Underdiagnosis and overtreatment:

provider practices for tuberculosis care in India

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I. ABSTRACT

Abstract (English):

Underdiagnosis and overtreatment: provider practices for tuberculosis care in India

Tuberculosis (TB) is the second leading infectious disease killer worldwide after COVID-19. Accounting for more than a quarter of the global TB incident cases, India shoulders the greatest TB burden in the world. High quality TB care includes early and accurate diagnosis, followed by rapid initiation of the correct drug regimen, patient support, and management of relevant comorbidities. The Indian private healthcare sector is large and unregulated; it treats half of Indian TB patients, with evidence suggesting that the quality of care they receive is suboptimal. Standardized patients (SPs) are increasingly used in low-income countries to assess quality of medical care. In this manuscript-based thesis, I assessed quality of TB care and provider practices across outpatient primary care settings in India's private sector. Using secondary data from a series of SP studies conducted in India, I studied if providers empirically prescribed anti-TB medications on the basis of clinical and chest X-ray (CXR) findings, and examined their propensity to prescribe potentially harmful medications or treatment regimes. Specifically, I conducted secondary analyses of data for a total of over 6,500 SP-provider visits in two cities with the aim to calculate unbiased prevalence estimates of inappropriate care and overprescription using inverse-probability-weighting based on the overall sampling strategy. SPs presented one of four case scenarios: case 1 consisted of a classic symptomatic case of presumptive TB who had 2-3 weeks of cough and fever, case 2 additionally presented with a chest CXR and 1 week of broad-spectrum antibiotic treatment ordered by another provider, with no improvement, case 3 also carried a positive microbiological test (sputum microscopy), and case 4 presented with suspected multidrug resistant (MDR) TB with 4 weeks of cough and fever, and history of incomplete TB treatment in the past. Among SP cases who presented to providers with typical TB symptoms and an abnormal CXR (case 2), 182 of 795 (25%; 95% confidence interval [CI]: 21-28%) of interactions resulted in ideal correct management, where the provider prescribed a microbiological test (sputum smear, Xpert MTB/RIF or culture) and did not offer a concurrent prescription for a steroid or antibiotic (more specifically of quinolone or anti-TB treatment [ATT]). Of all case 2 presentations, 210 of 795 (23%; 95% CI: 19-26%) resulted in potential empiric TB treatment, with a prescription or dispensation of ATT. A total of 140 of 795 (13%; 95% CI: 10-16%) of case 2 interactions resulted in a prescriptions/dispensation of ATT and additionally, a prescription for confirmatory microbiological

testing, either via sputum smear microscopy, Xpert MTB/RIF, or culture. Across all case presentations, 749 of 6685 (12%; 95% CI: 11-14%) SP visits were prescribed quinolones and 512 of 6685 (6%; 95% CI: 5-7%), steroids. When ATT was prescribed, a majority of group 1 ATT regimens (consisting of the first-line oral anti-TB drugs, isoniazid, rifampicin, ethambutol and pyrazinamide) were a four-drug fixed-dose combination –236 of 418 (64%; 95% CI: 57-70%). I also analyzed whether private pharmacists managed people with presumptive TB appropriately. In a cross-sectional study conducted over two survey rounds in Patna, I looked at two SP cases presenting at pharmacies: first, a patient presenting with 2-3 weeks of pulmonary TB symptoms (pharmacy case 1), and second, a patient with microbiologically confirmed pulmonary TB (pharmacy case 2). Ideal management for both cases were defined a priori as referral to a healthcare provider without dispensing antibiotics (including ATT) or steroids or both. Only some pharmacies correctly managed patients with presumed TB, but most correctly managed a case of confirmed TB. Across both rounds of data collection, 331 of 936 (35%; 95% CI: 32-38%) of interactions were correctly managed; at baseline, 215 of 500 (43%; 95% CI: 39-47%) of interactions were correctly managed whereas 116 of 436 (27%; 95% CI: 23-31%) were correctly managed in the second round of data collection. We saw a decrease in correct case management between case 1 and case 2 by 20 percentage points from baseline to round 2 in our difference-in-difference analysis. Pharmacies did not dispense anti-TB drugs for either case or either round. Absence of a confirmed diagnosis is a key driver of antibiotic misuse and could inform antimicrobial stewardship interventions. Overall, this body of work contributes to fill some knowledge gaps regarding how private providers manage TB in urban India and factors that drive empirical management and use of inappropriate medications. This could help design and implement tailored interventions aimed to promote the rational use of medicines and diagnostics. These findings hold implications for the design and implementation of effective quality improvement programs for TB.

II. RÉSUMÉ

Résumé (français):

Sous-diagnostic et surtraitement: pratiques des prestataires de soins de santé pour la tuberculose dans l'Inde urbaine

La tuberculose (TB) est la deuxième maladie infectieuse la plus meurtrière dans le monde après le COVID-19; représentant plus d'un quart des cas de tuberculose, l'Inde supporte la plus grande charge de la tuberculose dans le monde. Les soins de qualité dans le domaine de la tuberculose comprennent un diagnostic précoce et précis, suivi de l'instauration rapide d'un traitement médicamenteux adapté, du soutien du patient et de la prise en charge des comorbidités pertinentes. Le secteur privé des soins de santé en Inde est vaste et non réglementé; il traite la moitié des patients indiens atteints de tuberculose, et les preuves suggèrent que la qualité des soins qu'ils reçoivent est sous-optimale. Les patients standardisés (PS) sont de plus en plus utilisés dans les pays à faible revenu pour évaluer la qualité des soins médicaux. Dans cette thèse par articles, j'ai examiné la qualité des soins de la tuberculose et les pratiques des prestataires dans les établissements de soins primaires ambulatoires du secteur privé en Inde. En utilisant des données secondaires provenant d'une série d'études SP en Inde, j'ai évalué si les prestataires prescrivent empiriquement des médicaments antituberculeux sur la base des résultats cliniques et des radiographies pulmonaires (CXR), et leur propension à prescrire des médicaments ou des régimes de traitement potentiellement dangereux. Plus précisément, j'ai effectué des analyses secondaires des données pour un total de plus de 6 500 interactions PS-prestataire dans deux villes dans le but de calculer des estimations de prévalence non biaisées de soins inappropriés et de prescription excessive en utilisant une pondération inverse de la probabilité basée sur la stratégie d'échantillonnage globale. Les PS se sont présentés sous l'une des quatre formes suivantes: le cas 1 est un cas symptomatique classique de tuberculose présumée qui présente une toux et une fièvre depuis 2 à 3 semaines, le cas 2 présente en outre un antécédent de radiographie thoracique et une semaine de traitement antibiotique à large spectre prescrit par un autre prestataire, sans amélioration, le cas 3 présente également un test microbiologique positif (microscopie des expectorations), et le cas 4 est un adulte suspect de tuberculose multirésistante (MDR) qui présente une toux et une fièvre depuis 4 semaines avec un historique de traitement antituberculeux incomplet. Parmi les cas de PS qui se sont présentés aux prestataires avec des symptômes typiques de la TB et un CXR anormal (cas 2), 182 des 795

(25%; intervalle de confiance [IC] 95% : 21-28%) interactions ont abouti à une prise en charge idéale correcte, où le prestataire a prescrit un test microbiologique (frottis d'expectoration, Xpert MTB/RIF ou culture) et n'a pas proposé une prescription concomitante de stéroïde ou d'antibiotique (plus spécifiquement de quinolone ou de traitement anti-TB [ATT]). Sur l'ensemble des présentations de cas 2, 210 sur 795 (23%; IC 95%: 19-26%) ont donné lieu à un traitement antituberculeux empirique potentiel, avec une prescription ou une délivrance d'ATT. Un total de 140 interactions sur 795 (13%; IC 95%: 10-16%) ont donné lieu à une prescription ou à une dispensation de ATT et à une prescription de tests microbiologiques de confirmation, soit par microscopie du frottis d'expectoration, soit par GeneXpert MTB/RIF, soit par culture. Sur l'ensemble des présentations de cas, 749 des 6685 (12%; IC 95% : 11-14%) PS se sont vus prescrire des quinolones et 512 des 6685 (6%; IC 95% : 5-7%), des stéroïdes. Lorsque la ATT était prescrite, la majorité des régimes de ATT de première intention étaient une combinaison à dose fixe de quatre médicaments - 236 sur 418 (64%; IC 95%: 57-70%). J'ai également analysé si les pharmaciens privés prenaient en charge de manière appropriée les personnes présentant une présomption de tuberculose. Dans une étude transversale répétée à Patna, j'ai examiné deux cas standardisés de patients se présentant en pharmacie: d'abord, un patient présentant des symptômes de tuberculose pulmonaire depuis 2 à 3 semaines (cas 1 de pharmacie), et ensuite, un patient présentant une tuberculose pulmonaire confirmée microbiologiquement (cas 2 de pharmacie). La prise en charge idéale pour les deux cas était définie a priori comme l'orientation vers un prestataire de soins de santé sans dispenser d'antibiotiques ou de stéroïdes ou les deux. Seules quelques pharmacies ont correctement pris en charge les patients atteints de tuberculose présumée, mais la plupart ont correctement pris en charge un cas de tuberculose confirmée. Sur les deux cycles de collecte de données, 331 interactions sur 936 (35%; IC 95%: 32-38%) ont été correctement gérées; au départ, 215 interactions sur 500 (43%; IC 95%: 39-47%) ont été correctement gérées alors que 116 interactions sur 436 (27%; IC 95%: 23-31%) ont été correctement gérées lors du deuxième cycle de collecte de données. Les pharmacies n'ont pas délivré de médicaments antituberculeux pour les deux cas. Nous avons constaté une diminution de la prise en charge correcte des cas entre le cas 1 et le cas 2 de 20 points de pourcentage entre le début et le deuxième tour dans notre analyse de différence dans la différence. L'absence de diagnostic confirmé est un facteur clé de la mauvaise utilisation des antibiotiques et pourrait servir de base à des interventions de gestion des antimicrobiens. Dans l'ensemble, ce travail contribue à combler certaines lacunes dans les connaissances sur les comportements des prestataires privés dans les zones urbaines de l'Inde, aidant ainsi à concevoir et à mettre en œuvre des interventions adaptées visant à promouvoir l'utilisation rationnelle des

médicaments et des diagnostics. Ces connaissances sont nécessaires pour concevoir et mettre en œuvre des programmes efficaces d'amélioration de la qualité pour la tuberculose.

III. ACKNOWLEDGEMENTS

Having the opportunity to learn with and from exceptional students and faculty such as those of McGill University's Department of Epidemiology, Biostatistics and Occupational Health was definitely worth the effort and investment. I would like to express my sincere gratitude to my supervisor, Dr. Madhukar Pai, not only for guiding me throughout my doctoral training and providing me with amazing opportunities in global health, but also for giving me the privilege to join his amazing team. It is thanks to my outstanding colleagues and their continuous support that the last years have been so special. To that end, I am particularly grateful to Sophie Huddart and Giorgia Sulis who both encouraged and mentored me throughout this process. I am also deeply indebted to Caroline Vadnais for her support and meticulous reading of this colossal work.

I offer my profound appreciation to all my research collaborators and co-authors without whom this thesis would have never seen the light. My deepest thanks go to my committee members, Drs. Jishnu Das and Amrita Daftary, for sharing their feedback and providing me with new and broader perspectives. I am also deeply indebted to my colleagues Benjamin Daniels, Ada Kwan and our amazing study team in India, who all tirelessly work to improve the lives of people with TB and who made these analyses possible. It's a privilege to work with talented and compassionate colleagues who are also dear friends, thank you.

I am extremely grateful for receiving the FRQS Doctoral Fellowship and the AGBU Graduate Student Award along with additional financial support from the McGill Faculty of Medicine and Health Sciences, the McGill International TB Centre and McGill Global Health Programs.

I would like to extend my heartfelt thanks to my parents for encouraging and supporting me at each step of the way; you are my biggest champions. I am endlessly grateful for the mentors who led me here, the friends who got me through and my family, for everything. Thanks to Sascha in particular, the most supportive of partners.

I also thank the many TB champions who have shared their stories and their strength with myself and the TB community. To that end, I would like to dedicate this thesis to my dear friend Deepti Chavan, whose courage, strength and kindness have inspired me throughout every step of this journey. You are an incredibly special person.

IV. PREFACE AND CONTRIBUTION OF AUTHORS

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

Manuscript 1: Do private providers initiate anti-tuberculosis therapy on the basis of chest radiographs? A standardised patient study in urban India

I developed the study design and objectives with input from Dr. Madhukar Pai. I wrote the study protocol, drafted the manuscript and all authors provided critical feedback.

Manuscript 2: Using standardised patient methodology to assess inappropriate use of quinolones and corticosteroids for tuberculosis by private practitioners in urban India

I developed the study design and objectives with input from Dr. Madhukar Pai. I designed and performed the analysis with input from Dr. Madhukar Pai and Benjamin Daniels. I interpreted the results and drafted the manuscript; all authors provided critical feedback.

Manuscript 3: Anti-tuberculosis prescriptions in the private Indian healthcare sector: an analysis of trends using standardised patient methodology

I developed the study design and objectives with input from Dr. Madhukar Pai. I designed and performed the analysis with input from Benjamin Daniels. I interpreted the results and drafted the manuscript; all authors provided critical feedback.

Manuscript 4: Use of standardised patients to assess tuberculosis case management by pharmacies in Patna, India: a repeat cross-sectional study

I developed the study design and objectives with input from Benjamin Daniels and Dr. Madhukar Pai. I designed and performed the analysis with input from Benjamin Daniels. I interpreted the results and drafted the manuscript; all authors provided critical feedback.

V. STATEMENT OF ORIGINALITY

The four manuscripts that form this thesis are all original scholarship and provide unique contributions to knowledge. All four of my chapters offer analyses of large standardized patient (SP) studies conducted over three survey rounds from 2014-2019 in India. These studies make use of the SP methodology to generate more accurate and less biased estimates of quality of care metrics for a set of clinical conditions that do not require antibiotic treatment and are frequently encountered in primary care across low- and middle income countries (LMICs). Hence, this is a significant improvement over commonly employed methodologies such as prescription audits, patient exit interviews and direct observation of patient-provider visits. This work also sets the stage for the use of SPs in future research investigating antibiotic prescribing practices in greater depth.

VI. LIST OF ABBREVIATIONS

AFB	acid-fast bacillus
ARTI	acute respiratory tract infection
ATC	anatomical therapeutic chemical
ATT	anti-tuberculosis treatment
AYUSH	Ayurveda, Yoga, Unani, Siddha, or Homeopathy
BMGF	Bill and Melinda Gates Foundation
CXR	chest X-ray
DiD	difference in difference
DOTS	directly observed treatment, short course
DST	drug susceptibility test
FDC	fixed dose combination
FQ	fluoroquinolones
HRZE	isoniazid, rifampicin, pyrazinamide and ethambutol
INR	Indian rupee
ISTC	International Standards for TB Care
LMIC	low- and middle-income country
MBBS	Bachelor of Medicine, Bachelor of Surgery
MDR	multidrug resistant
NGO	non-governmental organization
NSP	National Strategic Plan
NTP	National TB Programme
NTEP	National TB Elimination Programme
OR	odds ratio
OTC	over-the-counter
PPIA	Private Provider Interface Agency
PPM	public-private mix
PR	prevalence ratio
RCT	randomized controlled trial
RNTCP	Revised National TB Control Programme

RR	rifampin-resistant
Smear	Sputum smear microscopy
SP	standardized patient
STCI	Standards for TB Care in India
TB	tuberculosis
UHC	universal health coverage
USAID	United States Agency for International Development
WHO	World Health Organization
WHP	World Health Partners
WRD	WHO-recommended rapid diagnostic
Xpert MTB/RIF	Xpert Mycobacterium tuberculosis/rifampicin

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CHAPTER 1: LITERATURE REVIEW

1.1 INTRODUCTION

Good health is a function of the utilization of healthcare services and the quality of healthcare. In the field of global health, there is growing awareness of the need to go beyond coverage of services and improve the quality of care. Every year, it is estimated that more than eight million people in low and middle-income countries (LMICs) die from conditions which are entirely treatable by their respective health systems. Poor quality care is estimated to account for 60% of deaths amenable to healthcare.[1]

Tuberculosis (TB) is a prime example that illustrates the importance of quality of care. With TB affecting an estimated 9.9 million people (95% uncertainty interval (UI): 8.9-11 million) in 2020, equivalent to 127 cases (UI: 114-140) per 100,000 population, TB is the second leading killer worldwide due to a single infectious agent. Despite being curable, TB unnecessarily caused 1.5 million deaths in 2020.[2] It is estimated that 50% of TB deaths are due to poor quality TB care.[1]

Within this grave global epidemic, made worse by the ongoing COVID-19 pandemic, India has the highest burden of TB cases and deaths. The World Health Organization (WHO) estimates that India accounted for 27% of the 10M incident cases, and 38% of global TB deaths among HIV-negative people and for 34% of the combined total number of TB deaths in HIV-negative and HIV-positive people. Research in this context shows that poor and highly variable quality of medical care is a concern in general[3-5], and TB care is no different; less than half of providers knew which diagnostics to order for patients with TB symptoms, and less than a third knew the correct treatment regimen to prescribe once a diagnosis had been made.[6] Patient pathway studies for TB have shown long, convoluted paths to care,[7] with an average of three healthcare providers seen over 55 days from onset of symptoms to diagnosis and treatment.[8] There is also poor adherence to International Standards for TB Care, with the private sector performing significantly worse compared to the public sector.[6] As outlined in these standards, high quality care in TB includes early and accurate diagnosis, followed by rapid initiation of the correct drug regimen, patient support, and management of relevant comorbidities.

However, assessing quality of TB care is challenging. Many quality of TB care evaluations have relied on patient self-reporting surveys, questionnaire-based surveys of provider knowledge, and prescription/chart analyses. Unfortunately, these methods are prone to significant biases and thus may

not reflect actual, real-world practice.[3,5,9-12] To address these issues, standardized patients (SPs) are increasingly used in resource-constrained countries to assess quality of medical care.[4,5,11] In an SP study, locally recruited individuals are trained to portray pre-specified medical conditions using a standardized script with contextually and biomedically appropriate symptom descriptions. SP studies seek to understand how providers diagnose and treat patients and thus, provide critical data on the quality of clinical care, as opposed to provider knowledge alone. Compared to other methods, SP studies can provide an accurate assessment of provider practice that is free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of healthcare providers.[12,13] This method allows researchers to understand how providers would behave under different counterfactual possibilities.

1.2 GLOBAL EPIDEMIOLOGY OF TB IN THE AGE OF COVID-19

TB is a communicable disease and is one of the leading causes of death worldwide. Until the COVID-19 pandemic emerged in 2020, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. TB is caused by *Mycobacterium tuberculosis*; transmission of the bacillus occurs when people who are sick with TB expel aerosolized bacteria into the air (e.g. by coughing). The disease typically affects the lungs (pulmonary TB) but can affect other body sites (extrapulmonary TB). About a quarter of the world's population is estimated to be infected with *M. tuberculosis*, with more cases among men than women.[14,15]

TB is curable and preventable. About 85% of people who develop TB disease can be successfully treated with a 6-month 4-drug regimen of antibiotics. Moreover, regimens of 3-6 months can be used to treat TB infection itself, avoiding a progression from latent infection to active disease.

Universal health coverage (UHC) is essential in ensuring that all those with disease or infection can access these lifesaving treatments. Addressing TB determinants such as poverty, undernutrition, HIV infection, smoking and diabetes, will also reduce the number of people acquiring infection and developing disease and subsequent TB-related mortality. Certain countries (e.g. Tonga, Slovakia, Oman, Jordan) have already reduced their burden of TB disease to fewer than 10 cases and less than 1 death per 100 000 population per year; further innovative research is needed to reduce the number of new cases each year (TB incidence) worldwide to the levels already achieved in such low-burden settings.[15]

A majority of TB cases in 2020 were in the WHO regions of South-East Asia (43%), Africa (25%) and the Western Pacific (18%), with smaller proportions in the Eastern Mediterranean (8.3%), the Americas (3.0%) and Europe (2.3%). Of the 30 high TB burden countries, 8 accounted for two thirds of the global total: India (26%), China (8.5%), Indonesia (8.4%), the Philippines (6.0%), Pakistan (5.8%), Nigeria (4.6%), Bangladesh (3.6%) and South Africa (3.3%) – (Figure 1-1).[15]

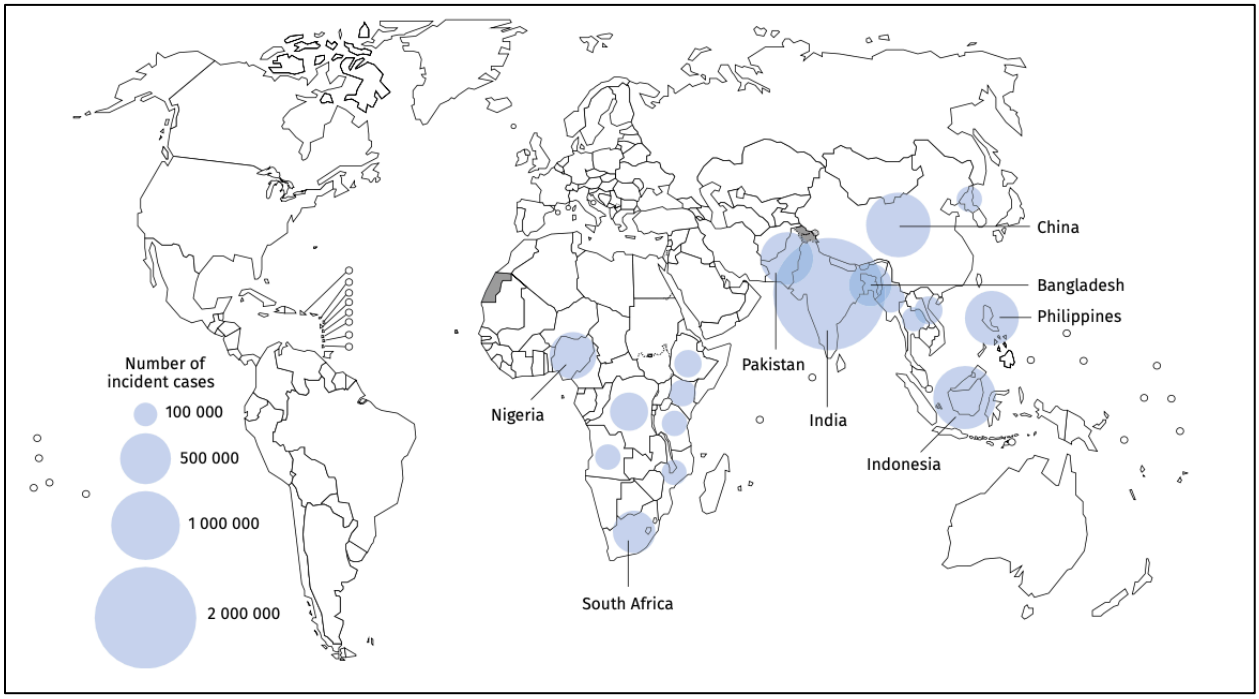
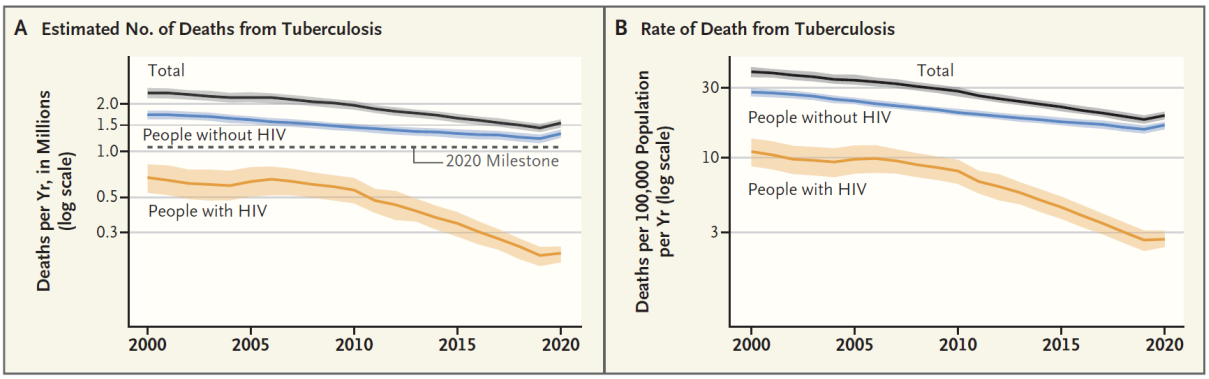


Figure 1-1: *Estimated TB incidence in 2020, for countries with at least 100,000 incident cases. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

The COVID-19 pandemic resulted in over 500 million cases worldwide[16], millions of excess deaths and severe disruptions to essential health services including TB services. New estimates from the WHO show that the full death toll associated directly or indirectly with the COVID-19 pandemic (described as "excess mortality") was approximately 14.9 million (range 13.3 million to 16.6 million) between 1 January 2020 and 31 December 2021.[17] The disruptions produced by the pandemic causing a large global drop in the number of people newly diagnosed with TB and reported in 2020, compared with 2019. There was a sharp decrease in people newly diagnosed (incident cases), from 7.1 million to 5.8 million between 2019 and 2020, representing an 18% reduction.[15] TB mortality has also increased because of reduced access to care; in 2020, there were roughly 1.5 million tuberculosis deaths worldwide, representing the first year-over-year increase in tuberculosis deaths since 2005 (Figure 1-2).[18]



Global Trends in the Estimated Number of Tuberculosis Deaths and Tuberculosis Mortality, 2000 to 2020.

From the Global Tuberculosis Report 2021.[2] Shaded areas represent uncertainty intervals. The horizontal dashed line in Panel A shows the 2020 milestone of the End TB Strategy.

Figure 1-2: *Global trends in the estimated number of tuberculosis deaths and tuberculosis mortality, 2000 to 2020. From the Global Tuberculosis Report 2021. Shaded areas represent uncertainty intervals. The horizontal dashed line in Panel A shows the 2020 milestone of the End TB Strategy. (Source: Pai et al. NEJM, 2021); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[18]

A similar pattern in TB case notifications was also evident in five of the six WHO regions, with particularly large absolute and relative reductions in the regions of South-East Asia and the Western Pacific. These two regions jointly accounted for much (84%) of the global reduction in notifications of incident TB between 2019 and 2020. Sixteen countries accounted for 93% of the total global drop of 1.3 million, with India (41%), Indonesia (14%), the Philippines (12%) and China (8%) contributing the most to the global drop between 2019 and 2020. The largest relative reductions in annual notifications between 2019 and 2020 were seen in Gabon (80%), the Philippines (37%), Lesotho (35%), Indonesia (31%) and India (25%). Figure 1-2 shows the 30 countries that are in each of the three global lists of high-burden countries for TB, HIV-associated TB, and multidrug- or rifampicin-resistant TB (MDR/RR-TB). While there is substantial overlap among the three lists, 49 countries are in at least one of them, with each list accounting for 86-90% of the estimated global TB incidence in 2019 (Figure 1-3).[15]

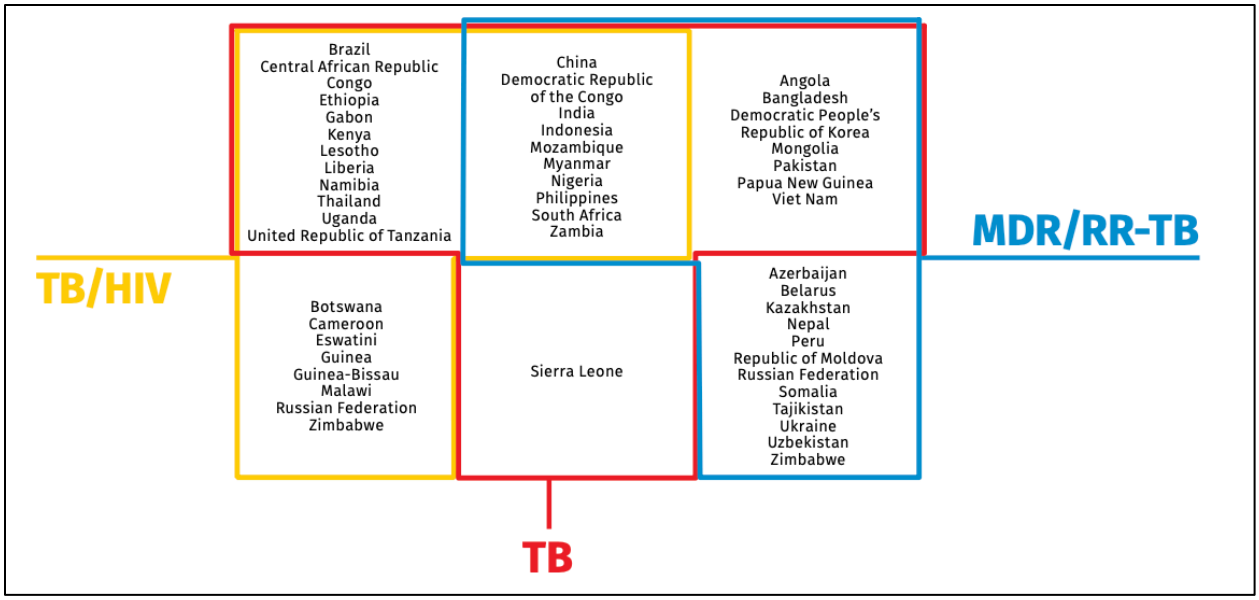


Figure 1-3: *The three global lists of high-burden countries for TB, HIV-associated TB and MDR/RR-TB to be used by WHO in the period 2021-2025, and their areas of overlap. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021; reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

Globally, there are gaps between the estimated TB incidence and the number of people newly diagnosed with TB and reported to the health system. In 2020, there are still over 4 million missing cases worldwide.[15] Of those notified cases, only 2 out of 5.8 million cases were diagnosed with WHO-recommended rapid diagnostics (WRDs) in 2020; smear microscopy is still widely used and uptake of WRDs remains slow with over half of all notifications clinically diagnosed.[15] Such gaps in diagnostic capacity has an impact of the attainability of goals set out in the WHO's End TB Strategy (2016–2035), which aims to end the global tuberculosis epidemic by 2035. Particularly, the target "to increase access to rapid and accurate detection of TB worldwide by 2025" is far removed from the current diagnostic realities; using WRDs as an initial test for TB is currently only occurring in 33% in instances, and the goal is set to be 100% by 2025 (see Table 1-1).[15] These differences are due to a number of reasons including the underreporting of people diagnosed with TB, inability to access healthcare, and lockdown measures.

Table 1-1: *Summary of diagnostic gaps in ability to attain the goals of the End TB strategy. (Source: Nazir Ismail, WHO, (Personal communication))* [15]

End TB Target: Objective 1 - Increase access to rapid and accurate detection of TB

Notified vs Bact confirmed	**Current**	**2020**	**2025**
WHO Rapid Diagnosyics as initial tests	33%	80%	100%
Bacteriologically confirmed TB	48%	80%	90%
Policy with WRD as initial test	53%	100%	100%

Estimated vs Notified	59%		90%
Gap: 3-4 million / annum			

Ten countries collectively accounted for 74% of the global gap between estimated TB incidence and the number of people newly diagnosed with TB and reported in 2022 (Figure 1-4). The top three contributors in this regard were India (24%), Indonesia (11%) and the Philippines (8.3%).[15]

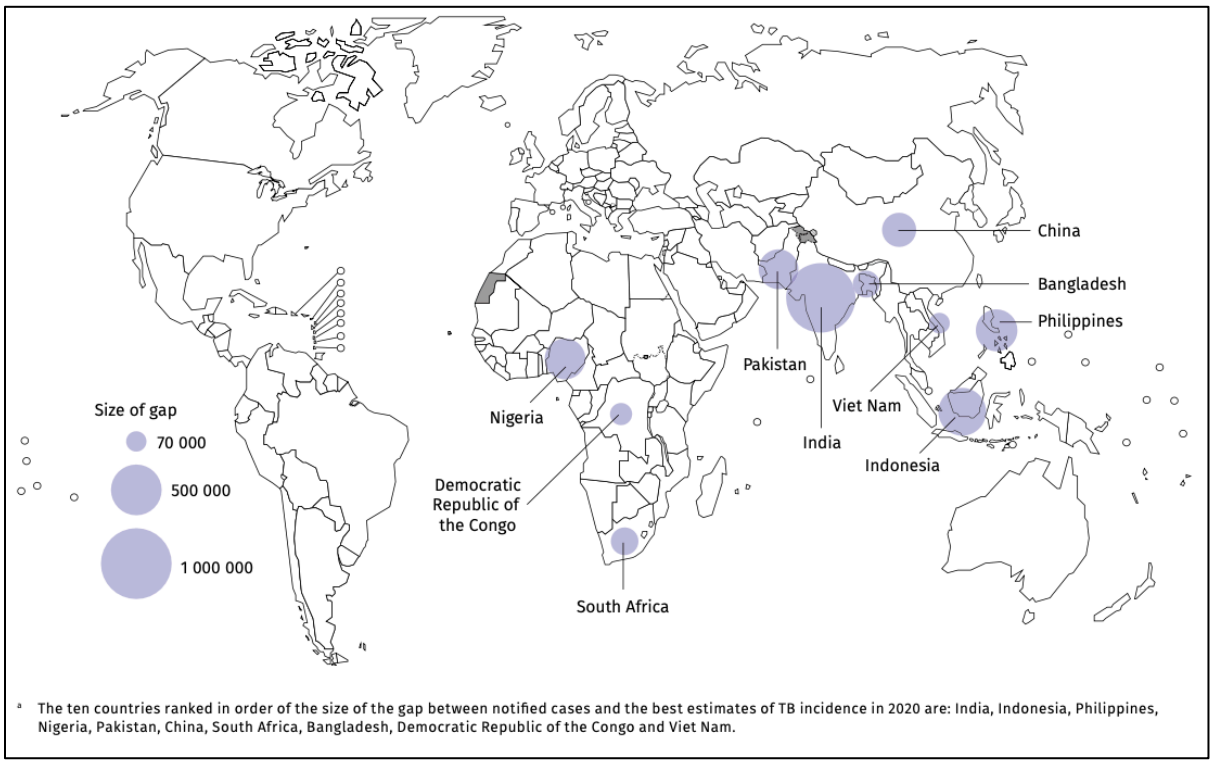


Figure 1-4: *The ten countries with the largest gaps between notifications of new and relapse (incident) TB cases and the best estimates of TB incidence, 2020. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021; reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

There is also a need to increase the percentage of cases confirmed bacteriologically in many countries. The increased uptake of WRDs (rapid molecular tests or culture) is critical because it allows people to be correctly and promptly diagnosed, is necessary to test for drug resistance, and ensures that the most effective treatment regimen can be selected as early as possible. Among the 4.8 million people diagnosed with pulmonary TB worldwide in 2020, only 59% were bacteriologically confirmed (Figure 1-5). Diagnostic testing utilization was lowest in low-income countries, and highest in high-income countries (median, 81%) where there is greater access to the most sensitive diagnostic tests.[15]

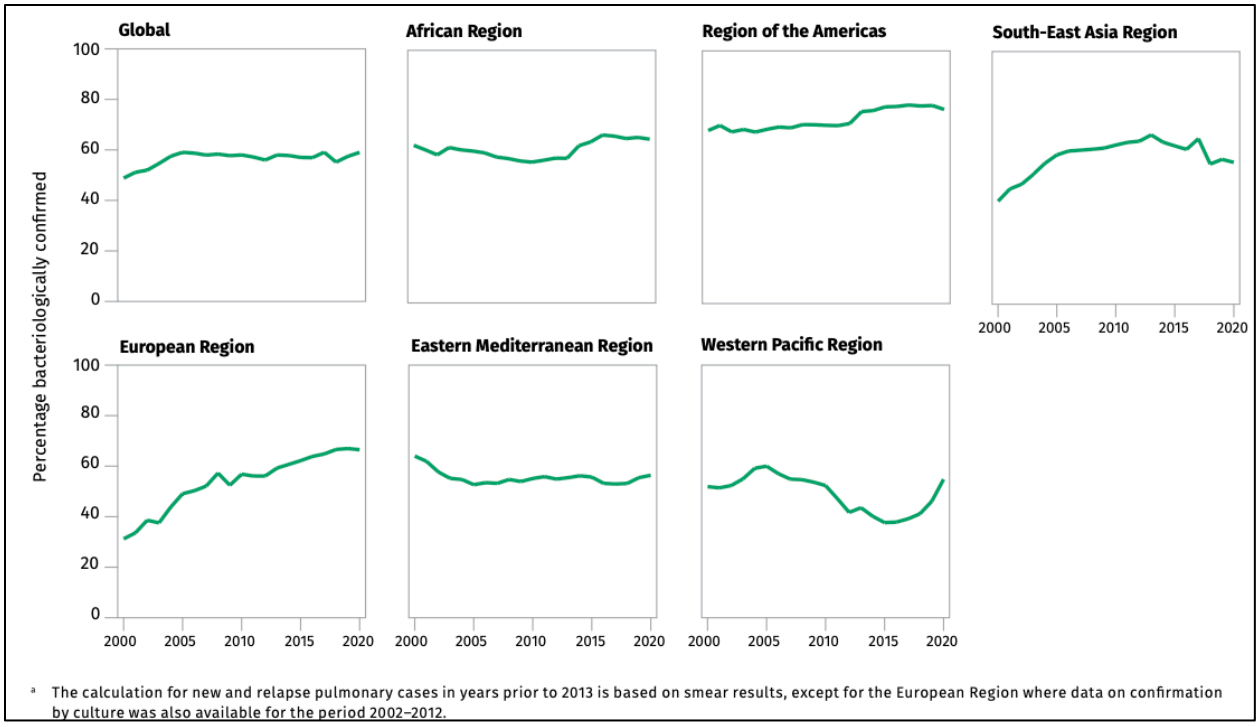


Figure 1-5: *Percentage of new and relapse pulmonary TB cases with bacteriological confirmation, globally and for WHO regions, 2000-2020. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

1.3 EPIDEMIOLOGY OF TB IN INDIA

Tuberculosis is one of India's major public health problems and the country is home to the world's largest TB epidemic. In 2020, India accounted for 26% of the incident TB cases globally, with and incidence rate of 192 cases per 100,000 of population. It also accounted for 38% of global TB deaths among HIV-negative people and for 34% of the combined total number of TB deaths in HIV-negative and HIV-positive people. Moreover, in 2020, India accounted for a 24% of global gap between estimated TB incidence and the number of people newly diagnosed with TB and reported.[15]

In 2022, India released the results of a national prevalence survey, and the prevalence of microbiologically confirmed PTB in ≥ 15 years age was estimated at 316 per 10,000 population (95% CI: 290-342) in the country.[9] The majority (64%) of symptomatic individuals did not seek healthcare services. Among the 36% of survey participants who sought care for their symptoms, there was equal preference for public and private facilities.[19]

Prior to the COVID-19 pandemic, India was witnessing an increase in notification: January and February 2020 saw a 6% increase in notifications compared to the same months in 2019, i.e. some 411,000 case notifications. However, case notifications tumbled thereafter, with a decrease in notifications of 38% overall and 44% in the private sector. Many efforts were made to mitigate these losses, and by December 2020, the gap had almost been closed: a total of 1,805,670 patients were notified, 11% more than the estimated projection made in April (Figure1-5). A quarter of these cases were detected through active TB case-finding. The private sector contributed to 549,000 patients, some 31% of total notifications, up 3% from 2019. In 2019, 96% of the detected cases were put on treatment with a cure rate of 89% and despite COVID-19, 95% of the 1,805,670 TB cases diagnosed in 2020 were put on treatment.[20] There is still a lot to learn and understand about the impact of TB during the COVID pandemic. However, while it appears that this gap in detection has all but been closed, it remains unclear to what extent the "losses" can be attributed to cases not being identified and thus reported vs. actual lower rates of TB incidence. The effect of the pandemic on delayed diagnosis in India remains elusive. These trends are captured in Figure 1-6 below.

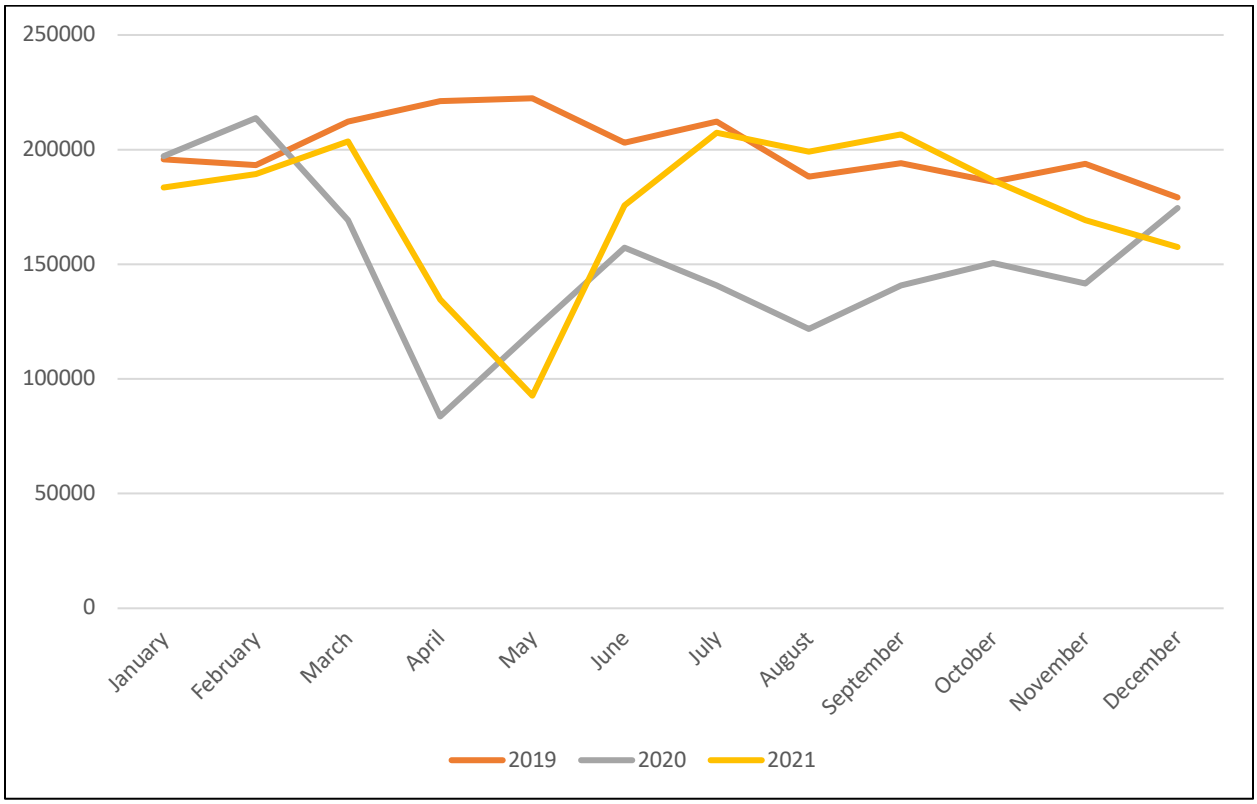


Figure 1-6: *Month-wise trend of TB notification in India from 2019 to 2021. (Source: National TB Elimination Program, India, 2021); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[20]

1.4 TB IN THE PRIVATE SECTOR

In 2021, the United Nations Secretary General progress report illustrated that there was a need to "scale up engagement and leverage the capacity of private and other unlinked public healthcare providers in the delivery of TB prevention, diagnosis and care services to reach the missing people with TB, including children, especially in countries with a large private sector".[21]

The WHO's End TB Strategy (2016–2035) aims to end the global tuberculosis epidemic by 2035. The strategy includes targets to reduce absolute mortality by 95% and incidence by 90% between 2015 and 2035, and to make sure that tuberculosis-affected families no longer have to bear catastrophic tuberculosis-related costs by 2030[22]. In turn, the WHO End TB Strategy's 2nd component combined engagement of private providers with that of civil society organizations and "communities", as well as public non-national TB programme (NTP) providers to provide "bold policies and supportive systems". It remains critical to ensure private provider engagement is prioritized, given that action in this area will drive success in reaching the targets under Pillar 1- "Integrated, patient-centered TB care and prevention" to ensure universal and early access to quality diagnosis and care.[23]

The literature on private healthcare in LMICs is vast.[24] Private providers are an important source of healthcare for all socio-economic strata; while persons of less-poor means tend to make more use of formal and qualified providers, the poor typically turn to informal and unqualified providers. In the South-East Asian region, the lion's share of outpatient primary care is provided by the private sector, some 50-70% (Figure 1-7).[23]

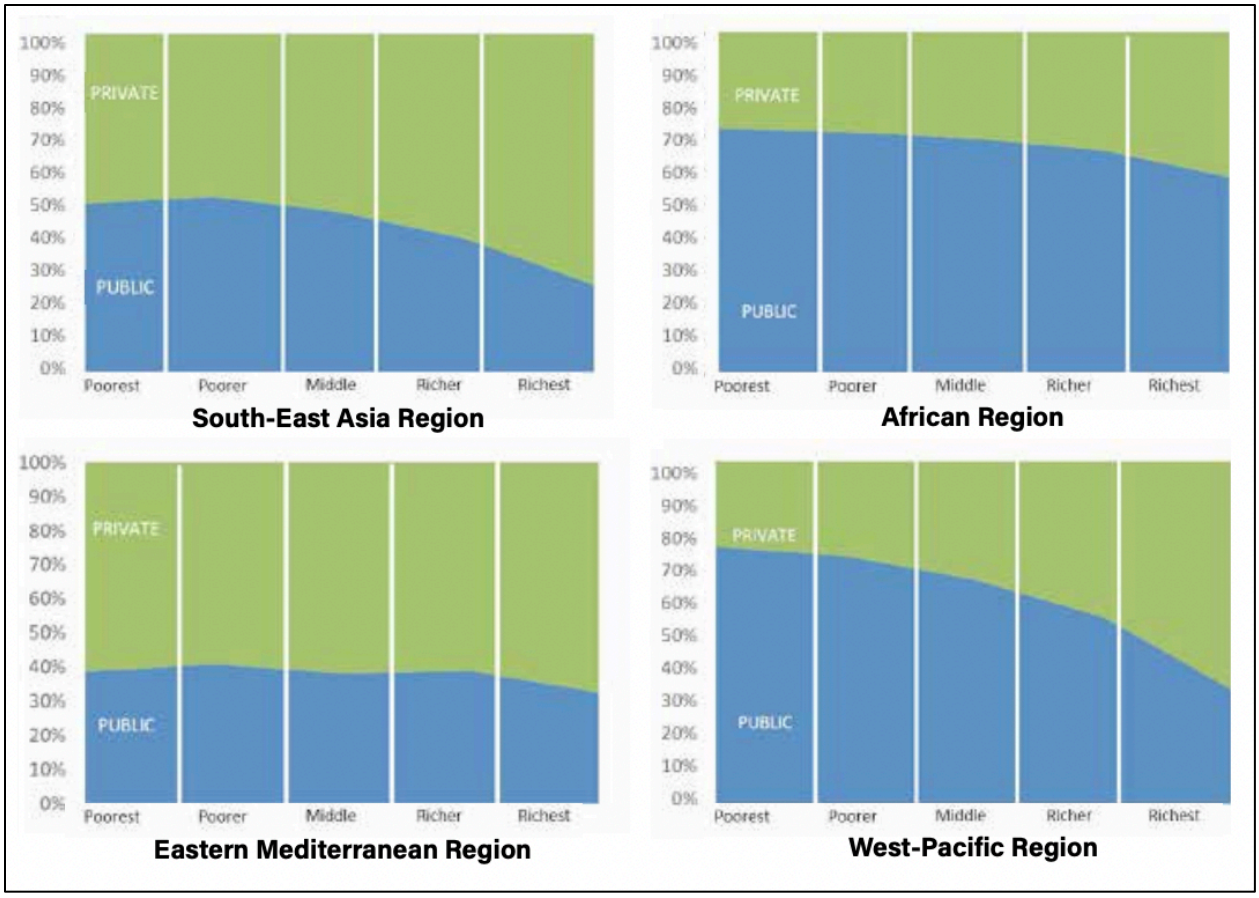


Figure 1-7: *Ownership ratio by who region, weighted by country population from year of most population survey. (Source: Engaging Private Health Care Providers in TB Care and Prevention: A Landscape Analysis. Geneva: World Health Organization, 2018; reuse permitted under the terms of the Creative Commons CC BY 4.0)*[23]

Since 2002, the national TB program in India has outlined various plans to engage private providers, but these were never prioritized. Despite various United States Agency for International Development (USAID) and Global Fund projects calling attention to the need, from 2003, consecutive Joint Monitoring Missions noted the same lack of attention to the issue.[25] Eventually however, in 2012, the fundamentals of a new approach towards engagement of the private sector were planned. Amongst other tactics, these included the development of a case-based electronic TB case notification system (now called Nikshay)[26], a ban on inaccurate but widely used serological tests,[27] and making TB notification mandatory.[28] There was also the decision to move to daily drug regimens as opposed to intermittent regimens, fixed dose combinations (FDCs) of anti-TB drugs, and a common standard of TB care in India which helped align publicly available regimens with those commonly used in the private sector.[29,30]

India's National Strategic Plan for TB (2017-2025) calls for a six-fold increase to two million private notifications per year by 2020.[31] This laudable goal is indicative of a larger attitude shift towards private provider engagement by the Revised National TB Control Programme (RNTCP), now renamed the National TB Elimination Programme (NTEP).[32] A total of 13% of the US$36 million Global Fund program was allocated to three principal recipients dedicated to scaling up private provider engagement across 40 cities in 2018-2020. A World Bank credit of US$400 million has been largely focused on support for private provider engagement since 2019 for these initiatives.[23]

Private provider notifications have increased significantly in recent years (Figure 1-8), even if they fall short of the ambitious targets set by the national strategic plan. Private providers notified 680,948 TB cases in 2019, representing more than three times the total for 2015. A total of 31% of all notifications and 26% of the estimated total TB incidence were reported in the private sector in 2019. The issue being that while notifications have increased, the majority of patients did not receive program-supported diagnostics, TB drugs or social support. Treatment success – defined as the proportion of cases registered in a given year (excluding cases placed on a second-line drug regimen) that successfully completed treatment without bacteriological evidence of failure – was also toted at 71% for the 2018 cohort, raising some concerns about the validity of the latest estimate for privately managed patients.[23]

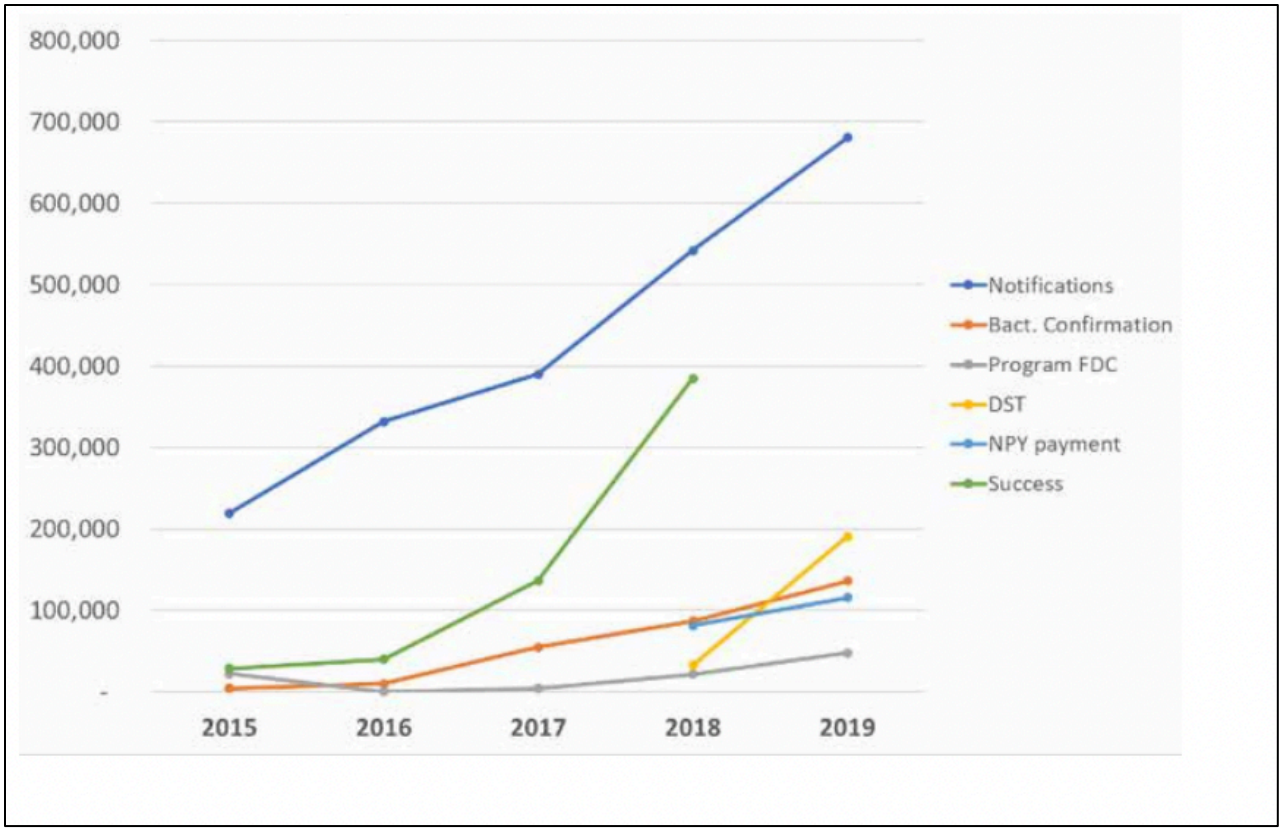


Figure 1-8*: Trend in private TB notifications and coverage of program services in India, 2015-2019. (Source: Engaging Private Health Care Providers in TB Care and Prevention: A Landscape Analysis. Geneva: World Health Organization, 2018); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[23]

There is evidence that quality of TB care in the private sector falls short of international standards in many ways and is in urgent need of improvement.[33] The evidence comes from systematic reviews on the quality of TB care or surrogates of quality indicators such as diagnostic delays, analyses of TB care cascades, and newer SP studies that directly measure quality of TB care. Some issues highlighted by these sources point to low rates of TB testing by private providers, even when patients present with archetypal TB symptoms; low rates of referral to the national TB program; private providers prefer to empirically manage with antibiotics and order tests later; chest x-rays are the preferred tests for TB; microbiological tests are rarely used; use of drug susceptibility testing (DST) in the private sector is very low; there is limited capacity to support patients with adherence and treatment completion; and high costs of care, with 50% of the total costs experienced before TB is diagnosed.[23]

1.5 THE MISSING MILLIONS

Ten countries collectively accounted for 74% of the global gap between estimated TB incidence and the number of people newly diagnosed with TB and reported in 2020 (Figure 1-9). Among the top three contributors was India at 24%. There are several reasons why such gaps in reporting may occur including the underreporting of people diagnosed with TB, especially by private providers, and underdiagnosis, owing to people with TB being unable to access healthcare or not being diagnosed when they do. This dismal reality was exacerbated by the onset the COVID-19 pandemic in 2020, and efforts to recover levels of case detection achieved previously are of particular importance in these countries.[15]

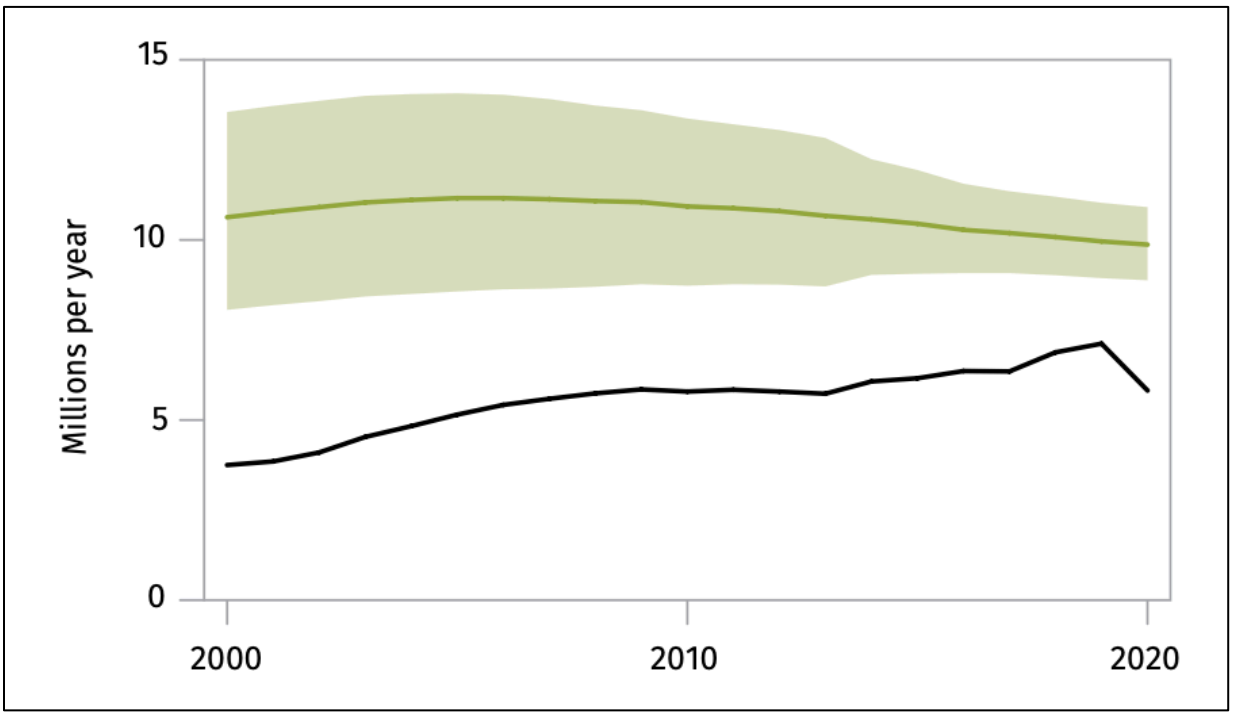


Figure 1-9: *Global trends in notifications of people newly diagnosed with TB (black) and the estimated number of incident TB cases (green), 2000-2020. Shaded areas represent the uncertainty intervals. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

India was by far the largest contributor to the global shortfall in TB notifications in 2020 as compared to 2019 with a 41% decrease in notifications (Figure 1-10). The substantial reduction in TB case detection and reporting likely reflects both supply- and demand-side disturbances to TB services. The reasons for these disruptions range from a reduced health system capacity to continue to provide services, to less

willingness and ability to seek care in the context of lockdowns and associated restrictions on movement, or concerns about the risks of going to healthcare facilities during an epidemic surge. A general stigma associated with similarities in the respiratory symptoms and transmission patterns related to TB and COVID-19 could also have contributed.[15]

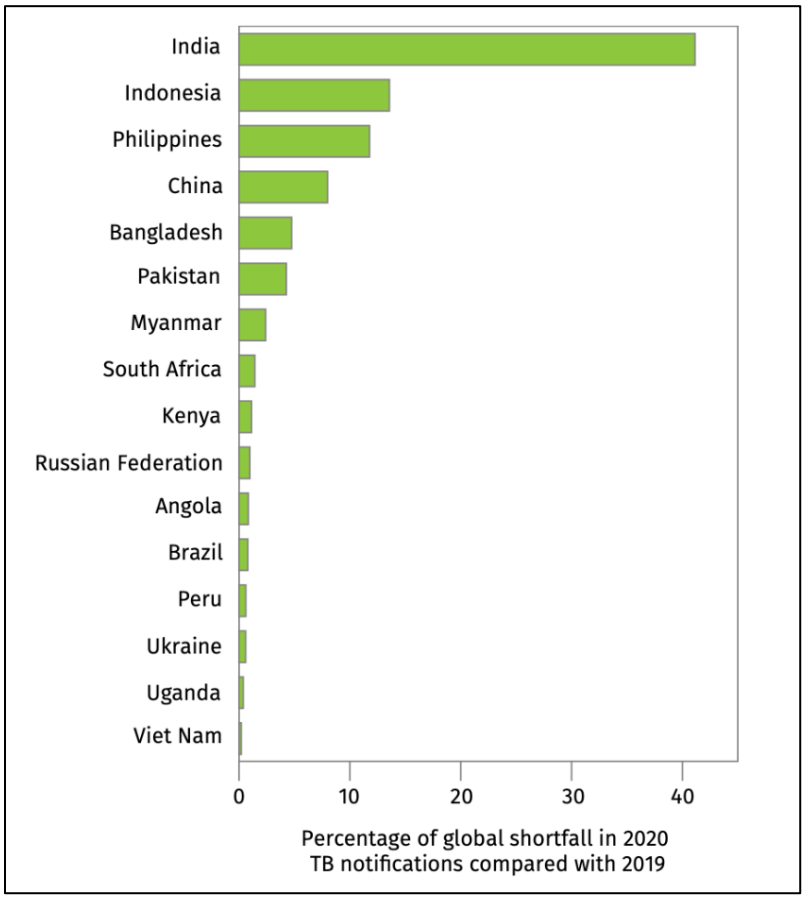


Figure 1-10: *16 countries with the largest contributions to the global shortfalls in TB notifications in 2020 as compared with 2019. (Source: Global Tuberculosis Report, 2021. Geneva, Switzerland: WHO, 2021; reuse permitted under the terms of the Creative Commons CC BY 4.0)*[15]

Whereas standardised TB treatment and service in India is delivered by the public sector, early diagnosis and treatment are hindered by the presence of a large and unregulated private healthcare sector with varying degrees of quality.[8,34-36] Poor diagnostic practices in this sector prolong tuberculosis transmission by delaying case detection,[37,38] whereas a general lack of counselling and support of treatment adherence hampers successful, relapse-free cure.[35] Moreover, most cases treated in the private sector are never notified to public health authorities.[39] India is not alone in harbouring "missing" TB patients in a vast and unregulated private sector; in 7 countries with 62% of the total missing cases, private providers account

for 65-85% of initial care seeking, yet they contributed just 19% of TB notifications, equivalent to just 12% of estimated incidence (Figure 1-11).[40]

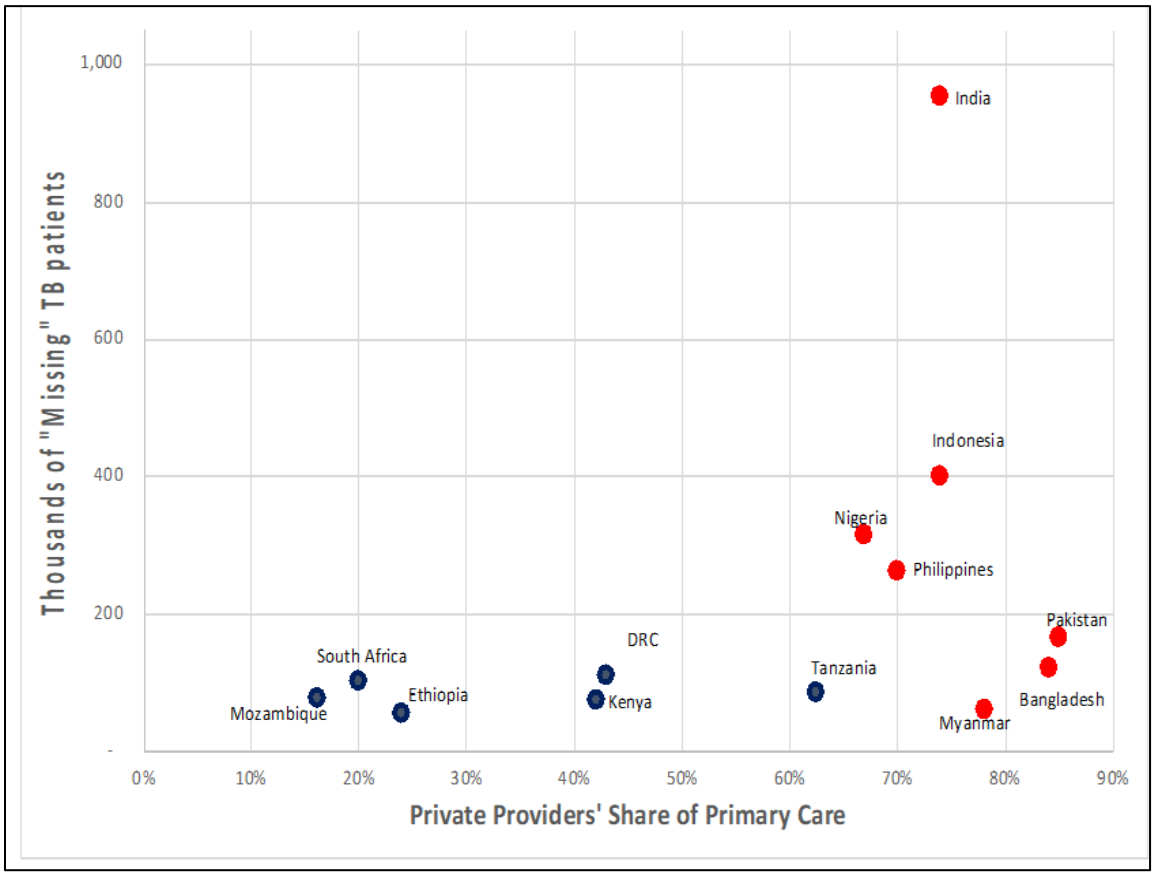


Figure 1-11: *Private share of primary care in 13 countries with the most "missing" TB patients (excluding China). (Source: Guy Stallworthy, Bill & Melinda Gates Foundation (Personal communication))*

Estimating the number of TB patients treated by the private sector is difficult, but models suggest that an estimated 2.2 million patients were being treated in the private sector in 2014 in India (Figure 1-12).[41] This conservative estimate assumed that only 50% of diagnoses in the private sector genuinely have tuberculosis, and were treated with TB medicines for an average of 4 months.

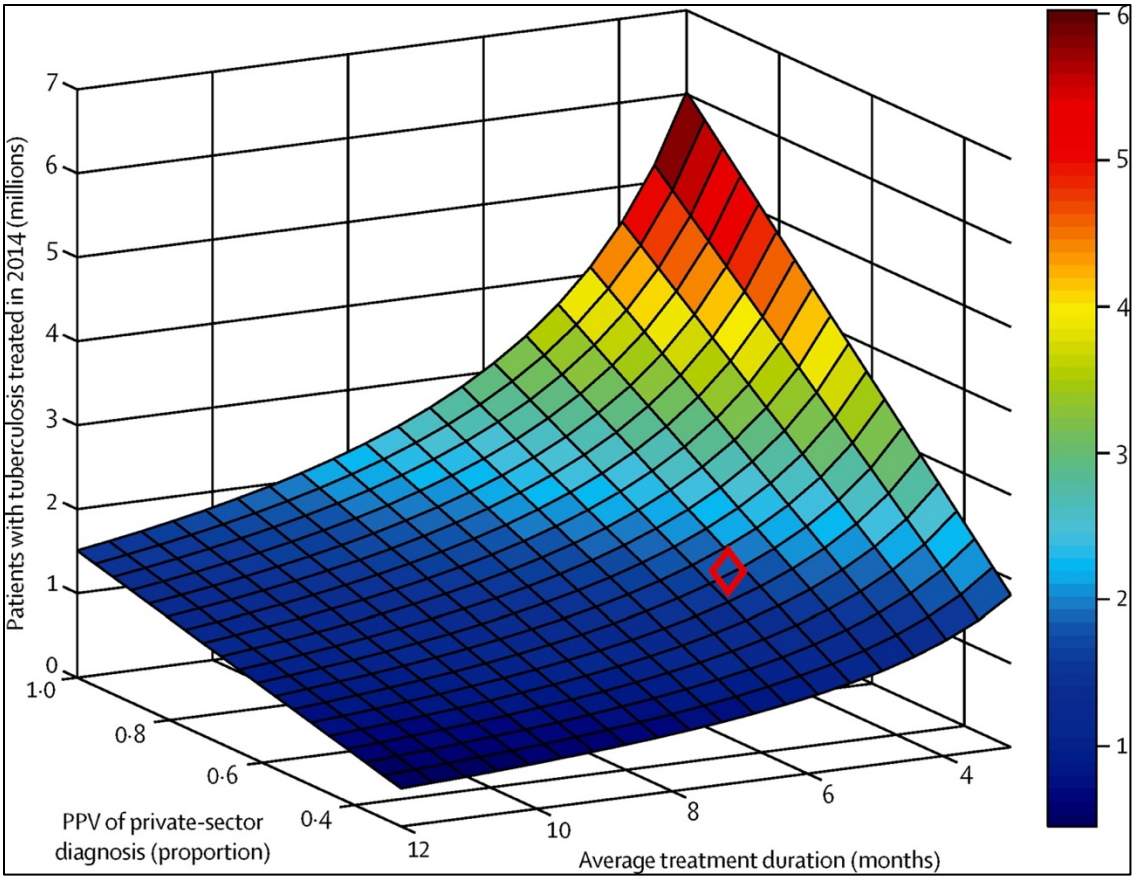


Figure 1-12: *Implications of treatment volume in 2014 for tuberculosis burden managed by the private sector in India. (Source: Arinaminpathy et al, Lancet Infectious Diseases (2016); reuse permitted under the terms of the Creative Commons CC BY 4.0)* [41]

1.6 QUALITY OF PRIMARY CARE

Improving the quality of primary healthcare via provider performance improvement is a crucial objective set by multiple policymakers and health practitioners, particularly in resource-poor settings. Recently, a systematic review identified 499 published studies on quality improvement initiatives spanning 79 LMICs over the last fifty years.[42] The breadth of these studies was vast, covering a large range of clinical presentations, outcomes, behaviors, locations, sectors, and intervention types.

However, limited generalizable insights can be made regarding healthcare provider performance improvement, despite the scale of the available data. There are several reasons for this knowledge gap.[43,44] First, the comparability of individual study definitions of "quality" are not usually collapsible. Quality is measured in a myriad of ways, from structural indicators to process indicators to patient outcomes; the capacity to benchmark these changes against the actual needs of patients is often lacking.

Second, studies are generally not transportable, meaning they are bound to context-specific outcomes targeted by the intervention and are challenging to translate to other settings. Third, other studies made use of second-hand accounts such as interviews only, or they used medical records, which can create "big data biases" where the magnitude of estimation error increases with the size of the dataset.[45,46] There was a scarcity of studies which collected data specifically for the purpose of evaluation of provider performance.

Many of the studies identified by the systematic review for inclusion were of poor quality; only one third of the studies included had a "low or moderate" risk of bias, two thirds used a true control group, and around 40% were randomized, with randomization becoming more popular in more recent studies.[47] Many projects were short in duration, spanning from a few months to a year, and those that were lengthier only continued for a maximum of 6 months post-intervention, questioning the sustainability of such efforts.

Only 17 prior studies have explored healthcare provider performance improvement in the private sector in LMICs using high quality research methods in randomized interventions. Figure 1-13 illustrates this using a meta-analysis forest plot. Only eight of these studies were set exclusively in urban contexts and none took place in urban India specifically. The trial by Das et al (2016)[48] was the only rigorous randomized controlled trial (RCT) study on healthcare performance conducted in the rural Indian private sector. In light of ongoing trends of population urbanization, alongside the appearance of drug-resistant variants of tuberculosis as well as novel diseases like COVID-19, it has become critically important to fill these knowledge gaps with research on provider performance in the private urban Indian sector.[49-52]

These gaps in knowledge have been recognized and from them, more generalizable method of learning from intervention programs have been developed. The study in India was conducted by a member of this thesis committee (Das) with an informal provider training program in rural West Bengal. In that study, general and multidimensional definitions of quality were developed and measured with knowledge vignettes, clinical observations, and standardized patient audits. Underlying medical conditions and metrics were not revealed to the training team, and the study was randomized and follow-up conducted after 9 months.[48] This rigorous approach produced high quality, generalizable insights that could be transferred to other settings, and has contributed to a re-imagining of how to understand healthcare quality more broadly.[53]

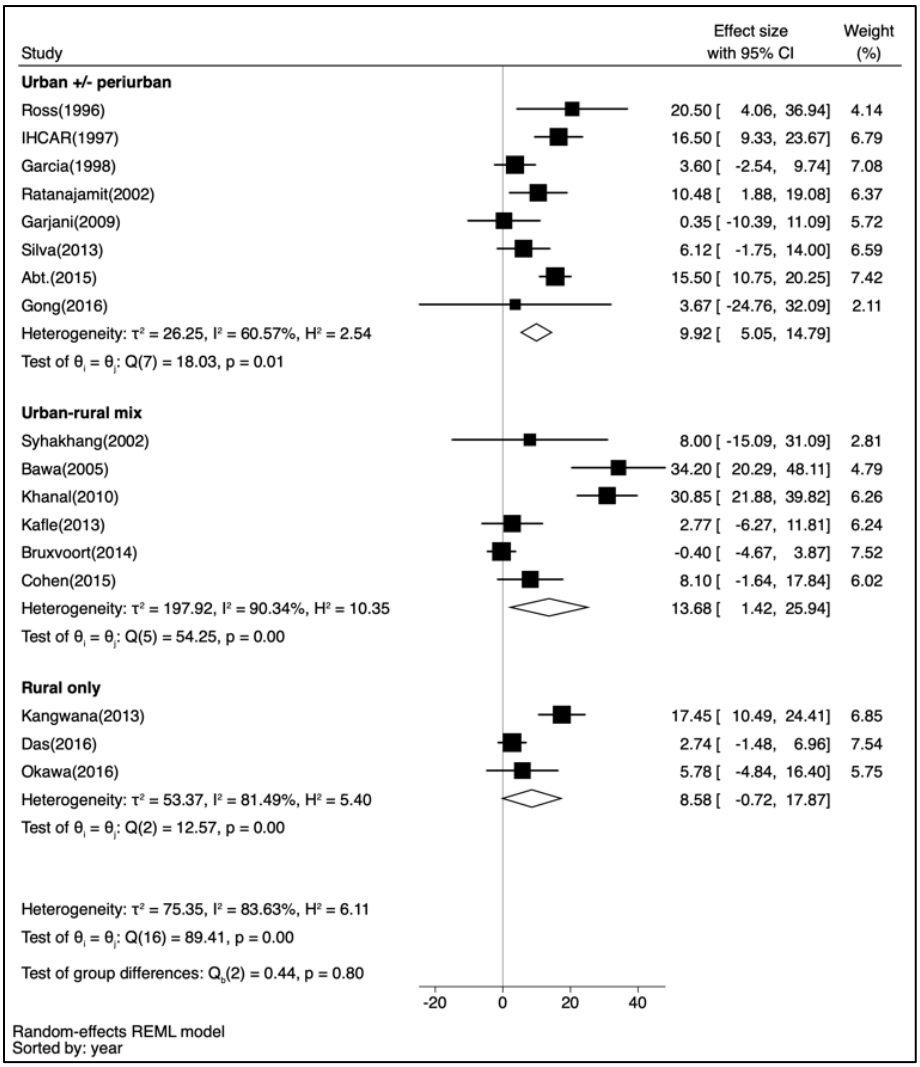


Figure 1-13: *High quality RCTs with LMIC private providers are rare. (Source: Rowe et. Al. Lancet Global Health (2018); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[42]

1.7 QUALITY OF CARE AND TB

In a landmark Lancet Commission entitled "High quality health systems (HQSS) in the Sustainable Development Goals era: Time for a revolution", the authors asserted that providing health services (i.e. coverage) without guaranteeing a minimum level of quality is ineffective, wasteful, and unethical.[1] Instead, health systems globally are in need of high quality health systems that optimize healthcare in each given context by consistently delivering care which improves or maintains health, by being both

respected by society, and by responding to ever evolving population needs.[1] More than 8 million people annually in LMICs die from conditions that are treatable and upwards of 60% of deaths from conditions amenable to healthcare are due to poor quality care, with the residual deaths resulting from under-utilization of the health system itself.[1]

The report lists TB as a key and recurring example of the need to go beyond coverage alone and focus on the quality of care. TB is a prime example that illustrates the importance of quality of care. With TB disease affecting an estimated 9.9 million people (95% UI: 8.9-11 million) in 2020, equivalent to 127 cases (UI: 114-140) per 100,000 population, TB is the second leading killer worldwide due to a single infectious agent; despite being curable, TB unnecessarily caused 1.5 million deaths in 2020.[2] It is estimated that 50% of TB deaths are due to poor quality TB care with the remaining 476,047 deaths due to non-utilization of healthcare services.[1] Using already existing tools coupled with improving the quality of care, 50% of all TB deaths or 900,000 TB deaths could be prevented annually.[1] TB is an entirely curable, bacterial infection for which we have policies, tools and technologies and despite this, 50% of deaths in association with TB occur in patients actively seeking medical care, embodying a grave health systems failure.

Cascades of care for TB at the global level clearly illustrate poor quality. Kim et al. analyzed the cascades of TB care across 30 high TB burden countries and reported that only 1 in 2 patients successfully completed the care cascade (Figure 1-14).[54]

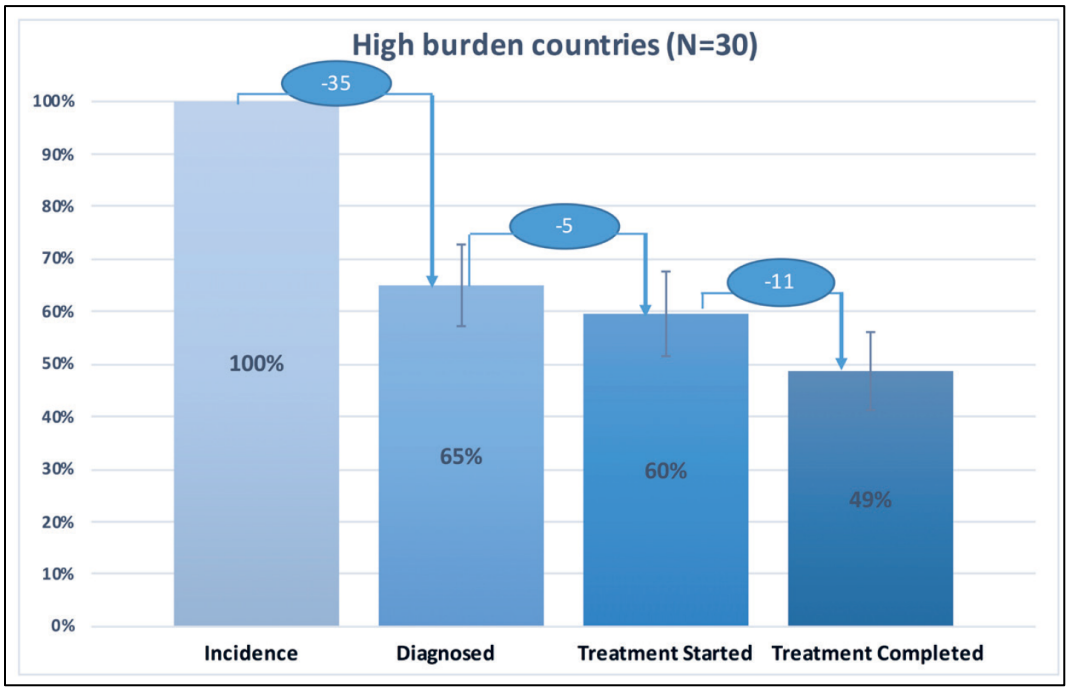


Figure 1-14: *TB care cascade for 30 high-burden countries, 2015. Diagnosed: 100 × [(sum of total of new and relapse cases and cases with unknown previous tuberculosis treatment, 2015)/(estimated number of incident cases (all forms), 2015)]. Treatment Started: 100 × [(sum of outcomes for all new and relapse cases: cohort size and outcomes for previously treated patients: cohort size, 2015)/(estimated number of incident cases (all forms), 2015)]. Treatment Completed: 100 × [(sum of outcomes for all new and relapse cases: treatment success (cured or treatment completed) and outcomes for previously treated patients: treatment success (cured or treatment completed)/ (estimated number of incident cases (all forms), 2015)]. (Source: ,Kim et al, J Global Health (2019); reuse permitted under the terms of the Creative Commons CC BY 4.0)* [54]

A similar finding emerged in the work of Kendall et al.[55] where the cascades of care for drug-resistant TB were analyzed. Currently, fewer than 1 in 4 individuals with MDR- or RR-TB worldwide receive corresponding treatment, and only an estimated 1 in 8 are successfully treated (Figure 1-15).[55] These cascade analyses clearly illustrate poor quality of TB diagnosis and follow-up.

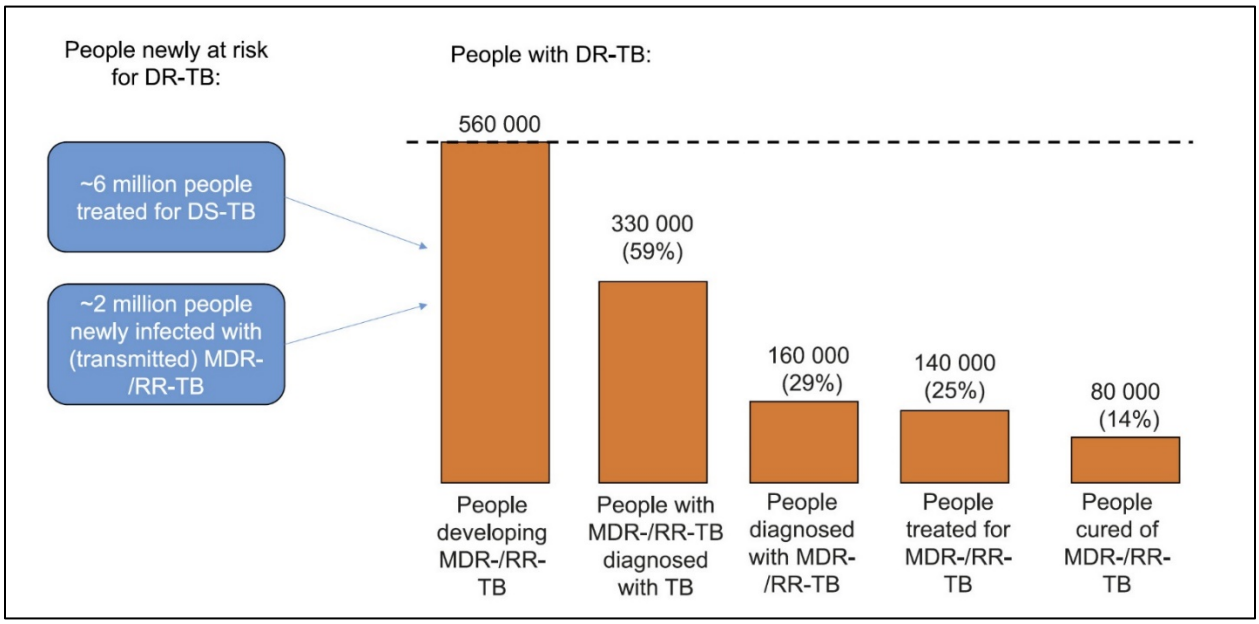


Figure 1-15: *Cascade of care for drug-resistant TB worldwide. The boxes to the left show an estimate of the people at risk to develop either transmitted or acquired rifampin-resistant (RR) or multidrug-resistant (MDR) TB. The orange bar chart shows the people with active MDR- or RR-TB (estimates for 2016, based on aggregation of often-limited country-level data[56]) who are lost at the stages of TB diagnosis, drug resistance diagnosis, initiation of treatment, and completion of curative treatment. (Source: Kendall , et al, Int J Tuberc Lung Dis (2019)); reuse permitted under the terms of the Creative Commons CC BY 4.0)* [55]

As Figure 1-16 illustrates, there are many reasons for poor quality, from under-funded national TB programs, to limited uptake of new tools. Enhanced integration at every level of the health system is necessary to ensure TB patients are promptly diagnosed and initiated on effective treatment. Links

between clinical and laboratory service delivery points are essential to strengthen the diagnostic capabilities of TB care providers. Moreover, there are opportunities to improve quality at the first point of contact care for TB patients even when it occurs outside of the TB care system – general clinics, dispensaries and informal providers should all be engaged. Other notable drivers of inferior quality are under-funding of national TB programs, and inadequate implementation of system-wide evidence-based policies, as confirmed by evidence syntheses of care costs,[57] surveys on implementation of TB policies,[58] and market analyses of access to new TB tools.[59,60] Thus, increasing both the coverage and the quality of TB services across the entire care continuum is required to decrease TB mortality and incidence substantially.[61]

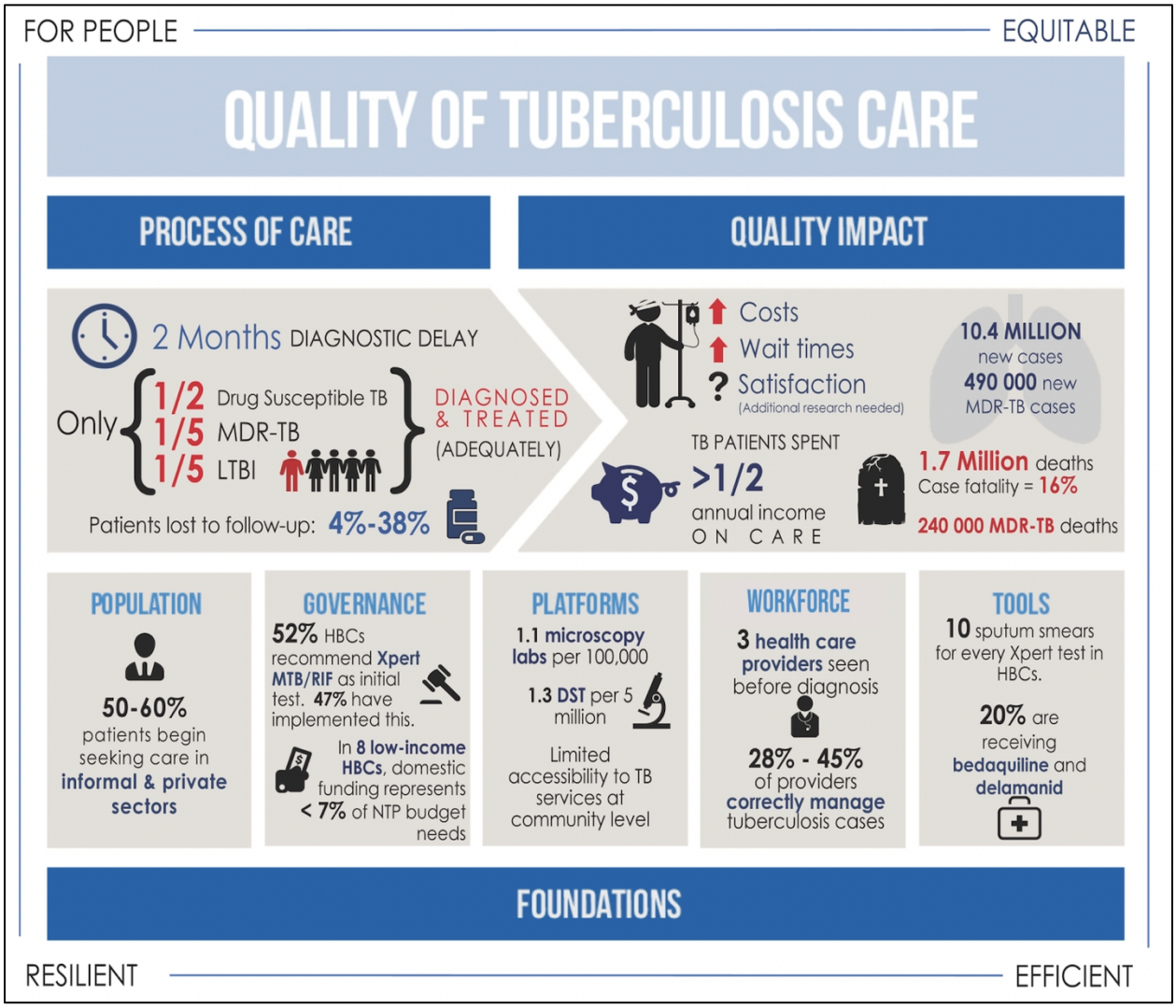


Figure 1-16: *Dimensions of quality of TB care, and barriers that undermine optimal service quality. (Source: Reid et al, Journal of Clinical Tuberculosis and Other Mycobacterial Diseases (2020)); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[61]

1.8 STANDARDIZED PATIENT METHODOLOGY

Assessing quality of TB care is challenging since the majority of past quality of TB care evaluations have relied on recall-based patient surveys, questionnaire surveys of provider knowledge, and prescription/chart analyses. Table 1-2 summarizes the aforementioned quality measurement methods across their abilities to assess provider knowledge and practice, to provide limitations and biases when considering each method, and to outline illnesses that can be captured. These methods are unfortunately subject to significant biases and thus may not reflect real-world practices.[3,5,9-12] This is especially true in the highly fragmented and variable private sector.

To address these issues, standardized patients (SPs) are increasingly used in to assess quality of medical care, particularly in low resource settings.[4,5,11] Standardized patients have emerged as close to a 'gold standard' for measuring the quality of clinical care by allowing care to be benchmarked against pre-existing standards. The success of SP methodology lies in its counterfactual manipulations of the possibilities available to real care-seekers – especially those paths not taken up by them – through which real responses can be elicited from real providers. The method works well to elicit responses from the provider through conditional manipulations of SP behavior.[62] Compared to other methods, SP studies can provide an accurate assessment of provider practice that is free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of healthcare providers.[12,13] This method allows researchers to understand how providers would behave under different counterfactual possibilities.

Table 1-2: *Summary of quality measurement methods across their abilities to assess provider knowledge and practice, to provide limitations and biases when considering each method, and to outline illnesses that can be captured (Source: Kwan et al. BMJ Global Health 2019;reuse permitted under the terms of the Creative Commons CC BY 4.0)*[63]

Measure of Quality	Measures Knowledge	Measures Practice	Accounts for Case-Mix	Accounts for Patient-Mix	Limitations and biases when considering each method	Illnesses Covered
Provider Vignettes	Yes	No	Yes	Yes	By design: Vignettes measure the maximum a provider can do and is affected by social desirability bias. Very easy to include as a survey when research team is already conducting health facility surveys; however, vignettes can overestimate provider practice.	All
Patient Exit Interviews	No	Yes	Yes	No, but can account for service-mix	By design: Exit interviews measure the maximum a patient recalls and is affected by social desirability bias. Challenges exist with sampling patients and ensuring high rates of participation, and providers may not always refer to clinical or technical procedures by name with patients.	All; however, recruitment of patients is more difficult if research team is interested in rarer health conditions or patient characteristics.
Direct Clinical Observation	No	Yes	No	No	Direct observation is biased by Hawthorne effects; however, Leonard and Masatu (2007) show big	Limited in two ways: (A) "serious" illnesses like unstable angina will show up on a sporadic

					Hawthorne effects begin to decline with the time spent observing (3). Costs of paying enumerators to observe for long periods of time can be high and may not be relevant for rarer conditions. Ethical challenges exist for data collectors who observe bad or harmful practices being performed on real patients.	basis, and (B) the observer never knows what the patient actually has—and doctors frequently make incorrect diagnoses.
Medical Record or Chart Abstraction	No	Yes	No	No	Although appropriate in settings with very strong records, LMIC settings typically have incomplete, varied (paper, books, electronic), or no records in low-resource settings. Records if they exist also often only measure patients after a specific diagnosis is made and do not accurately or consistently reflect patient-provider interactions.	More relevant for provider actions that occur after diagnosis is made and for conditions where health records are kept. If records exist and are high quality, this method can be better for conditions where patients visit providers for multiple, sequential visits (e.g., chronic conditions)
Standardized Patients	No	Yes	Yes	Yes	Assesses one-time interaction (and not follow-up or subsequent visits) to a single facility or provider. More extensive planning, recruitment, and training costs, and significant capacity and skill in implementation is needed to address the details in conducting such a study.	Limited to (A) diseases that don't have any obvious physiological symptoms (which cannot be mimicked), and (B) conditions that don't require invasive exams—particularly in LMICs.

There is very wide variation in the quality of TB-related care amongst providers. Table 1-3 shows the proportion of 'correct management' of SPs with classic TB symptoms by both private (non-NTP) and public providers in five countries.[23] Standardized patient studies show gaps in cascades of care, and poor quality of care in both public and private sectors, with private sector performing comparatively worse.[4,37,38,42,43]

Across countries, only about a third of SPs with presumed TB were managed correctly at the primary care level in the private sector an, in India, most were not referred.[38,65-68]

Table 1-3: *Summary of correct management and referral patterns of SP studies conducted in the public and private sectors. (Sources: Das et al. (2015); Kwan et al. (2018); Daniels et al. (2017); Sylvia [64] et al. (2017); Christian et al. (2018); Boffa j 2021; Rosapep l 2022); reuse permitted under the terms of the Creative Commons CC BY 4.0)*[37,38,65-68]

Setting - Sector	% Correctly Managed	% Referred
Delhi, India – *private sector*	21%	10%
Mumbai, India – *private sector*	37%	15%
Patna, India – *private sector*	33%	10%
Nairobi, Kenya – *public & private sectors*	33-40% Public: 79% asked for sputum test Private: 36% asked for sputum test	4-10%
Rural China (3 provinces) – *public sector*	28%, village clinics 38%, township centers 90%, county hospitals	28%, village clinics 18%, township centers 5%, county hospitals
South Africa – *public sector* **(Western & Eastern Cape)**	43% got TB and HIV tests 84% got sputum TB tests	
South Africa – *private sector* **(KZN & Cape Town)**	43%	57%
Nigeria – private sector **(Lagos & Kano)**	31% in clinical facilities	

Because SP studies capture actual practice rather than knowledge, they have allowed researchers to estimate the 'know-do gap', i.e. the difference between what providers know (i.e. knowledge, as measured by vignettes) and what providers do in their actual, real-life practice (as measured by SP studies). Data from four countries convincingly show a large know-do gap (Table 1-4). Providers often report better knowledge about TB management than what they display when SPs visit them.

Table 1-4: *Summary of 4 studies comparing the 'know-do gap 'in TB care – the difference between what providers know (i.e. knowledge, as measured by vignettes) and what providers do in their actual, real-life practice (as measured by SP studies); (Sources:* Boffa et al; Kovacs et al*;* Das et al; Sylvia et al); *reuse permitted under the terms of the Creative Commons CC BY 4.0)*[37,64,67,69]

Location	Vignettes (knowledge)	SPs (practice)
South Africa (Boffa et al)	80%	43%
Senegal (Kovacs et al)	81%	68%
India (Das et al)	77%	10%

China (Sylvia et al)	76%	32%

Due to the complexity and variability of the private sector, interventions designed to address quality of care in India require flexible, dynamic solutions which can work to address the problem from multiple angles.[70] From this challenge, SPs have emerged as a close to 'gold standard' for measuring the quality of clinical care across a wide variety of settings as possible. This method resolves problems of patient mix across healthcare providers and allows care to be benchmarked against pre-defined standards, allowing for flexibility across regional standards and nuance. While SPs are not real patients, their presence in a study is not meant to exactly replicate reality. Rather, the success of the SP methodology lies in its ability to conduct counterfactual manipulations of the possibilities available to real care-seekers. The method is especially useful for those paths not taken up – through which real responses can be elicited from real providers. Thus, their success is not predicated on their ability to act as direct substitutes for real patients and the subsequent validity of their findings do not rely on their ability to imitate real patients. In a study where SPs returned to providers for follow-ups when asked, it was demonstrated that the SP method worked well to elicit responses from the provider through conditional manipulations of SP behavior. In tandem with observational methods, which are better suited to understand what choices real people make and how these can affect the direction of diagnosis and treatment, SPs can thus help parse out how quality of care emerges for the "patient" as a shared history between care-seeking individuals and care providers.

Each SP can be observed at many different providers, and thus, the study design allows for representative and completeness of data. This novel method was first used in a population-based sample in a low/middle-income country setting by Das et al. (2012)[71,72] and has since then been used in quality of care studies in multiple countries and for conditions ranging from TB to malaria to family planning. Care practices and decision-making has been used in a variety of context. In Figure 1-20 for instance, one such study in India reported that there were no clear patterns and wide variation in usage across cities (Mumbai vs. Patna) and provider types (formal vs. informal) and case presentation.[73] This figure reports the proportion of SP interactions in which various TB care management practices were observed. An extensive literature documents the validity and benefits of this approach.[62,72-75]

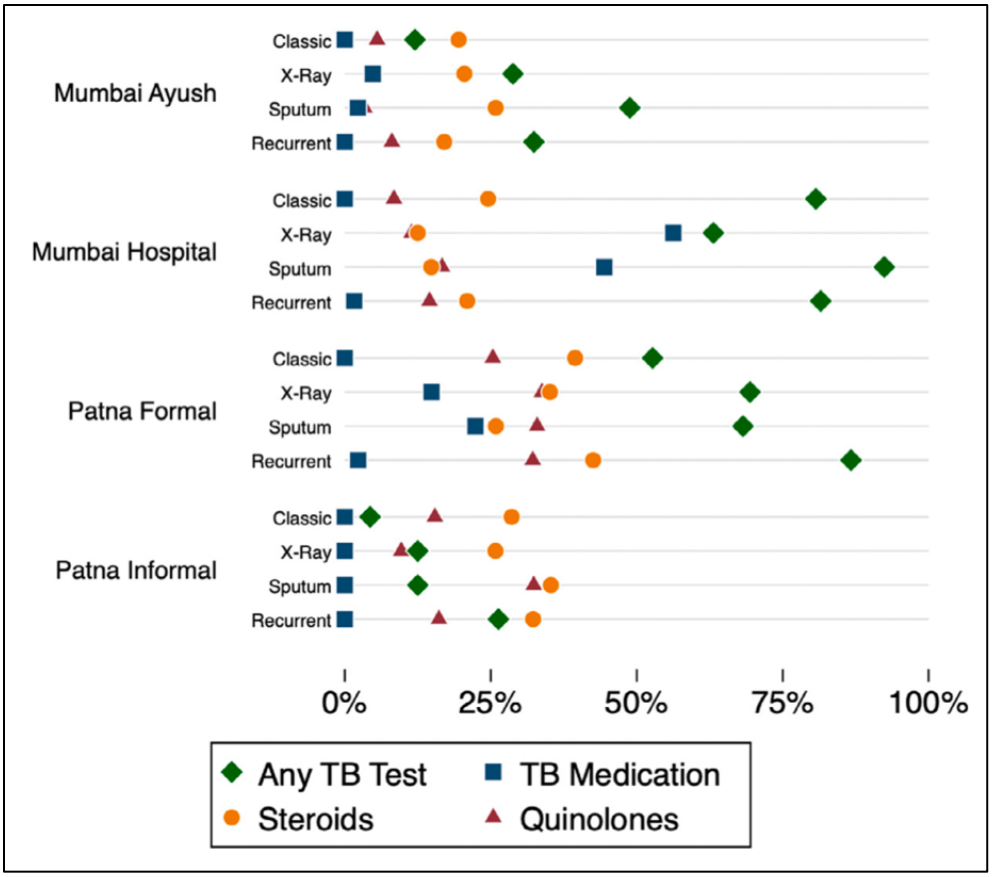


Figure 1-17: *TB-related testing, anti-tb medication, and contraindicated medication use by case presentation at private providers in urban India for all case presentations. (Source: Daniels et al, Journal of Clinical Tuberculosis and Other Mycobacterial Diseases (2019); reuse permitted under the terms of the Creative Commons CC BY 4.0).*[73]

Nonetheless, the SP method has its limitations and challenges. Thus far, the method has been limited to a one-time interaction with a provider and has not yet been validated for multiple, sequential visits to the same provider. This might be particularly important for certain chronic conditions. The SP method is also not feasible for conditions that require physical signs to be evident such as trauma or pregnancy. As for assessing quality of care for childhood conditions, the SP method has been used with and without a real children present, which requires different, yet precise precautions.[76] Moreover, the SPs are trained to present their symptoms and history in a manner that should not lead the provider in a wrong direction; however, in real-life situations, many patients have difficulty presenting the symptoms and history of their disease in a clear manner, and the provider could be misled. In other words, the muddled picture some patients may give of their symptoms may misrepresent their underlying conditions compared to a clear presentation delivered by an SP. Additionally, the identity of SPs themselves may lead to different findings.

For example, quality estimates from a more educated SP population may not be generalizable to a less educated patient population since the two groups are likely to express themselves differently. Ethical considerations are also paramount, since both providers and SPs could be subject to harm in the conduct of the research. Initial scoping of the setting and proper mitigation strategies must be put in place.

A detailed manual and toolkit (https://gh.bmj.com/content/bmjgh/4/5/e001669/DC1/embed/inline-supplementary-material-1.pdf?download=true) on how to conduct SP studies has been developed by the QuTUB consortium (https://www.qutubproject.org/).

1.9 RESEARCH GAPS ADDRESSED BY THIS THESIS

While previous SP studies have shown overall poor quality of TB care in the Indian private sector,[3,4,6,8-10,1416] my thesis will build upon these findings by investigating four critical questions among an unprecedented larger sample, and over a longer time period:

(1) Do private providers start TB treatment purely on the basis of their clinical judgement and chest radiography without microbiological confirmation?

(2) Do private providers manage presumptive or confirmed TB patients with medications that can suppress TB symptoms and potentially worsen/delay TB detection, such as corticosteroids or quinolones?

(3) What kind of TB drug regimens are typically prescribed by private providers in India? How often are irrational drug combinations used?

(4) When faced with patients with TB symptoms, do private pharmacists refer them for TB testing or do they dispense antibiotics or anti-TB drugs over-the-counter?

1.10 OBJECTIVES

In my manuscript-based thesis, I will assess quality of TB care and provider practices across outpatient primary care settings in India's large and unregulated private sector. More specifically, using secondary data from a series of SP studies in India, I will seek to evaluate if providers empirically manage TB on the basis of clinical and CXR findings, whether they prescribe potentially harmful medications, and whether

private pharmacists manage people with presumptive TB appropriately. These insights are needed in order to design and implement effective quality improvement programs for TB.

My research work will address this issue through four main objectives (i.e. chapters) as outlined below:

Part 1: Understanding quality of TB care among private providers

Objective 1: To perform an analysis of a dataset compiled from SP studies in order to investigate providers' care decisions based on abnormal chest X-ray across healthcare providers

> *Specific aim 1.1:* To estimate the overall proportion of SP-provider interactions that resulted in the initiation of anti-TB treatment based on abnormal chest X-ray alone (without microbiological tests ordered)
>
> *Specific aim 1.*2: To identify provider- and patient-level factors associated with prescription of anti-TB medications based on abnormal chest X-ray alone

Objective 2: To perform an analysis of a dataset compiled from SP studies in order to investigate providers' patterns in quinolone and corticosteroid dispensation across healthcare providers

> *Specific aim 2.1:* To estimate the overall proportion of SP-provider interactions that resulted in prescription or dispensing of quinolones and corticosteroids, respectively, for various types of TB case presentations
> *Specific aim 2.*2: To identify provider- and patient-level factors associated with quinolone and corticosteroid dispensation, respectively

Objective 3: To perform an analysis of a dataset compiled from SP studies in order to investigate providers' patterns in anti-TB treatment (ATT) across healthcare providers

> *Specific aim 3.1:* To estimate the overall proportion of SP-provider interactions that resulted in prescription or dispensing of ATT, for various types of TB case presentations, and identify the proportion of ATT regimens that were irrational
> *Specific aim 3.*2: To identify provider- and patient-level factors associated with various types of ATT dispensation, respectively

Part 2: Understanding quality of TB care among private pharmacists

Objective 4: To perform an analysis of survey data compiled from SP studies conducted 5 years apart, among pharmacies in Patna, India

Specific aim 4.1: To calculate the proportion of pharmacy interactions that resulted in ideal management

Specific aim 4.2: To calculate the proportion of interactions resulting in antibiotic, quinolone, and corticosteroid dispensation, respectively

Specific aim 4.3: To compare the changes in medical advice and drug dispensing practices of pharmacists for SPs presenting with symptoms suggestive of pulmonary TB disease in Patna, India, after a 5-year follow-up by case

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CHAPTER 2: DO PRIVATE PROVIDERS INITIATE ANTI-TUBERCULOSIS THERAPY ON THE BASIS OF CHEST RADIOGRAPHS? A STANDARDISED PATIENT STUDY IN URBAN INDIA

2.1 PREFACE

As highlighted in Chapter 1, understanding and measuring the proportion of patients seeking care who receive empiric treatment for TB (without microbiological confirmation) is a key step to developing targeted and effective quality-improvement interventions, and this is especially true for patients who are put on treatment based on an abnormal chest radiograph. In the Indian private sector particularly, there is evidence that quality of TB care falls short of international standards in many places and is in urgent need of improvement. The evidence comes from systematic reviews on the quality of TB care or surrogates of quality indicators such as diagnostic delays, long patient pathways, analyses of TB care cascades, and newer SP studies that directly measure quality of TB care. Some issues highlighted by these sources point to low rates of TB testing by private providers, low rates of referral to the national TB program, and empirical management with antibiotics. Chest radiographs are indicated as a preferred tests for many private providers.

This study is the first to make use of multiple rounds of SP data, across two large urban Indian settings to provide insights into the prevalence and behaviours associated with empiric treatment based on a CXR abnormality.

This work is part of a larger series of papers to be published by the QuTUB consortium (https://www.qutubproject.org/), funded by the Gates Foundation. It will soon be submitted for publication.

2.2 TITLE PAGE

Do private providers initiate anti-tuberculosis therapy on the basis of chest radiographs? A standardised patient study in urban India

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2.3 ABSTRACT

Introduction

The initiation of TB treatment based on results of WHO-approved microbiological diagnostics an important marker of good quality tuberculosis (TB) care. This study makes use of a unique opportunity presented by largescale SP studies, where simulated patients presented with abnormal chest radiograph (CXR) to healthcare providers in Patna and Mumbai, to answer the question whether private providers start anti-TB therapy on the basis of CXR and clinical examinations.

Methods

This study uses the standardized patient (SP) methodology to generate accurate and unbiased estimates of empiric treatment for patients presenting to primary care providers in urban India with an abnormal CXR. A total of 795 SP interactions were done over three survey rounds, from 2014 to 2020, in two cities. All estimates clustered standard errors at the provider level, and were inverse-probability-weighted based on the study sampling strategy, resulting in city-round-representative interpretations of all outcome measures.

Results

Amongst SPs who presented to a provider with an abnormal CXR, 182 of 795 (25%; 95% CI: 21-28%) interactions resulted in ideal management, where the provider prescribed a microbiological test and did not offer a concurrent prescription for a corticosteroid or antibiotic (including anti-TB medications). In contrast, 210 of 795 (23%; 95% CI: 19-26%) interactions were prescribed anti-tuberculous medications. 140 of 795 (13%; 95% CI: 10-16%) of interactions resulted in a prescriptions/dispensation of ATT (anti-tuberculosis treatment) plus a prescription for confirmatory microbiological testing.

Conclusion

This research shows that one in five SPs with abnormal CXR were prescribed ATT by private providers. It contributes novel insights to the prevalence and behaviours associated with empiric treatment based on CXR abnormality. It stands as a reminder of the balance physicians in the Indian context need to find between not losing their patients altogether to follow-up and being able to trust their laboratories while providing the proper regimen and care to their patients. A more detailed qualitative inquiry into their

practices and decision-making rationale, coupled with engaging them in anti-microbial stewardship and lab strengthening measures, are likely to have impacts in timely and appropriate management of TB, and other respiratory infections.

2.4 INTRODUCTION

An important marker of high quality tuberculosis (TB) care is the initiation of TB treatment based on the results of WHO-approved microbiological diagnostics. Nearly 60% of the 4.8 million people diagnosed with pulmonary TB worldwide in 2020 were microbiologically confirmed. This proportion has remained virtually unchanged since 2005, with a slight increase from 57% out of a total of 6.0 million notified TB cases in 2019. Remaining patients are diagnosed clinically, that is, based on signs and symptoms, abnormalities on chest radiographies or other non-microbiological tests.[1] The microbiological detection of TB is critical because it allows patients to be correctly diagnosed, is a prerequisite to test for drug resistance and ensures that the most effective treatment regimen is initiated, based on the individualized pattern of drug resistance.

The WHO thus urges National TB Programs (NTPs) to make use of WHO recommended diagnostics (WRDs) that are more sensitive than smear microscopy and prioritize the increase in the percentage of TB cases confirmed bacteriologically. As part of the WHO's updated guidelines for the use of molecular assays intended as initial tests for the diagnosis of TB, among adults and children in the general population with signs and symptoms of pulmonary TB or CXR with lung abnormalities or both, Xpert MTB/RIF or Xpert Ultra (Cepheid, Sunnyvale, CA, USA) or TrueNAT MTB (Molbio Diagnostics, India) should replace smears as the initial test for pulmonary TB.[2]

A balance in ideal clinical decision-making with the limitations imposed by real-world care settings may lead physicians to initiate the treatment of presumptive TB patients in the absence of a bacteriologically confirmed diagnosis, frequently referred to as empirical TB treatment. Drivers of empiric management of TB include, amongst other factors, a high burden of disease, difficulty in accessing sputum TB testing, easy access to antibiotics, clinical presentations suggestive of TB, and excessive reliance on non-specific tests such as CXRs, and widespread antimicrobial abuse, especially in private and informal health sectors.[3] While not all cases of TB can be microbiologically confirmed, it is important for healthcare providers to make a serious effort at getting a confirmation. TB symptoms are neither sensitive nor specific, and tests such as chest radiographs and other clinical features lack specificity, with the implication that an incorrect diagnosis of TB could lead to unnecessary TB treatment. Empiric treatment can potentially result in overtreatment with 6 months of a potentially toxic treatment, added costs to patients and the health system, and a missed opportunity to correctly diagnose and treat other diseases that might mimic TB.

India is the biggest consumer of antibiotics, and antibiotic abuse has worsened during the pandemic (Sulis et al PLOS Med). Private providers in India are known to rely on clinical diagnosis and empiric treatment initiation.[4,5] In India, only 16% of all private TB notifications in 2018 were bacteriologically confirmed cases, suggesting widespread empirical management.[6] Prior research shows that there is variety in the patterns of diagnostic algorithms employed by providers; these include clinical diagnosis without TB diagnostic tests or clinical diagnosis with a CXR suggestive of TB, with low utilization of microbiological tests and high rates of empirical treatment across different kinds of providers.[7,8] Studies have suggested that some physicians are distrustful of diagnostics, whether they be "new" as in Xpert MTB/RIF – WHO endorsed in 2010 – or more antiquated methods such as smear microscopy. Private and informal providers in these contexts decide to rely rather on their experience and clinical acumen; they can also be swayed by explicit or implicit economic motivation. Moreover, TB drug prescription data analyses have found that the amount of TB medications sold in the private sector is two to three fold that of the number of notified patients.[9] Despite this disjunct, it remains impossible to link this directly to the potential for overtreatment of TB since true TB burden is measured in terms of numbers of patients, not volumes of anti-TB drugs sold in the market.[10]

It remains unclear how much empiric treatment on the basis of clinical suspicion and/or abnormal chest CXR is occurring. If someone presented with typical TB symptoms and an abnormal CXR in urban India, to what extent do providers prescribe anti-tuberculosis treatment (ATT) without first ordering a confirmatory microbiological test? Most cases in the private sector are not bacteriologically confirmed and coupled with the fact that there are more anti-TB medicines sold than there are cases that are notified, it is highly likely that providers are initiating treatment without sufficient investigations.

In this study, we employed the standardized patient (SP) methodology to directly address this exact question. Building off our previous work,[8,11-16] this study made use of a unique opportunity presented by large-scale SP studies, with SPs presenting with abnormal CXR to healthcare providers in Patna and Mumbai in three consecutive rounds of surveys with aims to better describe inappropriate care decisions and patterns of prescriptions and treatments practices based on CXR abnormalities among formally trained private practitioners in these two cities.

Context

Before examining the variation of diagnostic practices in these two cities, it is important to understand their respective TB burdens and the scale of the private sectors. Mumbai is the relatively wealthy and cosmopolitan capital of the state of Maharashtra. As per the latest census (2011)[17], it is home to 12 million inhabitants, with an annual per capita income of 180,000 Indian Rupees (INR) (equivalent to US$ 2,440). In contrast, Patna is the capital of the state of Bihar and one of India's least developed states, with a recorded per capita income of 30,441 INR (US$ 412). The population of urban Patna is 2 million.[17]

In 2019, 106,189 and 191,294 patients with TB were officially notified in Bihar and Maharashtra, respectively.[18] Within the public sector, in Bihar, 43,139 (40.6%) cases were confirmed via microbiological confirmation whereas 79,039 (41.3%) were confirmed in Maharashtra.[18] A country-wide prevalence survey conducted between 2019-2021 indicated that the prevalence of microbiologically confirmed pulmonary TB among population aged ≥ 15 years was observed to be 327 (95% CI: 236-417) per 100,000 population in Patna and 161 (95% CI: 105-218) per 100,000 population.[19] In this survey, all eligible study participants underwent symptom screening using a standard questionnaire and chest X-ray screening; participants with chest symptoms suggestive of TB and/or with past history of TB and/or currently on TB treatment and/or having an abnormal chest X-ray were eligible for sputum examination. The diagnostic algorithm in the survey highlighted the importance of using molecular tests in diagnosing TB given that 33% of cases were exclusively diagnosed based on a molecular test.[19] Molecular tests, when combined with a diagnosis by smear and culture methods, increased the detection rate to 78.4%. Moreover, it was also found that 42.6 % of the TB cases in the survey would have been missed if CXR had not been included.[19]

Data on how many cases were diagnosed empirically within the private sector of each of these two cities does not exist, though the country-wide survey indicated that 67% and 66% presented in the private sector in Bihar and Maharashtra, respectively.[19] In 2018, only 16% of all private notifications were bacteriologically confirmed across the country.[6] The reasons for which this happens despite the availability of microbiological diagnostic tools has yet to be properly explored in these contexts. In terms of the coverage of molecular testing across the country, as of 2020, the number of rapid molecular machines increased from 1,547 modules in 2019 to 3,147 in 2022. 72 rapid molecular testing platforms were housed in Bihar and 335 machines in Maharashtra.[19]

While both cities have public clinics and hospitals, it is within the largely unregulated private sector where most patients decide to seek care.[19] It is important to note that the structure of the private sector is very different between both these cities. Informal providers in Mumbai are mainly AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy) practitioners, while in Patna informal providers tend to be those with other or no qualifications at all. Formal providers in Patna who are MBBS-qualified (Bachelor of Medicine, Bachelor of Surgery, an undergraduate medical degree), tend to operate detached, single-provider clinics, whereas in Mumbai, providers also work in several multi-provider facilities or in hospitals, in addition to their personal clinics. These sites generally contain a mix of MBBS providers, general medicine MD providers, and MD specialists as well as AYUSH practitioners.

This present study will focus solely on MBBS-trained, formal providers in each of these two cities, as they are the practitioners who have the ability to prescribe microbiological testing as shown in our previous work[15], thus examining their propensity to prescribe microbiological diagnosis prior to the commencement of any treatment is of interest. Our previous SP work also found very low rates of anti-TB drug prescription by AYUSH and informal providers (who, legally, are not allowed to prescribe ATT), while formal providers accounted for a large majority of ATT prescriptions.[15]

2.5 METHODS

Study Design and Data Collection

The objectives of this study are to better describe inappropriate care decisions, patterns of prescriptions and treatments practices based on CXR abnormalities among formally trained private practitioners in Patna and Mumbai. To do so, we analyzed unique SP data collected in three survey rounds in these two cities amongst formal providers. Data was collected from a quality of TB care (QuTUB: https://www.qutubproject.org/) surveillance study, funded by the Bill and Melinda Gates Foundation (BMGF), from 2014-2019; the first round was from 2014-2015, the second 2016-2018, and the final round 2019-2020.

The methods of data collection used are described in detail in our baseline survey report.[15] Data was collected to inform and study two Private Provider Interface Agency (PPIA) programs being established by non-governmental organizations (NGOs) in Mumbai and Patna, which were not the focus of this study.[20,21] Throughout, we retained the full sample of healthcare providers, not distinguishing between those in the

PPIA and those outside. The program is only mentioned here since the weighting scheme applied to reach representative sample was based on participation in the PPIA program. Preliminary analysis of data separating the two are currently in progress and can be found in an unpublished brief to BMGF.[22]

Assessing quality of TB care, and within that, reasons for which empirical diagnoses are chosen over microbiological diagnoses, can be challenging. Generally, quality of care studies have relied on recall-based patient surveys, questionnaire surveys of knowledge, and prescription/chart analyses. Unfortunately, these methods are prone to significant biases and thus may not reflect genuine practice.[23-28] To overcome some of these issues, standardized patients (SPs) are increasingly used in LMICs (low-and middle income countries) to assess quality of medical care and the SP method was validated assessing TB quality of care in urban India.[8,13,25,28] Compared to other methods, SP studies can provide an accurate assessment of provider practice that is free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of health care providers.[26,29]

SP Recruitment and Characteristics

Methods of SP recruitment, script development, SP training, provider sampling and assignment of SP cases to providers was previously outlined by our team, and available as an open-access manual and toolkit.[15] Briefly, the research team recruited staff from the local community and provides each SP with a single fixed script (example script in supplementary, S6-Figure 2) for a disease case scenario. These SPs are then extensively trained them to present discreetly at a large number of real healthcare practitioners, posing as a real care-seeker. Each provider's actions and management approach was documented in a structured exit questionnaire (Appendix Y), completed within 1-2 hours of the scheduled visit with a sampled provider. Quality metrics were calculated and reported, including duration of the encounter, history questions asked, diagnoses given or suspected, laboratory tests ordered, treatments recommended/prescribed/dispensed, and price paid by the SP.

Over the course of the three rounds of data collection in each of the two cities, a total of 39 individuals (16 females and 23 males) were recruited and hired as SPs. A total of 13 of these individuals were hired as SPs in both cities, 17 were hired for Mumbai only and 9 for Patna alone.

In Mumbai, 30 individuals (11 female) conducted fieldwork between April 2015 and December 2019. SPs were originally from the states of Bihar (9), Madhya Pradesh (3), Delhi (2) and Maharashtra (16). Primary

languages spoken by the SPs included Angika (1), Bengali (1), Bhojpuri (1), Hindi (9), Malwi (1), Magahi (4), and Marathi (12). In Patna, 22 individuals (10 female) conducted fieldwork. SPs were originally from the states of Bihar (18), Delhi (2) and Madya Pradesh (2). Primary languages spoken by the SPs included Angika (3), Bengali (1), Bhojpuri (4), Hindi (7), Maithili (1), Malwi (1) and Magahi (5).

All potential SPs underwent a health screening questionnaire and checkup, with the resulting cohort of actors of seemingly healthy status. This was important as it assured that the SPs had no apparent health conditions that could confound the case presentation and interaction with healthcare providers. While the SPs were specifically recruited to fit each case scenario and corresponding narrative, they differed in age, sex, height, and weight. The average age of all the SPs was 32. The youngest was 21 and the oldest was 58. The 23 males weighed 50 to 76 kilograms and were 1.55 to 1.84 meters tall. The 16 females weighed 46 to 73 kilograms and were 1.42 to 1.67 meters tall.

Case Presentations

The SP actors in each round were trained to portray one of four different health presentations as designed by a multidisciplinary team of medical anthropologists, health economists, epidemiologists and local clinical experts, the methods of which are described elsewhere.[15,16] This novel method was first used in an LMIC-based, population-based sample by Das et al. (2012), and has since been utilized in quality of care studies in multiple countries and for a variety of clinical case presentations. An extensive literature documents the validity and benefits of this approach.[11,14,30]

This study will only look at two of the four case presentations, with the bulk of the focus being on case 2. All case presentations are detailed below in Table 2-1.

In brief, case 1 consisted of a classic symptomatic case of presumptive TB who had had 2-3 weeks of cough and fever. Case 2 was a presumptive TB case who had 2-3 weeks of cough and fever as well, but additionally presented with a CXR and had received broad-spectrum antibiotic treatment for one week as ordered by another provider, with no improvement.

Table 2-1: *Standardised patient case scenario descriptions.*

CASE DESCRIPTION	PRESENTATION OF PATIENT	EXPECTED CORRECT CASE MANAGEMENT

CASE 1	Classic case of presumed tuberculosis with 2–3 weeks of cough and fever	Presents with presumptive tuberculosis, for the first time, to a private health-care provider, saying "Doctor, I have cough that is not getting better and some fever too"	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 2	Classic case of presumed tuberculosis in a patient who has had 2–3 weeks of cough and fever. The patient has taken a broad-spectrum antibiotic (amoxicillin) given by another health-care provider for 1 week with no improvement. He also carries an abnormal chest CXR suggestive of tuberculosis	Presents after an initial, failed (empirical) treatment for symptoms with broad-spectrum antibiotics and a diagnostic CXR, saying "I have cough and fever which is not getting better. I went to a doctor and took the medicines he gave me and have also had an CXR done." The chest CXR and blister pack for the antibiotics are shown if the provider asks	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 3	Chronic cough with a positive sputum smear report for tuberculosis from a public health facility	Presents with evidence of microbiologically confirmed tuberculosis, saying "I am having cough for nearly a month now and also have fever. I visited [the local government hospital] and they gave me some medicines and did a sputum test." The sputum report is shown if the provider asks	Either referral to a public DOTS center, a qualified provider or specialist, or (in the case of a qualified private provider) initiation of treatment with standard, four-drug, first-line anti-tuberculosis therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol [the HRZE regimen])
CASE 4	Chronic cough and, if asked, elaborates a history of previous, incomplete treatment for tuberculosis, which would raise the suspicion of multidrug-resistant tuberculosis	Presents as a previously treated patient with tuberculosis with recurrence of the disease (i.e., suspicion of drug resistance), saying "Doctor, I am suffering from a bad cough. One year ago I had got treatment in [the local public hospital], and it had got better. But now I am having cough again"	Recommendation for any drug-susceptibility test (culture, line probe assay, or Xpert MTB/RIF MTB/RIF) or referral to a public DOTS center or qualified provider

More specifically, for case 2, the SP carried a digital CXR dated within the last 10 days with evidence of abnormalities, and a blister pack of amoxicillin with him/her. The antibiotic is only shown when the provider asks for it without prompting. The SP begins the interaction by saying: "Doctor, I have had cough and fever. It is not getting better, even though I went to a doctor and took medicines also."

The same CXR film and same radiologist report was used for all rounds, both in Patna and Mumbai; male and female actors had corresponding sex-specific reports (supplementary S2-Figure 1-4). The letterhead on which the report was prepared as per the location deployed. The CXR film itself showed an ill-defined patchy parenchymal opacity with the accompanying report stating that the abnormality was possibly due to "Pulmonary Koch's" (as TB is often reported on radiology reports in India) (S2-Figure 1-4]. We decided to include both the report and the film since we did not expect all practitioners to be able to read the film, for the sake of uniform and consistent interpretation of radiological findings. We wanted to eliminate any possibility that a provider may incorrectly read the CXR film and conclude that there were no abnormalities present. Both the film itself and the accompanying report contained information that could have been indicative of other respiratory conditions (e.g. bacterial pneumonia) which would require further clinical investigation and microbiological testing to diagnose.

Provider Sampling Framework

The primary data collection for this study in Mumbai and Patna was conducted by urban TB programs funded by the BMGF and implemented by PPIAs in each city. These PPIAs were World Health Partners (WHP) in Patna and PATH in Mumbai. Each of these organizations were mapping, recruiting, and enrolling private sector providers into provider networks in both cities.[31] Between 2015 and 2019, the QuTUB Project team completed three rounds of quality or care monitoring across the planned PPIA pilot cities of Mumbai and Patna, completing a total of 6,452 SP-provider interactions with primary care providers over the course of the study. A lane-by-lane mapping exercise[31] resulted in a list of private sector providers in Mumbai and Patna, and this resulting universe was then restricted based on eligibility criteria for the SP study: providers eligible for the study were those who were known to see adult outpatients with respiratory symptoms in the private health sector. The description of the PPIA program served to support sampling weights applied to achieve the urban area estimates for Mumbai and Patna (described below).

Amongst formal providers across both cities, 701 providers were visited, resulting in a total of 4,166 SP interactions (case 1: 1,818, case 2: 795, case 3: 701, case 4: 852). In round 1 of data collection (2014-2015),

717 visits were made in Patna and 637 in Mumbai. In the following round (2016-2018), 761 visits were conducted in Patna vs. 635 interactions in Mumbai. The final round of visits (2019-2020) resulted in 674 and 742 visits amongst formal providers in Patna and Mumbai, respectively. In Patna, there were 963 case 1 presentations and 855 case 2 presentations. In Mumbai, SPs presented as case 1,390 times and as case 2, 405 times.

Weighting

Based on the sampling strategy outlined above, the city-level estimates of the behavioural characteristics in Mumbai and Patna were extrapolates from the sampling frame to the full population of private healthcare providers in each city. To calculate averages and differences within and across cities, we utilized inverse probability weights to satisfy the following:

1. Each city-case combination (Patna case 1, Mumbai case 2, etc.) has a total sum of weights equal to one. Therefore, each case is equally weighted within each city, and the two cities have equal total weights.

2. Within each city-case combination, the sum of weights for (A) MBBS-qualified (formal) and above and (B) non-MBBS-qualified (informal) providers is exactly equal to each group's prevalence in the city as a whole.

3. Within each city-case-qualification group, the relative total weights for (A) PPIA and (B) non-PPIA providers are exactly proportional to each group's prevalence in that city and provider qualification stratum.

4. Each round of the study is exactly proportional to the number of visits completed within that round.

By satisfying these conditions, the weight on each interaction was calculated such that our estimates took the values that they would have had if we had sampled exactly at random from the city as a whole, assuming that our sample is representative of that provider mix. There are 96 weighting groups: one for each city, case, qualification, PPIA status, and round (2 * 4 * 2 * 2 * 3).

Under the assumption that the providers we sampled from our sampling frames were representative of similar providers throughout the city, the resulting estimates were thus representative of the choice of a random provider within the city for each case presentation. Thus, when a statistic is to be reported in this

study in the form "X of Y interactions (N%)", Y is the whole number of interactions observed, X is the whole number of interactions in which an outcome or characteristic occurred, and N is the population-level estimate calculated using the weights detailed above. Table 2-2 details the weights employed for case 2 presentations, by type of provider and city with S2-Table 2 in the Appendix detailing case 1 weighting as well.

Table 2-2*: Sampling and weighting distributions for case 2 within formal providers surveyed.*

			Weighting Group			
Round	SP Case		Patna Formal Non-PPIA	Patna Formal PPIA	Mumbai Formal Non-PPIA	Mumbai Formal PPIA
Round 1 (2014-2015)	Case 2	n	70	28	69	53
	-	weight	0.01274152	0.00386048	0.01387193	0.00080824
Round 2 (2016-2018)	Case 2	n	112	45	76	60
	-	weight	0.00796345	0.00240208	0.01259425	0.00071395
Round 3 (2019-2020)	Case 2	n	94	41	90	57
	-	weight	0.00948837	0.00263643	0.01063515	0.00075152

PPIA=public private interface agency.

Outcome Definitions

For each case, and following quality of care outcomes used in previously published studies, we benchmarked our main outcome, expected correct case management, on Indian Standards for TB Care.[32] We focused primarily on referral and diagnostic behaviours regardless of superfluous prescription of any medication. Based on national guidelines, the recommendation is to order a microbiological test or refer the patient for further management, rather than dispense any further medications or Group 1 anti-tuberculosis treatment (ATT), specifically (supplementary S2-Figures 5-6). Since we measured ordering a test or referring the SP, rather than ordering a test only, this definition of correct case management utilized in previous SP studies assessing quality of TB care, is broader.[30] For each presentation, we outlined correct case management using a "lenient" approach based on Indian Standards for TB Care,[32] meaning we focussed on referral and diagnostic behaviour only.

We operationalized management of case 2 using three binary outcome definitions. First, we defined an ideal standard of care as a (1) prescription for any microbiological test (sputum smear, Xpert MTB/RIF or another molecular TB test (e.g. TrueNAT) or culture) and no concurrent prescription or dispensation of a steroid or any antibiotic/antimicrobial drug (more specifically of quinolone or anti-TB medication). The

following two definitions of empiric management were of progressively conservative nature; (2) a prescription for ATT was dispensed/prescribed, and (3) a prescription for anti-TB medication and an additional simultaneous prescription indicated for confirmatory microbiological testing, either via sputum smear microscopy, Xpert MTB/RIF, or culture. These three definitions are summarized in Table 2-3.

Table 2-3*: Definitions of empiric treatment practices for tb and proportions by case type.*

	Referral for sputum smear	*Referral Xpert MTB/RIF or another molecular TB test*	*Referral for Culture/DST*	*Corticosteroid*	*Quinolone*	*Any Antibiotic*	*Anti-TB Medication (isoniazid, rifampicin, ethambutol, pyrazinamide)*
Definition 1: Ideal management	Yes	Yes	Yes	No	No	No	No
Definition 2: Empiric treatment with ATT	No	No	No	-	-	-	Yes
Definition 3: Empiric treatment with ATT with concurrent microbiological testing	Yes	Yes	Yes	-	-	-	Yes

DST=drug-susceptibility testing

Identification of Medicines

Medicines dispensed or prescribed to the SPs were coded into pre-determined categories of interest (e.g., corticosteroids, antibiotics). To assess drug use, all labelled medicines prescribed by the pharmacies were digitized and stored and then coded by three co-authors with expertise in TB (AS & AS) and infectious diseases (GS). The authors were blinded from any provider identifying details, and they identified and categorized medicines as steroids, anti-TB drugs, quinolones, or other broad-spectrum antibiotics under maker-checker procedure, whereby dual-approval was needed by two separate people for each coding. Quinolone antibiotics were defined as Anatomical Therapeutic Chemical (ATC) codes beginning with

J01M, and corticosteroids, both inhaled and systematic, defined as ATC codes beginning with H02, R01, or R03. Anti-tuberculosis treatment (ATT) was defined as the dispensation of any of the four group 1, i.e. first-line oral anti-TB drugs: Isoniazid, Rifampicin, Ethambutol or Pyrazinamide. The category "other antibiotic" included all antibiotics other group 1 ATTs and quinolones. Discrepancies in categorization between coders were resolved by consensus. Finally, while loose or unlabeled pills were dispensed in some interactions, no further attempts were made to identify them as it was not feasible to perform chemical drug assays at scale.

Statistical Analysis

We reported proportions for outcomes of interest, namely our 3 articulations of empiric treatment practices amongst other clinical management factors, and population mean estimates computed using inverse probability weighting[33] with corresponding 95% CIs. The weights were calculated such that each of the 96 city-case-round combination contributed equally to overall estimates and corresponded to the sampling framework of private-sector providers listed from the mapping exercise in both cities. We also presented findings over time (from baseline to endline of survey).

In addition to using these weights to estimate population likelihoods, we used them to calculate weighted prevalence ratios (PRs) in a multivariate model by using log-binomial regression comparing variation in factors associated with treatment based on abnormal CXR, by city, and clustering at the provider level. These methods are preferred to logistic regression estimation to directly estimate PRs from cross-sectional studies since odds ratios overestimate the PR, particularly when the outcome is not rare.[34,35] The associations between predictors of interest and practices will be presented as a PR as a more interpretable alternative to the odds ratio. We take the perspective that a quality outcome in a given interaction reflects a combination of inputs that vary at provider, patient and facility levels. We presented both univariate and multivariate models for factors of interest, with the multiple regression framework specified as below (Equation 1):

equation 1:

$$logit(Management_{ijklt}) = \alpha + \beta_0 + \beta_1 Provider_{jt} + \beta_3 Patient_{kt} + \beta_4 Site_{lt} + \varepsilon_{ijklt}$$

where $Management_{ijklt}$ is one of the three empiric treatments by provider i to patient j at health facility k at time t; $Provider_{jt}$ is a vector of provider characteristics at time t; $Patient_{kt}$ is a vector of patient

characteristics at time t; $Site_{lt}$ is a vector of facility characteristics at time t; and ϵ is an error term. Relevant provider characteristics included patient yield; patient characteristics included disease demographic factors and clinical presentation; and facility characteristics included city. The final multivariate model only included variables that were shown to potentially impact care management outcomes in our previous work[11,15] or would reasonably have contributed to care management practices.

In an analysis comparing Case 1 to Case 2 directly amongst providers who had seen both cases, odds ratios were calculated. This choice was made given that the cases were matched.

All estimates clustered standard errors at the provider level, and were inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures. Reported estimates represent the expected likelihood of the outcome occurring if a provider were chosen at random from the population of providers within each respective city and within each round's time period. In order to look at time trends between rounds, we conducted weighted pair-wise t-tests and linear regressions to test for time trends.

Variables of Interest

The regressions comprised the following binary or dummy predictors: clinal examination performed (yes vs. no); invasive treatment offered (yes vs. no); medical history taken (yes vs. no); study site (Patna (ref) vs. Mumbai); patients waiting in office (yes vs. no); round of data collection (round 1 (ref) vs. round 2 vs. round 3); treatment counselling performed (yes vs. no). We presented these as a univariate regression individually, and a full multivariate model with all co-variates.

All data analyses were performed with Stata 15 (Stata, College Station, TX).

Patient and Public Involvement

While our study aligns with patient-centred care, no real tuberculosis patients were involved in study recruitment or conduct.

Ethics

Ethical approvals for this study were granted by the McGill University Health Centre in Montreal, Canada (REB No. 14-137-BMB) and the Subcommittee for the Ethical Approval of Projects at the Institute for Socioeconomic Research on Development and Democracy in Delhi, India.[8] Ethics committees approved a waiver from obtaining informed consent from providers in Patna and Mumbai under the Government of Canada Panel on Research Ethics, as well as a study by Rhodes and colleagues (2012) on ethical aspects of standardized patient studies commissioned by the US Department of Health and Human Services,[36] and study specific rationale of waiver is detailed elsewhere.[15] All individuals who participated as standardised patients were hired as staff and trained to protect themselves from any harmful medical interventions, such as avoiding injections, invasive tests, or consuming any drugs.

2.6 RESULTS

Amongst case 2 interactions, SPs who presented an abnormal CXR, 210 of 795 (25%; 95% CI: 21-28%) of interactions resulted in ideal management, where the provider prescribed a microbiological test (sputum smear, Xpert MTB/RIF or culture) and did not offer a concurrent prescription for a steroid or antibiotic (more specifically of quinolone or anti-TB medication). Of all case 2 presentations, 182 of 795 (23%; 95% CI: 19-26%) followed in a prescription or dispensation of ATT. A total of 140 of 795 (13%; 95% CI: 10-16%) of interactions resulted in a prescriptions/dispensation of ATT plus a prescription for confirmatory microbiological testing, either via sputum smear microscopy, Xpert MTB/RIF, or culture. These three outcomes are summarized in Table 2-4.

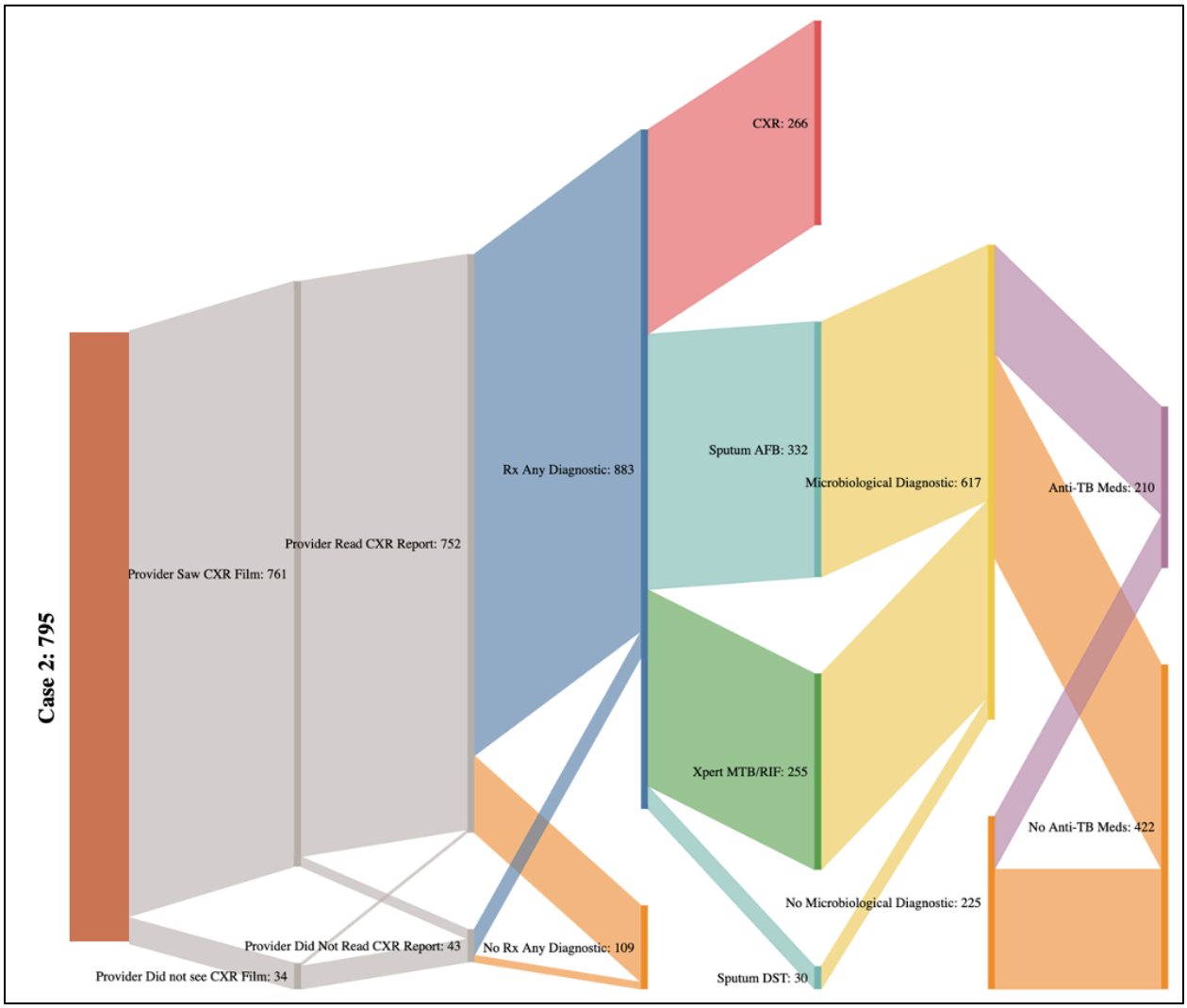
Table 2-4: *Proportion of interactions resulting in outcomes of interest, weighted.*

	n	Proportion	95% CI
Definition 1: ***Ideal management***	210	25%	21-28%
Definition 2: ***Empiric management with ATT***	182	23%	19–26%
Definition 3: ***Empiric management with ATT with concurrent microbiological testing***	140	13%	10-16%

ATT= anti-TB treatment

Diagnostic Flow

When we look at a diagnostic care cascade for this same patient presentation (Figure 2-1), we see that a vast majority [761 of 795 (96%; 95% CI: 95-98%)] of providers looked at the CXR film, while 752 of 795 (95%; 95% CI: 93-97%) read the CXR report itself. A total of 686 of 795 (83%; 95% CI: 80-86%) of interactions resulted in any diagnostic test being ordered, and 266 of 794 (32%; 95% CI: 28-36%) interactions resulted in a new CXR being ordered, even though the patient would have presented with an abnormal film and a report. Moreover, 332 of 792 (43%; 95% CI: 39-48%) sputum smears, 255 of 794 (22%; 95% CI: 19-25%) Xpert MTB/RIFs and 30 of 791 (4%; 95% CI: 2-6%) cultures were prescribed. Of the 474 of 795(53%; 95% CI: 49-57%) microbiological tests ordered, 210 of 632 (30%; 95% CI: 25-34%) interactions also prescribed or dispensed ATT medications. Only 70 of 790 (12%; 95% CI: 9-15%) interactions resulted in a referral.



CXR= chest radiography; DST= drug-susceptibility testing; AFB= acid-fast bacillus.

Figure 1: Diagnostic care cascade of patients presenting with an abnormal CXR and the subsequent diagnostic algorithm by which they travel through, with the dispensation (or not) of ATT regimens they are dispensed as the endpoint. these represent raw counts.

Comparison of Case 2 vs. Case 1

Providers' behaviours differed upon the addition of a CXR on patient presentation; when comparing providers who saw both case 1 and case 2 (n=1178 & n=749, respectively (Figure 2-2)), the case 2 SPs carrying the CXR report resulted in increased odds of ideal management (OR 7.6; 955 CI: 5.15-11.2; p < 0.001) as well as higher odds of prescribing sputum smear (OR 4.93; 95% CI 3.80–6.39; p < 0.0001) and Xpert MTB/RIF (OR 7.43; 95% CI 4.97-11.1; p < 0.0001) and a lower likelihood of CXR (OR 0.28; 95% CI 0.22–0.35; p < 0.0001) ordering, as compared to case 1 presentation. It should be noted that medicines were very frequently prescribed or dispensed in both cities, and we did not penalize the use of additional or unnecessary medications against the provision of correct management. Notwithstanding, providers were more likely to prescribe or dispense a quinolone (OR 1.3; 95% CI 0.96-1.75; p =0.0863) to case 2 presentations, but less likely to order a steroid (OR 0.52; 95% CI 0.31-0.85; p = 0.0091) or other antibiotic (not quinolone or ATT) (OR 0.3; 95% CI 0.24-0.37; p < 0.0001). No statistically significant association was seen for empiric management (across both definitions) since only 1 of 1,818 case 1 interactions resulted in the prescription/dispensation of an ATT.

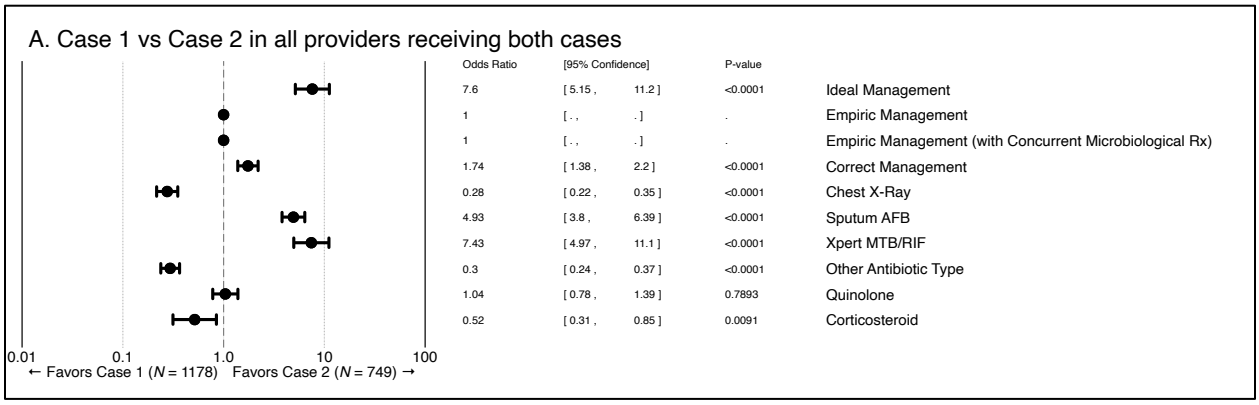
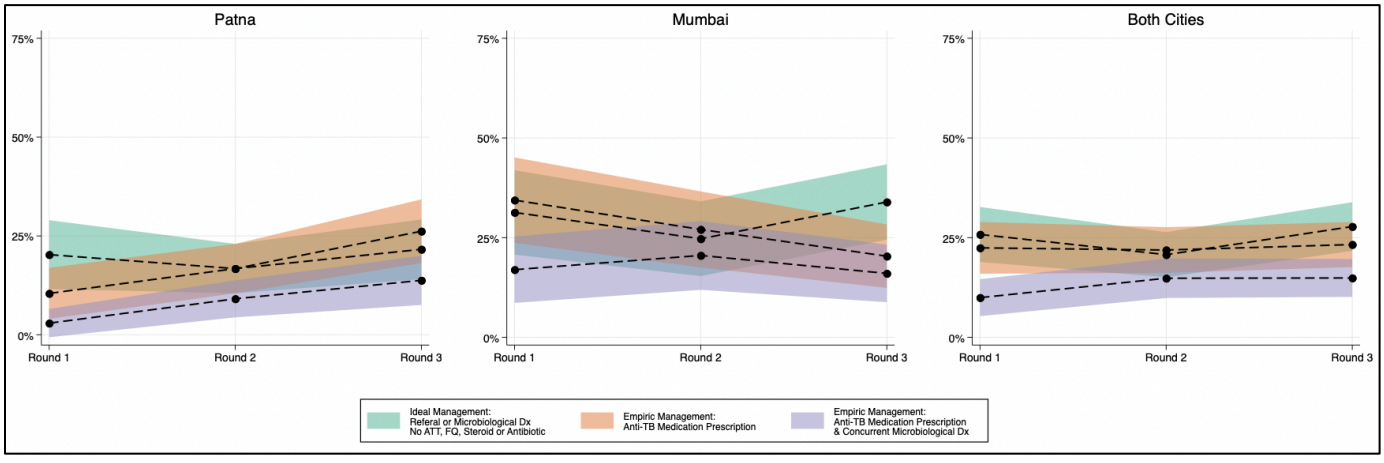


Figure 2-2: *Quality of care differences between SP case scenarios presenting to the same provider calculated in a linear regression model, with standard errors clustered at the provider level. Case 1= 1,178 interactions; case 2=749 interactions.*

Management Outcomes Over Time

If we consider these outcomes over time (Figure 2-3), we see that in Mumbai, the prevalence of ideal management changed from 32 of 122 (31%; 95% CI: 21-42%) of interactions at baseline to 30 of 136 (25%; 95% CI: 15-34%) in the subsequent round of data collection, to 44 of 147 (34%; 95% CI: 24-43%) in the final round of data collection. Empiric treatment of presumptive TB with ATT decreased from 54 of 122 (34%; 95% CI: 24-45%) interactions at baseline, to 46 of 136 (27%; 95% CI: 17-37%) in round 2 and 34 of 147 (20%; 95% CI: 12-28%) at endline data collection, with this decreasing linear trend being statistically significant (β=-0.07, 95%CI: -0.134- (-0.0064)). There was an increase over time in concurrent prescription of a microbiological diagnostic in addition to ATT, 32 of 122 (17%; 95% CI: 9-25%) of interactions at baseline, then subsequently 38 of 136 (21%; 95% CI: 12-29%), and finally, 29 of 147 (16%; 95% CI: 9-23%).

In Patna, ideal management was seen in 18 of 98 (20%; 95% CI: 11-29%) of interactions at baseline, increased to 28 of 157 (17%; 95% CI: 10-23%) and 30 of 135 (22%; 95% CI: 14-29%) at the second and final round of data collection, respectively. Empiric management of case 2 was observed in 11 of 98 (10%; 95% CI: 4-17%) interactions to begin and increased to 28 of 157 (17%; 95% CI: 10-23%) and 37 of 135 (26%; 95% CI: 18-34%); here an increasing, linear trend over time was observed (β=0.078, 95%CI: 0.028-0.129). The prescription/dispensation of ATT with a script for a simultaneous diagnostic test was observed in 3 of 98 (3%; 95% CI: 1-7%) interactions and then 17 of 157 (9%; 95% CI: 4-14%) and 21 of 135 (14%; 95% CI: 7-20%) in later rounds; this upward trend was statistically significant over time (β=0.054, 95%CI: 0.018-0.090).



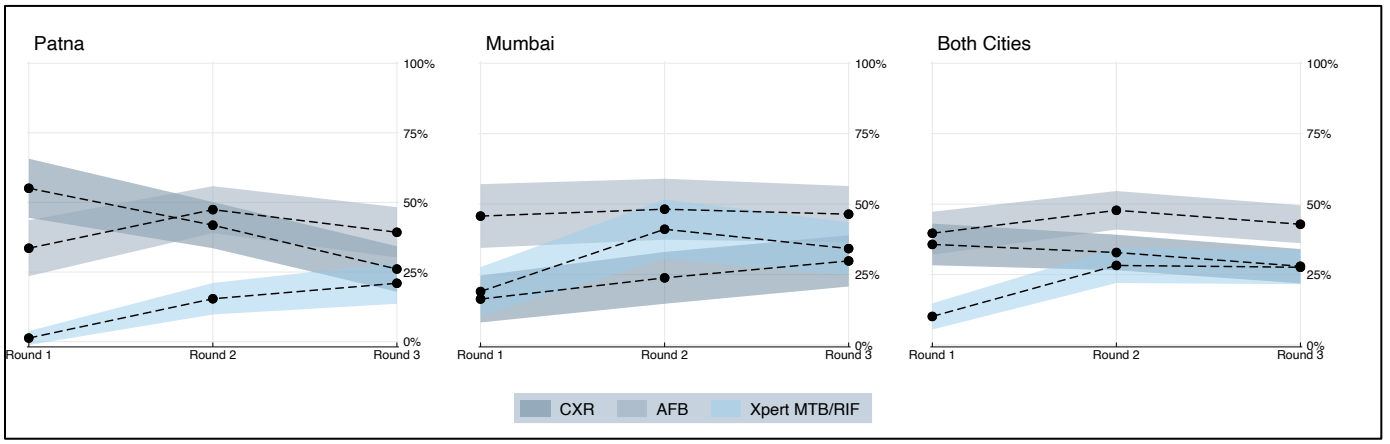
Dx= diagnosis; ATT=anti-TB treatment; FQ= fluoroquinolone.

Figure 2-3: *Weighted changes in empiric treatment practices by city and round of data collection. Round 1: 2014-2015, round 2: 2016-2018, round 3: 2019-2020.*

Diagnostic Practices Over Time

Looking at trends over time in diagnostic practices in both cities (Figure 2-4), in Mumbai there was an increase in recommendation for repeat CXR in case 2, first observed in 24 of 122 (16%; 95% CI: 8-25%) interactions at baseline, then 35 of 136 (24%; 95% CI: 15-33%) and finally, 51 of 147 (30%; 95% CI: 20-39%). Despite the SP presenting with an existing CXR, this increase in CXR prescriptions by providers is statistically significant over time (β=0.066, 95%CI: 0.023-0.129). Smear prescriptions stayed relatively similar over time: 49 of 122 (46%; 95% CI: 34-57%) interactions in round 1, (48%; 95% CI: 37-59%) of interactions in round 2, and (46%; 95% CI: 36–56%) of interactions in round 3 An Xpert MTB/RIF diagnostic saw an initial increase from 41 of 122 (19%; 95% CI: 10-28%) of interactions at baseline to 77 of 136 (41%; 95% CI: 30-52%) in the second round of the survey; it then decreased to 70 of 147 (35%; 95% CI: 25-44%) of interactions in the final round.

Patna saw decreased repeat CXR recommendations over time, from 53 of 98 (55%; 95% CI: 44-66%) to 70 of 157 (42%; 95% CI: 33-50%) and 33 of 134 (26%; 95% CI: 18-34%) interactions at study end; these changes were significant over time (β=0.145, 95%CI: -0.213 –(-0.077)). Sputum smear microscopy prescriptions were seen in 34 of 98 (34%; 95% CI: 23-44%) interactions initially, then increased to 77 of 157 (47%; 95% CI: 39-56%), before decreasing to 54 of 134 (39%; 95% CI: 30-48%). Xpert MTB/RIF was only ordered for 1 of 98 (1%; 95% CI: 1-4%) interactions at baseline and increased over time, from 34 of 157 (15%; 95% CI: 10-21%) in round 2 to 32 of 134 (21%; 95% CI: 14-28%) in the final round; this increase of uptake of Xpert MTB/RIF was significant over time (β=0.0985, 95%CI: 0.590-0.138).



CXR=chest radiograph; AFB=acid-fast bacillus,

Figure 2-4: *Weighted changes in diagnostic patterns by city and round of data collection. Round 1: 2014-2015, round 2: 2016-2018, round 3: 2019-2020.*

Factors Associated with Management Practices of Case 2

Some factors were associated with increased prevalence of ideal management of a case of presumptive TB with an abnormal CXR in the multivariate analysis (Figure 2-5); interactions in Mumbai were more likely to result in ideal management compared to those that took place in Patna (weighted aPR 1.54, 95% CI: 1.11-2.13). The provider performing a clinical exam and taking the SP's medical history were behaviours less likely to be associated with non-ideal management (weighted aPR 0.52, 95% CI: 0.38-0.70), and (weighted aPR 0.48, 95% CI: 0.35-0.67), respectively. In Figure 2-6, we see that treatment counseling was associated with empiric management of the case with ATT (weighted aPR 5.12, 95% CI: 3.70-7.07). When we also considered concurrent prescription of a microbiological diagnostic with dispensation of ATT (Figure 2-7), we see that clinical examination (weighted aPR 3.89, 95% CI: 1.26-11.97) and treatment counseling (weighted aPR 5.18, 95% CI: 3.30-8.15) were both associated with the outcome in the multivariate model.

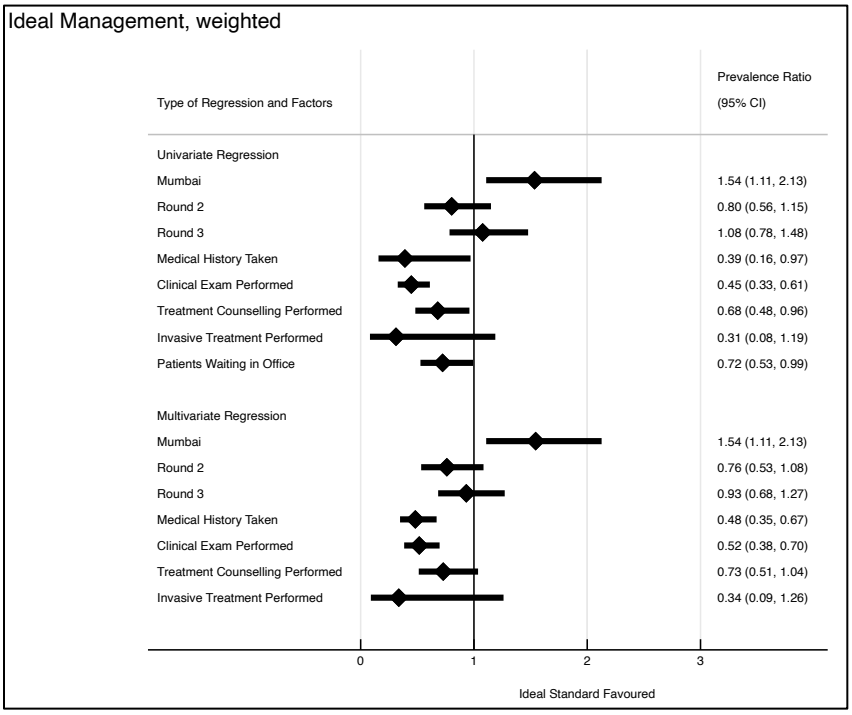


Figure 2-5: *Factors associated with ideal management amongst formal providers. Prevalence ratios (PRs) were calculated by using log-binomial regression; standard errors were clustered at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures; the adjusted prevalence ratios (aPR) in the multivariate model adjusted for all variables included in the univariate regression.*

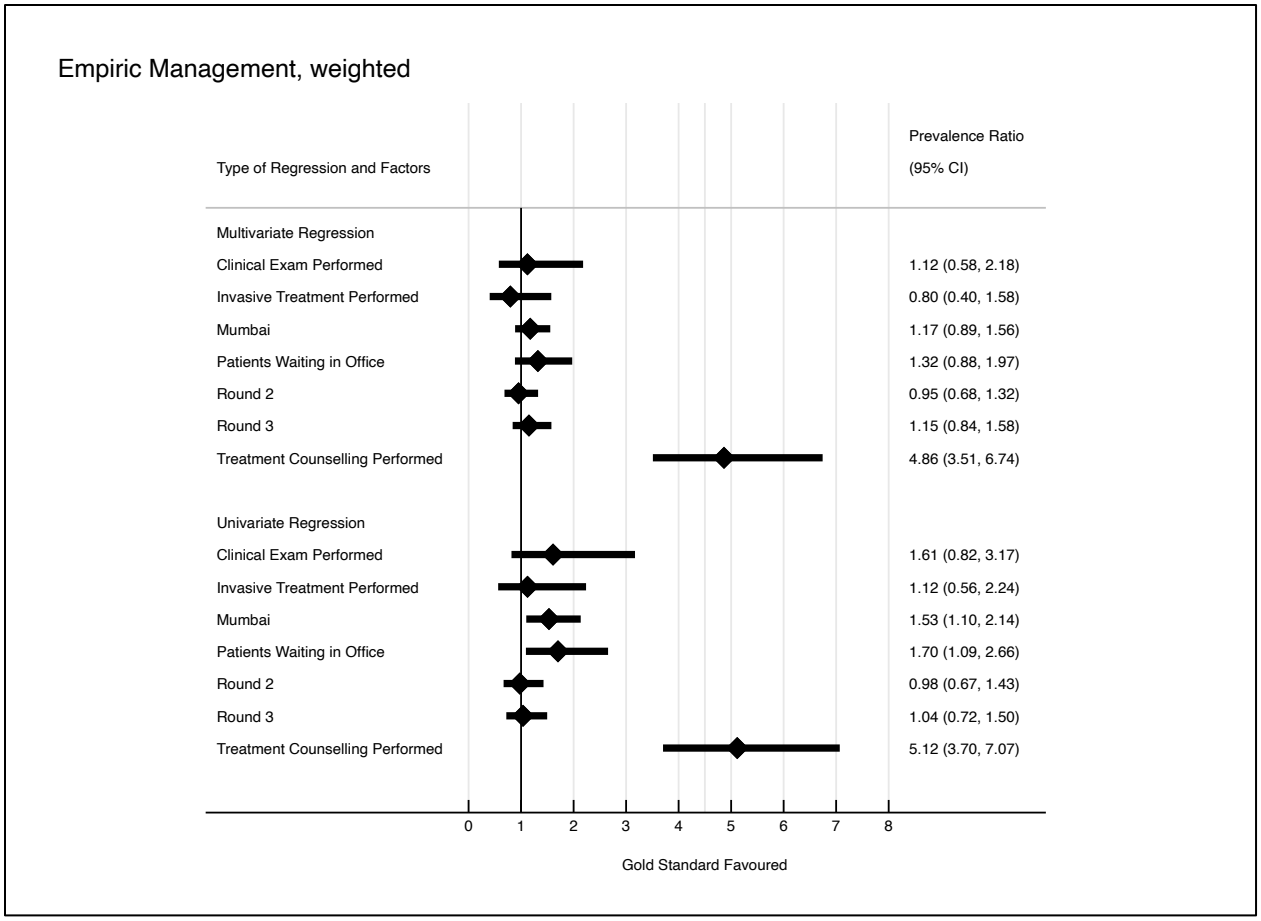


Figure 2-6: *Factors associated with empiric management with ATT amongst formal providers. prevalence ratios (PRs) were calculated via prevalence ratios (PRs) by using log-binomial regression; standard errors were clustered at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures; the adjusted prevalence ratios (aPR) in the multivariate model adjusted for all variables included in the univariate regression.*

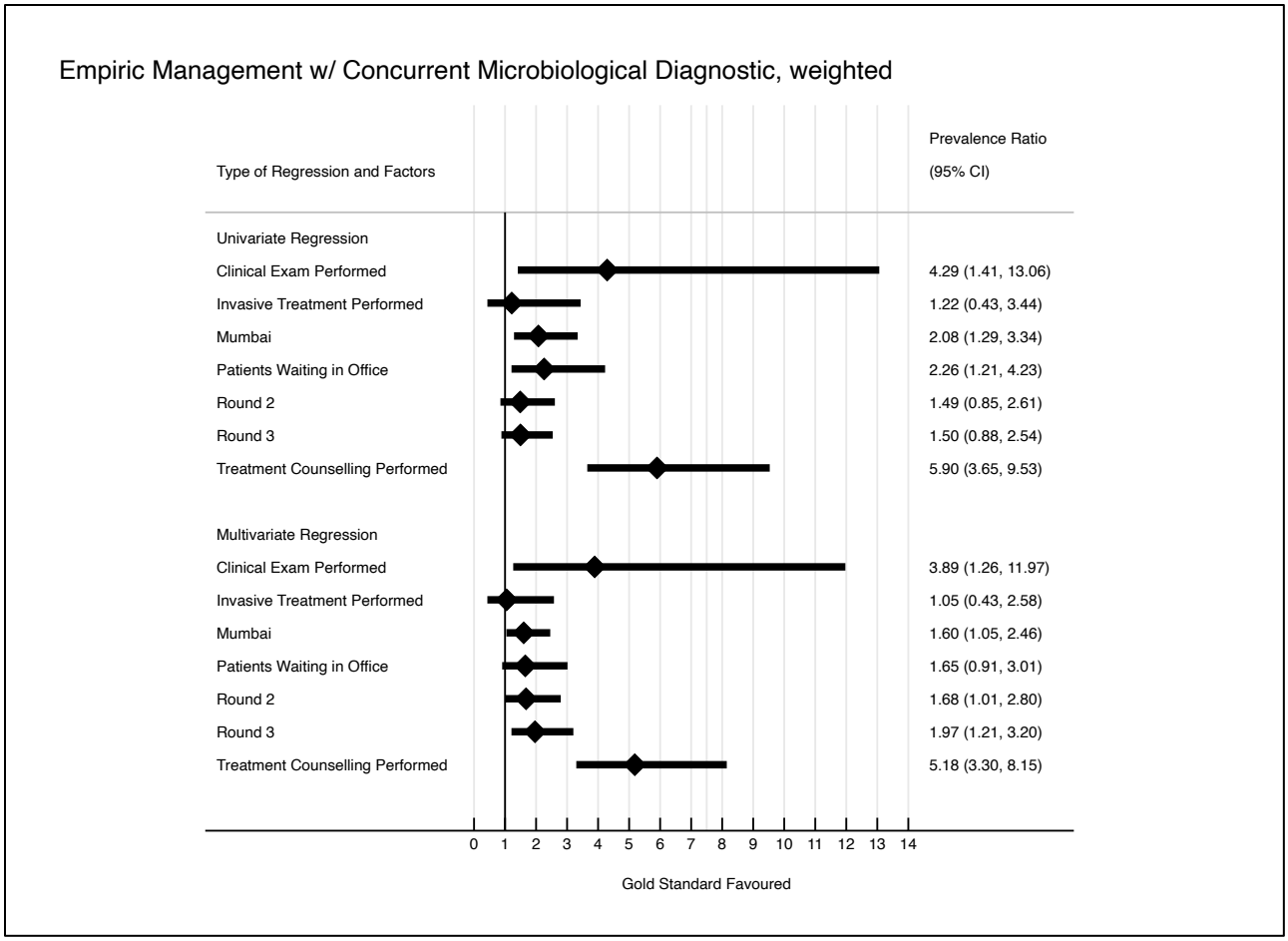


Figure 2-7: *Factors associated with empiric management with concurrent microbiological diagnostic amongst formal providers. prevalence ratios (PRs) were calculated via prevalence ratios (PRs) by using log-binomial regression; standard errors were clustered at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures; the adjusted prevalence ratios (aPR) in the multivariate model adjusted for all variables included in the univariate regression.*

2.7 DISCUSSION

This study adds to a growing body of evidence surrounding behaviours around empiric management of TB. It makes an effort to explore these patterns of decision-making in the context of an abnormal CXR presentation. Taking advantage of the SP methodology, the study explains how initial management of people presenting to the Indian formal private healthcare sector with TB symptoms and an abnormal CXR could be associated with the practice of dispensing ATT without microbiological confirmation. Such behaviours could potentially compromise the timely diagnosis of TB, miss drug-resistance, and result in

inappropriate drug regimens. We discuss the implications of the study findings on quality of TB care more broadly while suggesting opportunities for laboratory and health systems strengthening.[37]

Despite case 2 patients presenting with evidence of an ambiguous respiratory infection, without a definite indication for TB specifically (no cavitation for instance) and with proof of an ineffective course of antibiotics, antibiotics and anti-TB medications were prescribed to one in five standardized patients in both Patna and Mumbai. While we know that globally approximately 40% of reported TB cases are treated empirically[1] and that this number is likely even larger in the Indian private sector, with upwards of 80% empirically treated in 2018 in the private health sector,[6] it remains challenging to define how much empiric overtreatment is too much and to target an appropriate amount of empiric treatment against an ideal standard. This is due to the fact that it remains unclear at what point the risks and costs of potential overtreatment outweigh the benefits of empiric treatment for some patients.[38] Given that we know that culture, the gold standard in molecular diagnostic, has imperfect sensitivity as a reference standard,[39] and that there is a general limitation in the ability of current bacteriological tools to efficiently diagnose cases with subclinical and incipient forms of TB,[40] we are unable to know exactly what the prevalence of culture-negative pulmonary TB is within any given population and thus anticipate how much empiric treatment is truly justifiable. It is likely that in patients without HIV coinfection, culture-negative TB is likely an early disease state on the continuum between *M. tuberculosis* infection and active disease, which could advance to culture-positive disease if left untreated with ATT. Patients with negative sputum cultures may have culture-negative TB disease that would benefit from empiric treatment, and the judgment of experienced clinicians is a valuable tool for recognizing high-risk, sputum negative TB presentations.[41-44] In one particular study where more than 12,000 individuals were tested for TB with a highly sensitive assay in a community setting, in parallel with characterization of health facility-diagnosed cases and community-representative controls, universal testing identified both highly symptomatic individuals with high bacillary burdens (37%) and people with trace-positive sputum (63%) who were mainly culture negative but had features that distinguished them from the TB-negative controls used in the study's design.[45]

In the absence of microbiological tools to parse out various disease states, a better understanding of the clinical presentation of culture-negative pulmonary TB could increase clinicians' awareness and dictate appropriateness of initiating empiric treatment, facilitating the recognition of PTB at an early state, and leading to early treatment initiation, which in turn could reduce the development of transmissible disease.[46] This is particularly important because treatment of culture-negative PTB can be shorter than

that of culture-positive PTB (4 vs. 6 months, respectively).[47,48] There is also the risk of deferring treatment in patients with risk factors for mortality or poor follow-up, which might prompt some physicians into action. However, it seems that most clinically diagnosed, culture-negative patients were found to be less sick than the typical TB case based on symptoms and inflammatory markers; this implies that treatment could have been deferred in these patients without grave consequence.[35] In addition, patients with advanced HIV, a comorbidity which might prompt many clinicians to proactively treat empirically, shows a reduced benefit in reducing mortality for empiric TB treatment.[38,49]

Our findings are very much in line with various ethnographic and qualitative research studies suggesting that multiple pressures drive the empirical practices we observed. These include the use of medications as diagnostic tools, a desire to provide rapid symptom relief to patients, insecurity about the accuracy of available TB tests and apprehension of loss of clients in private practice.[5,50,51] Prior work has shown that physicians in this context oftentimes rely on low cost pharmaceuticals as diagnostic tools, privileging symptom relief above diagnostic certainty in their delivery of care.[5,6,51] This is also a concern with widespread empirical use of antimicrobials in India, and has been demonstrated in SP studies as well.[52] In our study, interactions where SPs were asked to return for more medicines were more likely to receive treatment prior to microbiological diagnosis, suggesting empiric antibiotic therapy may have been used as a diagnostic tool in this context. Private providers in India tend to be cautious in ordering tests among patients with limited means, since these often require out-of-pocket expenditures. Further, providers aimed to provide symptom relief to their patients, yet wanted to make sure they would be able to gauge their progress in a subsequent visit. The ordering of non-specific treatments prior to microbiological diagnosis, coupled with will multiple patient visits and providers seen, results in diagnostic delays.[6] This behaviour was mitigated when providers put in more effort, and interactions were subject to a more thorough clinical examination, whether via physical exam or more detailed history taking. This thus demonstrates that some physicians were likely assessing the likelihood of an infection with the evidence they gathered, prior to dispensing medications. This highlights the importance of comprehensive history-taking and comprehensive physical assessments in mitigating the appropriate use of therapeutics for respiratory infections.

The behaviours observed may also suggest that providers might be wary of reliance on microbiological diagnosis as a tool in isolation. Prior evidence suggests that physicians also gravitate towards a multi-pronged approach to diagnostics, using clinical in conjunction with various modern diagnostics, to provide

a diagnosis.[5,50,51,53] Descriptive analysis of these combinations suggested that providers may have used microbiological tests as an "add-on" test rather than as "replacement". Xpert has been widely regarded as a game changer in the global fight against TB, but its impact on case finding and management in high burden countries is likely to be constrained by low adoption by private providers, or by empirical treatment.[3] Although broader uptake of Xpert can have implications on detection of rifampicin resistance, utilization of the tool as frontline diagnostic poses challenges in the private sector. Existing evidence regarding its impact is primarily from the public sector, and studies examining the integration of Xpert into clinical decision-making are limited.[20] It was found that Xpert, compared to smear microscopy, increased the number and proportion of microbiologically confirmed TB case notifications and reduced the delay in treatment initiation. However, it did not significantly increase overall case notifications and did not have a significant impact on patient-relevant health outcomes such as mortality, tuberculosis-related morbidity, and successful treatment completion. These mixed findings are believed to be driven by high levels of empirical treatment, which may be partially replaced by Xpert.[20,54,55] Inability to do microscopy or Xpert (as in sputum-scarce patients), substandard clinical training, and high likelihood of one-off encounters with patients might also drive the initiation of empirical treatment.[3,56,57] This distrust in the accuracy of microbiological test may be tapered as the sensitivity of available diagnostic tests increases and the probability of false negative results become less likely. As health systems transition to assays with higher sensitivity, such as Xpert Ultra MTB/RIF, clinicians may benefit from guidance on how to adapt their diagnostic intuition accordingly and recalibrate their own threshold for empiric treatment.[38]

Despite presenting with an abnormal CXR, case 2 SPs were often asked to get yet another CXR and a sputum AFB smear, respectively. This may point to distrust in the quality of the laboratory services present in either city, especially from labs that are unfamiliar to the provider. For smear diagnostics, there may be human resource barriers to guideline adherence, namely that laboratory diagnostics from an unknown providence do not engender confidence because of lack of skill in conducting microscopy, or general laboratory skills; the quality of the result they are presented with may be called into question. Another possible explanation is that private providers often have close relationships with laboratories and pharmacies, and these are based on financial incentives and relationships built over time.[51] Thus, providers may ask for tests to be done at their preferred laboratories, even if patients have reports from other labs.

While usage of Xpert MTB/RIF does not require skilled technicians in the same way, there could be fears that the accessibility of the test or delays in turnaround times would induce loss of the patient prior to diagnosis. Pre-treatment loss to follow-up in the Xpert MTB/RIF context can be due to high staff turnover, inconsistent and delayed specimen transport to Xpert MTB/RIF testing sites, time delays in obtaining results, high costs of the test, and the inability to track and follow-up with patients with positive TB test results.[51,58,59] Since these tests were almost always conducted offsite, even if test turn-around times were just a few hours, patients were often asked to return for test results and further management in the following days, a practice that can lead to loss to follow-up.[53,60] High cost of Xpert MTB/RIF in the private health sector might put off patients who cannot afford them, and they might never return to the providers who ordered the test.[61] There is also the issue that there are practical obstacles which limit full reliance on Xpert technology despite the low skill level required,[62] namely that maintenance issues may force health facilities to send specimens to distant labs and cause several-day delays; such delays would increase a physicians' propensity to choose empiric treatment for high-risk patients.[38] In our study, it was observed that overall there was an increased utilization of Xpert MTB/RIF over time, though it remains unclear if there is a subsequent effect on empiric management. While it has been shown that Xpert MTB/RIF leads to more bacteriologic confirmation among patients treated for TB,[54] the effect of Xpert MTB/RIF on the accuracy of empirical diagnosis remains more elusive.[3] As clinicians grow more comfortable with using Xpert MTB/RIF to rule out TB, there is some evidence that empiric treatment declines over time after Xpert MTB/RIF introduction.[63]

Thus, decisions around empirical treatment of TB have to be put within a larger health ecosystem, where providers want to be able to provide care to their patients with the tools most readily accessible to them, rather than one in which the providers are blamed for mismanagement. Making WHO-endorsed tests more affordable in the private market, linking privately managed patients with free diagnostic testing in the public sector, laboratory network strengthening, and building confidence between providers and laboratories is integral to the practice of favouring microbiological diagnosis over empirical treatment alone. In Mumbai and Patna, PPIA programs have attempted to (i) make available high quality diagnostic tests to private providers through incentives, subsidies and eventually free of cost, (ii) provide free TB drugs and adherence support mechanisms to TB patients to maximise treatment completion and (iii) facilitate reporting of TB patients to India's National Tuberculosis Elimination Programme. Following the success of these initiatives, private sector engagement has subsequently seen massive expansion across the country, accompanied by an increase in the Government of India's pledged budget for TB, as well as

support from the World Bank and the Global Fund.[64] Due in part to these efforts, the private sector contribution to TB notifications grew from 7% in 2014 to 28% in 2019.[18] Such progress represents crucial steps in achieving comprehensive coverage of private providers in India.[65]

Providers were more cautious to treat with ATT prior to microbiological diagnosis in Mumbai compared to Patna. The repercussions of empiric treatment without concurrent microbiological testing can be grave, specifically for its potential implications of inappropriate regimen dispensation on antimicrobial resistance. In Mumbai for instance, the epidemiological data is very clear that there is a large prevalence of drug resistance within the city; [66,67]Mumbai is known to have a high proportion of MDR-TB with quinolone resistance and advanced TB resistance profiles.[68,69] Mumbai contributed 22% of TB cases of the total of 10, 621 patients with MDR-TB were diagnosed in Maharashtra in 2019.[69-71] Prescription of antibiotics prior to initiating a TB test, and especially prescription of quinolones, carries the risk of delaying TB diagnoses by masking symptoms and thus delaying test taking and/or diagnostic confirmation.[72,73] Antibiotics such as quinolones and steroids are known to affect TB disease and its symptoms, often masking symptoms and delaying diagnosis.[74] [75,76] Inappropriate use of quinolones is further associated with quinolone-resistance[77,78] and are among the most widely used antibiotics in India.[79] Our findings have potential implications for quality of care in TB and antimicrobial stewardship generally. It is essential to optimise antibiotic use in order to mitigate antimicrobial resistance and infectious disease transmission, and protect patient safety.[80,81]

Notwithstanding its contributions, this study had several limitations to acknowledge. First, while the study was a population-weighted assessment of average behaviours for these provider types and cities, it was not necessarily representative of the provider mix that patients may face if they were to choose to visit different types of providers and findings may not replicate in other settings. Patient choices in provider visitation might be influenced by gender, socio-economic status, etc. and these patient-level arbiters of care decisions could not be captured in this study design. Second, we did not directly inquire on rationale and thus may not be able distinguish appropriate medicine use from misuse in a holistic sense. As alluded to early, clinicians' judgement would play a role in either city context with care decisions reflecting a balance between epidemiological likelihood of TB, and valid fears of patient loss to follow-up, transmission potential, etc. Third, observed practice only reflected what healthcare providers did when they came across a completely new patient seeking medical care in during an initial visit. Although it was feasible in a pilot study to send back SPs for repeated interactions with the same provider,[14] SPs have not

yet been routinely used to construct standardized measures that include follow-up visits to providers, therefore longitudinal assessment and understanding of provider behaviours of any given patient presentation is impossible. Fourth, this study only covered private practitioners in urban areas in India and cannot be extended to rural areas; these results and our corresponding interpretations may not be generalizable to contexts outside of other high-TB burden, urban cities in India. In addition, SPs cannot measure the quality of care received over the entire treatment phase of TB care, because they are not in fact ill; therefore if any clinical indicators are assessed during any visit, physicians might act contrary to indication – even when a medical diagnostic result is provided (e.g. if the provider sees a healthy patient who lives in a polluted city with no cough, or fever or visible weight loss, they may ignore abnormal chest X-ray results, etc.). Moreover, since a proportion of SP-provider interactions resulted in direct dispensing of unlabelled medicines, certain drugs could not be identified, thus potentially leading to underestimation of the extent of antibiotic and other medicine dispensation. Furthermore, the intent of the overall study was not to inquire about this very particular question; as such our design would surely have been strengthened if we had been able to have an exact counterfactual presentation of the case 2. Specifically, we would have been able to expect direct comparability if we provided some SPs with a normal CXR. Finally, with the advent of the global COVID-19 pandemic, the landscape of respiratory diseases worldwide has most likely changed since our study was conducted.[82-84]

2.8 CONCLUSION

This research contributes novel insights to the prevalence and behaviours associated with empiric treatment based on CXR abnormality. It stands as a reminder of the balance physicians in the Indian context need to find between not losing their patients altogether to follow-up and being able to trust their laboratories while providing the proper regimen and care to their patients. A more detailed inquiry into their practices and decision-making rationale, coupled with engaging them in antibiotic stewardship and lab strengthening measures, are likely to have impacts in timely and appropriate management of TB, and other respiratory infections.

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S2-1

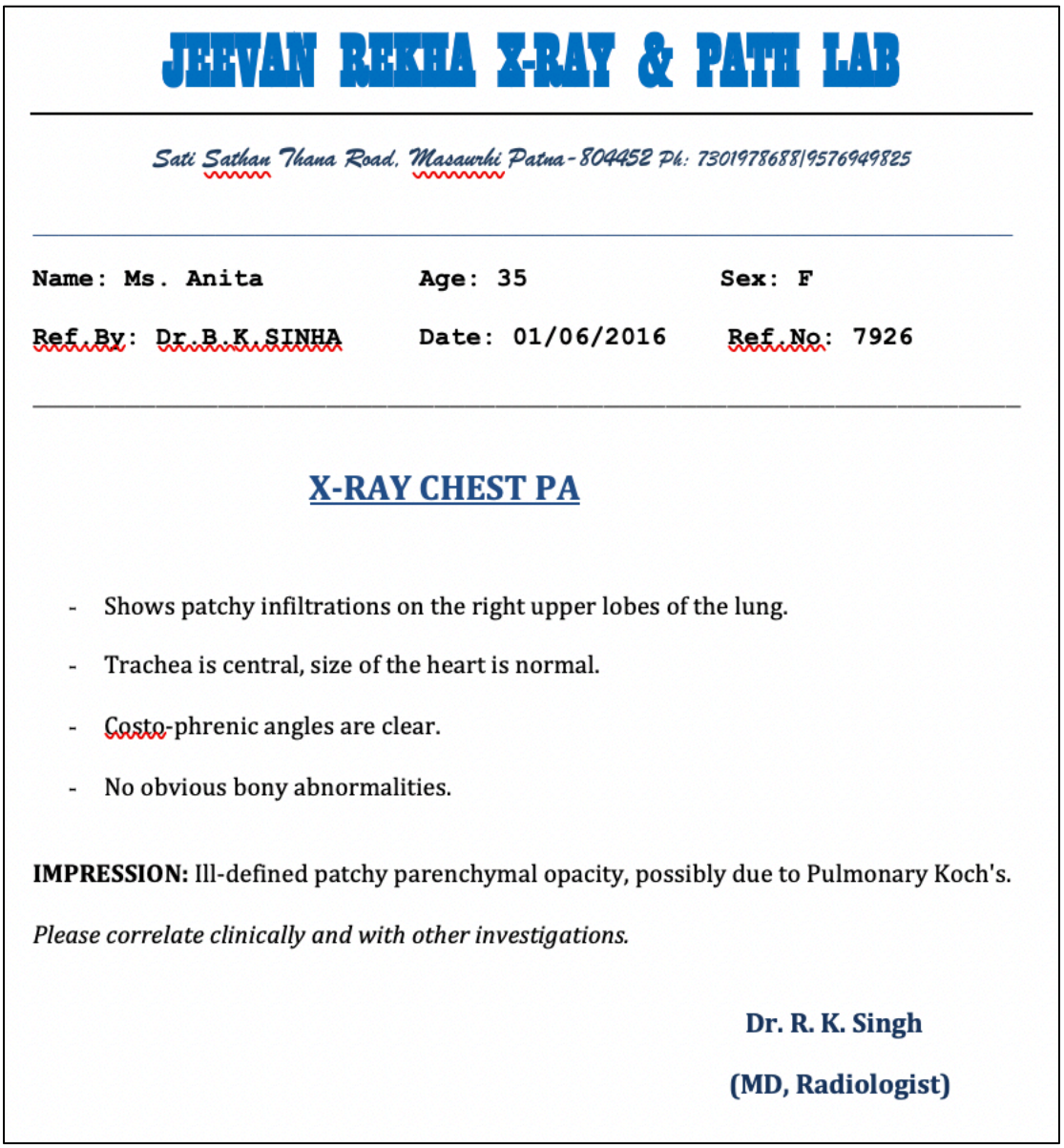
S2-Table 1: *Standardised patient variable descriptions.*

	Measurement method
Provider level- variables	
Qualification of provider	Recorded in provider data
Provider younger than 30 years of age	Assessed by standardized patient
Provider 30–50 years of age	Assessed by standardized patient
Provider older than 50 years of age	Assessed by standardized patient
Provider male	Observed by standardized patient
Patients waiting on arrival	Observed by standardized patient
Patients waiting on departure	Observed by standardized patient
Provider has clinic assistant	Observed by standardized patient
Process indicator	
Provider used cell phone	Observed by standardized patient
Other people in room during interaction	Observed by standardized patient
Television on during interaction	Observed by standardized patient
Essential checklist %	Calculated from standardized patient data
Time with provider (min)	Measured by standardized patient
Did the provider create a private environment?	Assessed by standardized patient
Did the provider explain about your illness?	Assessed by standardized patient
Did the provider explain your treatment plan?	Assessed by standardized patient
Did you like this doctor?	Assessed by standardized patient
Would you go to this doctor again?	Assessed by standardized patient
Did the provider seem knowledgeable about your illness?	Assessed by standardized patient
Did the provider address your worries seriously?	Assessed by standardized patient

How would you rate the provider? (1–10)	Assessed by standardized patient
Quality outcome	
Correct management	Calculated from standardized patient data using Indian NTP guidelines
Correct Treatment based on Mx Dx	Calculated from standardized patient
Referred case	Reported by standardized patient
Tuberculosis suspicion	Reported by standardized patient
Chest CXR	Reported by standardized patient
Sputum acid-fast bacillus	Reported by standardized patient
Xpert MTB/RIF MTB/RIF	Reported by standardized patient
Anti-tuberculosis treatment	Determined by analysis team
Quinolone	Determined by analysis team
Other antibiotic	Determined by analysis team
Steroids	Determined by analysis team

S2-Table 2: *Sampling and weighting distributions for cases 1 & 2 within formal providers surveyed.*

			Weighting Group			
Round	SP Case		Patna Formal Non-PPIA	Patna Formal PPIA	Mumbai Formal Non-PPIA	Mumbai Formal PPIA
Baseline	Case 1	n	253	136	134	171
	-	weight	0.00352532	0.0007948	0.00714301	0.00025051
	Case 2	n	70	28	69	53
	-	weight	0.01274152	0.00386048	0.01387193	0.00080824
Round 1	Case 1	n	215	89	117	156
	-	weight	0.0041484	0.00121453	0.00818088	0.0002746
	Case 2	n	112	45	76	60
	-	weight	0.00796345	0.00240208	0.01259425	0.00071395
Round 2	Case 1	n	189	81	122	155
	-	weight	0.00471908	0.00133449	0.0078456	0.00027637
	Case 2	n	94	41	90	57
	-	weight	0.00948837	0.00263643	0.01063515	0.00075152



JEEVAN REKHA X-RAY & PATH LAB

Sati Sathan Thana Road, Masaurhi Patna-804452 Ph: 7301978688|9576949825

Name: Ms. Anita Age: 35 Sex: F

Ref.By: Dr.B.K.SINHA Date: 01/06/2016 Ref.No: 7926

X-RAY CHEST PA

- Shows patchy infiltrations on the right upper lobes of the lung.
- Trachea is central, size of the heart is normal.
- Costo-phrenic angles are clear.
- No obvious bony abnormalities.

IMPRESSION: Ill-defined patchy parenchymal opacity, possibly due to Pulmonary Koch's.

Please correlate clinically and with other investigations.

Dr. R. K. Singh

(MD, Radiologist)

S2-Figure 1: *Example of CXR report carried by female SPs during data collected in 2016.*

RITE DIAGNOSTICS & LABORATORIES

The right results, every time

Address : Shop No 41, Sukur Garden, Manorama Nagar Road, Thane West, , Thane, Maharashtra - 400601,India

Timing : 8 am to 2 pm & 5 pm to 10 pm (Sunday 8 am to 2 pm) Mobile : 7045577530,7506218520

Name: Ms Mamta **Age: 35** **Sex: F**

Ref By: Dr.A.K.MEHTA **Date: 18/02/2017 ID NO:10131**

X-RAY CHEST PA

- Shows patchy infiltrations on the right upper lobes of the lung.
- Trachea is central, size of the heart is normal.
- Costo-phrenic angles are clear.
- No obvious bony abnormalities.

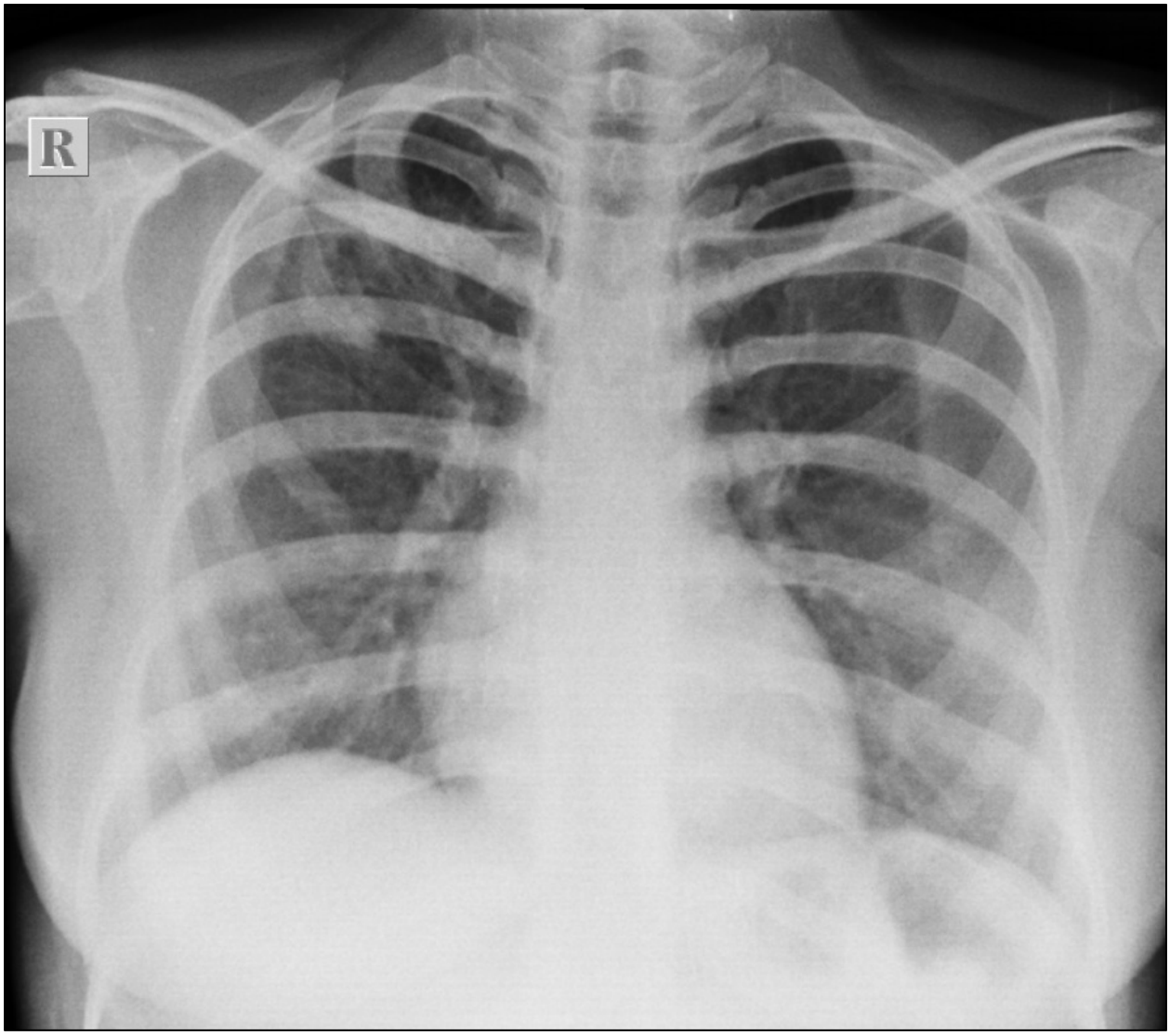
IMPRESSION: Ill-defined patchy parenchymal opacity, possibly due to Pulmonary Koch's.

Please correlate clinically and with other investigations.

Dr. R. Manohar

(MD, Radiologist)

S2-Figure 2: *Example of CXR report carried by female SPs during data collected in 2018.*



S2-Figure 3: *Example of CXR imaging carried by female SPs.*

JEEVAN REKHA X-RAY & PATH LAB

Sati Sathan Thana Road, Masaurhi Patna-804452 Ph: 7301978688|9576949825

Name: Mr. Anil Kumar Age: 35 Sex: M

Ref.By: Dr.B.K.SINHA Date: 01/06/2016 Ref.No: 7929

X-RAY CHEST PA

- Shows patchy infiltrations on right upper lobe of the lung.
- Increased brocho-alveolar markings.
- Trachea is central, size of the heart is normal.
- Costo- phrenic angles are clear. No obvious bony abnormalities.

IMPRESSION:? Pulmonary koch's.

Please correlate clinically and with other investigations.

Dr. R. K. Singh

(MD, Radiologist)

S2-Figure 4: *Example of CXR report carried by male SPs during data collected in 2016.*

RITE DIAGNOSTICS & LABORATORIES

The right results, every time

Address : Shop No 41, Sukur Garden, Manorama Nagar Road, Thane West, , Thane, Maharashtra - 400601,India

Timing : 8 am to 2 pm & 5 pm to 10 pm (Sunday 8 am to 2 pm) Mobile : 7045577530,7506218520

Name: Mr. Ravi Kumar Age: 35 Sex: M

Ref.By: Dr.A.K.MEHTA Date: 18/02/2017 ID No: 10131

X-RAY CHEST PA

- Shows patchy infiltrations on right upper lobe of the lung.
- Increased brocho-alveolar markings.
- Trachea is central, size of the heart is normal.
- Costo- phrenic angles are clear. No obvious bony abnormalities.

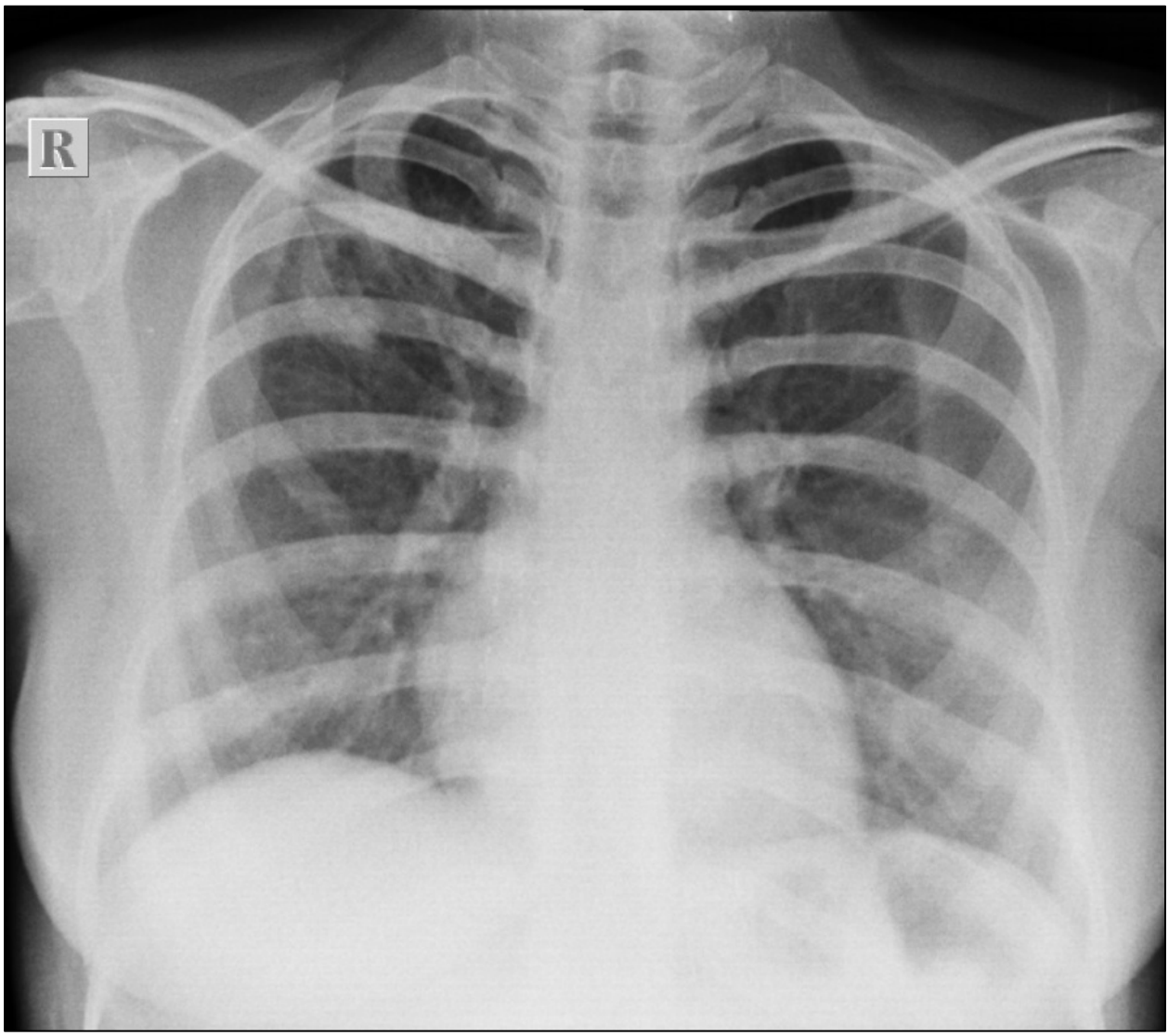
IMPRESSION:? Pulmonary koch's.

Please correlate clinically and with other investigations.

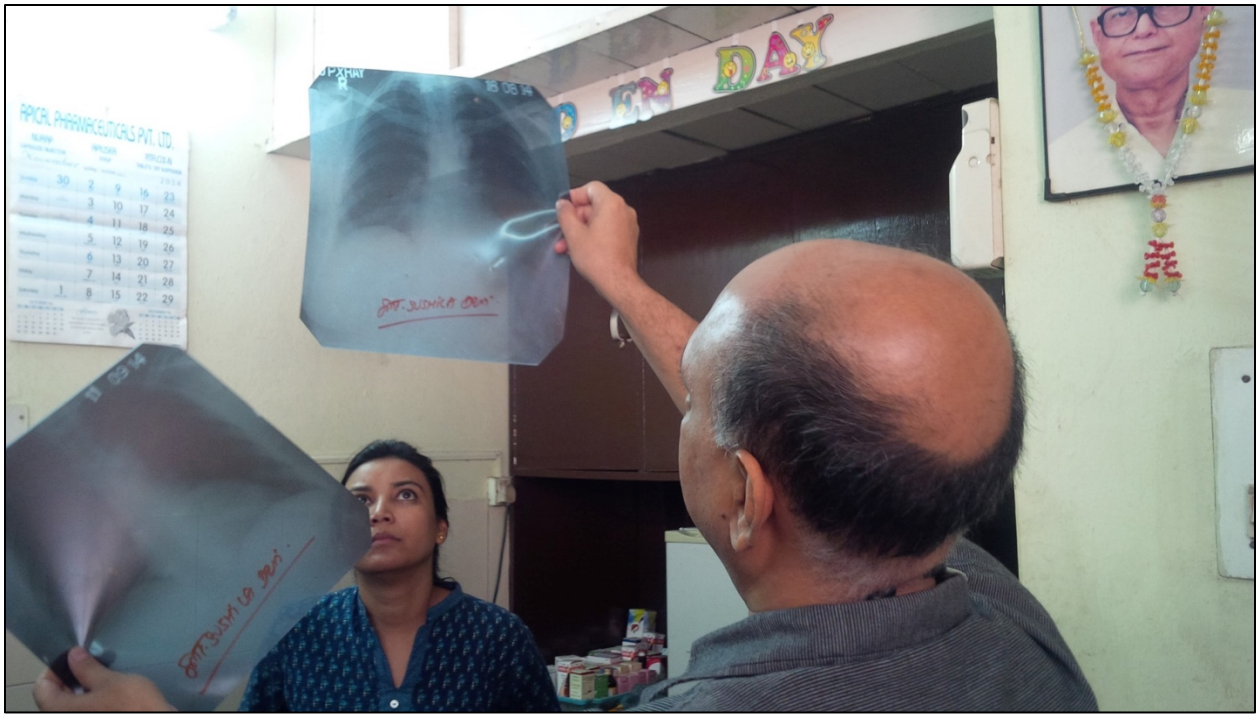
Dr. R. Manohar

(MD, Radiologist)

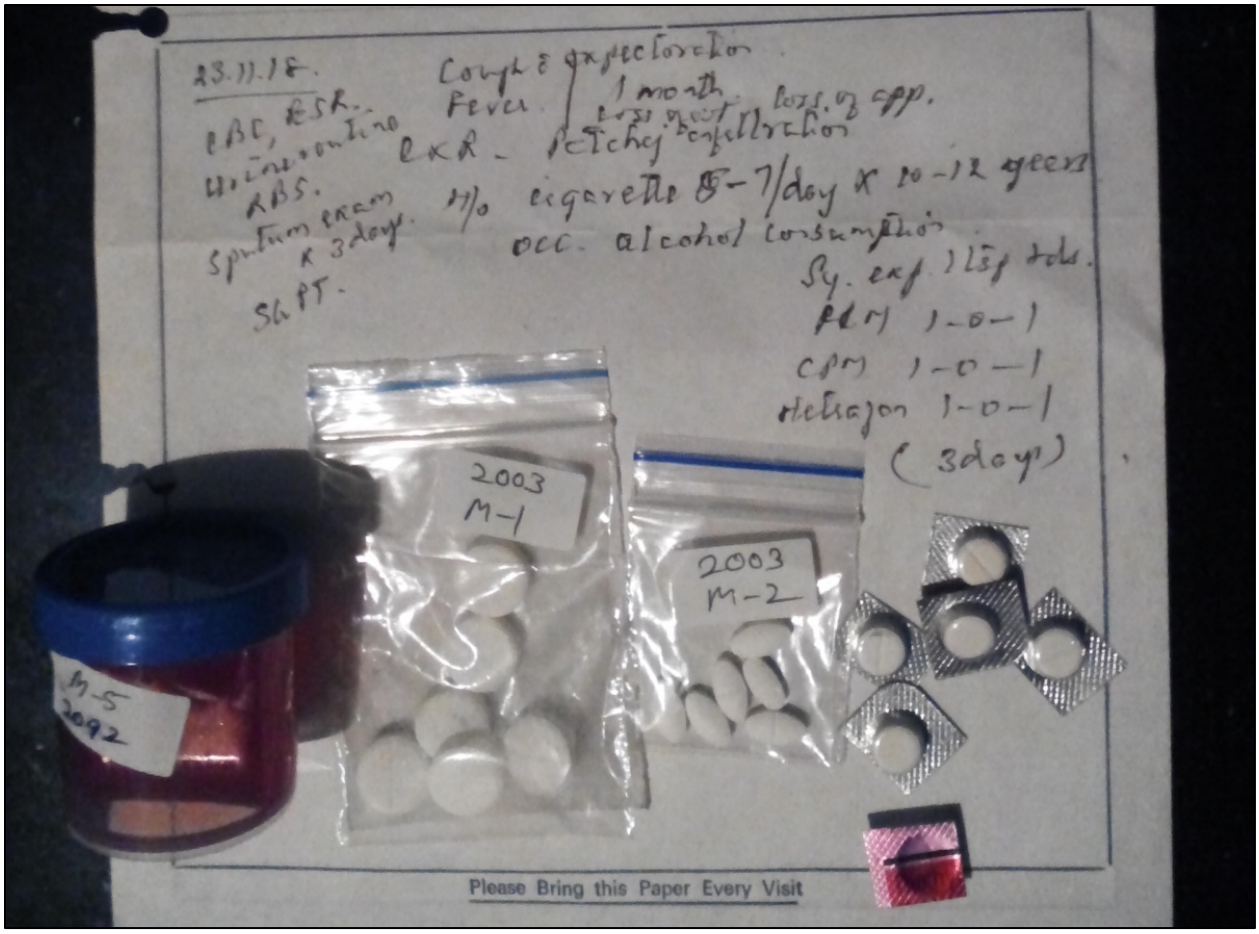
S2-Figure 5: *Example of CXR report carried by male SPs during data collected in 2018.*



S2-Figure 6: *Example of CXR imaging carried by male SPs.*



S2-Figure 7: *CXR from a typical general practitioner in Patna (permission given).*



S2-Figure 8: *Example of a prescription and subsequent, dispensed loose & unlabelled pills given to a case 2 presentation in Mumbai.*

CHAPTER 3: USING STANDARDISED PATIENT METHODOLOGY TO ASSESS INAPPROPRIATE USE OF QUINOLONES AND CORTICOSTEROIDS FOR TUBERCULOSIS BY PRIVATE PRACTITIONERS IN URBAN INDIA

3.1 PREFACE

My study in Chapter 2 indicated that approximately a quarter of patients seeking care with evidence of an abnormal CXR were prescribed ATT. I was next interested in understanding what other medications were being prescribed across different types of case presentations. Specifically, I was interested to know the proportion of patients who received a corticosteroid or quinolone, two medicine categories where abuse could have problematic implications for the diagnosis and treatment of TB.

In this manuscript, I report the results of a large analysis SP study, performed over multiple time points from 2014-2019. The objective of this study was to investigate patterns in quinolone and corticosteroid dispensation and prescription across healthcare providers, in cases of presumed or confirmed TB.

This work is part of a larger series of papers to be published by the QuTUB consortium (https://www.qutubproject.org/), funded by the Bill and Melinda Gates Foundation. It will soon be submitted for publication.

3.2 TITLE PAGE

Using standardised patient methodology to assess inappropriate use of quinolones and corticosteroids for tuberculosis by private practitioners in urban India

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3.3 ABSTRACT

Introduction

Acute respiratory tract infections (RTIs) are among the most common conditions managed in primary care. When TB diagnosis is not considered when patients present with a persistent cough, patients may be erroneously treated with quinolones or corticosteroids, which might provide temporary symptomatic relief but delay or mask TB diagnosis.

Methods

The objective of this study was to perform an analysis of a dataset compiled from standardized patient (SP) studies in order to investigate patterns in quinolone and corticosteroid dispensation and prescription across healthcare providers, in cases of presumed or confirmed TB. Making use of the standardized patient (SP) methodology, this study employs actors who portray four different case presentations to providers in urban India. A total of 6,685 SP interactions were done over three survey rounds, from 2014 to 2020, in two cities. Estimates clustered standard errors at the provider level, and were inverse-probability-weighted based on the study sampling strategy, resulting in city-round-representative interpretations of all outcome measures.

Results

Across all case presentations and two cities, 749 of 6,685 (12%; 95% CI: 11-14%) interactions resulted in the prescription of quinolones and 512 of 6,685 (6%; 95% CI: 5-7%) were corticosteroids. In Patna, 511 of 2,732 (19%; 95% CI: 17-20%) interactions resulted in the prescription of a quinolone vs. 238 of 3,953 (6%; 95% CI: 5-8%) in Mumbai. A total of 210 of 2,732 (7%; 95% CI: 6-8%) interactions resulted in the prescription of a corticosteroids in Patna, vs. 302 of 3,953 (6%; 95% CI: 5-6%) in Mumbai.

Conclusion

In this study, standardized patient (SP) methodology was employed to shed light on prescription practices of corticosteroids and quinolones amongst private practitioners in urban India. One in ten SP interactions resulted in the use of quinolones and about one in twenty interactions resulted in the use of steroids. These might mask TB detection in the private sector, and this study highlights the importance of monitoring of dispensation of both quinolones and corticosteroids, as both constitute potentially harmful consequences when deployed unnecessarily.

3.4 INTRODUCTION

Acute respiratory tract infections (RTIs) are among the most common conditions managed in primary care.[1] Antibiotics, such as quinolones, and corticosteroids are known to affect TB disease and its symptoms, often masking the latter and delaying diagnosis and specific treatment.[2-4] Research, including our work in the previous chapter, shows a propensity for providers to underdiagnose and overtreat presumptive TB patients, with microbiologically confirmed cases remaining scarcer than those empirically diagnosed, and with providers oftentimes using medicines themselves as a diagnostic tool.[5] When TB diagnosis is not considered when patients present with a persistent cough, patients may be erroneously treated with quinolones or corticosteroids, which might provide temporary symptomatic relief but delay or mask TB diagnosis.[6]

Antimicrobial resistance (AMR) is a major public health and security concern worldwide.[7] With drug-resistant bacterial infections on the rise globally, there is also growing focus on drug-resistant TB, its diagnosis and treatment.[8] Quinolones are key second-line antibiotic drugs for the treatment of multi-drug resistant TB (MDR-TB), also used to treat other respiratory tract infections.[7] Their broad application poses a potential risk for selecting quinolone-resistant strains of *M. tuberculosis* in case TB disease is misdiagnosed.[6] Their monotherapy in patients with TB disease can cause quinolone drug resistance.[9,10]

Based on data reported by 105 countries and territories, the average proportion of MDR-TB patients with *M. tuberculosis* strains also resistant to one of the quinolones was 20.1% (95% CI 15.5-25.0%).[11] Increasing quinolone resistance is a concern because it undermines newer, shorter drug regimens that include quinolones (e.g. four-month, rifapentine-based regimens with moxifloxacin, recently endorsed by the WHO).[12] Additionally, the widespread use of quinolones also poses broader issues related to the emergence of resistant strains among bacteria other than MTB; in particular quinolones are a class of antibiotics that have a high potential for selecting resistance.[13]

There are two main pathways that may result in the development of resistance to quinolones: 1) their use within inappropriate TB regimens and 2) their use for other respiratory infections, and the subsequent risk for the emergence of resistant TB.[6] Quinolones are among the most widely used antibiotics in India, and India consumes more antibiotics than any other country in the world.[14] During the coronavirus disease

2019 (COVID-19) pandemic, antibiotic consumption in India has dramatically increased, raising concerns about anti-microbial resistance.[15]

Corticosteroids have potent anti-inflammatory and immunosuppressive effects; as such, they are among the most commonly used medicines to control inflammation across various indications, from infections to autoimmune diseases and malignancies [16] They are commonly prescribed to address many respiratory conditions such as asthma, bronchiolitis, cystic fibrosis and some forms of tuberculosis.[16] More recently, corticosteroids have become a key component of the treatment of COVID-19 associated with hypoxia[17], and the excessive use of corticosteroids for COVID-19 patients, along with comorbidities such as diabetes, are likely drivers of an upsurge of an otherwise very rare fungal disease (mucormycosis), and is suggestive of the rampant misuse of corticosteroids across clinical indications.[18] In particular, three quarters of Indian patients in a study conducted during the first wave of COVID-19 in 2020 received corticosteroids (with more than 60% receiving inappropriate therapy).[19]

Steroids are often used as an adjunct in the treatment of some forms of TB, most notably to prevent complications, such as constrictive pericarditis, hydrocephalus, pleural adhesions, focal neurological deficits and intestinal strictures, among others.[20] However, in undiagnosed presumptive TB cases, corticosteroids may also mask clinical symptoms of TB by promoting weight gain and reducing fever temporarily,[21] may interfere with the diagnosis itself by limiting the body's ability to respond to immune-based TB tests,[22,23] and – when given without anti-TB treatment – corticosteroids could actually promote the progression from latent infection to active TB disease.[4] In addition, the concurrent administration of anti-TB drugs and corticosteroids causes pharmacokinetic interactions that hinder efficacy of both drugs thus impairing clinical outcomes.[24-28]

Building off our previous work,[29-35] the objective of this study was to perform an analysis of a dataset compiled from SP studies in order to investigate patterns in quinolone and corticosteroid dispensation and prescription across healthcare providers, in cases of presumed or confirmed TB.

3.5 METHODS

Context

Mumbai is the relatively wealthy and cosmopolitan capital of the state of Maharashtra. As per the latest census (2011), it is home to 12 million inhabitants, with an annual per capita income of 180,000 INR (US$2,440). In contrast, Patna is the capital of the state of Bihar and one of India's least developed states, with a recorded per capita income of 30,441 INR (US$412). The population of urban Patna is 2 million.

In 2019, 106,189 and 191,294 patients with TB were officially notified in Bihar and Maharashtra, respectively.[36] Within the public sector, in Bihar, 43,139 (40.6%) cases were confirmed via microbiological confirmation whereas 79,039 (41.3%) were confirmed in Maharashtra.[36] The recent national prevalence survey estimated the prevalence of TB in Maharashtra state to be 161 per 100,000 population, and 327 per 100,000 for Bihar state. The overall national prevalence was estimated to be 316 per 100,000.[37] The National TB Prevalence Survey (2019-21) reported that there were many missing TB case in 2021; it was found that in Bihar 3.15 TB cases were missed per 1 case notified to the public system. In Maharashtra, the number of missing cases was 0.86 for every case notified.[37]

Though both cities have government-run public clinics and hospitals, it is within the largely unregulated private sector where most patients decide to seek care. It is important to note that the structure of the private sector is very different between both cities. Informal providers in Mumbai are mainly AYUSH (Ayurveda, Unani, Siddha, homeopathy) practitioners while in Patna informal providers tend to be those with other or no qualifications at all. Formal providers in Patna who are MBBS-qualified tend to operate detached, single-provider clinics, whereas in Mumbai, they additionally work in numerous multi-provider facilities or in hospitals. These sites generally contain a mix of MBBS providers, specialists with higher qualifications as well as AYUSH practitioners.

Study Design

Data was collected in three survey rounds in two cities, Patna and Mumbai, was analysed to investigate patterns in quinolone and corticosteroid dispensation and prescription across healthcare providers, in cases of presumed or confirmed TB. Data was collected from a quality of TB care surveillance study from 2014-2019 – the first round was from 2014-2015, the second 2016-2018, and the final round 2019-2020.

Standardized patients (SPs) are increasingly used in low-income countries to assess quality of medical care to bypass other methods which are prone to biases and thus may not reflect genuine practice.[31,38,39] Compared to other methods, SP studies can provide an accurate assessment of provider practice that is

free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of healthcare providers.[40,41]

Case Presentations

The SP actors in each round were trained to portray four different health presentations as designed by a multidisciplinary team of medical anthropologists, health economists, epidemiologists and local clinical experts, the methods of which are described elsewhere.[34,35]

Case presentations are detailed in Appendix (S3-Table 1). In sum, case 1 consisted of a classic symptomatic case of presumptive TB who had had 2-3 weeks of cough and fever. Case 2 was a presumptive TB case who had had 2-3 weeks of cough and fever, but additionally presented with a completed CXR and 1 week of broad-spectrum antibiotic treatment ordered by another provider, with no improvement – this SP case was the primary focus of our analysis. The SP carried a digital chest X-ray dated within the last 10 days with evidence of abnormalities, and the blister pack of amoxicillin with him/her. The SP began the interaction by saying: "Doctor, I have had cough and fever. It is not getting better, even though I went to a doctor and took medicines also." Case 3 presented similarly to case 2 but additionally carried a positive microbiological test (sputum microscopy). Case 4 presented as an adult multidrug resistant (MDR) TB suspect with 4 weeks of cough and fever. It should be noted however that none of our 4 SP cases required quinolone or corticosteroids, and therefore any use would have been inappropriate in all of the SP interactions.

SP Recruitment and Characteristics

Recruitment of SPs, script development, SP training, provider sampling and assignment of SP case providers was previously outlined by Kwan et al.[34] and will thus not be described in detail here. Briefly however, in an SP study, locally recruited individuals are trained to portray pre-specified medical conditions using a standardized script with contextually and biomedically appropriate symptom descriptions. SP studies seek to understand how providers diagnose and treat patients and thus, provide critical data on the quality of clinical care, as opposed to provider knowledge alone.

Over the course of the three rounds in each of the two cities, a total of 39 individuals (16 females and 23 males) were recruited and hired as SPs. A total of 13 of these individuals were hired as SPs in both cities, 17 were hired for Mumbai only and 9 for Patna alone.

In Mumbai, 30 individuals (11 female) conducted fieldwork between April 2015 to December 2019. For these interactions, 20 SPs (8 female) were case 1, 8 SPs (4 female) were case 2, 8 SPs (2 female) were case 3, and 12 SPs (3 female) were case 4. SPs were originally from the states of Bihar (9), Madhya Pradesh (3), Delhi (2) and Maharashtra (16). Primary languages spoken by the SPs included Angika (1), Bengali (1), Bhojpuri (1), Hindi (9), Malwi (1), Magahi (4), and Marathi (12).

In Patna, 22 individuals (10 female) conducted fieldwork. For these interactions, 18 SPs (6 female) were case 1, 7 SPs (4 female) were case 2, 7 SPs (3 female) were case 3, and 7 SPs (3 female) were case 4. SPs were originally from the states of Bihar (18), Delhi (2) and Madya Pradesh (2). Primary languages spoken by the SPs included Angika (3), Bengali (1), Bhojpuri(4), Hindi (7), Maithili (1), Malwi (1) and Magahi (5).

All potential SPs underwent a health screening questionnaire and checkup, with the resulting cohort of actors of seemingly healthy status. This was important as it assured that the SPs had no apparent health conditions that could confound the case presentation and interaction with healthcare providers. While the SPs were specifically recruited to fit each case scenario and corresponding narrative, they differed in age, gender, height, and weight. The average age of all the SPs was 32. The youngest was 21 and the oldest was 58. The 23 males weighed 50 to 76 kilograms and were 1.55 to 1.84 meters tall. The 16 females weighed 46 to 73 kilograms and were 1.42 to 1.67 meters tall.

Sampling Framework

The primary data collection for this study in Mumbai and Patna was conducted by urban TB programs funded by the Bill and Melinda Gates Foundation (BMGF) and implemented by Private Provider Interface Agencies (PPIAs) in each city. These PPIAs were World Health Partners (WHP) in Patna and PATH in Mumbai. Each of these organizations was mapping, recruiting, and enrolling private sector providers into provider networks in both cities. A lane-by-lane mapping exercise resulted in a list of private sector providers in Mumbai and Patna and this resulting universe was then restricted based on eligibility criteria for the SP study: providers eligible for the study were those who were known to see adult outpatients with respiratory symptoms in the private health sector. Throughout, we retained the full sample of

healthcare providers, not distinguishing between those in the PPIA and those outside, as they were not the focus of this study.[42,43] The description of the program served to support sampling weights applied to achieve the urban area estimates for Mumbai and Patna (described below). Preliminary analysis of data separating the two are currently in progress and can be found in an unpublished brief to the BMGF.[44]

Weighting

The city-level estimates of the behavioural characteristics in Mumbai and Patna were able to extend from the sampling frame to the full population of private healthcare providers in each city based on the sampling strategy outlined above. We utilized inverse probability weights to calculate averages and differences within and across cities, satisfying the following:

1. Each city-case combination (Patna case 1, Mumbai case 2, etc.) has a total sum of weights equal to one. Therefore, each case is equally weighted within each city, and the two cities have equal total weights.

2. Within each city-case combination, the sum of weights for (A) MBBS-qualified (formal) and above and (B) non-MBBS-qualified (informal) providers is exactly equal to each group's prevalence in the city as a whole.

3. Within each city-case-qualification group, the relative total weights for (A) PPIA and (B) non-PPIA providers are exactly proportional to each group's prevalence in that city and provider qualification stratum.

4. Each round of the study is exactly proportional to the number of visits completed within that round.

The weight on each interaction is calculated such that our estimates take the values that they would have had if we had sampled exactly at random from the city as a whole, assuming that our sample is representative of that provider mix. There are 96 weighting groups: one for each city, case, qualification, PPIA status, and round (2 *4 *2 * 2 * 3).

Under the assumption that the providers we sampled from our sampling frames are representative of similar providers throughout the city, the resulting estimates are thus representative of the choice of a random provider within the city for each case presentation. Thus, when a statistic is to be reported in this

study in the form “X of Y interactions (N%)”, Y is the whole number of interactions observed, X is the whole number of interactions in which an outcome or characteristic occurred, and N is the population-level estimate calculated using the weights detailed above. Table S3- 1 details the weights employed for each case presentation by type of provider and city.

Identification of Medicines

Labeled medicines dispensed and prescriptions given to the SPs were coded into pre-determined categories of interest (e.g., corticosteroids, antibiotics). In order to assess drug use, all labelled medicines prescribed by the pharmacies were digitized and stored and then coded by three co-authors with expertise in TB (AS & AS) and infectious diseases (GS). Blinded from any provider identifying details, they identified and categorized medicines as steroids, anti-TB drugs, quinolones, or other broad-spectrum antibiotics under maker-checker procedure, whereby dual-approval was needed by two separate people for each coding. Quinolone antibiotics were defined as Anatomical Therapeutic Chemical (ATC) codes beginning with J01M, and corticosteroids, both inhaled and systematic, defined as ATC codes beginning with H02, R01, or R03. Anti-tuberculosis treatment (ATT) was defined as the dispensation of any of the four group 1, i.e. first-line oral anti-TB drugs: Isoniazid, Rifampicin, Ethambutol or Pyrazinamide. The category “other antibiotic” included all antibiotics other group 1 ATTs and quinolones. Discrepancies in categorization between coders were resolved by consensus. Finally, loose or unlabeled pills were dispensed in some interactions, but no further attempts were made to identify them as it was not feasible to perform assays at scale.

Statistical Analysis

The results are presented in four sections. In the first section, we provide a brief overview of the sampled providers, the sampling framework as well as the corresponding weights utilized. In the second, we describe overall standards of care, focusing on medicine prescription patterns, in Patna and Mumbai as well as these trends over time. Next, we look at factors associated with prescription of quinolones and corticosteroids, respectively. In the final section, we present a quantitative bias analysis of outcome misclassification.

We reported proportions of dispenses/prescribed quinolones and corticosteroids computed using inverse probability weighting with corresponding 95% CIs. The weights were calculated such that each of the 96

city-case-round combinations contributed equally to overall estimates and corresponded to the sampling framework of private sector providers listed from the mapping exercise in both cities.

In addition to using these weights to estimate population likelihoods, we used them to calculate weighted prevalence ratios (PRs) by using log-binomial regression comparing variation in factors associated with dispensation of quinolone or corticosteroids, respectively, adjusting for round and city, and clustering at the provider level. These methods are preferred to logistic regression estimation to directly estimate PRs from cross-sectional studies since odds ratios overestimate the PR, particularly when the outcome is not rare. The associations between predictors of interest and practices will be presented as a PR as a more interpretable alternative to the odds ratio. In order to look at time trends between rounds, we conducted weighted pair-wise t-tests and linear regressions to test for time trends.

We take the perspective that a quality outcome in a given interaction reflects a combination of inputs that vary at provider, patient and facility levels. We presented both univariate and multivariate models for factors of interest. In the multiple regression framework:

$$logit(Quinilone/Steroid_{ijklt}) = \alpha + \beta_0 + \beta_1 Case_{it} + \beta_2 Provider_{jt} + \beta_3 Patient_{kt} + + \beta_4 Site_{lt} + \varepsilon_{ijklt}$$

where $Quinilone/Steroid_{ijklt}$ is the corticosteroid or quinolone given by provider I to patient j at health facility k at time t; $Provider_{jt}$ is a vector of provider characteristics at time t; $Case_{it}$ a vector of case presentations at time t; $Patient_{kt}$ is a vector of patient characteristics at time t; $Site_{lt}$ is a vector of facility characteristics at time t; and ϵ is an error term. Relevant provider characteristics included provider age, and sex; patient characteristics included case presentation and some demographics; and facility characteristics included facility size, level of care, formal or informal, management, as well as community characteristics. The final model only included variables that were shown to potentially impact care management outcomes in our previous work[29,34] or would reasonably have contributed to care management practices.

All estimates were clustered standard errors at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures. Reported estimates represent the expected likelihood of the outcome occurring if a provider were chosen

at random from the population of providers within each respective city and within each round's time period. All data analyses were performed with Stata 15 (Stata, College Station, TX).

Variables of Interest

The regressions comprised the following binary or dummy predictors: study site (Patna (ref) vs. Mumbai); case presentation (case 1 (ref) vs. case 2 vs. case 3 vs. case 4), provider qualification (informal providers (ref) vs. formal providers); round of data collection (round 1 (ref) vs. round 2 vs. round 3); any diagnostic test ordered (yes vs. no); medical history taken (yes vs. no); clinical exam performed (yes vs. no); microbiological test performed (yes vs. no); treatment counselling performed (yes vs. no); invasive treatment performed (yes vs. no); and patients waiting in office (yes vs. no). We presented these as a univariate regression individually, and a full multivariate model with all co-variates.

Patient and Public Involvement

While our study aligns with patient-centred care, no tuberculosis patients were involved in study recruitment or conduct.

Ethics

Ethical approvals for this study were granted by the McGill University Health Centre in Montreal, Canada (REB No. 14-137-BMB) and the Subcommittee for the Ethical Approval of Projects at the Institute for Socioeconomic Research on Development and Democracy in Delhi, India.[32] Ethics committees approved a waiver from obtaining informed consent from providers in Patna and Mumbai under the Government of Canada Panel on Research Ethics, as well as a recent study by Rhodes and colleagues (2012) on ethical aspects of standardized patient studies commissioned by the US Department of Health and Human Services,[45] and study specific rational of waiver is detailed elsewhere.[34] All individuals who participated as standardised patients were hired as staff and trained to protect themselves from any harmful medical interventions, such as avoiding injections, invasive tests, or consuming any drugs.

3.6 RESULTS

Overview of Sampled Providers

Overall, 6,685 SP visits (case 1: 3,083; case 2: 1,129; case 3: 1,042; case 4: 1,431) at 1,321 providers in Patna and Mumbai were completed over a 4-year period. During the first round of data collection, 2,655 visits were made (Patna: 1,019; Mumbai: 1,636). In the second round 2,614 SP visits (Patna: 1,039; Mumbai: 1,575) were conducted. In the last round of data collection, 1,416 SP visits (Patna: 674; Mumbai 742) took place. In total, 5,675 medicines were prescribed or dispensed across all case presentations and cities. The sampling and weighting distributions for all cases by provider type are detailed in the supplement (S3-1).

Medicine Prescription Patterns

Across all 4 case presentations and 2 cities, 749 of 6,685 (12%; 95% CI: 11-14%) interactions resulted in the prescription of quinolones and 512 of 6,685 (6%; 95% CI: 5-7%) were corticosteroids. In Patna, 511 of 2,732 (19%; 95% CI: 17-20%) interactions resulted in the prescription of a quinolone vs. 238 of 3,953 (6%; 95% CI: 5-8%) in Mumbai. A total of 210 of 2,732 (7%; 95% CI: 6-8%) interactions resulted in the prescription of a corticosteroids in Patna, vs. 302 of 3,953 (6%; 95% CI: 5-6%) in Mumbai. It must be noted however that these prescriptions do not include any unlabelled tablets which accounted for 1,738/6,685 (16%; 95% CI: 15-17%) and unlabelled injections: 3/6,685 (0%; 95% CI: 0-0%).

Figure 3-1 details prescription practices by case and city. In Mumbai, quinolones were dispensed in 109 of 1,824 (6%; 95% CI: 5-8%) of case 1 interactions, 40 of 644 (6%; 95% CI: 4-9%) of case 2, 25 of 553 (6%; 95% CI: 3-9%) of case 3 and 64 of 932 (6%; 95% CI: 4-9%) in case 4. Quinolones were prescribed in Patna to 247 of 1,259 (20%; 95% CI: 17-22%) of case 1 presentations, 92 of 485 (19%; 95% CI: 15-23%) of case 2, 91 of 489 (19%; 95% CI: 15-23%) of case 3 and 81 of 499 (16%; 95% CI: 13-20%) of case 4.

Steroids were prescribed in Mumbai to 167 of 1,824 (6%; 95% CI: 5-8%) of case 1 presentations, 29 of 644 (4%; 95% CI: 3-6%) of case 2, 45 of 553 (6%; 95% CI: 4-8%) of case 3 and 61 of 932 (5%; 95% CI: 3-7%) of case 4. In Patna, corticosteroids were dispensed/prescribed to 124 of 1,259 (9%; 95% CI: 7-11%) of case 1 interactions, 28 of 485 (7%; 95% CI: 4-9%) of case 2, 28 of 489 (7%; 95% CI: 4-10%) of case 3 and 30 of 499 (6%; 95% CI: 3–8%) of case 4 interactions.

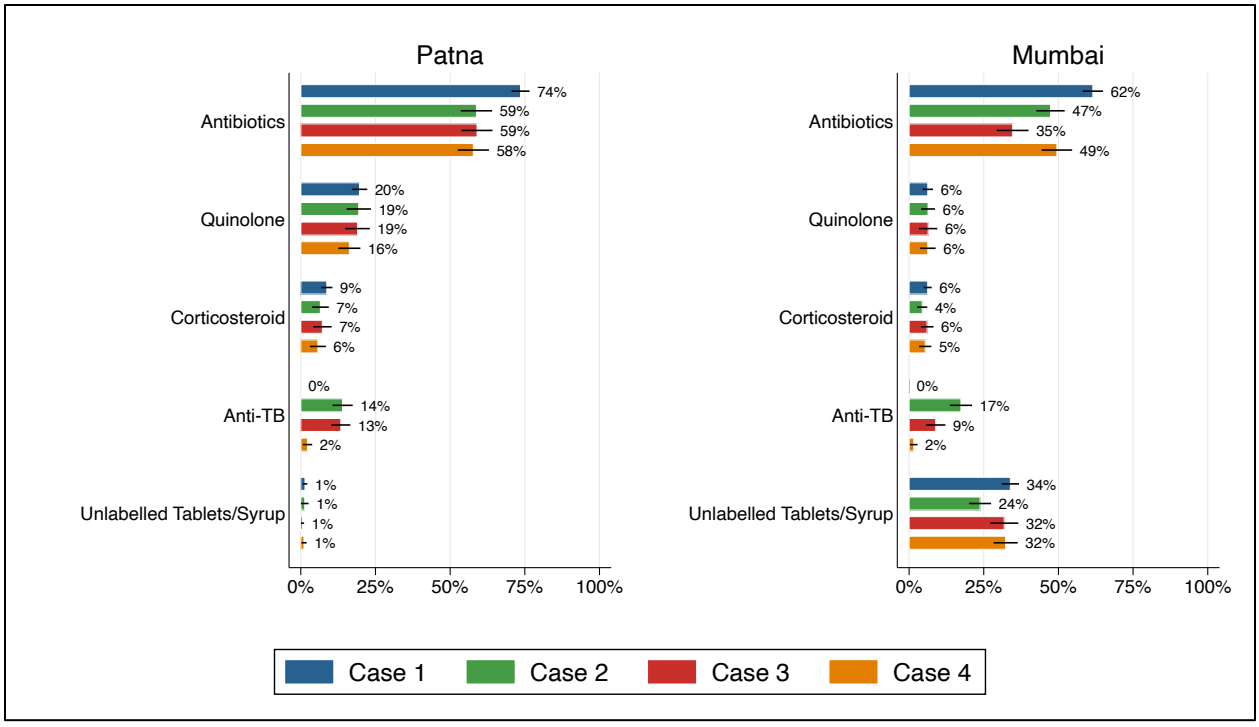

Figure 3-1: *Medicines prescribed/dispensed corticosteroids by case and city, weighted. **Anti-tb=Group 1 ATT medicines, Antibiotics=Any antibiotic dispensed.*

The most commonly prescribed quinolones and corticosteroids by city, respectively, are detailed in the appendix (S3-Figure 1 and S3-Figure 2). In Patna the following quinolones were prescribed most often: ciprofloxacin 53 of 747 (10%; 95% CI: 6-13%), levofloxacin 272 of 511 (52%; 95% CI: 47-58%), ofloxacin 68 of 511 (12%; 95% CI: 9-16%), ofloxacin + cefixime 49 of 511 (9%; 95% CI: 6-12%), and levofloxacin + azithromycin 15 of 511 (3%; 95% CI: 1-4%). In Mumbai, results were levofloxacin 69 of 236 (39%; 95% CI: 29-50%), moxifloxacin 28 of 236 (7%; 95% CI: 2-12%), ofloxacin 21 of 236 (9%; 95% CI: 3-15%), ciprofloxacin 9 of 236 (6%; 95% CI: 0-12%), and ofloxacin + cefixime 8 of 236 (2%; 95% CI: 0-4%). These are detailed in figure S3-Figure 1 of the supplementary. As for corticosteroids, in Patna, results were betamethasone 68 of 209 (28%; 95% CI: 19-36%), prednisolone 46 of 209 (22%; 95% CI: 14-30%), dexamethasone 43 of 209 (27%; 95% CI: 17-37%), deflazacort 28 of 209 (10%; 95% CI: 5-15%), methylprednisolone 11 of 209 (6%; 95% CI: 2-10%), and in Mumbai, deflazacort 28 of 209 (10%; 95% CI: 5-15%), dexamethasone: 43 of 209 (27%; 95% CI: 17-37%), prednisolone 46 of 209 (22%; 95% CI: 14-30%), methylprednisolone 11 of 209 (6%; 95% CI: 2-10%). These are detailed in the supplementary (S3-Figure 2).

When we consider what concurrent prescription/dispensation is occurring (Figure 3-2), we see that there is very little overlap between drug categories of interest. Amongst case 1, 44 of 3,083 (1.4%; 95% CI: 1-2%) of interactions received a quinolone and a corticosteroid. Among case 2, 7 of 1,129 (0.6%; 95% CI: 0-2%) of interactions received a quinolone and a corticosteroid, 30 of 1,129 (3%; 95% CI: 2-4%) received ATT and a quinolone, and only 4 of 1,129 (0.4%; 95% CI: 0-1%) a corticosteroid and ATT. A total of 10 of 1,042 (0.8%; 95% CI: 0-2%) of case 3 presentations received a quinolone and a corticosteroid, 23 of 1,042 (2%; 95% CI: 1-3%) ATT and a quinolones and 4 of 1,042 (0.2%; 95% CI: 0-1%) a corticosteroid and ATT. Case 4 interactions received a quinolone and a corticosteroid in 13 of 1,431 (0.9%; 95% CI: 0-2%) of instances and a ATT and a quinolones in 10 of 1,431 (0.7%; 95% CI: 0-1%) of interactions.

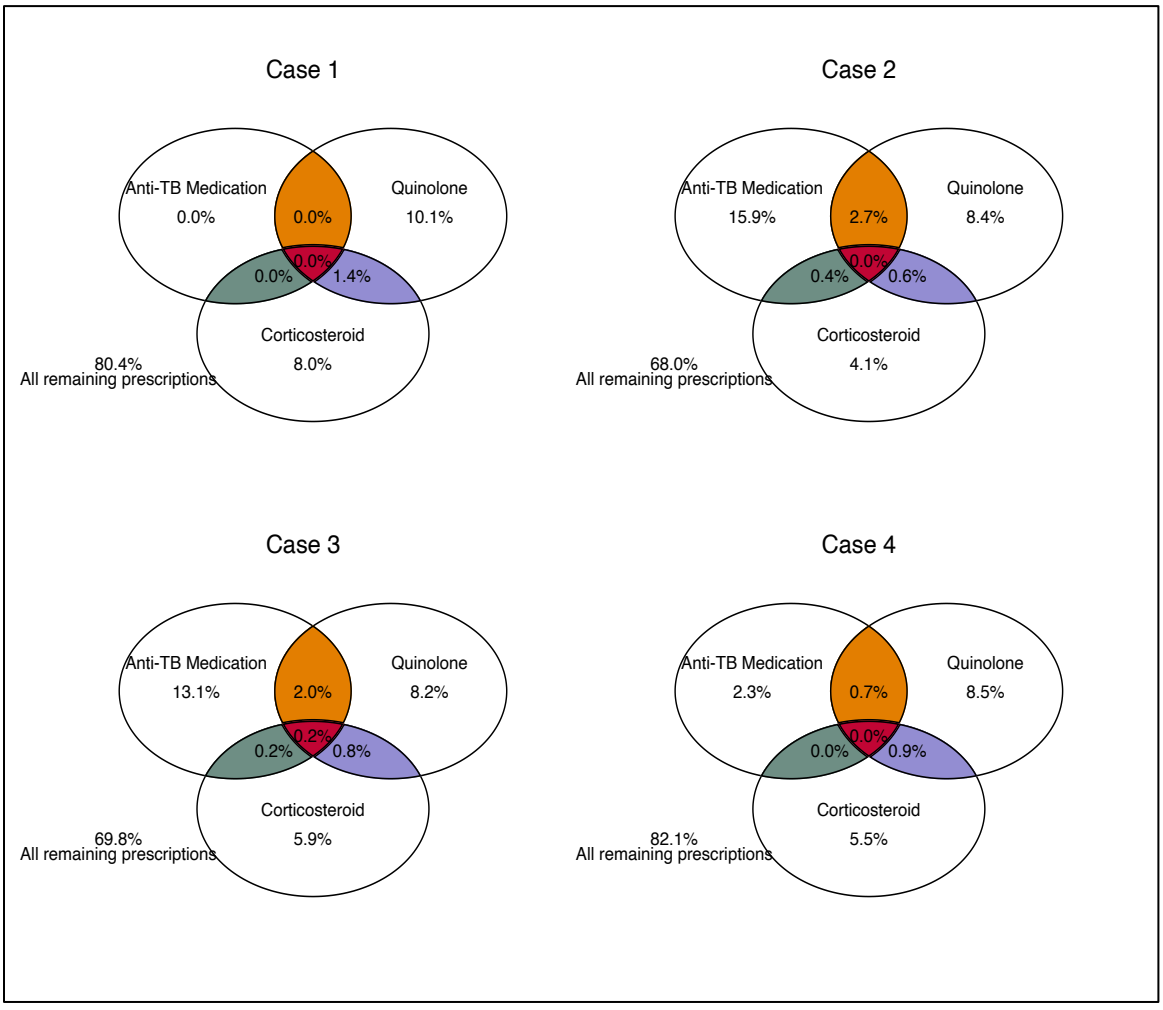

Figure 3-2: *Overlap in prescription patterns of ATTs, quinolones & steroids, by case.*

If we consider these outcomes over time (Figure 3-3), we see that in Mumbai there is an increase over time in antibiotic dispensation from 776 of 1.636 (42%; 95% CI: 38-46%) of interactions at baseline to 828 of 1,575 (48%; 95% CI: 44-52%) in the subsequent round of data collection, to 470 of 742 (54%; 95% CI: 50-59%) in the finalrRound of data collection; this increase was significant over time (β=0.0605, 95% CI: 0.0255-0.0957). Steroids were prescribed/dispensed in 88 of 1,636 (4%; 95% CI: 3-5%) of interactions at baseline, 181 of 1,575 (10%; 95% CI: 8-11%) in round 2 and 33 of 742 (3%; 95% CI: 1-4%) in round 3 data collection. Quinolones were prescribed in 117 of 1,636 (8%; 95% CI: 5-10%) of interactions at baseline, then subsequently 77 of 1575 (5%; 95% CI: 4-7%), and finally 44 of 742 (6%; 95% CI: 4-8%).

In Patna, there were decreases over time of prescriptions of both corticosteroids and quinolones, but only the former was significant over time (β=-0.0286, 95%CI: -0.0479 – (-0.009)). Steroid dispensation was seen in 224 of 1,019 (22%; 95% CI: 18-25%) of interactions at baseline and increased to 168 of 1,039 (16%; 95% CI: 13-19%) and 119 of 674 (18%; 95% CI: 14-21%) at the second and final round of data collection, respectively. Steroids were observed in 100 of 1019 (10%; 95% CI: 7-13%) of interactions to begin and increased to 79 of 1,039 (7%; 95% CI: 5-9%) and 31 of 674 (4%; 95% CI: 2-6%). The prescription/dispensation of antibiotics, generally, increased over time; a script for any antibiotic was observed in 691 of 1,019 (59%; 95% CI: 54-63%) of interactions and then 659 of 1,039 (55%; 95% CI: 51-59%) and 519 of 674 (73%; 95% CI: 69-77%), in later rounds. We see that the latter prescriptions increased significantly over time (β=0.0731, 95%CI: 0.0416-0.105).

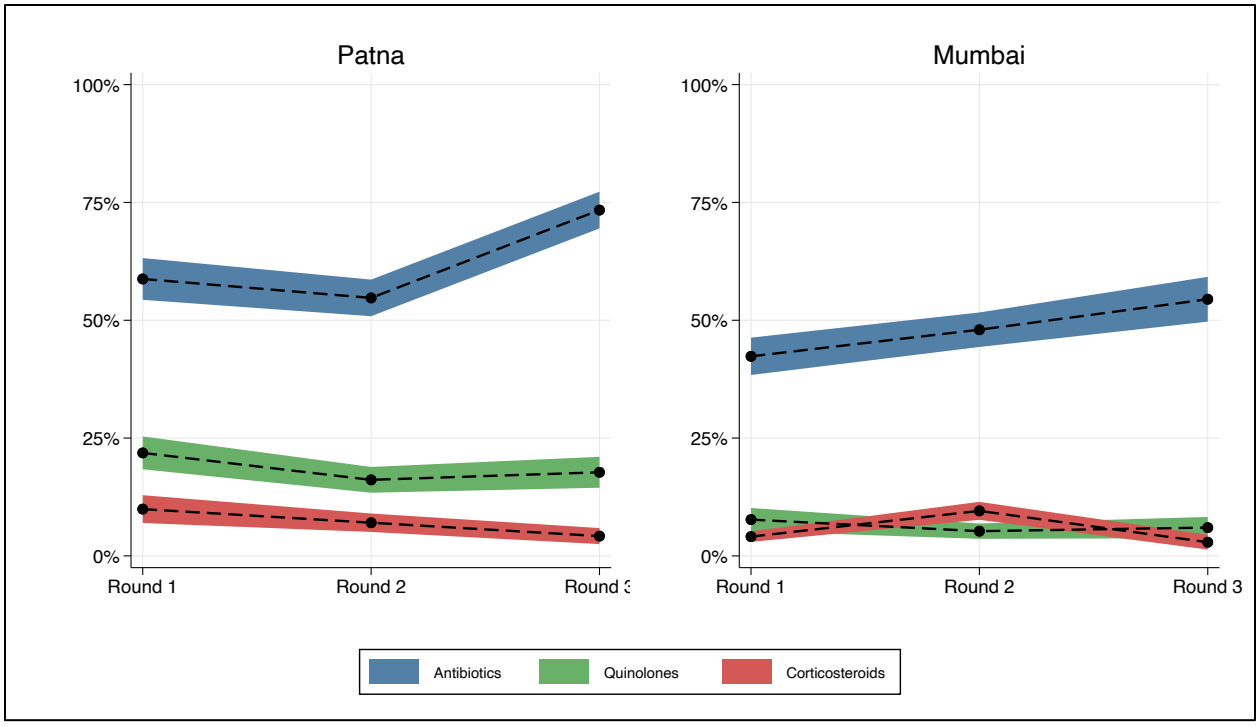

Figure 3-3: *Weighted changes in dispensation/prescription of antibiotics, corticosteroids and quinolones patterns by city and round of data collection. Round 1: 2014-2015, round 2: 2016-2018, round 3: 2019-2020*

Within the formal sectors (Figure 3-4), we see that there is a decrease over time in antibiotic dispensation from 954 of 1,354 (63%; 95% CI: 59-67%) of interactions at baseline to 960 of 1,396 (63%; 95% CI: 60-67%) in the subsequent round of data collection to 989 of 1,416 (64%; 95% CI: 61-67%) in the final round of data collection. Steroids were prescribed/dispensed in 63 of 1,354 (3%; 95% CI: 2-4%) of interactions at baseline, to 57 of 1,396 (4%; 95% CI: 2-5%) in round 2 and 64 of 1,416 (4%; 95% CI: 2-5%) at endline data collection. Quinolones prescriptions decreased significantly over time within the formal sector over each round of the survey (β=-0.0351, 95%CI: -0.052 – (-0.0182)); 237 of 1,354 (19%; 95% CI: 16-23%) of interactions resulted in quinolone dispensation at baseline, then 167 of 1,396 (13%; 95% CI: 11-15%), and finally 163 of 1,416 (12%; 95% CI: 10-14%).

Among informal providers, corticosteroid dispensation was seen in 125 of 1,301 (12%; 95% CI: 9-15%) of interactions at baseline to 203 of 1,218 (13%; 95% CI: 11-16%) at the second round of data collection. Quinolones were observed in 104 of 1,301 (9%; 95% CI: 7-12%) of interactions to begin and fell to 78 of 1,218 (8%; 95% CI: 6-11%). A script for any antibiotic was observed in 513 of 1,301 (36%; 95% CI: 32-40%)

of interactions at baseline, and then 527 of 1,218 (38%; 95% CI: 34-41%) in later rounds. It should be noted that informal providers were not surveyed in the final round of data collection.

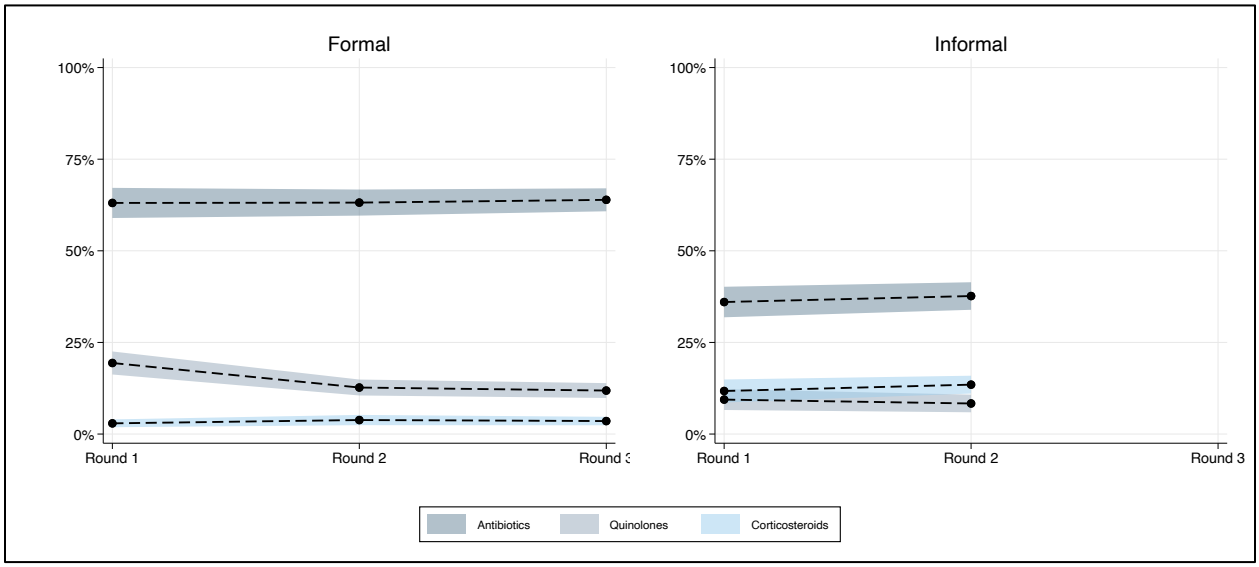

Figure 3-4: *Weighted changes in dispensation/prescription of antibiotics, steroids and quinolones patterns by provider qualification and round of data collection. Round 1: 2014-2015, round 2: 2016-2018, round 3: 2019-2020.*

Factors Associated with Dispensing of Quinolones and Steroids

Figure 3-5 details factors that were associated with quinolone prescribing, in univariate associations and then the multivariate model. In the full multivariate model, we saw that performing a clinical exam (weighted aPR 1.86, 95% CI: 1.18-2.92) and formal providers (weighted aPR 1.53, 95% CI: 1.09-2.16) were more likely to dispense quinolones. Conversely, the study site of Mumbai (weighted aPR 0.35, 95% CI: 0.24-0.52), and later study rounds, were associated with less quinolone prescriptions. For rounds 2 and 3, compared to round 1, we found a weighted aPR 0.74 (95% CI: 0.61-0.88) and aPR 0.67 (95% CI: 0.54-0.84), respectively.

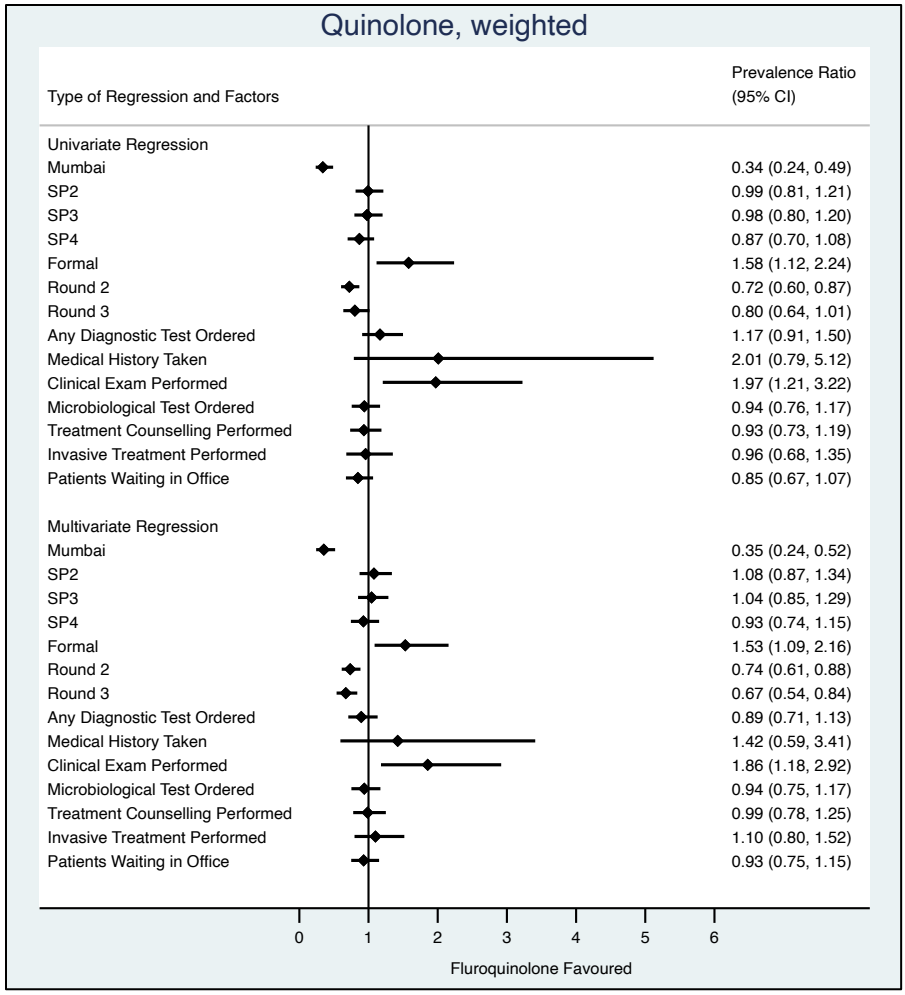

Figure 3-5: *Factors associated with quinolone prescriptions, weighted. prevalence ratios (PRs) were calculated via log-binomial regression; standard errors were clustered at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures; multivariate model after adjusting for other variables.*

Figure 3-6 details factors that were associated with corticosteroid prescribing. In the multivariate model, we saw that providers who offered invasive exams, such as blood glucose test (weighted aPR 1.79, 95% CI: 1.18-2.70) and performed a clinical examination (weighted aPR 1.91, 95% CI: 1.38-2.65) were associated with corticosteroid prescription. Providers who ordered any diagnostic test (weighted aPR 0.32, 95% CI: 0.23-0.42), were formal providers (weighted aPR 0.37, 95% CI: 0.23-0.58), and practiced in Mumbai -compared to Patna- (weighted aPR 0.66, 95% CI: 0.47-0.94), were less likely to prescribe a corticosteroid.

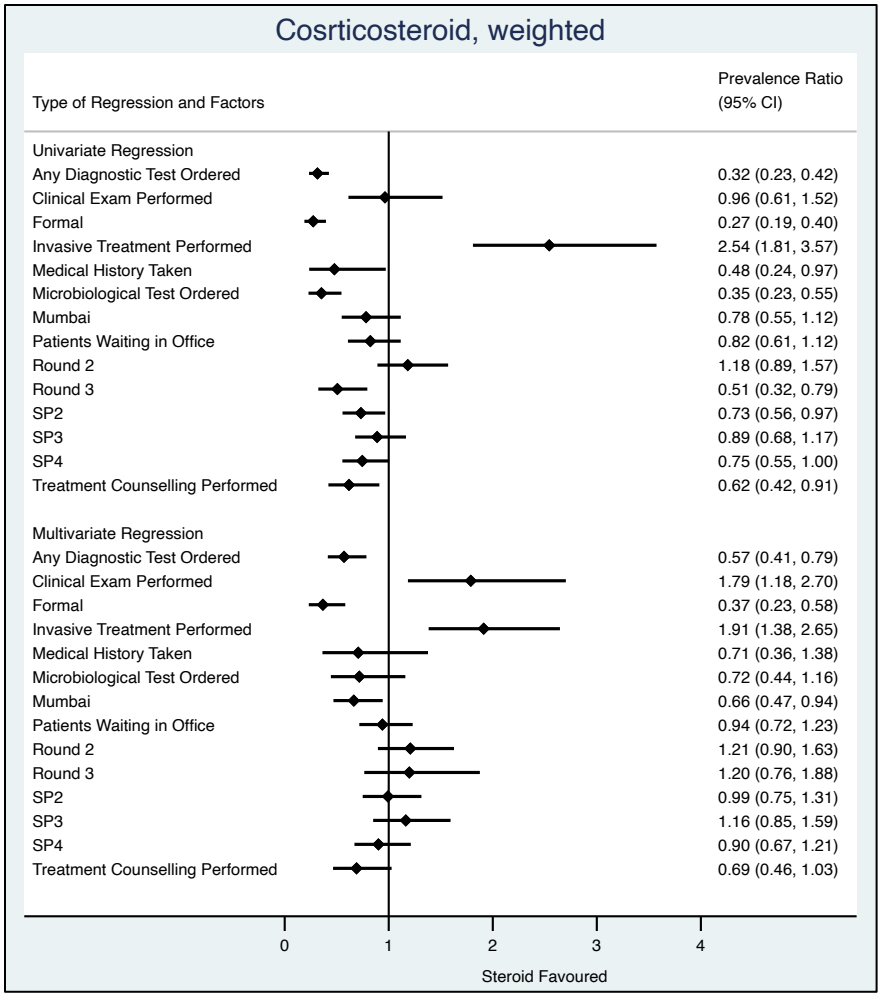

Figure 3-6: *Factors associated with steroid prescriptions, weighted. Prevalence ratios (PRs) were calculated via log-binomial regression; standard errors were clustered at the provider level, and inverse-probability-weighted based on our sampling strategy to arrive at city-round-representative interpretations of our outcome measures; the adjusted prevalence ratios (aPR) in the multivariate model after adjusting for other variables.*

3.7 DISCUSSION

In this study, we built off our previous work[29-35] and employed standardized patient (SP) methodology to shed light on prescription practices of corticosteroids and quinolones amongst private practitioners in urban India. We found that across all case presentations and both cities, 749 of 6,685 (12%; 95% CI: 11-14%) interactions resulted in the prescription of quinolones and 512 of 6,685 (6%; 95% CI: 5-7%) in corticosteroids. Thus, one in ten SP interactions resulted in the use of quinolones and about one in twenty

interactions resulted in the use of steroids. We discuss the implications of these prescriptions in the Indian private sector on patient outcomes, health systems and public health, generally.

Quinolones are an essential component of some TB regimens, particularly for drug-resistant disease, and they are also a component of emerging, four-month regimens for drug-sensitive TB.[46] Quinolone exposure is a recognized risk factor for the development of quinolone resistance in many nosocomial as well as community-acquired pathogens.[47-50] Higher probability of quinolone-resistant MTB in patients with a history of respiratory infections has been attributed to widespread quinolone usage in these individuals.[51-55] A meta-analysis evaluating the association of prior quinolone usage and the development of resistance in MTB reports a three-fold higher risk of quinolone-resistant MTB in patients prescribed quinolone before TB diagnosis.[6] Prolonged quinolone exposure (defined as more than 10 days of treatment), or multiple quinolone prescriptions have been highlighted as significant risk factors for the development of quinolone resistance in MTB.[54,56,57] Many treatment guidelines in TB-endemic countries continue to include quinolone as first-line treatment due to the fact that high global resistance rates amongst respiratory pathogens to alternative agents, including macrolides, limit options.[52] A recent review of global quinolone resistance rates reports a much higher odds ratio for quinolone resistance in MDR-TB as compared to non-MDR-TB.[58] Such resistance is associated with the use of a second-line therapy including quinolone in the management of MDR-TB[58,59] and is attributed to inadequate treatment protocols.[60]

Mumbai is known to have a high proportion of MDR-TB with quinolone resistance and other severe forms of DR-TB,[61,62] and contributes 22% of TB cases reported in the state of Maharashtra.[36,63] In that light, our study showed some promise with management of the disease across case types. The high burden of drug resistant TB in Mumbai is reflected in the prevalence of quinolone prescribed. In Patna, 511 of 2,732 (19%; 95% CI: 17-20%) interactions resulted in the prescription of a quinolone vs. 238 of 3,953 (6%; 95% CI: 5-8%) in Mumbai, and our multivariate model also showed that providers were less likely to prescribe a quinolone in Mumbai (weighted aPR 0.35, 95% CI: 0.24-0.52) compared to Patna. Regulation of antibiotic sales is known to be tighter in Mumbai than Patna, and that might explain some of the results we found.

In poor health systems where there is a gap in vaccine coverage, hygiene practices, and health education of communities, antibiotics are often used as a substitute for poor policy control and regulations to fill practice gaps in managing infections.[64] Such usage is promoted by physician behaviour and market forces. Moreover, physicians may be incentivized financially by pharma detailers in high TB burden countries.[65]

There is also the issue that private hospitals may also rely on the sale of medicines to generate income.[66] Inappropriate TB treatment by inadequately trained professionals, physicians, pharmacists, and allied health workers, particularly in the private sector, is common in weak healthcare systems.[66] In high TB burden countries, up to 30% of patients receive ciprofloxacin,[67] an agent not recommended for use in TB.[56]

Yet another contributor to the increased consumptions of quinolone and subsequent resistance healthcare systems is the lack of availability of reliable antibiotic susceptibility data,[64] both for MTB and for other bacterial infections; this gap is all the more apparent in the private sector where the scale of resistance to quinolones is difficult to ascertain. A combination of poor quality laboratory data, inadequate surveillance strategies, and imperfect awareness of resistance epidemiology among healthcare workers lead to the overuse of quinolone in respiratory illnesses.[68] Studies aimed at filling this gap in knowledge, especially in the private sector, would be essential in creating awareness and more evidence-informed practices for therapeutic regimens across respiratory infections.[68]

More corticosteroids were prescribed in the informal sector (weighted aPR 0.37, 95% CI: 0.23-0.58) compared to the formal sector. This is disconcerting given that undiagnosed presumptive TB cases, corticosteroids may also mask clinical symptoms of TB, delaying diagnosis of TB,[21] and the ubiquity of the informal private sector. Healthcare providers without formal medical training are several times more widespread and accessible than qualified doctors. For example, there are 30 informal providers for each public doctor in rural West Bengal[69] and, in rural areas, they are sought for up to 75% of primary care visits.[30] In addition, it has been shown that marginalised and impoverished communities disproportionately rely on informal providers, as costs of care and access barriers are much lower than formal providers.[70]

Despite its contributions and merits, this study has several limitations. While the study was a population-weighted assessment of average behaviours for these provider types and cities, it is possible that it was not statistically representative of the provider mix that patients face. Choices in provider visitation might be informed by gender, socio-economic status etc. and these patient-level arbiters of care decisions, could not be captured in this study design. Second, since we did not directly inquire on physicians' rationale for prescription, we were not able discriminate appropriate medicine use from misuse in a holistic sense. As alluded to previously, clinicians' judgement would play a role in either city context with care decisions

reflecting a balance between epidemiological likelihood, and valid fears of patient loss to follow-up, transmission potential etc. Third, what we observed only reflected what healthcare providers did when they came across a new patient seeking medical care in during an initial visit. SPs in this context have not yet been used to construct standardized measures that include follow-up visits to providers, therefore longitudinal assessment and understanding of provider behaviours of any given patient presentation, is impossible. Fourth, this study only extended to private practitioners in urban areas in India and cannot be extended to rural areas; these results and our corresponding interpretations may not be generalizable to contexts outside of other high-TB burden, urban cities in India. In addition, SP methodology, as deployed, cannot measure the quality of care received over the entire treatment phase of TB care, because they are not in fact ill. Therefore, if any clinical indicators are assessed during any visit, physicians might act contrary to indication – even when a medical diagnostic result is provided (e.g. if the provider sees a healthy patient who lives in a polluted city with no cough, or fever or visible weight loss, they may ignore abnormal chest X-ray results, etc.). Moreover, since a proportion of SP-provider interactions resulted in direct dispensing of unlabelled medicines, certain drugs could not be identified, thus potentially leading to underestimation of the extent of antibiotic and other medicine dispensation. Conducting chemical analyses of all loose pills to determine the fraction that was quinolone or corticosteroid would have been ideal, but this would have been cost prohibitive. Next, we were unable to correct for misclassification in our coding of the outcome; however, when we considered misclassification of the outcome, we saw no material difference in estimates, meaning that we are not very concerned that these would alter our interpretations at most, the non-differential misclassification of the outcome, would slightly temper the effect seen towards the null, but the magnitude of the effect would stay relatively similar. Finally, with the advent of the global SARS-CoV-2 global pandemic, the landscape of respiratory diseases worldwide has most likely changed since our study was conducted.[71-73]

3.8 CONCLUSION

In this study, standardized patient (SP) methodology was employed to shed light on prescription practices of corticosteroids and quinolones amongst private practitioners in urban India. One in ten SP interactions resulted in the use of quinolones and about one in twenty interactions resulted in the use of steroids. These might mask TB detection in the private sector. This study highlights the importance of monitoring of dispensation of both quinolones and corticosteroids, as both constitute potentially harmful consequences when deployed unnecessarily.

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S3-1

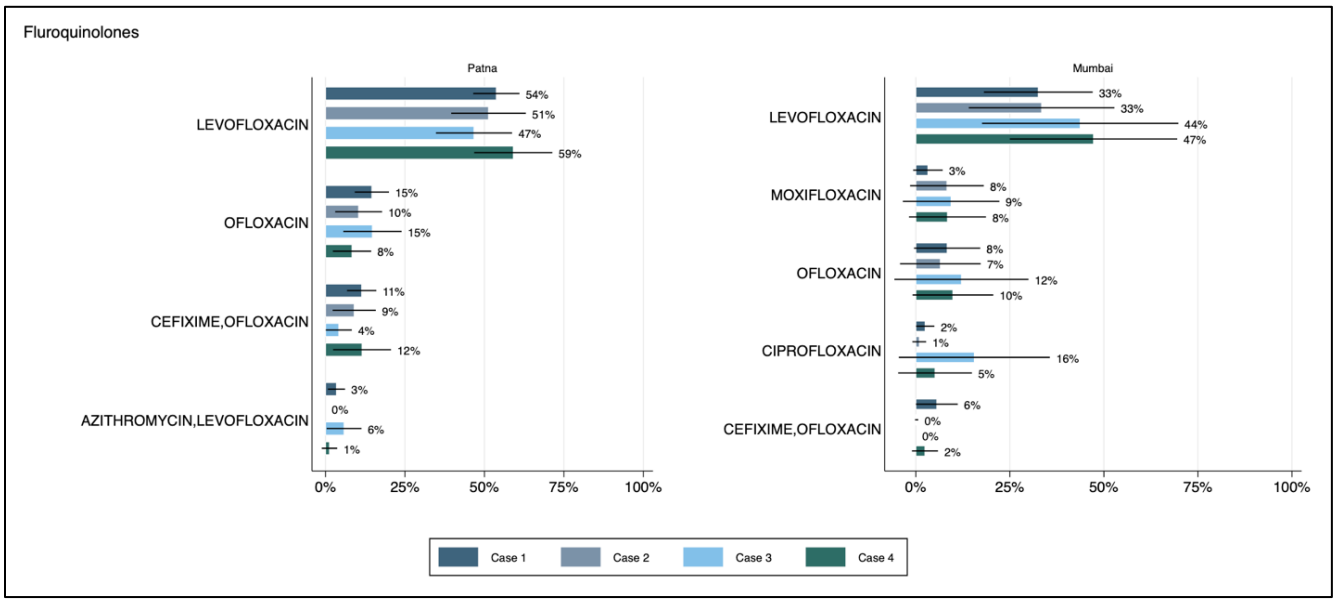
S3-Table 1: *Standardised patient case scenario descriptions.*

	CASE DESCRIPTION	PRESENTATION OF PATIENT	EXPECTED CORRECT CASE MANAGEMENT
CASE 1	Classic case of presumed tuberculosis with 2–3 weeks of cough and fever	Presents with presumptive tuberculosis, for the first time, to a private health-care provider, saying "Doctor, I have cough that is not getting better and some fever too"	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 2	Classic case of presumed tuberculosis in a patient who has had 2–3 weeks of cough and fever. The patient has taken a broad-spectrum antibiotic (amoxicillin) given by another health-care provider for 1 week with no improvement. He also carries an abnormal chest CXR suggestive of tuberculosis	Presents after an initial, failed (empirical) treatment for symptoms with broad-spectrum antibiotics and a diagnostic chest CXR, saying "I have cough and fever which is not getting better. I went to a doctor and took the medicines he gave me and have also had an CXR done." The chest CXR and blister pack for the antibiotics are shown if the provider asks	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 3	Chronic cough with a positive sputum smear report for tuberculosis from a public health facility	Presents with evidence of microbiologically confirmed tuberculosis, saying "I am having cough for nearly a month now and also have fever. I visited [the local government hospital] and they gave me some medicines and did a sputum test." The sputum report is shown if the provider asks	Either referral to a public DOTS center, a qualified provider or specialist, or (in the case of a qualified private provider) initiation of treatment with standard, four-drug, first-line anti-tuberculosis therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol [the HRZE regimen])
CASE 4	Chronic cough and, if asked, elaborates a history of previous, incomplete treatment for tuberculosis, which would raise the suspicion of multidrug-resistant tuberculosis	Presents as a previously treated patient with tuberculosis with recurrence of the disease (i.e., suspicion of drug resistance), saying "Doctor, I am suffering from a bad cough. One year ago I had got treatment in [the local public hospital], and it had got better. But now I am having cough again"	Recommendation for any drug-susceptibility test (culture, line probe assay, or Xpert MTB/RIF MTB/RIF) or referral to a public DOTS center or qualified provider

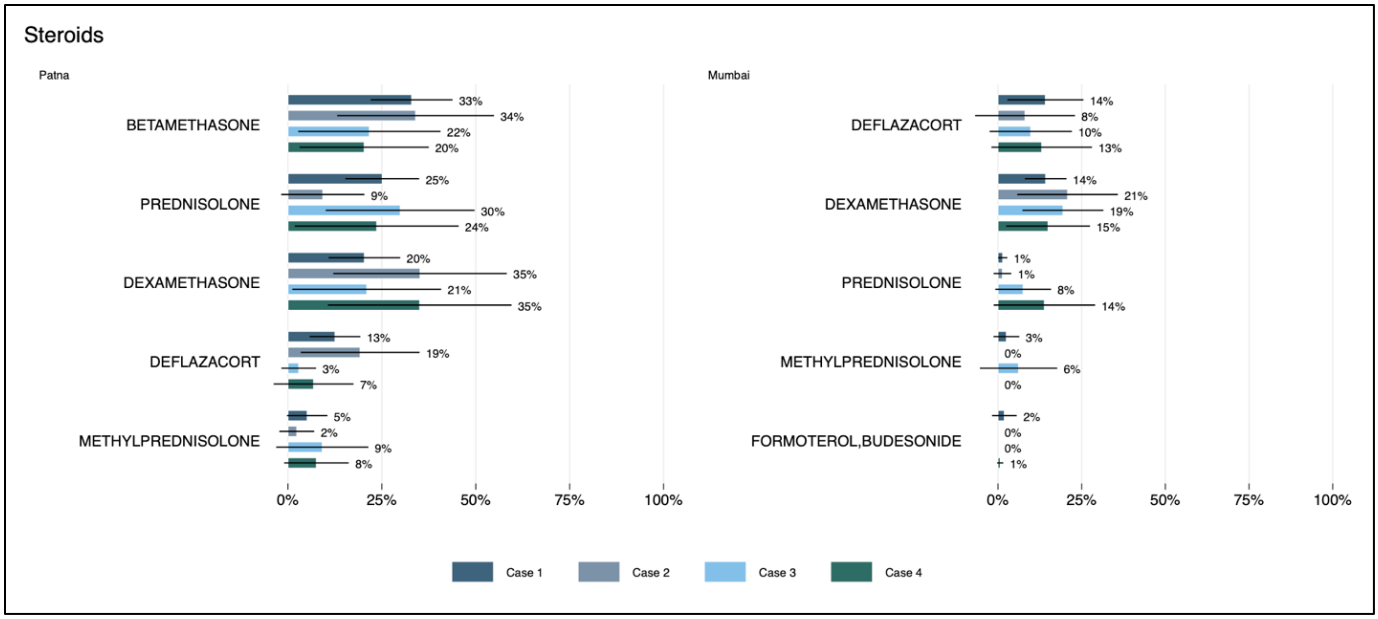
S3-Table 2: *Sampling and weighting distributions for all case types within all providers surveyed by round.*

		WEIGHTING GROUP							
ROUND	Case	Patna Informal Non-PPIA	Patna Informal PPIA	Patna Formal Non-PPIA	Patna Formal PPIA	Mumbai Informal Non-PPIA	Mumbai Informal PPIA	Mumbai Formal Non-PPIA	Mumbai Formal PPIA
		n *weight*	*n* *weight*	*n* *weight*	*n* *weight*	*n* *weight*	*n* *weight*	*n* *weight*	*n* *weight*
ROUND 1 (2014-2015)	Case 1	91	93	253	136	412	87	134	171
	-	0.003713	0.000893	0.002042	0.00046	0.001136	0.000422	0.003538	0.000124
	Case 2	20	20	70	28	104	21	69	53
	-	0.016892	0.004152	0.007379	0.002236	0.0045	0.001747	0.006872	0.0004
	Case 3	20	20	77	33	103	22	28	51
	-	0.016892	0.004152	0.006708	0.001897	0.004543	0.001667	0.016934	0.000416
	Case 4	18	20	85	35	206	44	30	101
	-	0.018769	0.004152	0.006077	0.001789	0.002272	0.000834	0.015805	0.00021
ROUND 2 (2016-2018)									
	Case 1	55	57	215	89	383	87	117	156
	-	0.006143	0.001457	0.002402	0.000703	0.001222	0.000422	0.004053	0.000136
	Case 2	27	28	112	45	92	22	76	60
	-	0.012513	0.002966	0.004612	0.001391	0.005087	0.001667	0.006239	0.000354
	Case 3	30	27	107	45	101	18	41	51
	-	0.011261	0.003076	0.004827	0.001391	0.004633	0.002038	0.011564	0.000416
	Case 4	25	29	105	43	190	47	41	93
	-	0.013514	0.002864	0.004919	0.001456	0.002463	0.00078	0.011564	0.000228
ROUND 3 (2019-2020)									
	Case 1			189	81			122	155
	-			0.004719	0.001334			0.007846	0.000276
	Case 2			94	41			90	57
	-			0.009488	0.002636			0.010635	0.000752
	Case 3			90	40			86	52
	-			0.00991	0.002702			0.01113	0.000824
	Case 4			98	41			100	80
	-			0.009101	0.002636			0.009572	0.000535

S3-Figure 1: *Example of quinolones and corticosteroid prescribed to SP presenting as case 3.*



S3-Figure 2: *Most common quinolone prescriptions by case and city.*



S3-Figure 3: *Most common corticosteroid prescriptions by case and city.*

CHAPTER 4: ANTI-TUBERCULOSIS PRESCRIPTIONS IN THE PRIVATE INDIAN HEALTHCARE SECTOR: AN ANALYSIS OF TRENDS USING STANDARDISED PATIENT METHODOLOGY

4.1 PREFACE

My study in Chapter 3 outlined the patterns in prescribed corticosteroids and quinolones in two urban Indian settings and Chapter 2 indicated that approximately a quarter of patients seeking care with evidence of an abnormal CXR were prescribed ATT. I was next interested in understanding how frequently ATT was prescribed across various SP case presentations and what kinds of ATT regimens were prescribed.

In this manuscript, I report the results of a large analysis SP study, performed over multiple time point from 2014-2019. I once again employ standardized patient (SP) methodology to assess ATT prescribing practices in two urban Indian settings among private healthcare providers. I additionally describe concurrent prescription of ATT with certain medicines of interest.

This work is part of a larger series of papers to be published by the QuTUB consortium (https://www.qutubproject.org/), funded by the Bill and Melinda Gates Foundation. As such, the manuscript will soon be submitted for publication.

4.2 TITLE PAGE

Anti-tuberculosis prescriptions in the private Indian healthcare sector: an analysis of trends using standardised patient methodology

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4.3 ABSTRACT

Introduction

Understanding the private drug market for anti-tuberculosis treatment (ATT) and ensuring correct ATT regimens is critically important both from a public health perspective and for improving individual patient health outcomes.

Methods

We employed standardized patient (SP) methodology to assess ATT prescribing practices in two urban Indian settings among private healthcare providers. We additionally described concurrent prescription of ATT with certain medicines of interest. Making use of the standardized patient (SP) methodology, this study employs actors who present four different case to care providers in urban India. A total of 6,685 SP interactions were done over three survey rounds, from 2014 to 2020, in two cities. Estimates clustered standard errors at the provider level, and were inverse-probability-weighted based on the study sampling strategy, resulting in city-round-representative interpretations of all outcome measures.

Results

Across 6,685 interactions, ATT was prescribed in 418 (7%; 95% CI: 6-8%). When we consider the types of regimens typically prescribed for TB treatment, taking into account the underlying selection into our survey with weighting, we see that a majority of the prescriptions were made for a complete group 1 anti-tuberculosis treatment (ATT) regimen in the form a four-drug FDC of HRZE – some 236 of 418 (64%; 95% CI: 57-70%). Next, drugs were dispensed as a complete first line regimen with a two-drug FDC pill, supplemented with 2 additional loose pills (of varying composition, but typically of Rifampicin and Isoniazid). This prescribing pattern was seen amongst 67 of 418 (15%; 95% CI: 10-20%) of prescribed ATTs. Loose pills were prescribed in a minority of cases, 8 of 418 (2%; 95% CI: 0-4%).

Conclusion

Making use of data obtained from a standardized patient study, our results provide insights on the types of ATT typically dispensed in the Indian private healthcare sector. Promisingly, the data suggests that the vast majority of the regimens sold were four-drug, fixed-dose combinations, a preferred regimen format. Continuing to monitor that this trend holds true across India is of the upmost importance, as medicine formats are critical in minimizing prescription errors, and simplifying TB treatment regimens.

4.4 INTRODUCTION

Worldwide, it is estimated that private markets deliver millions of doses of anti-TB drugs.[1] Understanding the private drug market for anti-tuberculosis treatment (ATT) and ensuring correct ATT is critically important both from a public health perspective and for improving individual patient health outcomes. This is because private health sector is dominant in 7 of the top 10 countries ranked by TB incidence.[2] In these seven countries, home to 57% of global TB incidence and over 62% of missing cases, private providers are the destination for an average of 75% (range: 67-84%) of initial care seeking, and private expenditure represents 61-74% of total expenditure on health with private markets delivering 15-54% of total anti-TB drugs.[2] Yet, private notifications represent just an average of 23% (range: 12-28%) of total notifications and 16% (range: 3-21%) of estimated incidence.[2]

While in the public sector TB treatment practices are typically based on World Health Organization (WHO) recommendations, centrally approved and uniformly applied by National TB Programs (NTP), no such consistency can be found in the highly fragmented private sector where decision-making is made at the healthcare provider and/or patient level and may not always be entirely evidence based.[3] The private medicine markets are usually unregulated, with scant procedures in place to monitor and ensure evidence-informed prescribing patterns for TB regimens.[3] The consequences of this can be grave, from heightened risks of patient mortality to creating threats for developing drug resistance.[4]

One way to limit the emergence of drug resistance attributable to inadequate or incorrect drug intake is with the introduction of simplified short-course multidrug chemotherapy in the form of fixed-dose combinations (FDCs). The use of FDC tablets against tuberculosis is recommended by WHO as a tool to help ensure effective treatment of tuberculosis patients as they simplify the prescription of drugs, reduce pill burden, and improve the management of quality-assured drug supply.[5] Patients prescribed these pills have to take considerably fewer pills (3-4 individual pills instead of 9-16 individual pills per day in the intensive phase), thus making treatment easier, aiding adherence, and limiting the risk of drug-resistant tuberculosis arising as a result of inappropriate drug selection, under-dosing, and monotherapy.[6]

In India, it is estimated that 54% of annual TB first line treatment course equivalents were sold through non-NTP channels, i.e. the Indian private sector.[7] One study has shown that the lion's share of TB

treatment was dispensed not as separate drugs, but rather as combination pills, accounting for over 96% of private sector TB treatment in 2017.[7]

These findings were based on drug sales and should be corroborated with alternative means. In this study, we employ the standardized patient (SP) methodology to assess ATT prescribing practices in two urban Indian settings among private healthcare providers. We additionally describe concurrent prescription of ATT with certain medicines of interest.

4.5 METHODS

Context

The data collection methods used are described in greater detail in survey report conducted at baseline.[8] Briefly, the Bill and Melinda Gates Foundation (BMGF) India Country Office along with city and state governmental partners, have implemented two Private Provider Interface Agency programs in Mumbai and Patna since 2014 in an effort to increase case notifications and improve TB management by engaging private sector actors. It is within this larger context that a quality of care surveillance project was conducted by our team (PIs: Pai and Das), in both cities, funded by BMGF. Throughout, we retained the full sample of healthcare providers, not distinguishing between those in the PPIA and those outside, as they were not the focus of this study.[9,10] The program is only referenced here since the weighting scheme employed to reach representative sample was based on participation in the PPIA program. Initial analysis of program-desegregated data are currently in progress and can be found in an unpublished brief to the BMGF.[11]

Patna is the capital of the state of Bihar and one of India's least developed states, with a recorded per capita income of 30,441 INR (US$412). The population of urban Patna is 2 million.[12] Mumbai, in contrast, is the relatively wealthy and cosmopolitan capital of the state of Maharashtra. As per the latest census (2011), it is home to 12 million inhabitants, with an annual per capita income of 180,000 INR (US$2,440).

The recent national prevalence survey estimated the prevalence of TB in Maharashtra state to be 161 per 100,000 population, and 327 per 100,000 for Bihar state. The overall national prevalence was estimated to be 316 per 100,000.[14] The National TB Prevalence Survey (2019-21) also reported that there were many

missing TB case in 2021; it was found that in Bihar 3.15 TB cases missed per 1 case notified to the public system. In Maharastra, the number of missing cases was 0.86 for every case notified.[14] In 2019, 106,189 and 191,294 patients with TB were officially notified in Bihar and Maharashtra, respectively.[13] Within the public sector, in Bihar, 43,139 (40.6%) cases were confirmed via microbiological confirmation whereas 79,039 (41.3%) were confirmed in Maharashtra.

Both cities have government-run public clinics and hospitals, but it is within the largely unregulated private sector where most patients decide to seek care. It is important to note that the structure of the private sector is very different between both these cities. Informal providers in Mumbai are mainly AYUSH (Ayurveda, Unani, Siddha, homeopathy) practitioners while in Patna informal providers tend to be those with other or no qualifications at all. Formal providers in Patna who are MBBS-qualified tend to operate detached, single-provider clinics, whereas in Mumbai, they additionally work in numerous multi-provider facilities or in hospitals. These sites generally contain a mix of MBBS providers, specialists with higher qualifications as well as AYUSH practitioners.

Study Design

We analyzed unique SP data collected in three survey rounds in two cities, Patna and Mumbai, to investigate patterns in ATT prescribing practices across healthcare providers, in cases of presumed or confirmed TB. Data was collected from a quality of TB care surveillance study from 2014-2019 – the first round was from 2014-2015, the second 2016-2018, and the final round 2019-2020.

Case Presentations

In each round of data collection, SP actors were trained to portray four different health presentations as designed by a multidisciplinary team of medical anthropologists, epidemiologists, health economists, and local clinical experts, the methods of which are described elsewhere.[8,20]

Case presentations are detailed in Appendix (S4-Table 1). In sum, case 1 consisted of a classic symptomatic case of presumptive TB who had had 2-3 weeks of cough and fever. Case 2 was a presumptive TB case who had had 2-3 weeks of cough and fever, but additionally presented with a completed CXR and 1 week of broad-spectrum antibiotic treatment ordered by another provider, with no improvement – this SP case was the primary focus of our analysis. The SP carried a digital chest X-ray dated within the last 10 days with evidence of abnormalities, and the blister pack of amoxicillin with him/her. The SP began the

interaction by saying: “Doctor, I have had cough and fever. It is not getting better, even though I went to a doctor and took medicines also.” Case 3 presented similarly to case 2 but additionally, carried a positive microbiological test (sputum microscopy). Case 4 presented as an adult with suspected multidrug resistant (MDR) TB with 4 weeks of cough and fever, and previous history of incomplete ATT.

SP Recruitment and Characteristics

Kwan et.al. previously outlined the recruitment of SPs, script development, SP training, provider sampling and assignment of SP case providers was previously outlined[8] and will thus not be described in detail here. Briefly however, locally recruited individuals were trained to portray pre-specified medical conditions using a standardized script with contextually and biomedically appropriate symptom descriptions.

Over the course of the three rounds in each of the two-cities, a total of 39 individuals (16 females and 23 males) were recruited and hired as SPs. A total of 13 of these individuals were hired as SPs in both cities, 17 were hired for Mumbai only and 9 for Patna alone.

In Patna, 22 individuals (10 female) conducted fieldwork and within these interactions, 18 SPs (6 female) were case 1, 7 SPs (4 female) were case 2, 7 SPs (3 female) were case 3, and 7 SPs (3 female) were case 4. SPs were originally from the states of Bihar (18), Delhi (2) and Madya Pradesh (2). Primary languages spoken by the SPs included Angika (3), Bengali (1), Bhojpuri(4), Hindi (7), Maithili (1), Malwi (1) and Magahi (5).

In Mumbai, 30 individuals (11 female) conducted fieldwork between April 2015 to December 2019. For these interactions, 20 SPs (8 female) were case 1, 8 SPs (4 female) were case 2, 8 SPs (2 female) were case 3, and 12 SPs (3 female) were case 4. SPs were originally from the states of Bihar (9), Madhya Pradesh (3), Delhi (2) and Maharashtra (16). Primary languages spoken by the SPs included Angika (1), Bengali (1), Bhojpuri (1), Hindi (9), Malwi (1), Magahi (4), and Marathi (12).

The potential SPs underwent a health screening questionnaire and checkup. The resulting group of actors were of seemingly healthy status. This specification was important as it assured that the SPs had no apparent health conditions that could confound the case presentation and interaction with healthcare providers. While the SPs were specifically recruited to fit each case scenario and corresponding narrative, they differed in age, gender, height, and weight. The average age of all the SPs was 32. The youngest was

21 and the oldest was 58. The 23 males weighed 50 to 76 kilograms and were 1.55 to 1.84 meters tall; the 16 females weighed 46 to 73 kilograms and were 1.42 to 1.67 meters tall.

Sampling Framework

The primary data collection for this study in Mumbai and Patna was conducted by urban TB programs funded by the Bill and Melinda Gates Foundation (BMGF) and implemented by Private Provider Interface Agencies (PPIAs) in each city. These PPIAs were World Health Partners (WHP) in Patna and PATH in Mumbai. Each of these organizations was mapping, recruiting, and enrolling private sector providers into provider networks in both cities. A lane-by-lane mapping exercise resulted in a list of private sector providers in Mumbai and Patna and this resulting universe was then restricted based on eligibility criteria for the SP study: providers eligible for the study were those who were known to see adult outpatients with respiratory symptoms in the private health sector. The description of the program serves to support sampling weights applied to achieve the urban area estimates for Mumbai and Patna (described below).

Overall, 6,685 SP visits (case 1: 3,083, case 2: 1,129, case 3: 1,042, case 4: 1,431) at 1,321 providers in Patna and Mumbai were completed over a 4-year period. During the first round of data collection, 2,655 visits were made (Patna: 1,019; Mumbai: 1,636). When the second round was conducted 2,614 SP visits (Patna: 1,039; Mumbai: 1,575). In the last round of data collection, 1,416 SP visits (Patna: 674; Mumbai: 742) took place.

In total 5,675 medicines were prescribed or dispensed across all case presentations and cities. The sampling and weighting distributions for all case types by provider type are detailed in the supplementary (S4-1).

Weighting

Based on the sampling strategy outlined above, the city-level estimates of the behavioural characteristics in Mumbai and Patna extrapolate from the sampling frame to the full population of private healthcare providers in each city. To calculate averages and differences within and across cities, we utilized inverse probability weights to satisfy the following:

1. Each city-case combination (Patna case 1, Mumbai case 2, etc.) has a total sum of weights equal to one. Therefore, each case is equally weighted within each city, and the two cities have equal total weights.

2. Within each city-case combination, the sum of weights for (A) MBBS-qualified (formal) and above and (B) non-MBBS-qualified (informal) providers is exactly equal to each group's prevalence in the city as a whole.

3. Within each city-case-qualification group, the relative total weights for (A) PPIA and (B) non-PPIA providers are exactly proportional to each group's prevalence in that city and qualification stratum.

4. Each round of the study, are exactly proportional to the number of interactions completed in each round.

By satisfying these conditions, the weight on each interaction is calculated such that our estimates take the values that they would have had if we had sampled exactly at random from the city as a whole, assuming that our sample is representative of that provider mix. There are 96 weighting groups: one for each city, case, qualification, PPIA status, and round (2 *4 *2 * 2 * 3).

Under the assumption that the providers we sampled from our sampling frames are representative of similar providers throughout the city, the resulting estimates are thus representative of the choice of a random provider within the city for each case presentation. Thus, when a statistic is to be reported in this study in the form "X of Y interactions (N%)", Y is the whole number of interactions observed, X is the whole number of interactions in which the outcome occurred, and N is the population-level estimate calculated using the weights detailed above.

Statistical analysis

We report proportions of dispensed ATT computed using inverse probability weighting with corresponding 95% CIs. The weights were calculated such that each of the 96 city-case-round combinations contributed equally to overall estimates and corresponded to the sampling framework of private sector providers listed from the mapping exercise in both cities. All estimates were clustered standard errors at the provider level, and inverse-probability-weighted based on our sampling strategy to

arrive at city-round-representative interpretations of our outcome measures. In order to look at time trends between rounds, we conducted weighted pair-wise t-tests and linear regressions to test for time trends. Reported estimates represent the expected likelihood of the outcome occurring if a provider were chosen at random from the population of providers within each respective city and within each round's time period. All data analyses were performed with Stata 15 (Stata, College Station, TX).

Identification of medicines

Labeled medicines dispensed and prescriptions given to the SPs were coded into pre-determined categories of interest (e.g., corticosteroids, antibiotics). In order to assess drug use, all labelled medicines prescribed by the pharmacies were digitized and stored and then coded by three co-authors with expertise in TB (AS & AS) and infectious diseases (GS). Blinded from any provider identifying details, they identified and categorized medicines as steroids, anti-TB drugs, fluoroquinolones, or other broad-spectrum antibiotics under maker-checker procedure, whereby dual-approval was needed by two separate people for each coding. Quinolone antibiotics were defined as Anatomical Therapeutic Chemical (ATC) codes beginning with J01M, and corticosteroids, both inhaled and systematic, defined as ATC codes beginning with H02, R01, or R03. Anti-tuberculosis treatment (ATT) was defined as the dispensation of any of the four group 1, i.e. first-line oral anti-TB drugs: Isoniazid, Rifampicin, Ethambutol or Pyrazinamide. When we examined these ATT regimes, we defined them based on their composition but not based on the dosages. While dosages are important, accurate data were not available in this regard, so we solely focused on composition. We also differentiated between "complete" vs. "incomplete" regimens, with the former indicating that the provider had not indicated all four drugs within the group 1 first-line oral anti-TB drug classification. The category "other antibiotic" included all antibiotics other group 1 ATTs and quinolones. We also had an additional category indicated as "unknown"; for these medicines, the brand or generic name of the medicine in addition to its component salts, were not known. Therefore, they were designated as ATT regimens of unknown composition.

Discrepancies in categorization between coders were resolved by consensus. Finally, loose or unlabeled pills were dispensed in some interactions, and we made no further attempts to identify them as it was not feasible to perform chemical assays at scale.

Patient and Public Involvement

While our study aligns with patient-centred care, no tuberculosis patients were involved in study recruitment or conduct.

Ethics

Ethical approvals for this study were granted by the McGill University Health Centre in Montreal, Canada (REB No. 14-137-BMB) and the Subcommittee for the Ethical Approval of Projects at the Institute for Socioeconomic Research on Development and Democracy in Delhi, India.[21] Ethics committees approved a waiver from obtaining informed consent from providers in Patna and Mumbai under the Government of Canada Panel on Research Ethics, as well as a recent study by Rhodes and colleagues (2012) on ethical aspects of standardized patient studies commissioned by the US Department of Health and Human Services,[22] and study specific rational of waiver is detailed elsewhere.[8] All individuals who participated as standardised patients were hired as staff and trained to protect themselves from any harmful medical interventions, such as avoiding injections, invasive tests, or consuming any drugs.

4.6 RESULTS

Across both cities, 6,685 interactions were completed: 2,732 in Patna and 3,953 in Mumbai. There were 3,083 presentations of case 1, 1,129 of case 2, 1,042 of case 3 and 1,431 of case 4. An ATT was prescribed in 418 of 6,685 (7%; 95% CI: 6-8%) SP interactions.

These interactions resulted in the prescription of 5,675 medicines in total; Table 4-1 shows the ATT medicines that were prescribed and dispensed across both cities. Across interactions, ATT was prescribed in 418 of 6,685 (7%; 95% CI: 6-8%); 167 ATT regimens were prescribed/dispensed in Patna vs. 251 in Mumbai.

Table 4-1: *ATT prescriptions by case and city.*

		SP CASE				
CITY	ATT (Anti-TB treatment)	SP1	SP2	SP3	SP4	**Total**
PATNA						**2284**
	ATT Prescribed/dispensed	0	76	82	9	167
	None	1162	306	288	361	

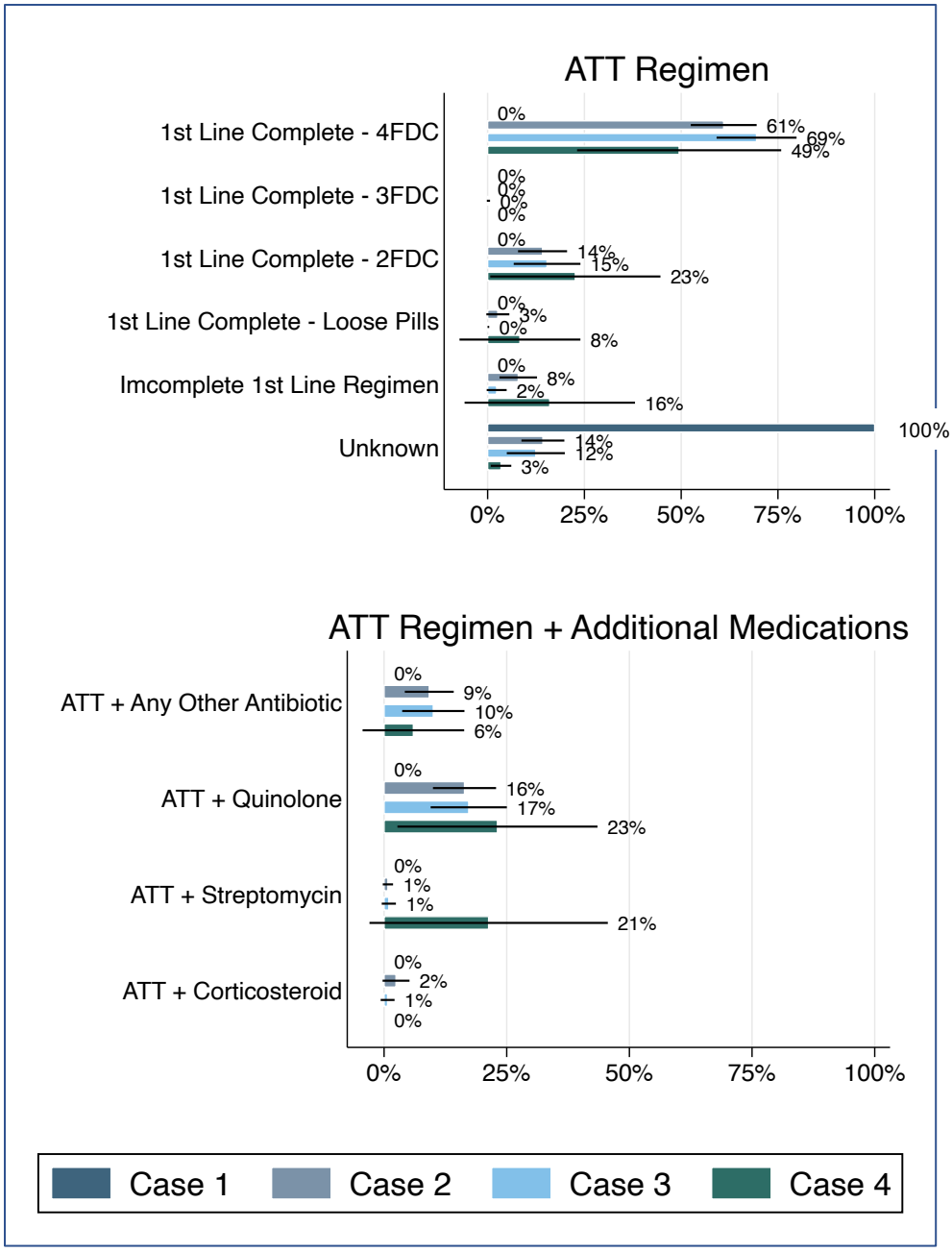
MUMBAI						**3391**
	ATT Prescribed/dispensed	1	137	79	34	251
	None	1717	348	313	762	
		2880	867	762	1166	**5675**

It was reassuring to note virtually no ATT prescriptions among SP1 cases (presumed or suspected TB). But ATT use increased among SP2 cases (SPs with TB symptoms and abnormal CXR), and SP3 cases (confirmed TB cases).

When we consider the types of regimens typically prescribed for TB treatment, taking into account the underlying selection into our survey with weighting, we see that a majority of the prescriptions were made for a complete group 1 anti-tuberculosis treatment regimen in the form of a four drug FDC of HRZE – some 236 of 418 (64%; 95% CI: 57-70%) – Figure 4-1. Next, drugs were dispensed as a complete first line regimen with a two FDC pill, supplemented with 2 additional loose pills (of varying composition, but typically of Rifampicin and Isoniazid) – this prescribing pattern was seen amongst 67 of 418 (15%; 95% CI: 10-20%) of prescribed ATTs. Loose pills were prescribed in a minority of cases, 8 of 418 (2%; 95% CI: 0-4%). The remaining pills were either of unknown composition (89 of 418 (13%; 95% CI: 9-15%)), incomplete (17 of 418 (6%; 95% CI: 3-10%)) or composed of a three salt FDC with the addition of a fourth drug to complete to regimen in of 1 of 418 instances (0%; 95% CI: 0-1%)).

When we examined how many ATT regimes were concurrently prescribed (Figure 4-1), we saw that in 5 of 418 (2%; 95% CI: 0-3%) of instances, corticosteroids were additionally added to a script. In addition, we saw that 58 of 418 (17%; 95% CI: 12–22%) of interactions where an ATT was prescribed, a quinolone was also indicated. Streptomycin – a group B second-line injectable agent recommended for the treatment of RR-TB and MDR-TB only under certain circumstances – was added to the ATT regimen in 14 of 418 (2%; 95% CI: 0-4%) and the addition of any antibiotic other that an anti-TB drug or quinolone was seen in 36 of 418 (9%; 95% CI: 6-13%) of interactions.

In the appendix we can see these prescription patterns segregated by city (S4-Figure 1).

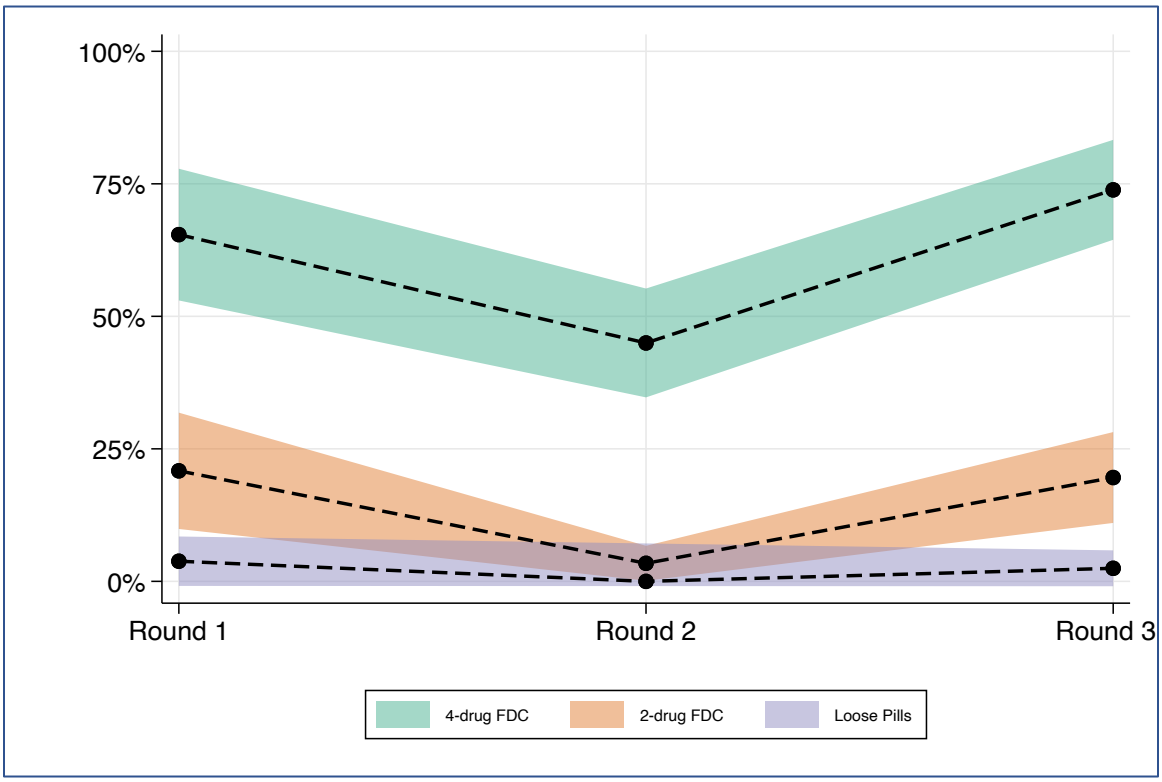


ATT=anti-tb treatment; FDC=fixed-dose combination.

Figure 4-1: *Proportions of ATT regimen by case type and proportions of medicines prescribed in addition to ATT.*

We then considered the different format of ATT prescribed over time amongst ATT regimens of known composition and all four group 1 ATT medicines indicated (Figure 4-2). We see that 4-drug FDCs changed from 72 of 125 (65%; 95% CI: 53-78%) at baseline to 60 of 161 (45%; 95% CI: 35-55%) and finally to 104 of 132 (74%; 95% CI: 64-83%) in the final round of data collection. The proportion of 2-drug FDCs was 40 of 125 (21%; 95% CI: 10-32%) at baseline, 5 of 161 (3%; 95% CI: 0-7%) at midline and finally, 22 of 132 (20%;

95% CI: 11-28%) at endline. Prescription/dispensation of loose pills went from 6 of 125 (4%; 95% CI: -1-9%), to 0 of 161 (0%; 95% CI: 0-0%) and finally to 2 of 132 (2%; 95% CI: 1-6%). None of these portrayed any evidence of statistically significant trends over time.



ATT=anti-tb treatment; FDC=fixed-dose combination.

Figure 4-2: *Changes in ATT regimen types over time. Round 1: 2014-2015, round 2: 2016-2018, round 3: 2019-2020, amongst complete ATT regimens of known composition.*

4.7 DISCUSSION

The results of our analysis shed light on the types of ATT are prescribed or dispensed in the Indian private healthcare sector in two urban centers. Making use of data obtained from standardized patient methodology, we were able to ascertain what a typical provider in each of these urban settings generally prescribes. While some historical studies have shown some disconcerting evidence of inappropriate treatment regimens in the Indian private sector, with one study indicating vast heterogeneity in regimens to presumptive patients,[23,24] our study is suggestive of an improvement in prescription practices for TB compared to these previous studies; the majority of providers prescribed the standard, four-drug (HRZE), fixed-dose combinations, rather than loose pills in their prescription of ATTs. These findings are consistent

with more recent literature suggesting private providers overwhelmingly prescribing combination products, i.e. FDCs.[7] Such dosage forms are critical in minimizing prescription and dosing errors, and simplifying TB treatment regimens.[25]

The use of standardized patients in our study allows us to reflect on actual real-world practice. This is in contrast to other studies where intent and knowledge rather than practice was evaluated. In such studies, practitioners were asked to write a prescription and specify drugs, dosage and duration of treatment based on clinical vignettes, then assessed the appropriateness of the regimens.[23,24] In a more recent study conducted in Mumbai city, the main question posed to private practitioners was *"Please write a prescription for a previously untreated adult case of sputum-positive pulmonary tuberculosis weighing 50 kg"*. In addition, practitioners were also asked a question to understand their prescribing practices in the treatment of MDR-TB (*"Please write a prescription for a previously untreated adult case of multidrug-resistant tuberculosis resistant to isoniazid and rifampicin and weighing 50 kg"*). Survey questionnaire administered to practicing general practitioners attending a continuing medical education programme in India indicated that only 6 of the 106 respondents wrote a prescription with a correct drug regimen and 106 doctors prescribed 63 different drug regimens. There was tendency to overtreat with more drugs for longer durations.[23] This is problematic because poor prescribing practice is a major factor fuelling the MDR-TB epidemic.[26,27] Only 5 of the 106 respondents could write an appropriate prescription with a minimum of 3 new second-line drugs in the right doses for a right duration. The quality of prescriptions for MDR-TB was even more dismal than those for drug-susceptible TB; over a third of respondents only added a single second-line drug, this single drug being a quinolone in 70% of such prescriptions. This combination of MDR and additional quinolone resistance — pre-XDR TB — is a direct result of inappropriate and indiscriminate quinolone use and a majority of the prescriptions reported by the practitioners would serve only to amplify resistance.[23] Data from the same hospital in Mumbai reported 30% of all MTB cultures to be quinolone resistant.[28]

Our findings are in line with other studies which suggest that drugs sold in a single salt account for only a small proportion (2-3%) of overall TB treatment volumes in the private sector, and have remained roughly constant over time.[7] The dominance of blister-packed FDCs in the private TB drug market could have positive implications for future implementation of existing treatment adherence support mechanisms in the private sector, where, unlike the public sector, there is a lack of formalized adherence support for patients.[7] This is especially critical in the private sector. Group 1 anti-tuberculosis treatment regimens are

typically 6 months in duration, the dearth of treatment support for privately treated patients creates concern for treatment completion among privately treated patients. In an aim to address these concerns, novel adherence tools (e.g. 99DOTS, call centers, smart pill boxes) are being engineered specifically for use with blister packaging for FDCs to facilitate adherence support.[29] Such mechanisms are already widely available in India, where patients can have daily contact with a call-centre-based adherence tracking system.[29] These could be used even in the private context to address adherence monitoring to privately-notified TB patients, and are facilitated by the emergence of new, low-cost adherence support mechanisms.

The concurrent prescription of a quinolone or streptomycin in addition to an ATT regimen was seen in our study. Specifically, for case 4 (recurrent TB), we saw that providers added streptomycin to the regimen, often without a DST request; private providers may also consider streptomycin, even more than quinolones, as a first line drug, likely based on the past history of TB regimens. Thus, it seems that most MDR-TB patients are not receiving sufficient MDR-TB treatment in either the public or private sectors.[30] The finding of significant quinolone usage for both TB and non-TB indications is consistent with the increasing incidence of quinolone-resistant TB in certain countries.[28] As the demand for both quinolones and other second line drugs expands in the private sector, regulatory and oversight approaches will become all the more important to protect both lives and drugs.[3]

The Schedule H1 notification of the Government of India on August 30, 2013, an amendment to the Drugs and Cosmetics Rules of 1945, came into effect in March of 2014. This schedule imposes certain conditions in the dispensing of listed medicines, including ATTs, which are somewhat midway between Schedule H – which stipulates retail distribution only against a valid prescription – and Schedule X – that requires prescription in duplicate, separate license requirement and meticulous storage and dispensing records. The intention of this schedule is primarily to control the rampant use through over-the-counter (OTC) dispensing of antibiotics in India. People prefer to approach friendly neighborhood pharmacies for minor symptoms, which are more than ready to oblige by handing over small quantities of various drugs, including supply of antibiotics for 2-3 days, for immediate symptom relief.

Self-prescribing of antibiotics – when patients take antibiotics without first consulting a medical doctor by using leftover antibiotics from previous treatments or getting antibiotics at the pharmacy without a prescription – occurs commonly in India.[31] This increases the risk for resistance due to inappropriate or

unnecessary use. While this practice is likely done in good faith, the long-term consequences can be grave; easy availability coupled with irrational prescribing of antibiotics by doctors at all levels contributes to increasing resistance to antibiotics and increasing drug resistant TB cases in India.[32] The promotion of antibiotic stewardship is needed to curtail such use but the study of the impact of the enactment of Schedule H1 notification is difficult to ascertain.[31] One study conducted in Andhra Pradesh revealed that antibiotics continued to be sold without prescription, even after the education program on schedule H1. The SPs in this study successfully obtained antibiotics from 78% pharmacies and only 22% of pharmacists objected to dispensing antibiotics without a prescription.[33]

Despite contributing to some encouraging news about the improvement of ATT regimen dispensing in the Indian private sector, this study had several limitations to acknowledge. First, while the study was a population-weighted assessment of average behaviours for these provider types and cities, it was not necessarily statistically representative of the provider mix that patients face if patients choose to visit different types of providers on average and might not replicate in other settings; choices in provider visitation might be informed by gender, socio-economic status etc. and these patient-level arbiters of care decisions, could not be captured in this study design. Second, we did not directly inquire on rationale and thus may not be able distinguish appropriate medicine use from misuse in a holistic sense. Clinicians' judgement would play a role in either city context with care decisions reflecting a balance between epidemiological likelihood, and valid fears of patient loss to follow-up, transmission potential, etc. Third, observed practice only reflected what healthcare providers did when they came across a completely new patient seeking medical care in during an initial visit. SPs have not yet been used to construct standardized measures that include follow-up visits to providers, therefore longitudinal assessment and understanding of provider behaviours of any given patient presentation, is impossible. Fourth, this study only covered private practitioners in urban areas in India and cannot be extended to rural areas; these results and our corresponding interpretations may not be generalizable to contexts outside of other high-TB burden, urban cities in India. In addition, we were unable to perfectly differentiate between single pill FDCs and co-blistered drugs, though both have the advantage of simplifying TB treatment, compared with single salt (i.e. loose pill) formulations. Moreover, our data does not allow to determine dosage in an accurate way and variation in dosing practices within the private sector has been indicated in other studies.[23,24,34] This is due to the fact that most providers do not provide a script for ATT beyond a few weeks. We cannot therefore establish exact prescribing behaviors or the rationale behind those behaviors with our data. This shortcoming is however one that is important to address. The volatility in dosage patterns mimics that

previously seen in the public sector; even with standardized regimens, dosage errors can be common,[35] and dosage heterogeneity only raises the likelihood that private providers may make mistakes or that their patients will be confused. Just as WHO and the Global Drug Facility (GDF) helped to rationalize dosing in the public sector,[36] so regulators may be able to use market authorization to rationalize private markets. Some guidance from WHO on this issue, geared specifically to an audience of national regulatory authorities, would seem appropriate. Manufacturers may be persuaded via provider demand to only make the dosage strengths and formulations recommended by WHO or the NTPs.[37] Finally, with the ongoing COVID-19 global pandemic, the landscape of respiratory diseases worldwide has most likely changed since our study was conducted, and has most definitely worsened antimicrobial abuse in many settings.[38-40]

4.8 CONCLUSION

Making use of data obtained from standardized patient study, our results provide insights on the types of ATT typically dispensed in the Indian private healthcare sector. Promisingly, the data suggests that the vast majority of the regimens prescribed were four-drug, fixed-dose tablets, a preferred regimen format. Continuing to monitor that this trend holds true across India is of the upmost importance, as such medicine formats are critical in minimizing prescription errors, and simplifying TB treatment regimens.

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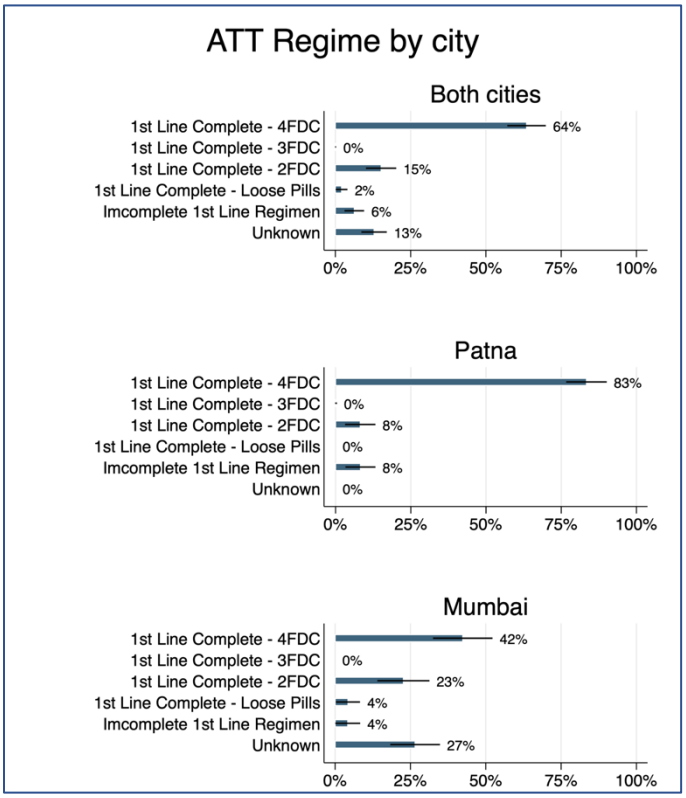
S4-1

S4-Table 1: *Standardised patient case scenario descriptions.*

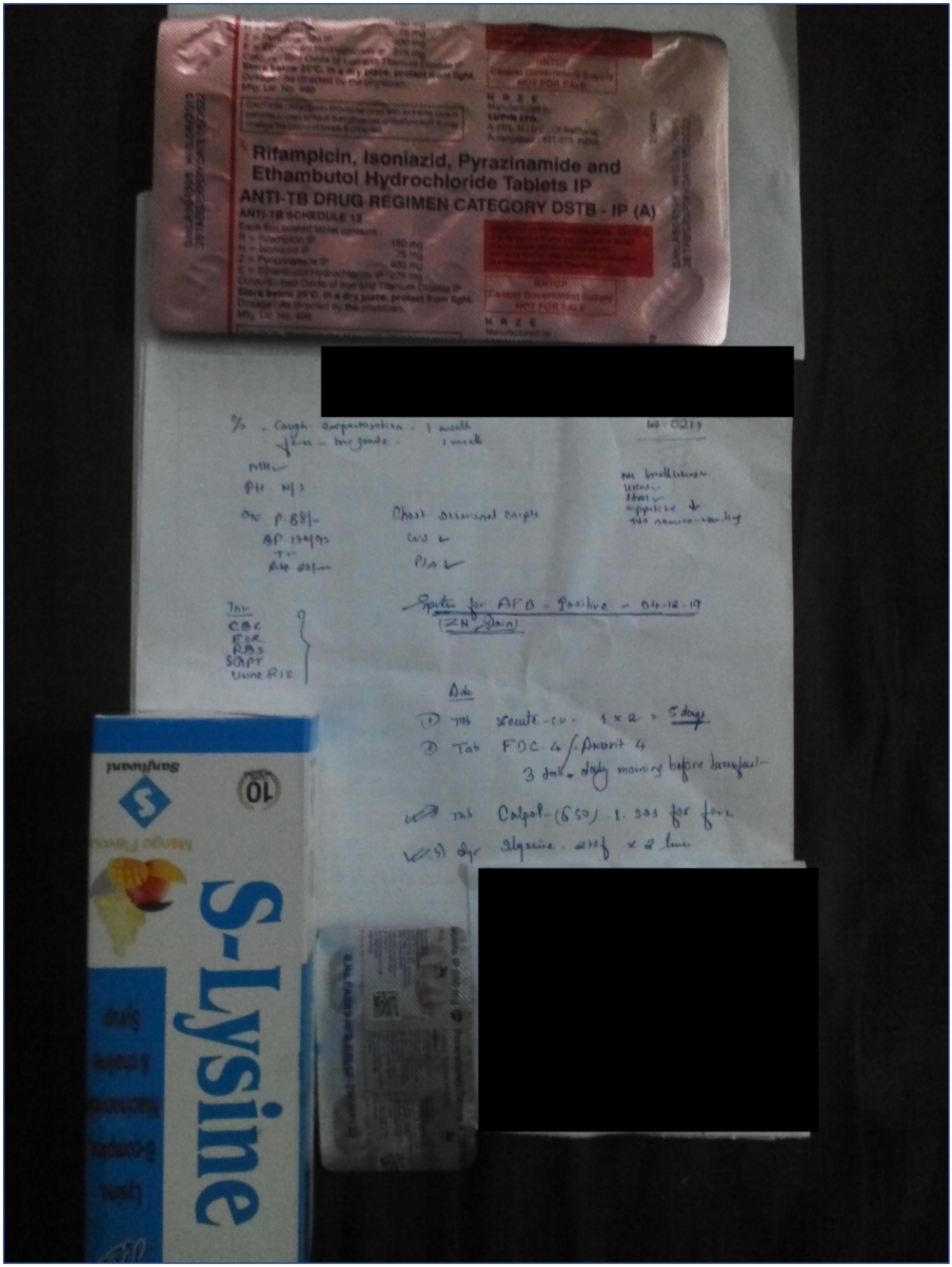
	CASE DESCRIPTION	PRESENTATION OF PATIENT	EXPECTED CORRECT CASE MANAGEMENT
CASE 1	Classic case of presumed tuberculosis with 2–3 weeks of cough and fever	Presents with presumptive tuberculosis, for the first time, to a private health-care provider, saying "Doctor, I have cough that is not getting better and some fever too"	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 2	Classic case of presumed tuberculosis in a patient who has had 2–3 weeks of cough and fever. The patient has taken a broad-spectrum antibiotic (amoxicillin) given by another health-care provider for 1 week with no improvement. He also carries an abnormal chest CXR suggestive of tuberculosis	Presents after an initial, failed (empirical) treatment for symptoms with broad-spectrum antibiotics and a diagnostic chest CXR, saying "I have cough and fever which is not getting better. I went to a doctor and took the medicines he gave me and have also had an CXR done." The chest CXR and blister pack for the antibiotics are shown if the provider asks	Recommendation for sputum testing, chest radiograph, or referral to a public DOTS center or qualified provider
CASE 3	Chronic cough with a positive sputum smear report for tuberculosis from a public health facility	Presents with evidence of microbiologically confirmed tuberculosis, saying "I am having cough for nearly a month now and also have fever. I visited [the local government hospital] and they gave me some medicines and did a sputum test." The sputum report is shown if the provider asks	Either referral to a public DOTS center, a qualified provider or specialist, or (in the case of a qualified private provider) initiation of treatment with standard, four-drug, first-line anti-tuberculosis therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol [the HRZE regimen])
CASE 4	Chronic cough and, if asked, elaborates a history of previous, incomplete treatment for tuberculosis, which would raise the suspicion of multidrug-resistant tuberculosis	Presents as a previously treated patient with tuberculosis with recurrence of the disease (i.e., suspicion of drug resistance), saying "Doctor, I am suffering from a bad cough. One year ago I had got treatment in [the local public hospital], and it had got better. But now I am having cough again"	Recommendation for any drug-susceptibility test (culture, line probe assay, or Xpert MTB/RIF MTB/RIF) or referral to a public DOTS center or qualified provider

S4-Table 2: Sampling and weighting distributions for all case types within all providers surveyed by round.

		WEIGHTING GROUP							
ROUND	Case	Patna Informal Non-PPIA	Patna Informal PPIA	Patna Formal Non-PPIA	Patna Formal PPIA	Mumbai Informal Non-PPIA	Mumbai Informal PPIA	Mumbai Formal Non-PPIA	Mumbai Formal PPIA
ROUND 1 (2014-2015)									
	Case 1	91	93	253	136	412	87	134	171
	-	0.003713	0.000893	0.002042	0.00046	0.001136	0.000422	0.003538	0.000124
	Case 2	20	20	70	28	104	21	69	53
	-	0.016892	0.004152	0.007379	0.002236	0.0045	0.001747	0.006872	0.0004
	Case 3	20	20	77	33	103	22	28	51
	-	0.016892	0.004152	0.006708	0.001897	0.004543	0.001667	0.016934	0.000416
	Case 4	18	20	85	35	206	44	30	101
ROUND 2 (2016-2018)	-	0.018769	0.004152	0.006077	0.001789	0.002272	0.000834	0.015805	0.00021
	Case 1	55	57	215	89	383	87	117	156
	-	0.006143	0.001457	0.002402	0.000703	0.001222	0.000422	0.004053	0.000136
	Case 2	27	28	112	45	92	22	76	60
	-	0.012513	0.002966	0.004612	0.001391	0.005087	0.001667	0.006239	0.000354
	Case 3	30	27	107	45	101	18	41	51
	-	0.011261	0.003076	0.004827	0.001391	0.004633	0.002038	0.011564	0.000416
	Case 4	25	29	105	43	190	47	41	93
ROUND 3 (2019-2020)	-	0.013514	0.002864	0.004919	0.001456	0.002463	0.00078	0.011564	0.000228
	Case 1			189	81			122	155
	-			0.004719	0.001334			0.007846	0.000276
	Case 2			94	41			90	57
	-			0.009488	0.002636			0.010635	0.000752
	Case 3			90	40			86	52
	-			0.00991	0.002702			0.01113	0.000824
	Case 4			98	41			100	80
	-			0.009101	0.002636			0.009572	0.000535



S4-Figure 1: *ATT regimen type by city.*



S4-Figure 2: *Example of ATT prescription given to SP in Patna.*

CHAPTER 5: USE OF STANDARDISED PATIENTS TO ASSESS TUBERCULOSIS CASE MANAGEMENT BY PHARMACIES IN PATNA, INDIA: A REPEAT CROSS-SECTIONAL STUDY

5.1 PREFACE

Chapters 2 to 4 outline care practices amongst physicians (both formally and informally trained). I was also interested in understanding how TB care was handled in urban pharmacy settings, since pharmacies are often the first point of contact for many patients in these settings. There have been numerous attempts to engage pharmacists in TB care, treatment education, and screening and referral in India and while this study is not aimed to parse out the individual impact of each respective intervention, we would expect them to have had an impact on practice amongst pharmacists.

In this manuscript, I assess 'over-the-counter' medical advice and drug dispensing practices of pharmacists for standardized patients presenting with classic symptoms of pulmonary TB and with those with sputum smear positive pulmonary TB disease and examine how practices have changed over time. I evaluate how and whether pharmacies are improving practices for suspected TB in 2019 compared to a baseline study conducted in 2015.

This work is part of a larger series of papers to be published by the QuTUB consortium (https://www.qutubproject.org/), funded by the Bill & Melinda Gates Foundation. As such, the manuscript will soon be submitted for publication.

5.2 TITLE PAGE

Use of standardised patients to assess tuberculosis case management by pharmacies in Patna, India: a repeat cross-sectional study

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5.3 ABSTRACT

Introduction

As the first point of care for many healthcare seekers in resource-restrained settings, private pharmacies are positioned to play an important role in case detection and referral of tuberculosis (TB). However, inappropriate management by pharmacies often contributes to delayed diagnosis and over-the-counter (OTC) treatments with previous studies in India showing that pharmacies commonly dispense cough syrups, bronchodilators, anti-histamines and broad-spectrum antibiotics OTC, rather than referring patients to the appropriate provider for TB testing and treatment.

Methods

In this study, we assessed medical advice and OTC drug dispensing practices of pharmacists for standardized patients presenting with classic symptoms of pulmonary TB (case 1) and for those with sputum smear positive pulmonary TB disease (case 2), and examined how practices have changed over time in a single, urban site in India. We examined how and whether pharmacies are improving practices for TB compared to a baseline study conducted in 2015 in the city of Patna. The proportion of interactions that resulted in correct or ideal management, as well as the proportion of interactions resulting in antibiotic, quinolone, and corticosteroid are presented, with standard errors clustered at the provider level. To assess the difference in case management and the use of drugs across the two cases by round, a difference in difference (DiD) model was employed.

Results

A total of 936 SP interactions were completed over both rounds of survey. Our results indicate that across both rounds of data collection, 331 of 936 (35%; 95% CI: 32-38%) of interactions were correctly managed. At baseline, 215 of 500 (43%; 95% CI: 39-47%) of interactions were correctly managed whereas 116 of 436 (27%; 95% CI: 23-31%) were correctly managed in the second round of data collection. Ideal management, where in addition to a referral, patients were not prescribed any potentially harmful medications, was seen in 275 of 936 (29%; 95% CI: 27-32%) of interactions overall, with 194 of 500 (39%; 95% CI: 35-43%) of interactions at baseline and 81 of 436 (19%; 95% CI: 15-22%) in round 2. No pharmacy dispensed anti-TB medications without a prescription. On average, the difference in correct case management between case 1 vs. case 2 dropped by 20 percent points from baseline to the second round of data collection. Similarly, ideal case management decreased by 26 percentage points between rounds. This is in contrast

with the dispensation of medicines, which had the opposite effect between rounds; the difference in dispensation of quinolones between case 1 and case 2 increased by 14 percentage points, as did corticosteroids by 9 percentage points, antibiotics by 25 percentage points and medicines generally by 30 percentage points.

Conclusion

Our standardised patient study provides valuable insights into how pharmacies in an urban Northern Indian city changed their treatment of patients with tuberculosis symptoms or with confirmed tuberculosis over a 5-year period. We saw that overall, pharmacy performance has weakened over time. Importantly, however, no over-the-counter dispensation of anti-TB medications occurred in either survey round. As the first point of contact for many care seekers, continued and sustained efforts to engage with Indian pharmacies should be prioritized.

5.4 INTRODUCTION

Tuberculosis (TB) is a leading infectious cause of death globally, with cases projected to rise even more due to the disruptions caused by the COVID-19 pandemic.[1] In 2020, 5.8 million new cases of TB were notified, though a substantial amount of cases were never detected, reported or offered appropriate treatment.[2] These "missing" patients, who are either undiagnosed or not notified to the TB programme, comprise around 4.1 million cases yearly and result in continued community transmission, undermining national and global TB control efforts.[3]

India has the world's highest burden of tuberculosis (TB) and "missing patients" globally.[2] In high-incidence settings, it has been shown that patients with TB frequently experience delays before obtaining a diagnosis.[4] On average, a patient with TB visits three providers, experiencing a delay of 55 days before being diagnosed and initiating TB treatment.[4,5] With over 750,000 retail outlets in India, private pharmacies could play an important role in case detection and referral with the potential to plug early leaks in the TB care cascade and reducing transmission and incidence, by strengthening the steps between symptom screening, diagnosis and case notification.[6,7] In India, private pharmacies are an attractive access point for medical services with their long operating hours, drug inventory, lack of queues and consultation fees.[8,9] Given their ubiquity, accessibility and trusted role in local communities,[10] pharmacies are frequently the first point of contact for patients soon after they develop symptoms of TB.[11-13] In this context, up to 40% of patients who were ultimately diagnosed with TB visited a private pharmacy prior to medical assessment and TB diagnosis, with 25% of patients continuing to seek advice from pharmacies even after diagnosis, preferring to avoid doctor consultations. [14-16]

While private pharmacies are positioned to play an important role in case detection and referral, inappropriate management often contributes to delayed diagnosis and TB-specific treatment.[14] Previous studies in India have shown that pharmacies commonly dispense cough syrups, bronchodilators, anti-histamines and antibiotics over-the-counter (OTC), rather than referring patients to the appropriate provider for TB testing and treatment.[17-19] Such practices of self-medication and poor referral practices can delay TB diagnosis.[4,5] Pharmacies that dispense inappropriate antibiotics to patients with TB may also contribute to the development of antimicrobial resistance (AMR). Private pharmacies have thus been identified as key stakeholders in both TB and AMR control efforts.[12]

In a standardized patient study by Satyanarayana et al. from our group conducted in 2015, it was found that while no pharmacy dispensed anti-TB medications without a prescription, 319 (27%) of 1,200 (95% CI: 24-29%) interactions resulted in broad-spectrum antibiotic dispensing, across all interactions.[18] The results also suggested that the use and misuse of antibiotics are influenced by drug category and the information that care seekers present. Findings also showed that 38% of the pharmacies dispensed antibiotics or corticosteroids to people with TB symptoms but no test results. In addition, there was dispensation of quinolones in 7% and corticosteroids in 5% of interactions.

Since this baseline study, there have been numerous attempts to engage pharmacists in TB care, treatment education, and screening and referral,[1,19-23] and while this study was not aimed to parse out the individual impact of each respective intervention, we did expect them to have changed practice amongst pharmacists in these settings to some extent.

In this study, we assessed over-the-counter medical advice and drug dispensing practices of pharmacists for standardized patients presenting with classic symptoms of pulmonary TB and for those with sputum smear positive pulmonary TB disease, and examined how practices have changed over time in Patna, surveying the majority of the same provider (92% same pharmacies). Specifically, we assessed how and whether pharmacies are improving practices for suspected TB compared to a baseline study conducted in 2015 compared to the same provider behaviours in 2019.[18]

5.5 METHODS

Context

Patna is the capital of the state of Bihar and one of India's least developed states, with a recorded per capita income of 30,441 INR (US$412). The population of urban Patna is 2.0 million city inhabitants. In 2019, 106,189 patients with TB were officially notified in Bihar.[1] Within the public sector, 43,139 (40.6%) cases were confirmed via microbiological testing. The National TB Prevalence Survey (2019-21) reported a TB prevalence of 327 per 100,000 in Bihar state, and also showed that there were many missing TB cases in 2021; it was found that 3.15 TB cases were missed per 1 case notified to the public system.[24]

Study Design

We assessed the medical advice and drug dispensing practices of pharmacies for standardised patients presenting with either presumptive TB (case 1) or microbiologically confirmed tuberculosis (case 2). By assessing the difference in antibiotic use across the two cases for the same pharmacists, we broke down the relative importance of antibiotic misuse arising from the lack of diagnosis (case 1) versus antibiotic use despite a confirmed diagnosis for which antibiotics are contraindicated (case 2).

Assessing quality of TB care can be challenging. Many quality of TB care evaluations have relied on recall-based patient surveys, questionnaire surveys of knowledge, and prescription/chart analyses. Unfortunately, these methods are prone to significant biases and thus may not reflect genuine practice. To bypass these issues, standardized patients (SPs) are increasingly used in low-income countries to assess quality of medical care.[25-27] Compared to other methods, SP studies can provide an accurate assessment of provider practice that is free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of health care providers.[28,29]

To set the benchmark for what pharmacists should do when faced with such patients, the guidelines from the Government of India's TB Control program and the Indian Pharmaceutical Association were used.[30] These guidelines specify that pharmacies should counsel patients about tuberculosis, identify and refer persons with tuberculosis symptoms to the nearest public health facilities for tuberculosis testing, and play a part in the provision of tuberculosis treatment. Therefore, pharmacists adhering to these guidelines should have referred the standardised patients to healthcare providers without dispensing either antibiotics or corticosteroids, both of which require a prescription.

Recruitment of SPs, script development, SP training, provider sampling and assignment of SP case providers was previously outlined by Satyanarayana[18] and will thus not be re-described here.

Standardised Patient Presentations

Case presentations are summarized in Table 5-1. Standardised patients trained as case 1 presented to pharmacists with 2-3 weeks of cough and fever and sought relief directly from the pharmacy (i.e. seeking medicines). This case presentation could be indicative of TB or other chronic respiratory infections. While an antibiotic might be warranted for some of these conditions, giving one to the SP would not be correct management without a prescription from a doctor, rather, a referral for TB testing would be.

Standardised patients trained as case 2 presented with 1 month of cough and fever and a tuberculosis positive laboratory report from a recent sputum smear test from a government healthcare provider. While tuberculosis was indeed confirmed by the laboratory report, the standardised patients would present as a naïve patient, and make it clear that they did not fully understand what the report said. The pharmacist should in this situation recognize the futility of broad-spectrum, short-term antibiotic dispensation but could still offer them (e.g. if driven by profits) since the presenting SP has made their confusion with their diagnosis of TB clear.

Neither of the standardised patient cases presented with drug prescriptions. After each pharmacy visit, standardised patients were debriefed with a structured questionnaire within 1 h of the visit.

Table 5-1: *Standardised patient case descriptions.*

	Case description	**Presentation of standardised patient**	**Expected case management**
Case 1	Classic case of presumed tuberculosis with 2–3 weeks of cough and fever and directly seeking care from a pharmacist or pharmacist	Case 1 presents with the opening statement, "Sir, I have cough and fever that is not getting better. Please give me some medicine." At presentation, this case has had a 2–3 week cough, which occurred more during early morning and night, accompanied by a 2–3 week, on-and-off, low-grade fever. The patient was producing sputum that did not contain any blood. The case would admit to a loss of appetite and to his or her clothes becoming a bit loose if prompted by the pharmacist. If the pharmacist asked about taking medicines for this illness, the patient would say no	Verbal or written referral to a DOTS centre or a health-care provider without dispensing any antibiotics (including anti-tuberculosis drugs and quinolones) or corticosteroids
Case 2	Chronic cough with a positive sputum smear report for tuberculosis from a government dispensary and directly seeking care from a pharmacist or pharmacist	Case 2 presents with a positive sputum smear result visiting a pharmacist, presenting with the opening statement, "Sir, I am having cough for nearly a month now and also have fever." While showing a positive sputum report to the pharmacist, the patient continues, "I went to the government dispensary and they asked me to get my sputum tested. I have this report. Can you please give me some medicine?" At presentation, this case has had a cough for 1 month and produces sputum without blood, accompanied by a 1 month, on-and-off, low-grade fever, which was more during evening times. Similar to Case 1, the case would admit to a loss of appetite and to his or her clothes becoming a bit loose if prompted by the pharmacist. If the pharmacist asked about taking medicines for this illness, the patient would say no	Verbal or written referral to a DOTS centre or a health-care provider without dispensing any antibiotics (including anti-tuberculosis drugs and quinolones) or corticosteroids

DOTS=directly observed treatment, short-course.

SP Training

The training of SPs ensured that they (a) correctly presented the cases, (b) correctly recalled the interaction with the pharmacy staff, and (c) avoided detection. The first two aims were achieved through classroom training in case presentation and testing of recall, as well as mock interviews and dry runs that were supervised in the field. For the third aim, SPs were taught to avoid detection by the following methods. First, our recruitment strategy ensured that SPs came from low-income areas or slums from the same cities in which the project was located, and the areas from which they came were far from the field sites. This meant that their clothing, mannerisms, and speech were very close to the ordinary patients who visited pharmacists, but they would not have been personally known in the study areas. Second, previous observations in pharmacies and pharmacist shops were conducted by supervisors in order to observe the patterns of interaction (e.g., mode of address), and we ensured that SPs approximated those patterns of interaction. Third, during the training, SPs were taught to internalize completely the characters and the details of their mock stories through which the character was made alive to them. In mock interviews during training, supervisors would add unscripted questions with regard to family or neighborhood that SPs could answer spontaneously because they were of the actual social background that was being approximated in the characters they were portraying. Finally, dry runs were conducted in which the supervisor was present in the shop on the pretense of buying something such as toothpaste or an over-the-counter cough syrup and thus could watch the interaction and offer corrections later.

Selection of Pharmacies, Standardised Patient Visits and Study Size

In the 2014 round, SPs completed 395 interactions with pharmacies in Patna. In the repeat survey, standardized patients were sent to 260 randomly sampled pharmacies in Patna between October 2019 and January 2020, resulting in a fixed sample size of 805 additional interactions (1,200 between baseline and second survey). This sample size was large enough to allow a precise estimate of the outcome of interest using the Clopper-Pearson exact method (i.e. proportion of visits resulting in ideal management, assumed to be 10% of case 1 interactions 60% of case 2 interactions based on previous study)[15] within a confidence interval of 8.30-11.70% and 57.16-62.79%, respectively. If it is assumed that the various PPIA initiatives were effective and resulted in a 10% increase in correct management, this sample size would allow an estimate of the prevalence difference between 5.51-14.49% for case 1 and 4.33-15.67% for case 2.

In urban Patna (defined as Patna, Danapur, and Phulwarisharif blocks), a lane-by-lane mapping exercise conducted between January and August 2014 served as a complete list of pharmacies that were operating in these areas at the time. Additionally, urban TB programs implemented by Private-Provider Interface Agencies (PPIAs) were recruiting and enrolling pharmacists or pharmacist assistants into TB referral and treatment networks in Patna. The geographical frame covered all 40 wards in Danapur block, all 28 wards in Phulwari Shariff block, and 34 wards selected in collaboration with the PPIAs out of 73 wards in Patna block. For both of the random samples in Patna, we provided a reserve list, which could replace originally sampled pharmacists found to be permanently closed at the time of data collection for the purposes of surveillance. The same catchment area and mapping used in the baseline study (2014) was used in the survey in 2019; 92% of the providers visited at baseline were revisited in the 2019 survey.

Identification of Drugs Given by Pharmacists

Guidelines for pharmacies are specified under the Ministry of Health and Family Welfare's Drugs and Cosmetics Rules Act, 1945.[31] Schedule H and Schedule H1 contain all antibiotics and corticosteroids. Schedule H drugs cannot be given to patients without a prescription from a qualified medical practitioner. In 2013, regulations were further tightened, with anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) and some quinolones (such as moxifloxacin and levofloxacin, used in the treatment of tuberculosis) listed on a newly created Schedule H1. For H1 drugs, pharmacies require both a prescription from a qualified medical practitioner and a separate register to record the name and address of the prescriber, the patient, the names of the drugs and the quantity supplied.[32,33]

In order to assess drug use, at baseline, all labelled medicines prescribed by the pharmacies were digitized and stored and then coded by two doctors with expertise in TB (SS) and infectious diseases (RS). In the repeat survey, coding was replicated by a well-trained team of staff, who had worked on the previous survey. Blinded from provider identifying details, they identified and categorized medicines as corticosteroids, anti-TB drugs, quinolones, or other broad-spectrum antibiotics under maker-checker procedure, whereby dual-approval was needed by two separate people for each coding. Finally, loose or unlabeled pills were dispensed in some interactions, and we made no further attempts to identify them as it was not feasible to perform chemical assays of pills at scale.

Data Sources

All datasets from individual SP studies are freely accessible from Dr. Pai's QuTUB consortium (https://www.qutubproject.org/), funded by the Bill & Melinda Gates Foundation.

Definition of Main Outcomes

We operationalized our two main, binary outcomes in one of two ways. First, we defined correct case management as verbal or written referral to a DOTS centre or to a healthcare provider, regardless of medicines dispensed. We then defined ideal case management for both cases as a verbal or written referral to a DOTS centre or to a healthcare provider without dispensing any antibiotics (including anti-tuberculosis drugs and quinolones) or corticosteroids.

Statistical Analysis

The proportion of interactions that resulted in correct or ideal management, as well as the proportion of interactions resulting in antibiotic, quinolone, and corticosteroid, will be presented. The unit of analysis is a pharmacy-SP interaction irrespective of who (pharmacy owners, pharmacists, or pharmacy assistants) the standardised patient interacted with. Whether the case was correctly managed was assessed from a tuberculosis perspective, consistent with Standards for Tuberculosis Care in India and International Standards for Tuberculosis Care. We employed ordinary least squares regression to assess differences in outcomes by case.

To assess the difference in case management and the use of drugs across the two cases by round, a difference in difference (DiD) model was employed. DiD is a non-experimental statistical technique used to estimate treatment effects by comparing the change (difference) in the differences in observed outcomes between treatment and control groups, across pre-treatment and post-treatment periods.[34] It is commonly used to recover the causal effect of interest from observational study data — where the experimental design is out of the researcher's control and usually subjected to unobserved confounders and some form of selection bias. DiD is a combination of time-series difference – comparing outcomes across pre-treatment and post-treatment periods – and cross-sectional difference – comparing outcomes between treatment and control groups.[34] In this case, the treatment effect can be estimated by subtracting the average change in the control group from the average change in the treatment group.

With repeated, cross-sectional data gathered in our surveys, the regression model can be defined as:

$$y_{it} = \beta_0 + \beta_1 P_t + \beta_2 T_i + \beta_3 (P_t * T_i) + u_{it}$$

where *y* is the outcome of interest (ideal or correct case management for instance), *P* is a dummy variable for the second round of data collection in our survey and *T* is a dummy variable for the treatment group – i.e. cases 1 or 2. The interaction term, $P \times T$, is equivalent to a dummy variable equal to 1 for observations of case 2 and in the second round of data collection.

The coefficients can be interpreted as follows:

- β_1: Average change in the outcome from the first to the second survey round that is common to both cases
- β_2: Average difference in outcome between the two cases that is common in both rounds of the survey
- β_3: Average differential change in the outcome from the first to the second survey round of case 2 relative to case 1

All estimates clustered standard errors at the provider level.

Ethics

Ethical approvals for this study were granted by the McGill University Health Centre in Montreal, Canada (REB No. 14-137-BMB) and the Subcommittee for the Ethical Approval of Projects at the Institute for Socioeconomic Research on Development and Democracy in Delhi, India.[17] Ethics committees approved a waiver from obtaining informed consent from providers in Patna and Mumbai under the Government of Canada Panel on Research Ethics, as well as a recent study by Rhodes and colleagues (2012) on ethical aspects of standardized patient studies commissioned by the US Department of Health and Human Services,[35] and study specific rational of waiver is detailed elsewhere.[36] All individuals who participated as standardised patients were hired as staff and trained to protect themselves from any harmful medical interventions, such as avoiding injections, invasive tests, or consuming any drugs. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

5.6 RESULTS

Our results, detailed in Table 5-2, indicate that across both rounds of data collection, 331 of 936 (35%; 95% CI: 32-38%) of interactions were correctly managed; at baseline, 215 of 500 (43%; 95% CI: 39-47%) of interactions were correctly managed whereas 116 of 436 (27%; 95% CI: 23-31%) were correctly managed in the second round of data collection.

Ideal management, where in additional to a referral, patients were not prescribed any potentially harmful medications, was seen in 275 of 936 (29%; 95% CI: 27-32%) of interactions overall, with 194 of 500 (39%; 95% CI: 35-43%) of interactions at baseline and 81 of 436 (19%; 95% CI: 15-22%) in round 2.

Table 5-2: *Summary statistics of main outcomes.*

	Full sample	Baseline (2014-2015)	Round 2 (2018-2019)
Correct Case Management	0.35	0.43	0.27
	331	215	116
	(0.478)	(0.496)	(0.442)
Ideal Case Management	0.29	0.39	0.19
	275	194	81
	(0.456)	(0.488)	(0.389)
N	*936*	*500*	*436*

mean coefficients; counts; sd in parentheses; correct case management = verbal or written referral to a DOTS centre or a healthcare provide; ideal case management = verbal or written referral to a DOTS centre or a healthcare provider without dispensing any antibiotics (including anti-tuberculosis drugs and quinolones) or corticosteroids

If we further look at our main outcomes by case (Table 5-3), we see that correct case management was observed in 39 of 250 (16%; 95% CI: 12-21%) of case 1 interactions at baseline and 20 of 218 (9%; 95% CI: 6-14%) in round 2. At baseline, case 2 was correctly managed in 176 of 250 (70%; 95% CI: 64-76%) of interactions and dropped to 96 of 218 (44%; 95% CI: 38-51%) of interactions in the second round of the survey.

Baseline saw ideal case management in 33 of 250 (13%; 95% CI: 10-18%) of case 1 presentations, as compared to 13 of 218 (6%; 95% CI: 4-10%) in round 2. Case 2 was ideally managed in 161 of 250 (64%;

95% CI: 58-70%) of interactions at baseline and only 68 of 218 (31%; 95% CI: 25-38%) in the subsequent round.

Table 5-3: *Summary statistics of main outcomes by case.*

		Case 1		Case 2	
	Full sample	Baseline (2014-2015)	Round 2 (2018-2019)	Baseline (2014-2015)	Round 2 (2018-2019)
Correct Case Management	0.35	0.16	0.09	0.7	0.44
	331	39	20	176	96
	(0.478)	(0.364)	(0.289)	(0.457)	(0.498)
Ideal Case Management	0.29	0.13	0.06	0.64	0.31
	275	33	13	161	68
	(0.456)	(0.339)	(0.237)	(0.48)	(0.464)
N	*936*	*250*	*218*	*250*	*218*

mean coefficients; counts; sd in parentheses

Figure 5-1 details other outcomes of interest, and most notably, medicine prescriptions by case. Case 1 interactions resulted in the dispensation of medicine of any type in 202 of 250 (81%; 95% CI: 75-85%) at baseline and 189 of 218 (87%; 95% CI: 82-91%) of interactions at round 2. A total of 88 of 250 (35%; 95% CI: 30-41%) of case 2 presentations were dispensed medicine at baseline, versus 154 of 218 (71%; 95% CI: 64-76%) in round 2. Dispensation of an antibiotic was seen in 143 of 250 (57%; 95% CI: 51-63%) of case 1 interactions at baseline, and 148 of 218 (68%; 95% CI: 61-74%) at endline. Case 2 SPs were dispensed antibiotics in 50 of 250 (20%; 95% CI: 16-25%) interactions in round 1 and 122 of 218 (56%; 95% CI: 49-62%) of interactions in round 2. A total of 56 of 250 (22%; 95% CI: 18-28%) of case 1 SPs were dispensed quinolone at baseline and 11 of 218 (5%; 95% CI: 3-9%) in the second round. For case 2, quinolones were dispensed in 20 of 250 (8%; 95% CI: 5-12%) of interactions at baseline and 10 of 218 (5%; 95% CI: 3-8%) in the later round. Steroids were given to 34 of 250 (14%; 95% CI: 10-18%) case presentations in round 1 and then to 21 of 218 (10%; 95% CI: 6-14%) of interactions in the next round of data collection. A total of 12 of 250 (5%; 95% CI: 3-8%) of case 2 interactions were given a corticosteroid, in contrast to 22 of 218 (10%; 95% CI: 7-15%) in round 2. Importantly, there were no over-the-counter ATT medicines dispensed by any pharmacy, across both cases and both rounds.

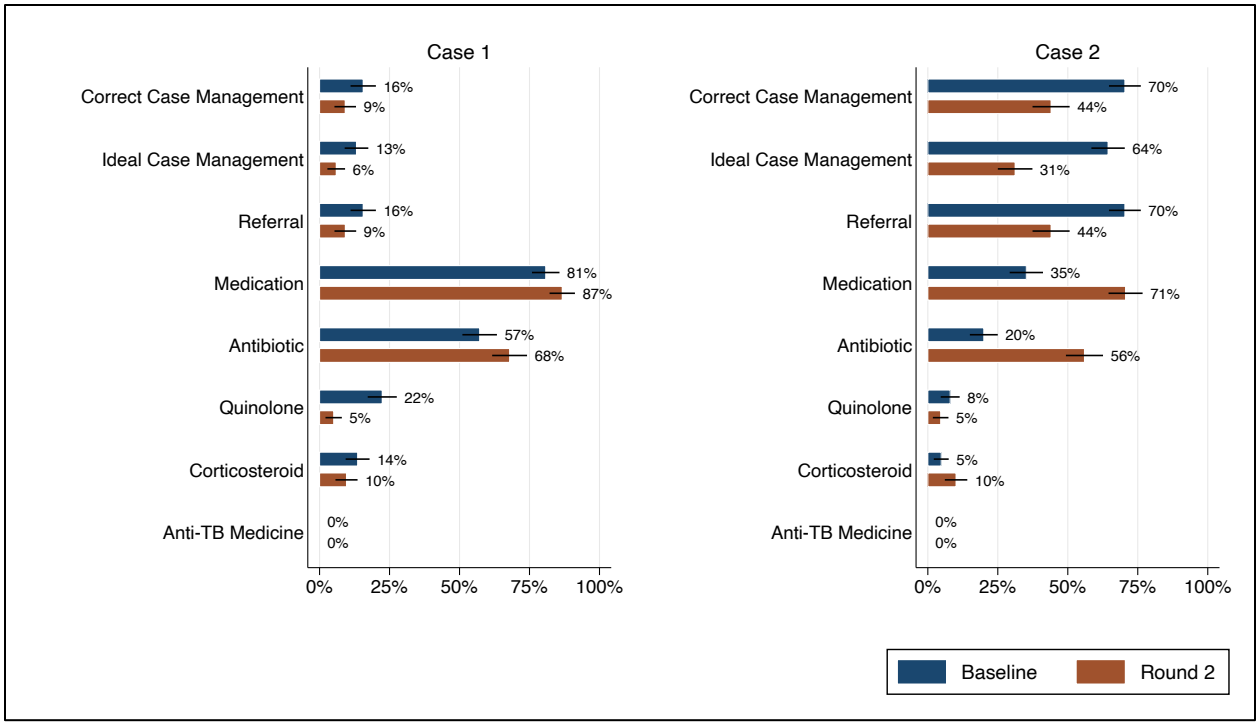

Figure 5-1: *Proportion of treatment outcomes by case and round of data collection. All estimates are clustered at the provider level.*

If we further breakdown components of correct and ideal case management, we can see patterns in referral and dispensation of antibiotic or a corticosteroid. In Figure 5-2, we see that referrals occurred more often at baseline than in round 2, especially in the management of case 2.

Amongst those who did not refer at baseline, we see that case 1 was managed in the following way: 67 of 250 (27%; 95% CI: 22-33%) of interactions received no antibiotic or corticosteroid; 7 of 250 (3%; 95% CI: 1-6%) received a corticosteroid only; 111 of 250 (44%; 95% CI: 38-51%) received an antibiotic only; and 26 of 250 (10%; 95% CI: 7-15%) received both an antibiotic and corticosteroid.

In round 2, 53 of 217 (24%; 95% CI: 19-31%) did not receive an antibiotic or corticosteroid, 3 of 217 (1%; 95% CI: 0-4%) a corticosteroid only, 125 of 217 (58%; 95% CI: 51-64%) an antibiotic only, and 16 of 217 (7%; 95% CI: 5-12%) an antibiotic and a corticosteroid.

Among pharmacist who were presented with case 2 presentations who did not refer at baseline, 31 of 250 (12%; 95% CI: 9-17%) did not dispense an antibiotic or corticosteroid, 5 of 250 (2%; 95% CI: 1-5%) gave a corticosteroid only, 31 of 250 (12%; 95% CI: 9-17%) an antibiotic only, and 7 of 250 (3%; 95% CI: 1-

6%) an antibiotic and corticosteroid only. In round 2 of data collection, among those pharmacist who did not refer, 27 of 218 (12%; 95% CI: 9-17%) interactions additionally did not dispense a corticosteroid or antibiotics, 0 of 218 (0%; 95% CI: 0-2%) a corticosteroid only, 77 of 218 (35%; 95% CI: 29-42%) an antibiotic only, and 18 of 218 (8%; 95% CI: 5-13%) both an antibiotic and a corticosteroid.

Of those providers who referred, case 1 presentations were dealt with in the following ways: at baseline 33 of 250 (13%; 95% CI: 10-18%) solely referred, without the concurrent prescription of an antibiotic or corticosteroid, 0 of 250 (0%; 95% CI: 0-2%) referred and prescribed a corticosteroid only, 5 of 250 (2%; 95% CI: 1-5%) referred and dispensed an antibiotic, and 1 of 250 (0%; 95% CI: 0-2%) provided an antibiotic, corticosteroid and referral. In round 2, for case 1 presentations who were referred, 13 of 217 (6%; 95% CI: 4-10%) did not receive an additional antibiotic or corticosteroid, 0 of 217 (0%; 95% CI: 0-2%) received a corticosteroid only, 5 of 217 (2%; 95% CI: 1-5%) an antibiotic only, and 2 of 217 (1%; 95% CI: 0-3%) an antibiotic, corticosteroid and referral.

For case 2 presentations where providers referred SPs, at baseline 164 of 250 (66%; 95% CI: 60-71%) only referred, 0 of 250 (0%; 95% CI: 0-2%) gave out a corticosteroid, 12 of 250 (5%; 95% CI: 3-8%) an antibiotic and 0 of 250 (0%; 95% CI: 0-2%) a referral, antibiotic and corticosteroid. At endline, 68 of 218 (31%; 95% CI: 25-38%) only referred, 1 of 218 (0%; 95% CI: 0-3%) gave only a corticosteroid, 24 of 218 (11%; 95% CI: 8-16%) only an antibiotic, and 3 of 218 (1%; 95% CI: 0-4%) referred and prescribed an antibiotic and corticosteroid.

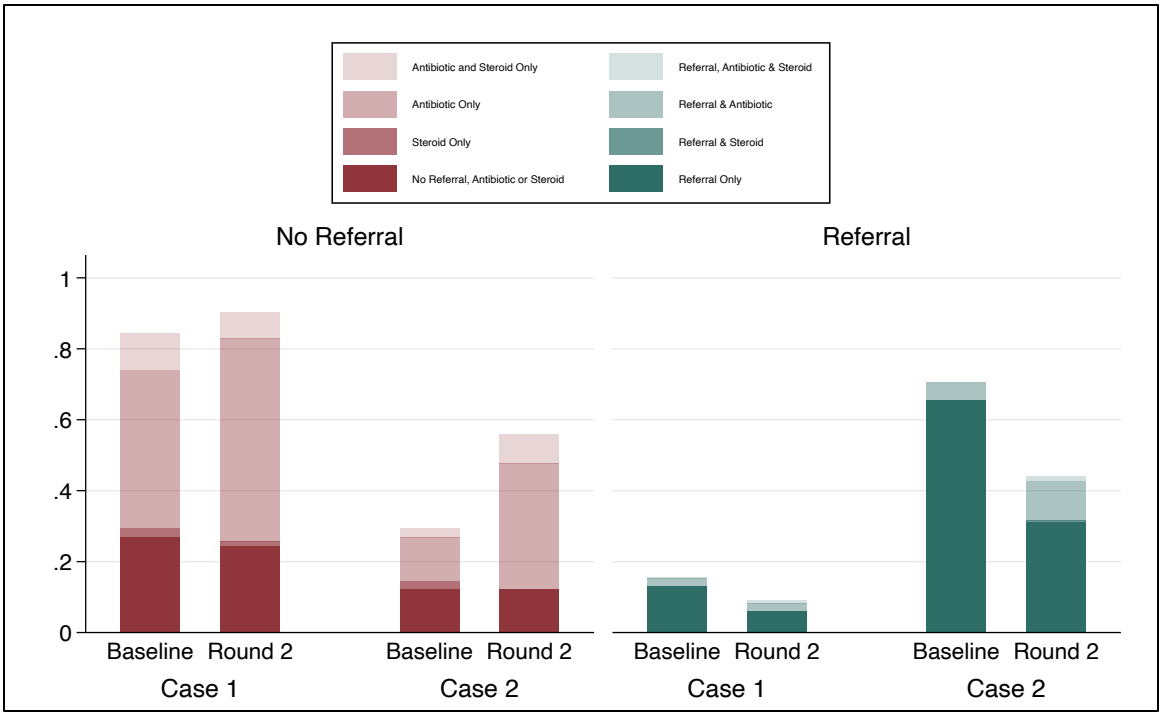

Figure 5-2: *Changes in referral patterns over round of data collection and dispensation patterns of quinolones and steroids.*

We then compared our outcomes of interest for each case by round (Figure 5-3). We see that for case 1, providers were more likely to both correctly and ideally manage a case at baseline than in the second round of data collection (OR 0.55; 95% CI: 0.32-0.95 and OR 0.42; 95% CI: 0.22-0.79, respectively). Providers were more likely to prescribe a corticosteroid (OR 0.18; 95% CI: 0.09-0.35) or quinolone (OR 0.67; 95% CI: 0.43-1.06) to SPs as compared to round 2, though the latter was not statistically significant. Providers were however more likely to prescribe any medication or antibiotic in the second round (OR 1.55; 95% CI: 1.04-2.31 and OR 1.58; 95% CI: 1.14-2.20, respectively).

Case 2 witnessed a similar pattern between rounds. Ideal management was more likely to be seen in round 1 of data collection (OR 0.25; 95% CI: 0.17-0.36), as was correct management (OR 0.33; 95% CI: 0.23-0.47). Quinolones were also more likely to be prescribed in the first round of the survey, but this was not statistically significant (OR 0.55; 95% CI: 0.25-1.24). The prescription of any medication (OR 4.43; 95% CI: 3.09-6.35), an antibiotic (OR 5.08; 95% CI: 3.42-7.55) and a corticosteroid (OR 2.23; 95% CI: 1.10-4.50) was more likely to be seen in round 2 than round 1.

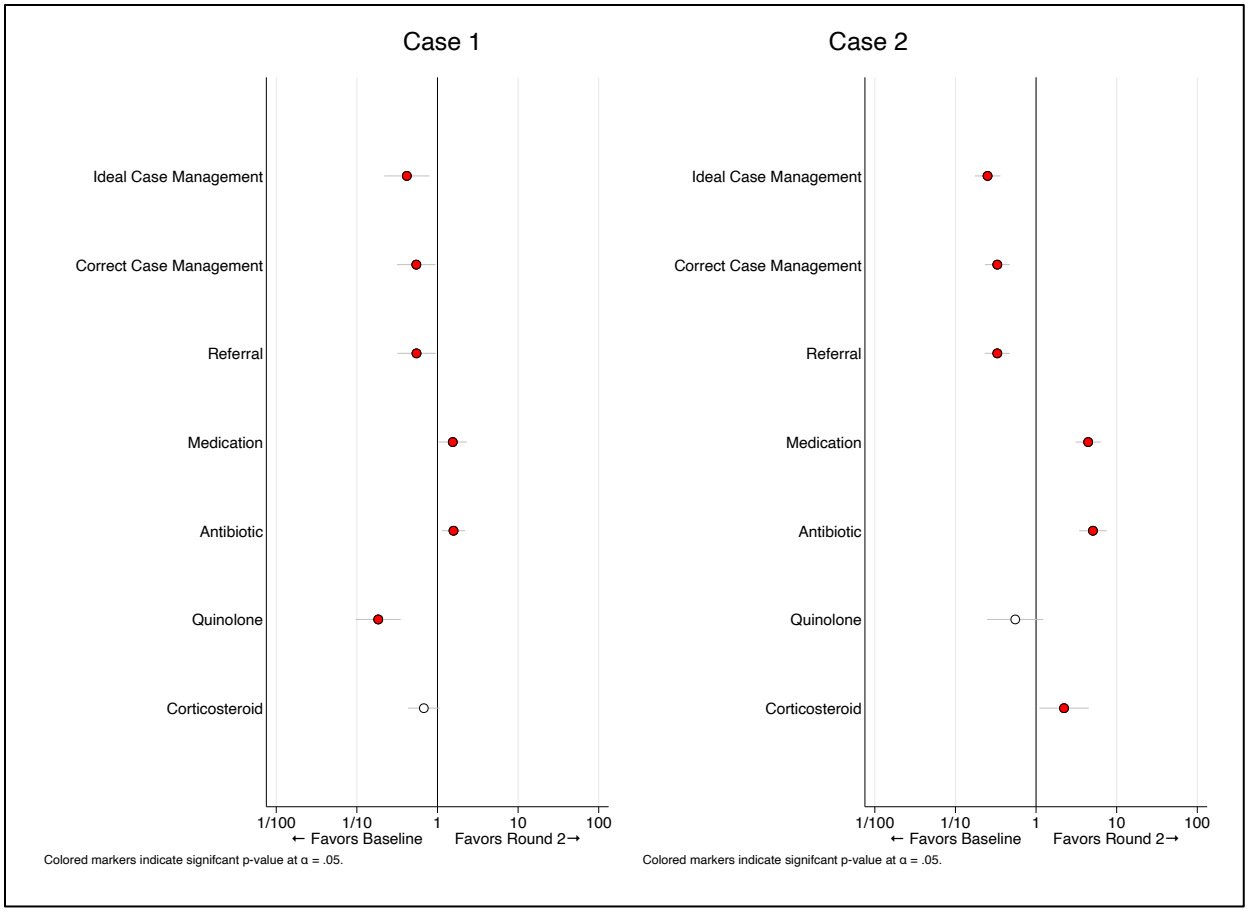

Figure 5-3*: Outcome changes over time for each respective case; estimates were calculated with an OLS regression, with standard errors clustered at the pharmacy level.*

We then conducted a difference-in-difference analysis to capture the significant differences in outcomes across the two case presentations, which occur between the baseline and endline periods (Figure 5-4 and Table 5-4).

On average, the difference is correct case management between case 1 and case 2 dropped by 20 percent points from baseline to the second round of data collection. Similarly, ideal case management decreased by 26 percentage points. We also see that this is in contrast to the dispensation of medicines, which had the opposite effect between rounds; the difference in dispensation of quinolones between case 1 and case 2 increased by 14 percentage points, as did corticosteroids by 9 percentage points, antibiotics 25 percentage points and medicines generally by 30 percentage points. This highlights the asymmetry in referral rates which constitute the major reason why ideal case management was applied at baseline more than round two, despite the relative impact of prescription of antibiotics and corticosteroids.

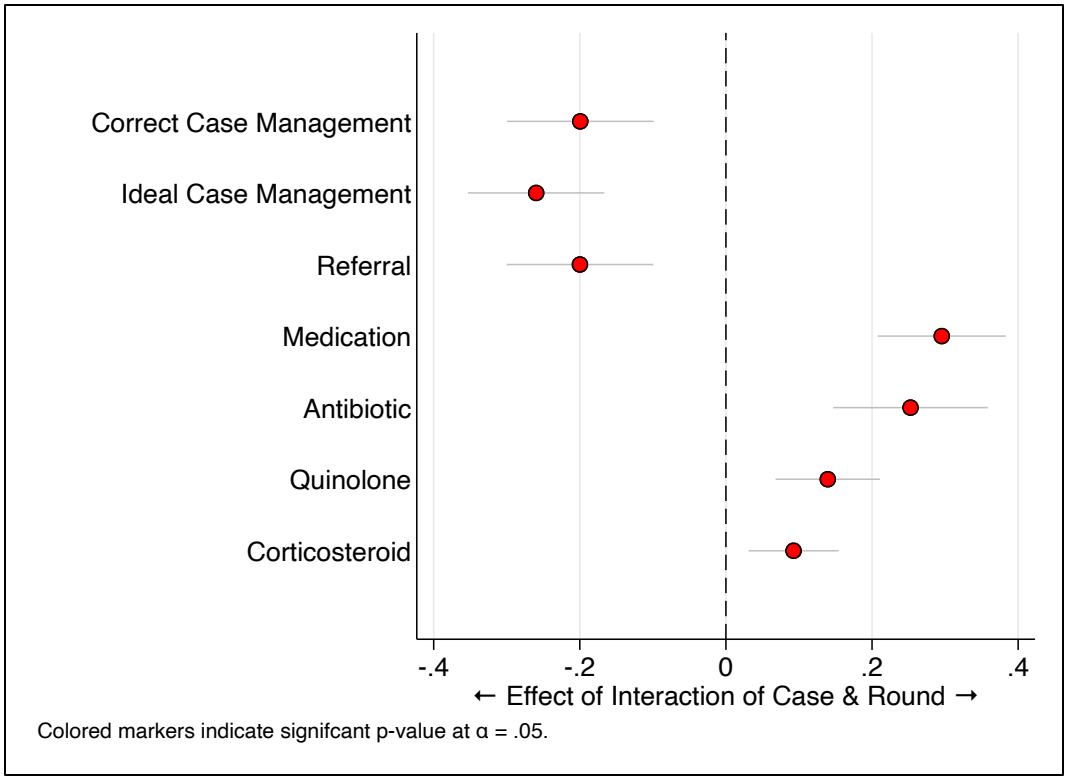

Figure 5-4: *Differences-in-difference model by case and round, with standard errors clustered at the provider level.*

Table 5-4*: Differences-in-difference model by case and round, with standard errors clustered at the provider level.*

	CONTROL		**TREATMENT**		**DIFFERENCE-IN-DIFFERENCE**
	Baseline	Difference	Baseline	Difference	
	Mean	Coef.	Mean	Coef.	Coef.
	(SE)	(SE)	(SE)	(SE)	(SE)
	Clusters	Clusters	Clusters	Clusters	Clusters
VARIABLE	N	N	N	N	N
CORRECT CASE MANAGEMENT	0.16	-0.06**	0.7	-0.26***	-0.20***
	(-0.02)	(-0.03(	(-0.03)	(-0.04)	(-0.05)
	250	258	250	250	260
	250	468	250	468	936
IDEAL CASE MANAGEMENT	0.13	-0.07***	0.64	-0.33***	-0.26***
	(-0.02)	(-0.03)	(-0.03)	(-0.04)	(-0.05)
	250	258	250	250	260

	250	468	250	468	936
REFERRAL	0.16	-0.06**	0.7	-0.26***	-0.20***
	(-0.02)	(-0.03)	(-0.03)	(-0.04)	(-0.05)
	250	258	250	250	260
	250	467	250	468	935
MEDICATION	0.81	0.06**	0.35	0.35***	0.30***
	(-0.02)	(-0.03)	(-0.03)	(-0.04)	(-0.04)
	250	258	250	250	260
	250	468	250	468	936
ANTIBIOTICS	0.57	0.11***	0.2	0.36***	0.25***
	(-0.03)	(-0.04)	(-0.03)	(-0.04)	(-0.05)
	250	258	250	250	260
	250	468	250	468	936
QUINILONE	0.22	-0.17***	0.08	-0.03	0.14***
	(-0.03)	(-0.03)	(-0.02)	(-0.02)	(-0.04)
	250	258	250	250	260
	250	468	250	468	936
CORTICOSTEROID	0.14	-0.04*	0.05	0.05**	0.09***
	(-0.02)	(-0.02)	(-0.01)	(-0.02)	(-0.03)
	250	258	250	250	260
	250	468	250	468	936

We also assessed whether or not providers that demonstrated higher or poorer quality practices were more likely to shut down over time or move. We saw no impact of attrition on the outcome (S5-Figure 2). In addition, we explored the question of whether or not providers who with good quality behaviours in the first round continued to engaged in good quality behaviours in the second round. The effect of consistency of behaviours amongst same providers can be seen in the appendix (S5-Figure 3).

5.7 DISCUSSION

To our knowledge, this is the first study to examine changes in pharmacy practices over a period of time in a community that had been exposed to efforts directed at greater engagement and training of private health providers. Since we returned after a 5-year period to almost all the same providers initially assessed (some 93%), the findings provide a basis upon which we can judge the merit of current efforts for private sector engagement. Our findings suggested marked improvements as well as disconcerting declines in quality of care, complementing our recent study that assessed tuberculosis management by healthcare

providers.[17] On the one hand, we found that no pharmacy dispensed group 1 anti-tuberculosis treatment medicines. However, when we looked at other metrics of quality, we did not see such comforting findings. Our findings show that ideal case management, where a patient was not only referred but also not dispensed a harmful medication was observed in 33 of 250 (13%; 95% CI: 10-18%) of case 1 presentations at baseline and 13 of 218 (6%; 95% CI: 4-10%) in round 2. Ideal management increased with the addition of more information to the case presentation, with case 2 being ideally managed in 161 of 250 (64%; 95% CI: 58-70%) of interactions at baseline and 68 of 218 (31%; 95% CI: 25-38%) in the subsequent round. Since standardised patient methodology systematizes the presentation of the underlying clinical presentation across different providers,[37] the results can be considered reliable, valid, and comparable across pharmacies.

A key repeat finding is that none of the pharmacies in our study dispensed group 1 anti-tuberculosis drugs without a prescription. Fortunately, any concerns regarding the use of anti-tuberculosis drugs by pharmacies seem to be unfounded and reports that pharmacies are sources for TB resistance via the inappropriate dispensation of anti-tuberculosis are unlikely. While we did not have the opportunity to conduct qualitative research on pharmacy decision-making, it is possible that TB drugs, unlike antibiotics and corticosteroids, are considered toxic, and that tuberculosis requiring long-term treatment might play a part in pharmacies being cautious about OTC use of ATT drugs. Perhaps it may be in part due to the proactiveness of the Indian National Tuberculosis Control Program in including tuberculosis drugs under Schedule H-1, subsequently requiring providers to maintain a register and report these prescriptions.[38]
Our results indicate a decline in progress between rounds of data collection by case. If we define outcomes as successful based on referral, we see that the propensity to refer patients – the primary metric used to evaluate correct treatment in each study – faced a decline from baseline. This decline in referral rates with concurrent upsurge prescription of potentially harmful medicines is disconcerting; the increased use of quinolones and corticosteroids is especially worrying because these drugs delay tuberculosis diagnosis.[39,40] Miller et al. reviewed the literature on SP studies among pharmacies for TB, and showed similar poor quality of care across various settings (Table 5-5).[23]

Table 5-5: *Examples of TB case presentations and management of TB in standardised patient studies.*[23]

Examples of TB case presentations and management of TB in standardised patient studies.

Study	Case presentation	Management	
		Referred	Sold an antibiotic
Miller and Goodman 2017, India [40]	'I have had cough and some fever for 3–4 weeks. We have had a relative staying with us who has TB. Can you suggest something?'	46%	16%
Satyanarayana et al. 2016 (case 1), India [30]	'I am having cough for nearly a month now and also have fever.' Whilst showing a positive sputum report to the chemist, the patient continues, 'I went to the government dispensary and they asked me to get my sputum tested. I have this report. Can you please give me some medicine?'	16%	37%
Satyanarayana et al. 2016 (case 2), India [30]	`I have cough and fever that is not getting better. Please give me some medicine.'	67%	16%
Vu et al. 2012, Vietnam [41]	SP claimed to be suffering from cough and fever for 4 weeks. No improvement had occurred after two 10-day courses of antibiotics (amoxicillin followed by spiramycin). SP had been in contact with a TB patient. Anti-TB drugs were requested. (The paper does not provide the verbatim script).	46%	41%

Quinolones are also an integral part of multidrug-resistant tuberculosis treatment regimens and emerging regimens, so such suboptimal OTC use of this class of medications are of concern.[40] The widespread use of antibiotics and corticosteroids for respiratory symptoms also has implications for community-acquired infections more generally. Inappropriate use of quinolones is a major risk factor for producing highly resistant Gram-negative enteric bacteria, resulting in an increased risk of diarrhoeal illness, bacteraemia, and other infections, especially in India.[41] Pharmacies often dispense antibiotics for clients with chronic cough without referral for TB testing, with the expectation of improving client retention.[14,18] This problem could possibly be addressed by supplying pharmacies with referral slips, which could allow pharmacies to dispense a product while maintaining their position relative to client expectations of action.[42] The use of broad spectrum antibiotics for respiratory symptoms identified in our study might contribute to resistant strains of common respiratory pathogens.[43] Unnecessary use of corticosteroids is associated with an increased risk of developing lower respiratory tract infection, cellulitis, herpes zoster, and candidiasis, in addition to potentially delaying treatment.[44]

In countries with a high burden of tuberculosis, private pharmacies are frequently the first point of care seeking for individuals with TB indicative symptoms.[13,15,16,45,46] This holds true in India. India has a high rate of drug-resistant pathogens, likely driven by rampant antibiotic misuse, a high burden of infectious diseases, easy access to antibiotics, and a fragmented, unregulated, privatized healthcare system. While all antibiotics, anti TB medications, and corticosteroids in India are listed in Schedule H under the Ministry of Health and Family Welfare Department of Health's Drugs and Cosmetics Rules, 1945, and dispensing them requires a valid prescription, due to weak enforcement, pharmacists readily give antibiotics to patients without prescriptions, as shown in our previous SP surveys of pharmacies in India.[18,47] The quality of TB care by pharmacies in low-income and middle-income countries (LMICs) has been shown to be low in other contexts, with lack of TB knowledge among pharmacy staff, inappropriate sales of antibiotics and

anti-TB medications, and lack of systems to facilitate referrals for TB testing.[14,18,23] Most pharmacies are not linked to national tuberculosis programmes (NTPs) but establishing structured mechanisms for the referral of individuals with presumptive TB, not just the mandatory notification of ATT purchases, from pharmacies to private or NTP-associated facilities for testing could help to identify the millions of missing patient who develop TB yearly but were not diagnosed and reported to NTPs.[48]

Even as rates of ideal management went down over time, management of case 2 (where a diagnosis was confirmed) over case 1 (which relied on symptoms alone) were higher by 5-fold at both time points. This suggests best practices can be supported by a confirmed diagnosis. But, given that a high proportion of SPs were poorly managed even in light of a confirmed diagnosis, significantly greater inquiry into pharmacy practices and interventions that address incorrect practices are needed. This warrants much stronger engagement with the private pharmacy sector, who, in light of broader PPM initiatives, may be neglected. This underscores the fact that the use of antibiotics is mediated by drug category and the information that patients present, something that was observed in our first study, and while this effect was tapered in subsequent round, it still holds true.

Confirmed diagnoses dictate what pharmacists do, and sharp increases in ideal management and large decreases between case 1 and case 2 in antibiotic use are indicative of that. This large difference suggests that the main challenge faced by pharmacists is confusion about the likely diagnosis. Better training regarding tuberculosis symptoms and encouraging early referrals for patient with tuberculosis symptoms might help. The TB PPM Learning Network has worked on a simple infographic tool that could be adapted by countries and used to educate pharmacies on the dos and don’ts while dealing with people with TB cough as the primary complaint (Figure 5-5).

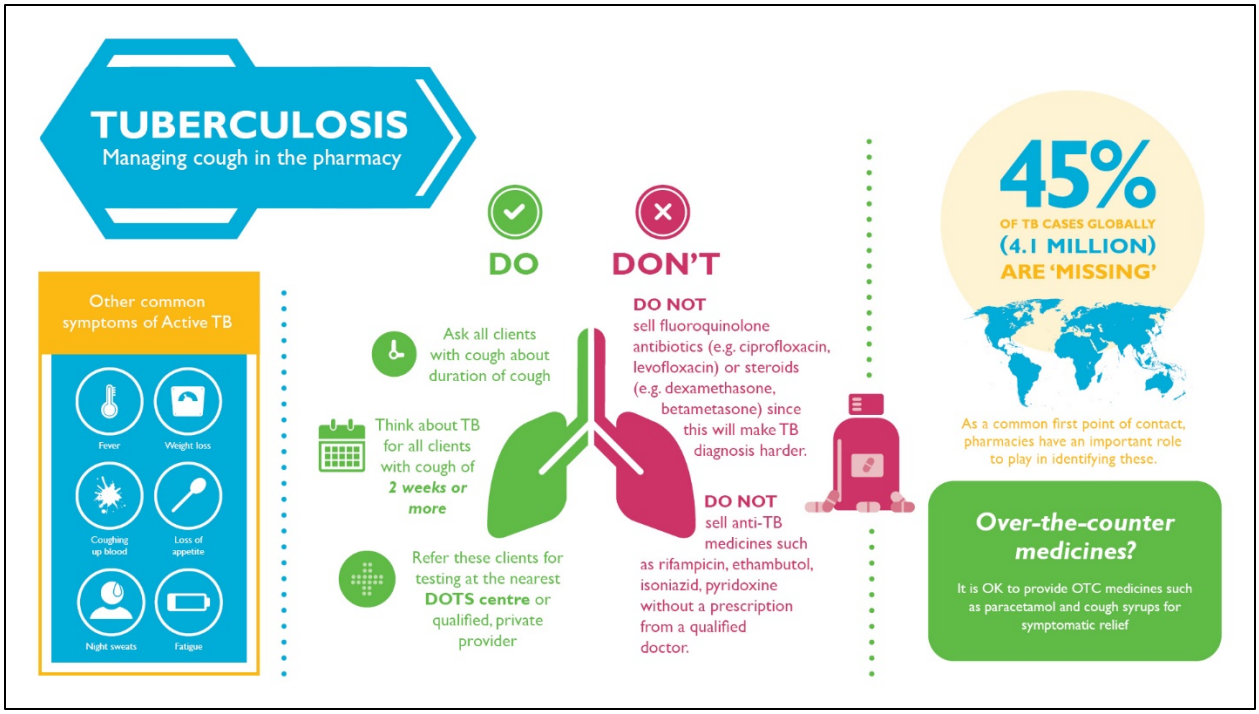

Figure 5-5: *Dos and don'ts of managing cough in a pharmacy setting. (Source: https://www.tbppm.org/)*

Since it was beyond the scope of our study to conduct qualitative research, it is unknown why some pharmacists give antibiotics. Moreover, it is unclear whether the variation in our data is explained by the qualification of the person providing advice in pharmacies. A typical pharmacy in India has a qualified pharmacist, and many other helpers and assistants who are not qualified in pharmacy science. It is unclear what advice pharmacists provide vis-à-vis their helpers, since SP studies are unable to discern the exact qualifications of the person interacting with the standardized patients. There are some clues within the qualitative literature, suggesting that a combination of other factors might also be at play, including pharmaceutical industry marketing techniques, business models followed by local providers, and active demand from patients for medicines.[49] It has been shown that the reciprocal relationships between the retail private pharmacists, private providers, medical representatives and the prevalence of kickbacks (financial incentives) influenced pharmacist drug-stocking patterns.[50] Overstock, near-expiry, and undersupply are additional factors which may explain the misuse of antibiotics and restricted drugs.[47,49]

Engaging with the private sector in TB management is important; encouraging NTPs to develop strong public-private partnerships is highlighted by the WHO as a top priority in the End TB strategy.[51] Given that 50% of India's TB is managed outside of the public sector,[52,53] engagement with private providers is

essential. The Revised National TB Control Programme (RNTCP) has implemented public-private mix (PPM) programmes through private-provider interface agencies (PPIAs)[54] These initiatives should extend to the pharmacy system as well, since, despite engagement of the private sector, our work shows that those efforts may be missing the mark. Additional work is needed to uncover why this is happening, that provider practise may not be responding to the incentives and trainings being doted out, meaning a better evaluation and revisiting of those initiatives may be needed. Robust and effective private sector engagement is ultimately predicated on behavioural change on the part of providers, which may not be as simply resolved through trainings alone. Lessons learnt from an evaluation of pharmacy interventions have shown that to properly retain pharmacists in such initiatives over time, a package of incentives was required that included not only monetary incentives but also training in TB and the opportunity to interact with influential stakeholders in ways which were seen by pharmacy owners as beneficial to their businesses. This is particularly true due to the fact that there is pressure from clients themselves; clients expect to receive a tangible outcome such as medication from a visit to a pharmacy, even in the absence of diagnostic testing.[42] Creating sustainable, long term linkages between pharmacies and referral facilities are vital success, and information should flow in both directions.[20] This would be facilitated by digital tracking tools for pharmacies to facilitate information sharing and real-time updates and received feedback on the number of their referred clients attending testing sites and the number diagnosed with TB.[42]

Our study is not without limitations. First, our repeat study could only be conducted in one city, Patna, so our findings may not be generalizable to other cities in India and our study does not provide evidence on how pharmacists in rural areas manage patients with tuberculosis or tuberculosis symptoms. Second, our study reflects what happens when pharmacists receive a completely unknown patient as opposed to a known, regular client, or a client who returns to the pharmacist after one round of ineffective treatment, as would be expected from many community pharmacies; such familiarity could well have mediated some of the behaviours. Third, differences between case 1 and case 2 outcomes could reflect variation in the standardised patient profile themselves; we could not assess this possibility given that different standardised patients were assigned to the two cases with no crossover. In other studies however, it has been shown that inclusion of standardised patient characteristics has little effect on estimated coefficients and coefficients remain stable when we account for standardised patient sex, height, and weight.[18] Also, our SP studies could not identify whether the interactions were done with qualified pharmacists or their

helpers/assistants. It is likely that most interactions were with pharmacy staff rather than qualified pharmacists.

5.8 CONCLUSION

Our standardised patient study provides valuable insights into how pharmacies in an urban Northern Indian city changed their treatment of patients with tuberculosis symptoms or with confirmed tuberculosis over a 5-year period. We saw that overall, pharmacy performance weakened over time. Importantly, however, no over-the-counter dispensation of anti-TB medications occurred in either survey round. As the first point of contact for many care seekers, continued and sustained efforts to engage with Indian pharmacies should be prioritized.

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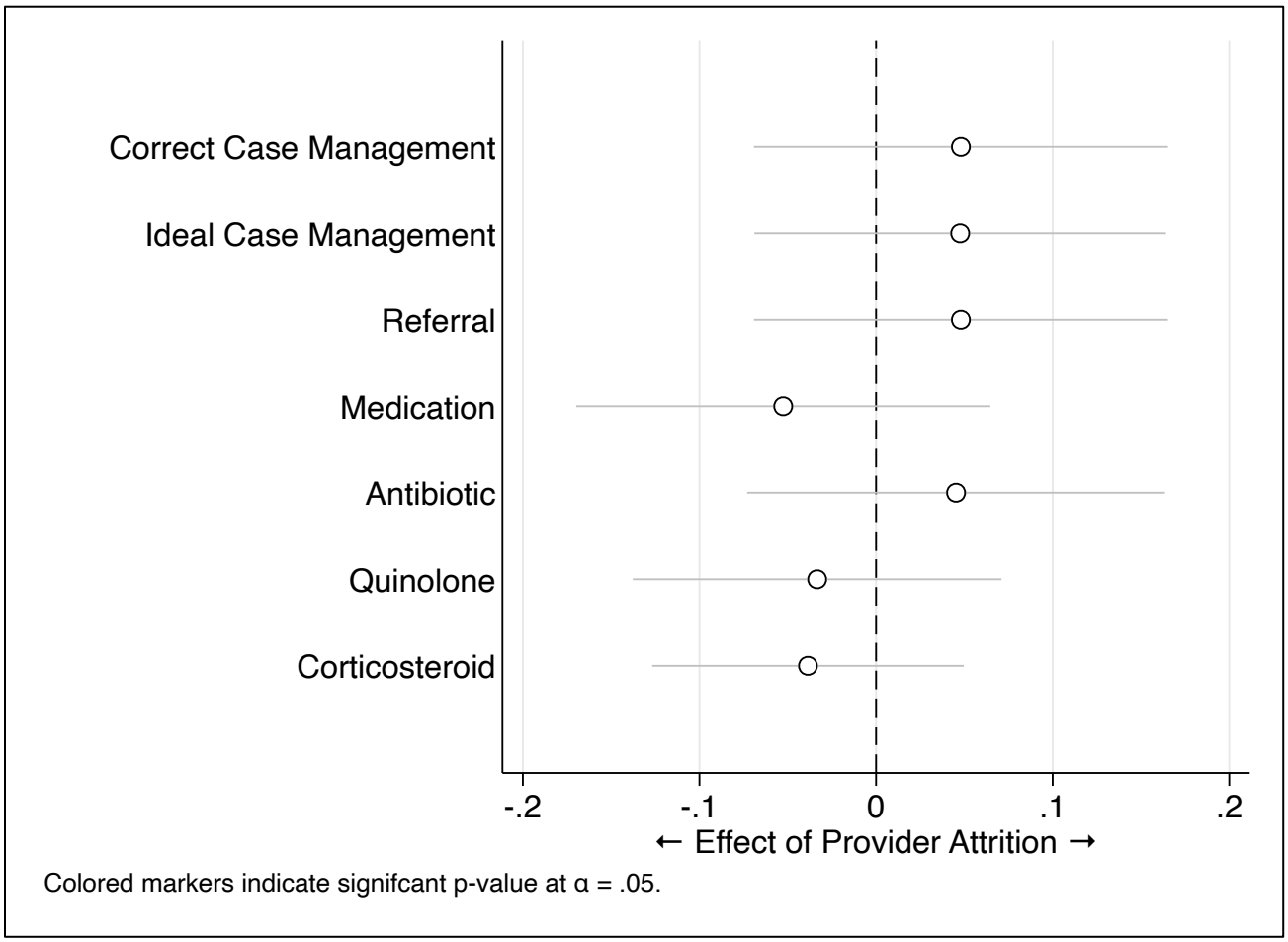
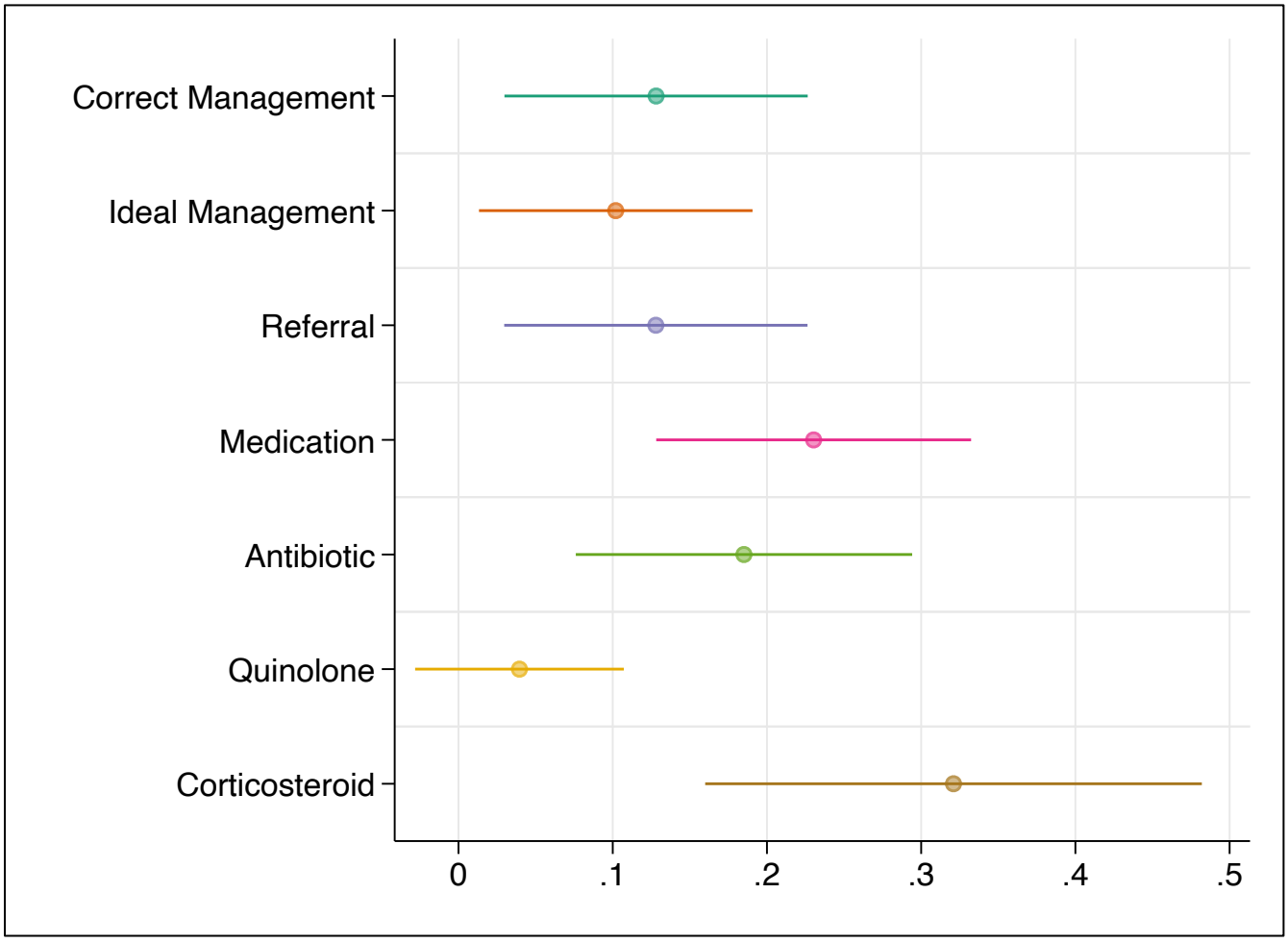
S5-1

S5-Figure 1: *Example of pharmacy in pharmacy in urban India.*



S5-Figure 2: *Impact of attrition on outcome calculated using a linear regression model, with standard errors clustered at the provider level.*



S5-Figure 3: *Consistency of behaviours amongst same providers, calculated using a linear regression model, with standard errors clustered at the provider level.*

CHAPTER 6: SUMMARY AND CONCLUSIONS

TB is the second leading infectious disease killer worldwide after COVID-19. Accounting for more than a quarter of the global TB incident cases, India has the greatest TB burden in the world. High quality TB care includes early and accurate diagnosis, rapid initiation of the correct drug regimen, patient support, and management of relevant comorbidities. The Indian private healthcare sector is large and unregulated; it treats half of Indian TB patients, with evidence suggesting that the quality of care they receive is suboptimal. SPs are increasingly used in low-income countries to assess quality of medical care. In this manuscript-based thesis, I assessed quality of TB care and provider practices across outpatient primary care settings in India's private sector. Using secondary data from a series of SP studies conducted in India, I analyzed if providers empirically prescribe anti-TB medications on the basis of clinical and chest X-ray (CXR) findings, and their propensity to prescribe potentially harmful medications or treatment regimes. Specifically, I conducted secondary analyses of data for a total of over 6,500 SP-provider interactions in two cities with the aim to calculate unbiased prevalence estimates of inappropriate care and over-prescription using inverse-probability-weighting based on the overall sampling strategy. I additionally looked at behaviours amongst pharmacies in urban Patna using data from 936 SP-provider interactions. My thesis produced several insights into how private providers, including private pharmacies, manage people with TB or symptoms of TB in urban India.

6.1 SUMMARY OF RESULTS

The results of Chapter 2 indicated that among SP cases who presented to providers with typical TB symptoms and an abnormal CXR (case 2), 182 of 795 (25%; 95% CI: 21-28%) of interactions resulted in a ideal correct management, where the provider prescribed a microbiological test (sputum smear, Xpert MTB/RIF or culture) and did not offer a concurrent prescription for a corticosteroid or antibiotic (more specifically of quinolone or anti-TB medication, or ATT). Of all case 2 presentations, 210 of 795 (23%; 95% CI: 19-26%) resulted in potential empiric TB treatment, with a prescription or dispensation of ATT. A total of 140 of 795 (13%; 95% CI: 10-16%) interactions resulted in a prescriptions/dispensation of ATT and additionally, a prescription for confirmatory microbiological testing, either via sputum smear microscopy, Xpert MTB/RIF, or culture. Specifically, our finding that one in five SPs with an abnormal CXR were prescribed ATT by private providers is important evidence of fairly widespread empirical management of TB, and might help explain the low rates of bacteriological TB diagnoses in the Indian private health sector. A more detailed qualitative inquiry into provider practices and decision-making rationale, coupled with engaging them in anti-microbial stewardship and lab strengthening measures (e.g. free or subsidized WHO recommended rapid diagnostics) are likely to have impacts in timely and appropriate management of TB, and other respiratory infections.

In Chapter 3, we found that across all case presentations, 749 of 6,685 (12%; 95% CI: 11-14%) SPs were prescribed quinolones and 512 of 6,685 (6%; 95% CI: 5-7%), corticosteroids. Our findings show that one in ten SP interactions resulted in the use of quinolones and about one in twenty interactions resulted in the use of steroids. These provider practices might mask TB detection in the private sector, and highlight the need for greater provider education about the potential harms of quinolones and corticosteroids, as both carry potentially harmful consequences when deployed unnecessarily. Better regulation of these medicines in the private market might also help.

In Chapter 4, when ATT was prescribed, a majority of group 1 ATT regimens were a four-drug, fixed-dose combination – some 236 of 418 (64%; 95% CI: 57-70%). Our findings are promisingly in that this is a preferred regimen format; continuing to monitor that this trend holds true across India is of the upmost importance since these medicine formats are critical in minimizing prescription errors, and simplifying TB treatment regimens.

Finally, I also analyzed whether private pharmacists manage people with presumptive TB appropriately. The repeat cross-sectional study amongst pharmacists in Patna in Chapter 5 found that 331 of 936 (35%; 95% CI: 32-38%) of interactions were correctly managed; at baseline, 215 of 500 (43%; 95% CI: 39-47%) of interactions were correctly managed whereas 116 of 436 (27%; 95% CI: 23-31%) were correctly managed in the second round of data collection. We saw a decrease in correct case management between case 1 and case 2 by 20 percentage points from baseline to round 2 in our difference-in-difference analysis. Pharmacies did not dispense anti-tuberculosis drugs for either case or round. Our findings on how private pharmacies manage TB show that sustained efforts to engage with Indian pharmacies should be prioritized, since they are often the first point of contact for patients.

Overall, this body of work contributes to fill some knowledge gaps regarding private provider behaviors in urban India, thus helping to design and implement tailored interventions aimed at promoting the rational use of medicines and diagnostics. These insights are needed in order to design and implement effective quality improvement programs for TB in the private sector.

6.2 IMPLICATIONS OF KEY FINDINGS & SUGGESTIONS TO ADDRESS THEM

Insights from each study could be helpful for quality improvement in the Indian private sector for TB care. All the key findings from research on quality of TB care in the Indian private sector, including this thesis, have been summarized in Table 6.1, where I also offer potential suggestions for improvement. The key findings, which are recurring in both this thesis and other works, are: (1) low rates of TB testing by private providers, even when patients present with typical TB symptoms; (2) low rates of referral to NTP; (3) private providers prefer to empirically manage with antibiotics and order tests later; (4) in private pharmacies, low rates of ideal management of people with TB or suspected TB; (5) CXR is the preferred tests for TB & sputum-based tests rarely used; (6) use of DST in the private sector is very low, even among patients with history of anti-TB therapy; (7) empirical anti-TB treatment on the basis of an abnormal CXR is fairly widespread; (8) use of steroids and quinolones is fairly widespread; (9) when anti-TB medicines are prescribed, they generally tend to be four-drug, fixed dose combinations (HRZE); (10) what providers know and what they do in practice are often very different ('know-do gap'); (11) there is limited capacity of private providers to support patients with adherence and treatment completion; (12) there are high costs of care, with 50% of the total incurred before TB is diagnosed; (13) private providers are disengaged from government; (14) impact of private sector interventions wane over time; (15) there is wide heterogeneity of care practices; (16) the information conveyed by patients impacts provider care decisions.

Table 6-1: *Summary of key findings and suggestions for their improvement.*

Key findings	***Potential suggestions for improvement***
(1) Low rates of TB testing by private providers, even when patients present with typical TB symptoms	• Provide continuing medical education, preferably digitally delivered, to providers on updated information in TB diagnosis and management, including Standards for TB Care in India • Engage providers via public-private mix (PPM) programs which can make TB testing more affordable and accessible to private providers • Support private providers with sample collection and transport from their clinics • Create and facilitate linkages between providers and trusted laboratories • Reduce the cost of WHO recommended TB tests in the private market • Employ field officers (e.g. detailers) to visit providers for intermittent reminders and for behavioural change communication • Provide human resource support to make it easier to test and notify TB cases

(2) Low rates of referral to NTP	• Support private providers, via intermediary and community-based agencies • Offer greater incentives for referrals both financial and non-monetized • Provide online, mobile-based referral tools • Make sure that referring providers receive information about their patients and that they are engaged in providing follow-up care during anti-TB therapy
(3) Private providers prefer to empirically manage with antibiotics and order tests later	• Enforce regulatory oversight of medications (e.g. Schedule H1 enforcement) • Offer e-health services for patient tracking to mitigate loss to follow-up • Increase accessibility between private/public sector e-health platforms (ex: Nikshay) so patient history is available • Engage providers via public-private mix (PPM) programs which can make TB testing more affordable and accessible to private providers • Support private providers with sample collection and transport from their clinics • Strengthen laboratories to engender confidence in quality and speed of service
(4) In private pharmacies, low rates of ideal management of people with TB or suspected TB	• Educate pharmacies via pharmaceutical associations and other professional societies • Strengthen enforcement of Schedule H1 to limit the abuse of restricted antibiotics and drugs • Incentivize referrals • Facilitate dialogue and mutually beneficial relationships between pharmacies and health care providers
(5) CXR - preferred tests for TB; sputum tests rarely used	• Build confidence in laboratory quality, to increase use of microbiological tests such as sputum microscopy • Expand access to molecular testing options and make WHO recommended rapid tests more affordable • Facilitate sample transport • Create networks of trusted providers and laboratories • Offer private GPs free molecular testing via public TB clinics
(6) Use of DST in the private sector is very low, even among patients with history of anti-TB therapy	• Strengthen existing laboratory capabilities to increase use of cultures, line probe assays and Xpert MTB/RIF • Capitalize on laboratory infrastructure developed for COVID-19 molecular testing and repurpose for TB • Expand access to Xpert MTB/RIF in both public and private sectors • Educate providers on importance of antimicrobial stewardship • Lower costs to both operators and patients when DST indicated • Offer private GPs free drug-resistance testing via public TB laboratories
(7) Empirical anti-TB treatment on the basis of an abnormal CXR is fairly widespread	• Expand education programs to cover the risks of overtreatment • Create better laboratory networks and make it easier for private providers to access microbiological testing for their patients

	• Engage providers via public-private mix (PPM) programs which can make TB testing more affordable and accessible to private providers • Enforce stronger regulations for ATT
(8) Use of steroids and quinolones is fairly widespread	• Expand education programs to cover the risks of potentially harmful medicines like steroids and quinolones • Enforce a stronger regulatory framework for dispensation of steroids and antibiotics • Strengthen enforcement of Schedule H1 to limit the abuse of restricted antibiotics and drugs
(9) When anti-TB medicines are prescribed, they generally tend to be four-drug, fixed dose combinations (HRZE)	• Continue incentivizing pharmaceutical companies to make and market FDCs • Give private patients government FDCs from the public sector at no cost • Communicate market needs for expansion of digital adherence technologies to support treatment (smart pill boxes, SMS reminders, 99DOTS, video DOT, etc.) • Provide data to providers on success of FDCs from a patient perspective
(10) What providers know and what they do in practice are often very different ('know-do gap')	• Provide continuing medical education for providers • Periodically audit providers and provide them with feedback, so they can improve their performance • Provide anonymous feedback from SP studies to providers about their performance given a clinical presentation • Address market failures that increase the practice gap (e.g. expensive WHO recommended tests in the private sector that reduce their uptake)
(11) Limited capacity of private providers to support patients with adherence and treatment completion	• Partner with NGOs, TB survivors, and local community organizations to provide patient-centered care and offer peer counseling to TB patients • Engage providers via public-private mix (PPM) programs which can offer adherence support to patients via call centers, counselors, and digital adherence technologies (e.g. SMS reminders; video DOT, smart pill boxes, etc.) • Connect TB patients with TB survivors who can accompany them during their treatment • Provide direct cash benefits to TB patients throughout their TB treatment • Provide mental health and nutritional support during treatment
(12) High costs of care, with 50% of the total incurred before TB is diagnosed	• Engage providers via public-private mix (PPM) programs which can offer free TB tests and drugs from the public sector • Provide direct cash benefits to TB patients at diagnosis and throughout their TB treatment

	• Link TB patients to other social security benefits they may be entitled to (e.g. direct benefits transfers, social insurance, free food rations, etc.)
(13) Private providers are disengaged from government	• Create an overall national policy on PPM for TB • Create policy, regulations, enablers (such as simplified digital systems) and enforcement mechanisms for notification of TB cases • Create policy, regulations and enforcement mechanisms regarding sales of anti-TB drugs and inappropriate diagnostics • Create policy and systems for quality assurance of healthcare practitioners and facilities (such as licensing, certification, registration, accreditation) • Create policy, systems and specialist staff dedicated to contracting and purchasing health services packages
(14) Impact of private sector interventions wane over time	• Engage with the private sector in a sustained manner over time, rather than as a short-term partnership • Continuously seek to understand patient and provider preferences • Establish and nurture relationships • Negotiate viable and mutually beneficial value propositions • Train providers as necessary, but efficiently • Ensure private patients have access to quality-assured diagnostics • Ensure simple models of notification, recording and reporting, often via support provided by an intermediary like an NGO or community • Ensure private patients have access to quality-assured, appropriate drugs
(15) There is wide heterogeneity of care practices	• Ensure diagnostic and treatment algorithms are as per national and international standards of TB care • Integrate notification, recording and reporting with the national data system • Build stronger regulatory capacity for diagnostics, laboratories, and medicines
(16) The information conveyed by patients impacts provider care decisions	• Promote health literary and self-advocacy • Create patient-centered systems • Provide mechanisms for feedback of care delivery

6.3 STRENGTHS AND LIMITATIONS

This work is strengthened by its scale and the SP methodology used. To the best of my knowledge, this is the largest analysis of standardized patient interactions ever published, allowing me the statistical power to ask very specific questions which have otherwise been impossible to assess. As previously highlighted, the SP methodology has the following benefits over other approaches to determining quality of healthcare. Compared to other methods, SP studies can provide an accurate assessment of provider practice that is free from observation bias, less vulnerable to recall bias and allows for valid quality comparisons across different types of healthcare providers.[12,13] This method allows researchers to understand how providers would behave under different counterfactual possibilities.

However, it is important to note the limitations of this work. First, although the studies were population-weighted assessments of average behaviours for these provider types and cities, findings are not necessarily statistically representative of the provider mix that patients face if they were to choose to visit different types of providers. The choices in provider visitation might be informed by gender, socio-economic status, etc. Due to the design limitations of the SP method, such patient-level influencers of care decisions, could not be captured in this study design. Second, we did not conduct qualitative research and thus were not able distinguish appropriate medicine use from misuse in a way that considers a provider's clinical judgement as a whole. A provider's judgement and experience could play a role in either city. Care decisions can reflect a balance between epidemiological likelihood of TB, and valid fears of patient loss to follow-up, transmission potential, etc. Third, the practices that were observed only reflected what healthcare providers did when they came across a completely new patient seeking medical care during an initial visit. Although it was feasible in a pilot study to send back SPs for repeated interactions with the same provider, SPs have not yet been routinely used to construct standardized measures that include follow-up visits to providers, and certainly not at the scale that was used in these studies. Longitudinal assessment and understanding of provider behaviours for the same patient over time was not captured in any of these studies. Fourth, these studies only covered private practitioners in urban areas in India. Findings cannot be extended to rural areas, and results and corresponding interpretations may not be generalizable to contexts outside other high-TB burden, urban cities in India. In addition, SPs cannot measure the quality of care received over the entire treatment phase of TB care, because of their cross-sectional nature and the fact that SPs are not in fact ill; therefore if any clinical indicators are assessed during any visit, physicians might act contrary to indication – even when a medical

diagnostic result is provided (e.g. if the provider sees a healthy patient who lives in a polluted city with no cough, or fever or visible weight loss, they may ignore an abnormal chest X-ray results). Also, since the SP methodology cannot measure long-term outcome such as treatment adherence or completion, it only provides a partial picture of the quality of TB care. For a more complete view, it is necessary to conduct cascades of care and longitudinal cohort studies on patient-important outcomes. Moreover, since a proportion of SP-provider interactions resulted in direct dispensing of unlabelled medicines, certain drugs could not be identified, thus potentially leading to underestimation of the extent of antibiotic and other medicine dispensation. Finally, with the ongoing global COVID-19 pandemic, the landscape of respiratory diseases worldwide has most likely changed since our study was conducted.

6.4 DIRECTIONS FOR FUTURE RESEARCH

Generating more and higher quality data on private provider behaviours and practices is essential to the design and implementation of effective quality improvement interventions. In many LMICs like India, where the private sector plays a major role in healthcare delivery, it is important to gather specific data on prescribing practices among private practitioners and actively involve them in targeted programs aimed at promoting the rational use of medicines, diagnostics, etc.

The SP methodology offers interesting opportunities to further explore practices beyond the specific behaviours I was interested in investigating across chapters 2-5. For instance, new SP clinical presentations and conditions representing common infections such as community-acquired pneumonia or COVID-19 could be developed and used in future research to better evaluate the adherence to national and international guidelines and determine the appropriateness of therapeutic choices. This approach could also prove valuable in assessing the impact of tailored qualitive improvement interventions. Additionally, fostering the transition from paper-based to electronic documentation and establishing minimum quality standards for prescription and diagnostic records in both private and public sectors would be import to produce accurate and nationally representative periodic evaluations of prescribing patterns, diagnostic practices and provider care decisions. Because antibiotic, and more specifically, quinolone use, is closely intertwined with the emergence of resistance strains, improving our knowledge on the amount of antibiotics used in human medicine and other sectors along with their underlying determinants is a global priority. The irrational use of corticosteroids poses similar challenges globally, and would thus it would also be useful to know the real extent of their dissemination. For antibiotics, corticosteroids and other potentially harmful medicines discussed in this thesis, action is needed to rapidly diminish their indiscriminate application for both presumptive and confirmed TB and COVID-19 cases. Both these indications alone are likely contributing to substantial overuse across the globe.

This thesis has also brought to light additional research questions that would enhance our understanding of TB care in the Indian private sector. We had first envisioned to compliment our SP studies with qualitative and ethnographic research on why providers treat empirically, why they give out FQ or steroids, etc. This, however, was not possible due to the onslaught of the COVID-19 pandemic – field visits would have been altogether impossible. Next, SP research to directly compare quality of TB care in the private sector versus public sector in India would have been interesting. Specifically, it would be important

to see how these sectors compare in Patna specifically, as this work is already underway in Mumbai. It would also be interesting to understand decision-making rationale from the patients' perspective; for example, understanding why patients prefer private sector care despite the obvious issues including suboptimal quality of care and higher costs. I could also envision designing new SP cases that mimic COVID-19 to see if providers confuse TB with COVID-19, or whether they are more likely to test for COVID-19 than TB. Moreover, it would be good to understand how the syndemic diseases of TB and COVID-19 could benefit from synergies in healthcare offerings, or if, rather, an antagonistic relationship emerges between the two diseases. In other words, to understand if and how one (likely COVID-19) is prioritized in terms of treatment, diagnosis, funding etc. I would also be interested to perform a 'know-do-gap' analysis in Patna by directly comparing clinical vignettes to the SP study findings between the same providers.

6.5 CONCLUSION

To improve TB patient outcomes, India must first accurately address its quality of care issues. This work is a step forward in understanding the experiences and outcomes of TB patients in the understudied Indian private sector and promotes the use of modern methodological techniques to minimize bias when estimating quality of care metrics. More studies need to be undertaken to generate new accurate data and take action accordingly. Through consistent efforts to improve quality of care, India can succeed in curbing its TB epidemic.

6.6 SUPPLEMENTARY

ISERDD **SP2 Exit Questionnaire** **"Santosh/Laxmi"**

Provider ID: ☐☐☐☐☐☐☐☐☐ **Form No:** ☐☐☐☐

	Cover Page				
CP1	City Name शहर का नाम	**PATNA**	**CP2**	City ID शहर की आई डी	**2**
CP3	Facility Name फैसिलिटी का नाम				*English*
CP4	Facility ID फैसिलिटी आई डी	☐☐☐☐☐☐☐☐☐			
CP5	Provider Qualification प्रोवाइडर की डिग्री	*No Degree=01, RMP=02, BAMS=03, BIMS=04, BUMS =05, BHMS/DHMS=06 BEHMS/BEMS=07, MBBS=08, MBBS+MD=09, Chemist=10, Other=11, Unknown= 99*			☐☐
CP6	Provider Name प्रोवाइडर का नाम				*English*
CP7	Provider ID प्रोवाइडर की आई डी	☐☐☐☐☐☐☐☐☐			
CP8	Interviewer name साक्षात्कारकर्ता का नाम		**CP9**	Interviewer ID साक्षात्कारकर्ता की आई डी	☐☐

	Visits	**Visit 1** पहला विज़िट	**Visit 2** दूसरा विज़िट	**Visit 3** तीसरा विज़िट
CP10	Date (DD/MM/YYYY) सर्वे की तारीख	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
CP11	SP Name एस पी का नाम			
CP12	SP ID एस पी आई डी	☐☐	☐☐	☐☐
CP13	Arrival Time (hh:mm) पहुँचने का समय	☐☐:☐☐	☐☐:☐☐	☐☐:☐☐
CP14	Case Completion केस पूरा हुआ *Yes=1, No=2*	☐	☐	☐
CP14a	If no, give reason यदि नहीं कारण दीजिए।	☐	☐	☐
	Waited 3 hours = 1; Provider in town but not coming to clinic = 2; Provider out of town = 3; Clinic locked = 4; Provider no longer practicing = 5; Provider migrated= 6; Address was not correct = 7; Visited the provider before = 8; Made appointment = 9			
CP14b	Days until appointment? कितने दिन बाद अपोइंटमेंट मिला?	☐☐	☐☐	☐☐
CP14c	Departure Time (hh:mm) जाने का समय	Fill if case completed तभी भरें, यदि केस पूरा हो गया हो		☐☐:☐☐
CP14d	Total Time with Provider प्रोवाइडर के साथ कुल समय	Fill if case completed तभी भरें, यदि केस पूरा हो गया हो	☐☐ (mm) :	☐☐ (ss)

CP15	Do you know if you went to the correct clinic location? क्या आपको पता है कि आप सही क्लीनिक पर गये?	*1=Yes; 2=No; 3=Don't know*	☐
CP16	Did you see the sampled provider? क्या आपने सेम्पल प्रोवाइडर को दिखाया?	*1=Yes; 2=Did not see sampled provider; 3=Don't know; 4=Not assigned*	**4**
CP16a	What was the name of the provider you saw? जिस प्रोवाइडर को आपने दिखाया उसका नाम क्या था?		*if unknown write -99*
CP17	In which age group do you think the provider falls? आपके हिसाब से प्रोवाइडर किस उम्र का लगता है?	*1=Under 30, 2=Between 30 and 50, 3=Above 50*	☐
CP18	Provider Gender प्रोवाइडर का लिंग	*1=Male पुरुष, 2=Female महिला*	☐
CP19	How many patients were waiting when you reached the clinic? जब आप क्लीनिक में पहुँचे तब कितने रोगी इन्तजार कर रहे थे?		☐☐
CP20	How many patients were in the clinic when you left? जब आप क्लीनिक से बाहर निकले तब कितने रोगी बाकी थे?		☐☐
CP21	Did the provider have a compounder? क्या प्रोवाइडर के पास कम्पाउंडर था?	*1=Yes; 2=No; 3=don't know*	☐
CP22	Did the provider/compounder take your name, address? क्या प्रोवाइडर/कम्पाउंडर ने आपका नाम, पता लिखा?	*1=Yes; 2=No; 3=don't know*	☐
CP23	Did the provider/compounder take your phone number? क्या प्रोवाइडर/कम्पाउंडर ने आपका फोन नम्बर लिया?	*1=Yes; 2=No; 3=don't know*	☐

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S6-Figure 1: *Example exit questionnaire used in SP study.*

STANDARDIZED CASE 1: CLASSIC CASE OF SUSPECTED TB (WITH NO ANTIBIOTICS OR X-RAY)
स्टैन्डराईज्ड केस 1: क्लासिक केस ऑफ सस्पेक्टेड टी बी (बिना एन्टीबायोटिक या एक्स-रे)

Ravi (Male)

Ravi is a 35 year old male who has studied up to 10th standard. He is the owner of a small tea shop. Today, in the morning like any other day, when he leaves for his work, his wife Rekha, handing him his lunch box asks, "Why are you not eating your lunch properly - you leave most of it uneaten every day?" Ravi replies, "I have cough and seem to have lost my appetite." Ravi's family is small. It consists of his wife and two children, aged six (daughter) and four (son) and they live in a two-room house, which he owns. His business at the tea stall is doing well as he is able to earn on average rupees 8000– 10000 per month. Generally Ravi keeps good health. He has not had any major health problems or any chronic Illness. His wife and children too are in good health. But since last 2-3 weeks, he is suffering from cough, which is more or less present during early morning and night, and it also has expectoration though that does not have any color in it and is clear. He also has low-grade mild fever, on and off, which gets worse during the evening time. But since this problem started he feels a bit tired and also has lost some weight, as his clothes have gotten a bit loose. He does not suffer from any associated chest or body pain. He smokes 4-5 *beedis* during the day since last 8-10 years and drinks alcohol once or twice in the month. His relationship with his wife is good. He loves her very much. He has a cheerful and an easy going personality, but today his face bears a tense look as he is worried about his cough and fever and visits a doctor nearby.

रवि (पुरुष)

रवि एक 35 साल का व्यक्ति है जिसने 10वीं कक्षा तक पढ़ाई की है। रोजगार के लिये वह अपनी चाय की दुकान चलाता है। जिसे वह खोलने के लिये हर रोज की तरह आज भी अपने घर से निकलता है और निकलते समय उसकी पत्नी रेखा खाने का डिब्बा देते हुये बोलती है कि''क्या बात है आजकल आप खाना ठीक से नहीं खा रहे हो''? रवि कहता है ''मुझे खाँसी है और भूख भीकम लग रही है''। रवि का छोटा परिवार है, जिसमें उसकी पत्नी और दो बच्चे है, लड़की की उम्र 6 साल और लड़के की 4 साल है। रवि दो कमरे के खुद के मकान में रहता है। रवि की चाय की दुकान ठीक चलती है जिससे वह औसतन 8 से 10 हजार रुपये महीना कमा लेता है।

आमतौर पर रवि का स्वास्थ्य अच्छा रहता है,उसे किसी भी तरह की तकलीफ और कोई लम्बी बिमारी नहीं है। उसकी पत्नी और बच्चों का स्वास्थ्य भी अच्छा है। लेकिन रवि को पिछले 2–3 हफ्तों से खाँसी है, जो सुबह और रात के समय ज्यादा होती है।उसकी खाँसी के साथ बलगम भी आता है जिसका कोई रंग नहीं है, वह साफ है। खाँसी के साथ उसे हल्का बुखार रहता है जो चढ़ता–उतरता है, लेकिन अक्सर शाम के समय ही ज्यादा होता है। जब से उसे यह तकलीफ शुरु हुई है तब से उसे थकावट महसूस हो रही है।उसे लगता है कि उसकाकुछ वजन कम हो गया है क्योंकि उसके कपड़े ढीले हो गये है। उसे इस तकलीफ में किसी भी तरह का छाती का दर्द और बदन दर्द नहीं है।

वहदिन में 4 से 5 बीड़ी पीता हैऔर उसकी यह आदत पिछले 8–10 सालों से है। महीने में एक या दो बार शराब का सेवन भी कर लेता है। उसके अपनी पत्नी के साथ अच्छे सम्बन्ध है।वहउसे बहुत प्यार करता है। वह हंसमुख और मिलनसार स्वभाव का व्यक्ति है, लेकिन आज उसके चेहरे पर अपनी खाँसी और बुखार को लेकर थोड़ी परेशानी है जिसको लेकर वह नजदीक के डॉक्टर के पास गया है।

1

S6-Figure 2: *Example narratives used SP study (continued on next pages).*

STANDARDIZED CASE 2: CLASSIC CASE OF SUSPECTED TB, ALREADY TREATED WITH ANTIBIOTICS AND CARRYING X-RAY

स्टैन्डराईज्ड केस 2: क्लासिक केस ऑफ सस्पेक्टेड टी बी, पहले से ही एन्टीबायोटिक दवाई के साथ किया गया इलाज और छाती X-ray साथ ले जाना

Santosh (Male)

Santosh is a 40 year old male who has studied up to 10th standard. He works as a salesman in a garment shop and gets rupees 8000 – 10000 as monthly salary. Santosh's family is small. It consists of his mother, wife and two children, aged twelve (daughter) and ten (son) and they live in a small house which has two rooms, a separate kitchen and bathroom built on a 25 square yard plot which he owns. His children attend a nearby government school.

Generally Santosh keeps good health. He has not had any major health problems or any chronic Illness. His wife and children too are in good health. But since last 1 month he has been suffering from cough, which is more or less present during the day, and has expectoration though that does not have any color in it and is clear. He also has a low grade mild fever, on and off, which gets worse during the evening. But since this problem started he feels a bit tired and also has lost some weight, as his clothes have gotten a bit loose. He does not suffer from any associated chest or body pain.

Around two weeks back, he went to a doctor who asked him to get an X-Ray done and had given him some capsules. He got the x-ray done but then was scared to go back and was feeling better with the medicines. He feels that the cough is again becoming worse so he has brought the x-ray and empty capsule blister pack. He wants to ask if there is any reason to be worried. He smokes 4-5 beedis during the day since last 15-20 years and drinks alcohol once or twice in the month. His relationship with his wife is good. He loves her very much. He has a cheerful and an easy going personality.

सन्तोष(पुरुष)

सन्तोष 40 साल का व्यक्ति है जिनकी स्कूली शिक्षा 10वीं तक है और पिछले कई सालों से कपड़े की दुकान पर सेल्स मेन का काम करते है जिसके लिये उन्हें 8–10 हजार रुपये महिना तनख्वाह मिलती है। सन्तोष का एक छोटा परिवार है जिसमें इनकी माँ, पत्नी और दो बच्चे लड़की 12 वर्ष और लड़का 10 वर्ष का है। दोनों बच्चे पास के सरकारी स्कूल में पढ़ते है। सन्तोष स्वयं के 25 गज के मकान में रहता है जिसमे दो कमरे और किचन बाथरुम है।

आमतौर पर सन्तोष का स्वास्थ्य अच्छा रहता है, उसे किसी भी तरह की तकलीफ और कोई लम्बी बिमारी नहीं है। उसकी पत्नी और बच्चों का स्वास्थ्य भी अच्छा है। लेकिन सन्तोष पिछले एक महीने से खाँसी से परेशान है जो सुबह के समय ज्यादा होती है। उसकी खाँसी के साथ बलगम भी आता है जिसका कोई रंग नहीं है, वो साफ है। उसे हल्का बुखार जो चढ़ता–उतरता रहता है पर अक्सर शाम के समय ही ज्यादा रहता है। जब से उसे यह तकलीफ शुरु हुई है तब से उसे थकावट महसूस हो रही है। उसे लगता है कि उसका कुछ वजन कम हो गया है क्योंकि उसके कपड़े ढीले हो गये है। उसे इस तकलीफ में किसी भी तरह का छाती का दर्द और बदन दर्द नहीं है।

डो हफ्ते पहले सन्तोष ने नजदीक के प्राईवेट डॉक्टर को दिखाया जिसने उसे एक हफ्ता केप्सूल खाने के लिये दिये और एक छाती का एक्स–रे कराने को कहा। उसने एक्स–रे करवा लिया पर दोबारा डॉक्टर के पास जाने में डर रहा है मगर उसको दवाई से थोड़ा आराम आ गया। सन्तोष को लग रहा है कि अब उसकी खाँसी ज्यादा होती जा रही है इसलिये आज काम पर जाते वक्त सन्तोष ने अपनी दवाई का खाली पत्ता और एक्स–रे अपने थेले में रखा और सोचा कि आज समय निकाल कर डॉक्टर के पास जरूर जाऊँगा और पूछूंगा कि कहीं कोई चिन्ता की बात तो नहीं है? पिछले 15–20 सालों से सन्तोष रोज दिन में 4 से 5 बीडी पी लेता है और महीने में एक या दो बार शराब का सेवन भी कर लेता है। सन्तोष अपनी पत्नी के प्रति बहुत वफादार है और उससे बहुत प्यार करता है। वह हंसमुख और मिलनसार स्वभाव का व्यक्ति है।

STANDARDIZED CASE 3: PATIENT WITH TB SYMPTOMS AND A POSITIVE SPUTUM SMEAR RESULT ("TB CASE")

स्टैन्डराईज्ड केस 3: एक मरीज जिसको टी बी के लक्षण है और उसका सपूटम स्मियर रिजल्ट पॉजिटिव है ("टी बी केस")

Ramesh (Male)

Ramesh is a 25 year old male from Bihar and has studied up to 12th standard from his village. He came to Patna 5-6 years back in search of job and since then he has been working as a messenger boy in a courier company. He earns rupees 8000 to 9000 in a month from this work. He lives in a rented room, which he shares with other two people. He sends money every month to his family back in the village. Ramesh's family is small. It consists of his father, mother, wife and a three year old child. Generally Ramesh keeps good health. He has not had any major health problems or any chronic Illness. His parents, wife and child too are in good health. But since last one month he is suffering from cough which is more or less present during early morning and night, and it also has expectoration though that does not have any color in it and is clear. He also has low grade mild fever, on and off, which gets worse during the evening time. But since this problem started he feels a bit tired and also has lost some weight, as his clothes have gotten a bit loose. He does not suffer from any associated chest or body pain. And for this problem, he had visited a government hospital once and where they gave him some pills for the fever and asked him to undergo sputum test, which he did at the hospital itself. He has got the test results with him, and someone at his office suggested that he should see a private doctor. He is going to a private doctor and has brought along with his sputum report. He smokes 4-5 *beedis* during the day since last 6-7 years and drinks alcohol once or twice in the month.

रमेश(पुरुष)

रमेश25 साल का व्यक्ति है जो बिहार का रहने वाला है। उसनेगाँव में रह कर बारहवीं कक्षा तक पढाई की है। रोजगार के लिये वह पिछले 5–6 सालों से दिल्ली में रह रहा है और एककुरियर कम्पनी में मेसेन्जर बॉय का काम करता है। वह एक किराये के कमरे में दो लोगो के साथ मिलकर रहता है। उसकेपरिवार में बुढ़े माँ–बाप, बीबी और एक बच्चा है जो गाँव में ही रहते है।रमेश की औसतन आय 8000 से 9000 रुपये है। वहगाँव हर महिने अपने माँ–बाप को पैसा भेजता है।

वैसेतो रमेश स्वस्थ रहता है उसे कभी कोई लम्बी बिमारी नहीं रही और ना ही उसके परिवार में किसी को कोई लम्बी बिमारी नहीं हुई है। रमेशको पिछले एक महिने से खाँसी और बुखार है,खाँसीसुबह और रात के समय ज्यादा होती है। उसकी खाँसी के साथ बलगम भी आता है जिसका कोई रंग नहीं है, वह साफ है।खाँसी के साथ उसे हल्का बुखार रहता है जो चढ़ता–उतरता है, लेकिन अक्सर शाम के समय ही ज्यादा होता है।जब से उसे यह तकलीफ शुरु हुई है तब से उसे कमजोरी महसूस हो रही है और उसे लगता है कि उसका वजन कम हो गया है, क्योंकि उसके कपड़े ढीले हो गये है।

इस तकलीफ के लिये रमेशने एक बार सरकारी अस्पताल में दिखाया था, जहाँउसे बुखारकी दवाई दी और थूक की जॉच करवाने के लिये कहा,जो कि उसने वहाँ सेही करवा ली।उसेउसके ऑफिस में किसी व्यक्ति ने प्राइवेट डॉक्टर को दिखाने की सलाह दी और वह अपनी थूक जॉच की रिपोर्ट को लेकर डॉक्टर के पास गया है।

रमेश दिन में 4 से 5 बीडी पी लेता है उसकी यह आदत पिछले 6–7 सालों से है। महिने में एक या दो बार शराब का सेवन भी कर लेता है।

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STANDARDIZED CASE 4: A CASE OF SUSPECTED MDR-TB (PREVIOUS HISTORY OF TB TREATMENT)
स्टैंडर्ड केस 4: एम आर डी – टी बी (पहले टी बी का इलाज़ लिया हुआ है)

Suraj (Male)

Suraj is a 38 year old male who has studied up to 10th standard while he was living with his uncle (Chacha) in the city. He works in a General Store and earns rupees 7000 to 8000 in a month. He lives in the city in a rented two room house with his wife and three children, aged 13 (boy), 10 (girl) and 6 (boy) and all of them are studying in a government school. His parents are back in the village where his father has a small piece of land.

Suraj had developed a cough last year for which he went to a government hospital near his house where after a sputum test and chest x-ray he was diagnosed with TB. He was given 6 or 7 different types of tablets and had to take them on alternate days. (ek din chod kar). He took the treatment for 4 to 5 months and then stopped as he felt better. But after stopping the medication he had mild cough, which used to subside on its own. His family has been keeping well and none of them have ever had any of his symptoms.

But since last one month, he is suffering from cough, which is more or less present during early morning and night, and he also has expectoration in which he has seen flecks of blood once or twice in a month. He also has low grade mild fever, on and off, which gets worse during the evening time. But since this problem started he feels a bit tired and also has lost some weight, as his clothes have gotten a bit loose. He does not suffer from any associated chest or body pain. He has tried some home remedies and cough syrup from a local chemist for the problem. However, the cough had not subsided. He has misplaced other medical records. He smokes 4-5 *beedis* during the day since last 10-12 years and drinks alcohol once or twice the month.

सूरज (पुरुष)

सूरज 38 साल का व्यक्ति है जिसने शहर में अपने चाचा के पास रहकर 10वीं कक्षा तक पढ़ाई की है। सूरज के माता–पिता के पास गाँव में खेती के लिए छोटी सी जमीन है। सूरज अपनी पत्नी और तीन बच्चों के साथ जिनकी उम्र 13 (लड़का), 10 (लड़की) और 6 (लड़के)साल की है जो किराये के दो कमरों के मकान में रहते है। सूरजएक किराना की दुकान (जनरल स्टोर) में काम करता है जहाँ उसेमहीने के 7000 से 8000 रूपये तनख्वाह मिलती है। उसकेतीनों बच्चे सरकारी स्कूल में पढ़ते है।

सूरज को पिछले साल खाँसी हो गयी थी जिसके लिये उसने घर के पास ही एक सरकारी अस्पताल से इलाज कराया था। वहाँ थूक और एक्स–रे की जाँच के बाद पता चला की उसे टी बी है।वहाँ से 6–7 तरह की दवाईयाँ मिलती थी, जिन्हे एक दिन छोड़कर खाना होता था। उसने यह इलाज 4–5 महीनेलिया और फिर बन्द कर दियाक्योंकि उसे लगा कि उसे आरामआ गया है। इलाज छोड़ने के बाद सूरज को बीच–बीच में खाँसी हो जाती थी मगर वह अपने आप ही ठीक हो जाती थी। सूरज की पत्नी और बच्चों का स्वास्थ्य अच्छा है और किसी को भी कोई लम्बी बिमारी नही रही।

लेकिनपिछले एक महीने से सूरज को फिर से खाँसी और बुखार की परेशानी हो रही है।खाँसी के साथ बलगम भी आता है जिसमें पिछले महिने में एक–दो बार लाल रंग के धब्बे भी दिखाई दिये है।उसे हल्का बुखार है, जो चढ़ता–उतरता रहता है पर अक्सर शाम के समय ही ज्यादा रहता है। जब से उसे यह तकलीफ शुरु हुई है तब से उसे थकावट महसूस हो रही है। उसे लगता है कि उसका कुछ वजन कम हो गया है क्योंकि उसके कपड़े ढीले हो गये है। उसको किसी भी तरह का छाती और बदन दर्द नहीं है। सूरज ने पिछले महीने कैमिस्ट से खाँसी का सिरपऔर कुछ घरेलू उपचार किये जिससे उसकी खाँसी में कुछ आराम नहीं आया। उसके सभी मेडिकलरिकार्डकहीं खो गये है।

सूरज दिन में 4 से 5 बीड़ी पीता है और उसकी यह आदत पिछले 10–12 सालों से है। महिने में एक या दो बार शराब का सेवन भी कर लेता है।

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