Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study

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Summary

Background India has the highest number of patients with tuberculosis and multidrug-resistant tuberculosis in the world. We used a transmission model to project the emergence of drug resistance in India due to incorrect tuberculosis management practices in multiple sectors, including public and private providers, chemists, and non-allopathic practitioners.

Methods We constructed a dynamic Markov model to represent India's tuberculosis epidemic, including a probabilistic framework reflecting complex treatment-seeking pathways. Underlying drug resistance and the acquisition of drug resistance during treatment were included. India-specific epidemiological data, including tuberculosis management practices, were obtained from published literature. Outcomes, which included annual risk of infection, incidence of new disease, prevalence of untreated tuberculosis, and tuberculosis-related mortality, were stratified by underlying drug resistance, as well as by health sector to understand how each sector contributes to the emergence of drug resistance.

Findings If tuberculosis management practices across sectors in India remain unchanged over the next 20 years, we estimated a 47% increase in the incidence of isoniazid resistance, a 152% increase in multidrug-resistant tuberculosis incidence, a 242% increase in prevalent untreated multidrug-resistant tuberculosis, and a 275% increase in the risk of multidrug-resistant tuberculosis infection. By 2032, an estimated 85% of multidrug-resistant tuberculosis will be primary multidrug-resistant tuberculosis compared with only 15% in 2012. The public sector contributed 87% of acquired multidrug-resistant tuberculosis, related to irregular adherence; the remainder came from the private sector, related to treatment non-completion. Chemists and non-allopathic practitioners do not treat with rifampicin, but because of the high rates of inappropriate isoniazid-containing regimens, and treatment non-adherence, this would generate isoniazid resistance.

Interpretation We predict a gradual transformation from the current epidemic of drug-susceptible tuberculosis to a drug-resistant epidemic. Evidence-based strategies to improve provider practices and patient adherence across health sectors are urgently needed to prevent this.

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Introduction

The emergence of drug-resistant tuberculosis has the potential to reverse progress made to reduce tuberculosis-related morbidity and mortality over the past 20 years. Of particular concern are multidrug-resistant strains resistant to isoniazid and rifampicin, the two most effective tuberculosis drugs. Drug resistance emerges as a result of inadequate tuberculosis treatment, which might be an incorrect combination of tuberculosis drugs, inadequate dose or duration, or irregular drug-taking. These problems can occur in any setting, but are particularly prevalent in poorly regulated non-public sectors. To date, only a few studies have examined how patient and health-care provider behaviour within non-public sectors contributes to the drug-resistant tuberculosis epidemic.

India had the largest estimated burden of tuberculosis (2·8 million cases) and rifampicin-resistant or multidrug-resistant tuberculosis (130 000 cases) in the world in 2015.[1] India has a complex health-care system with at least three non-public sectors, including private allopathic providers (ie, private practitioners of western medicine), chemists (pharmacists), and informal health-care providers. Informal providers, or non-allopathic providers, refer to all practitioners of alternative medicine, which include ayurvedic and homoeopathic practitioners. Inappropriate tuberculosis care practices have been documented in all sectors, including prescription of inadequate tuberculosis regimens, low doses or reduced duration, and high rates of treatment non-completion or poor adherence by patients.[2–5] Thus, both public and non-public sectors might contribute to India's drug-resistant tuberculosis epidemic.

Computer simulation models offer a method to quantify how inappropriate practices in the different sectors might contribute to the development of drug-resistant tuberculosis. The primary objective of our

Research in context

Evidence before this study

We reviewed published literature (without restrictions on publication date or language) by searching MEDLINE (PubMed) using the search terms "India" and "tuberculosis" for studies done in India relevant to tuberculosis treatment and diagnostic practices across different sectors, treatment-seeking and treatment-taking behaviours among patients with tuberculosis, and factors associated with drug-resistant tuberculosis. Our searches identified considerable published evidence on the situation of tuberculosis treatment (current practice including regimens, adherence, and outcomes) in India. We also identified several systematic reviews on the effect of various regimens and treatment outcomes on the emergence of drug resistance. Random-effect meta-analyses were done to produce estimates for all model variables from studies identified in our search. Furthermore, we re-analysed data from our own published systematic reviews to obtain more accurate estimates for the effect of different drug regimens on treatment outcomes, stratified by underlying drug resistance. Our primary objective was to provide an estimate of the effect of inappropriate management practices, in multiple health sectors, on the overall tuberculosis epidemic and multidrug-resistant tuberculosis epidemic in India, as this has not been done before. No other studies have been published on this topic.

Added value of this study

There have been several modelling studies published in recent years examining the tuberculosis epidemic in India. One study found that improving non-multidrug-resistant tuberculosis cure rates would decrease overall incidence and mortality from tuberculosis, but have little effect on multidrug-resistant tuberculosis rates. Another found that national scale-up of universal rapid drug susceptibility testing could greatly reduce the numbers of multidrug-resistant tuberculosis cases between 2015 and 2025. However, this study only focused on the public sector. A third study modelled how different health-care system interventions might affect patient care-seeking pathways and the tuberculosis epidemic in India, but did not examine the emergence of drug resistance. By contrast, our study examined the complex health system-related issues across all sectors, and how these issues—including lengthy delays in care-seeking—affect the emergence of drug resistance in India.

If the state of tuberculosis care in India remains unchanged over the next 20 years, our model projected a modest increase in isoniazid-resistant tuberculosis and a nearly two-fold increase in rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis, and a substantial shift from a treatment-generated multidrug-resistant tuberculosis epidemic to one that is transmission-generated. The public sector was the largest contributor to drug-resistant tuberculosis, because the most patients with tuberculosis were treated in this sector, and because all patients received rifampicin as part of standard therapy, whereas non-public providers were less likely to prescribe rifampicin. We found the main driver of acquiring drug resistance during treatment in the public sector was irregular adherence (ie, patients were not taking medication regularly, but did complete the treatment), whereas in the non-public sector it was treatment non-completion.

Implications of all the available evidence

Concerns about quality of tuberculosis care in non-public health sectors are common in many low-and-middle-income countries. This study suggests that although non-standard or inappropriate tuberculosis management treatment practices by providers and patients in all sectors—public and non-public—contribute to the emergence of drug resistance, correcting issues in the public system will probably have the largest effect on the multidrug-resistant tuberculosis epidemic. Furthermore, the issues affecting each sector are not identical. For example, irregular adherence is a larger problem in the public sector, whereas high treatment non-completion rates are found in the non-public sectors. Evidence-based strategies to improve provider practices and patient adherence in all health sectors are urgently needed to arrest an emerging multidrug-resistant tuberculosis epidemic in India.

study was to estimate the effect of different inappropriate management practices overall and in different health sectors on the emergence of drug resistance in India. Our secondary objective was to estimate the benefit of correcting these practices in each sector.

Methods

Model design

We constructed a dynamic tuberculosis transmission Markov model using decision analysis software (TreeAge Professional, 2014), as described in detail elsewhere[6] and in the appendix. The model represented India's tuberculosis epidemic, which included a probabilistic framework reflecting complex treatment-seeking pathways (appendix). Model variables related to the natural history of tuberculosis were derived from published studies (appendix). India-specific epidemiological data, including tuberculosis management practices, were also obtained from published literature (table 1). Several key pathogenetic variables were refined through model calibration (appendix). We adjusted these key variables until the model predicted a drug-susceptible tuberculosis epidemic that matched the 2012 WHO-estimated tuberculosis incidence and prevalence rates in India (appendix).[8] Drug resistance was then incorporated by stratifying the initial population—representing the full population of India—by underlying drug resistance (drug susceptible, isoniazid resistant [but not multidrug resistant], and rifampicin resistant or multidrug resistant).[9] We did not calibrate variables associated with development of

See Online for appendix

drug-resistant tuberculosis because of the absence of robust historic data regarding drug-resistant tuberculosis trends in India. However, we incorporated transmission variables for drug-resistant tuberculosis estimated through calibration in a tuberculosis modelling study by another group using India-specific data.[37] HIV was not explicitly considered because of the low and declining percentage of patients with tuberculosis co-infected with HIV (roughly 4%) in India.[1]

People with active tuberculosis in our model could seek care in public (the Revised National Tuberculosis Control Program) or non-public health sectors; non-public sectors were divided into private allopathic doctors, chemists (those who dispense tuberculosis drugs), and informal providers (appendix). Information regarding how individuals initially access the health system was obtained from a large general population sample from India[11] and supplemented with data from another source (table 1, appendix).[12] The probability that individuals with active tuberculosis were treated varied by sector (table 1). If no tuberculosis drugs were given, an individual could seek care from another provider, with up to a maximum of three attempts, after which they would no longer seek care and remain untreated. We used three attempts since it was the average number of health-care providers consulted by patients with tuberculosis before diagnosis in India according to a systematic review.[10] Full details on the probabilities of seeking care at the end of three health-seeking attempts are provided in the appendix. Patients made a maximum of three attempts to receive tuberculosis treatment. After up to three attempts at diagnosis (or first round of treatment), 17·3% (95% CI 13·3–18·4) of individuals ended up in the private sector, of which 91·8% (79·6–96·2) were diagnosed with tuberculosis; 64·1% (64·1–68·4) of individuals were in the public sector, of which 96·4% (94·5–98·8%) were diagnosed; 3·3% (2·3–4·4) were treated by chemists, of which 34·1% (28·2–43·9) received tuberculosis drugs; and 15·4% (10·9–17·9) were in the informal sector of which 97·5% (91·4–99·5) did not receive tuberculosis drugs (table 1, appendix). Those who were diagnosed and treated were assigned a total delay of 57·5 days between onset of symptoms and starting tuberculosis treatment, during which time they were infectious to others (table 1).[10] This delay applied to all sectors since sector-specific data for these delays was not identified in published literature.

A correct tuberculosis regimen for initial treatment consisted of at least three drugs in the initial phase (containing both isoniazid and rifampicin); rifampicin for at least 6 months; and correct dose of rifampicin. Patients receiving tuberculosis drugs from any type of provider could be prescribed or dispensed incorrect regimens, and could also take treatment irregularly or incorrectly (table 1). These errors in turn affected the risk of treatment failure, relapse, and acquired drug resistance during treatment (appendix).

	Number or proportion of individuals	Source(s)
General epidemiological variables for India		
Background mortality (death due to non-tuberculosis causes per year)	0·8%	The World Bank, 2016[7]
Initial tuberculosis incidence rate in 2012 (per 100 000 population)	176	WHO, 2013[8] (adjusted during model calibration)
Proportion of patients with tuberculosis who had pulmonary tuberculosis	80%	WHO, 2013[8]
Proportion of patients with tuberculosis who were smear-positive	66·5%	WHO, 2013[8]
Proportion of new patients with tuberculosis with any non-multidrug isoniazid resistance	10·1% (6·2–15·2)	WHO, 2008[9]
Proportion of previously treated patients with tuberculosis with any non-multidrug isoniazid resistance	19·4% (17·1–21·9)	WHO, 2008[9]
Proportion of new patients with tuberculosis with any rifampicin-resistant or multidrug-resistant tuberculosis	2·6% (2·3–3·6)	WHO, 2008[9]
Proportion of previously treated patients with tuberculosis with any rifampicin-resistant or multidrug-resistant tuberculosis	18·1% (15·9–20·6)	WHO, 2008[9]
All sectors		
Average mean total delay (patient delay plus health system)	57·5 days (36–118)	Sreeramareddy et al, 2014[10]
Proportion seeking care at each health sector (per attempt)		
Public	34·8%	International Institute for Population Sciences, 2007; Vijayan et al, 2014[11,12]
Private	12·3%	International Institute for Population Sciences, 2007; Vijayan et al, 2014[11,12]
Chemist	19·3%	International Institute for Population Sciences, 2007; Vijayan et al, 2014[11,12]
Informal	33·6%	International Institute for Population Sciences, 2007; Vijayan et al, 2014[11,12]
Public sector		
Proportion treated on first encounter	73·1% (69·6–84·6)	Ananthakrishnan et al, 2012; Selvam et al, 2007; Suganthi et al, 2008[13-15]
If treated, prescribed treatment with three or more drugs and over 6 months of rifampicin	100%	Assumed
Substandard dose of rifampicin prescribed	32·4% (23·8–42·3)	Mishra and Mulani, 2013[2]
Poor quality rifampicin dispensed (eg, because of poor storage conditions or past expiry)	6·5% (4·5–9·2)	Ramachandran et al, 2013[16]
Private sector		
Proportion treated on first encounter	53% (34·4–62·7)	Achanta et al, 2013; Baxi and Shah, 2006; Datta et al, 2010; Krishnan et al, 2009; Roy et al, 2005; Singla et al, 1998; Uplekar et al, 1996; Vandan et al, 2009[5,17-23]
No tuberculosis drugs given	0	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2-5]
If treated, monotherapy (isoniazid and rifampicin not given)	0·5% (0–1·6)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2-5]

(Table 1 continues on next page)

	Number or proportion of individuals	Source(s)
(Continued from previous page)		
If treated, with two drugs	2·7% (1·7–4·6)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Isoniazid plus rifampicin	59·0% (19·0–86·7)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Isoniazid plus any drug other than rifampicin	15·0% (0–39·3)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Rifampicin plus any drug other than isoniazid	26·0% (12·8–59·3)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
If treated, treatment with three or more drugs	97·0%	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Correct doses, but duration of rifampicin <6 months	1·7% (0–2)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Correct duration but low dose of rifampicin	25·3% (12–38)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Correct dose and duration	72% (52–88)	Mishra and Mulani, 2013; Singla et al, 1998; Udwadia et al, 2010; Yadav et al, 2012[2–5]
Informal sector		
Referred to public or private providers	66·2% (54·2–76·5)	Anandhi et al, 2002[24]
Proportion treated with tuberculosis drugs on first encounter, among those who are not referred to other providers*	80% (58·7–92·4)	Anandhi et al, 2002[24]
Chemist prescribing†		
Refer to other providers (any type)	25%	Assumed
Proportion treated with tuberculosis drugs, among those who are not referred to other providers†	5%	Assumed based on findings from Satyanarayana et al, 2016[25]
Chemist dispensing errors (if correct prescription given by private or informal doctors)‡		
Poor quality rifampicin	8·9% (4·5–15·1)	Bate et al, 2013[26]
Dispensing on a daily or weekly basis (increased probability of short treatment)	50·0% (50–64)	Rajeswari et al, 2002[27]

(Table 1 continues on next page)

If a patient did not respond to treatment, relapsed, or did not complete their first treatment, our model assumed patients treated in the public sector remained in the public sector for re-treatment, and were re-treated correctly (appendix). However, patients treated in non-public sectors could switch providers after initial treatment for their second round of treatment. The probabilities for seeking re-treatment with the different types of provider, and the probabilities of treatment errors in non-public sectors remained unchanged as initial treatment. Patients who received a second round of treatment always received tuberculosis drugs, regardless of which sector they visited. A maximum of two rounds of treatment with tuberculosis drugs could be given.

In the initial year of analysis, individuals in latent and active tuberculosis states could have drug-susceptible, isoniazid-resistant, or rifampicin-resistant or multidrug-resistant tuberculosis, based on WHO estimates of the prevalence of drug resistance in new and previously treated patients with tuberculosis.[9] Some individuals could acquire drug resistance during treatment, and some could become infected with a drug-resistant strain of tuberculosis. Untreated drug-resistant cases generated secondary drug-resistant infections, but with a slight reduction in transmission (appendix) based on several published studies[38–41] that have found drug-resistant tuberculosis to be less infectious (appendix). Not all individuals were diagnosed or received treatment with tuberculosis drugs when they sought care (table 1). If they received no tuberculosis drugs, they could spontaneously be cured or die, but could not acquire drug resistance (appendix).

Outcomes

The base case analysis began in 2012 and assumed no changes in provider or patient behaviours, and projected epidemiological outcomes for India in 2032. Outcomes were stratified by underlying drug resistance and included annual risk of infection, incidence of new disease, prevalence of untreated tuberculosis, and tuberculosis-related mortality. Patients with drug resistance were stratified according to whether this was primary (from transmission) or acquired (during treatment) resistance. Outcomes were also stratified by health sector to understand how each sector contributes to the emergence of drug resistance.

Sensitivity analysis

We considered scenarios where a single inappropriate tuberculosis management practice or barrier in each sector was corrected within the model, while keeping all other variables constant, and sequentially removed each type of error in each sector from the model until there was no more acquired drug resistance. By doing so, we were able to estimate the benefit of correction of each error.

Due to the insufficient published evidence for the effect of multiple errors, the base case analysis did not estimate the effect of sequential errors (ie, a provider error followed by a patient error). In sensitivity analysis, we investigated the effect of combining provider errors with patient errors on projected outcomes—overall and by sector. In another sensitivity analysis, we estimated the outcomes that would result if only one sector provided treatment for all tuberculosis cases. These additional scenarios were first modelled with existing non-standard treatment practices and then modelled to correct the most important inappropriate management practice causing acquired drug resistance. Although published evidence suggests

informal doctors and chemists do not prescribe rifampicin in India,[25] we considered an alternative scenario in sensitivity analysis where all patients with tuberculosis went to these providers and were prescribed rifampicin. Finally, a probabilistic sensitivity analysis reporting 95% uncertainty ranges (UR), generated from 10 000 Monte Carlo simulation trials, was done to quantify the combined uncertainty when key variables were varied simultaneously. Distributions were defined with reported or calculated CIs around point estimates obtained from the literature. All values reporting ranges in table 1 and the appendix were defined as distributions and used in the probabilistic sensitivity analysis. Probability variables were defined by β distributions and non-probability variables were defined by normal distributions.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, and data interpretation, or writing of the report. All authors had full access to the data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Without any changes to patient behaviours or existing treatment practices, the model projected a 76% increase in isoniazid-resistant tuberculosis and a doubling of the multidrug-resistant tuberculosis incidence over the 20-year period (table 2). The annual risk of tuberculosis infection would also slightly increase, with a slight drop in risk of drug-susceptible tuberculosis infection, and an increase in risk of drug-resistant infections (table 2). The increase in multidrug-resistant tuberculosis incidence was associated with a 242% increase in prevalence of untreated multidrug-resistant tuberculosis, and a 275% increase in risk of multidrug-resistant tuberculosis infection, so that by 2032, we predicted that 85% of multidrug-resistant tuberculosis infections would be from primary transmission, compared with only 15% in 2012. The relative contributions to acquired isoniazid-resistant and multidrug-resistant tuberculosis in patients who did not respond to treatment, relapsed, did not complete treatment, or had irregular treatment adherence, by health sector are summarised in table 3 and the appendix. The public sector accounted for most of the multidrug-resistant tuberculosis cases because most patients treated with rifampicin were treated by public sector providers, and many had irregular treatment adherence. The two most important factors associated with acquired multidrug-resistant tuberculosis were no response to initial treatment and irregular adherence. The risk of acquired isoniazid resistance was much higher in patients treated by chemists or informal providers, and slightly higher in those treated in the private sector than in the public sector (table 3). However, the risk of acquired multidrug-resistant tuberculosis was higher in the public sector than in all other sectors.

	Number or proportion of individuals	Source(s)
(Continued from previous page)		
Patient-level behaviours (only arise when a correct regimen is given)		
Take monotherapy (any sector)	4·7% (1·9–10·3)§	Uplekar et al, 1998[28]
Take two drugs (any sector)	9·3% (5·1–16·0)¶	Uplekar et al, 1998[28]
Treatment not completed		
Public providers	6% (5·9–6·1)	Central TB Division, 2014[29]
Non-public providers	40% (39–44)	Ambe et al, 2005; Reed et al, 1990; Tandon et al, 2002; Uplekar et al, 1998 (assumed patients had self-administered therapy)[28,30-32]
Take therapy irregularly		
Public providers	39% (37·0–40·7)	Gopi et al, 2007 (assumed as partial adherence to directly observed therapy)[33]
Non-public providers	10% (8–10)	Kulkarni et al, 2013; Zaman et al, 2014[34,35]

Data are n or n (95% CI). 95% CIs were estimated using the DerSimonian and Laird random effects method for meta-analysis when there were two or more studies.[36] When there was only one study present, the 95% CI was derived from the study sample data. These estimates and their associated 95% CI (when available) were used to specify the β distributions used in the probability sensitivity analysis. *When patients were treated with tuberculosis drugs in the informal sector, 55% received monotherapy with streptomycin alone. The remainder (45%) received isoniazid with either streptomycin or ethambutol.[23] †When patients were treated with tuberculosis drugs by chemists, 55% received streptomycin only, and 45% received isoniazid with either streptomycin or ethambutol (we assumed this was the same as for informal providers). ‡When patients with tuberculosis presented to private chemists with a tuberculosis prescription, 5% were assumed to be referred to public sector for dispensing. §Of these, we assumed that a third received isoniazid, a third received rifampicin, and a third received some other drug (eg, streptomycin or ethambutol). ¶Of these, we assumed that a third received isoniazid and rifampicin, the remainder received either isoniazid or rifampicin (half of each) in combination with some other drug (eg, streptomycin or ethambutol).

Table 1: **Model key India-specific input variables**

Changes with the largest effect on projected outcomes are shown in table 4 (see appendix for all secondary analyses). The biggest reduction in mortality would occur if all patients were diagnosed and treated during the first encounter, although this would have little effect on drug resistance. The biggest reduction of isoniazid resistance would occur if all patients with tuberculosis were treated in the public sector—this would also reduce mortality, but would increase multidrug-resistant tuberculosis because of the consistent use of rifampicin. Correction of irregular adherence in patients treated in the public sector would have the largest effect on multidrug-resistant tuberculosis incidence. In other sectors, increased completion of treatment by patients treated by private providers would reduce mortality and isoniazid resistance, but have little effect on multidrug-resistant tuberculosis incidence. The largest reduction of tuberculosis morbidity and mortality in patients treated by chemists, and by informal providers, would occur if these providers referred all patients with tuberculosis to public or private allopathic providers. However, if informal providers and chemists stopped treating patients with tuberculosis drugs (even non-standard treatment), there would be greater mortality with a small decrease in isoniazid resistance.

	Drug-sensitive tuberculosis (95% UR)	Isoniazid-resistant tuberculosis (95% UR)	Multidrug-resistant tuberculosis (95% UR)	All tuberculosis (95% UR)	Percentage of all cases due to drug-resistant tuberculosis (95% UR)
Annual risk of infection (%)					
2012	1·7% (1·6–1·8)	0·2% (0·2–0·3)	0·08% (0·07–0·09)	2·0% (1·9–2·2)	14·0% (12·3–20·5)
2032	1·5% (1·4–1·7)	0·4% (0·3–0·5)	0·3% (0·2–0·4)	2·2% (1·9–2·6)	31·8% (19·2–47·4)
Incidence (per 100 000)					
2012 total incidence	156·4 (150·0–161·9)	15·1 (9·9–21·1)	3·9 (3·1–4·8)	175·4 (163·1–187·8)	10·8 (6·9–15·9)
2012 incidence of acquired drug resistance	..	3·8 (2·4–5·5)	3·9 (2·7–5·4)	..	..
2032 total incidence	136·7 (128·6–145·8)	26·6 (18·8–34·8)	14·1 (11·2–16·0)	177·4 (158·5–196·6)	22·9 (15·3–32·1)
2032 incidence of acquired drug resistance	..	3·3 (2·2–4·9)	4·6 (3·3–6·1)	..	..
Prevalence (per 100 000)					
2012 untreated	350·3 (334·3–364·3)	42·2 (28·3–58·1)	14·0 (11·9–16·3)	406·5 (374·5–438·7)	13·8 (9·2–19·9)
2032 untreated	320·6 (300·6–340·5)	59·0 (43·2–77·0)	48·0 (38·8–58·4)	427·6 (382·6–475·9)	25·0 (17·2–35·4)
Mortality (deaths per 100 000)					
2012	24·6 (23·2–25·8)	3·0 (2·0–4·1)	1·7 (1·5–1·9)	29·3 (26·7–31·8)	16·0 (11·0–22·5)
2032	21·2 (19·0–23·5)	5·9 (4·3–7·4)	7·5 (5·8–8·9)	34·6 (29·1–39·8)	38·7 (25·4–56·0)

The 95% UR gives the 2·5th percentile and 97·5th percentile of the range of estimated outcomes from 10 000 Monte Carlo simulations done in probability sensitivity analysis. UR=uncertainty range.

Table 2: **Annual risk of infection, incidence, prevalence, and mortality, by underlying drug resistance, in 2012 and 2032 estimated by model projection**

	Percentage of all patients with tuberculosis treated with tuberculosis drugs in the sector	Number of patients with drug-sensitive tuberculosis who received treatment (95% UR)	Number of patients with drug-sensitive tuberculosis who acquired isoniazid-resistant tuberculosis during treatment (95% UR)	Percentage of patients with drug-sensitive tuberculosis who acquired isoniazid-resistant tuberculosis during treatment (95% UR)	Overall percentage of all isoniazid-resistant tuberculosis acquired because of tuberculosis treatment in each sector	Total number of patients with drug-sensitive and isoniazid-resistant tuberculosis who received treatment (95% UR)	Number of patients with drug-sensitive and isoniazid-resistant tuberculosis who acquired multidrug-resistant tuberculosis during treatment (95% UR)	Percentage of patients with drug-sensitive and isoniazid-resistant tuberculosis who acquired multidrug-resistant tuberculosis during treatment (95% UR)	Overall percentage of all acquired multidrug resistance due to tuberculosis treatment in each sector
Public	68·2%	99 (92–107)	1·7 (1·1–2·5)	1·7% (1·2–2·3)	51·5%	123 (109–137)	4·0 (2·9–5·4)	3·3% (2·7–3·9)	87%
Private	15·3%	24 (21–27)	0·6 (0·5–0·9)	2·5% (2·4–3·3)	18·2%	29 (24–34)	0·6 (0·4–0·8)	2·1% (1·7–2·4)	13%
Chemist*	2·3%	3 (3–4)	0·1 (0·07–0·2)	3·3% (2·3–5)	3·0%	4 (3–5)	0	0	0
Informal*	14·2%	22 (19–26)	0·9 (0·5–1·4)	4·1% (2·6–5·4)	27·3%	27 (22–32)	0	0	0
Total	100%	148 (135–164)	3·3 (2·2–5·0)	2·2% (1·6–3·0)	100%	183 (158–208)	4·6 (3·3–6·2)	2·5% (2·1–3·0)	100%

All numbers per hypothetical population of 100 000 people. The 95% UR gives the 2·5th percentile and 97·5th percentile of the range of estimated outcomes from 10 000 Monte Carlo simulations done in probability sensitivity analysis. *We assumed that chemists and informal providers did not prescribe rifampicin. UR=uncertainty range.

Table 3: **Acquired drug resistance projected after 20 years under base case scenario, by health sector**

When the effect of patient treatment adherence factors were combined with incorrect provider treatment practices in all sectors, the incidence and mortality rates due to drug-susceptible tuberculosis and isoniazid-resistant tuberculosis increased slightly, but the mortality rates due to multidrug-resistant tuberculosis increased substantially (table 5). Results from hypothetical scenarios where all patients sought care from only one sector (eg, all patients seen by the public sector only) are shown in the appendix. The findings from these scenarios suggest that if more patients were treated by chemists or informal providers, the emergence of drug resistance would be much greater than in the base-case scenario, particularly if these sectors use rifampicin.

Discussion

Our tuberculosis transmission model projected minor changes in overall risk of infection, incidence, or prevalence of tuberculosis in India over 20 years, given current use, and frequency of inappropriate management practices by patients and providers within the different health sectors. However, if these practices are not corrected, we project the tuberculosis epidemic will shift gradually from one that is predominantly drug susceptible to one with increasing

	Incidence (per 100 000 people)			Mortality (per 100 000 people)		
	Drug-sensitive tuberculosis	Isoniazid-resistant tuberculosis	Multidrug-resistant tuberculosis	Due to drug-sensitive tuberculosis	Due to isoniazid-resistant tuberculosis	Due to multidrug-resistant tuberculosis
No change (base case)	136·7	26·6	14·1	21·2	5·9	7·5
All sectors						
All patients seeking care in the public sector	131·0	22·4	14·7	14·1	3·5	7·8
All patients diagnosed and start treatment on first diagnostic attempt*	132·3	26·7	13·7	18·1	5·9	7·3
Public sector						
All patients treated in the public sector complete treatment (100% adherence)	136·2	26·3	14·0	20·6	5·7	7·4
No irregular adherence in patients treated in the public sector	136·7	26·6	13·3	20·8	5·8	6·8
Private sector						
All patients treated in the private sector complete treatment	135·3	25·5	14·0	19·5	5·3	7·4
Chemists						
Chemists refer all suspected tuberculosis cases to private and public providers for diagnosis and treatment	134·0	25·5	14·3	18·3	5·2	7·6
Informal sector						
Informal practitioners refer all suspected tuberculosis cases to private and public providers for diagnosis and treatment	136·3	24·6	14·6	19·6	4·7	7·8

Corrections with the greatest epidemiological impact are shown by major category of drug resistance. Correction of the following problems made very little difference in these outcomes compared with the base case analysis: drug quality improved at a regulatory level; private allopathic doctors prescribe correct tuberculosis drugs; chemists who fill private doctors, prescriptions dispense only monthly drug doses (ie, no daily or weekly dispensing); patients treated in the private sector do not selectively take drugs (ie, no monotherapy or taking only two of the prescribed drugs); when chemists dispense drugs without a prescription, they dispense all correct tuberculosis drugs.
*Total delay before to treatment initiation was only 38·1 days (reflects health system delay only).

Table 4: **Secondary analysis of projected tuberculosis incidence and mortality after 20 years after correction of major problems identified in each health system sector**

drug resistance. In particular, multidrug-resistant tuberculosis in India will shift from being mainly acquired during treatment to being mainly acquired through primary transmission. Our study is not alone to find such a substantial transition; Suen and colleagues[42] also projected that by 2035, over 60% of new multidrug-resistant tuberculosis cases will result from transmission rather than be acquired during treatment.

This is the first study, to our knowledge, to examine the effect of tuberculosis management and patient adherence on emergence of drug resistance in all major health-care sectors in India. One strength of this study is that the major health-care sectors involved in the treatment of tuberculosis in India were accounted for, with a comprehensive analysis of how various treatment practices in these sectors might affect acquired and transmitted drug resistance. An additional strength was that many variables used in the modelling were based on an extensive review of the scientific literature, including a recent systematic review,[10] and were India-specific.

This study had several limitations. The health-care system in India is complex, and despite the development of a comprehensive model to reflect this, capturing all options for patients seeking care for tuberculosis was difficult. Furthermore, the health-care landscape in India is highly heterogeneous and is variable at a subnational level; for example, there is stronger presence of informal practitioners in rural settings compared with urban settings, where the presence of private allopathic doctors is more prevalent. Our model aimed at representing the average landscape across India, and thus simplified the experiences of patients with tuberculosis across the country. In our base case analysis, patients were assumed to have only one barrier or error, but in reality, patients can have multiple barriers, or errors. This limitation was explored in our sensitivity analysis, but interpretation should be cautious as no evidence for how compounded errors truly affect treatment outcomes has been published.

Several modelling studies have been published in the past few years examining the tuberculosis epidemic in India. Suen and colleagues[42] found that improving non-multidrug-resistant tuberculosis cure rates would decrease overall incidence and mortality from tuberculosis, but have little effect on multidrug-resistant tuberculosis rates. Sachdeva and colleagues[43] found that national scale-up of universal rapid drug-susceptible tuberculosis could greatly reduce the numbers of multidrug-resistant tuberculosis cases between 2015

	Incidence (per 100 000 people)			Mortality (per 100 000 people)		
	Drug-sensitive tuberculosis	Isoniazid-resistant tuberculosis	Multidrug-resistant tuberculosis	Due to drug-sensitive tuberculosis	Due to isoniazid-resistant tuberculosis	Due to multidrug-resistant tuberculosis
Base case scenario (single inappropriate practice)	136·7	26·6	14·1	21·2	5·9	7·5
Combined inappropriate provider and patient treatment practice*						
All sectors	134·2	27·5	19·9	21·6	6·5	11·9
Public sector only	135·1	27·0	17·3	21·2	6·2	9·9
Private sector only	136·2	26·9	15·2	21·2	6·1	8·4

*We assumed that one provider substandard treatment practice (rifampicin for less than 6 months; rifampicin dosage less than standard; monotherapy; or only two drugs) could be combined with one patient treatment adherence factor (selectively taking only one or two drugs; irregular adherence; or non-completion). The probability of having a specific combination of errors is the product of the independent probabilities of the two errors. We assumed that the probability of the treatment outcomes (death, failure, relapse, non-completion, and acquiring drug resistance) was simply the sum of the respective probabilities from each error. For example, if a patient received rifampicin for less than 6 months and had irregular adherence, then the probability of treatment failure would be the sum of the probability of treatment failure of receiving a short regimen and having irregular adherence.

Table 5: **Sensitivity analysis of projected tuberculosis incidence and mortality after 20 years (combined inappropriate provider and patient treatment practices)**

and 2025. However, their study only focused on the public sector. Mandal and colleagues[44] modelled how different health-care system interventions might affect patient care-seeking pathways and the tuberculosis epidemic in India but did not examine the emergence of drug resistance. By contrast, our study examined the complex health system-related issues across all sectors, and how these issues affect the emergence of drug resistance in India.

Our modelling study suggests that tuberculosis treatment in the public sector contributes substantially to acquired multidrug-resistant tuberculosis in India. One possible reason for this finding is the use of a thrice weekly intermittent schedule of treatment, which is associated with a high rate of irregular adherence (estimated at 39% in published studies, table 1). Other studies have suggested the reasons for poor adherence in India are multifactorial, including but not limited to poor provider–patient interactions, inaccessibility to treatment centres (eg, operating hours, distance), insufficient social support, increased financial strain, comorbid conditions, and social stigma.[45–47]

Another important finding was the contribution of pre-existing isoniazid mono-resistance to the emergence of multidrug-resistant tuberculosis because the standardised WHO regimens for new and previously treated patients have high rates of failure and relapse with amplification to multidrug resistance.[48] This finding emphasises the need for routine drug susceptibility testing for all individuals diagnosed with tuberculosis, regardless of their treatment history, to ensure drug resistance is identified and an appropriate regimen is prescribed. The finding that non-public health-care services might substantially contribute to isoniazid-resistant tuberculosis suggests that barriers in all health sectors must be addressed to prevent further emergence of multidrug-resistant tuberculosis in India.

The landscape of tuberculosis care has changed enormously in India over the past two decades, with rapid expansion of diagnosis and treatment, especially the use of rifampicin in the public sector. A large number of studies have described important barriers to existing treatment practices in both public and private health sectors in India—many of which could generate drug resistance. Our aim was to assemble these estimates and use them to project the effect of inappropriate management practices on overall epidemiological trends and the potential benefit of their correction. The next step will be to analyse the effect of interventions to improve inappropriate tuberculosis management practices and adherence issues that we have identified as important contributors to the epidemic of drug resistance. Potential interventions include scaling up effective public–private strategies to improve tuberculosis management,[49] implementing local initiatives to increase tuberculosis case notification from private and informal sectors to ensure diagnosed patients receive appropriate treatment,[50] and introducing patient-centred strategies (eg, reminder systems) to improve treatment adherence.[51] Evidence-based strategies to improve provider practices and patient adherence, and ultimately reduce the burden of drug-resistant tuberculosis in all relevant health sectors are urgently needed.

Contributors

ASP and CV conceived the study idea. SL, OO, ASP, CV, and DM contributed to the study design. SL, OO, and DM did the literature reviews and data analysis. All authors contributed to data interpretation, writing the manuscript,and approved the final version of the paper.

Declaration of interests

CV and ASP are employed by the United States Agency for International Development. All other authors declare no competing interests.

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