Treatment as diagnosis and diagnosis as treatment: empirical management of presumptive tuberculosis in India

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SUMMARY

BACKGROUND: Mismanagement of TB is a concern in the Indian private sector, and empirical management might be a key contributor.

OBJECTIVE: To understand factors associated with empirical diagnosis and treatment of presumed TB in India’s private sector and examine their effects on TB care.

DESIGN: In this ethnographic study, 110 private practitioners of varying qualification who interacted with TB patients (90 in Mumbai and 20 in Patna) were interviewed, and a subset was observed while providing clinical care. Interviews and observations were analysed for indicators of empirical diagnosis and treatment.

RESULTS: All non-specialist practitioners began antibiotic treatment, especially quinolones, for persistent cough before prescribing a test. Several factors contribute to empirical management. These include a common practice use of medications as diagnostic tools, a desire to provide rapid symptom relief to patients, a desire to manage illness costs effectively, uncertainty about the presentation of TB, the effects of broad spectrum antibiotics on TB symptomology, and uncertainty about the accuracy of available TB tests.

CONCLUSION: Empiricism in general and in TB care is widespread in the urban private sector in India. Ethnography might offer useful insights for addressing this in public-private mix models.

KEY WORDS: tuberculosis; India; private sector; empiric management; fluoroquinolones

IN 2014, INDIAN TUBERCULOSIS (TB) patients accounted for approximately one fourth of the 9 million new cases annually, and nearly a million of the estimated 3 million annually ‘missed’ cases.1 TB incidence in India is not declining as quickly as expected.2 At the same time, drug resistance rates have increased, especially in urban hotspots such as Mumbai,3–5 where extensively drug-resistant and totally drug-resistant strains have also been reported.6

Experts suggest that engaging with the Indian private sector is essential for TB control;7–15 however, relatively little is known about the private sector. Previous research has suggested that the private sector is unregulated in structure, and has reported various non-standard practices as well as reluctance to become involved in public-private mix (PPM) projects.8,16–19 The private sector includes physicians ranging in degree from ‘a bachelor of medicine and bachelor of surgery (MBBS) degree, to degrees based on traditional systems of medicine such as Ayurveda or Unani, to distance education courses with six months of training to no medical training at all’.20,21 A study of households in Delhi showed that 70% of health visits were to private sector providers, and among visits to the private sector, nearly a third were to providers with little or no training.22 Moreover, 80% of primary health care visits have been shown to be in the private sector.20 An earlier study revealed a similar pattern in Mumbai.18

Recent work also shows that about 50% of patients seek anti-tuberculosis treatment outside the public sector.23 Studies on the quality of private sector TB care show a diversity of treatment regimens and diagnostic tools used.24–26 Among private providers, there is no unified protocol for diagnosis, and treatment regimens provided to patients often do not meet international standards.27 Private sector management of TB has been shown to be characterised by high rates of non-standard drug regimens, dosages and treatment durations.24,25,28,29 Such variability in care can generate multidrug-resistant TB (MDR-TB) and increase the cost of care for patients.

In 2013, MDR-TB accounted for approximately 2.2% and 15% of new and relapse cases, respectively, globally.3 The World Health Organization estimated that there were 62 000 MDR-TB cases in India in 2013.30 Resistance to second-line drugs, such as fluoroquinolones (FQs), due to their use as broad

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spectrum antibiotics prior to TB diagnosis, intensifies this challenge. Widespread empirical treatment of several infections with quinolones contributes to patterns of resistance that bypass many of the second-line drugs and delay appropriate treatment. \(^{32-36}\) FQ resistance is a defining feature of extensively drug-resistant TB (XDR-TB). The study population included 150 hours of clinical observation and 75 semi-structured interviews or follow-up conversations with physicians, and treatment, including 143 semi-structured interviews suggested, and deeper investigation confirmed, to effect empirical treatment. These included the utility and trustworthiness of local laboratory services, the cost-effectiveness of laboratory diagnostics as compared to drug treatments, locally salient and qualification-specific understandings of TB epidemiology, patients’ needs, providers’ diagnostic paradigms, processes for ordering a test and receiving a laboratory result, and familiarity with the range of tests available for TB.

AM conducted clinical observation in seven clinics, in three of which he asked patients to give entrance and exit interviews. During clinic observation we focused on practitioner and patient interaction, particularly with requests for laboratory-based tests, presenting patients with the diagnosis, referrals, changes in practice across patient visits, the type of medicine distributed or prescribed by the practitioner, and the type of clinical examination performed by the practitioner. We began clinical observation after at least two interviews with the practitioners and observed clinics in 5-h time slabs over at least 3 consecutive days. Although observation may have affected the type of care provided, we combined interview with observation and multiple visits to reduce any distortion. Moreover, providers are likely to have adjusted their practice to bring it closer to their assumed ideal under observation, in which case our results are likely to underemphasise the extent of empirical diagnosis and treatment instead of overestimating it.

We also observed and participated in six pulmonary care Continuing Medical Education (CME) events, organised as part of the PPIA intervention, which included physicians from a broad array of qualifications in Mumbai. We selected CMEs in which at least one chest physician was present and giving a lecture. At CMEs, we focused both on the message shared by the chest physicians and the kind of interactions (questions, visual aids, networking opportunities) that unfolded there.

Semi-structured interviews allowed for flexibility in conversation, while clinical observations presented
in situ examples of reported behaviour. Interviews were conducted in Hindi or English and were reviewed on a weekly basis to provide insights for follow-up interviews. Notes were also taken to document non-verbal communication, clinical practice and setting characteristics.

Data analysis
We analysed the data with the help of detailed descriptions of diagnostic practices, settings, interactions and examination practices between emerging themes, research goals, actors and diagnoses. Survey results were triangulated with clinical observation and group discussion in CME meetings. Identities and locations have been masked to protect participant identities. We transcribed and cross-checked notes and audio files. As primary care providers in our sample rarely maintain medical records or follow written protocols, we did not review any records or written protocols.

On a weekly basis, we reviewed interviews and observations to generate a unique list of themes to add to existing themes. As data accumulated, we continued to examine it for themes and cross-checked those themes with new and existing interviewees as well as observations. We looked for repetitions and variations in interview content and contexts (claims made before and after a comment about empirical treatment and diagnosis). We also analysed for interview themes in clinical practice, particularly during observations, and focused our analysis on themes that occurred in both interviews and observation. We then searched for connections between themes and consulted key informant practitioners for their feedback on our analysis.

Ethics
The study was approved by the Research Ethics Board at McGill University Health Centre, Montreal, QC, Canada. An information sheet was made available for participants. All participants provided oral consent to participate in the study, and their data were anonymised.

RESULTS

Treatment strategies
All sampled MBBS, Bachelor of Ayurveda, Medicine and Surgery (BAMS), Bachelor of Homeopathy, Medicine and Surgery (BHMS) and Bachelor of Unani, Medicine and Surgery (BUMS) physicians (n = 105, Table) in both conversation and practice began by symptomatically treating pulmonary conditions based on patient history and clinical observation. Although diagnostic services were never more than 1 km from the clinic, physicians felt that their patients needed and desired drug treatment before testing. They often referred to patients’ remarks, ‘doctor, I have to go to work tomorrow,’ as evidence of what they considered was the need for rapid relief and patients’ readiness to choose another practitioner if asked for a test in lieu of treatment on their first visit. Although the number of MBBS physicians in the sample was limited, the diagnostic practices of the 13 MBBS physicians resembled those of the other practitioners. We found no significant differences in the general pattern of care in terms of age, degree (except Doctor of Medicine [MD]), years of training, years of practice or sex.

One BAMS physician commented:

I work in a slum and my patients can spend a bit of money, but not all at once and they prefer not to spend on health care. I can treat them (with drugs) for a week or I can send them for tests, it is the same cost. I must first try to treat and help them save the money.

Another BHMS physician a few kilometers away reiterated his view that empirical treatment is in the patient’s financial best interest:

<table>
<thead>
<tr>
<th>Physician type</th>
<th>Characteristics</th>
<th>Sample size</th>
<th>Method</th>
</tr>
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<tbody>
<tr>
<td>MD/MD Chest</td>
<td>Post-graduate training in medicine, with or without specialisation</td>
<td>5</td>
<td>Observation during CME event (n = 1) Interviews (n = 6)</td>
</tr>
<tr>
<td>MBBS</td>
<td>Medical degree from an accredited medical school of biomedicine</td>
<td>13</td>
<td>Observation during a CME event (n = 2) Interviews (n = 13)</td>
</tr>
<tr>
<td>BAMS</td>
<td>Medical degree from an accredited school of Ayurveda—an Indian medical system derived from Sanskrit medical texts</td>
<td>55</td>
<td>Observation during CME event (n = 3) Interviews (n = 73) Clinics observed (n = 3)</td>
</tr>
<tr>
<td>BHMS</td>
<td>Medical degree from an accredited school of homeopathy—a form of alternative medicine popularised by Hahnemann in early nineteenth century Europe and United States</td>
<td>34</td>
<td>Observation during CME event (n = 1) Interviews (n = 45) Clinics observed (n = 3) Patient interviews (n = 65)</td>
</tr>
<tr>
<td>BUMS</td>
<td>Medical degree from an accredited school of Unani—an Indian medical system derived from Greek and Arabic medical texts</td>
<td>3</td>
<td>Observation during a CME event (n = 1) Interviews (n = 6) Clinics observed (n = 1)</td>
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MD = Doctor of Medicine; CME = continuing medical education; MBBS = Bachelor of medicine, Bachelor of surgery; BAMS = Bachelor of Ayurveda, Medicine and Surgery; BHMS = Bachelor of Homeopathy, Medicine and Surgery; BUMS = Bachelor of Unani, Medicine and Surgery.
Patients do not accept a test on the first visit. If they do not become well then we can ask for tests but not on the first few visits, especially before our treatment has had time to work. Most likely, the problem is just an everyday infection anyway.

This BHMS physician refers to the practice of distributing one or two doses of medicines per visit and charging only a small fee (usually INR30–70, equivalent to US$0.45–1.05). Of the 90 non-MBBS practitioners AM interviewed in Mumbai, 89 (98.9%) distributed allopathic medicines in this fashion. By comparison, a single complete blood count (CBC) test often costs more than 1 week of treatment.

Another BAMS physician who practises near the middle of a large North Mumbai slum is a good example of diagnostic practices across Mumbai, and highlights the ways physicians change drug prescriptions over time.

I do not usually suspect TB at first. On a first visit, I give amoxi-clavulanate (amoxicillin and clavulanate potassium). I give 3 days of amoxi-clavulanate, a painkiller, a bronchodilator and an anti-pyretic. I ask the patient to come back in 3 days. They almost always come back, and if they feel a little better I keep going with the amoxicillin-clavulanate but if they do not feel any better I change to azithromycin. I give them that for 3 days and ask them to come for follow-up. If that too does not work, I change again to ofloxacin for another 3 days. If a patient does not feel better after the ofloxacin I will try to tell the patient about tests. Sometimes they are willing to get tested, but other times it scares them or they are suspicious of me. If they look willing, I’ll ask for a complete blood count, an erythrocyte sedimentation rate, and a chest X-ray. If the laboratory results look bad, like if there is a shadow on the X-ray, I either start TB medicines or I refer the patient to the public sector or a chest specialist. But I will not think about TB before my regimen fails.

Although he and many others are aware of the high TB burden in Mumbai and in India more generally, none of the non-allopathic physicians reported that they regularly suspect TB on a first visit with history of chronic cough. ‘I will not think TB unless the problem persists for some time despite treatment,’ was considered a rule of thumb. Thus, passage of time and multiple failed empirical broad-spectrum antibiotic trials were necessary before practitioners considered TB.

Uncertainty around tuberculosis and accuracy of tests

The insidious nature of TB, its multiple manifestations, and its diversity of often vague symptoms further complicates diagnosis. An MBBS physician in Patna explained:

A surgeon in Mumbai commented,

I am a surgeon, so I did not think I would find much TB in my practice, but often when I am doing surgery, like an exploratory surgery, we find TB in the abdomen. It is not uncommon to find out the patient has TB rather than some gastrointestinal problem.

While it is already well-known that Indian private practitioners underuse sputum smear microscopy testing, which is known to lack sensitivity, the underlying reasons are less well understood. One BHMS physician who practises in east central Mumbai explained why sputum smears were less important for him:

I do not see so much value in a smear. My patients, even if they do produce sputum, do not usually give a good sample. I can see cavities on an X-ray so what more can a sputum smear tell me? It is a yes/no test. It is the very end of my diagnostic plan and even then I already more or less know it is TB. What more can sputum tell me?

Such criticism also extends to the Xpert® MTB/RIF assay (Cepheid Inc, Sunnyvale, CA, USA). An MBBS doctor in Mumbai commented:

But why should I use Xpert? It only tells if the patient is rifampicin susceptible or not, but it does not tell me anything else. It is better to give first-line drugs and see if the patient responds. After some time we will know if the first-line drugs are working and if they do not we know we need to move on. Xpert tells us about rifampicin quickly but what we really need is a culture and that takes time. In Mumbai, Xpert is not enough to decide on a proper second-line regimen.

No practitioner reported empirical treatment with first-line anti-tuberculosis drugs as the preferred option. Those who reported suspecting TB, often after months of fever, preferred to administer a chest X-ray, complete blood count, erythrocyte sedimentation rate, or occasionally a smear for acid-fast bacilli for confirmation. None reported or were observed starting first-line drugs without administering a chest X-ray; however, treatment was occasionally started in the context of negative tests. An MD practising in Mumbai’s large central slum explained:

If I see a patient who is not responding to anything, then I think of TB. Even if the tests are inconclusive I have to treat her with TB drugs. She is probably infectious. So many of my patients have a negative sputum smear but a positive X-ray. In Mumbai maybe half of my patients are negative...
on a sputum smear. Many do not even produce sputum.

**TB as fever disease**

Providers frequently noted the ubiquity of cough in urban India and paucity of sputum production among their patients to highlight their emphasis on fever as a diagnostic criterion for TB. This lack of productive cough combined with increased concern about extra-pulmonary TB makes cough less important. One BAMS practitioner commented:

> For me TB is a fever disease. Sometimes (it is characterised by) cough, of course, but in Mumbai there is so much pollution a long-term cough can be from allergy or irritation or chronic obstructive pulmonary disease. Everyone coughs. When symptoms include rising fever in the evening, then I think about TB. When a patient has unexplained weight loss and fever that does not respond to antibiotics I think: ‘Maybe it’s diabetes, maybe it’s typhoid, maybe it is TB,’ in that order. I run a sugar test and treat for typhoid, but if it still persists I begin to think about TB.

Another BHMS practitioner explained,

> Sometimes, anti-tuberculosis drugs may be used with fever and unresolved gastric pain. If symptoms improve we think it is maybe TB. How else can we confirm the diagnosis? The patient is not coughing or producing sputum.

TB as a fever disease with multiple effects becomes an explanation after physicians become confused. A BAMS practitioner who treats more than 100 patients a day from a small clinic shared his thoughts on diagnosis.

> If I have a patient with pyrexia of unknown origin, which means with fever for 15 days or a month, I begin to wonder how I will diagnose him. It could be so many things, no? Patients are troubled and I am troubled, but before this I cannot order a test because I have not tried my best. If I can change my antibiotics and find one which works then I have a diagnosis, pyrexia of unknown origin responding to x or y or z. Then I know a diagnosis and I can just continue that course. Cough is not a diagnosis for me.

Only seven of a total 105 non-MD physicians kept written patient records to document treatment or changes in patient status over time. In addition, as none followed written treatment protocols, each patient receives idiosyncratic care as symptoms emerge. Based on our results, the Figure provides a schema of the likely drivers that contribute to empirical management.

**DISCUSSION**

India has the largest number of privately managed TB patients in the world, and the engagement of private providers is critical for TB control. This, in turn, requires a sound understanding of how private practitioners manage persons with presumed TB. Our study results suggest that empirical treatment with antibiotics of all classes, including FQs and anti-tuberculosis drugs, occurs due to multiple pressures and drivers. We present these pressures as three interrelated groups: treatment strategies, uncertainty generated by TB biology, and symptomologies affected by treatment and TB biology.

Treatment strategies are affected by pressures such as the need to provide rapid symptom relief to patients, the risk of losing patients in a competitive private health care marketplace, patients’ limited financial capability, easy availability of antibiotics that are often less expensive than tests, and the use of drugs that are mildly active against TB as broad spectrum antibiotics. Second, the TB biology, its ability to affect various parts of the body, its lack of a
unique and clearly defining symptom, and its slow onset and progression, make a ‘treat with antibiotics and wait’ perspective a clinical possibility. Third, pressures affected by the combination of treatment strategies and TB biology include the perception that large numbers of TB patients do not have cough or produce sputum, the paucity of bacteria present on sputum smear examination, a concern about Xpert’s ability to only detect rifampicin resistance in a context of severe forms of drug-resistant TB, and diagnostic and referral delays when symptoms perceived by practitioners do not align with international standards.

A recent study of quality of TB care in India assessed using standardised (simulated) patients showed widespread use of broad-spectrum antibiotics and poly-pharmacy, and very little testing for TB. Even when standardised patients were presented with a history of all classic TB symptoms, less than 10% underwent sputum smears or chest X-rays on their initial visit. These findings correlate well with our research findings and underscore the need for ethnographic work to supplement conventional research on quality of care.

The three factors our results reveal help make sense of the disorganised TB-related practices in urban India. The empirical use of quinolones and drugs such as amoxicillin-clavulanate as treatment and diagnostic tools may delay microbiological diagnosis, as these drugs have weak activity against TB or provide temporary symptomatic relief and delay the diagnostic work-up. These drugs may mask symptoms such as fever, cough or sputum production, which many practitioners take to be key signs of TB. These now complex symptomologies and a rule of thumb that a physician ought to suspect TB only if the patient’s condition worsens despite treatment with antibiotics blur the line between empirical diagnostic practices and empirical treatment.

In addition, patients who do not improve are likely to change physicians, and each new physician might begin the process of elimination again through initiating treatment with an antibiotic that they view as more potent. Even for patients who do not choose a new provider, the lack of record keeping or systematised treatment protocol leaves the progression of disease and previous treatments to the memory of physicians and patients. These practices create a cycle in which less expensive diagnostic tests such as sputum smear fail to identify TB due to low bacteria count. Without recourse to sputum-based microbiological tests, the empirical use of anti-tuberculosis drugs and the observation of patient progress seems an expeditious and economical solution.

Although these results present a seemingly unbreakable cycle between treatment practice and biology, stronger regulation of antimicrobial sales and distribution in India has been proposed as one solution to the problem of empirical diagnosis and treatment. The general physicians sampled suggested that sales by pharmacists of FQs in the government of India’s H1 schedule (i.e., restricted drug list) have decreased since the enforcement of the H1 legislation; however, this does not reflect the common practice of in-clinic dispensing of unlabelled quinolones by primary care providers. As we have no adequate way of knowing how legislation has affected the in-clinic distribution of FQs and other antibiotics, medical representatives (pharma detailers) and pharmaceutical companies may be good actors within the private sector to incentivise the proper use and distribute information on the masking quality of these drugs against TB presentation. In addition, regulation may account for the strong preference for amoxicillin-clavulanate in Mumbai, where H1 is enforced, and FQs in Patna, where the law is implemented less regularly.

Similarly, to reduce the masking of TB that empirical treatment might produce, public health messages in high TB burden settings ought to emphasise the effects of empirical antibiotic use on TB and the utility of record keeping combined with diagnostic protocols such as history checklists to monitor progress and suspect TB more quickly. As newer anti-tuberculosis drugs, such as linezolid and bedaquiline, or regimens such as PA-824, moxifloxacin (M) and pyrazinamide (Z) [PaMZ], reach the market, an effort should be made to reserve them for only TB by focusing on their use in TB rather than for their broader effects. If these drugs are used as broad-spectrum antibiotics as the FQ class is, their potential to revolutionise anti-tuberculosis treatment may be lost. These results also suggest that public health messages about standardised procedures that rely on cough as the defining criteria of TB might be adjusted to emphasise cough alongside other criteria in areas where air pollution, smoking, respiratory infections and empirical antibiotic use are commonplace.

These practices of empirical diagnostic and treatment may be one factor in reducing both the clinical impact and the uptake of Xpert. The ubiquity of empirical diagnostic practices further emphasise the need for a reliable, rapid and inexpensive test for TB. Furthermore, work to improve the quality of laboratory facilities to include patient counselling on how to produce sputum is necessary to disrupt assumptions regarding patients’ inability to produce sputum. More attention should be paid to creating inexpensive, multiplexed tests that fit into a panel for a respiratory and/or fever clinical syndrome, instead of focusing only on TB.

* Four chemists sampled for another study confirmed the physicians’ assumption.
Finally, empirical diagnosis and treatment practices and their effects reiterate the need for methods that can trace the connections between heterogeneous diagnosis and treatment practices in the private sector and TB control through public-private partnerships. The results presented here show the important links between multiple pressures that drive empirical practices and help suggest areas for intervention that account for actors on the ground who are caught between the pressures of private practice, patient needs and clinical uncertainties regarding TB. Ethnographic methods trained on TB suggest that careful messaging, attention to providers’ care practices and the need for diagnostic testing that is both rapid and affordable are all necessary to address the causes and effects of empirical practice.

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**CONTEXTE :** Une mauvaise prise en charge de la tuberculose (TB) est une préoccupation dans le secteur privé en Inde et le traitement empirique pourrait y contribuer largement.

**OBJECTIF :** Comprendre les facteurs associés à un diagnostic et à un traitement empirique d’une TB présumée dans le secteur privé en Inde et examiner leurs effets sur la prise en charge de la TB.

**SCHEMA :** Dans cette étude ethnographique, 110 praticiens privés de qualification variable qui ont vu des patients TB (90 à Mumbai et 20 à Patna) ont été interviewés et un sous-groupe a été observé pendant qu’ils prodiguaient des soins. Les entretiens et les observations ont été analysés à la recherche d’indicateurs de diagnostic et de traitement empirique.

**RESULTATS :** Tous les praticiens non spécialistes ont mis en route un traitement antibiotique, surtout de quinolones, pour une toux trainante avant de prescrire un test. Plusieurs facteurs contribuent à une prise en charge empirique. Ce sont notamment : une pratique répandue qui consiste à recourir à des médicaments comme outils de diagnostic, le désir d’offrir un soulagement rapide des symptômes des patients et de gérer la maladie de façon économique, l’incertitude à propos des signes cliniques de TB, les effets des antibiotiques à large spectre sur les symptômes de la TB et l’incertitude relative à l’exactitude des tests TB disponibles.

**CONCLUSION :** L’empirisme en général et dans la prise en charge de la TB est répandu dans le secteur privé urbain en Inde. L’ethnographie peut offrir des éclairages utiles pour gérer ce problème grâce à un modèle de collaboration public-privé.