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# The burden of transmitted multi-drug resistance among epidemics of tuberculosis: A transmission model

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## Abstract

**Background—**Multidrug-resistant tuberculosis (MDR-TB) can be acquired through *de novo* mutation during TB treatment or through transmission from other individuals with active MDR-TB. Understanding the balance between these two mechanisms is essential when allocating resources for MDR-TB.

**Methods—**We constructed a dynamic transmission model of an MDR-TB epidemic, allowing for both treatment-related acquisition and person-to-person transmission of resistance. We used national TB notification data to inform Bayesian estimates of the fraction of each country's 2013 MDR-TB incidence that resulted from MDR transmission rather than treatment-related MDR acquisition.

**Findings—**Global estimates of 3·5% MDR-TB prevalence among new TB notifications and 20·5% among retreatment notifications translate into an estimate that resistance transmission rather than acquisition accounts for a median 96% (95% UR: 68–100%) of all incident MDR-TB, and 61% (16–95%) of incident MDR-TB in previously-treated individuals. The estimated percentage of MDR-TB resulting from transmission varied substantially with different countries' notification data; for example, we estimated this percentage at 48% (30–75%) of MDR-TB in Bangladesh, versus 99% (91–100%) in Uzbekistan. Estimates were most sensitive to estimates of the transmissibility of MDR strains, the probability of acquiring MDR during tuberculosis treatment, and the responsiveness of MDR TB to first-line treatment.

**Interpretation—**Notifications of MDR prevalence from most high-burden settings are most consistent with the vast majority of incident MDR-TB resulting from transmission rather than new



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treatment-related acquisition of resistance. Merely improving the treatment of drug-susceptible TB is unlikely to greatly reduce future MDR-TB incidence. Improved diagnosis and treatment of MDR-TB – including new tests and drug regimens – should be highly prioritized.

## Background

An estimated 480,000 people developed incident multidrug-resistant tuberculosis (MDR-TB) in 2013.[1] The prevalence of MDR is generally much higher among TB patients who have been previously treated for TB than among treatment-naive patients. This disparity is widely assumed to suggest that a large proportion of MDR-TB arises from selection of drug resistance mutations during previous ineffective TB treatment, as opposed to transmission of pre-existing MDR strains.[2–5] This interpretation has major implications for the control of MDR-TB: if most MDR arises from ineffective treatment of drug-susceptible TB, then better treatment of susceptible strains should be the focus in preventing additional cases of MDR-TB.[6,7] Previous transmission modeling analyses, which illustrated the difficulty of controlling established MDR-TB epidemics, urged programs to improve the treatment of drug-susceptible TB.[8] Over time, however, the predominant etiology of incident MDR-TB shifts from acquisition of resistance during treatment to direct person-to-person transmission of MDR strains,[9] and there is a point at which MDR-TB epidemics cannot be contained without early and effective treatment of drug-resistant TB.[10] This evolving balance between treatment-related acquisition and primary transmission of MDR therefore has critical public health implications: when MDR-TB epidemics are driven by primary transmission, resources must increasingly be allocated to MDR-TB treatment and ongoing development of novel regimens (to make MDR-TB treatment shorter, cheaper, and more tolerable[11]), rather than to treatment of drug-susceptible TB alone.[11–13] Where this balance currently stands in most high-burden settings is uncertain.

The World Health Organization (WHO) publishes widely-cited estimates of the prevalence of MDR-TB among notified new and previously treated cases. These estimates have known weaknesses,[14,15] but they are nonetheless widely used for country-level planning (as no better estimates exist for most countries). Unfortunately, these estimates of MDR-TB prevalence cannot be directly translated into estimates of the proportion of MDR-TB incidence that reflects primary transmission. For example, when individuals are infected with drug-resistant strains and subsequently develop MDR-TB disease in an area where drug susceptibility testing is not routinely performed for new cases, these patients will be initially notified as drug-susceptible, and only after failing initial treatment might they be notified as (previously treated) MDR-TB. Molecular epidemiologic studies have variably found that from <25%[16,17] to >80%[18] of MDR-TB clinical isolates are genetically clustered, but incomplete sampling biases these numbers as an estimate of transmitted disease.[19] To understand how current notification data regarding the prevalence of MDR-TB would translate into the estimated proportion of MDR-TB that arises from prior TB treatment versus from MDR transmission, a mechanistic understanding of MDR-TB transmission in the context of TB notification practices is required. We therefore created a dynamic transmission model of an MDR-TB epidemic to convert the notified prevalence of MDR-TB into estimates of the separate contributions of resistance transmission and treatment-related resistance acquisition to incident MDR-TB cases.

# Methods

## Model structure

We constructed a deterministic compartmental model of a historical (through 2012) adult pulmonary TB epidemic involving a drug-susceptible strain (i.e. a weighted average of all non-MDR strains) and an MDR strain in a homogeneous adult population (Figure 1). Similar to previously-published models,[20,21] susceptible individuals could be infected with either strain, resulting either in immediate progression to active disease (which, after a subclinical phase, progressed to care-seeking and TB treatment) or in latent infection (a non-infectious state with a continuous ongoing probability of reactivation and progression to active, infectious disease). In this historical model of high-burden countries, we assumed that, at the population level, treatment for MDR-TB was negligible, consistent with global estimates that <20% of incident MDR-TB was treated prior to 2013[1] and <10% through at least 2009.[22] Thus, individuals diagnosed with TB were treated with first-line therapy in the primary analysis, although sensitivity analysis was performed for alternative scenarios in which 25% or 50% of all people who failed initial therapy were treated with appropriate second-line therapy, with little difference in outcomes (see supplementary material, section 1c). Probabilities of treatment outcomes – including cure, treatment failure (with or without acquired resistance), and apparent cure with subsequent relapse (also with or without acquired resistance) – depended on a patient's resistance status (MDR or DS) and treatment history (treatment-naïve DS or previously-treated DS). Previously-treated individuals were assumed to have worse outcomes because of accumulated resistance to isoniazid or other single drugs, more advanced disease, or patient characteristics that contributed to their initial failure.

It was possible for MDR to be acquired during any course of TB treatment. The outcome of DS TB treatment was determined through a series of events (illustrated in Figure S1); the probability of each subsequent event was conditional on the preceding events. First, early bacteriologic response (i.e. an expected initial decline in bacterial burden leading to culture conversion) either was or was not achieved. Second, an MDR mutant either was or was not selected. Third, treatment either was or was not completed. Finally, with a probability conditional on each of the steps above, relapse after treatment either did or did not occur. Acquisition of resistance was more likely for previously-treated patients (who were more likely to already harbor resistance to some drugs in a regimen) than for treatment-naïve patients, and for patients who failed to achieve early bacteriologic response (for initial reasons unrelated to MDR, e.g., large bacillary burden or inadequate doses of drug) than for patients in whom early bacteriologic response to treatment was achieved. If *de novo* MDR mutation occurred, the probability of subsequent relapse to new active MDR-TB was high. Preexisting MDR-TB also could, rarely, respond to first-line therapy, but then also had a high probability of relapse.

## Model simulations

We generated a series of model simulations to account for uncertainty related to the transmissibility, natural history, and treatment of TB and MDR-TB; each simulation used a specific set of parameters sampled from the ranges shown in Table 1. Then, as described in

detail below, we weighted each simulation based on its fit to notified TB data. We evaluated the resulting weighted set of simulations to generate estimates of how TB and MDR-TB notifications would best translate into estimates of the proportion of incident MDR-TB that reflected transmitted, as opposed to treatment-acquired, MDR-TB. We generated a total of 1,000,000 simulations for consideration as follows: First, for model parameters not related to drug resistance, we took 2000 Latin hypercube samples[23] uniformly distributed on either the arithmetic or logarithmic scale (i.e., uniform or truncated exponential distributions), across plausible ranges for a medium- to high-burden setting (Table 1), to generate 2,000 equilibrium epidemics of drug-susceptible TB. Further details are in the Supplementary Material, section 1b. We then similarly sampled a different 500 sets of drug resistance-related parameters for each initial drug-susceptible epidemic and allowed acquisition of MDR-TB during treatment of DS-TB (and subsequent transmission from person to person) to start at a specific point in time 20–60 years in the past. We evaluated the resulting MDR-TB epidemic at five-year intervals up to sixty years (beyond which our reported results were stable), with the primary analysis performed after twenty years of MDR emergence[18] and with sensitivity analysis for other durations. The probability of acquiring resistance was sampled over a wide range, considering values of up to 10% per treatment course for new patients and even higher values for those previously treated (even if they initially responded appropriately to a second course of treatment) and those without an initial rapid bacteriologic response to treatment (in whom ongoing bacterial replication under antibiotic pressure may promote selection of drug resistance). We assumed that the MDR strain had a transmissibility relative to the drug-susceptible (DS) strain that was bounded from zero (no MDR transmission) to one (equivalent transmissibility of both strains).[24]

Among all 1,000,000 simulations generated, those with TB incidence between 20 and 1400 per 100,000 per year, TB prevalence between 20 and 1200 per 100,000, and MDR-TB in at least 0·1% of new TB notifications, were considered consistent with plausible epidemiological scenarios for a medium- to high-TB-burden setting, and were retained for consideration in comparison to present-day notification data.

## Model calibration

After reducing the initial simulations to this broadly plausible set, we applied a Bayesian melding process[25] to translate TB notification estimates from WHO into corresponding estimates of the fraction of MDR-TB incidence that resulted from MDR transmission. To achieve this aim, we first took all plausible simulations, generated as described above, as an uninformative prior distribution of epidemic trajectories consistent with existing knowledge about TB epidemiology, natural history, and treatment practices in medium-to-high-burden settings. Then, in order to prioritize the simulations most consistent with a given set of notification data, we assigned each simulation a weight, based on a joint likelihood that represented how closely the simulation replicated the notification data of interest, including proportions of new and retreatment cases with MDR-TB and the WHO-estimated TB incidence and prevalence. Using this generalizable framework, we evaluated both a “global” scenario (fit only to the global estimates of MDR-TB prevalence, among new and among retreatment notifications) and “country-level” scenarios (fitting the same generalizable model to country-level estimates of both MDR-TB, as done for the global scenario, and total

TB burden). We evaluated country-level scenarios for six countries representing a variety of geographic settings, TB and MDR-TB burdens, and retreatment-to-new MDR prevalence ratios, as shown in Table 2. We also applied the country-specific process to notification estimates for all countries for which WHO reported a TB incidence >40/100,000/year, at least 10 TB notifications, and nonzero prevalence among new TB notifications in 2013. Eleven countries (notably including China) were excluded on the basis that appropriate fits could not be obtained while assuming stable TB natural history parameters and no second-line treatment through 2013 (see supplementary material, section 2a, for details).

Details of model calibration are described in supplementary material section 1b. Results are reported as a median value, weighted by the likelihood (with weighted 2·5$^{th}$ and 97·5$^{th}$ quantiles as the bounds of the 95% uncertainty range (UR)).

## Sensitivity analyses

For each model parameter, we computed partial rank correlation coefficients for the correlation of the parameter (simultaneously adjusted for all other model parameters) with the percentage of MDR incidence that resulted from MDR transmission rather than MDR acquisition during prior treatment in the same individual. We computed these correlation coefficients among all plausible simulations for a medium-to-high-TB-burden country as described above, and, for each of the six representative countries shown in Table 2, among the subset of simulations that fell within that country's WHO-reported uncertainty intervals for each of the four notification measures considered, as shown in Table 2. We also performed illustrative sensitivity analysis for the variation in a specific parameter (rate of TB diagnosis and treatment initiation) between individual countries, by restricting our set of simulations based on country-level estimates of that parameter and recalculating our primary result (see Supplementary material).

Then, in addition to the sensitivity analyses noted above related to time since MDR emergence and availability of second-line MDR treatment, we also considered the impacts of non-equilibrium TB epidemiology and of epidemic heterogeneity. To evaluate the impact of the declining overall TB incidence seen over the past decade in much of the world,[1,26] we first reduced the TB reactivation rate linearly by 2% per year and determined the resulting percent of incident MDR-TB that resulted from transmission. We then repeated a similar analysis in which the declining overall TB incidence instead results from a 1%/year linear decrease in the TB transmission rate. Both of these scenarios approximately replicated the observed 1·5% annual decline in TB incidence that is currently estimated.[1] Finally, we tested the sensitivity of our results to our assumption of population homogeneity by evaluating the impact of MDR hotspots on the fraction of MDR-TB that results from MDR transmission. For each homogeneous-model simulation, we increased the acquisition and transmission of resistance within a hotspot, and decreased those of the background population, by random amounts, calibrating the hotspot population size to achieve equal average MDR incidence in the heterogeneous and homogeneous populations (details in supplement, section 1c). All analyses were performed in R version 3·1·2.[27]

### Role of the funding source

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

### Ethical approval

This study did not involve human subjects and did not require ethics or IRB approval.

## Results

Of the one million potential TB epidemics we simulated, 315,567 simulations had plausible TB incidence and prevalence for a medium-to-high burden setting and were retained for consideration. Figure 2 shows the estimated proportion of incident MDR-TB representing transmission of resistance rather than selection of resistance during previous treatment in each of those 315,567 “plausible” simulations (see also Figure S2). In the 15% of these plausible simulations in which fewer than half of MDR infections resulted from transmission, the ratio of MDR prevalence among retreatment versus new notifications was extraordinarily high (median 37, IQR 24–61). Among the remaining 85% of plausible simulations, the retreatment-to-new MDR prevalence ratio was 7 (IQR 4–12), similar to the reported median ratio of 6 (IQR 5–11) across WHO notifications in 2013 from all countries with TB incidence >40/100,000/year and >10 cases/year.[28]

In this transmission model, the global estimates of 3·5% (95% CI: 2·2–4·7%) MDR-TB prevalence among new TB notifications and 20·5% (95% CI: 13·6–27·5%) among retreatment notifications[1] corresponded to a median 95·9% (95% UR: 68·0–99·6%) of all incident MDR-TB, and 61·3% (95% UR: 16·5–95·2%) of incident MDR-TB among previously treated individuals, resulting from MDR transmission (Figure 2, inset). When separate fits were generated for the notification data of representative individual countries (Table 2), the estimated percentage of incident MDR-TB that resulted from MDR transmission ranged from 48% in a setting (Bangladesh) where MDR prevalence is estimated to be far higher (15 times higher) among retreatment than among new TB cases, to >75% in multiple countries representing a range of TB and MDR prevalence and more typical ratios of MDR in retreatment versus new TB patients, and to 99% in a setting (Uzbekistan) with very high (23%) MDR prevalence among new TB cases. Among the 92 medium- to high-burden countries whose notification data could be adequately fit, the median proportion of incident MDR estimated to arise from transmission rather than treatment-related acquisition was 92% (IQR 82–97% and full range 24% to >99% for individual countries’ median estimates) (Table S4).

Both before and after notification-data-based constraints were applied, the estimated contribution of transmission to MDR incidence was highly sensitive to the transmissibility of MDR strains (figure 3). Before applying notification-data constraints (figure 3A), parameter values that caused a shift in overall tuberculosis epidemiology to more recent transmission rather than reactivation (eg, a higher proportion of infections progressing

rapidly to active disease, or a slower reactivation rate) also increased the relative amount of transmitted versus treatment-acquired MDR TB. Once only simulations consistent with a given country's notification data were considered (figure 3B), the proportion of MDR TB that resulted from MDR TB was also sensitive to the probability of acquiring resistance during treatment and to assumptions about the responsiveness of MDR infections to first-line therapy.

Given the sensitivity of estimates to MDR strain fitness and to per-treatment probabilities of acquiring resistance, we re-evaluated our results after restricting our initial broad sampling ranges for these parameters in order to verify that our original estimates were not driven by inclusion of extreme parameter values. Data are sufficiently limited and variable that we considered the original ranges to better represent the uncertainty in our estimates, but a probability of acquired resistance 0·1%–2% per new-patient treatment[28] and an MDR-TB transmissibility of 0·5–0·8 relative to DS-TB[24] are supported by data. With these restrictions, the estimated percentages of incident MDR-TB reflecting MDR transmission in the global-average scenario were 94·4% (95% UR: 76·4–98·8%) when restricted by per-treatment resistance acquisition, 96·2% (95% UR: 81·6–99·5%) when restricted by MDR strain fitness, and 94·9% (95% UR: 83·5–98·7%) when restricted by both, versus 95·8% (95% UR: 68·0%–99·6%) without the restrictions as above. Additional sensitivity analyses – (a) varying the time period over which MDR is assumed to emerge, (b) adding appropriate second-line treatment for up to half of MDR-TB patients, (c) reducing the TB reactivation or transmission rate in order to generate a declining epidemic, and (d) including a high-MDR-TB-incidence "hotspot" on a background of lower incidence – each caused no more than 2% variation in the point estimate for the fraction of incident MDR-TB cases resulting from MDR transmission (see Figure S4).

## Discussion

This population-based transmission model of MDR-TB epidemics, which aims to translate notification data into estimates of MDR transmission, suggests that current estimates of MDR-TB prevalence among TB notifications are most consistent with a hypothesis that over 80% of incident MDR-TB in most present-day epidemic settings results from transmission of MDR-TB rather than selection of *de novo* resistance during previous treatment of the index case. To the extent that these notification data are accurate and our model is an adequate representation of TB transmission dynamics, these findings suggest that better treatment of drug-susceptible strains alone is unlikely to curb MDR-TB epidemics in most settings. Our estimates of MDR-TB transmission are robust to a wide array of sensitivity analyses and assumptions about the transmissibility of MDR strains, MDR-TB treatment practices, and TB natural history at the population level. These results should prompt further research to validate the findings of this model-based analysis and to improve these estimates by developing more accurate surveillance measures of drug resistance and by clarifying TB natural history and transmission-related parameters. A predominance of MDR transmission as the etiology of new MDR cases should motivate the global TB community to expand resource outlays and infrastructure for the rapid diagnosis and effective treatment of MDR-TB.

Although epidemiologic and molecular estimates of transmitted MDR-TB vary, a predominance of MDR transmission as suggested by our model has been observed in some clinical settings. Transmission in high-incidence urban settings can result in extensive MDR-TB strain clustering,[29] and a large fraction of MDR isolates in a small country can even arise from transmission of a single strain.[30] Molecular epidemiologic analyses have demonstrated transmitted MDR clusters even in previously treated patients whose initial infection was documented to be drug susceptible,[16] and across wide geographic and temporal separation.[31] Worldwide spread of MDR strains of the Beijing lineage has also been observed, and even when sampling is global and avoids bias from local outbreaks, clustering has been observed among 42% to 100% of MDR isolates within any single Beijing clonal complex.[18] Other molecular epidemiologic studies have yielded much lower estimates of MDR clustering, [16,17] but genotypic clustering is an imperfect and lower-bound estimate of MDR transmission (especially when sampling coverage is incomplete and study duration is short). This principle is evidenced by the finding that even MDR-TB cases with no history of previous TB treatment – and thus no opportunity to acquire MDR in any way other than through transmission – did not belong to any identified cluster in many studies.[32–34] The profound geographic heterogeneity of MDR-TB, particularly when observed within single jurisdictions and clinical catchment areas,[35,36] is similarly consistent with high rates of ongoing MDR transmission. Settings (e.g. New York City,[37] or more recently, Baltic states[38]) that have achieved rapid control of MDR are generally characterized by prioritization of MDR-TB detection and treatment. Importantly, of all notified TB patients worldwide who have MDR, over half have never before been treated,[1] a finding that is also consistent with this analysis.

If, as our results suggest, most MDR-TB is the result of MDR transmission, then reducing transmission through early and effective treatment of MDR-TB is essential to preventing incident MDR-TB and controlling MDR-TB epidemics. Although treating a case of MDR-TB costs five to ten times more than treatment of DS-TB,[39] the cost-effectiveness and affordability of MDR-TB treatment should be reconsidered in light of the population-level impact of ongoing widespread MDR transmission. Despite the challenges of treating MDR-TB, this analysis nevertheless offers hope that MDR-TB can be contained, as current MDR treatment coverage and MDR treatment outcomes both have much room for improvement through ongoing pharmacologic and programmatic innovations, whereas further improving DS-TB treatment outcomes on a population level is arguably more difficult.

Our model, which sought to translate estimates of notified MDR prevalence into the estimates of MDR transmission that are most consistent with current WHO notification data, is dependent upon the accuracy and precision of those data. To the extent that the quality of those data is variable or the WHO-reported confidence intervals are too narrow, so also are our model-based estimates of MDR transmission. These findings should motivate improved notification data – upon which updated and improved estimates of MDR transmission could be generated. In addition, our study has limitations common to model-based analyses. Our model's assumptions, including population homogeneity, static TB treatment practices, and uniform transmissibility of MDR strains, necessarily simplify a complex reality. Although our sensitivity analyses suggest that these simplifying assumptions do not drive our primary results, our quantitative estimates may be inaccurate in settings where our model

formulation does not align with local TB epidemiology. For example, we did not explicitly incorporate HIV (though we calibrate our model to increased TB incidence in HIV-endemic countries); HIV may alter the balance of MDR acquisition versus transmission by increasing the probability of acquiring drug resistance,[40] increasing the rate of progression to active TB after transmission events,[41] increasing nosocomial MDR-TB transmission through clustering in healthcare settings,[42] and increasing TB mortality (which may reduce MDR-TB transmission). Our model also may not fit well to settings in which TB epidemiology and treatment practices are rapidly changing. Such settings may include those where MDR-TB may be rapidly emerging as the result of poor treatment practices (e.g., Somalia[43]), or those where the DS-TB epidemic has been declining steeply since MDR-TB emerged (e.g., China[44]). Furthermore, we did not model specific historical circumstances in individual countries (e.g., prisons in the former Soviet Union) but rather aimed to create a generalizable platform for translation of notification data into estimates of MDR transmission. Future studies should evaluate the degree to which these findings hold in specific settings, especially those with rapidly changing MDR-TB epidemics or unique historical features that merit customized modeling efforts. We also assumed MDR to be a uniform entity and did not explicitly incorporate resistance profiles to individual drugs or transmission of monoresistant strains, although we capture their individual-level impact through poorer treatment outcomes including more frequent MDR acquisition for previously-treated DS-TB cases among whom single-drug-resistance is more prevalent. Relatedly, because our model considers the historical development of MDR epidemics before widespread second-line treatment, second-line drug resistant does not impact our model's results and was not included, although second-line drug resistance has an important impact on the ability to treat MDR-TB using current standard second-line regimens. Finally, the probability of acquiring resistance during treatment was important in sensitivity analyses but has little supporting data to inform its value.[28,45] Further studies of drug resistance acquisition during treatment could be helpful in this regard.

This mechanistic model of TB treatment and drug resistance suggests that existing notifications are most consistent with today's MDR-TB epidemic being predominantly (>80%) an epidemic of MDR transmission. A preponderance of transmission is consistent with both observed MDR-TB epidemiology and historical successes in MDR-TB control. If, as our model suggests, only a small fraction of MDR-TB incidence results directly from previous treatment, then incremental improvements in DS-TB treatment are unlikely to bend the epidemic curve of MDR-TB in most settings. By contrast, expansion of MDR-TB treatment availability, along with improvement in MDR-TB treatment outcomes, has tremendous potential to limit the spread of MDR-TB in the future. If the current MDR-TB epidemic is to be controlled, expanding effective MDR-TB treatment while developing novel rapid drug susceptibility tests and more tolerable, less resource-intensive drug regimens for MDR-TB should be prioritized by the global public health community.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Panel: Research in context

### Evidence before this study

We performed a PubMed search, updated through September 15, 2015, for "((((selected OR acquired OR amplified) OR (primary OR transmit* OR index OR cluster)) and tuberculosis)) AND (resistan*[Title/Abstract] OR MDR*[Title/Abstract])", and reviewed reference lists of relevant results for additional relevant citations.

Transmission of MDR-TB is recognized in some settings as a common reason for first-line treatment failure,[1] MDR outbreaks,[2,3] and drug resistance among treatment-naïve individuals[4] and children,[5] but the much higher prevalence of MDR-TB in previously-treated individuals than in new cases has been taken as informal and indirect evidence of low transmission levels. Molecular epidemiologic analyses of strain clustering often identify likely transmission relationships in only a minority of MDR-TB cases,[6–11] but these methods have known biases that could greatly underestimate the proportion of incident MDR-TB that reflects transmission. Apart from these molecular epidemiologic analysis, we found no other estimates (model-based or otherwise) of how many MDR-TB cases among all or previously-treated TB patients are attributable to selection of resistance during that individual's previous treatment versus MDR transmission.

### Added value of this study

This mechanistic model of the etiology of incident MDR-TB translates estimates of MDR-TB prevalence based on notifications into estimates of the proportion of incident MDR-TB that reflects transmission of MDR strains. In providing such analysis calibrated to country-level and global epidemiology, we show that current notification data are most consistent with MDR transmission dominating in most settings.

### Implications of all the available evidence

A predominance of MDR-TB transmission as the cause of new MDR-TB cases, even those that arise in individuals with a history of TB treatment, highlights the need for prevention of MDR-TB transmission as a focus of MDR-TB control efforts.

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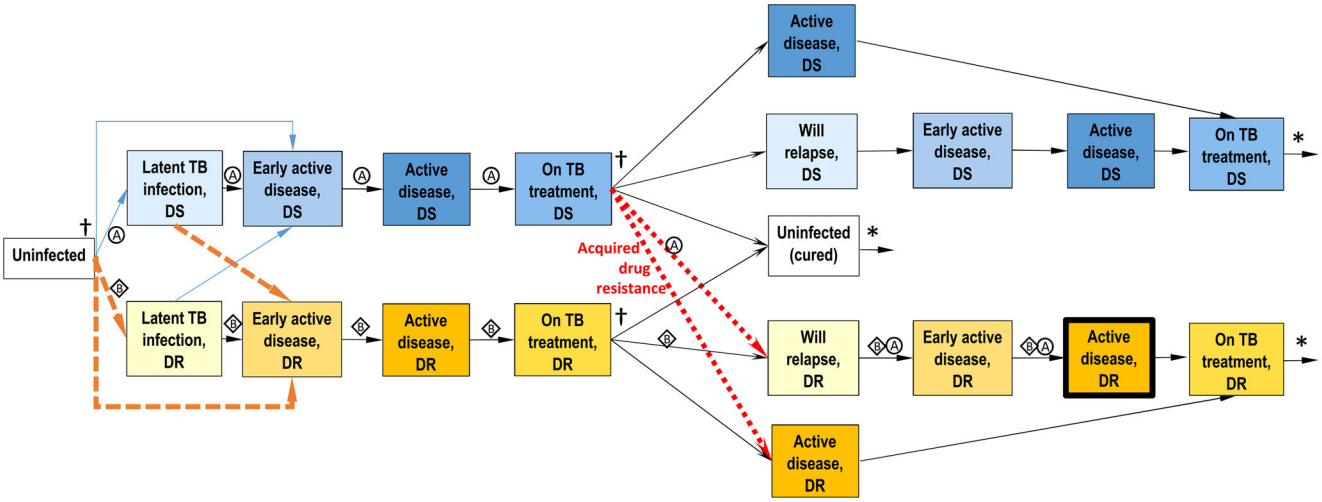
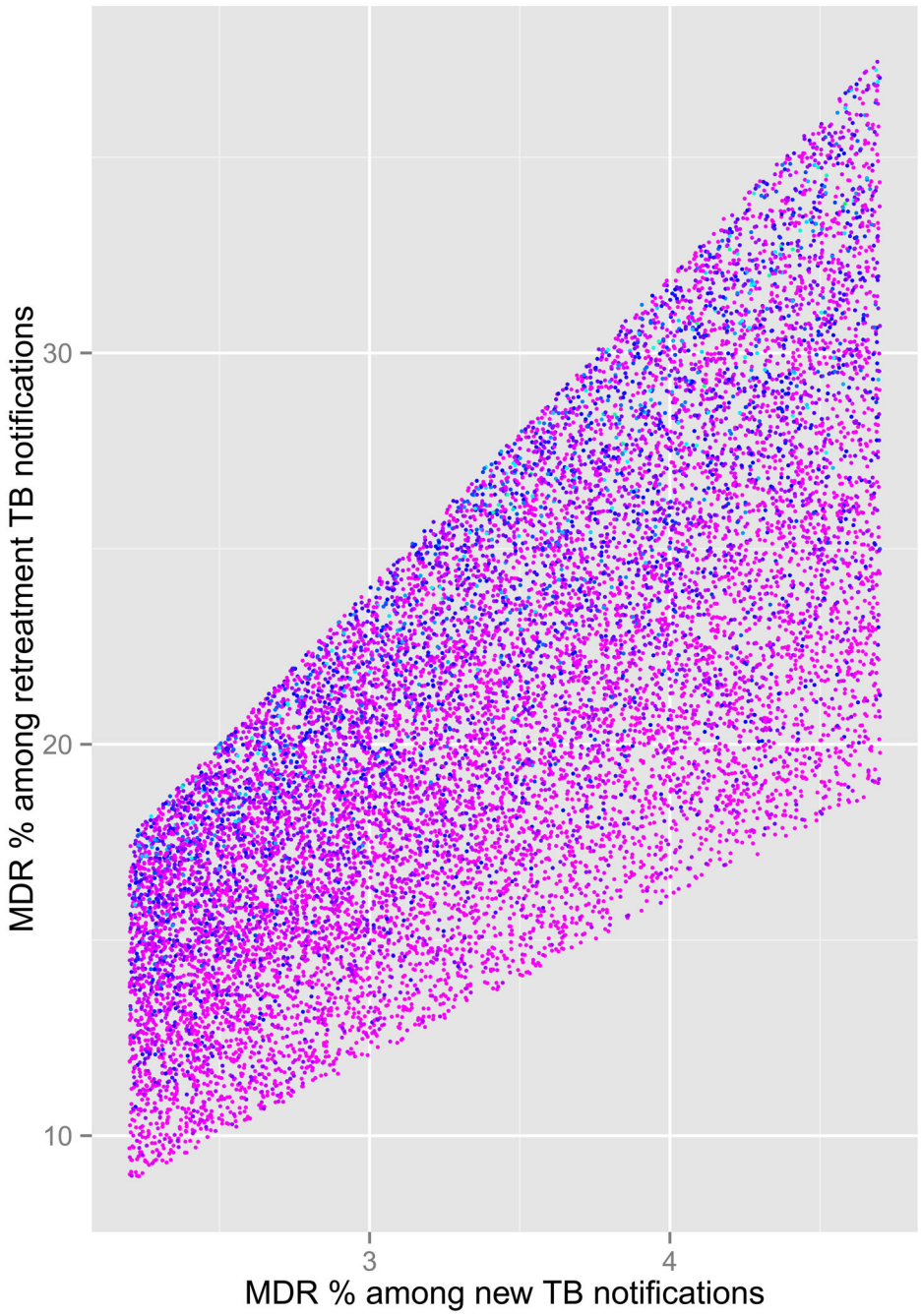



**Figure 1. Model structure**

This simplified schematic of the model shows progression through stages of tuberculosis infection, disease, and treatment, and shows opportunities to develop drug-resistant (DR) tuberculosis (TB) via either acquisition or transmission of resistance. The arrows labeled as pathway “A” show how drug resistance in a previously treated case may result from prior treatment, and the arrows labeled as pathway “B” show how drug resistance in a previously treated case may result from transmission of resistance (with subsequent failure of the initial course of standard treatment). MDR-TB in a previously treated case, indicated by the box with a heavy outline, can result from either acquired (pathway A) or transmitted (pathway B) resistance.

Asterisks (*) indicate that transitions through these states, including possibilities for reinfection, proceed as for states of the same name to the left (denoted with daggers (†)). Not shown here, but also included in the model, are subdivisions into treatment-naïve and treatment-experienced compartments (with differing probabilities of each treatment outcome; see Figure S1), and death and spontaneous cure (either of which can occur from any active disease or treatment state).



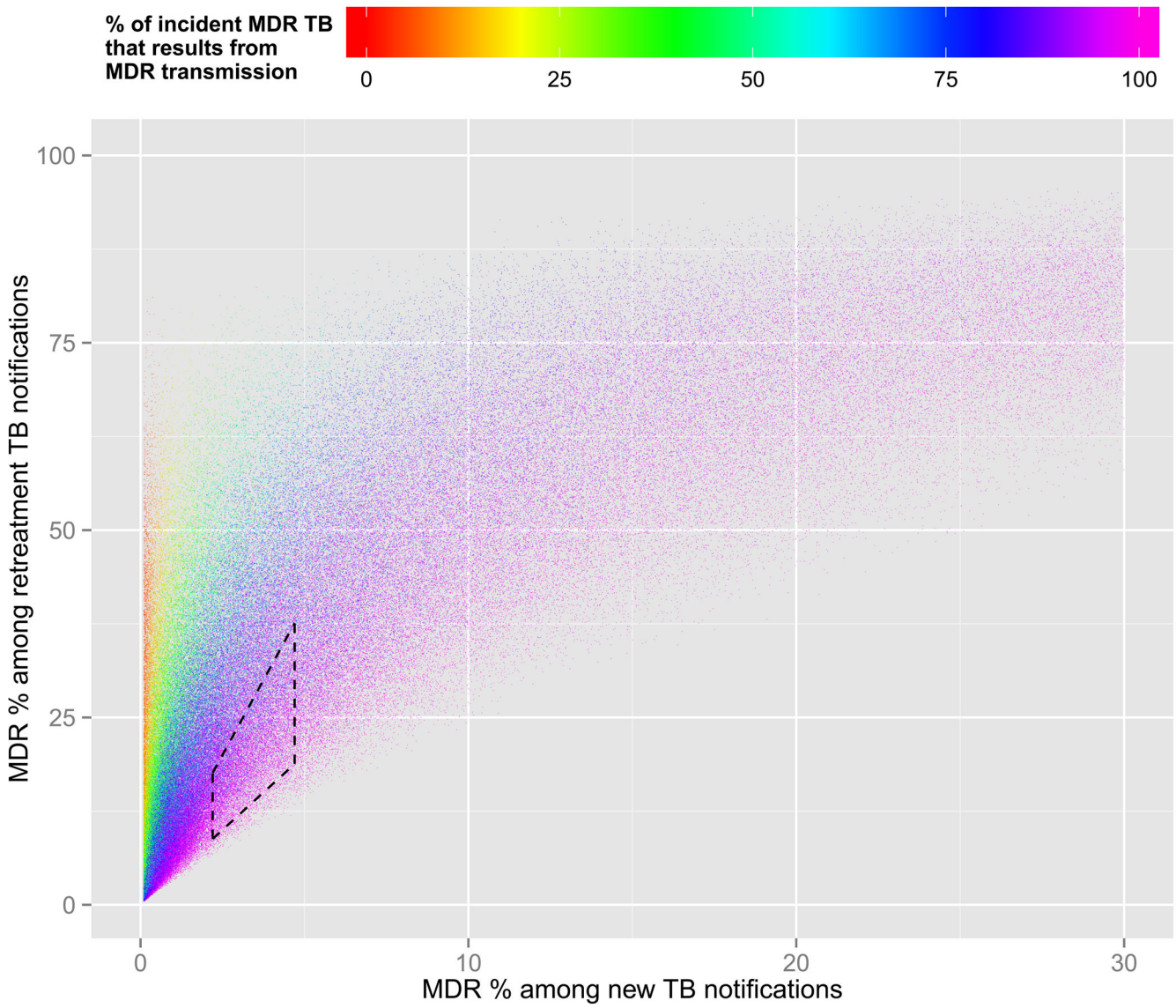



**Figure 2. Converting multidrug-resistant tuberculosis (MDR-TB) notifications into estimated percentage of incident MDR-TB due to MDR transmission**

Shown is the estimated percentage of incident MDR-TB reflecting MDR transmission (rather than acquisition during previous treatment in the same person) across all simulations (upper left) and within the estimated prevalence of MDR among notifications globally (namely, MDR prevalence of 2·2–4·7% among new TB notifications and four to eight times higher MDR prevalence among retreatment notifications (inset)). Current global notifications were most consistent with a vast majority of MDR-TB cases reflecting transmission (median 96%, 95% uncertainty range: 68–100%) (inset). Treatment-related acquisition of resistance was high only when the ratio of MDR prevalence in retreatment versus new notifications was extremely high (red and yellow dots). The same trends are illustrated in line graphs without a color scale in Figure S2.

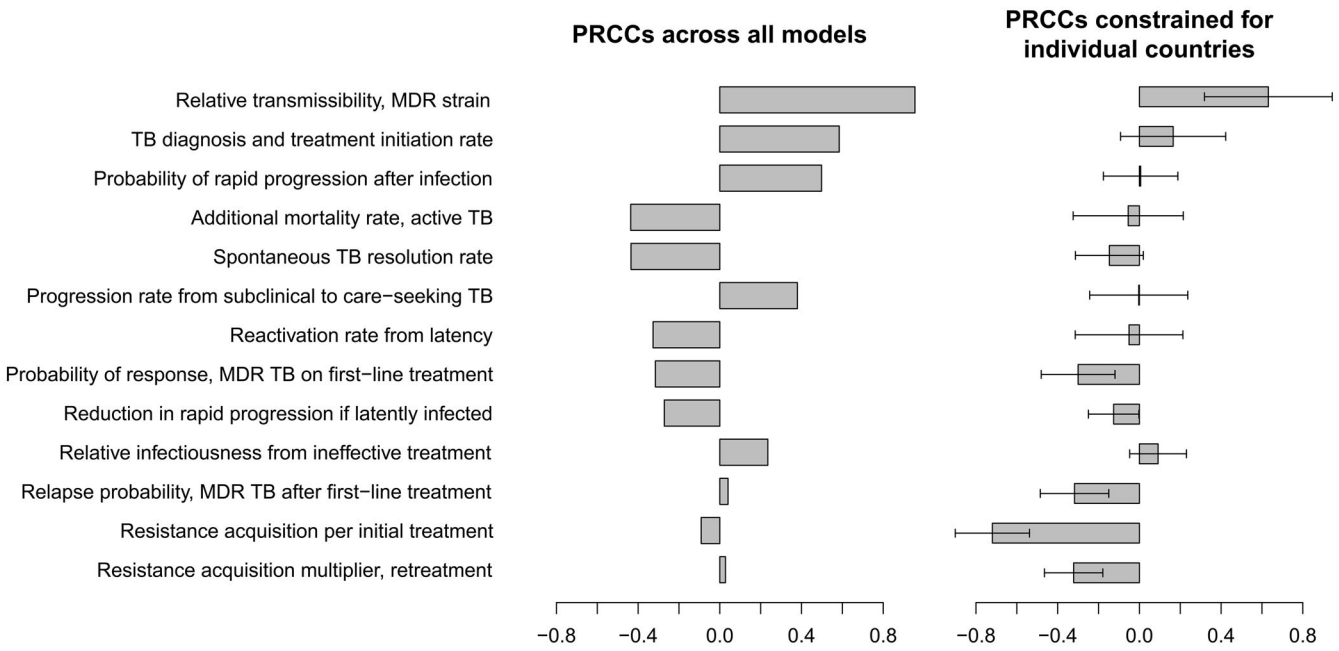



**Figure 3. Partial rank correlation coefficients (PRCCs)**

with the fraction of incident MDR-TB cases resulting from MDR transmission, after adjusting for other parameters. PRCCs were calculated both without notification constraints (Panel 1) and within the notification-based tolerance ranges for each of the representative countries shown in table 2 (Panel 2, mean and SD of PRCCs over six countries). Parameters that had either a PRCC > 0.2 across all models or a mean PRCC >0.2 across the six countries are shown in the figure.

## Table 1

Model parameters

| Parameter | Sampled range | References and notes |
|---|---|---|
| Baseline mortality rate (year$^{-1}$) | 0·015–0·025 | Life expectancy at age 15 = 55–82 |
| TB Transmission coefficient (annual secondary infections produced in a susceptible population, per active DS-TB case, [persons/year]) | 8–14 *a* | Calibrated to target TB incidence range *b* |
| Relative transmissibility of MDR versus DS strain | 0–1 | Uninformative prior |
| Probability of acquiring resistance per new-patient treatment course | 0·00025–0·1 *a* | 28 *b* |
| Multiplier for probability of acquiring resistance, retreatment | 1–10 *a* | 45 *b* |
| Multiplier for probability of acquiring resistance, if failing treatment | 1–4 *a* | *b* |
| Additional mortality rate from active TB (year$^{-1}$) | 0·1–0·4 *a* | 46 *b* |
| Spontaneous resolution rate of active TB (year$^{-1}$) | 0·08–0·32 *a* | 6,46 *b* |
| Fraction of new TB infections progressing rapidly to active disease | 0·04–0·18 | 47 |
| Reduction in rapid progression if latently infected | 0–0·86 | 47,48 |
| Reactivation rate from latent to early-active TB (year$^{-1}$) | 0·0005–0·0020 *a* | 48 –51 *b* |
| Rate of progression from early-active to clinical active TB (year$^{-1}$) | 0·7–2·8 *a* | 52,53 |
| TB diagnosis and treatment initiation rate (year$^{-1}$) | 0·5–2·0 *a* | 54 |
| Relative infectiousness and mortality of early-stage active TB | 0·11–0·44 *a* | 55 *b* |
| Relative infectiousness and mortality of TB on ineffective treatment (without appropriate bacteriologic response), versus no treatment | 0–1 | *b* |
| Relative mortality of TB on effective treatment, versus no treatment | 0–0·2 | 1 *b* |
| Fraction of patients with initial bacteriologic response to first-line therapy (includes those who will relapse with or without acquired resistance): | | |
| -treatment-naïve, DS-TB | 0·97–1·00 | 1 |
| -treatment-experienced, DS-TB | 0·88-[treatment-naïve rate] | 1 |
| -MDR-TB | 0–0·5 | 56 –58 |
| Fraction of patients lost to follow-up from first-line therapy | | |
| -Initial treatment | 0–0·08 | 1 |
| -Retreatment | [Initial treatment value]-0·16 | 1 |
| Fraction of treatment-responsive patients who relapse after first-line therapy | | |
| -Initial treatment, if no preexisting or acquired MDR | 0·01–0·09 *a* | 28,59 |
| -Retreatment, if no preexisting or acquired MDR | 1–4x[initial-treatment fraction] *a* | 45,59 |
| -Preexisting or acquired MDR-TB | 0·6–1 | 57 |
| Relapse probability multiplier if treatment not completed | 1–9 *a* | 28,59,60 |
| Average time to relapse (years) | 0·5–4·5 *a* | 59 |

*a* indicates parameter sampled from a uniform distribution on a logarithmic scale (i.e. from a truncated exponential distribution) as further described in SI; all others were sampled from uniform distributions on an arithmetic scale over the indicated range

*b* Additional details about parameter estimation are provided in supplement, section 1b.2

**Table 2**

Model calibration and estimates of transmitted MDR-TB for six representative countries with disparate MDR-TB notification data

| Representative country | Bangladesh | Ethiopia | Malawi | Peru | Philippines | Uzbekistan |
|---|---|---|---|---|---|---|
| **Features of notification data** | High TB, moderate MDR, **very high ratio** | Moderate TB, moderate MDR, moderate ratio | Moderate TB, **low MDR**, high ratio | Moderate TB, **high MDR**, moderate ratio | **High TB,** moderate MDR, moderate ratio | Low TB, **very high MDR, low ratio** |
| **TB prevalence, per 100,000** | | | | | | |
| **WHO*** | 402 (210–656) | 211 (170–257) | 135 (67–226) | 124 (110–142) | 438 (385–495) | 120 (61–199) |
| **Model*** | 355 (259–467) | 227 (194–268) | 207 (168–246) | 179 (138–234) | 441 (383–487) | 120 (89–150) |
| **TB incidence, per 100,000/year** | | | | | | |
| **WHO** | 224 (119–253) | 224 (188–276) | 156 (152–168) | 164 (77–283) | 292 (261–331) | 80 (68–97) |
| **Model** | 222 (198–249) | 201 (164–238) | 157 (148–165) | 121 (108–139) | 289 (261–319) | 80 (66–93) |
| **MDR among new TB cases, %** | | | | | | |
| **WHO** | 1.4 (0.7–2.5) | 1.6 (0.9–2.8) | 0.4 (0.1–1.0) | 3.9 (3.6–4.2) | 2.0 (1.4–2.7) | 23 (18–29) |
| **Model** | 1.2 (0.3–2.1) | 1.5 (0.5–2.4) | 0.3 (0.1–0.8) | 3.9 (3.6–4.2) | 2.0 (1.3–2.6) | 27 (23–31) |
| **MDR ratio: % among retreatment cases to % among new cases** | | | | | | |
| **WHO** | 20.7 (17.1–24.3) | 7.5 (3.5–13.1) | 12.0 (8.0–17.3) | 9.0 (8.5–9.5) | 10.5 (8.0–14.5) | 2.7 (2.3–3.1) |
| **Model** | 20.5 (17.4–24.4) | 8.1 (5.2–13.7) | 12.1 (8.7–17.4) | 9.0 (8.5–9.5) | 10.1 (7.7–13.4) | 3.0 (2.7–3.4) |
| ***Model estimate of transmitted MDR* (% of incident MDR cases (95% UR))** | **48% (30–75%)** | **92% (58–99%)** | **82% (56–97%)** | **95% (79–100%)** | **76% (51–98%)** | **99% (91–100%)** |

* WHO estimates are shown as reported point estimate (reported uncertainty interval). Model estimates are shown as the weighted median (95% uncertainty range).