Reframing and unpacking 'irrational' antibiotic use

REFRAMING AND UNPACKING 'IRRATIONAL' ANTIBIOTIC USE: A Structural and Socio-Ecological Perspective on Antibiotic Resistance in India

DISSERTATION

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Dedication

This dissertation would not have been possible without Sana Hirata, my life partner and editor-in-chief. Your never ending support, encouraging edits, tedious and meticulous transcriptions, and positive affirmations made this PhD go more smoothly than I ever could have imagined.

I would also like to dedicate this dissertation to my parents, Manoj and Veena Nair, and my brilliant sister, Priya Nair, who could probably have completed this PhD in half the time. Thank you all for being such a steadfast source of support in my life, even from 7,000 miles away.

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Executive Summary

The overuse of antibiotics is often deemed as an "irrational" practice that limits the effectiveness of antibiotics by contributing to antimicrobial resistance (AMR), especially in emerging economies or low-and-middle-income countries such as India. One multi-country study from low-income and lower-middle-income countries (LMICs) found that children received an average of 25 antibiotic prescriptions in the first five years of life. However, care seeking behavior is often governed by structural factors and socio-ecological environments that are not adequately accounted for in the discourse around AMR. My thesis explores the social and structural forces influencing prescription and consumption behavior in LMICs like India, and critically examines behavioral, structural, and policy interventions to address antibiotic misuse in India.

Chapters 1 and 2 examine findings from a mixed-methods knowledge, attitudes, and practices study that explores provider perceptions governing antibiotic use in a district in West Bengal. Doctors scored highest in questions assessing knowledge (77.3%) and attitudes (87.3%), but performed poorly in practices (67.6%), indicating a clear gap between knowledge and practice. Many doctors knew that antibiotics were not indicated for viral infections, but over 87% (n = 82) reported prescribing them in this situation. Nurses, pharmacy shopkeepers, and informal providers were more likely to perform poorly on the survey compared to allopathic doctors (OR: 10.4, 95% CI 5.4, 20.0, $p<0.01$). The role of pharmaceutical company representatives as a source of knowledge was particularly salient as 30.8% (n = 118) of all providers reported relying on these representatives as a major source of information about antibiotics.

Key informant interviews and qualitative findings in Chapter 2 further explained individual behavioral motivations behind some of these prescription practices. Among allopathic providers, inconsistent follow up, lack of testing facilities, risk of secondary infections, and unhygienic living conditions have a major influence on the decision to antibiotics. Pharmaceutical company representatives actively network with informal health providers and formal healthcare providers alike, and regularly visit providers even in remote areas to market newer antibiotics. Allopathic doctors and informal health providers frequently blame the other party for being responsible for antibiotic resistance, and yet both display interdependence in referring patients to one another.

Chapter 3 is a systematic review of the current evidence landscape on interventions to influence antibiotic prescriptions by health professions in outpatient settings within low-and-middle-income and lower-middle-income countries. Behavioral interventions were classified as persuasive, enabling, restrictive, structural, or bundle (mix of different interventions). In total, 3,514 abstracts were screened and 42 studies were selected for full-text review, with 13 studies included in the final narrative synthesis. Our review found that enabling or educational interventions alone may not be sufficient to overcome the ingrained incentives to link revenue generation to sales of antibiotics, and hence, inappropriate prescription or misuse of antibiotics. Multi-faceted, bundle interventions, in contrast, appear to be very effective at changing prescription behavior among healthcare providers, including drug sellers or pharmacists.

Chapter 4 outlines the results of a qualitative study with 23 semi-structured, in-depth interviews with a variety of key informants with diverse backgrounds in academia, non-government organizations, policy, advocacy, pharmacy, medicine, and others. The goal was to complement the systematic review and assess the use and effectiveness of policy or behavioral interventions. Data were charted into a framework matrix and analyzed using a hybrid, inductive and deductive thematic analysis according to the socio-ecological model. As outlined in chapter 3, there was a similar recognition by key informants from all backgrounds that educational interventions targeting individual or interpersonal interactions were largely ineffective, and policy interventions needed to incorporate behavioral nudge interventions, improve the healthcare infrastructure and embrace task shifting to rectify staffing disparities in rural areas. Key informants also expressed a need to adopt a hub-and-spoke model to target informal providers via existing networks with formal providers and pharmaceutical company representatives, incorporate smart regulation for antibiotic use, and leverage pharmaceutical companies in decoupling sales and incentives.

Finally, chapter 5 takes a deeper dive into the national action plan to combat AMR in India. While the NAP-AMR successfully mirrors the Global Action Plan and lays out ambitious goals, the lack of financial allocations across states, poor enforcement, and inadequate multi-sectoral coordination have hampered progress. The central government should emulate the successes of the Kerala State Action Plan in promoting a One Health approach and effectively coordinating between public and private sector actors to implement antibiotic stewardship initiatives.

Introduction

In the early 20th century, the average life expectancy at birth was 47 years and infectious diseases were a leading cause of death worldwide [1]. The discovery of penicillin in 1928 ushered in a brand new age of novel antibiotics that changed the leading causes of death in high-income countries from communicable to mostly non-communicable diseases [1]. However, in predominantly low-income and low-and-middle-income countries (LMICs) like India, we now see a double disease burden, where neglected and communicable diseases that are easily preventable continue to exact a heavy toll and non-communicable diseases such as cancer and cardiovascular disease cause further morbidity and mortality [2].

At the same time, the World Health Organization (WHO) warns that antibiotic resistance (ABR) is accelerating and rising to unprecedented levels around the world due to overuse in humans, animals, and the environment, creating conditions where minor injuries might once again be deadly [3]. Without urgent and coordinated action, the accelerating pace of ABR combined with the stagnating pipeline for new antibiotics will pose new threats and may reverse rapid gains in life expectancy and reductions in morbidity and mortality due to infectious diseases.

Fortunately, the issue is considered a top priority for multilateral health agencies, national governments, and the private sector alike, with the WHO spearheading the development of a global action plan to combat antimicrobial resistance (AMR) [4]. Pharmaceutical companies, such as Takeda and GlaxoSmithKline, have also launched efforts to prioritize the issue [5]. 23 leading biopharmaceutical companies have come together to invest more than $1 billion in an AMR action fund to support smaller biotech companies and provide industry expertise to support the development of 2-4 novel antibiotics by 2030 [6]. However, the AMR Benchmark Report, published annually by the Access to Medicine Foundation, finds that even though there is improvement since 2018 in how pharmaceutical companies are tackling AMR, the clinical pipeline of antibiotics for priority infections remains limited and does not match the scale required to meet the global challenge of AMR [7].

While antibiotic resistance is a global problem that requires urgent coordination between national governments and multilateral agencies, the problem is of particular concern in LMICs such as India. Even though high-income countries such as the United States have far higher per capita rates of antibiotic consumption, India was the world's largest consumer of antibiotics for human health in 2010 with a total consumption of 12.9 x 10^9 units (10.7 units per person), followed by China at 10.0 x10^9 units (7.5 units per person) [8-9].

According to The State of the World's Antibiotics 2021 Report by the Center for Disease Dynamics, Economics & Policy (CDDEP), antibiotics continue to be prescribed and dispensed for viral infections, a phenomenon that was heightened during the COVID-19 pandemic, and resistance to first-line antibiotics is a common trend, due in large part to the 165% increase in use of antibiotics for human health between 2000 and 2015 [9]. As the devastating second wave of the COVID-19 pandemic that swept through India demonstrated, poor healthcare equipment and infrastructure, inadequate vaccine coverage, poor air quality, inadequate hygiene and sanitation, and other social determinants of health leave millions vulnerable to infection [10]. One study analyzing the first wave of the COVID-19 pandemic in India found that "COVID-19 likely contributed to about 216 million excess doses (95% CI: 68.0 to 364.8 million; $P = 0.008$) of total antibiotics and 38.0 million excess doses (95% CI: 26.4 to 49.2 million; $P < 0.001$) of azithromycin between June and September 2020" [11].

Antibiotic overuse in India certainly worsened during the COVID-19 pandemic, but it is part and parcel of everyday life, with antibiotics easily available and dispensed over-the-counter, despite seemingly stringent regulations on paper, and routine prescriptions in primary healthcare [12]. Antibiotic overuse in this context is often deemed as 'irrational,' given the fact that antibiotics are not appropriate or useful for viral infections. However, the use of terms like 'irrational' often fail to acknowledge and address vital social determinants and drivers of antibiotic misuse, which often occur in the context of failing health systems, major disparities in access, and socio-economic factors that require quick periods of recovery to prevent a loss in income and family well-being [13].

Access to healthcare varies widely between states and territories within India. At the federal level, regulatory and policy decisions are made by the Ministry of Health and Family Welfare, but the roles and responsibilities of healthcare provision and delivery are managed at the state level [14]. The health system is largely decentralized and pluralistic, with a motley mix of public and private providers. The government system provides free access to healthcare, which is organized by sub-centers in very rural areas (1 per 3000-5000 population), primary health centers (1 per 20,000-30,000 population), community health centers (1 per 80,000-120,000), and finally district hospitals or larger medical colleges [15]. Government institutions are staffed by a variety of practitioners, including but not limited to allopathic medical doctors, nurses, pharmacists, and traditional practitioners of Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa and Homoeopathy (collectively known as AYUSH practitioners) [14-15]. However, the vast majority of patients pay out-of-pocket to access private hospitals and private practitioners, who can range from allopathic medical doctors to informal or traditional practitioners without any biomedical training.

Antibiotic use in India is far more complicated than high-income settings, given the interplay between private and government institutions, pharmacy shops, and a wide array of practitioners with and without formal medical training. This dissertation takes a systems level perspective to critically examine antibiotic use and misuse at each level of the healthcare system.

Chapter 1 explores the knowledge, attitudes, and practices (KAP) related to antibiotic use among allopathic medical practitioners, informal providers, nurses, and pharmacy shopkeepers in the Indian State of West Bengal. Chapter 2 complements this perspective with an in-depth qualitative study examining the drivers and incentives behind this prescription behavior with the same groups of providers. In addition, this study incorporates a patient perspective as well through semi-structured in-depth interviews with patients accessing care at primary health centers and hospitals across Paschim Bardhaman district in West Bengal. Chapter 3 moves beyond drivers and analyzes behavioral interventions to address antibiotic misuse in LMICs by conducting a systematic review of the literature. The chapter looks at various restriction, enabling, behavioral and structural interventions and presents a narrative synthesis of the efficacy, feasibility, and impact of these interventions.

Despite conducting an exhaustive review of the literature from LMICs, there were few studies looking specifically at interventions targeting informal providers, AYUSH practitioners, and primary healthcare, since the vast majority focused on antibiotic stewardship interventions in inpatient settings. In order to meet this gap in the literature, Chapter 4 presents the results of a qualitative study with various key informants who work with these populations, including but not limited to representatives from non-government institutions, policy stakeholders, academics, medical doctors, among others. Finally, Chapter 5 takes a deep dive into AMR policy in India and adopts a critical perspective on the strengths and implementation gaps in the national action plan on AMR in India.

The five chapters, in concert with one another, present a holistic picture of the behavioral and socio-ecological drivers of antibiotic misuse in India, critically examine a variety of interventions to address misuse, and make a case for reframing antibiotic misuse as a health systems and socio-ecological issue rather than an individual or behavioral issue related to "irrational" prescriptions or use.

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Chapter 1:

Knowledge, perceptions and practices related to antibiotic use: a mixed methods case study from West Bengal, India.

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Abstract

Introduction

Antibiotic misuse is widespread and contributes to antibiotic resistance, especially in less regulated health systems such as India. Although informal providers are involved with substantial segments of primary healthcare, their level of knowledge, attitudes, and practices is not well documented in the literature.

Objectives

This quantitative study systematically examines the knowledge, attitudes, and practices of informal and formal providers with respect to antibiotic use.

Methods

We surveyed a convenience sample of 384 participants (96 allopathic doctors, 96 nurses, 96 informal providers, and 96 pharmacy shopkeepers) over a period of 8 weeks from December to February using a validated questionnaire developed in Italy. Our team created an equivalent, composite KAP score for each respondent in the survey, which was subsequently compared between providers. We then performed a multivariate logistic regression analysis to estimate the odds of having a low composite score (<80) based on occupation by comparing allopathic

doctors (referent category) with all other study participants. The model was adjusted for age (included as a continuous variable) and gender.

Results

Doctors scored highest in questions assessing knowledge (77.3%) and attitudes (87.3%), but performed poorly in practices (67.6%). Many doctors knew that antibiotics were not indicated for viral infections, but over 87% (n = 82) reported prescribing them in this situation. Nurses, pharmacy shopkeepers, and informal providers were more likely to perform poorly on the survey compared to allopathic doctors (OR: 10.4, 95% CI 5.4, 20.0, p<0.01). 30.8% (n = 118) of all providers relied on pharmaceutical company representatives as a major source of information about antibiotics.

Conclusions

Our findings indicate poor knowledge and awareness of antibiotic use and functions among informal health providers, and dissonance between knowledge and practices among allopathic doctors. The nexus between allopathic doctors, pharmaceutical company representatives, and informal health providers present promising avenues for future research and intervention.

Introduction

Antibiotics have been a crucial development in the evolution of medical treatment, effectively reducing the morbidity and mortality from bacterial diseases that were previously left untreated [1]. However, irrational use of antibiotics (including veterinary antimicrobial misuse/overuse, environmental contamination, nosocomial transmission, suboptimal point of care diagnostics, and suboptimal dosing) has contributed to the emergence and selection of resistant bacteria [2]. Consequently, World Health Organization (WHO) has warned that the world is entering a "post antibiotic" era where even minor infection and injury, previously manageable with antimicrobials, will cost lives [3].

It is well known that knowledge of antibiotics is quite poor among patients and the general public in multiple countries [4–10]. Among healthcare providers, antibiotics are routinely prescribed for acute upper respiratory tract infections [11–13], despite clinical evidence to the contrary. The misuse of antibiotics is particularly striking in India, which is ranked as one of the world's largest consumers of antibiotics for human health [14]. Most private pharmacies in India are operated by unqualified persons rather than trained and licensed pharmacists, which exacerbates the practice of disbursing medicines normally not available over-the-counter without a prescription from an appropriate medical practitioner. The Drugs & Cosmetics Act and Rules provide regulatory enforcement to the sale of antimicrobials in India, as well as a mandate to identify unlicensed pharmacies, and unqualified medical practitioners and prescribers [15]. The rules state that only qualified medical practitioners can prescribe medicine, but this is often not the case as many informal health providers (IHPs), who do not hold formal medical degrees and are untrained in allopathic medicine, disburse antibiotics as part of their regular practice [16].

However, there is limited evidence regarding the perceptions and drivers of antibiotic misuse in the Indian setting [17–21], and there are no published studies focusing on the Knowledge, Attitudes and Practices (KAP) of antibiotic use from West Bengal. We were unable to find any recent studies that comprehensively assess the KAP of formal and informal providers alike in relation to antibiotic use in India. Understanding local knowledge, attitudes and practices regarding antibiotics will be the first step in constructing a template for effective antibiotic stewardship and effective infection control measures. Such a template is essential in planning future interventions for antibiotic resistance throughout India.

This study addresses these gaps in the literature by systematically examining the prescribing patterns of informal and formal providers, and assessing how informal providers differ from allopathic doctors in knowledge, attitudes and practices in Paschim Bardhaman district, located in the state of West Bengal, India.

Materials and methods

A self-administered 38-question KAP survey tool was provided to allopathic doctors, informal healthcare providers, nurses, and pharmacy shopkeepers, in order to establish the knowledge,

attitudes, and practices related to antibiotic use in Paschim Bardhaman district of West Bengal. Appropriate antibiotic use was defined as the right antibiotic at the right time, in the right dose, and for the right duration [22]. The questionnaire was adapted from a validated, self-administered, cross-sectional questionnaire used in Italy, and revised based on a literature review. The final questionnaire was pre-tested prior to data collection, and covered a broad range of domains assessing the KAP of participants, including but not limited to common uses of antibiotics and prescription practices, among other factors. Face validity was established using a panel of experts who thoroughly reviewed the questionnaire and concluded that it measures the traits of interest. Additionally, we field-tested the questionnaire to understand how well the instrument is able to collect the intended information. We also conducted a Cronbach's alpha test to assess internal reliability: the alpha score of 0.75 indicated moderate reliability of the questionnaire.

Recruitment and sampling

The study team adopted a convenience sampling methodology to recruit participants for the KAP survey due to resource limitations. Based on a study describing antibiotic prescription practices for acute, uncomplicated respiratory tract infections [23], we assumed a prevalence of irrational antibiotic usage (overuse and inappropriate choice of antibiotics for treatment of viral infections) among health care personnel of 50% with alpha = 5%, design effect of 1%, and 5% acceptable margin of error. The minimum sample size was calculated at 384. The sampling frame was subsequently stratified among the four groups of healthcare providers: 96 allopathic doctors, 96 informal healthcare providers, 96 nurses, and 96 pharmacy shopkeepers. It must be noted that while the intent was to assess the KAP of pharmacists, we could not ascertain whether participants were licensed pharmacists, as many shops dispensing antibiotics were not licensed pharmacies. We have included all participants who were interviewed at pharmacies as "pharmacy shopkeepers" in the study. With this sample size, the power of the study to detect a 20% difference in composite scores between allopathic doctors, informal healthcare providers, nurses, and pharmacy shopkeepers was 82% based on a normal approximation with continuity correction. 60% of doctors had a low composite KAP score (<80) in comparison to 80% of all

participants in the other occupation groups. We considered a two-sided confidence interval of 95%, with a sample size of 96 in each occupational group.

The primary health system in India is organized into primary, secondary, and tertiary levels, with subcentres (SCs) and primary health centres (PHCs) constituting the first point of entry, community health centres and smaller sub-district hospitals constituting secondary care, and medical colleges and district hospitals constituting tertiary care within the government system. The study team systematically started at the primary health centre and subcentre levels to target informal healthcare providers and allopathic practitioners working at the grassroots level, and worked their way upwards to block primary health centres (BPHCs) and Asansol District Hospital (ADH), the main secondary care referral centre in the district. In total, all 8 administrative blocks of Paschim Bardhaman district were covered. BPHCs and associated PHCs were sampled from Khandra, Kelejora, Laudoha, Akalpur, Bahadurpur, Panagarh, Raniganj and Pithaikeary.

Data collection and analysis

Data collection took place over a period of approximately 8 weeks from December to February following an initial one month period of planning and field mapping. We continuously approached participants to attain our target sample size of 384 respondents. In total, we approached 494 people to participate in the survey, and 110 declined to participate, yielding a response rate of 77.7%. The most commonly cited reason for declining was a lack of interest in the study. All study participants were assured of confidentiality and informed that the data would be de-identified at entry. Participants were only identified by an ID number in the database and participant names only appeared in the consent forms. Survey responses for all 384 participants were collated in Excel and data was analyzed in SPSS. Each Likert scale question received a maximum of 5 points for the most accurate answer, and 1 point for the least accurate answer. As such, there was a maximum possible score of 32, 45, and 20 in the knowledge, attitudes, and practice sections respectively, and a maximum total composite score of 97. Our team created an equivalent, composite KAP score for each respondent in the survey, which was subsequently compared between providers. We then performed a multivariate logistic regression analysis to

estimate the odds of having a low composite score (<80) associated with occupation (comparing the referent category of allopathic doctors with all other study respondents), adjusted for age (included as a continuous variable) and gender (male or female). While gender was significantly associated with low score in the univariable analysis, age showed no significant relationship. However, we still chose to include age in the final model. The level of significance was set at a p-value<0.05, and a 95% confidence interval was calculated for all odds ratio calculations. Apart from checking the level of skewedness and kurtosis, the normality of variables was also assessed using a test of normality (Shapiro-Wilk test) in SPSS.

Results

Demographic characteristics

Over 90% of the participants were between 26 and 60 years of age (Table 1). Amongst pharmacy shopkeepers, 9.4% (n = 9) were between the ages of 18–25 years; our field observations suggested that several of these workers were not actually licensed pharmacists, but rather apprentices or relatives of small business owners. They were not asked to provide documentary evidence of their qualifications. The mean age of all participants in the study was observed at 41.7 years (± 10.9 years). Of the 19 variables related to KAP questions, only 4 had 100% complete data. The remaining 15 variables had a median (IQR) of 3 (2–6) records missing in the database out of 384 records for each variable.

	Allopathic* (N = 96) N (%)	Informal providers* (N = 96) N (%)	Nurses* (N = 96) N (%)	Pharmacy shopkeepers* (N = 96) N (%)	Total (N = 384) N (%)
Age group (years)					
18–25	0 (0)	1 (1.0)	3 (3.1)	9 (9.4)	13 (3.4)
26–35	36 (37.5)	14 (14.6)	32 (33.3)	23 (24.0)	105 (27.3)
36–45	19 (19.8)	41 (42.7)	38 (39.6)	37 (38.5)	135 (35.2)
45–60	35 (36.5)	33 (34.4)	23 (24.0)	20 (20.8)	111 (28.9)
>60	6 (6.2)	7 (7.3)	0 (0)	7 (7.3)	20 (5.2)
Mean + SD age (years)					
	42.5 ± 11.5	44.2 ± 10.1	39.9 ± 10.2	40.2 ± 11.2	41.7± 10.9
Gender					
Male	76 (79.2)	95 (99)	0 (0)	93 (96.9)	264 (68.8)
Female	20 (20.8)	1 (1)	96 (100)	3 (3.1)	120 (31.3)
Work setting					
PHC	31 (32.3)	0 (0)	61 (63.5)	11 (11.5)	103 (26.8)
District hospital	61 (63.5)	2 (2.1)	35 (36.5)	0 (0)	98 (25.5)
Private hospital	0 (0)	1 (1.0)	0 (0)	0 (0)	1 (0.3)
Private clinic	3 (3.1)	90 (93.8)	0 (0)	2 (2.1)	95 (24.7)
Pharmacy	0 (0)	3 (3.1)	0 (0)	81 (84.4)	84 (21.9)
Others	1 (1.0)	0 (0)	0 (0)	2 (2.1)	3 (0.8)
Work experience (months)					
1–11	13 (13.5)	0 (0)	3 (3.1)	4 (4.2)	20 (5.2)
12–60	29 (30.2)	12 (12.5)	29 (30.2)	21 (21.9)	91 (23.7)
61–120	17 (17.7)	9 (9.4)	23 (24.0)	17 (17.7)	66 (17.2)
>120	37 (38.5)	75 (78.1)	41 (42.7)	54 (56.3)	207 (53.9)

*All four prescriber groups had statistically significant differences for each demographic characteristic (chi square: p-value < 0.001)

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Table 1. Demographic characteristics of health provider sub-groups.

Overall, the vast majority of participants (68.8%) were male: the proportions of informal health providers and pharmacy shopkeepers were heavily skewed towards men, whereas nurses were entirely female. While doctors and nurses were overwhelmingly drawn from the government setup (either Asansol District Hospital or PHCs), almost all of the informal health providers (93.8%) were interviewed at their private clinic and 84.4% of pharmacy shopkeepers were interviewed at their pharmacy shop. Furthermore, just over half of participants (53.9%) had over 10 years of work experience, a finding that was particularly notable among informal health providers (78.1%) who claimed to rely heavily on experience for decision making in their professional work.

Dissonance between knowledge and practice

The 38-point survey questionnaire provided a holistic overview of the knowledge, attitudes, and

practices related to antibiotic use. The most pronounced finding was the dissonance between knowledge and practices, wherein participants could correctly identify appropriate uses of antibiotics, and yet fail to apply these findings in practice.

As a starting point, all doctors claimed to prescribe antibiotics in their practice. Several patients were given at least one antibiotic for a multitude of reasons: some claimed it was due to patient demands, while others claimed to use antibiotics as a precautionary measure to prevent against secondary infections. Nearly all (95.7%) informal health providers and half of pharmacy shopkeepers who were interviewed reported prescribing antibiotics at their workplace.

Similarly, when asked how frequently health providers prescribe or provide an antibiotic for symptoms of common cold or sore throat (Fig 1), over 88% of allopathic doctors and 85% of informal health providers responded by saying they did this for at least some of their patients. We considered "none of my patients" as the only acceptable and appropriate response for all providers. Clinical guidelines indicate that antibiotics are ineffective for symptoms of the common cold; as a result, any antibiotic prescriptions for these symptoms would be considered inappropriate [24].

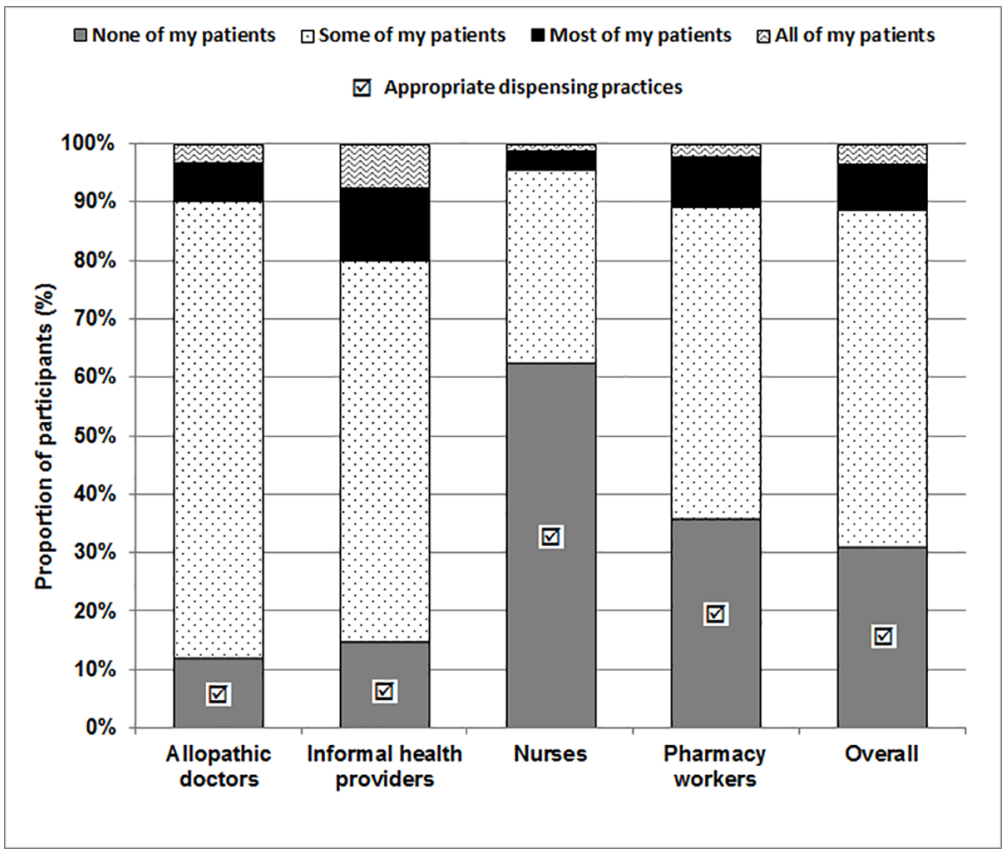

Figure 1. Proportion of healthcare providers dispensing antibiotics for a cold or sore throat.

Furthermore, 7.4% of informal health providers claimed they prescribed or provided an antibiotic to all of their patients for symptoms of a common cold or sore throat.

Attitudes are very similar across respondent groups

Interestingly, 95.9% of informal health providers, 98.9% of nursing staff, and 94.8% of pharmacy shopkeepers claimed that knowledge of antibiotics was important to them in their role as a health provider, even though none of these groups are legally permitted to prescribe antibiotics independently. Where knowledge of antibiotics was highly valued, participants stated that their most utilized sources of information were medical textbooks, pharmaceutical company representatives (PCRs), and allopathic doctors (in the case of informal health providers).

Knowledge differences between provider groups

All four groups of participants were asked whether antibiotics were useful for viral infections and whether antibiotics were indicated to reduce the symptoms of pain and inflammation as part of the knowledge assessment. As Fig 2 below indicates, the levels of knowledge of allopathic doctors contrasted strongly with the other three groups as expected. 76.1% of allopathic doctors either strongly disagreed or disagreed with the statement that antibiotics were useful for viral infections, and these were combined as "no" responses in Fig 2. Neutral answers were included as "yes" responses, as a neutral response to such a question does not concur with current medical guidelines [24]. A few senior doctors who responded incorrectly later qualified their answers by suggesting that a lack of follow-up opportunities and the likelihood of developing a secondary infection occasionally required the use of antibiotics even during viral infections. Similar sentiments were expressed by allopathic doctors when they were asked whether antibiotics were indicated to alleviate the symptoms of pain and inflammation: a few doctors explicitly stated that inflammation can be caused by a bacterial infection, which would necessitate the use of antibiotics even in the absence of confirmation from laboratory testing.

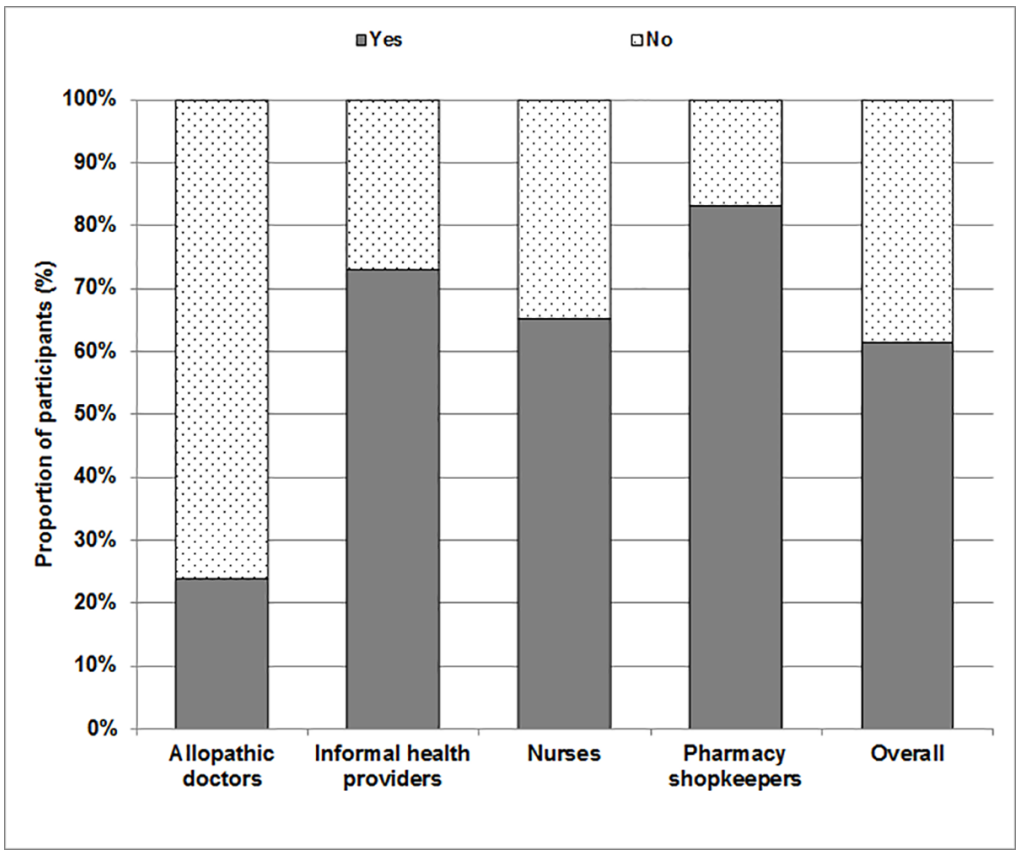

Figure 2. Proportion of healthcare providers expressing agreement with the statement that antibiotics are useful for viral infections.

Knowledge of contraindications of antibiotics during pregnancy

Most allopathic doctors confidently completed the survey questionnaire without much hesitation. However, the most challenging question for allopathic doctors inquired which antibiotic was contraindicated in pregnancy, with three possible single-select options: Amoxicillin, Ciprofloxacin, and Gentamicin. The U.S. Food & Drug Administration classifies Gentamicin as a Category D drug, indicating that there is positive evidence of fetal risk in humans [25]. By contrast, Ciprofloxacin is classified as a Category C drug, which indicates that there are no adequate and controlled studies in humans despite animal reproduction studies indicating adverse effects. The correct answer (Gentamicin) was selected by a mere 43.8% of doctors, while another 43.8% of doctors incorrectly identified Ciprofloxacin. Only 17.7% of pharmacy shopkeepers correctly identified Gentamicin, while 54.2% claimed they did not know. Informal health

providers and nurses similarly had little idea about Gentamicin and its links to potential birth defects, even though we frequently observed IHPs providing Gentamicin during field observations.

Awareness regarding the importance of a full course of antibiotics

One of the more interesting questions in our study was an assessment of the respondent's awareness around the full course of antibiotics. As Fig 3 below demonstrates, an overwhelming proportion of all respondents either strongly disagreed or disagreed with the practice of stopping a full course before it was complete. However, this also reflected a sharp dissonance between knowledge and practice, as we found that all four groups of respondents frequently disbursed shorter, 3-day courses of antibiotics rather than a full course.

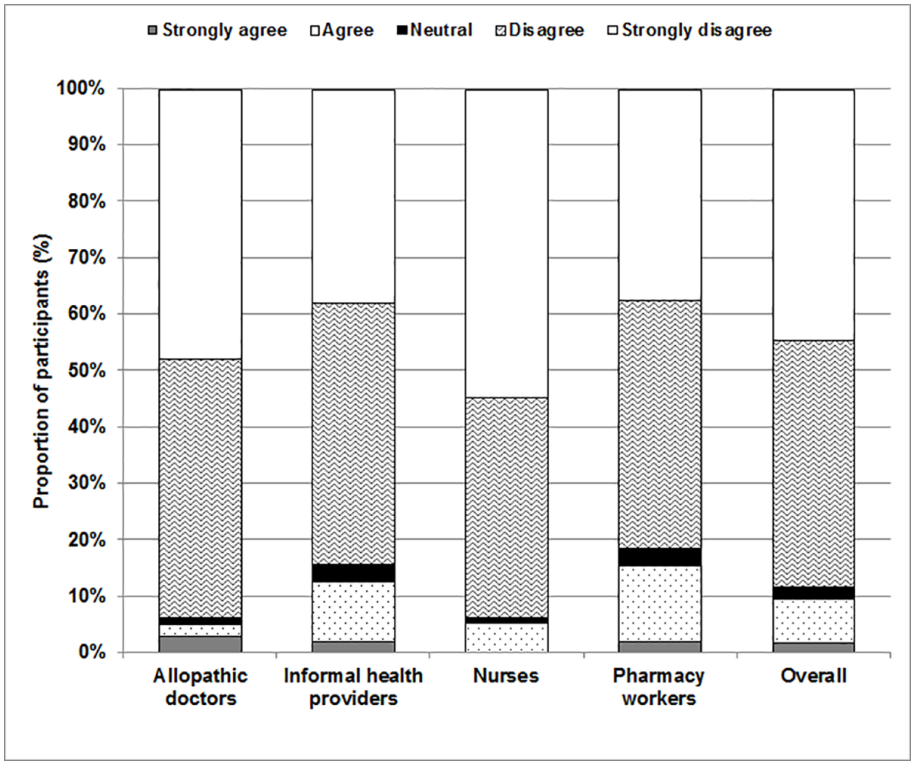

Figure 3. Proportion of healthcare providers who find it appropriate to stop taking antibiotics prior to the completion of the full course.

Composite KAP scores

Our team conducted a more detailed analysis of the knowledge, attitudes, and practices by creating a composite KAP score for each respondent in the survey, which has been presented as average percentage scores for ease of comparison below in Table 2.

Occupation	Knowledge Mean % (SD)	Attitudes Mean % (SD)	Practice Mean % (SD)	Composite KAP score Mean % (SD)
Allopathic doctor	77.3 (12.7)	87.3 (7.7)	67.6 (11.1)	79.9 (6.9)*
Informal health providers	56.9 (11.5)	80.0 (9.6)	71.2 (11.6)	70.6 (7.8)*
Nurses	63.4 (11.2)	79.9 (9.2)	75.5 (12.6)	73.5 (7.2)*
Pharmacy shopkeepers	57.8 (9.7)	79.3 (9.6)	72.1 (12.8)	70.7 (7.0)*

*Statistically significant difference in composite scores between occupational groups ($p<0.001$)

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Table 2. Average percent scores for knowledge, attitudes, and practices by occupation.

One-way ANOVA testing determined that there was a statistically significant difference in average scores of knowledge, attitude and practice questions between the four occupational groups. As evidenced in Table 2, allopathic doctors scored highest in questions assessing knowledge (77.3%) and attitudes (87.3%), and yet, this knowledge did not translate into practice. Allopathic doctors performed most poorly (67.6%) when asked about their practices with respect to antibiotic use and prescriptions.

We also conducted a multivariate logistic regression analysis, adjusting for age and gender, and found that the odds of having a low composite score in non-allopathic practitioners was 10.4 (95% CI 5.4, 20.0) times greater than allopathic doctors ($p<0.001$). Thus, our study found that non-allopathic practitioners were significantly more likely to perform poorly on the survey.

Discussion

Our study represents one of the few attempts in the literature to assess the knowledge, attitudes, and practices of all providers interacting with antibiotics in the Indian context, including allopathic doctors, nurses, pharmacy shopkeepers, and informal health providers. While doctors

outperformed other formal and informal healthcare providers in the knowledge and attitudes components of the survey, their comparatively poor performance in the practice section of the survey is concerning. This may be due to the fact that many doctors across India prescribe antibiotics in PHC settings as a precautionary measure to compensate for diagnostic uncertainty due to lack of availability of point-of-care diagnostic tests, poor infection control, and inadequate sanitation practices [26]. Additionally, informal practitioners, nurses, and pharmacy shopkeepers are not legally entitled to prescribe antibiotics, which may have prompted them to answer less candidly on practice-related questions in comparison to doctors.

Other studies [11–13, 18–20] have focused predominantly on the KAP of medical students or clinicians in tertiary care hospitals, which address a limited part of the antibiotic dispensing pathway and leave out the crucial role played by informal providers. These studies generally report poor practices even among medical students and allopathic practitioners: for instance, Khan et al. found that only 77.3% (n = 75) of respondents were aware that bacteria were not responsible for causing colds and flu [20]. Another study by Gautham et al. compares the knowledge, practices and relationships of informal providers in two districts in Northern and Southern India [27], and finds their role has evolved differently in the two disparate market settings. The study documents not just wide variations in knowledge, but also interesting and mutually beneficial referral links with private doctors.

While the presence of informal providers is particularly salient in India, such providers can be found in every health system, according to the WHO [28]. A systematic review conducted by Sudhinaraset et al. finds that people across developing countries use informal providers due to convenience, affordability, and social and cultural preferences; many providers across countries such as Vietnam and Bangladesh reported poor adherence to national guidelines with respect to antibiotic use [29]. In developed economies such as the United States, antibiotics are only prescribed by graduate physicians, but similar problems persist with respect to inappropriate overuse of antibiotics: recent studies estimated that at least 30% of all antibiotic prescriptions in outpatient settings in the United States are considered inappropriate, and 50% of all antibiotic prescriptions for respiratory tract infections are inappropriate [30–31]. The authors found that inappropriate prescription practices were linked to a multitude of factors, including clinical factors, demographic characteristics of patients, severity of illness, previous infection history,

compromised immune response, geographic region, among others [30]. Multi-center studies conducted across the United States, Scotland, Switzerland, Sweden, Slovenia, Spain, France, and England examined knowledge, attitudes, and practices related to antibiotic use among medical students and found that the vast majority wished to acquire more knowledge about choosing appropriate antibiotic treatment [32–34]. Moreover, many relied on Wikipedia more than formal peer-reviewed sources or textbooks for guidance on antimicrobial use [33].

In our context, many providers relied on pharmaceutical company representatives as a source of information regarding new antibiotics and associated uses. This may stem from an inadequate focus on antibiotics and drivers of antibiotic resistance in the medical curriculum. Our findings further indicate that there is poor knowledge and awareness of antibiotic uses and functions among informal providers and a strong dissonance between knowledge and practices among formal healthcare providers. This is supported by other studies as well: Das et al. have demonstrated significant quality gaps between private and public providers of primary health care in other Indian states, noting incorrect medical diagnoses, incorrect treatments, and inconsistent adherence to clinical checklists [35]. Similarly, Scaioli et al used the original questionnaire adapted in our study on a convenience sample of students from medical, dental, nursing, and other health professions in Italy and found that health professionals do not practice what they know: in other words, high levels of knowledge do not translate into appropriate attitudes and practices with respect to antibiotic use [36]. We found that allopathic doctors treated common illnesses such as cold, cough, fever, and watery loose stools with antibiotics without clinical indication, largely due to risk aversion in the context of diagnostic uncertainty and lack of robust follow-up.

As for informal providers, Bloom et al. note in their study on informal providers in health markets in Nigeria and Bangladesh that the behavior of informal providers is governed predominantly by the institutional context in which they operate and the emergence of such informal markets represents broader failures in the public health delivery system to meet the needs of the impoverished [37]. This may explain the high rates of antibiotic use among informal providers in our context, since many areas of the district are inadequately covered by existing public facilities. Previous studies have advocated for re-training and “formalizing” the informal health providers by empowering them to practice allopathic medicine as “social physicians,”

given concerns around equity and access to care for rural populations [38, 39]. However, the evidence on training programs is uncertain: Das et al. recently examined the impact of training informal healthcare providers in West Bengal and found that while the training increased correct case management rates, it did not reduce unnecessary antibiotic use [40]. Rather than focusing solely on training, future efforts must work to strengthen the existing public health infrastructure.

The Government of India has also embraced this idea and announced a Bridge Program in Community Health for Nurses and Ayurveda practitioners under the flagship National Health Mission in order to enhance the capacity of mid-level care providers [41]. Initiatives like this can be scaled up to improve the capacity of the existing public health infrastructure to meet patient demands. We argue that these kinds of initiatives provide a unique opportunity to enhance awareness around antibiotic resistance while ensuring equitable access to antibiotics when required. Balancing the demands between access and overuse of antibiotics is the big challenge for policy makers at present.

In order to better tackle the growing threat of resistance, India also adopted the National Action Plan on Antimicrobial Resistance (2017–21) in April [42]. The objectives include reducing infections, enhancing awareness, strengthening surveillance, improving rational use, promoting research and supporting neighboring countries in the collective fight against infectious diseases. However, the National Plan does not account for the role of PCRs and informal providers with respect to antibiotic use. Trainings should be initiated for PCRs who have been largely ignored in the scientific literature around antibiotic resistance. In Paschim Bardhaman district, the vast majority of participants surveyed indicated that they relied on pharmaceutical company representatives as a source of medical knowledge.

Future efforts to curb antibiotic resistance should involve advocacy with pharmaceutical firms in order to tap into the strong, pre-existing networks of PCRs and reorient their efforts to promote a more responsible message around antibiotics; regulation may also be useful in addressing the issue. These efforts to involve PCRs and informal health providers can form a critical community-level component of antibiotic stewardship programs moving forward, in addition to emphasizing antibiotic resistance in the curriculum for continued medical education, increasing access to cost-effect point-of-care diagnostics to aid doctors in decision making, increasing the

use of prescription audits in primary care settings, and enforcing the legal framework around over-the-counter use of antibiotics. Current initiatives to tackle ABR in Asia aim to set up surveillance systems, regulate the sale of antibiotics, and introduce national guidelines for antibiotic use, but fail to take into account patient perceptions and expectations from health providers as a major driver for ABR. Any effort to tackle antibiotic resistance must also include patient education and counseling, as patient demands are a major driver for overuse of antibiotics among formal and informal health providers alike. Several recent studies demonstrate that the Internet and social media, in particular, can be an effective resource for disseminating high quality health information to improve antibiotic stewardship in the community [43–44]. Future interventions must consider social media within their communication strategy to promote appropriate use for antibiotic-related information seeking in the general population.

Limitations

This study had several limitations due to resource constraints. Firstly, given the use of convenience sampling in the survey design, our findings must be interpreted with caution when generalized to Paschim Bardhaman district despite the sample size of 384 participants. The use of convenience sampling limits the generalizability of the results at the study population level and may introduce the potential for selection bias in the study. Secondly, the overall population being studied may not be representative: for instance, we were not able to ascertain whether pharmacy shopkeepers were licensed or operating informally; thus, the "pharmacy shopkeepers" sample may not be representative of the overall population of pharmacists in the region. Finally, self-reported data always comes with limitations. We were unable to cross-check survey responses with actual prescription practices, and social desirability bias may have played a role in undermining the credibility of our results. This may explain why doctors performed more poorly than informal providers in the "practices" section of the validated questionnaire. Given the vastly limited literature from this region of India, we believe the study adds value in understanding the scope of the problem, but we recommend that future studies should be undertaken with a robust study design in mind.

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Chapter 2

"Without antibiotics, I cannot treat": A qualitative study of antibiotic use in Paschim Bardhaman district of West Bengal, India

This paper has been peer reviewed and published in PLoS ONE.

Abstract

Background

Misuse of antibiotics is a well-known driver of antibiotic resistance. Given the decentralized model of the Indian health system and the shortage of allopathic doctors in rural areas, a wide variety of healthcare providers cater to the needs of patients in urban and rural settings. This qualitative study explores the drivers of antibiotic use among formal and informal healthcare providers as well as patients accessing care at primary health centers across Paschim Bardhaman district in West Bengal.

Materials and methods

We conducted 28 semi-structured, in-depth interviews with four groups of healthcare providers (allopathic doctors, informal health providers, nurses, and pharmacy shopkeepers) as well as patients accessing care at primary health centers and hospitals across Paschim Bardhaman district. Qualitative data was analyzed using the framework method in an inductive and deductive manner.

Results

Our results indicate that patients demand antibiotics from healthcare providers and seek the fastest cure possible, which influences the prescription choices of healthcare providers, particularly informal health providers. Many allopathic doctors provide antibiotics without any clinical indication due to inconsistent follow up, lack of testing facilities, risk of secondary infections, and unhygienic living conditions. Pharmaceutical company representatives actively

network with informal health providers and formal healthcare providers alike, and regularly visit providers even in remote areas to market newer antibiotics. Allopathic doctors and informal health providers frequently blame the other party for being responsible for antibiotic resistance, and yet both display interdependence in referring patients to one another.

Conclusions

A holistic approach to curbing antibiotic resistance in West Bengal and other parts of India should focus on strengthening the capacity of the existing public health system to deliver on its promises, improving patient education and counseling, and including informal providers and pharmaceutical company representatives in community-level antibiotic stewardship efforts.

Introduction

Global antibiotic consumption, expressed in defined daily doses (DDDs), increased by 65% from 21.1 billion DDDs to 34.8 billion DDDs between 2000 and 2015, largely driven by rising consumption in low- and middle-income countries, according to a recent study published in Proceedings of the National Academy of Sciences [1]. The World Health Organization (WHO) also issued a warning that the world is entering a "post antibiotic" era where minor infections or injuries, previously manageable with antibiotics, will cost lives [2].

In response to the growing threat of resistance, India adopted the National Action Plan on Antimicrobial Resistance (2017–21) in April 2017, following the WHO's leadership toward a global action plan on antimicrobial resistance [3]. While the National Action Plan seeks to reduce infections, strengthen surveillance, promote research, and improve rational use of antibiotics, the mechanisms outlined in the plan are yet to be fully implemented, as healthcare systems and budgets vary significantly across states in India. In October 2018, Kerala became the first state to launch a sub-national action plan to contain antibiotic resistance [4].

The Drugs & Cosmetics Act and Rules regulate over-the-counter (OTC) use of antibiotics in India and provide a mandate to identify unlicensed pharmacies, and unqualified medical practitioners [5]. Despite these provisions however, informal health providers (IHPs) who lack formal medical degrees and training in allopathic medicine can be commonly found in rural areas

where coverage of primary health centers (PHCs) is more limited. While urban areas have multiple private and public hospitals, rural areas lack access to quality health care. The formal medical system is comprised of a network of sub-centers and PHCs, as well as district and tertiary care hospitals. These hospitals are staffed by formally trained nurses, doctors, and pharmacists. However, in more rural areas where the coverage of PHCs is sub-optimal, unqualified IHPs function as the first point of contact for patients in the community. These providers often lack formal schooling and operate their own clinics after observing medical doctors in practice.

The evidence regarding knowledge, attitudes, and practices (KAP) related to antibiotic use in the Indian setting is limited [6–9], with no published studies from West Bengal. A few studies have attempted to establish the level of knowledge of patients and medical students or healthcare providers, but they do not adequately address the role of IHPs with respect to antibiotic use [10–16]. The WHO recognizes that the "systematic neglect of cultural factors is one of the biggest obstacles to achieving better health outcomes and better standards of living worldwide" [17]. The contextual approach used in this study across multiple users in order to understand prescription and usage choices is one of the added values of this study.

This study took place in Paschim Bardhaman district of West Bengal, which consists of an urban city centre and eight administrative blocks. The Asansol Municipal Corporation manages urban primary healthcare in the city centre. Healthcare in the rest of the subdivision is managed by West Bengal's Ministry of Health via village sub-centres, PHCs, and block primary health centres (BPHCs). Asansol District Hospital (ADH) is the secondary care referral centre. The total number of registered pharmacies is estimated to be above 300, with a significant number of unregistered pharmacies also present.

The main thematic objectives of the study were:

1. To understand perceptions and vocabularies of illness among patients seeking care
2. To uncover patient expectations from healthcare providers while seeking care
3. To understand knowledge of appropriate antibiotics and perceptions of antibiotic use among formal and informal healthcare providers, and

4. To understand the drivers for various antibiotic prescription choices.

Materials and methods

This qualitative study was designed as a follow-up to a KAP survey conducted by our team in the same district. The self-administered survey was adapted from a validated tool used in Italy and contained 38 questions. 384 healthcare providers completed the survey, including 96 nurses, 96 medical doctors, 96 pharmacy shopkeepers, and 96 IHPs, who were recruited through convenience sampling. The findings from the survey are published separately in PLOS ONE [18]. We found that doctors had superior knowledge of antibiotic uses and functions in comparison to other groups, but this knowledge did not translate into practice as many prescribed or provided antibiotics for illnesses such as the common cold (which does not require a course of antibiotics). Furthermore, IHPs routinely provided antibiotics to patients who visited their private clinics, despite the fact that only licensed medical doctors are allowed to prescribe antibiotics under Indian law. This qualitative study uncovered some of the drivers for these prescription choices and explored the discrepancies between knowledge and practices among formal and informal health providers through semi-structured, in-depth interviews. Our team purposively sampled providers who participated in the survey until we reached saturation. In addition, we also conducted semi-structured, in-depth interviews with patients seeking care in the outpatient departments (OPD) of PHCs and hospitals in order to understand patient vocabularies of illness and expectations from healthcare providers.

The interview guide was developed based on a literature review and analysis of existing studies from India, as well as consultations with medical doctors and nurses to understand the gaps in the medical literature around this issue. It was pilot tested with 4 medical doctors, 2 nurses, 2 patients, and 2 pharmacy shopkeepers prior to data collection, and revised iteratively as needed. We also consulted senior doctors who had worked on the issue of antibiotic resistance to see if any questions needed to be revised or added. Unlike the quantitative survey, this process was more informal for the qualitative study since the interview guide was designed as a flexible, semi-structured document which could be revised iteratively with each interview as needed.

In total, we purposively sampled 21 providers (6 allopathic doctors, 5 pharmacy shopkeepers, 5 IHPs, and 5 nurses) to take part in in-depth interviews after completing the survey. We were

unable to ascertain whether participants were licensed pharmacists, as many shops which dispensed antibiotics were not licensed pharmacies. For the purposes of our study, we were interested in understanding the KAP of individuals who dispensed medications to patients, which is why we have included all these providers together as pharmacy shopkeepers. In addition to healthcare providers, 7 patients were purposively sampled for inclusion in the study based on the following characteristics:

1. >18 years of age
2. Geographical location to garner broad representation
    1. Targeting areas from the OPD of ADH
    2. Targeting areas from PHCs and subcenters in excess of 5 km from the district hospital

In total, we approached 39 participants for in-depth interviews, and 11 participants declined to participate due to lack of time. Ethics approval was obtained from the Medecins Sans Frontieres Ethics Review Board as well as the Clinical Research Ethics Committee of Calcutta School of Tropical Medicine.

Data collection and analysis

Participants were approached for in-depth interviews until saturation was attained. In-depth interviews were conducted in English, Bengali or Hindi, depending on the preference of the participant. One of the interviewers was a trained qualitative researcher, while the other three were counselors working in information, education, and communication. The three counselors were extensively trained through mock interviews. Interviewers were trained to ask open ended questions using the interview guide, and follow up with probing questions without overtly leading the participant in order to avoid bias. All interviews happened face-to-face and participants were asked to select a convenient, quiet place for the interview. Since the interviews happened face-to-face, all interviewers were also trained to monitor their body language for inadvertent non-verbal cues which may lead the participant and bias the responses. Interviews were digitally audio-recorded and transcribed verbatim before being translated from Bengali or Hindi into English to facilitate analysis. Certain words or phrases which may have been lost in

translation (i.e. “halka phulka” antibiotics, which is loosely translated as light or low-power antibiotics) were included verbatim along with a translation. All participants provided written informed consent prior to participating in the interviews, and consented to unrestricted use of all data from the interviews, including quotes, for scientific purposes. In order to ensure confidentiality, any quotes attributed to patients in the following paper have been de-identified, using only basic demographic information that cannot be easily traced back to the participant.

Qualitative data was analyzed using the framework method, a robust and flexible method of summarizing qualitative data across cases and themes [19]. As an initial step to aid familiarization, the research team read and re-read each transcript, before carefully coding each transcript line-by-line. The coding process was both inductive and deductive, as some areas of inquiry (such as the role of informal health providers and pharmaceutical representatives) were predetermined from the literature review, while others emerged inductively from the data through the process of open coding. After reading a few transcripts, an initial coding framework emerged which was subsequently applied to all transcripts. Data which did not fit neatly into the coding framework was included in emergent, in-vivo codes and later reconciled in the framework matrix. The researchers completed this process of coding using NVIVO 11 software, but the final framework matrix was developed in Excel. Data was analyzed separately for formal healthcare providers, IHPs, pharmacy shopkeepers, nurses, and patients and also compared across these categories before being indexed and charted in the framework matrix. Ideally, we would have liked to conduct respondent validation through informal interviews with participants after data collection and analysis was complete in order to assess perceived accuracy of themes. However, this was not possible due to time and resource limitations. Instead, we relied on data triangulation for validation. In addition to analyzing and triangulating data between all respondents and within each respondent group, all four interviewers analyzed the data before arriving on a coding framework in consensus. Hence, data analysis was triangulated between different perspectives in order to minimize coder bias.

Results

We conducted a total of 28 in-depth interviews (5 pharmacy shopkeepers, 5 informal health

providers, 6 allopathic doctors, 5 nurses, and 7 patients accessing care at the OPD setting). All doctors claimed to prescribe antibiotics in their practice: some said it was due to an unhygienic hospital environment, while others said it was due to suspected infections, patient demands, or fears of a "secondary" or superadded infection. The results have been presented in two distinct categories: 1) knowledge, perceptions and practices of healthcare providers; and 2) patient perceptions and expectations from healthcare providers, in keeping with the objectives of the study.

Knowledge, perceptions and practices of healthcare providers

The following section explores the themes related to objectives 3 and 4, namely knowledge, perceptions and practices related to antibiotic use among healthcare providers.

Doctors perceived antibiotics to be a vital part of care and treatment

While some allopathic doctors clearly stated that they refused to prescribe antibiotics without clinical indication, others reiterated that antibiotics are necessary in order to get cured. For cases of simple diarrhea with no blood in the stool, one allopathic doctor mentioned that he routinely included Metronidazole in his prescriptions to facilitate an early recovery:

"*See*, *the difference between viral diarrhoea and bacterial diarrhoea is that viral diarrhoea has more severity*. *The stool comes out like water*, *especially in children… if you give medicine based on diagnosis*, *then things will get worse…first*, *I always write*: *'use boiled water.' #2*: *I give ORS*. *#3*: *if the patient is going to the latrine 3–5 times*, *then I add Metronidazole*. *Without asking anything else*. *Metronidazole*, *ORS*, *boiled water*. *And I give advice that you boil water before you drink*, *cover the water*, *eat smashed rice*, *etc*." [Male, 51, allopathic doctor]

Similarly, one allopathic doctor further noted that antibiotics always have a benefit, provided there is no gross misuse:

"*the benefit is always there*, *there's no harm from antibiotics…but if you use the same drug over and over again*, *resistance will develop and then the harm factor comes into play*" [Male, 28, allopathic doctor].

If the condition appears life threatening in any way, doctors prescribed antibiotics without hesitation and said they were necessary to get cured. Similar views were expressed by nurses, pharmacy shopkeepers, and IHPs: one IHP even stated that he disbursed antibiotics to every single patient who visited him. IHPs felt it was an important component for care and treatment even for patients presenting with fever symptoms:

"*if [the] patient is coming with fever [since] 2 or 3 days*, *and he [has] already taken Paracetamol*, *so definitely we should apply antibiotics- without antibiotics*, *it cannot be cured*" [Male, 39, IHP].

Informal providers prescribed antibiotics in order to retain patients

When asked why antibiotics were disbursed so readily, IHPs indicated that patients self-medicate frequently these days, and they can only fully recover if antibiotics are provided.

"*In this [day and] age*, *there are a lot of medicines [that] patients eat at home before coming here…and after that*, *if he comes to the doctor*, *[that] means he hasn't gotten better*, *[and] we have to apply antibiotic to them*. *Only then can they full recover*" [Male, 39, IHP].

There was a strong desire to retain the patient. IHPs perceived that patients demanded the fastest cure possible or switched providers, so antibiotics were seen as a necessary part of the treatment regimen:

"*everyone wishes that the patient will come to them more…suppose we say the patient will not be cured, he will right away go to another practitioner. It's better that we give antibiotics and control the disease. Without antibiotics, I cannot treat*" [Male, 45, IHP].

Perceived demands for "quick cures" influenced the use of antibiotics

Pharmacy shopkeepers were routinely pressured by patients to provide antibiotics:

"first [patients] will tell you to prescribe the medicine that can cure me quickly…they tell to give good medicine for quick recovery. This is not only the scenario [in] my place. This happens everywhere…we can start with Cifran, but Ampiclox works quickly. The patient does not have any patience" [Male, 48, pharmacy shopkeeper].

IHPs similar perceived that patients demand shorter courses of treatment:

"*we tell them that they should take the antibiotic for around 2–3 days, but then the patient says 'no, we just want a one-day course*'" [Male, 24, IHP].

Some nurses expressed surprise at how well patients could articulate certain names of medicines, despite their lack of knowledge around its uses and functions.

"*They are community people, so maybe they heard from someone. They heard stories like 'I took this, I took that,' and with that, they say the name. We feel shocked how nicely they say the name*" [Female, 35, nurse].

Nurses reiterated that patients were habituated to quick alleviation of symptoms from antibiotics purchased at medical shops, and demanded such antibiotics without adequate understanding of side effects, risks or uses. There was a widespread perception of patients being stubborn, illiterate and lacking in knowledge of antibiotics, illnesses or appropriate points of contact for care seeking, which made counselling even more difficult.

"*They [patients] don't know much about antibiotics…there is a course of antibiotics which they don't complete- after taking 2–4 [tablets]*, *they think it is done*" [Female, 53, nurse].

Antibiotics were prescribed to prevent secondary (superadded) infections

Doctors frequently mentioned that they prescribed antibiotics as a precautionary measure, which was linked to other factors such as unhygienic conditions at the patient's home, in addition to poor sanitation at health facility levels, lack of follow up, and diagnostic uncertainty.

"*I give antibiotics because I think my hospital…is not so sterile [hygienic]*. *So*, *I have to give an antibiotic*, *otherwise there are chances of an infection*" [Male, 60, allopathic doctor].

While some doctors reported only resorting to antibiotics after other drugs had failed, several others claimed they regularly prescribed an antibiotic as a precautionary measure:

"*In viral [infections]*, *there is no role for an antibiotic*. *Okay*? *But even then*, *we sometimes give an antibiotic*. *Ask me why…because in a viral infection*, *the antibodies are prepared in the body*, *but the viral [infection] is damaging your tissues*. *After it damages you*, *there is a secondary infection…there can be a bacterial infection*. *So to combat this secondary infection*, *we add [an] antibiotic*" [Male, 51, allopathic doctor].

Lack of adequate testing facilities contributed to "empirical" treatment

Most doctors reported prescribing antibiotics without conducting culture or sensitivity tests, either due to lack of adequate laboratory facilities or time:

"*usually*, *I believe on my clinical findings simply*. *If I see that there is some infection*, *I will usually give the empirical antibiotic"* [Male, 60, allopathic doctor].

Doctors at the PHC level typically examined at least 80–100 patients per day, and many reported that it was practically impossible to conduct lab tests before deciding to prescribe antibiotics on a patient-by-patient basis. As a result, they often engaged in "empirical" treatment, which is treatment based on clinical experience alone in the absence of complete information. In some cases, doctors had existing relationships with private labs or were part of a private-public partnership; they referred patients for diagnostic testing to these labs, but it was not clear how many patients returned with lab results for follow-up:

"*for the patients*, *we have [a] lab out here*. *We have got government rates…that functions in public-private partnership mode*, *so we send there"* [Male, 31, allopathic doctor].

Doctors preferred "empirical treatment" based on an assessment of symptoms. They prescribed basic medicines like paracetamol for fevers or salbutamol for coughs, before proceeding to amoxicillin, ampicillin, cloxacillin, and other antibiotics if the condition did not improve:

"*we first give you simple treatment*, *like I give you paracetamol if you are getting a fever*, *salbutamol for a cough…after that*, *I say to gargle*, *and if he doesn't get better even then*, *then I give antibiotics*. *And in that antibiotic*, *Amoxicillin is first*. *Amoxicillin*, *ampicillin*, *cloxacillin*" [Male, 51, allopathic doctor].

Even in cases where labs did exist, one doctor mentioned he questioned the authenticity of the reports as he found different reports for the same patients from some labs:

"*I personally won't trust the report of the culture-sensitivity over here…because [in a] few instances*, *I found different reports from them"* [Male, 31, allopathic doctor].

In most areas, we found that government doctors were working in conditions with highly limited lab support:

"*it's easier to say what is not available*. *Cultures and sputum tests are not available here*, *and 24 hour lab support is not there …people*, *as well as other resources*, *are not available*. *Only total counts and urine are done here*. *With urine*, *a culture is also not done*, *and this is a basic need where pediatric practice is concerned…there are a lot of limitations here at present*" [Male, 31, pediatric doctor].

Pervasive influence of pharmaceutical company representatives

Another salient theme which emerged from our interviews was the strong desire to acquire new knowledge, among formal and informal health providers alike. Pharmaceutical company representatives (PCRs), in particular, were seen as a key source of new knowledge, as many IHPs attended meetings and seminars organized by PCRs:

"*big companies like Cipla*, *Ranbaxy invite me and the speaker is a big doctor…if there is a new medicine*, *we get to know from PCRs*. *If PCRs don't come*, *then how will we know*?" [Male, 38, IHP].

Similarly, many doctors interacted with PCRs in order to get information about newer drugs on the market. Doctors recognized that PCRs often contributed to increasing resistance by demanding doctors prescribe their antibiotics: as one BPHC doctor lamented,

"*he [PCR] doesn't even know the use of clavulanic acid*, *but he dictates the doctor…because he works for a reputed 100-year-old multinational company*, *he thinks he has the right to dictate the doctor*!" [Male, 31, allopathic doctor].

It was also commonly noted among allopathic doctors that less than half the PCRs visiting them provided any real evidence for use of the drugs that were being recommended, even when doctors specifically asked for such clinical evidence:

"*only about 40 to 45% [of PCRs] provide evidence- real evidence*. *Even if you ask repeatedly*, *only about 50% will come up with [something]…either that or they don't turn up next time"* [Male, 31, pediatric doctor].

When asked about incentives presented by pharmaceutical company representatives, no doctors admitted to receiving any incentives of any kind.

We found that PCRs tapped into a very strong network of IHPs and regularly organized meetings and seminars:

"*like there is Franco India…these people like MR [medical representatives or PCRs] come and visit*. *What they do- they choose 10–20 doctors…and do a get-together…some companies also say…let us do a program in this hotel"* [Male, 45, IHP].

These meetings typically hosted up to 40–50 people at a time either at a hotel, district library, or a central location such as a park, and were organized by the regional association of IHPs. In addition, most IHPs relied on networks and referrals to sustain their practice, and acquired new knowledge through on-the-job training and the information provided by PCRs visiting their practice. In general, IHPs viewed PCRs as a very helpful source of information regarding antibiotics and perceived their visits positively.

Erosion of trust in doctor-patient relationship

Doctors routinely reported that they were worried about being blamed for faulty treatment by patients.

"*Mischievous people…make the matter worse…they will bring 10 people and stand here. They create chaos, and say the doctor has killed someone. Why has he killed the patient*?" [Male, 51, allopathic doctor].

Multiple doctors expressed fear for their lives, given the threats to personal well-being from angry patients. Some doctors also blamed the media:

"*one of the faults is also with the media…they create such a notion [that] doctors are…looting the patients, or they are only [here] for earning money from the patient. They are extracting so much from the patient*" [Male, 31, allopathic doctor].

Doctors in the government setup are usually given a non-practicing allowance, in order for them to focus on their duties in the government setup without the distractions of private practice. However, more than one doctor reported taking the non-practicing allowance and operating a

private practice anyway. During the course of an interview, one doctor mentioned he was losing several patients worth Rs. 250 each for every minute he was sitting here in the government setup.

"*As you can see, I am working and I work very fast…I also have a chamber [private practice]…if I did this much work in my chamber, I would get 250 rupees per patient, OK? … I don't know how many 250-rupee patients I am losing right now*" [Male, 51, allopathic doctor].

He took pride in his ability to take no more than 5–10 seconds per patient in the government setup, but claimed the same patient would be given 20–30 minutes in his private clinic. During our field observations, we observed another doctor referring his government patients to his own private clinic, claiming that they would receive much better care and medicines at his private clinic.

We also frequently noticed that formal and informal health providers alike would doubt patients and wonder whether they were actually in pain.

"*By calling him after 3 days, the benefit for us is that we can have a follow-up and see how the patient's response was. And how much his need is. If he's really in pain, then he will definitely come. And if he's just faking it, then he won't come again*" [Male, 51, allopathic doctor].

Doctors routinely prescribed longer antibiotic courses in blocks of 3 days due to perceived lack of treatment adherence and poor follow-up of patients

Given poor follow up and a perceived lack of patient adherence to treatment, many doctors preferred to prescribe a 3-day course of antibiotics for patients in order to improve the likelihood of the patient returning for follow up, irrespective of the required treatment duration. Doctors easily identified the need to complete the full course of antibiotics to prevent antibiotic

resistance, but many also felt the field reality dictated a shorter course of antibiotics to better gauge patient response to treatment:

"*We actually prescribe [antibiotics] for three days*. *We've got two intentions for that- one is after three days*, *the patient will come back to get the medicine*, *and we will know whether the medicine is responding or not*. *Another thing is- if you give a lot of medicine at once*, *the patient does not know what to do with all the medicine and throws it away…so*, *I ask my patients to take for 3 days*, *come after 3 days to show me*, *and then take for another 3 days*" [Male, 31, allopathic doctor].

Another doctor mentioned:

"*if I gave him 7 days of medicine*, *then it's necessary that he will eat it all…in the beginning*, *I used to prescribe for 5–7 days…they stopped eating it after 3 days*" [Male, 51 allopathic doctor].

Task shifting related to antibiotic prescriptions

At the PHC level, there is often a severe shortage of doctors, which puts the burden squarely on the nurses or doctors on deputation who are in charge of more than one PHC. As a result, nurses informed us that they handle the OPD and give antibiotics in the absence of a doctor:

"*whatever the patients say about signs and symptoms*, *then…based on my experience seeing the doctor giving and by searching from internet*, *I give antibiotics*" [Female, 35, nurse].

A few providers confirmed this by suggesting that, in some areas where doctors were lacking, the government had permitted nurses to provide antibiotics.

"*In some PHCs, we have sisters [nurses] who have been treating basic pneumonias…who have been given permission from the government's side to treat pneumonia before they access the doctor…such things can be done more frequently, rather than giving it in the hands of these unqualified practitioners*" [Male, 31, allopathic doctor].

Furthermore, pharmacists in the government setup often assumed the role of dispensing medications unofficially.

"*I can do the treatment for small illnesses… in that case, we don't need permission…if it is [a] simple allergic case like cough, cold, runny nose and if it is symptomatic, then I wait for 2–3 days. If it is not [getting cured] by anti-allergic drugs like Cetirizine, then in that case, I start an antibiotic*" [Male, 48, pharmacist].

Healthcare providers blamed one another for the problem of antibiotic resistance

Among the different groups of participants, blame shifting was a very common phenomenon, where the doctors blamed informal health providers and pharmacy shopkeepers, and the informal health providers blamed allopathic doctors for antibiotic resistance. One IHP exclaimed during the interview:

"*What you are seeing now is that allopathic doctors are injecting a 1-year-old child with 250 injections…after seeing the prescriptions, I am able to see the amount of powerful antibiotics that are being prescribed*" [Male, 48, IHP].

We frequently noticed denial of any personal responsibility from IHPs:

"*to stop this*, *only the allopathic doctors can do something*! *What can we do about this*? *Chemist shop owners also cannot do anything*. *Whatever the doctor writes*, *whatever is on the prescription*, *they give out*" [Male, 48, IHP].

Doctors, on the other hand, expressed frustration at the lack of legal action against "quacks" and over-the-counter use of antibiotics:

"*Raniganj is full of quacks*. *Everywhere you go*, *you will find quacks"* [Male, 31, allopathic doctor].

They claimed that patients were often resistant to a multitude of antibiotics, which left them with no choice but to resort to fixed dose combinations (FDCs) of antibiotics or other powerful antibiotics:

"*in this area*, *quack is there*. *So they're using antibiotics…I'll have to use a antibiotic or higher derivatives*. *Otherwise*, *the patient will not respond- because they are resistant"* [Male, 60, allopathic doctor].

This was also linked to difficulties in counselling patients- many doctors felt patients were less patient these days and simply desired the fastest cure possible without any hindrance. As a result, doctors often felt pressured to prescribe multiple medicines, such as Rantac, Albendazole, B vitamins, and other medicines which may not be directly relevant to the patient's condition, but would not necessarily harm the patient either.

"Halka-phulka" antibiotics [light or low-power antibiotics] were perceived as first aid treatment by IHPs

We commonly observed dissonance between attitudes and practices among IHPs, who claimed that antibiotics should be given if other medicines do not work on the one hand, but simultaneously disbursed multiple antibiotics in our presence with no clinical indication. FDCs of antibiotics were referred to as "double antibiotics" or "high antibiotics," and were disbursed in cases where diseases were unresponsive to a single antibiotic. IHPs routinely perceived antibiotics as first aid treatment:

"*if the patient is having excessive loose motion*, *I give 1–2 O2 [Ofloxacin-Ornidazole] tablets or something like that as first aid…otherwise, patient doesn't even come*" [Male, 45, IHP].

Most providers referred to these "first aid" antibiotics as halka-phulka antibiotics:

"*I give Paracetemol [for a fever patient]- I will have to give a halka phulka antibiotic along with that- ampicillin*, *amoxicillin I will have to give*" [Male, 48, IHP].

IHPs reported that most patients arrived at their clinics with minor illnesses, such as cold, cough, fever, vomiting, and stomach pain or watery loose stools mostly. Such illnesses do not typically require antibiotics for treatment.

IHPs perceived their work was appreciated by medical doctors

IHPs reported a strong relationship between informal and formal health providers: one IHP informed us that doctors often referred patients to him to administer particular injections or provide basic first aid, even as other doctors lamented the lack of legal action against IHPs:

"*There are lots of doctors in the market, so we send the patients to XYZ doctor…when they ask [the patient] who has sent you, they tell our name and the doctor comes to know that there is a doctor [IHP] who is practicing. If a patient goes to any surgeon doctor…if [they] write 10 injections, they also instruct the patient to visit me to push it [administer the injection]. So, in that way, patients also get help and we also earn Rs. 5–10 for injecting, so our work is also done. It is helpful for the patient that they don't need to go here and there- their work is done at [one] place and if [they] come to me, I push the injection*" [Male, 38, IHP].

Furthermore, most IHPs operated in areas that lacked medical staff and healthcare facilities. IHPs often functioned as the first point of contact for patients before referring them to particular private clinicians whom they held established relationships with. Many IHPs currently working in the field learned from doctors or nurses in private hospitals for a few years, prior to opening up their own clinic. As a result, most informal health providers had high self-confidence in their abilities and felt they were a crucial part of the medical system.

"*Doctors are…many of them are happy with us…in the night, we are the ones practicing in village after village. The doctor will give his time, visit, and then leave…the doctors support us as well*" [Male, 45, IHP].

Antibiotic choice is not guided by evidence

Doctors in the government setup generally claimed to prefer prescribing antibiotics which were available in that particular facility:

"*whatever medicine is available here, I write…first. If that doesn't work, then I prescribe from outside, which is more expensive"* [Male, 51, allopathic doctor].

Amoxicillin, Azithromycin, Ciprofloxacin, Penicillin, Cotrimoxazole, Doxycycline, Norfloxacin, Ofloxacin, Levofloxacin, and Metronidazole were commonly available and prescribed as a result. Metronidazole was a very common prescription for diarrheal patients, whereas fever patients or patients presenting with a cough and cold were usually given Paracetamol, before being given any antibiotics:

"*for cough, I give a Paracetamol…if he doesn't get better and says he still has a cough, then I prescribe antibiotics"* [Male, 51, allopathic doctor].

Generally, doctors voiced support for monotherapy over FDCs of antibiotics, claiming that FDCs were unnecessary for the patient and could lead to resistance:

"*monotherapy is better than combination therapy obviously…suppose one patient comes to you with a cold…and you prescribe him or her a medicine that contains 4 or 5 drugs, but actually, he needs 1 or 2 medicines. That is sufficient for her symptoms to subside"* [Male, 31, allopathic doctor].

When doctors resorted to FDCs however, they usually prescribed medicines from outside the facility, with the patients bearing the costs of the medicines themselves. Since generic medicines were provided as monotherapy in the government setup, one doctor mentioned combining 3–4 drugs at the same time, especially given poor perceptions of treatment adherence among patients:

"*I have to combine a lot of things…to get the cure, to get the result, because here the people will see the result. They won't take the entire duration of the treatment*" [Male, 28, allopathic doctor].

Furthermore, there was a widespread perception of lower quality of generic medicines in the government health setup among medical doctors. Brand-name medicines were assumed to be of higher quality and made patients recover more quickly:

"*you take the generic medicine*. *Maybe you get cured in 3–5 days…but the quality [of brand-name medicines] gives you a better treatment…you are getting cured within hours or something"* [Male, 28, allopathic doctor].

However, one doctor did state that generic medicines were more affordable and noted that brand names were only perceived to be of better quality due to marketing by PCRs:

"*a brand-name company has to invest at least 200% of the manufacturing charges of the drug for marketing*, *but generic doesn't have that situation*. *Along with that*, *another thing I heard from one friend is that if brand medicines get expired*, *the company takes it back…but for a generic medicine*, *if it gets expired*, *it is the shopkeeper's loss*" [Male, 31, allopathic doctor].

Some doctors even felt concerned about the regulations enforced upon doctors:

"*[rather than] compelling the doctor to [prescribe] generic medicines*, *the government should impose price controls on the medicines*" [Male, 31, allopathic doctor].

Knowledge of antibiotics and antibiotic resistance varies widely

When asked what were the various causes of antibiotic resistance, most doctors immediately identified incorrect duration, incorrect dose, lack of communication between doctors in

transitions of care, and self-medication by patients as causes. In addition, doctors understood that resistance was a naturally occurring phenomenon:

"*whenever a bacteria will take the antibiotic*, *any person's chances of resistance will increase*. *You are consuming antibiotics for no reason*, *so the bacteria mutates and changes…the more you prescribe antibiotics*, *the more the resistance develop*" [Male, 51, allopathic doctor].

Additionally, doctors mentioned that inadequate sanitation resulted in a dependence on antibiotics rather than focusing on prevention.

Among pharmacy shopkeepers and informal health providers, FDCs and "bhari-barkam" [heavy-duty or powerful] antibiotics were seen as being more prone to antibiotic resistance, and yet antibiotics were frequently dispensed to prevent other illnesses or multiple antibiotics were combined individually to create combinations of antibiotics. Some pharmacy shopkeepers had no idea what caused antibiotic resistance and attributed "bad weather" as a causal factor:

"*this much I know*. *Something related to weather leads to antibiotic resistance*" [Male, 43, pharmacy shopkeeper].

Despite the dissonance between knowledge, attitudes, and practices, pharmacy shopkeepers did believe antibiotic resistance posed a major threat in the future:

"*those who are sitting in the chemist shops- if [they] are not guided*, *then in the future*, *it will be more difficult*. *Today*, *AmoxiClav is working on me*, *but maybe tomorrow it will not*. *That is very*

bad, *very dangerous*. *Nowadays*, *[this is] what is happening in most of the chemist shops*" [Male, 31, pharmacy shopkeeper].

Patient perceptions and expectations from healthcare providers

Vocabularies of illness among patients and limited knowledge of antibiotics

Patients usually named environmental factors as being a cause of illness:

"*water…does not come clean*. *That's why we fall sick*. *Also*, *the population is so big*, *and there is pollution in the cities- it happens because of this*. *There are many reasons*, *but mostly*, *it's because of water*, *changing seasons*, *like this*" [Male, 31, patient].

It was further understood that illness could be seasonal, even if the cause was unknown:

"*whoever has an illness will have it*. *This happens normally once or twice in the year on its own*" [Male, 31, patient].

Finally, one patient also identified negligence as a factor:

"*the carelessness we have*, *that is the reason for the illness*. *Not paying attention to cleanliness*, *not paying attention to a small illness when it occurs…all this*" [Male, 28, patient].

In general, patients had no conception of what constituted an antibiotic. Patients appeared to draw distinctions between halka-phulka [light or lower-power] medicines and more powerful

medicines, and some even associated the name "antibiotic" with a faster cure, but there was no knowledge of functions and uses:

"*antibiotic means for cold*, *cough*, *fever…all this*" [Male, 38, patient].

Overall, patients had a very poor understanding of antibiotic resistance or associated causes.

Patients switched medical providers frequently in order to seek the fastest cure

Patients switched health providers frequently if the treatment was perceived as being too slow or ineffective. In addition, patients did not hesitate to approach a combination of Ayurvedic (traditional medicine), homeopathic and allopathic doctors- the underlying motivation was the best cure in the fastest amount of time. Some patients used Ayurvedic products such as "Chawanprash" (herbal paste), but preferred allopathic medicines over homeopathic treatments, as they were perceived to cure the disease more quickly. If the prescribed treatment was not working however, patients did not hesitate to switch providers:

"*I [went] to the first doctor but didn't get cured*. *Then*, *I [went] to another doctor and [took] 2–3 medicines*, *but I still [was not] cured*. *Again*, *I [went] to another doctor and [took] medicine for 3 months*, *but my condition didn't improve*. *Finally*, *if the medicine of the next doctor works for me*, *then I go to that doctor every time*" [Male, 50, patient].

IHPs also perceived that patients frequently switched health providers in an effort to seek the fastest cure possible- in order to retain the patient, informal health providers constantly sought feedback and gave in to perceived patient demands for antibiotics:

"*In today's age*, *if a patient comes*, *he does not even wait 2–4 days with one doctor*. *He wants quick relief …he changes doctors 2–3 times*. *If he does not get cured in one day*, *he will not come back to me tomorrow; he will go to a second doctor*. *If the second doctor does not cure within 2 days*, *he will go to a third doctor*. *He changes doctors 4–5 times- in today's day and age*, *the patient does not have any patience*" [Male, 39, IHP]

Patients' unmet expectations from healthcare providers

Patients who sought treatment expected to be treated with respect and provided more than a minute or two for consultation. One young mother informed us that she wished the doctor would actually touch and see if something was wrong, rather than simply prescribing medicines quickly based on his visual judgment. Patients noted that doctors, especially private practitioners, treated them more like business customers rather than patients. The same doctors who would hesitate to spend 5 minutes with a patient in a government setting would spend much longer observing the patient in private practice, but they would also prescribe more medicines and tests, which occasionally made patients suspicious of the motives behind such decisions:

"*if you come once*, *then you have to go again…the bigger doctors outside- they have high fees*, *and nowadays it feels like they make a customer out of us*" [Male, 31, patient].

Government health facilities were perceived as being inadequate

Patients confirmed what doctors, nurses, IHPs, and pharmacy shopkeepers already stated in terms of the government healthcare system being the last resort for patients. Patients preferred to reach out to IHPs who sat directly in their communities or self-medicate with over-the-counter "halka phulka medicines" [light or low power medicines] at chemist shops wherever possible.

When asked why the government health system was seen as a last resort, patients usually cited long wait times and lack of adherence to work timings on the part of doctors. However, patients perceived this as a normal associated cost of free care:

"*where you go without money*, *you will have to bear a little trouble*" [Male, 38, patient].

Additionally, there was a perception of better treatment if recipients were well connected politically:

"*here*, *there is still this thing with the local politicians*. *If you are referred by someone*, *then you will be treated well*. *If you've just come like that*, *then you'll be treated like normal*" [Male, 31, patient].

As a result, if patients perceived the problem to be relatively minor, such as a cold, cough, or watery loose stools, they preferred to visit a pharmacy shop or a local IHP.

Complaints about the public health setup came from all stakeholders and ranged from unhygienic conditions at the facility level to severe staff shortages to inadequate roads in and around PHCs.

"*See I don't cut or do anything here*. *The setup is lacking*. *I actually come here on deputation*. *There is no Medical Officer here*. *I was told to come for 6 months*, *and I have been doing it continuously for the past 2 years…the road here is so bad*, *so the silencer in my car broke*. *The Government tells us that doctors should come on time- do this*, *and do that- but for that*, *they will have to see the other facilities too*, *right*? *They have to see the roads and reduce the influence of politics*" [Male, 51, allopathic doctor].

Overall, all five groups of participants suggested numerous strategies to counter the threat of antibiotic resistance. Counseling of patients featured prominently among these strategies, along with encouraging patients to complete the full course of antibiotics:

"*public awareness is needed…make them aware that [they should] only use antibiotics when it is needed*. *Don't take antibiotics by yourself"* [Male, 51, allopathic doctor].

Strict legal action was suggested by doctors, nurses and a few pharmacy shopkeepers, especially in terms of banning OTC use of antibiotics and taking action against informal health providers. Additionally, continued medical education, trainings, workshops, and seminars were all suggested as ways to improve knowledge around antibiotic use in the medical community. All doctors who were interviewed reported attending at least some events organized by their medical colleges in their vicinity, and expressed enthusiasm for the role of continued medical education:

"*[continued medical education] is very important*! *This is very important not only for antibiotic resistance*, *but also [to cover] basic topics…until and unless your basics are clear*, *your treatment is all in vain*" [Male, 31, allopathic doctor].

Discussion

Our study analyzed data from semi-structured interviews with formal and informal healthcare providers as well as patients seeking care to understand knowledge, attitudes, perceptions, and practices related to antibiotic use in a particular district of West Bengal. While other studies have similarly reported poor knowledge of antibiotics among patients and the general community in multiple settings [20–24], we could not find any studies from this region which triangulate these findings with perceptions among healthcare providers. Other studies from India in the literature primarily focus on surveying medical students or clinicians at the tertiary level, without effectively taking into account the role of IHPs and PCRs [7–10, 12–16].

Our findings demonstrated that perceived demands for antibiotics influenced prescription behavior, particularly among IHPs. Moreover, healthcare providers conceded that PCRs played a critical role in influencing behavior. This has been reported across multiple countries and contexts: Workneh et al found that approximately half of the medical doctors sampled from and working in Northern Ethiopia reported that their prescription decisions were influenced by PCRs in the last year [25]. Similar results have been reported from Yemen, Pakistan, Peru, Saudi Arabia [26–28], as well as developed countries such as Germany [29]. Lieb and Scheurich reported that doctors who saw PCRs frequently in Bavaria, Germany had significantly higher total prescriptions and total daily doses [29]. In India, Waheed et al found that tangible rewards for doctors by PCRs led to prescription loyalty and Kothani et al found that newer antibiotics were used on recommendations made by PCRs who often relied on skewed studies [30–31]. However, virtually no studies examined the links between PCRs and IHPs.

We found that IHPs do not just provide care or antibiotics to patients; they are also well-organized and operate within active networks across multiple blocks in the district. IHPs reported that PCRs often leveraged these networks to market new antibiotics and organized conferences for IHPs, given their desire to acquire knowledge. This has not been well-documented in the region and presents promising avenues for further research and investigation.

Current initiatives to tackle ABR focus on implementing antibiotic stewardship at the hospital level, setting up surveillance systems, restricting access to over-the-counter antibiotics, and generating awareness among consumers. However, these networks of IHPs and PCRs are largely left out of these initiatives. Some studies examined the roles occupied by informal health providers in the community: the findings generally indicated poor quality of service provision, gaps in knowledge, and mixed results regarding efforts to retrain them [32–37]. Future research should examine the long-term impacts of such training and assess how IHPs and PCRs can be influenced to promote a more responsible message around antibiotic use. Four pharmaceutical companies, including Glaxo-Smith-Kline and Pfizer, recently reported separating pay from antibiotic sales volume for all sales staff, and similar initiatives can be implemented and rigorously assessed for national pharmaceutical firms in India [38].

More broadly, the reliance on IHPs reflects a lack of trust in the existing government health system as reported by patients in our study. In order to alleviate the lacunae in the public health system, policy makers must invest in improving existing infrastructure and increasing the presence of allopathic doctors at PHCs. Our study found that doctors lacked the resources to conduct culture investigations prior to prescribing antibiotics in many settings, which exemplifies how shortfalls in healthcare delivery can contribute to irrational use of antibiotics and subsequent antibiotic resistance.

We argue that improving the capacity of the existing public health system to deliver on its promises can indirectly influence antibiotic prescription decisions and form an important component of curbing antibiotic resistance. While the short-term risks posed by the lack of awareness around antibiotic uses and functions are largely self-evident, there is also a larger long-term risk at play. Our study uncovered a fraught relationship between doctors and patients, where doctors feared physical assault or worse if the treatment did not go as expected, and patients claimed doctors treated them more like business customers. This erosion of trust in the doctor-patient relationship is exacerbated by the lack of resources in the public health system and the unwillingness of doctors to shun private practice for government service. Strengthening the existing system is likely to go a long way in reducing the reliance of patients on informal health providers. Balancing the demands between access to and overuse of antibiotics remains a major challenge for policy makers at present.

Methodological considerations

It must be noted that while we attained saturation in the study as a whole, we did not attain saturation in each analytical sub-category (i.e. allopathic doctors, pharmacy shopkeepers, etc.) which must be explored in future studies. Furthermore, we were only able to include patients accessing care at health facilities. Future studies must look to also include patients who are unable to seek care. It is quite possible the care-seeking behavior of this segment of the population differs from patients accessing care at the hospital or PHCs.

Conclusions

Efforts to curb antibiotic resistance in West Bengal and other parts of India require a holistic

approach, including but not limited to strengthening the capacity of the existing public health system to deliver on its promises, improving patient education and counseling, and including IHPs and PCRs in community-level antibiotic stewardship efforts.

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Chapter 3

Behavioural interventions to address rational use of antibiotics in outpatient settings of low-income and lower-middle-income countries

This paper has been peer reviewed and published in Tropical Medicine & International Health.

Abstract (247 words)

Objectives

Our systematic review seeks to explore the current evidence landscape on interventions to influence antibiotic prescribing behavior of health professionals in outpatient settings in low-income and lower-middle-income countries, an underrepresented area in the literature.

Methods

The systematic review protocol for this study has been registered in PROSPERO (CRD42020170504). We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for studies relating to antibiotic prescribing of health professionals in outpatient settings in low-income and lower-middle-income countries. Behavioral interventions were classified as persuasive, enabling, restrictive, structural, or bundle (mix of different interventions). In total, 3,514 abstracts were screened and 42 studies were selected for full-text review, with 13 studies included in the final narrative synthesis.

Results

Out of the 13 included studies, five were conducted in Vietnam, two in Sudan, two in Tanzania, two in India, and two in Kenya. All studies were conducted in the outpatient or ambulatory setting, but eight took place in primary health centers, two in private clinics, and three in pharmacies. Our review found that enabling or educational interventions alone may not be sufficient to overcome the ingrained incentives to link revenue generation to sales of antibiotics, and hence, inappropriate

prescription or misuse of antibiotics. Bundle interventions appear to be very effective at changing prescription behavior among healthcare providers, including drug sellers or pharmacists.

Conclusions

Multi-faceted, bundle interventions that combine regulations enforcement with face-to-face education and peer influence may be more effective than educational interventions alone at curbing inappropriate antibiotic use.

Background

The advent of antibiotics has ushered in an era of increased life expectancy and reduced mortality and morbidity from infectious diseases [1]. Overuse of antibiotics and irrational prescriptions of antibiotics, especially in developing or emerging economies, has further compounded the problem of antibiotic resistance (ABR) [2]. One multi-country study from low-income and lower-middle-income countries found that children received an average of 25 antibiotic prescriptions through age 5 [2]. Given high rates of antibiotic overuse and misuse, the World Health Organization (WHO) warned in 2014 that ABR poses a serious threat in every region [3].

There have been several studies looking at the drivers of antibiotic resistance globally [4-13], but very few analyzing antibiotic stewardship or other behavioral interventions to address prescription behavior of healthcare providers in outpatient settings as drivers of antibiotic use [14-20]. Some of these reviews have either been overly broad in scope with a predominant focus on context over behavioral interventions, or have failed to include evidence from informal and private sector settings within healthcare in low-income and lower-middle-income settings. Healthcare providers, especially in low-income or other limited resource settings, can be formally trained (e.g. medical doctors, nurses, pharmacists) or informal (untrained medical practitioners or practitioners of alternative medicine). In India, for example, there is a government ministry for Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy (AYUSH) that is dedicated to training and providing alternative systems of medical care [21]. The focus on outpatient care is particularly important in low-income settings, where the relation between overburdened government

healthcare systems and burgeoning private, informal providers is poorly understood in the context of antibiotic consumption.

Most of the available evidence comes from developed countries and involves more complex multi-faceted strategies such as electronic decision support, electronic health record prompts and automated peer comparison interventions [14, 18, 19, 22]. However, it is unclear whether similar interventions are as effective or can be applicable in low-income or lower-middle-income countries. Such contexts often face a high burden of communicable diseases, which are not always amenable to expensive or high-tech interventions involving electronic health records [2, 19].

To that end, our systematic review explores the current evidence landscape on behavioral interventions influencing antibiotic prescribing behavior of health professionals in outpatient settings in low-income and lower-middle-income countries.

Methods

The systematic review protocol for this study has been registered in PROSPERO (CRD42020170504). We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for studies relating to antibiotic prescribing of health professionals in outpatient settings in low-income and lower-middle-income countries, including bibliographies of retrieved articles. Only articles published in English between 2001-2019 were included in the review. Articles published before the year 2001 were excluded as this was when the first global plans addressing antibiotic resistance emerged, and the objective of the systematic review was to examine the latest evidence on behavioral interventions to address antibiotic resistance [23].

Behavioral interventions were defined and classified as persuasive (prescription audits and feedback advice), enabling (education or guidelines on antibiotic use), restrictive (expert approval prior to using certain antibiotics), structural (introduction of a new diagnostic test or clinical algorithm to guide prescriptions), or bundle (mix of different interventions), based on a prior systematic review by Davey et al using the EPOC taxonomy [14, 24]. Randomized controlled trials, non-randomized controlled trials, time series, uncontrolled before-and-after studies, as well

as qualitative studies were included if they reported a distinct change in knowledge, attitudes and practices following an intervention to improve knowledge of antibiotic resistance among prescribers. Interventions focusing on microbiological tests, improving infection prevention and control, or hospital inpatients and nursing homes were excluded. Studies that did not have full-text articles available were excluded if the original authors were not contactable. The focus was on outpatient or ambulatory care in low-income and lower-middle-income countries, according to World Bank classification [25]. Studies focusing on malaria, HIV, malnutrition, or other infectious diseases without directly dealing with antibiotic stewardship were excluded.

Search results from PUBMED, EMBASE, and CENTRAL were imported into Excel with 4,521 entries in total. After removing duplicates, 3,514 remained. MN conducted a detailed title and abstract screen, and RM subsequently reviewed all titles and abstracts to identify interventions addressing antibiotic prescription behavior (see PRISMA diagram in Figure 1 below). Study data was extracted and study quality assessed independently by two of the authors.

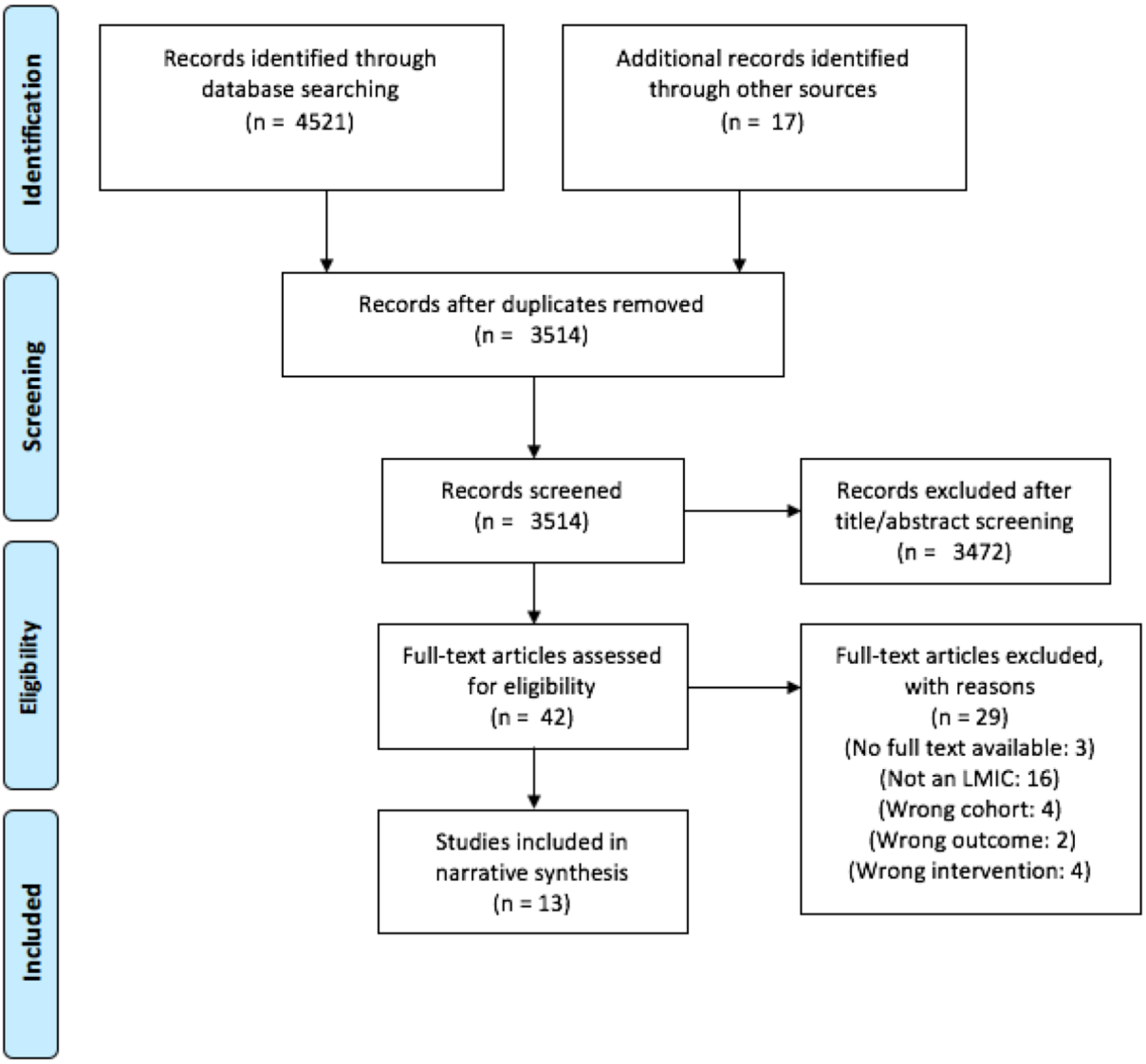

Figure 1. PRISMA diagram.

42 studies were identified for full-text review after an initial title/abstract screening. A pre-designed data extraction sheet was used to include information on study design, type of intervention, type of targeted behavior, participants, setting, methods, outcomes, and results to extract results. Two reviewers independently conducted full-text reviews of all 42 studies, and excluded 29 studies. The majority of studies were excluded due to misclassification as a low-income or lower-middle-income country: for instance, several studies were from China, which the World Bank currently classifies as an upper-middle-income country. 13 studies were included after

full-text review [26-38]. Given the heterogeneity in interventions and study designs, we have presented our results using a narrative synthesis approach without a meta-analysis.

Results

Out of the 13 included studies, five were conducted in Vietnam (one of these studies took place in both Vietnam and Thailand), two in Sudan, two in Tanzania, two in India, and two in Kenya. All studies were conducted in the outpatient or ambulatory setting, but eight took place in primary health centers (PHCs), two in private clinics, and three in pharmacies. Four studies involved public facilities, eight involved private facilities, and one study incorporated a mix of public and private facilities. Table 1 below details characteristics of included studies.

Table 1. Characteristics of studies examining behavioral interventions to address antibiotic resistance in ambulatory settings in low-income or lower-middle-income countries.

Authors	Type of study	Type of intervention	Description of intervention	Country	Year	Type of setting	Private or public sector	Effect of intervention

Kleczka et al [26]	Pre-post design	Bundle	Rubber stamp templates, clinical practice guidelines, low-budget smartphone, and one CME session per month	Kenya	2019	Outpatient: primary healthcare clinics	Private	Reduction in use of broad spectrum antibiotics and increase in use of narrow spectrum antibiotics
Das et al [27]	Randomized-controlled trial	Enabling	72 sessions and 150 teaching hours for informal providers over a 9-month period, covering medical conditions, triage, and avoidance of harmful practices.	India	2016	Outpatient: private clinics with informal providers	Private	No effect on use of unnecessary medicines or antibiotics

Lunn AD [28]	Pre-post design	Bundle	Multifaceted intervention: repeated process of audit and feedback, interactive training sessions, one-to-one case-based discussion, antibiotic guideline development, and coding updates	India	2018	Outpatient: NGO's PHC clinics	Primary care clinics (private NGO)	Marked reduction in antibiotic prescriptions for non-specific URTI

Hoa et al [29]	Randomized controlled trial	Enabling	Six training sessions on ARI management, six training sessions on ARI case scenario management, and poster distribution	Vietnam	2017	Outpatient: public and private personnel	Mixed	Significant improvement in knowledge and practice regarding antibiotic prescriptions

Korom et al [30]	Pre-post design	Bundle	Clinical guideline for management of uncomplicated urinary tract infection + peer-to-peer review of documentation + discussion of a recently published, peer-reviewed Kenyan study describing local AMR patterns	Kenya	2017	Outpatient: two semi-urban PHCs	Private	Significant improvements in ARI knowledge and prescription patterns

Rambaud-Althaus et al [31]	Cluster randomized controlled trial	Structural	Paper algorithm + electronic algorithm on a smartphone + control	Tanzania	2017	Outpatient: 9 PHCs (3 health centers and 6 dispensaries)	Public	Reduction in antibiotic prescriptions
Eltayeb et al [32]	Pre-post design	Bundle	Audit and feedback + audit and feedback along with guidelines and two seminars + audit and feedback along with academic detailing and a copy of guidelines	Sudan	2005	Outpatient: 20 health centers	Public	50% reduction in inappropriate antibiotic prescriptions

Shao et al [33]	Controlled, non-inferiority trial	Structural	ALMANACH algorithm available on paper and electronically, along with face-to-face supervision	Tanzania	2015	Outpatient: 4 PHCs	Private	80% reduction in antibiotic prescriptions
Awad et al [34]	Pre-post design	Bundle	1)No intervention (control); 2) audit and feedback; 3) audit and feedback + seminar; 4) audit and feedback + academic detailing	Sudan	2006	Outpatient: 20 health centers	Public	Multifaceted interventions were most effective in changing prescribing patterns

Chalker et al [35]	Randomized controlled trial	Bundle	Enforcement of regulations with local inspectors + education + peer review	Vietnam and Thailand	2005	Outpatient: 68 pharmacies in Hanoi and 78 pharmacies in Bangkok	Private	Significant improvements in Hanoi, reducing the dispensing of low dose antibiotics (69% vs. 90%), but the only significant improvement in Bangkok was the reduction in illegally dispensing steroids (25% vs. 44%) after the regulatory intervention.

Chuc et al [36]	Cluster randomized controlled trial with time series design	Bundle	Three interventions were applied sequentially: regulatory enforcement, education, and peer influence	Vietnam	2002	Outpatient: 68 pharmacies	Private	Significant reductions in dispensing antibiotics for ARIs
Chalker et al [37]	Randomized controlled trial	Bundle	Regulations enforcement, face-to-face education, and peer influence.	Vietnam	2002	Outpatient: 22 matched pair intervention and control pharmacies	Private	All three interventions were effective in changing knowledge and reported practice of drug sellers.

Phuong et al [38]	Randomized controlled trial	Bundle	Training on infectious diseases + provision of RDTs + combination of training and RDTs + control	Vietnam	2010	Outpatient: 12 PHCs	Public	RDTs improved the quality of diagnosis and decreased the prescription of antibiotics at the PHC level.

None of the included studies examined purely persuasive interventions, although similar components were included as part of a bundle intervention in nine studies [26, 28, 30, 32, 34-38]. Two studies were classified as enabling interventions that relied on continued medical education, other forms of education, or guidelines for antibiotic use [27, 29]. Two studies by Rambaud-Althaus et al and Shao et al utilized a new clinical algorithm for managing childhood illness and were hence classified as structural interventions: the former was a cluster randomized controlled trial conducted in programmatic conditions, while the latter was a controlled, non-inferiority controlled trial [31, 33].

Enabling interventions

All studies included in the review reported positive effects of the interventions through either increased knowledge around antibiotic use or reductions in inappropriate antibiotic prescriptions, with the exception of Das et al. This study found that informal providers who underwent 150 teaching hours over a 9-month period did not report any significant change in antibiotic

prescriptions [27]. Mean attendance at the 72 training sessions was 56% with no overlap from the control group, and the study found that informal providers in the intervention and control group prescribed fewer antibiotics than public sector providers and improved correct case management rates, despite no effect of the training program on the use of unnecessary medicines and antibiotics. This study highlighted that interacting with and training informal providers who operate outside the purview of the formal medical system did not lead to any increase in violation of rules or clinical practice, which has been a common critique and misconception among medical doctors in India according to Das et al.

The only other study classified as an enabling intervention in our systematic review was a two-armed cluster randomized controlled trial carried out by Hoa et al in a rural district in Vietnam [29]. The study participants included all medical staff (doctors, assistant medical doctors, nurses, and midwives) and pharmacy staff (drug sellers and pharmacists) working in public and private facilities within the district. In total, 144 healthcare providers were included in the intervention arm, while 160 were included in the control arm [29]. The interventions were conducted over seven months and included education around guidelines for appropriate antibiotic use, case scenario discussions, and poster distribution. The intervention group reported a 28% improvement in knowledge of acute respiratory infection etiology, and the mean improvement of 1.17 points in the total knowledge score within the intervention group was statistically significant. When presented with a mild ARI case scenario, practical competence improved by 20% in the intervention arm. However, there was no long-term follow up to assess whether the change in knowledge was sustained over time.

Structural interventions

Shao et al and Rambaud-Althaus et al utilized a new electronic algorithm (ALMANACH) for the management of childhood illness using mobile phones in Tanzania. Shao et al tested the algorithm in controlled settings and found that the use of the new algorithm achieved a better cure rate and a significantly lower rate of antibiotic prescription compared to routine practice (15% in the intervention arm vs. 84% in the control group) [33]. Rambaud-Althaus et al tested the same algorithm in programmatic conditions by randomizing nine primary healthcare facilities into three arms: paper algorithm, electronic algorithm using a smartphone, and a control group. The study

found that inappropriate antibiotic prescriptions dropped from 70% in the control arm to 26% in the paper algorithm and 25% in the electronic arm [31].

Bundle interventions

The majority of studies (n=9) within our systematic review were comprised of bundle interventions, which are multi-faceted interventions integrating elements of an educational or training component along with either a persuasive or structural intervention. Kleczka et al integrated rubber stamp templates for management of pre-specified medical conditions with clinical practice guidelines, one continued medical education session per month, and a low-budget smartphone to create a bundled intervention at nine private sector health facilities in the informal sector. The study found that feedback did not affect the number of antibiotics prescribed for UTIs, but increased the use of appropriate, narrow-spectrum antibiotics from 9.2% to 29.9% and reduced the use of broad-spectrum quinolones from 30% to 16.1% [26]. Two studies from Sudan, Awad et al and Eltayeb et al, utilized a pre-post design in 20 health centers to determine the impact of different multifaceted interventions: 1) no intervention, 2) graphs and explanations for audits of prescribing patterns, 3) audit and feedback along with seminars and a copy of guidelines, and 4) audit and feedback plus academic detailing along with a copy of guidelines [32, 34]. The former study focuses on prescription patterns for all diseases at one and three-month post-intervention, while the latter focuses specifically on sexually transmitted infections alone. The most effective intervention in both cases was the bundle intervention which combined audit and feedback with academic detailing through face-to-face educational meetings with prescribing experts and a copy of prescribing guidelines. Eltayeb et al reported a reduction of inappropriate prescriptions by 50% for this particular intervention, in comparison to 16% for audit and feedback alone.

Four studies focused on bundle interventions in Southeast Asia, specifically Vietnam and Thailand [35-38]. Phuong et al conducted a randomized controlled trial with primary health staff at 12 PHCs. Patients with acute undifferentiated fever (AUF) were recruited and PHCs were randomized to four intervention arms: 1) training on infectious diseases, 2) provision of rapid diagnostic tests (RDTs), 3) combination of RDTs and training on infectious diseases, or 4) control [38]. The study clearly demonstrated that the combined approach was more effective at reducing the prescription

of antibiotics in comparison to either the introduction of RDTs or training on infectious diseases on its own.

Chuc et al (2002) and Chalker et al (2002) both examined the effect of multi-faceted interventions on inappropriate antibiotic prescriptions as part of private pharmacy practice [36-37]. Chalker et al conducted a randomized controlled trial with 22 matched pair intervention and control private pharmacies using the following interventions: 1) regulations enforcement, 2) face-to-face education, and 3) peer influence. The study was one of the first to conduct a multi-intervention study in the private pharmacy sector in a low-income country and found a significant change in reported knowledge and practices: fewer drug sellers in the intervention group claimed they would sell antibiotics without a prescription, compared to the control group ($p=0.02$) [37]. Similarly, Chuc et al used four tracer conditions (uncomplicated acute respiratory infections, sexually transmitted disease, requests for the prescription-only drugs prednisolone, and a short course of cephalexin) in 68 randomly selected pharmacies in Hanoi and found that intervention pharmacies demonstrated decreased antibiotic dispensing and improved management of all tracer conditions [36]. Both studies espoused the value of multi-pronged interventions as an effective way to curb antibiotic misuse in private pharmacy practice. Another study by Chalker et al from 2005 examined the effectiveness of a similar multi-faceted intervention in 68 Hanoi pharmacies and 78 Bangkok pharmacies [35]. Three interventions (regulation enforcement with local inspectors, face-to-face education in Hanoi and large-group education in Bangkok; and voluntary peer review in Bangkok with compulsory peer review in Hanoi) were implemented sequentially with four months in between and the interventions resulted in significant improvements in Hanoi, but not Bangkok [35]. All indicators improved substantially in Hanoi, but Bangkok only demonstrated an improvement in dispensing of steroids after the regulatory intervention, which was not sustained.

Korom et al conducted a pre-post effectiveness trial in Kenya, which examined the effect of brief educational interventions, including 1) a clinical practice guideline, 2) peer-to-peer chart review, and 3) peer-reviewed literature detailing local AMR patterns, on the proportion of cases in which appropriate antibiotics were prescribed as per the guidelines [30]. Clinical adherence improved from 19% to 68% after all interventions [30]. Finally, Lunn AD measured the effect of a multifaceted intervention that involved audit and prescribing feedback, educational seminars, one-

on-one case-based discussions, guideline development, and a change in the way the disease is medically coded on reducing inappropriate antibiotic prescriptions in India [28]. The study reported a reduction in antibiotic prescriptions from 62.6% to 7.2%, and increased documentation of examination findings (52.7% to 95.6%). This intervention was particularly salient because it relied on low-cost resources in an NGO's outreach clinics in India [28].

Risk of bias

In order to assess the risk of bias in the selected studies, two reviewers independently utilized the Cochrane Risk of Bias criteria to indicate whether each study posed a high, low, or unclear risk of bias (see Table 2 below). Both reviewers discussed the studies after an independent analysis and reached a consensus regarding the criteria.

Table 2. Risk of bias across studies.

Authors	**Type of study**	**Selection bias (random sequence generation)**	**Selection bias (allocation concealment)**	**Reporting bias (selective reporting)**	**Performance bias (blinding of participants and personnel)**	**Detection bias (blinding outcome assessment)**	**Attrition bias (incomplete outcome data)**
Kleczka et al [26]	Pre-post design	High	High	High	High	High	High
Das et al [27]	Randomized-controlled trial	Low	Low	Low	Low	Unclear	Low

Lunn AD [28]	Pre-post design	High	High	High	High	High	Low
Hoa et al [29]	Randomized controlled trial	Low	Low	Low	High	Unclear	Unclear
Korom et al [30]	Pre-post design	High	High	High	High	High	Low
Rambaud-Althaus et al [31]	Cluster randomized controlled trial	Low	Low	Low	High	High	Low
Eltayeb et al [32]	Pre-post design	High	Low	Low	High	High	Low
Shao et al [33]	Controlled, non-inferiority trial	Low	Low	Low	High	High	Low
Awad et al [34]	Pre-post design	High	High	Low	High	High	Low

Chalker et al [35]	Randomized controlled trial	Low	Low	Low	High	High	Low
Chuc et al [36]	Cluster randomized controlled trial with time series design	Low	Low	Low	High	High	Low
Chalker et al [37]	Randomized controlled trial	Low	Low	Low	High	High	Low
Phuong et al [38]	Randomized controlled trial	Low	High	Low	High	High	Unclear

Other observations

Response shift bias is a common source of bias among non-randomized study designs (Kleczka et al, Lunn AD, Korom et al, Eltayeb et al, and Awad et al). In the study by Das et al, while the risk of bias according to traditional criteria was quite low, there was an additional risk because the impact of training was only estimated for those who expressed interest in the program, rather than all participants who were approached. Similarly, with Hoa et al's randomized controlled trial, there

was a difference in participation between private and public facilities which may have biased results; Korom et al's pre-post study only covered two outpatient sites and relied on a retrospective chart review to assess process measures in clinical encounters, which limits generalizability and discounts the possibility of assessments without adequate documentation. The average interval between intervention and outcome measurement for studies was 3.5 months, and the intervention follow-up period varied dramatically from 28 days (Shao et al) to 5 years (Phuong et al). In general, the durability of the interventions is unclear, because most studies did not assess the long-term impact of the intervention beyond 12 months.

Discussion

Our systematic review features studies from outpatient settings in low-income or lower-middle-income countries, with several studies focusing on the informal sector and pharmaceutical sector which is underrepresented in the literature on ABR from these regions. The study by Das et al is critical in illustrating the importance of improving the evidence base for behavioral interventions in the informal sector, which caters to 50-80% of primary healthcare visits in rural India and represents a major driver of antibiotic use in India [39-41]. While the educational intervention did not result in significant changes to rational antibiotic prescription behavior, it did improve correct case management, suggesting the informal sector can be reached for behavioral interventions, without cause for additional concern around worsening existing practices. Das et al indicate that the poor effect of the intervention on antibiotic prescriptions may result from the fact that the majority of providers earn profits through sales of medicines from wholesale providers or sales representatives, which may incentivize overtreatment.

Structural interventions addressing root causes and market-based incentives may be more effective at curbing inappropriate antibiotic prescriptions in such situations. Chalker et al and Chuc et al demonstrated the importance of moving beyond educational interventions to include multi-faceted, bundle interventions that combine regulations enforcement with face-to-face education and peer influence. Based on the 13 studies included in our final review, bundle interventions appear to be effective at changing prescription behavior among healthcare providers, including drug sellers or pharmacists. Arnold SR and Strauss SE reported similar results in their systematic review, which

analyzed 39 studies detailing the effect of "printed educational materials for physicians, audit and feedback, educational meetings, educational outreach visits, financial and healthcare system changes, physician reminders, patient-based interventions and multi-faceted interventions" in high-income contexts [22]. Their results suggested printed educational materials or audit and feedback alone resulted in limited or no changes in prescription behavior and multi-faceted or bundle interventions were the most effective in reducing irrational antibiotic use [22].

Other studies have also found that simply raising the awareness of ABR among consumers or prescribers in low-income and lower-middle-income settings may not be effective, because prescribers weigh a multitude of options when prescribing antibiotics: Pearson M and Chandler C found high levels of awareness in nine low-income settings did not translate into a reduction in misuse of antibiotics [42]. Prescription behavior was shaped by social determinants, such as the prevailing economic situation, decrepit health infrastructure, and inadequate hygiene and subsequent reliance on antibiotics as a substitute, further amplifying reliance on pharmaceutical representatives.

In resource-limited contexts within countries like India or Nigeria, successful and sustainable interventions should incorporate elements of audit and feedback or academic detailing interventions. Given the difficulties of implementing academic detailing interventions in resource-limited contexts, however, reinforcement seminars may be an effective alternative as suggested by Awad et al [34]. There is a need to evaluate the durability and sustainability of these interventions long-term, especially in limited resource settings, but multi-faceted interventions have a better track record to influence prescription behavior in this regard, compared to any single intervention. As Kleczka et al found, the use of routine data to measure and improve quality of healthcare is rare in low-income and lower-middle-income countries and simple technological interventions, such as rubber stamp templates and the use of smartphones, to deliver routine data in outpatient settings may also be an effective complement to educational or audit and feedback interventions in order to address knowledge-practice gaps within the health system.

Regulatory enforcement is often a major challenge in low-income settings, and may cause more harm than good in these settings: as Goodman et al note, overzealous regulatory enforcement may

have the unintended consequence of limiting access to urgently needed medicines, including antibiotics [43]. Rather than envisioning a top-down paradigm of regulatory enforcement, one possible way forward is to leverage multi-sectoral coordination and utilize a combination of provider incentives, indirect regulation through consumers, and public-private collaboration to incentivize rational prescription and dispensation of antibiotics [43-44]. In the Indian context for example, a potential way forward would be to link existing behavioral interventions or educational seminars with organized associations of informal providers and pharmacists, who function as the frontline providers in many rural areas. Adopting appropriate or rational prescription behavior requires a shift away from reliance on guidelines or educational interventions alone, and a broader recognition of the systemic factors driving prescription decisions, such as the use of antibiotics as a way to prevent future infections in the context of poor sanitation and infection control [41]. Structural interventions alone may offer some benefit compared to educational interventions, but they will be more effective and sustainable in concert with audit and feedback and other behavioral interventions that are integrated within the health system in limited resource settings.

Limitations

Given the heterogeneity of the studies, we were unable to conduct a meta-analysis and decided to opt for a narrative synthesis of the studies. We excluded national policy guidelines as they were determined to be outside the scope of behavioral interventions, and we did not include studies that focused simply on cost-effectiveness. Our review focused solely on prescription behavior, and did not take into account behavioral interventions targeting consumers or the general public- this has been adequately addressed by other reviews in high-income countries, but remains an area with limited scientific literature in low-income and lower-middle-income countries. Most of the studies included in the review measured changes over a short period of time and did not adequately account for long-term or sustainable changes in behavior. The generalizability of this review may be limited given the scope, but there are important lessons to be gleaned from the varied interventions in diverse low-income and lower-middle-income countries included in the review.

Conclusion

Multi-faceted interventions that integrate educational materials with audit and feedback or peer-to-peer comparison may be an effective method of reducing inappropriate prescriptions in limited-resource settings.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Chapter 4:

Exploring behavioral interventions and policy strategies to address antibiotic misuse within primary healthcare in India: a qualitative study

This paper is currently being peer reviewed in the SAGE Journal of Infection Prevention.

Abstract (295 words)

Introduction

Antimicrobial resistance poses a major public health threat. Despite Indian retail sector antibiotic consumption per capita increasing by approximately 22% between 2008 and 2016, empirical studies that examine policy or behavioral interventions addressing antibiotic misuse in primary healthcare are scarce. Our study aimed to explore this theme, particularly within the Indian private and informal sectors.

Methods

We conducted 23 semi-structured, in-depth interviews with a variety of key informants with diverse backgrounds in academia, non-government organizations, policy, advocacy, pharmacy, medicine, and others. Data were charted into a framework matrix and analyzed using a hybrid, inductive and deductive thematic analysis. Themes were analyzed and organized according to the socio-ecological model at various levels ranging from the individual to the enabling environment.

Results

Key informants largely focused on the importance of adopting a structural perspective to addressing socio-ecological drivers of antibiotic misuse. There was a recognition that educational interventions targeting individual or interpersonal interactions were largely ineffective, and policy interventions needed to incorporate behavioral nudge interventions, improve the healthcare

infrastructure and embrace task shifting to rectify staffing disparities in rural areas. Key informants also expressed a need to adopt a hub-and-spoke model to target informal providers via existing networks with formal providers and pharmaceutical company representatives, incorporate smart regulation for antibiotic use, leverage the role of pharmaceutical companies in decoupling sales and incentives, and strengthen enforcement of existing policies such as Schedule H1.

Conclusion

Prescription behavior is perceived to be governed by structural issues of access and limitations in public health infrastructure that create an enabling environment for antibiotic overuse. Interventions should move beyond a clinical and individual focus on behavior change with respect to AMR and aim for structural alignment between existing disease specific programs and between the informal and formal sector of healthcare delivery in India.

Introduction

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) as one of the top ten global health threats [1]. While antibiotic misuse and overuse as well as inadequate drug development pathways have been recognized as major drivers of antibiotic resistance, the patterns and drivers of antibiotic use vary significantly by region and are often influenced by socioeconomic factors, especially in low-and-middle-income countries (LMICs) such as India [1-2].

Much of the current literature on addressing AMR in LMICs has focused on antibiotic stewardship, defined as interventions that seek to measure and optimize the use of antibiotics; however, the predominant focus is on inpatient settings, where antibiotic stewardship committees can be readily established and compliance can be monitored [3-9]. Outpatient use is a significant driver of antibiotic resistance and antibiotic consumption per capita in the retail sector in India increased by approximately 22% between 2008 to 2016 [10]. Despite this, there are few evidence-based interventions to address antimicrobial misuse in primary healthcare or outpatient settings in LMICs

[11-14]. Most of these studies have found that antibiotic stewardship programs in primary healthcare are suboptimal, national guidelines ineffectively implemented, and multi-faceted interventions focused on specific diseases have been more effective at reducing antibiotic prescriptions compared to one-off educational interventions [11-14].

In the Indian context, antibiotic use in primary healthcare is difficult to contextualize without a concrete understanding of the decentralized and pluralistic model of healthcare delivery in rural and urban settings. India has a long-standing tradition of multi-tiered, pluralistic care seeking behavior. Outpatient care is provided free-of-cost at government facilities, and India's decentralized health system aims to provide one primary health center (PHC) for every 30,000 people and one community health center (CHC) for every 120,000 people [15]. In reality, however, there are far fewer facilities, and chronic shortages of doctors and other qualified providers is the norm in rural areas [16, 17].

In response, the Indian Government has periodically sought to train mid-level providers: the states of Chhattisgarh and West Bengal developed three-year diploma courses for modern and holistic medicine in rural areas [16]. In 2018, under the National Health Mission, the Government of India also launched a bridge program in community health for nurses and practitioners of holistic and traditional medicine such as Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa and Homoeopathy (AYUSH) [18-19]; for example, there are currently nearly 4000 AYUSH hospitals nationwide [20]. In rural areas in particular, AYUSH practitioners are actively employed within government health facilities to integrate traditional medicine with allopathic medicine, and improve doctor-patient staffing ratios [20].

Such limitations in the public sector often force a majority of patients to seek care in the private sector, access antibiotics over-the-counter at pharmacies as "quick cures" to alleviate symptoms, or visit informal providers in rural areas [21-24].

However, there are few, if any, empirical studies that examine policy or behavioral interventions to address AMR in primary healthcare, particularly with this group of traditional, AYUSH, private and informal providers in India [24-25]. Our study aimed to address this gap in the literature and

explore interventions and policy strategies to address antibiotic misuse in primary healthcare settings in the Indian context.

Methods

Design and data collection

Semi-structured, in-depth interviews were conducted with a wide variety of key informants focusing on India, including policy makers, non-profit leaders working in AMR, researchers, academics, allopathic medical practitioners, public health practitioners, among others. Through a literature review, we identified and contacted a list of key informants who worked in the area of antibiotic misuse in India. Subsequent snowball sampling was utilized to identify and recruit additional participants. Participants were continuously and purposively sampled until saturation was attained. In total, 53 participants were invited to participate in the study, with 6 key informants declining to participate due to a lack of time and 24 non-responders despite repeat e-mail requests.

The topics explored in the interview guide ranged from awareness of antibiotic dispensation practices in India, current research on antibiotic misuse, behavioral interventions to address misuse, national policies targeting AMR in India, the role and impact of pharmaceutical company representatives (PCRs) and the pharmaceutical industry on AMR, among other key domains (see Supplementary Material 2). Since the interview guides were semi-structured in nature, there was ample room to inductively draw upon emerging areas of inquiry from each new participant.

Each interview was transcribed verbatim and verified against the audio recording for transcription accuracy. Identifying information and names were redacted from each transcript. All interviews were conducted over Zoom in English, and no translation was required.

Data analysis

Data were analyzed using a framework matrix methodology, which incorporates flexible and robust approaches from thematic analyses and qualitative content analyses [26]. Each transcript

was read and re-read to aid familiarization with the data. The codebook was developed iteratively, using both an inductive and deductive approach: an initial set of codes were derived based on a review of the literature, interview guide, and familiarization with the first few transcripts, while emergent codes were added based on a review of each subsequent transcript. Each transcript data was indexed as an individual case in Microsoft Excel wherein each row represented an interviewee or case and each column represented a unique code.

Once all codes were saturated in the matrix, a cross-case comparison for each code was completed, detailed notes were referenced during the development of the codebook, and emergent thematic areas from the data were identified. The matrix allowed for a systematic comparison by case and code, enabling an analysis of higher-level themes across the entire dataset.

A social-ecological paradigm was utilized to better organize themes and present interventions related to antibiotic use at various interconnected levels: individual, interpersonal, organizational, community, and policy/enabling environment interventions [27-28]. Individual and interpersonal factors within the socio-ecological model examine individual characteristics and social networks between individuals; the organizational level includes institutions like hospitals that govern the development of regulations and behaviors; the community level in the model analyzes networks or relationships between organizations and institutions; and the policy/enabling environment level analyzes state, local laws and regulations [27].

Patient and public involvement

Patients or the public were not involved in the design, conduct, or implementation of this study. However, key informants represented various perspectives in non-governmental organizations, policy making, and medicine and public health, and were integral in informing the snowball sampling approach.

Ethics

The study was approved by the Maastricht University Ethics Review Board (FHML-REC/2020/044). All interviewees were provided with an information sheet, agreed to be audio

recorded, and each participant provided written informed consent by e-mail prior to participation in the interview.

Results

Semi-structured interviews were conducted with 23 key informants in total who represented a range of perspectives in academia, medicine, pharmacy, policy making, and non-profit advocacy within India, as demonstrated in Figure 1 below. Most respondents were part of academic institutions and several overlapped with government/policy making work and medicine.

Figure 1. Demographic profile of key informants; categories are not mutually exclusive.

61% of the respondents were female, and 39% were male; respondents ranged in age from 29 to 63 years old. The themes were analyzed and charted according to the social-ecological model and framework:

Individual or interpersonal level interventions

Educational or training interventions are largely ineffective in changing prescription behavior of individuals

Interventions that targeted individual or interpersonal interactions were perceived to inadequately recognize the context and influence of societal or systemic factors on behavior and were considered to be ineffective according to most key informants. Economic incentives, such as patient demands for quick cures, kickbacks from referrals to private networks, non-monetary and monetary rewards for antibiotic prescriptions from drug representatives or PCRs, and a desire to maximize profit under a capitalistic, market-driven model of healthcare delivery, were perceived as major drivers of antibiotic use and less amenable to behavior change from one-off educational or interventions targeting the individual: "*training improved correct management of the cases, but it didn't decrease unnecessary usage of medicines…doctors who are better tend to do the right thing more often, but they don't do the wrong thing less often*" (KII 22).

"*It's not a knowledge deficit that's happening here…for private providers especially, it's to their own economic detriment to sort of mitigate, mitigate against overuse. So I think it's a very difficult thing to ask private providers to put their livelihood on the line*" (KII 21).

One participant outlined how countries like the United Kingdom often leveraged nudge-based interventions: non-financial and behavioral interventions, such as recognizing medical practitioners who followed guidelines and reduced antibiotic use when it was not medically indicated as peer champions, were often successful in curbing misuse from an individual perspective.

Multi-pronged interventions, which combine knowledge enhancement with stronger regulations, audit and feedback, or peer-to-peer comparison, were perceived to be more effective in creating behavior change: "*I think it has to be a multi-pronged approach. And it has to be something that is continuously reinforced. But behavioral change is very tough*" (KII 20). However, key informants did note that even these multi-pronged interventions found limited success in sustaining behavior change over time since they were too focused on the individual or interpersonal interactions rather than the enabling environment in which these decisions occurred: "*The contextualization of these providers in the cosmos in which they function, that universe, one needs to look at that holistically. And then, consider multifaceted interventions that are focusing not just on these providers, but also on the other actors who influence what they are doing*" (KII 7).

Organizational level interventions

Other key informants focused more on interventions that occurred at the organizational level, such as antibiotic stewardship programs within health facilities.

<u>Antibiotic stewardship programs have not been implemented in the outpatient and private sector</u>

Key informants recognized that existing interventions often did not scale across different institutions and focused largely on inpatient settings alone. Even if a primary health care antibiotic stewardship pilot intervention existed, these largely ignored the role of a vast section of the primary healthcare workforce in the private sector: "*Nobody knows exactly what happens in there. And...it's even hard to identify them...you basically have to go and look for them in the street and knock on*

their door...if you don't know who to target, how can you intervene on what they're doing?" (KII 1).

Community-level interventions

Interventions that went beyond individual or institutional actors and analyzed the networks between these actors within the context of the broader community were classified as community-level interventions.

Adopting a hub-and-spoke model: targeting informal providers via existing associations and networks of formal providers

Key informants noted that informal providers already have strong collaborations and referral networks with formal providers, which can be leveraged for future interventions. They are extremely well-organized and have associations that coordinate with one another via WhatsApp groups: "*these guys are way more powerful and they're better organized [than] we think…[you could try to] convince one to let you in on his Whatsapp group*" (KII 18). Pharmaceutical companies have already tapped into these associations to increase sales of antibiotics in these unsaturated markets. A collaborative, multi-pronged intervention could tap into these existing networks and aim to disseminate knowledge to patients through trusted community leaders and religious leaders, while partnering with traditional healers, informal providers, and formal practitioners of allopathic medicine alike. These connections were often described as a hub-and-spoke approach to building educational networks:

"*How do you work with multiple stakeholders who have such diverse interests, not just across the human and veterinary health sectors, but also in terms of their you know, economic orientation, in terms of their professional background? We are dealing with informal providers, we're dealing with formal doctors, we realized that you can't just address informal providers, without bringing in doctors- the links between them are too strong and too close. So you know, we need to address them as...a kind of hub-and-spoke...because that's how they also function*" (KII 7).

Task shifting interventions could increase community service provision and simultaneously regulate use of antibiotics based on WHO AWaRe criteria

Given the limitations to healthcare access in India, especially in vast segments of rural India, restriction interventions should be cognizant of unintended consequences that further limit access for marginalized populations. A suggested better policy approach would be to leverage task shifting interventions to strengthen rural primary healthcare provision, while basing antibiotic availability according to the WHO AWaRe criteria: access group antibiotics that have lower potential for resistance should be widely available, watch group antibiotics should be more limited given their higher potential for resistance, and reserve group antibiotics should only be used as a last resort [29]. Auxiliary nurse midwives (ANMs), who work in primary health centers, were perceived by a few key informants as a crucial pillar in this strategy:

"*It's probably important when you look at the access, watch, and reserve list of antibiotics, to ensure that the access antibiotics are available…the ANM for example…know the villages, they know exactly what's going on…probably the government will have to have some kind of a primary list of access antibiotics based on certain science and protocols.*" (KII 13).

This kind of task shifting intervention could integrate informal providers as well: "*[policy makers] haven't tapped on to that sector to provide access to health care...so for example, for a common cold or cough or injury, it's fine to go to this kind of guy who can provide you first aid access, as long as he's trained, he's certified*" (KII 14).

Key informants noted that this approach could limit access to watch or reserve group antibiotics, empower frontline providers who already have strong connections in the community, and conserve important antibiotics without hampering access to necessary medicines for the community.

Policy/enabling level interventions

Key informants predominantly named systemic, policy-level interventions as promising avenues for curbing antibiotic misuse and enacting behavior change. These interventions largely focused on drug regulatory policies and market-based incentives for the retail and pharmaceutical sector and focused on the enabling environment that influenced individual, institutional, and community-based actors.

Leveraging the role of pharmaceutical companies and representatives

The role and influence of pharmaceutical company representatives varies widely across outpatient settings in different Indian states. While it is true that the nexus between the pharmaceutical industry and the medical profession "*begets more inappropriate prescribing*," PCRs occasionally function as "*medical science liaisons or medical advisors*" who engage doctors in a "*constant adaptation of knowledge of the recent data"* (KII 5). The incentives in this industry are entirely structured around maximizing profits from antibiotic sales, but several key informants who were also medical doctors reported that these interactions with PCRs also allowed them to learn about new drugs on the market. At present, PCRs have a fixed salary component and a variable component that increases based on the volume of sales, which can incentivize heavy marketing and over-prescription of antibiotics.

Key informants suggested working directly with pharmaceutical companies, such as GlaxoSmithKline (GSK), who have previously made pledges to delink sales from incentives for employees. "*In 2019, I think there were many pharma companies that decided to delink their sales with the profit, right? And GSK was one of them. But eventually, GSK went back on its own promise to delink sales with profit for the employees, because no other company was following suit*" (KII 14). This approach was largely recognized as an uphill battle as it ran counter to the motivations in a market-driven model of providing health and medicines, but there was some optimism for companies to follow suit and rebrand their healthcare approaches around conservation of antibiotics. One key informant named four concrete policy interventions that hold promise: *1) complete decoupling of incentives from antibiotic sales, 2) working with pharmaceutical company representatives to engage in science-based advocacy rather than product-based advocacy, 3) more real-world studies on antimicrobial susceptibility and sensitization of primary care physicians, and 4) sensitization of "quacks" or informal providers to acknowledge the harms of antibiotic overuse and understand when a referral to formal providers might be necessary* (KII 5).

Regulation has been somewhat effective in this regard, because the number of visits by pharmaceutical company representatives across outpatient departments has dramatically decreased: "*Again, if we talk about our state, because in the last four to five years, the number of MR [PCR] visits are much less nowadays"* (KII 8). This was partially due to better enforcement and availability of free or subsidized medicines within public hospitals, which reduced the demand or need for branded medicines by PCRs.

However, the challenges and barriers to large-scale changes in pharmaceutical regulation in India are significant. As some key informants mentioned, the pharmaceutical industry has deepened its presence in "*unsaturated*" rural and informal markets, which "*hold huge potential for expanding revenue segments*" (KII 7). Decoupling volume of sales from the salary would fundamentally alter the incentives for marketing and is unlikely to happen without "*very strong regulatory provisions*" (KII 12).

Inconsistent implementation of drug regulatory policies such as Schedule H1

India has strong regulations on paper that limit the prescriptions and sales of antibiotics, but implementation and enforcement have consistently lagged behind. "*If you think about the over-the-counter sale of antibiotics, this is technically forbidden in India, but it happens all the time....it's clear, everybody knows. I think it's pretty easy, because...antibiotics are sold over the counter everywhere...throughout drug stores at every corner*" (KII 1).

Schedule H1 came into effect as an amendment to the Drugs and Cosmetics Rules Act of 1945 and imposed restrictions on over-the-counter dispensing of certain antibiotics (mostly third and fourth generation cephalosporins, carbapenems, and newer fluoroquinolones) [30]. Under the policy, the drugs under this schedule contain a Schedule H1 warning label and chemists can only dispense the medications after checking a valid prescription and maintaining a separate register with details about the patient and prescribing doctor [30]. Drug inspectors have the authority to conduct surprise checks, but these are not regularly conducted, according to a senior authority and key informant from the Indian Pharmaceutical Association: "*schedule H1 [is]...checked sometimes by the drug inspectors...but maintenance of the Schedule H1 register only [entails] writing down the prescription regimen. Beyond that, [I have] not seen any [checks]*" (KII 11).

Poor enforcement and implementation of regulatory policies also impacts the manufacturing pipeline for antibiotics and the types of formulations which are available to the public, such as fixed dose combinations which tend to be more expensive than essential medicines which fall under price control orders, and are largely not evidence based. As one key informant noted, "*Why don't we curb the manufacturing of antibiotics? And why don't we become more serious about the FDCs [fixed-dose combinations] in the case of antibiotics?...look at the number of formulations*

which are available in India…the regulators are always ill equipped with the infrastructure, the number of drug inspectors" (KII 11).

Centralized drug procurement and standard treatment guidelines (STGs) for primary care

Key informants commonly named centralized drug procurement processes and standard treatment guidelines as a policy lever for reducing outpatient antimicrobial use, although this was perceived to be more effective in the public sector rather than the private sector. One key informant noted that antibiotics were often procured in parallel contracts despite the fact that these were not permitted within primary healthcare settings under the centralized procurement system. As of today, almost all states have an essential medicines list and a formal procurement system in place, and many have established evidence-based STGs in the government healthcare system.

However, adopting and following the guidelines is not always easy. Sensitizing doctors can be difficult as STGs are frequently perceived to "*encroach on their autonomy*" and limit empirical treatment based on clinical experience. Other barriers to adoption include unavailability of a physical copy of the guidelines in primary healthcare settings, and the fact that most guidelines are catered to inpatient settings within the public sector: "*The current guidelines for antimicrobial treatment in India are mainly thought for the inpatient setting...what is needed is a guideline for empirical treatment in the field"* (KII 1). Guidelines are inadequately followed in the public sector, but they were perceived to be even less commonly followed in the private sector. Key informants noted that they would need access to these guidelines along with training and incentives for compliance and enforcement:

"*I know it very well in West Bengal, that there are very clear guidelines on which antibiotics can be prescribed...but…there has yet to be a strong mechanism of either prescription audit or kind of digital prescriptions or whatever, in order to assess how far there is adherence*" (KII 12).

Supply-side interventions should target drug pricing policy and availability of antibiotics

One of the key themes emerging from our analysis detailed the need to control the supply of antibiotics. From this lens, changing the behavior of informal providers was seen as a lofty goal, since it was often governed by structural and market-based forces rather than knowledge deficits.

In contrast, supply-side interventions that control the availability of antibiotics were perceived as more promising: "*If they [antibiotics] are available off market, off prescription, free for everything, then the informal providers are just a small link in the chain...interventions targeting the informal providers for antibiotic prescribing should not focus on them, but rather should focus on their supply line, which is the pharmacies"* (KII 12). A regulatory system that controls the supply of antibiotics in the market would mitigate the need to change individual prescriber behavior in the informal sector.

The availability of generic medicines rather than brand-name antibiotics was seen as another key supply side intervention and policy lever to offset the influence of pharmaceutical companies. The current system allows for aggressive marketing by PCRs to ensure brand differentiation and market segmentation. Improving access to generic medicines and regulating the availability of antibiotics in the private sector may reduce cost for consumers and reduce the incentives for irrational prescriptions.

Inadequate access to antibiotics and healthcare is a larger problem than excess antibiotic use

From the perspective of an enabling environment, several key informants commonly noted that interventions must recognize the role of systemic and structural problems, such as inadequate hygiene and sanitation measures, poor public health infrastructure, inadequate access to antibiotics, and limited frontline healthcare staff (especially in rural areas), in creating endemic and problematic access barriers within the Indian healthcare system. "Irrational" antibiotic use in this regard was understood as a strategic response by healthcare providers to cope with inadequate access to healthcare for the vast majority of the Indian population. From this perspective, the term "irrational" was seen as a misnomer:

"*I think the white world calls it irrational practice. But how can you call it irrational when there are clearly good reasons for something that's taking place?...what are the reasons which are more structural in nature that kind of are encouraging this kind of practice, because anyone that I know, who is a physician...knows that we shouldn't be indiscriminately prescribing antimicrobials*" (KII 4).

"*Then, of course, in places like India, and any low and middle-income countries, as always, an issue of access and excess. So, you got rural places where there's hardly any healthcare facilities really...And if there is no pharmacy shop, what do you do? Then you go to a quack, right? Or you go to a native medicine person. And so all these are structural challenges, which actually prevent or rather inhibit forward movement in terms of action plans*." (KII 13)

These social determinants of antibiotic prescription behavior were seen as critical levers in understanding why healthcare providers dole out seemingly "irrational" prescriptions. There was also a concern that policy interventions must be cognizant of unintended consequences that could result from any policies that restrict access to antibiotics in the general population in the absence of a strong and functioning healthcare system.

Discussion

The importance of recognizing and addressing structural barriers to accessing high quality healthcare and understanding antibiotic use in the context of social determinants of health was a clear overarching theme across our interviews. Our results indicate that prescription behavior is perceived to be governed by structural issues of access and limitations in public health infrastructure that create an enabling environment for antibiotic overuse. Thus, from a socio-ecological perspective, interventions designed to improve knowledge of antibiotic use or educational interventions targeting individual or interpersonal interactions alone are unlikely to work, as there is a clear knowledge-practice gap even with interventions that successfully improve an individual's existing knowledge base.

This gap between knowledge and practice is well established in the global literature in AMR. For instance, Pearson and Chandler conducted more than 200 qualitative interviews and field observations in seven study sites across Ethiopia, India, Nigeria, the Philippines, Sierra Leone, and Vietnam [31]. Their study found that even when awareness of AMR was high among human and animal healthcare professionals, it did not translate into better practice and reduced prescribing. Contextual factors, such as improved infrastructure and regulation, were far more salient in reducing reliance on antibiotics. [31].

In India, the formal leadership of the Indian Medical Association advocates for a strict ban on antibiotic dispensing by informal providers, along with regulatory enforcement and punishment, in accordance with the provisions of the Indian Medical Council (IMC) Act of 1965, which makes it illegal for anyone without a university medical qualification to practice modern medicine [32-34].

Rather than wishing these frontline providers away in the context of lacking political will, our key informant interviews stated that this is both impractical and detrimental to public health and suggested a newer approach to empower formal and informal frontline providers, train and equip them with access group antibiotics, leverage existing connections and referral networks to private or public formal providers, and explicitly regulate access to watch or reserve group antibiotics.

In addition to a strengthened frontline healthcare workforce, additional investments must be made in implementing a routine prescription audit and feedback system in government primary healthcare centers, and building partnerships with academic and community-based organizations to establish hub-and-spoke models via associations of formal and informal providers, which could enable a thorough mapping of informal providers operating in the region.

Several studies have examined the behavior of private practitioners who treat tuberculosis, and the divergence in behaviors in terms of referrals to government hospitals [35-39]. McDowell and Pai found that even non-biomedical, AYUSH private practitioners frequently resorted to biomedical therapies, and almost 94% referred patients to a chest physician or the public sector [37]. Engel and van Lente found that effective integration of a public-private mix requires bridging diverse organizational cultures: the command-and-control style of the Revised National Tuberculosis Control Program, the professional monopoly of private practitioners that is aversive to control, and the community-oriented and participatory model of NGOs [38]. Many lessons for controlling AMR can be gleaned from tuberculosis treatment efforts in India in this regard, given the motley mix of public providers, private practitioners, and traditional healers in the TB care continuum

Finally, the pharmaceutical industry must be strategically engaged to counter the incentives for overprescribing, which are inherently built into the business model. Practices that leverage a firm's

desire for responsible stewardship-focused branding might be useful to engage companies like GlaxoSmithKline, which have previously expressed interest in taking action against AMR. The overall regulation of the pharmaceutical industry is another major policy area that requires additional oversight and intervention.

While the Government has enacted some regulations with respect to banning FDCs and enacting restrictive policies such as Schedule H1, their success has been a mixed bag with poor enforcement mechanisms and inadequate implementation across the country [40]. A 2018 study found that more than 60% of FDCs actually had no regulatory approval and many of the formulations were pharmacologically incompatible, reinforcing the need for better regulation and oversight of the pharmaceutical industry [41]. Regulatory recommendations inevitably face bureaucratic hurdles in implementation in a country as diverse and decentralized as India, but the Government has been able to implement and strictly enforce restrictions in areas it has deemed important, such as opioid access [42]. However, these have often created major access-related barriers for patients, and great care must be taken to ensure that patient rights to medicine are taken into account and existing disparities in access are not worsened.

The prevailing clinical focus on individual prescriber behavior in AMR must take into account the structural determinants that govern behavior from a socio-ecological perspective. As Broom et al detail in their examination of AMR from three different continents, an effective and sustainable approach to tackling AMR requires "solidaristic models that espouse collective responsibility and recognize relative opportunity to act rather than a continuation of the individualistic behavioral models that have, so far, proven largely ineffective" [43].

Limitations

While this study was able to meet a critical gap in the literature and incorporate unique insights from key informants, both academics and community-based advocates alike, it was not without limitations. Respondent validation through informal interviews with participants after data collection and analysis was not possible due to time and resource limitations. Even though 53 key informants were invited to participate, 57% declined the invitation to participate largely due to time constraints and non-response during the height of the COVID-19 pandemic; as a result, there

were more perspectives from academia and medicine or public health in comparison to government institutions and non-allopathic providers.

Conclusions

Behavior change interventions are very difficult to sustain without addressing structural barriers to accessing care that influence the policy and enabling environment. The healthcare delivery model within India offers unique opportunities to address structural barriers to accessing care and strengthen the existing delivery of primary and outpatient primary healthcare, while leveraging traditional and informal healthcare practitioners as a frontline workforce and improving regulatory efforts within the pharmaceutical industry.

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Supplementary Material 1: Codebook

1. Definition of antibiotic resistance
2. Drivers of antibiotic resistance
    1. Care-seeking behavior
    2. Types of antibiotics dispensed
    3. Prescription habits of private or informal providers
    4. Over-the-counter sale of antibiotics practices and policies
    5. Fixed-dose combinations practices and policies
    6. Role of pharmaceutical company representatives and incentives
    7. Social determinants or drivers of ABR
3. Access to antibiotics vs. excess antibiotics
4. Research gaps
5. Behavioral and policy Interventions:
    1. Need for multi-faceted interventions
    2. Strengthen the existing public health system

3. Improve data monitoring and surveillance
4. Centralized procurement and drug control policy improvements
5. National action plan policy strengths and weaknesses
6. Access and use of diagnostics
7. Leveraging existing networks between informal and formal providers
8. Task shifting
9. Standard treatment guidelines
10. Educational seminars
11. Antibiotic stewardship
12. AMR curriculum in medical training
13. Restriction interventions
14. Audit and feedback interventions
15. Academic detailing
16. mHealth or tech-based interventions
17. Patient or consumer education interventions

Supplementary Material 2: Key Informant Interview guide

1. Demographic details:
    1. Age, gender, occupation, years of experience, geographic region
2. Tell me about your current research. What does a typical day look like?
    1. Probes: How long have you been involved in this kind of work? What are your primary areas of focus in your research? What regions do you work in?
3. What is the role of formal and informal providers in a setting like India when it comes to antibiotic resistance?
    1. Probes: How would you define the informal sector? How are the formal and informal sectors structured in India? How do the informal sector and formal sector operate, especially with respect to antibiotic use and prescriptions?
4. How are antibiotics used and prescribed in the informal sector?
5. What types of interventions have been tried to address antibiotic use in the informal sector?

    1. Probes: What has been the level of success of such interventions? How have they been evaluated? Who are the actors behind these interventions? Who is funding these interventions? What is the level of priority assigned to these interventions? How are the interventions evaluated?
6. How do these interventions contrast with what's been attempted or tried in the formal sector in India?
7. What are some issues related to implementation of policies such as Schedule H-1?
8. What are the current gaps in research and knowledge regarding the informal sector and antibiotic prescriptions?
9. How does the informal sector interact with pharmaceutical representatives, if at all?
10. What are the best ways to engage the informal sector in antibiotic stewardship?
11. Which regions in India face the largest problems with respect to antibiotic prescription and use in the informal sector?
12. Who puts AMR on the agenda and how is the issue framed?
    1. Probes: By whom is it prioritized? What would it take to make it more of a priority on the national stage in India?
13. How are the national action plans to tackle AMR operationalized in India?
    1. Probes: What is the relationship between national plans and state-level plans? Which regions are doing well? Not so well? What changes, if any, are required?
14. Who else do you think I should speak with in this field?

Chapter 5

India's National Action Plan on Antimicrobial Resistance: A Critical Perspective

This paper has been peer reviewed and published in the Journal of Global Antimicrobial Resistance.

Abstract

Antimicrobial resistance is widely recognized as a global health threat that is projected to account for more deaths than cancer by 2050. The Government of India formulated a national action plan to tackle antimicrobial resistance (NAP-AMR), largely modeled on the World Health Organization's Global Action Plan on AMR. While the NAP-AMR successfully mirrors the Global Action Plan and lays out ambitious goals, we find that the lack of financial allocations across states, poor enforcement, and inadequate multi-sectoral coordination have hampered progress. A broader focus on improving infrastructure for water and sanitation, linking the issue of AMR to existing vertical health programs for HIV and TB, prioritizing infection prevention and control, strengthening the frontline healthcare workforce in rural and peri urban settings to reduce reliance on antibiotics, leveraging point-of-care testing and mobile app based mHealth interventions for diagnosis and surveillance, and adopting a socio-ecological approach to health and development would help create an enabling environment for concrete action on AMR in India.

Introduction

Antimicrobial resistance (AMR) has been recognized as a major global health threat by the World Health Organization (WHO), but the challenges are particularly stark in India [1]. There is widespread immunological resistance to commonly used broad-spectrum antibiotics, fluoroquinolones, as well as third-generation cephalosporins: studies have shown that over 70% of *Acinetobacter baumannii*, *E. coli*, and *Klebsiella pneumoniae* isolates, and over 50% of the isolates of *Pseudomonas aeruginosa* were resistant to third generation cephalosporins and fluoroquinolones [2].

Limited standardized surveillance data makes it even more challenging to monitor the extent and scope of resistance, and most of the data comes from published studies of healthcare associated infections in inpatient settings, scoping reports, prospective studies, and point prevalence surveys at select, large hospitals [3]. However, antibiotics are routinely prescribed for respiratory infections in primary care and outpatient settings in both the public and private sector [4–6]. A study in New Delhi, India by Kotwani et al. found that 39% of all patients attending private retail pharmacies and public facilities and 43% of patients visiting private clinics were prescribed at least one antibiotic [5].

Given this context, the Ministry of Health and Family Welfare (MoHFW) in India constituted three technical bodies (Intersectoral Coordination Committee, Technical Advisory Group and Core Working Group on AMR) to develop a national action plan on antimicrobial resistance (NAP-AMR) [7]. The NAP-AMR is largely modeled on the WHO's Global Action Plan (GAP) on AMR,

which was adopted by the World Health Assembly in 2015 [8]. In this paper, we examine the implementation, scope, and progress of the NAP-AMR in India with respect to the human sector.

Scope and coverage of the NAP-AMR: what is covered well and what is missing from the plan?

Political commitment for AMR in India has been building since 2011, when the health ministers of the South-East Asia Region's Member States articulated their commitment to tackle AMR through the Jaipur Declaration and prioritize it in national policy making. The NAP-AMR successfully integrates feedback from multiple stakeholders, including the Ministry of Health and Family Welfare, Ministry of Agriculture and Farmers Welfare, Department of Animal Husbandry Dairying and Fisheries, Ministry of Environment, and "clinicians and microbiologists, as well as international experts and policy makers from neighboring countries" [7]. It successfully models the Global Action Plan and follows a One Health approach, encompassing AMR in the context of human health, animal health, agriculture, and the environment. The six strategic priorities of the NAP-AMR include:

1. Improving awareness and understanding of AMR through effective communication, education and training
2. Strengthening knowledge and evidence through surveillance
3. Reducing the incidence of infection through effective infection prevention and control
4. Optimizing the use of antimicrobial agents in health, animals and food
5. Promoting investments for AMR activities, research and innovations
6. Strengthening India's international, national, and state level collaboration and leadership on AMR

Each strategic priority has several different key outputs and activities, with distinct short, medium, and long-term timelines [7]. While the plan is comprehensive in scope, it does not adequately take into account the nuances of pluralistic, multi-sectoral healthcare provision in India and fails to take into account the latest research on behavior change interventions and structural disparities in healthcare access.

Firstly, the plan relies heavily on individual knowledge, attitude, and practice (KAP) surveys across the general population and behavioral studies without establishing a clear repository for tracking this data. A standardized approach, led jointly by the central and state governments, would help in streamlining, collecting, and analyzing this data to better monitor trends over time. As Swaminathan et al note, standardized surveillance by government health agencies is more likely than individual surveys to bring about policy and practice changes in India [9].

Secondly, the indicators in the plan rely heavily on training, guidelines, and behavior change interventions that have seen limited success in India and other LMIC settings [10]. There is widespread variation in terms of compliance with standard treatment guidelines and educational efforts have not been consistently implemented across states; even where attempts have been made, frequent changes in governance of institutions, lack of time and enthusiasm, and a perceived encroachment on professional autonomy have presented major barriers to successful behavior change [6, 11].

In the NAP-AMR, there is an adequate focus on revising the curricula of professionals in human, animal, agricultural and environmental health, but the overarching emphasis is on behavior change

through campaigns rather than social compliance through nudge interventions or structural changes to the socio-ecological environment. For example, there is a strong emphasis on social mobilization campaigns and enhancing awareness of hand hygiene, but there is no mention of ensuring functional water and sanitation facilities in primary care institutions [7]. Existing initiatives should be closely linked to other sanitation programs such as *Swacch Bharat Abhiyan* [Clean India Mission]. While the plan does explicitly mention promoting "measures for overall health improvement and service delivery" in maternal health and immunization, a similar effort should be made to recognize the structural and socio-ecological impacts on behavioral changes and antibiotic prescriptions as a whole.

Additionally, while the plan does mention the need for antimicrobial stewardship at different levels, it does not recognize the diversity of outpatient care provision in India, nor does it provide clear mechanisms to coordinate activities between the public and private sector. The private sector is named as an entity for collaboration in microbiological surveillance and communication campaigns, but the system linkages to promote antimicrobial stewardship or track antibiotic use have not been detailed between the government sector and the traditional, informal, or private sectors. Given the diagnostic challenges in outpatient settings, scaling up use and access of point-of-care tests, such as C-reactive protein and procalcitonin, may reduce unnecessary antibiotic use. Electronic patient management algorithms utilizing similar interventions have documented clinically significant reductions in severe adverse events as well as unnecessary antibiotic use in other LMICs [12].

With respect to data monitoring and evaluation and surveillance measures, the NAP-AMR relies on a national network of laboratory-based surveillance at a few designated reference laboratories

in tertiary care medical institutions. While this Antimicrobial Resistance Surveillance & Research Network (AMRSN) has been a crucial step forward towards national surveillance, it is a reflection of tertiary care settings rather than community-based settings [13]. The patterns of antibiotic use and resistance differ widely between primary and tertiary care settings, with the understanding of drivers of antibiotic use at the community level extremely limited. As such, there is a clear need to scale up these surveillance networks to capture data from community-based settings [13]. Tracking and monitoring surveillance data from app-based platforms could be a crucial step forward in this regard. During the COVID-19 pandemic, India and China successfully launched and utilized mobile apps such as Aarogya Setu for contact tracing via Bluetooth [14]. Mobile, app-based platforms can be similarly leveraged as critical tools to disseminate information to private and public providers related to AMR patterns and antibiotic misuse, aiding the process of making a diagnosis, and improving surveillance and data collection efforts from community-based settings.

Finally, while the plan does briefly reference the crucial need to align AMR containment measures with existing vertical health programs (i.e. National Vector Borne Disease Control Program or National AIDS Control Organization), there are no supplementary, publicly available documents outlining the mechanisms for implementing these linkages. AMR containment is outlined as a cross-cutting, horizontal program that cuts across several sectors and government ministries, but it must be integrated at all levels in existing programs for dengue and malaria control, TB care, HIV care, among others.

Implementation gaps in the NAP-AMR

The five-year NAP-AMR (2017-2021) was intended as a pivotal blueprint for states to develop their own state action plans to tackle AMR, since health is a state subject in India. However, only three states/union territories have established state action plans: Kerala, Madhya Pradesh, and Delhi; financial constraints have impeded further implementation efforts as well [15].

While there have been significant legislative efforts to curb antibiotic misuse since 2017, including a ban on several fixed dose combinations, a ban on colistin as a growth promoter in animals, and establishing antibiotic residue standards for pharmaceutical effluents, implementation and enforcement of measures has been a challenge [15].

Several efforts have been made to restrict access to over-the-counter antibiotics, including the revamped and restrictive Schedule H1 policy, which was enacted prior to the introduction of the NAP-AMR [16-17]. Schedule H1 a) restricts the dispensing of certain drugs, including several third and fourth generation cephalosporins, carbapenems, newer fluoroquinolones and first- and second-line antitubercular drugs, to prescription-only, b) mandates adequate labeling of these drugs, and c) requires the maintenance of a separate register for these prescription-based sales. The NAP-AMR identifies the need to add regulatory interventions to further support Schedule H1 and review the categorization of newer antimicrobials under Schedule H1 [7].

One study by Farooqui et al. noted a significant decline in the quantum of antimicrobial use after Schedule H1 restrictions were imposed in 2014 based on retail sales data from 30 different regions in India [18]. However, implementation has varied widely across states, and Kerala has been one of the few states to successfully limit over-the-counter antibiotic sales and self-medication [18]. In other regions, implementation and enforcement of Schedule H1 has lagged far behind and has not

resulted in reductions of non-prescription, over-the-counter antibiotic use due to poor regulatory enforcement by drug inspectors and limited capacity [17].

Funding challenges and lack of multi-sectoral coordination at the central and state government levels have also been challenging. Given the conflicting priorities for state governments, there is a lack of separate financial allocations for AMR initiatives across different states in India, which creates a major impediment to progress at the national level [8]. The advent of the COVID-19 pandemic has made AMR even less visible, and further impeded progress; AMR is rarely, if ever, documented specifically as a cause of mortality or morbidity [19]. Without clear templates and governance structures to coordinate action between states, India is unlikely to make significant progress on AMR. Kerala offers a unique model for other states in this regard, because it has been able to coordinate public private partnerships, initiate and scale good antibiotic prescription practices across primary, secondary, and tertiary institutions, and coordinate activities via a statewide task force and a core committee at the state level [20]. Similar efforts should be encouraged by different state governments and financially supported by the central government.

Conclusion

While the NAP-AMR successfully mirrors the Global Action Plan and lays out ambitious goals, the lack of financial allocations across states, poor enforcement, and inadequate multi-sectoral coordination have hampered progress. The central government should emulate the successes of the Kerala State Action Plan in promoting a One Health approach and effectively coordinating between public and private sector actors to implement antibiotic stewardship initiatives. A broader focus on improving infrastructure for water and sanitation, linking the issue of AMR to existing vertical health programs for HIV and TB, prioritizing infection prevention and control,

strengthening the frontline healthcare workforce in rural and peri urban settings to reduce reliance on antibiotics, leveraging point-of-care testing and mobile app based mHealth interventions for diagnosis and surveillance, and adopting a socio-ecological approach to health and development would help create an enabling environment for concrete action on AMR in India.

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Conclusion

While the urgency of tackling antibiotic resistance is justified, the international community must pay closer attention to the critical influence of socio-ecological, behavioral, and structural drivers that govern antibiotic use. Till date, many of the interventions tailored to addressing antibiotic misuse in human health have focused inordinately on changing knowledge as a means of changing attitudes and practices toward antibiotic prescriptions. Overuse of antibiotics is too often framed as irrational use, implying a deficit in knowledge and understanding around the proper uses of antibiotics.

However, as chapters 2, 3 and 4 clearly illustrate, the drivers and practices related to antibiotic use in countries like India are far more complex, governed by the socio-economic context and an environment associated with diagnostic uncertainty and a lack of reliable access to healthcare services. There is an urgent need to view the use of antibiotics within the broader socio-political and economic context, considering the social dimensions beyond individual behavior. As Clare Chandler argues, conventional biomedical approaches to addressing AMR are often rooted in viewing individuals as the targets of interventions, governed by the belief that behavior is driven by choice devoid from context despite evidence to the contrary [1]. Prior qualitative work from India and other limited resource settings reinforces Chandler's premise that the reasons for individual prescription or consumption behavior are "beyond the control of individual patients or prescribers" and often conscious or rational decisions based on the underlying healthcare context [1-4]. Framing antibiotic resistance as an issue of individual and irrational behavioral choices removes responsibility from the state and risks relying on the same faulty logic that views diseases like obesity as a function of choice rather than responses to the built environment [5]. As Chapter

3 illustrates, interventions that solely focus on the individual often fail to alter behavior. Community-based and policy experts alike recognize the importance of the enabling environment in influencing prescription decisions and understanding the desire to purchase antibiotics as quick cures over the counter (see Chapter 4). While the World Health Organization appropriately recognizes the links between people, animals, plants, and their shared environment, the false dichotomy of "rational" vs "irrational" antibiotic use within the broader discourse around AMR in human healthcare fails to recognize the interconnected web of patients and prescribers in the underlying socio-political and structural context. Interventions that aim to educate consumers and prescribers on the dangers of antibiotic misuse not only presume a lack of awareness regarding antibiotics, but also frequently lack scale and viability. They do not recognize the social safety net limitations that prompt patients who rely on daily wage labor from seeking quick over-the-counter cures or the market-driven linkages between informal and formal healthcare providers that govern prescription decisions based on rational profit-seeking behavior, which have been detailed extensively in chapters 1-5.

Broom et al similarly examine this dynamic across varied institutional settings in three different continents and refer to the phenomenon of a 'marketisation ethic' with structural conditions that constraint individual capacity to act in the patient's best interest [6]. In settings like Australia as well as India, compliance with guidelines takes a backseat to the incentives of an immediate financial return in private sector hospitals in the form of pre-emptive treatment under fee-for-service healthcare models [6]. Chapter 2 details very similar findings from West Bengal, and highlights how patient demands, pharmaceutical industry influence, profit-driven prescription decisions, and a desire to quickly alleviate symptoms all coalesce to inform prescription and

consumption decisions related to antibiotics. Yet another parallel finding in Broom et al's data from Australia and India looks at the institutional response and diffusion of personal responsibility with respect to AMR. In West Bengal, we frequently heard blame shifting by different actors who diffused responsibility for poor practices from one actor to the next, one institution to another (see chapter 2); Broom et al similarly find a reticence to change individual practice until the institutional milieu regarding practices in agriculture, infection prevention and control, and hospital antibiotic use changes [6]. Under such conditions, focusing on individual behavior change is unlikely to contribute to any sustained change in practice. As long as patients are able to move from one provider to the next in a private market in search of "quick cures," clinicians are pressured to alleviate symptoms rapidly to minimize discomfort and retain the patient, pharmaceutical industry incentives are aligned to treat chronic long-term conditions rather than investing in a pipeline for new antibiotics, and hospital policies prioritize short-term patient outcomes over long-term impacts of antibiotic resistance, antibiotic practices will continue to be seen as "irrational" and the status quo is likely to continue. As Broom et al indicate, a "well-institutionalized solidaristic approach would require a broader personal and collective willingness to bear some of the costs of more judicious antimicrobial use," including an increased risk of negative patient outcomes in the short term in the absence of prophylactic broad spectrum antibiotic use [6].

Individual prescription or consumption behavior cannot be deemed "irrational" in the context of decrepit healthcare institutions, inadequate time for patient consultations, ineffective diagnostic testing, and vast healthcare shortages in limited resource settings in countries like India. National and international antimicrobial containment policies must prioritize scaling up infection and prevention control in rural and urban settings, ensure adequate staffing of healthcare facilities,

provide an adequate social safety net and a minimum basic standard of living for all residents, scale access to rapid diagnostic and point-of-care tests, and create an environment where patients and doctors alike are not pressured to quickly alleviate symptoms in the absence of a proper diagnosis. Compensation for healthcare practitioners and sales representatives should be decoupled from aggressive treatment or marketing of drugs such as antibiotics. A focus on systemic solutions to entrenched systemic barriers will mitigate against 'quick fix' solutions [6].

This thesis outlines how the reliance on informal healthcare providers or over-the-counter use in a fragmented and decentralized market is a symptom of poor access to healthcare in India, in an environment that faces drastic staffing shortfalls, medicine shortages, lack of diagnostics, and limited time with patients, which has only been heightened and rendered more visible by the COVID-19 pandemic. With images of funeral pyres running around the clock, shortages of oxygen cylinders, and hospitals packed beyond capacity, the COVID-19 pandemic exacted a heavy toll in India in 2021 [7]. However, the large death toll, high case counts, and limited numbers of vaccines or oxygen cylinders were an inevitable consequence of an underfunded system: India spends about $73 on healthcare per capita compared to a global average of $1,110 in 2018, and government facilities account for 10% of all hospitals, with private facilities only accessible to an elite minority in most regions [7]. During a crisis like the COVID-19, it is difficult to implement and enforce antibiotic stewardship practices when hospitals are overwhelmed. Even outside the Indian context, the COVID-19 pandemic resulted in widespread use of antibiotics in critically ill patients admitted to ICUs in China, France, and other countries [8]. And yet, a sustained investment in healthcare infrastructure, including adequate primary and tertiary care staffing, vaccines and therapeutics, and rapid diagnostic tests could have mitigated some of the issues faced during this crisis.

As Gautham and Shyamprasad detail in their analysis, India's chronic deficits in healthcare infrastructure and staffing date back to the first health policy drafted in 1946 by a body known as the Bhore Committee [9]. Prior to the formation of India as an independent nation in 1947, the region had a diverse cadre of Western medical providers that primarily fell into two classes: University graduates who underwent a 5.5 year training program and licentiates of medical practice (LMPs) who trained over a shorter period and graduated with a licentiate rather than an official medical degree. Based on the committee's own estimates, even though nearly two thirds of the 47,524 registered medical practitioners in the country at the time were LMPs, the Committee moved to abolish the licentiate programs and provide only one port of entry into the medical profession, which was to be the 5.5 year university degree (MBBS) [9]. Several members of the Committee had raised staunch concerns that an alternative and diverse cadre of healthcare workers was critical to meet healthcare coverage needs across India [9]. This proved to be a prescient observation as rural India today faces a shortage of formally trained medical doctors and nurses in primary health centers and sub-centers, and vast segments of the population rely instead on traditional healers and untrained informal providers who do not have any formal access to training programs in most states [10]. As the aforementioned chapters illustrate, some states like Chhattisgarh and West Bengal have responded to the shortfall by developing three year diploma courses for mid-level providers [9]. Even though the Indian Medical Association opposes such developments, state governments should expand access to short courses in order to effectively meet the needs of local conditions in rural India. There has been no political willpower to restrict informal providers from practicing, and they are often the only source of medical care in rural communities [10]. Training, recruiting, and certifying mid-level providers like informal

practitioners, traditional healers, auxiliary nurse midwives, and pharmacists would ease the burden in rural areas and provide adequate care in remote areas, and provide an upstream solution to rampant antibiotic misuse [9].

Beyond strengthening service delivery and healthcare provision, major reforms are needed in the pharmaceutical sector, including decoupling sales bonuses for antibiotics from salaries for sales staff and establishing public-private partnerships to build a pipeline for newer antibiotics. According to the Access to Medicine Foundations' 2020 Benchmark Report, 6 major pharmaceutical companies removed sales-based bonuses, but 16 have yet to take any meaningful action [11]. It is more common now for pharmaceutical companies to run AMR surveillance programs that track resistance patterns, but Pfizer is the first company to share the raw data on an open-access AMR online register [11]. However, companies are still reluctant to publicly disclose the amount of antibiotic residues discharged from production sites in wastewater [12].

Under the leadership of the World Health Organization, countries like India have made remarkable progress in establishing and adopting national action plans to tackle AMR in congruence with the global action plan, and yet, implementation has been woefully inadequate thus far (see Chapter 5). Political commitment at the state level has varied significantly between high performing states like Kerala and states like Bihar or Uttar Pradesh that have yet to convene stakeholders to establish a working state-level action plan. As Ranjalkar and Chandy state in their analysis of the national action plan, "lack of a separate financial allocation remains the greatest challenge for the implementation of NAPs and/or State Action Plans, not only in India but also in other LMICs," especially in the context of overburdened state governments and uncoordinated funding streams

[13]. Additionally, public-private sector coordination and initiatives that integrate civil society stakeholders as well as industry stakeholders will be critical.

Many of the solutions proposed in this thesis to enact social policy and structural change toward shifting the intervention landscape in AMR will take a long time, especially in a resource limited context like India. In the interim, the role of scaling up newer diagnostic tools, easy-to-use point-of-care tests, and integrating the latest research and discourse on AMR in medical and educational curricula should not be understated. A point-of-care test typically yields results quickly and is conducted near the patient, without any need for a centralized lab facility; it is estimated that the use of rapid tests for tuberculosis, community-acquired bacterial infections, and antenatal syphilis could prevent over 1 million deaths per year in the Global South [14-15]. Scaling up access to these tests would prevent unnecessary antibiotic use in the short term.

In order to truly make a meaningful difference in antibiotic use in the long term however, the solutions to addressing AMR need to expand beyond hospital-based settings, embrace the OneHealth paradigm to recognize the role of community and environmental spread, and be grounded in policy and systems change that recognize the role of social determinants in governing individual and institutional behavior.

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IMPACT STATEMENT

Antimicrobial resistance (AMR) has been a critical area of interest to the World Health Organization (WHO), national governments, and other large multi-lateral and international institutions. AMR is named as one of the top 10 threats to global public health, and one study estimates that it is poised to take more lives than cancer by 2050. The world is entering a "post antibiotic" era where even minor infections, which were previously managed with antibiotics, can be lethal. This is particularly true in low-and-middle-income countries (LMICs), such as India, where access to healthcare is limited, urban-rural disparities in healthcare are stark, and financial and political will is fragmented.

While the leadership of the WHO in modeling and developing a global action plan to tackle AMR has been pivotal in prompting the developing of national action plans and mobilizing political will, the current discourse around AMR is framed largely around individual issues related to prescription or consumption behavior rather than systemic barriers related to accessing care. This dissertation, "*Reframing and unpacking 'irrational' antibiotic use: a structural and socio-ecological perspective on antibiotic resistance in India*," examines the futility of focusing squarely on behavioral interventions, critically examines the gap between knowledge and practices related to antibiotic use, explores the limited engagement of diverse healthcare practitioners in interventions in a limited-resource setting like India, and analyzes policy limitations and recommendations moving forward.

The current literature in the global South contains extensive documentation of interventions designed largely to improve knowledge and behavior, or clinical interventions designed to reduce antibiotic use in inpatient care. However, there is limited evidence regarding effective

interventions in the outpatient setting and most studies lack a practical and critical examination of the policy context behind the interventions.

Taken as a whole, the five studies in this dissertation add several new insights while addressing a critical gap in the literature. The role of pharmaceutical company representatives in influencing decision making is well understood in the formal medical establishment, but this research was one of the first examinations of the reach of these representatives among informal health providers. Informal providers reported relying on pharmaceutical representatives for samples of new antibiotics and as a source of knowledge, which has important policy implications for a sector that is currently still ignored in national policy making within India. The studies also elucidate how informal medical providers often prescribe antibiotics due to market-driven incentives, such as the desire to alleviate symptoms quickly and retain patients, and function as the sole point of contact for patients in rural settings. Similarly, pharmacy shops and retailers are often the primary point of contact for patients who lack time or monetary resources to seek care from qualified medical practitioners.

The papers have policy-relevant implications for designing interventions and feasibly implementing a national action plan that appears comprehensive on paper, but lacks appropriate financial allocations, enforcement, political will, and depth. In particular, the papers make a case for actively involving the informal sector in decision making and interventions regarding antibiotic misuse. Until healthcare access and public health infrastructure drastically improves, a vast segment of India's population will continue to rely heavily on informal providers for access to care and this sector cannot be ignored in the broader decision making apparatus.

CURRICULUM VITAE

Mohit Manoj Nair was born in Mumbai, India on November 14, 1991. While he was born in India, he grew up in Japan and was educated in the United States. He obtained his Bachelor of Science degree from Cornell University and Master of Public Health (MPH) degree from Harvard T.H. Chan School of Public Health in the United States. After obtaining his MPH degree, he spent several years working in the humanitarian sector in South and Southeast Asia, conducting qualitative and mixed-methods research and evaluation studies for humanitarian non-profits such as Save the Children International and Medecins Sans Frontieres (MSF).

While working with MSF, Mohit conducted several field research studies examining the drivers of antibiotic use in West Bengal, the lived experiences of people on palliative care, and stigma and barriers to accessing care for people co-infected with HIV and visceral leishmaniasis. The widespread use and misuse of antibiotics in the local context sparked an interest to explore this further through a PhD. In late 2019, Mohit officially enrolled as an external PhD candidate at Maastricht University.

Mohit's doctoral thesis explores and critically examines the discourse around "irrational" antibiotic use in the global health context. The first two papers complement each other as a mixed-methods analysis of knowledge, attitudes, and practices towards antibiotic use in West Bengal. These papers build on the data collected from his work with MSF in West Bengal, and detail the gap between knowledge and practices regarding antibiotic misuse in the context of limited healthcare access in West Bengal. The third paper is a systematic review that provides a narrative synthesis and examination of the evidence regarding behavioral interventions to address misuse. The last

two papers involved virtual qualitative data collection with key informants and policy experts who either work in or are deeply knowledgeable about the Indian context.

As he was completing his PhD virtually from Seattle in the United States, Mohit was also working as a Social Research Scientist with Public Health Seattle-King County, evaluating large-scale early childhood education and criminal legal programs in the local county in Washington State. His work involved co-designing evaluation plans in partnership with community, monitoring and managing contracts for external evaluations, developing performance measures, conducting and analyzing qualitative data, and designing policy-relevant dissemination products.

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