy; model 3: GEE with logit link accounting for clustering by pharmacy.

References to Appendix

1. Rhodes KV, Miller FG. Simulated Patient Studies: An Ethical Analysis. *The Milbank Quarterly* 2012; **90**(4): 706-24.

2. Watson MC, Norris P, Granas AG. A systematic review of the use of simulated patients and pharmacy practice research. *International Journal of Pharmacy Practice* 2006; **14**(2): 83-93.

3. Das J, Kwan A, Daniels B, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. *The Lancet Infectious Diseases* 2015; **15**(11): 1305-13.

4. Satyanarayana S, Kwan A, Daniels B, 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.

Chapter 5. Discussion

5.1 Summary of results

We aimed to quantify antibiotic non-prescription, over-the-counter antibiotic dispensing in private pharmacies in a region of South India. The goal was to study the experience of actual patients, so the standardised patient methodology was used. Moreover, the medical conditions we considered – URI, diarrhoea, and fever – are all very common in most populations, thus representing situations were patients would be likely to visit their pharmacy. We also included both adult and child (by proxy) SPs, in order to compare their management at the pharmacy. Overall, we found that:

1. Antibiotics were dispensed for these conditions, contrary to the treatment outlined in international guidelines. For children, fixed dose combinations were very common. For adults, pharmacies rarely provided a full course of antibiotics, instead only dispensing a few pills from an entire tablet strip. Thus, dosing is inconsistent.
2. Pharmacies were least likely to provide antibiotics if they referred the SP to another provider, and most likely to do so if they asked more questions or spent a comparatively long time with the SP.
3. Even when antibiotics were not dispensed, many other prescription-only medications were provided without a prescription.
4. Overall, patient management was poor. Pharmacy staff spent very little time with patients and asked few questions.
5. Pharmacies do not treat adults and children identically, even when they present with the same symptoms. Though the number of antibiotics dispensed was similar (4.3% of adult interactions and 2.9% of paediatric interactions), adults received significantly more

medications overall, with 87.2% of adult interactions resulting in the provision of any medication, compared to 55.5% for children. Children were also asked slightly more questions. However, whether a pharmacy provided antibiotics to an adult SP was predictive of whether they did the same for a child SP, suggesting that adult and paediatric outcomes are correlated.

Notably, antibiotics were dispensed in only 3.6% [95% CI: 2.8%, 4.7%] of SP-pharmacy interactions in our study, which is considerably lower than other SP studies which have reported 15% to upwards of 40% of pharmacies dispensing non-prescription antibiotics.[86-89] This may reflect the fact that Udupi district, where our study was carried out, is relatively developed relative to the rest of the state and the country, with a higher median income and strong health indicators. However, we cannot draw any conclusions from our results alone.

5.2 Strengths and limitations

The primary advantage of our study was the experimental design. The SP methodology has been shown to be an effective way to measure quality of care in the Indian context.[89,95] We extend on previous SP studies in this setting by including three unique conditions, and representing all three in both the adult and paediatric populations. To our knowledge, this is the first SP study to directly compare the management of adults and children in Indian pharmacies, and we demonstrated that there may be differences in the way the two groups are treated.

The SP methodology also has some limitations. First and foremost, we do not know whether the individual the SP interacted with at the pharmacy was the pharmacist. SPs did not attempt to ask questions or gather any information about the qualification of the person they spoke to as this might have seemed unusual, thus increasing the risk that the SP would be detected. Previous research suggests that in India, pharmacists are often not available on-site, and the individuals working at the pharmacy are very underqualified.[76,77] Our results cannot be interpreted as representing what qualified Indian pharmacists do when faced with URI, diarrhoea, or fever. However, the aim of the study was to assess the true patient experience. If Indian patients often interact with non-pharmacists, specifically seeking out pharmacists in our study would not have been representative of actual practice.

Only male SPs were used, which means that we cannot examine potential differences in pharmacies' behaviour due to patient gender. A recent SP study conducted in Indian private healthcare facilities suggests that gender does not affect provider practice, but this has not been evaluated specifically in pharmacies.[96] The decision to use only male SPs was motivated by safety concerns, as SPs completed field visits alone.

This is a single site study, and as a result we cannot examine how demographic or geographic characteristics affect antibiotic dispensing. We also conducted a single visit, and the SP was an individual that the pharmacy had never seen before. The number of visits is more relevant for SP studies conducted in a primary care setting, where follow-ups are often necessary and more common.[95] In particularly small villages or remote areas, it is nonetheless plausible that pharmacy staff would recognise most members of the local community. They might have treated SPs differently due to the lack of an existing relationship, and our study design did not include any way to assess this.

Finally, we also note that adult individuals were used as proxy SPs for the paediatric SP case scenarios. Paediatric SP cases have been presented in absentia before, in both pharmacies and physicians' offices,[85,88,97] and appears to be an effective way to evaluate providers' management of children without putting a child at risk. This behaviour of parents or relatives seeking care for a child who is not present has been documented in India before,[98] so this may also be an effective way to represent patients' healthcare seeking behaviours. However, SPs in this study always presented the paediatric case first, followed by the adult case. It is possible that pharmacies' behaviour would have been different if the adult case was presented first, or if only one case was presented in each visit. We ensured that the two conditions presented were not identical, to avoid priming pharmacies with the first case, but did not conduct any visits with the adult case presented first.

5.3 Directions for future research

We hypothesised that the low frequency of non-prescription antibiotic dispensing was a result of Udupi's development status and healthcare coverage. At MAHE, local physicians noted that access to medical services is generally very good in Udupi, but we did not conduct a formal qualitative study to examine this. If patients can easily access and afford visits to clinics or hospitals, pharmacies may not feel the need to step into a prescribing role and may be more cautious with antibiotics because of the risk of side effects. However, to better understand the medical context in Udupi, further study is required, for example conducting qualitative interviews with physicians, pharmacists, and local drug regulators.

Additionally, if overall development status affects antibiotic dispensing, we might expect this behaviour to be more prevalent in underdeveloped, lower socioeconomic status regions of India. Regions of India are also culturally very diverse, which may be relevant. Data from outpatient centers in the U.S. and Europe demonstrate that antibiotic prescribing varies greatly according to region, and it has been hypothesised that this is partly explained by factors such as religiosity, education level, type of government, and general cultural attitudes.[99-101] An example of the potential relevance of culture is Switzerland, a land-locked country surrounded by France, Germany, and Italy: antibiotic prescribing in Swiss hospitals and outpatient centres appears to mimic the prescribing in the closest neighbouring country.[102,103] Due to the lack of thorough administrative data, it is difficult to examine these factors in the Indian setting. A multi-site SP study in India would provide better data to assess how demographic or cultural factors, such as population density, literacy, coverage of healthcare services, SES, or religion, affect pharmacy practice and antibiotic dispensing.

5.4 Conclusion

The results of our study confirm that antibiotics are provided without a prescription in Indian pharmacies, and in situations where they are not indicated, but also suggest that this practice may not be as prevalent throughout the country as previously thought. This highlights the heterogeneity of regions within a country as vast and complex as India. However, the poor overall patient management – marked by poor history-taking and the provision of many other unnecessary medications – observed in this study is consistent with previous studies. Non-prescription antibiotic dispensing is not the only potentially harmful practice in community pharmacies. Pharmacies are well-placed in the community to provide care in the form of advice, symptomatic medications, and referrals for further examination. While they should be a part of antimicrobial stewardship interventions in India, they can also be leveraged to improve overall patient outcomes. Overall, more research is needed to understand the complexity of factors that drive OTC antibiotic dispensing in this setting.

Appendix 1 – SP scripts

These scripts were designed for training purposes, for SPs to learn their character and to practice answering questions that pharmacies may ask them. It is possible that pharmacies would ask other questions not included in the script; SPs should answer to the best of their ability and describe the question asked to research staff following the visit. Scripts were developed in English and then translated into the local language, Kannada.

SP1 – adult URI + child diarrhoea

Umesh is a 25-year-old male who has studied up to 12th standard. He lives with his uncle and his aunt and their two children, a daughter (2 years; Anusha) and a son (5 years) in their two room house. He works as a waiter in a hotel and makes 10-15 thousand rupees per month. He is generally very healthy and has never had a major illness. He drinks a few times per month and smokes 2-3 cigarettes per day.

Opening statement: "Sir, my niece at home has diarrhoea. Please give me some medicines for her."

Q1: How old is the child?

A1: Two years.

Q2: How long has she had diarrhoea?

A2: Since the last day.

Q3: How many stools per day?

A3: Four in the last day.

Q4: Is there any blood or mucus in the stool?

A4: No.

Q5: Did she vomit in the last 6-8 hours?

A5: No.

Q6: Does she have a fever?

A6: No.

Q7: Is she passing urine as normal?

A7: Yes.

Q8: What foods and fluids has she received while sick?

A8: She is still eating normal household food, taking water.

Q9: Has she been given any medication?

A9: No.

Following statement: "And also for myself, since two days I have cough and fever. Can you help me also?"

Q1: How high is the fever?

A1: Not very high.

Q2: Is the fever constant?

A2: Yes.

Q3: Are you producing sputum when you cough?

A3: No.

Q4: Is there blood when you cough?

A4: No blood.

Q5: Do you have any throat pain?

A5: No.

Q6: Do you have any ear pain?

A6: No.

Q7: Do you have a runny or blocked nose?

A7: I have a runny nose.

Q8: Is anyone else in the house sick?

A8: My uncle has some cough since a few days.

Q9: Do you have any difficulty breathing or wheezing?

A9: No.

A10: Any chest pain?

A10: Also no.

SP2 – adult diarrhoea + child fever

Rahul is a 30-year-old male who has studied up to 10th standard. He lives with his wife and their one child, a son (3 years; Vishnu) in their one room house which he owns. He is a bar worker and earns on average 8-10 thousand rupees per month. He is generally very healthy and has never had a major illness. He drinks a few times per month and smokes 2-3 cigarettes per day.

Opening statement: “Sir, since four days my son has fever and chills. Can you give me some medicine for him?”

Q1: How old is he?

A1: Three years old.

Q2: What is the duration of the symptoms?

A2: Since four days, every other day.

Q3: Does he have a cough?

A3: No.

Q4: Does he complain of any pain?

A4: No.

Q5: Does he experience any seizures (fits) or fainting?

A5: No.

Q6: Is he sleeping and playing normally?

A6: He seems a little restless and weaker than usual.

Q7: Is he eating normally?

A7: Maybe eating a little less.

Following statement: “And for myself, I have diarrhoea. Can you help me also?”

Q1: How long have you had diarrhoea?

A1: Since the last day.

Q2: How many stools per day?

A2: Four in the last day.

Q3: Is there any blood or mucus in the stool?

A3: No.

Q4: Have you been vomiting?

A4: No.

Q5: Do you have a fever?

A5: No.

Q6: Is she passing urine as normal?

A6: Yes.

Q7: Have you been eating?

A7: I am still eating normal household food.

Q8: Have you taken any medication?

A8: No.

SP3 – adult fever + child URI

Ravi is a 25-year-old male who has studied up to 10th standard. He lives with his parents and grandparents and one 3 years old child (a girl; Meghna) in his parents' house. He works at a garment show room and earns on average 8-10 thousand rupees per month. He is generally very healthy and has never had a major illness. He drinks a few times per month and smokes 2-3 cigarettes per day.

Opening statement: "Sir, my niece at home has fever and cough. Can you give me some medicine for her?"

Q1: How old is she?

A1: Three years.

Q2: How long has she had the symptoms?

A2: Since two days.

Q3: How high is the fever?

A3: She has a low fever all day.

Q4: Is she coughing up sputum or blood?

A4: No.

Q5: Does she have a runny nose?

A5: Yes, since the two days.

Q6: Does she complain of any pain?

A6: No.

Q7: Does she have any difficulty breathing or wheezing?

A7: No.

Q8: Is she eating and drinking normally?

A8: Yes.

Q9: Is she still playing normally?

A9: Yes.

Q10: Is anyone else in the house sick?

A10: My uncle also has some cough.

Following statement: "And also for myself, I have fever since a few days that is not going away. I also get chills."

Q1: What is the duration of the symptoms?

A1: Since four days, every other day.

Q2: Do you have a cough?

A2: No.

Q3: Any pain?

A3: No.

Q4: Do you have a headache?

A4: No.

Q5: Do you experience any seizures (fits) or fainting?

A5: No.

Appendix 2 – instructions for SPs provided to field staff

SPs should remember:

1. The gender of the chemist.
2. Number of patients at the pharmacy when the SP arrived.
3. Amount of time (approximately) spent directly with the chemist. This can be measured by discreetly checking a watch or smartphone immediately before and after the visit.
4. Whether the chemist asked questions identified on the script, or any other questions.
5. Whether the chemist carried out any examinations.
6. Whether the chemist recommended any investigations or lab test.
    a. SP should refuse any injections/ invasive tests performed by the chemist during this encounter but should remember what was suggested.
    b. SP2 and SP3 should especially note whether a malaria test was suggested.
7. Whether the chemist provided a diagnosis, and what the diagnosis is.
8. If medications are provided, the SP must purchase the medications and remember the exact amount spent at the pharmacy. If SPs receive loose or unlabelled pills, they should ask for the name of the medicine, only if possible.
9. Medications must be preserved. After the SP leaves the pharmacy, medications should be placed in the labeled envelope corresponding to the pharmacy visited and brought back to KMC in Manipal.
10. SPs should call the local research assistant after the visit if any of the following occurs:
    a. Questions not identified on the script are asked.
    b. The SP thinks they made an error or were detected by pharmacy staff.
    c. Anything else out of the ordinary or that made the SP uncomfortable occurred.

Appendix 3 - SP exit questionnaire (from Epicollect 5)

Save your location (GPS coordinates automatically saved by application).

Chemist name

Chemist address

Chemist ID

Date of survey (automatically saved by application)

Time of visit (automatically saved by application)

Your (personal) name

SP ID number (1-3)

How much time did you spend with the chemist?

- ☐ Less than one minute
- ☐ One to two minutes
- ☐ Three to five minutes
- ☐ More than five minutes

How many other customers were at the pharmacy?

- ☐ None
- ☐ One or two
- ☐ Three to five
- ☐ More than five

Did the chemist advise you to see a provider?

- ☐ Yes
- ☐ No

If yes for referral, where? (Check NA if no referral).

- ☐ Private provider
- ☐ Government hospital
- ☐ NA

Did the chemist provide medicines for the child?

- ☐ Yes
- ☐ No

Did the chemist provide medicines for the adult?

- ☐ Yes
- ☐ No

Did you purchase the medicines provided?

- [ ] Yes
- [ ] No

Are the purchased medicines in the envelope?

- [ ] Yes
- [ ] No

Did the chemist give a receipt for medications?

- [ ] Yes
- [ ] No

Did the chemist provide any advice on how to use the medications?

- [ ] Yes
- [ ] No

How much (in Rs) did the medicines cost?

Did the chemist conduct any examinations?

- [ ] No
- [ ] Throat examination
- [ ] Pulse rate
- [ ] Blood pressure
- [ ] Temperature - with thermometer
- [ ] Temperature - with hand
- [ ] Other - tell RA on the phone

For the child scenario, what questions did the chemist ask? (Skip question if none)

- [ ] Age of the child
- [ ] How long has she had diarrhoea?
- [ ] How many stools per day?
- [ ] Blood or mucus in the stool?
- [ ] Any vomiting in the last 6-8 hours?
- [ ] Does she have a fever?
- [ ] Is she passing urine as normal?
- [ ] What food or fluids has she received while sick?
- [ ] Has she been given any medication?

For the adult scenario, what questions did the chemist ask? (Skip question if none)

- [ ] How high is the fever?
- [ ] Is the fever constant?
- [ ] Are you producing sputum when you cough?
- [ ] Is there blood when you cough?
- [ ] Do you have throat pain?
- [ ] Do you have ear pain?
- [ ] Do you have a runny or blocked nose?
- [ ] Is anyone else sick?
- [ ] Do you have difficult breathing or wheezing?
- [ ] Do you have chest pain?

Did the chemist ask any other questions?

- ☐ Yes - tell the RA on the phone
- ☐ No

Do you think you made any errors?

- ☐ Yes - tell the RA on the phone
- ☐ No

Do you think you were detected as an SP?

- ☐ Yes - tell the RA on the phone
- ☐ No

References

1. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infectious Diseases* 2014; **14**(1): 13.

2. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463.

3. Gandra S, Tseng KK, Laxminarayan R, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. 2018.

4. Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet (London, England)* 2016; **387**(10014): 168-75.

5. Goodman C, Miller R. Performance of retail pharmacies in low- and middle-income Asian settings: a systematic review. *Health Policy and Planning* 2016; **31**(7): 940-53.

6. Smith F. The quality of private pharmacy services in low and middle-income countries: A systematic review. *Pharmacy World & Science* 2009; **31**(3): 351-61.

7. Cosgrove SE, Carmeli Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. *Clinical Infectious Diseases* 2003; **36**.

8. Naylor NR, Silva S, Kulasabanathan K, et al. Methods for estimating the burden of antimicrobial resistance: a systematic literature review protocol. *Systematic Reviews* 2016; **5**(1): 187.

9. Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrobial Resistance & Infection Control* 2018; **7**(1): 58.

10. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2012; **18**(3): 268-81.

11. O'Neill J. The review on antimicrobial resistance. United Kingdom, 2016.

12. Rice LB. Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE. *The Journal of Infectious Diseases* 2008; **197**(8): 1079-81.

13. Zetola N, Francis JS, Nuermberger EL, Bishai WR. Community-acquired meticillin-resistant Staphylococcus aureus: an emerging threat. *The Lancet Infectious Diseases* 2005; **5**(5): 275-86.

14. Chopra I, Schofield C, Everett M, et al. Treatment of health-care-associated infections caused by Gram-negative bacteria: a consensus statement. *The Lancet Infectious Diseases* 2008; **8**(2): 133-9.

15. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. *Expert Review of Anti-infective Therapy* 2013; **11**(3): 297-308.

16. Zaidi AKM, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *The Lancet* 2005; **365**(9465): 1175-88.

17. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PLOS ONE* 2017; **12**(12): e0189621.

18. Lozano R, Fullman N, Abate D, et al. Measuring progress from 1990 to 2017 and projecting attainment to 2030 of the health-related Sustainable Development Goals for 195 countries and territories: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; **392**(10159): 2091-138.

19. Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *The Lancet Infectious Diseases* 2005; **5**(8): 481-93.

20. White NJ. Antimalarial drug resistance. *The Journal of clinical investigation* 2004; **113**(8): 1084-92.

21. Blower SM, Aschenbach AN, Gershengorn HB, Kahn JO. Predicting the unpredictable: Transmission of drug-resistant HIV. *Nature Medicine* 2001; **7**: 1016.

22. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015; **40**(4): 277-83.

23. World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva: WHO, 2015.

24. Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV. Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology* 2014; **13**: 42.

25. Zhao X, Drlica K. Mutant Selection Window Hypothesis Updated. *Clinical Infectious Diseases* 2007; **44**(5): 681-8.

26. Drlica K. The mutant selection window and antimicrobial resistance. *Journal of Antimicrobial Chemotherapy* 2003; **52**(1): 11-7.

27. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. *BMJ* 2017; **358**: j3418.

28. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340**: c2096.

29. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. *Emerging infectious diseases* 2002; **8**(4): 347-54.

30. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. *Emerging infectious diseases* 2004; **10**(3): 514-7.

31. WHO Collaborating Centre for Drug Statistics and Methodology. About the ATC/DDD system. https://www.whocc.no/ (accessed March 11, 2019 2019).

32. IQVIA. MIDAS®. https://www.iqvia.com/solutions/commercialization/geographies/midas (accessed March 11, 2019 2019).

33. IQVIA. Prescription information. https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information (accessed March 11, 2019 2019).

34. European Centers for Disease Control. Antimicrobial consumption database (ESAC-Net). https://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database (accessed March 11, 2019 2019).

35. World Health Organization. Community-based surveillance of antimicrobial use and resistance in resource-constrained settings. Report on five pilot projects. Geneva, Switzerland: WHO; 2009.

36. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious Diseases* 2011; **11**(9): 692-701.

37. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases* 2014; **14**(8): 742-50.
38. Adriaenssens N, Coenen S, Tonkin-Crine S, Verheij TJM, Little P, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. *BMJ Quality & Safety* 2011; **20**(9): 764.
39. Le Maréchal M, Tebano G, Monnier AA, et al. Quality indicators assessing antibiotic use in the outpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. *The Journal of antimicrobial chemotherapy* 2018; **73**(suppl_6): vi40-vi9.
40. Kallen MC, Prins JM. A Systematic Review of Quality Indicators for Appropriate Antibiotic Use in Hospitalized Adult Patients. *Infectious disease reports* 2017; **9**(1): 6821-.
41. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *JAMA* 2016; **315**(17): 1864-73.
42. Smith DRM, Robotham JV, Smieszek T, et al. Potential for reducing inappropriate antibiotic prescribing in English primary care. *Journal of Antimicrobial Chemotherapy* 2018; **73**(suppl_2): ii36-ii43.
43. Hawker JI, Smith GE, Morbey R, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations. *Journal of Antimicrobial Chemotherapy* 2014; **69**(12): 3423-30.
44. Versporten A, Muller A, Goossens H, Vankerckhoven V, Coenen S, Adriaenssens N. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. *Journal of Antimicrobial Chemotherapy* 2011; **66**(suppl_6): vi71-vi7.
45. Ministry of Health and Family Welfare. National Policy for Containment of Antimicrobial Resistance. New Delhi, India: Government of India, 2011.
46. Walia K, Ohri VC, Singh H. Antimicrobial Resistance Surveillance Network Annual Report. New Delhi, India: Indian Council of Medical Research, 2017.
47. Gandra S, Mojica N, Klein EY, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. *International Journal of Infectious Diseases* 2016; **50**: 75-82.

48. Gandra S, Joshi J, Trett A, Lamkang AS, Laxminarayan R. Scoping Report on Antimicrobial Resistance in India. Washington, DC: Center for Disease Dynamics, Economics & Policy, 2017.

49. India State-Level Disease Burden Initiative C. Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. *Lancet (London, England)* 2017; **390**(10111): 2437-60.

50. Dharmapalan D, Shet A, Yewale V, Sharland M. High Reported Rates of Antimicrobial Resistance in Indian Neonatal and Pediatric Blood Stream Infections. *Journal of the Pediatric Infectious Diseases Society* 2017; **6**(3): e62-e8.

51. Chaurasia S, Sankar MJ, Agarwal R, et al. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *The Lancet Global Health* 2016; **4**(10): e752-e60.

52. World Health Organization. Global Tuberculosis Report 2018. Geneva: WHO, 2018.

53. Ministry of Health and Family Welfare. National Action Plan on Antimicrobial Resistance. New Delhi, India: Government of India, 2017.

54. Mehta A, Hasan Farooqui H, Selvaraj S. A Critical Analysis of Concentration and Competition in the Indian Pharmaceutical Market. *PLOS ONE* 2016; **11**(2): e0148951.

55. McGettigan P, Roderick P, Kadam A, Pollock AM. Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship. *The Lancet Global Health* 2017; **5**(11): e1075-e6.

56. Ahmad A, Khan MU, Balkrishnan R. Fixed-dose combination antibiotics in India: global perspectives. *The Lancet Global Health* 2016; **4**(8): e521.

57. Shafiq N, Kumar G, Gautam V, Ray P, Malhotra S. Fixed-dose combinations of antimicrobials: A need for special attention. *Indian Journal of Medical Microbiology* 2016; **34**(2): 208-9.

58. Gautam CS, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. *British Journal of Clinical Pharmacology* 2008; **65**(5): 795-6.

59. Asensio A, Álvarez-Espejo T, Fernández-Crehuet J, et al. Trends in yearly prevalence of third-generation cephalosporin and fluoroquinolone resistant Enterobacteriaceae infections and antimicrobial use in Spanish hospitals, Spain, 1999 to 2010. *Euro Surveillance* 2011; **16**(40): 1-9.

60. Gandra S, Laxminarayan R, Klein EY, Pant S, Malhotra-Kumar S. Faropenem Consumption is Increasing in India. *Clinical Infectious Diseases* 2016; **62**(8): 1050-2.

61. World Health Organization. The treatment of diarrhoea: a manual for physicians and other senior health workers. Geneva: WHO, 2005.

62. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *The Lancet* 2003; **361**(9376): 2226-34.

63. World Health Organization. Management of pneumonia in community settings. Geneva: WHO & UNICEF, 2004.

64. 2015 Ct. Countdown to 2015: Building a future for women and children: the 2012 report. Geneva, Switzerland: World Health Organization, 2012.

65. Kotwani A, Roy Chaudhury R, Holloway K. Antibiotic prescribing practices of primary care prescribers for acute diarrhoea in New Delhi India. *Value Health* 2012; **15**.

66. Grills N, Porter G. Medication misuse in India: a major public health issue in India. *Journal of Public Health* 2015; **38**(2): e150-e7.

67. Kamat VR, Nichter M. Pharmacies, self-medication and pharmaceutical marketing in Bombay, India. *Social Science & Medicine* 1998; **47**(6): 779-94.

68. Nepal G, Bhatta S. Self-medication with Antibiotics in WHO Southeast Asian Region: A Systematic Review. *Cureus* 2018; **10**(4): e2428-e.

69. Shamsudeen SM, Priya RS, Sujatha G, Muruganandhan J, Manikandan K. Self-medication with antibiotics: A knowledge, attitude, and practice appraisal of 610 dental patients in Chennai, India, from 2016 to 2017. *Journal of education and health promotion* 2018; **7**: 66-.

70. Kotwani A, Holloway K. Access to antibiotics in New Delhi, India: implications for antibiotic policy. *Journal of Pharmaceutical Policy and Practice* 2013; **6**(1): 6.

71. Sudhinaraset M, Ingram M, Lofthouse HK, Montagu D. What Is the Role of Informal Healthcare Providers in Developing Countries? A Systematic Review. *PLOS ONE* 2013; **8**(2): e54978.

72. Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2013; (2).

73. Lowe RF, Montagu D. Legislation, regulation, and consolidation in the retail pharmacy sector in low-income countries. *Southern Med Review* 2009; **2**(2): 35-44.

74. All India Organisation of Chemists & Druggists. All India Organisation of Chemists & Druggists history. 2018. http://www.aiocd.net/ (accessed September 15 2018).

75. Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. Social determinants of antibiotic misuse: a qualitative study of community members in Haryana, India. *BMC Public Health* 2017; **17**(1).

76. Basak SC, van Mil JWF, Sathyanarayana D. The changing roles of pharmacists in community pharmacies: perception of reality in India. *Pharmacy World & Science* 2009; **31**(6): 612-8.

77. Sabde YD, Diwan V, Saraf VS, Mahadik VK, Diwan VK, De Costa A. Mapping private pharmacies and their characteristics in Ujjain district, Central India. *BMC Health Services Research* 2011; **11**(1): 351.

78. Ministry of Health and Family Welfare Government of India. The Drugs and Cosmetics Rules, 1945. 2013. https://mohfw.gov.in/sites/default/files/638332522.pdf (accessed January 4 2019).

79. Kotwani A, Wattal C, Katewa S, Joshi PC, Holloway K. Irrational use of antibiotics and role of pharmacists: an insight from a qualitative study in New Delhi, India. *Journal of Clinical Pharmacy Therapeutics June* 2012; **37**.

80. Travasso C. India draws a red line under antibiotic misuse. *BMJ* 2016; **352**: i1202.

81. Rethans J-J, Gorter S, Bokken L, Morrison L. Unannounced standardised patients in real practice: a systematic literature review. *Medical Education* 2007; **41**(6): 537-49.

82. Watson MC, Norris P, Granas AG. A systematic review of the use of simulated patients and pharmacy practice research. *International Journal of Pharmacy Practice* 2006; **14**(2): 83-93.

83. Xu T, de Almeida Neto Abilio C, Moles Rebekah J. A systematic review of simulated-patient methods used in community pharmacy to assess the provision of non-prescription medicines. *International Journal of Pharmacy Practice* 2012; **20**(5): 307-19.

84. Padget M, Guillemot D, Delarocque-Astagneau E. Measuring antibiotic consumption in low-income countries: a systematic review and integrative approach. *International Journal of Antimicrobial Agents* 2016; **48**(1): 27-32.

85. 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 Affairs* 2012; **31**(12): 2774-84.

86. Diwan V, Sabde Y, Bystrom E, De Costa A. Treatment of pediatric diarrhea: a simulated client study at private pharmacies of Ujjain, Madhya Pradesh, India. *The Journal of Infection in Developing Countries* 2015; **9**(1972-2680 (Electronic)): 505-11.
87. Shet A, Sundaresan S, Forsberg BC. Pharmacy-based dispensing of antimicrobial agents without prescription in India: appropriateness and cost burden in the private sector. *Antimicrobial resistance and infection control* 2015; **4**: 55-.
88. Miller R, Goodman C. Do chain pharmacies perform better than independent pharmacies? Evidence from a standardised patient study of the management of childhood diarrhoea and suspected tuberculosis in urban India. *BMJ Global Health* 2017; **2**(3).
89. Satyanarayana S, Kwan A, Daniels B, 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.
90. International Institute for Population Sciences. National Family Health Survey 4. 2016. http://rchiips.org/nfhs/about.shtml (accessed March 11 2019).
91. World Health Organization. Cough and cold remedies for the treatment of acute respiratory infections in young children. Geneva: WHO, 2001.
92. World Health Organization. Caring for the sick child in the community. Geneva: WHO, 2011.
93. World health Organization. Guidelines for the treatment of malaria, 3rd ed. Geneva: WHO, 2015.
94. Directorate of Census Operations. Census of India 2011, District Census Handbook Udupi. 2011. http://censusindia.gov.in/2011census/dchb/2915_PART_B_DCHB_UDUPI.pdf (accessed January 4 2019).
95. Das J, Kwan A, Daniels B, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. *The Lancet Infectious Diseases* 2015; **15**(11): 1305-13.
96. Daniels B, Kwan A, Satyanarayana S, et al. Use of standardised patients to assess gender differences in quality of tuberculosis care in urban India: a two-city, cross-sectional study. *The Lancet Global Health* 2019; **7**(5): e633-e43.
97. Mohanan M, Vera-Hernández M, Das V, et al. The know-do gap in quality of health care for childhood diarrhea and pneumonia in rural india. *JAMA Pediatrics* 2015; **169**(4): 349-57.

98. Johnston HB, Ved R, Lyall N, Agarwal K. Where do rural women obtain postabortion care? The case of Uttar Pradesh, India. *International family planning perspectives* 2003; **29**(4): 182-7.

99. Deschepper R, Grigoryan L, Lundborg CS, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? *BMC Health Services Research* 2008; **8**(1): 123.

100. Deschepper R, Stichele RV. The role of cultural aspects. Differences in antibiotics usage in Europe. *Pharmaceutisch Weekblad* 2001; **136**(22): 794-7.

101. Blommaert A, Marais C, Hens N, et al. Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study. *Journal of Antimicrobial Chemotherapy* 2014; **69**(2): 535-47.

102. Plüss-Suard C, Pannatier A, Kronenberg A, Mühlemann K, Zanetti G. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. *Journal of Hospital Infection* 2011; **79**(2): 166-71.

103. Achermann R, Suter K, Kronenberg A, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. *Clinical Microbiology and Infection* 2011; **17**(6): 855-61.