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PREDICTING OUTCOMES AND DRUG RESISTANCE WITH STANDARDIZED TREATMENT OF ACTIVE TB

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Abstract:

New WHO guidelines recommend initial treatment of active tuberculosis (TB) with a 6-month regimen utilizing rifampin throughout. We have modeled expected treatment outcomes, including drug resistance, with this regimen, compared to an 8-month regimen with rifampin for the first 2 months only, followed by standardized retreatment.

A deterministic model was used to predict treatment outcomes in hypothetical cohorts of 1000 new smear positive cases from 7 countries with varying prevalence of initial drug resistance. Model inputs were taken from published systematic reviews. Predicted outcomes included number of deaths, failures and relapses, plus the proportion with drug resistance. Sensitivity analyses examined different risks of acquired drug resistance.

Compared to use of the standardized 8-month regimen, for every 1000 new TB cases treated with the 6-month regimen we predict that 48-86 fewer persons will require retreatment, and 3-12 deaths would be avoided. However, the proportion failing or relapsing after retreatment is predicted to be higher, because with the 6-month regimen 50%-94% of failures and 3% - 56% of relapses will have MDR-TB.

We predict substantial public health benefits from changing from the 8-month to the 6-month regimen. However in almost all settings the current standardized retreatment regimen will no longer be adequate.

Background:

Since the early 1990's the World Health Organization (WHO) (1) and the International Union Against TB and Lung Disease (the Union) (2) have recommended use of a limited number of standardized drug regimens to treat active TB cases. This approach ensures that patients receive appropriate drugs in the right doses, for the correct length of time, and has been adopted in most low and middle income countries (3). Up to now two regimens have been recommended for new patients. The "8-month regimen" includes isoniazid, rifampin, pyrazinamide and ethambutol for 2 months followed by isoniazid plus ethambutol for 6 months (2HRZE/6HE). The "6-month regimen" includes isoniazid, rifampin, pyrazinamide and ethambutol for 2 months, followed by isoniazid plus rifampin for 4 months (2HRZE/4HR). The 6 month regimen has higher efficacy (4), but the 8 month initial regimen is preferred in countries where resource limitations preclude supervision of rifampin in the continuation phase (2). In view of the greater efficacy, the WHO has recently recommended that the 6-month regimen be used as standardized initial therapy in all countries (5).

For all previously treated patients who have failed, relapsed, or returned after failing to complete (defaulting) initial treatment, the WHO had recommended a single standardized retreatment regimen (1). This consisted of 2 months of streptomycin, isoniazid, rifampin, pyrazinamide and ethambutol, followed by one month of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 5 months of isoniazid, rifampin and ethambutol (2SHRZE/1HRZE/5HRE). WHO estimates that approximately 12% of all currently treated patients receive retreatment; meaning as many as 1.1 million individuals receive this regimen - given the total annual incidence of 9.2 million cases (3).

This standardized retreatment regimen was never tested in randomized trials (6), but rather was designed for use in sub-Saharan Africa for patients who had initially received the 8-month regimen and had very low likelihood of MDR (7). Use of the same retreatment regimen following the 6-month initial treatment has been particularly controversial (8;9), because treatment outcomes are poor in settings with high prevalence of initial drug resistance (10), and use of this regimen is associated with amplification of drug resistance (11;12). Surveillance information has consistently shown that the prevalence of drug resistance is higher among previously treated than new cases (13). However there is very limited and contradictory surveillance data linking drug resistance to detailed clinical histories, such as whether patients had previously defaulted, failed or relapsed after apparent cure (11;12;14;15). If the prevalence of drug resistance is very high in any of the retreatment sub-groups (failure, relapse or prior default) following the initial 6 month regimen, it would be inappropriate to treat them empirically with the current retreatment regimen.

This modeling exercise was undertaken in order to inform the treatment revision guidelines published by the WHO. These new guidelines have recently been made available, and now recommend that, in settings with no access to drug sensitivity testing, failures of initial treatment should be offered an empiric MDR regimen (5). Those who have relapsed and defaulted however will continue to be offered the standardized retreatment regimen.

We have used modeling to predict the treatment outcomes of failure, relapse, as well as the pattern of drug resistance associated with each of these outcomes - following initial therapy with one of two standardized initial regimens, and the current standardized retreatment regimen, in settings with varying levels of drug resistance

Methods:

Overview of model: A deterministic model representing a decision tree was developed to simulate hypothetical cohorts of 1000 smear positive active TB cases undergoing a single round of initial treatment and retreatment – all of which occurred within a year. New cases received either the standardized 8 or 6-month regimen; those who failed or relapsed received the standardized 8-month retreatment regimen. A simplified outline of the model is provided in the online supplement. Cohorts were modeled in 7 countries, selected to represent widely varying prevalence of initial drug resistance. The probability of transitioning at each decision node was determined from data found in the literature. Within each country the probability of cohort members starting with underlying drug resistance was determined by the drug resistance prevalence in that country from WHO reports (13). The probabilities of failure, relapse and acquired drug resistance were based on the regimen received (6 or 8-month) and the underlying drug resistance; these probabilities were taken from results of two recent systematic reviews and meta-analyses of randomized trials (16;17). Model predicted outcomes included deaths, the numbers who relapsed or failed initial therapy, began retreatment then failed or relapsed, and the proportion with drug resistance among failures or relapses. The total number of outcomes that occurred with each strategy was summed and compared using basic spread sheet analysis (Excel ®, 2007). Models were validated using published drug resistance data from countries that used either the 6 or 8-month regimens for new cases. Uncertainty in key parameters was addressed in sensitivity analysis (see section below).

HIV: In a recent meta-analysis there were very few randomized trials or cohort studies of treatment of HIV co-infected patients with underlying drug resistance (18), and too few patients with drug resistance for pooled estimates of outcomes (18). Therefore we assumed that model predicted outcomes would be similar for TB cases with HIV and without HIV. There is some evidence (19) that the acquisition of drug resistance may be increased in TB cases that are HIV positive. We explored this possibility in a sensitivity analysis in which we varied the risk of acquisition of drug resistance.

Initial drug resistance profiles: Prevalence of initial drug resistance in each country (Supplemental Table S1) was taken from the most recent WHO surveillance report on drug resistance (13). Initial drug resistance was categorized as: pan-susceptible, mono-isoniazid resistant, mono-streptomycin resistant, mono-ethambutol resistant, mono-rifampin resistant, poly-drug resistant (PDR) - defined as resistant to two or more drugs, but not meeting the definition of MDR, and MDR - (defined above). Mono-rifampin resistant cases were grouped with MDR cases. The mono-streptomycin resistance group was considered equivalent to pan-susceptible because streptomycin is not included in standardized initial treatment, except in Vietnam where streptomycin is used so this form of resistance was modeled with distinct treatment outcomes (4;20).

Modeling treatment: In TB programs in low and middle income countries, the pre-treatment drug resistance is not known to practitioners; all treatment is standardized and empiric. Therefore we assumed that standardized initial and retreatment regimens were given to all patients, regardless of underlying drug resistance profiles.

As shown in the supplemental figure, with initial treatment, new cases could be cured, die or fail during initial treatment. The proportion of the hypothetical cohort that died during initial treatment was 5.6% for all cases with either initial regimen (based upon global reported mortality during initial treatment in 2003 and 2004 for patients taking standardized initial treatment (10)), except for MDR cases as described below. A proportion of the cohort could fail, and the remainder were cured, of whom some could relapse. We assumed that all patients would complete treatment; the impact of non-completion (defaulters) was addressed in sensitivity analyses. Failure and relapse rates varied according to standardized initial treatment regimen received (8 or 6-month), and underlying drug resistance (see section below). Outcomes for MDR cases after initial standardized treatment were 25% spontaneous cure and 33% mortality In the absence of

other data, we assumed that TB cases with MDR have the same mortality and spontaneous cure rate as untreated cases in Europe in the pre-antibiotic era (21)). The remainder of MDR cases failed (42%).

We assumed that all failures and relapses would be detected and receive the standardized retreatment regimen. Those who required retreatment were reclassified according to their predicted post-treatment drug resistance profiles. Outcomes were modeled in a similar manner as for initial treatment, except that spontaneous cure of MDR-TB would not occur a second time (since we assumed the maximum reported value for spontaneous cure would occur during initial treatment). All retreatment cases could cure, die, or fail during retreatment, or relapse after cure, with probabilities determined by their pretreatment drug resistance, but independent of whether they required retreatment because of failure or relapse with initial treatment. Mortality during retreatment for all non-MDR cases was 7.8% (based upon global reported retreatment mortality in 2003 and 2004 for patients taking standardized retreatment (10)), and was 33% for MDR cases (21).

Failure/Relapse and Acquired Resistance rates: Treatment failure, relapse, and acquired drug resistance rates for the initial 6 and 8-month regimens, according to underlying initial drug resistance as defined above, were taken from a systematic review and meta-analysis of 57 published randomized trials (4). In order to address the problem of increased risk of acquired drug resistance associated with sub-optimal adherence in true program settings a sensitivity analysis was conducted (see below). There are no randomized trials reporting outcomes of the currently recommended standardized retreatment regimen(6). There are only 7 cohort studies that report bacteriologically confirmed outcomes in individual patients receiving the retreatment regimen; of these only 3 reported outcomes in INH resistant cases and none reported outcomes with other forms of drug resistance (6). Hence, probabilities of failure, relapse, and acquired drug resistance for the standardized retreatment regimen were assumed to be the same as the probabilities for the 6-month initial regimen. This assumption was investigated in sensitivity analysis (see below).

Outcomes Estimated: Using all of the above data, the total number of failures, relapses and deaths plus the resistance profile among those who relapsed or failed were predicted following initial treatment with the 6 or 8-month regimen and standardized retreatment.

Validation:
We applied published data on the prevalence of initial drug resistance (13), to compare prevalence predicted using our model with observed prevalence of MDR among failures and relapses in Peru (14) and Thailand (12), where the 6 month regimen was used, and Benin (15), where the 8 month regimen was used.

Sensitivity Analysis: Three sensitivity analyses were conducted. The first investigated the potential influence of defaulting by increasing the relapse rates with initial and retreatment regimens by 20% - well above the global average default rate (3). The second increased the probability of acquiring drug resistance during initial treatment by 25%. This sensitivity analysis provided insight into the possibility that the risk of acquired drug resistance would be higher in true program settings, or increased in HIV co-infected patients. The third sensitivity analysis increased the efficacy of the retreatment regimen by decreasing failure, relapse, and acquired drug resistance rates by 25%.

Results:
Predicted failures, relapses, and patterns of drug resistance among failures and relapses:
As shown in Table 1a the predicted number of failures of initial therapy was most strongly affected by the prevalence of initial drug resistance, although failures were more frequent with the 8-month regimen in all settings. However, the proportion with MDR would be much higher following initial treatment with the 6-

month regimen. In almost all countries, virtually all failures of standardized retreatment were predicted to have MDR – regardless of initial drug resistance or initial regimen.

Because of much higher relapse rates, the predicted total number of patients requiring retreatment will be much higher following the 8-month regimen, particularly with higher prevalence of initial drug resistance as shown in Figure 1. The proportion with MDR, or any form of drug resistance would be much lower among relapses than among failures with initial therapy, but much higher after standardized retreatment, as seen in Table 1b.

As summarized in Table 2, the majority of drug resistance after initial and retreatment was persistent - meaning that it had been present even before treatment, and simply persisted unchanged through-out therapy. However, some acquired drug resistance did occur - with the 8-month regimen this occurred more frequently but was usually mono-resistance, whereas with the 6-month regimen acquired drug resistance was less frequent, but more serious - as it was usually MDR.

The difference in drug resistance patterns was much greater between failures and relapses, than the differences in patterns with the different initial regimens, as demonstrated in Figures 2 and 3

Validation:
The predictions from this modeling study compare well with published surveillance data in a few countries. Among countries using the 6-month initial regimen (Figure 2), in Peru, the prevalence of MDR among failures of the 6-month regimen was 94% (14), close to our predicted prevalence of 87%. In Thailand, the prevalence of MDR was reported to be 86% in failures and 11% in relapses (12), compared to predicted values of 80% in failures and 21% in relapses. In Benin, where the 8-month regimen initial regimen was used, (Figure 3), our model predicted that 14% of failures and 1% of relapses would have MDR, compared to reported prevalence of 22% and 4% respectively (15).

Comparison of outcomes including deaths, with the two initial treatment approaches:
As seen in Table 3, deaths were most strongly associated with prevalence of drug resistant TB. In countries with high rates of initial drug resistance, a substantial proportion of deaths were due to MDR TB. However in the countries modeled with low prevalence of drug resistance, more than 80% of deaths occurred in persons with pan-susceptible strains. The most important gain from changing from the 8-month to the 6-month initial regimen would be 4-12 fewer deaths, as seen in Table 4. This reflects that only about half the number of patients would fail or relapse following the initial 6-month regimen, thereby avoiding the risk of mortality from a second episode of active TB.

Sensitivity Analysis: When relapse rates were increased by 20% (to reflect the impact of default rates) results were similar to the main analysis (see Supplemental Tables S2-S6). When the rates of acquired drug resistance during initial treatment were increased by 25%, even more MDR cases were predicted to develop with use of the 8-month regimen relative to the 6-month regimen (Supplemental Tables S7-S11). Even if the retreatment regimen was 25% more efficacious, results were not substantially altered (Supplemental Tables S12-S16).

Discussion:
The most important finding of this study is that in all countries modeled, following initial therapy with the 6-month regimen a very high proportion of failures and relapses are predicted to be drug resistant - more than half will have MDR. Changing from the 8-month to the 6-month regimen is predicted to result in

fewer deaths, and half as many patients requiring retreatment, but these are much more likely to have MDR. As a result the predicted rates of failure and relapse, and proportion with drug resistance among them, will be high if the same standardized retreatment is used.

Model inputs should have been accurate as they were taken from a meta-analysis of results of 57 randomized trials conducted in many settings that included a total of 19,801 patients (4). The algorithm developed for predicting the pattern of drug resistance in failures and relapses is simple, and the predictions were accurate in the few countries validated. This simple model (or Figure 3) could be used to predict drug resistance profiles among failures and relapses in countries that do not have surveillance data for retreatment patients. While awaiting surveillance data, these predicted patterns could be used to select appropriate regimens for patient with failure or relapse.

There are several limitations to this analysis. First, model inputs were taken from randomized trials which may underestimate the extent of acquired drug resistance in a true program setting. This limitation was addressed in sensitivity analysis however and a greater acquisition of drug resistance during initial treatment only led to increased MDR, especially with the 8-month regimen. Second, the risk of acquiring drug resistance in HIV positive TB patients was assumed to be the same as in HIV negative ones, because there is limited information on this point (18). Again, the potential impact of increased acquired drug resistance was addressed in sensitivity analyses, however predictions may not be accurate for high HIV burden settings. Third, default was not included in the primary analysis; as shown in the sensitivity analysis, higher default rates would result in more persons requiring re-treatment and more deaths. Default rates are higher in countries using the 8-month regimen (10). Therefore, assuming that a switch to a shorter regimen would in turn reduce the default rate and improve outcomes, the decision not to include default would tend to underestimate the advantages of switching from the 8-month to the 6-month regimen. Forth, we assumed that all failures and relapses would be detected and treated. This would result in an underestimate of mortality among failures and relapses - since it is unlikely they would all be detected under program conditions. Finally, the model also did not estimate transmission from failures and relapses resulting in secondary cases. These last two limitations would also underestimate the advantages of changing from the 8-month regimen

An obvious limitation is the lack of specific input data for treatment outcomes in patients with various forms of drug resistance receiving the standardized retreatment regimen. However, in a recent systematic review we could find no randomized trials, and only three reports of outcomes with the standardized retreatment regimen in three small cohorts, each with 30-40 patients with INH mono-resistance (6). Hence there are simply no published data available on which to base predictions.

This analysis has two major implications. First, we predict that changing from the standardized 8-month regimen to the 6-month regimen to treat new cases will result in fewer deaths, and substantially fewer patients who fail or relapse and therefore require retreatment. Differences will be greater in countries with higher levels of initial drug resistance. These findings provide strong support for the recommendation to switch from the 8 month to the 6-month initial regimen.

However, the most important implication is the need for a better retreatment strategy following initial therapy with the 6-month regimen. In almost all countries, more than half of all closely supervised patients who fail this initial regimen are predicted to have MDR-TB, while in countries with high prevalence of initial drug resistance more than half of relapses will have MDR. Because of this, we predict that the current retreatment regimen will have low efficacy in many settings.

The current retreatment strategy was designed empirically over 25 years ago (7), and is now used to treat at least one million patients annually. Given its origins, current widespread use, and the recent change in WHO recommendations (5) our findings support calls (8;9) for several changes: (i) Improved drug resistance surveillance linked to detailed clinical histories - this could be implemented rapidly to provide information to guide design of appropriate regimens in different settings; (ii) Access to drug sensitivity testing for all retreatment patients; and, (iii) Strengthened retreatment regimens. There can be no doubt that use of standardized regimens has enhanced access to treatment for patients in many settings. However the identification of standardized regimens that are the most efficacious and least toxic for patients requiring retreatment in all countries will take a concerted international effort. Surveillance studies, and a series of randomized trials will be needed to adequately evaluate the best options for retreatment, to resolve what is now the Achilles heel of the DOTS strategy.

Figure Legends:

Figure 1: Percentage of cohort requiring retreatment (failure and relapse of initial treatment) by prevalence of MDR in new cases. Each point represents one of the 7 countries included in the modeling. Diamonds: 6 month standardized regimen. Squares: 8 month standardized regimen
Blue vertical line: Global weighted mean of prevalence of MDR in new cases (2.9%)

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Legend:

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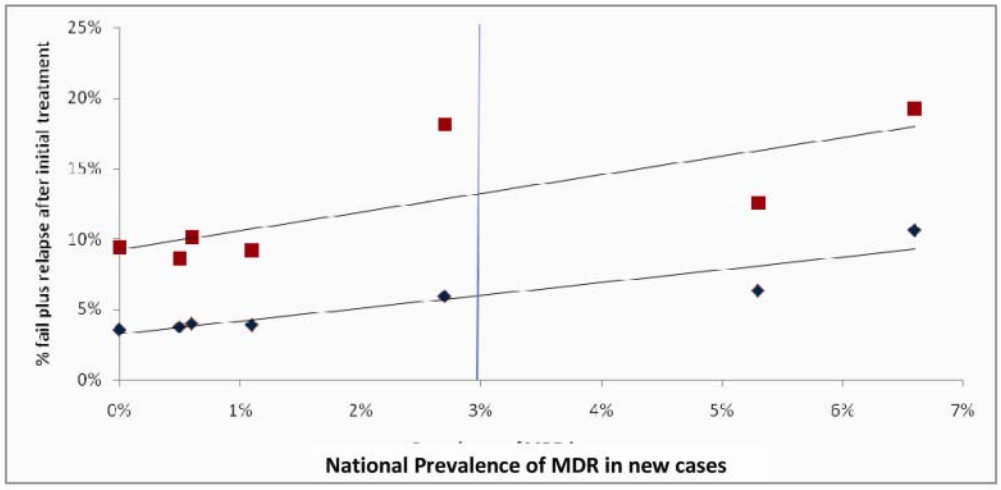

Figure 2: Percentage of failures and relapses with MDR following standardized initial treatment with 6-month regimen (2HRZ/4HR) and standardized retreatment - by national prevalence of MDR in new cases. Each point represents a one of the 7 countries included in the modeling.
Small filled squares with solid line: Failures during retreatment
Small filled diamonds with dashed line: Relapse after retreatment
Large unfilled squares with solid line: Failures during initial therapy
Large unfilled diamonds with dashed line: Relapse after initial therapy
Vertical line: National MDR prevalence in Thailand, with unfilled square representing reported MDR prevalence among failures (86%), and unfilled diamond reported MDR among relapses (11%) (12).

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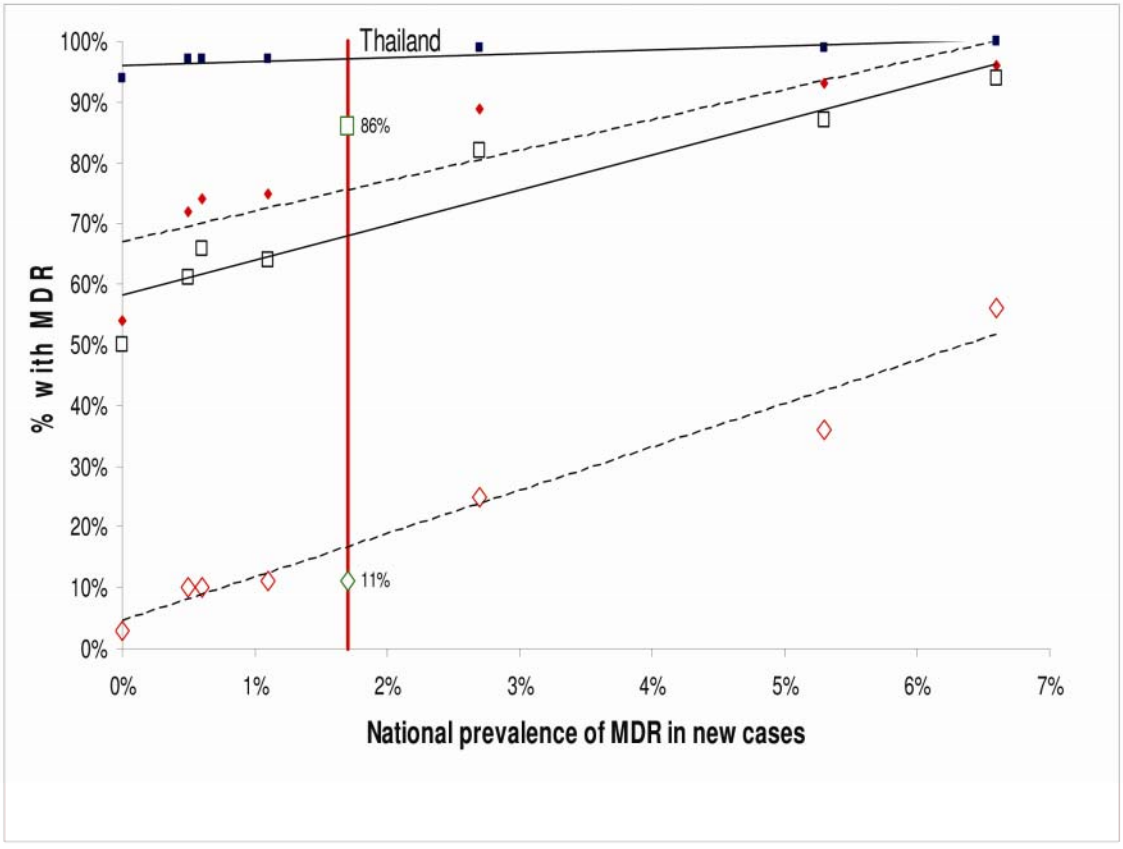

Figure 3: Percentage of MDR among failures and relapses following initial treatment with 8-month regimen (2HRZ/6HE) and standardized re-treatment – by national prevalence of MDR in new cases
Each point represents a one of the 7 countries included in the modeling.
Small filled squares with solid line: Failures during retreatment
Small filled diamonds with dashed line: Relapse after retreatment
Large unfilled squares with solid line: Failures during initial therapy
Large unfilled diamonds with dashed line: Relapse after initial therapy
Vertical line: National MDR prevalence in Benin, with unfilled square representing reported MDR prevalence among failures (22%), and unfilled diamond reported MDR among relapses (4%) (15).

Figure 3: Percentage of MDR among failures and relapses following initial treatment with 8-month regimen (2HRZ/6HE) and standardized re-treatment – by national prevalence of MDR in new cases. Each point represents one of the 7 countries included in the modeling.

Legend:
Small filled squares with solid line: Failures during retreatment
Small filled diamonds with dashed line: Relapse after retreatment
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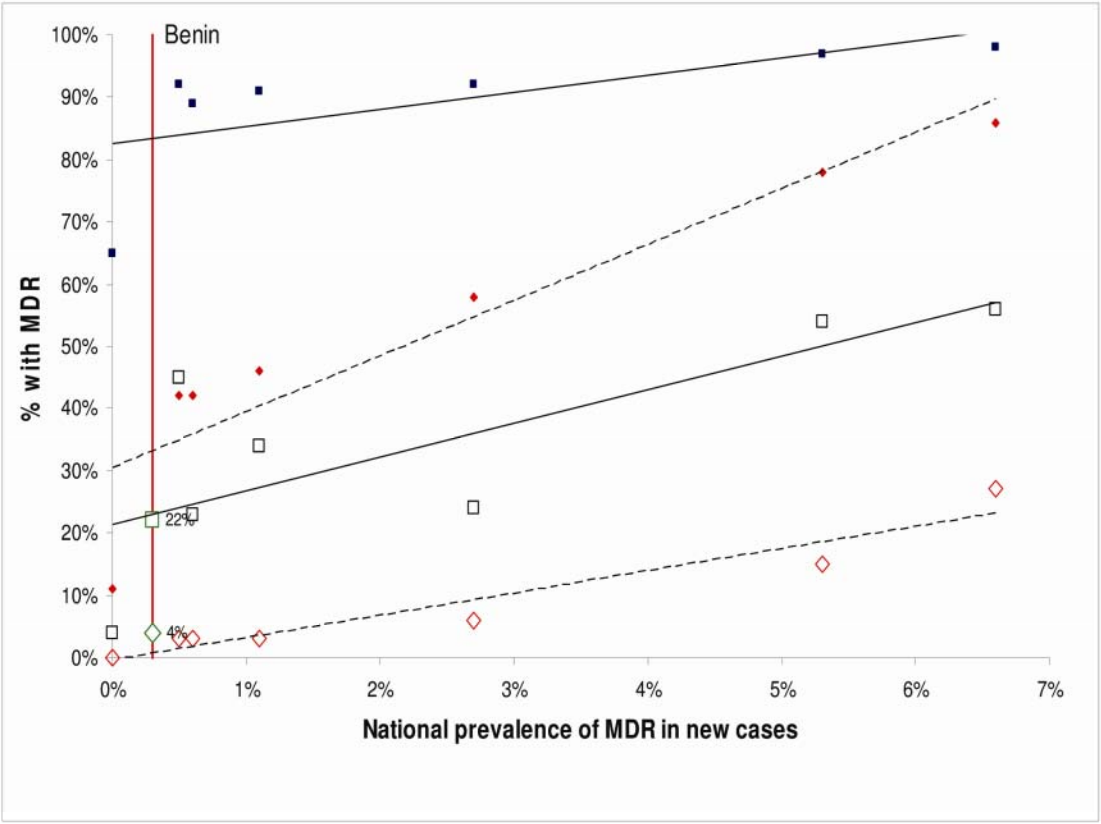

Supplemental Figure: Simplified schematic of modeling of initial TB treatment using either the 6 month or 8 month standardized regimen. 1000 new active TB cases from each country are stratified by their reported initial drug resistance pattern. To reflect what occurs in most low-middle income countries, all cases are modeled to receive standardized initial treatment, regardless of pre-treatment drug sensitivity. After a single course of standardized initial treatment, active cases can be cured, fail or die. Those cases that cure can then relapse. Relapse and failure rates vary according to underlying drug resistance. Cases that fail and relapse can acquire additional drug resistance according to user defined probabilities. All cases that fail and relapse are regrouped according to their post-treatment drug resistance and modeled to receive standardized retreatment. The 6 month and the 8 month initial regimen are evaluated separately, using different failure and relapse rates depending on the regimen. User defined probabilities from the literature determine the path followed through the model by the hypothetical population.

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Authors contribution statements:
Olivia Oxlade: Wrote protocol, conducted analyses, drafted and revised the manuscript, including approval of the final version. No conflicts of interest declared.
Kevin Schwartzman: Participated in the data analysis, and made critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.
Madhukar Pai: Made critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.
Jody Heymann: Made critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.
Andrea Benedetti: Participated in the data analysis, and made critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.
Sarah Royce: provided input on study protocol, made critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.
Dick Menzies: Formulated idea, reviewed analyses, critical revisions to the manuscript, including approval of the final version. No conflicts of interest declared.

Table 1: Predicted number of FAILURES or RELAPSES and respective drug resistance pattern during standardized initial treatment followed by standardized retreatment

(Hypothetical cohorts of 1,000 new cases in each country start initial therapy with one of two standardized regimens.)

1A: FAILURES*

	Initial Treatment					Retreatment			
Country	Initial Regimen	Total number of patients who fail Initial Tx (and will start retreatment)	Drug resistance pattern in patients who fail initial therapy			Total number of patients who fail retreatment	Drug resistance pattern in patients who fail retreatment		
			Pan-sensitive+	Any resistance (except MDR)	MDR-TB		Pan-sensitive	Any resistance (except MDR)	MDR-TB
Dominican Republic	2HRZE/**6HE**	66	1%	43%	56%	26	0%	2%	98%
	2HRZE/**4HR**	42	2%	4%	94%	26	0%	0%	100%
Peru	2HRZE/**6HE**	30	3%	43%	54%	11	1%	3%	97%
	2HRZE/**4HR**	19	5%	8%	87%	11	0%	1%	99%
Viet Nam	2HRZE/**6HE**	46	2%	74%	24%	9	1%	8%	92%
	2HRZE/**4HR**	17	4%	13%	82%	9	0%	1%	99%
UR Tanzania	2HRZE/**6HE**	9	12%	54%	34%	3	3%	6%	91%
	2HRZE/**4HR**	7	16%	20%	64%	3	1%	2%	97%
Nicaragua	2HRZE/**6HE**	13	8%	69%	23%	3	3%	9%	89%
	2HRZE/**4HR**	7	14%	20%	66%	3	1%	2%	97%
Gambia	2HRZE/**6HE**	6	20%	35%	45%	2	4%	5%	92%
	2HRZE/**4HR**	6	18%	21%	61%	2	1%	2%	97%
Kenya	2HRZE/**6HE**	8	14%	82%	4%	1	10%	25%	65%
	2HRZE/**4HR**	5	22%	28%	50%	1	2%	4%	94%

Table 1b: RELAPSES*

Country	Initial Regimen	Relapses After Initial Treatment				Relapses after retreatment			
		Total Number of patients who relapse after Initial Tx (and start retreatment)	Pan-sensitive	Any resistance (except MDR)	MDR-TB	Total relapses after retreatment	Pan-sensitive	Any resistance (except MDR)	MDR-TB
Dominican Republic	2HRZE/**6HE**	126	36%	37%	27%	29	4%	10%	86%
	2HRZE/**4HR**	65	30%	14%	56%	26	2%	2%	96%
Peru	2HRZE/**6HE**	96	60%	25%	15%	14	11%	10%	78%
	2HRZE/**4HR**	44	55%	9%	36%	12	6%	2%	93%
Viet Nam	2HRZE/**6HE**	135	34%	61%	6%	13	9%	33%	58%
	2HRZE/**4HR**	42	45%	30%	25%	10	6%	6%	89%
UR Tanzania	2HRZE/**6HE**	83	76%	21%	3%	5	35%	19%	46%
	2HRZE/**4HR**	33	80%	8%	11%	4	20%	5%	75%
Nicaragua	2HRZE/**6HE**	88	69%	29%	3%	5	32%	26%	42%
	2HRZE/**4HR**	33	77%	13%	10%	4	19%	7%	74%
Gambia	2HRZE/**6HE**	80	79%	18%	3%	4	41%	16%	42%
	2HRZE/**4HR**	32	83%	7%	10%	3	23%	5%	72%
Kenya	2HRZE/**6HE**	86	71%	29%	0%	3	51%	38%	11%
	2HRZE/**4HR**	31	83%	15%	3%	2	35%	12%	54%

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*Cases that die while on treatment are excluded from above calculations. All percents rounded to whole numbers.

Table 2. Percentage of failures and relapses that are predicted to have *persistent* or *acquired* drug resistance after standardized initial and retreatment regimens*

Country	Initial Regimen	Among **failures** of retreatment			Among **relapses** after retreatment		
		Pan-sensitive	Any form of resistance		Pan-sensitive	Any form of resistance	
			Persistent	Acquired		Persistent	Acquired
Dominican Republic	2HRZE/**6HE**	0%	94%	6%	4%	91%	4%
	2HRZE/**4HR**	0%	99%	1%	2%	97%	1%
Peru	2HRZE/**6HE**	1%	93%	7%	11%	84%	5%
	2HRZE/**4HR**	0%	99%	1%	6%	93%	1%
Viet Nam	2HRZE/**6HE**	1%	77%	22%	9%	78%	13%
	2HRZE/**4HR**	0%	97%	3%	6%	92%	2%
UR Tanzania	2HRZE/**6HE**	3%	83%	14%	35%	58%	7%
	2HRZE/**4HR**	1%	96%	3%	20%	77%	2%
Nicaragua	2HRZE/**6HE**	3%	76%	22%	32%	58%	10%
	2HRZE/**4HR**	1%	95%	4%	19%	78%	3%
Gambia	2HRZE/**6HE**	3%	86%	10%	41%	54%	5%
	2HRZE/**4HR**	1%	96%	3%	23%	74%	2%
Kenya	2HRZE/**6HE**	10%	28%	61%	51%	36%	12%
	2HRZE/**4HR**	2%	89%	8%	35%	60%	5%

* Persistent drug resistance is defined as resistance that exists at the start and remains throughout treatment. Acquired drug resistance is defined as resistance that is amplified or occurs de novo during a course of treatment. All percents rounded to whole numbers.

Table 3: Predicted number of DEATHS and drug resistance among deaths after standardized initial treatment followed by standardized retreatment

(Hypothetical cohorts of 1,000 new cases in each country start initial therapy with one of two standardized regimens.)

Country	Initial Regimen	Total number of deaths during initial and retreatment	Drug resistance pattern among those who died during initial and retreatment		
			Pan-sensitive	Any resistance (except MDR)	MDR
Dominican Republic	2HRZE/**6HE**	125	34%	12%	55%
	2HRZE/**4HR**	120	33%	8%	58%
Peru	2HRZE/**6HE**	89	60%	7%	33%
	2HRZE/**4HR**	85	59%	5%	35%
Viet Nam	2HRZE/**6HE**	85	49%	28%	21%
	2HRZE/**4HR**	73	55%	22%	22%
UR Tanzania	2HRZE/**6HE**	67	87%	6%	7%
	2HRZE/**4HR**	64	86%	3%	9%
Nicaragua	2HRZE/**6HE**	67	84%	9%	7%
	2HRZE/**4HR**	63	84%	6%	9%
Gambia	2HRZE/**6HE**	66	89%	3%	8%
	2HRZE/**4HR**	63	89%	2%	8%
Kenya	2HRZE/**6HE**	63	90%	10%	0%
	2HRZE/**4HR**	59	92%	7%	1%

†All percents rounded to whole numbers.

Table 4: Summary of outcomes with standardized initial treatment and retreatment regimens
(Hypothetical cohorts of 1,000 new cases in each country start initial therapy with one of two standardized regimens.)

Country	**Initial Regimen**	**Outcomes after initial treatment**	**Outcomes after initial and retreatment -** (Total number from original hypothetical cohort of 1000 new cases)		
		Total number of patients who relapse or fail	Deaths:	Relapse or fail, and survive with MDR-TB:	Relapse or fail, and survive with any other form of DR-TB (not MDR)
Dominican Republic	2HRZE/**6HE**	192	125	50	3
	2HRZE/**4HR**	106	120	51	0
	Difference*	86	5	-1	3
Peru	2HRZE/**6HE**	125	89	21	2
	2HRZE/**4HR**	63	85	22	1
	difference	62	4	-1	1
Viet Nam	2HRZE/**6HE**	181	85	16	5
	2HRZE/**4HR**	59	73	17	1
	difference	122	12	-1	4
UR Tanzania	2HRZE/**6HE**	92	67	5	1
	2HRZE/**4HR**	39	63	6	0
	difference	53	4	-1	1
Nicaragua	2HRZE/**6HE**	101	67	4	1
	2HRZE/**4HR**	40	63	5	0
	difference	61	4	-1	1
Gambia	2HRZE/**6HE**	86	66	4	1
	2HRZE/**4HR**	38	63	5	0
	difference	48	3	-1	1
Kenya	2HRZE/**6HE**	94	63	1	1
	2HRZE/**4HR**	36	59	2	0
	difference	58	4	-1	1

┼ All numbers rounded to whole numbers.

* Difference is positive if outcome more frequent with 8-month regimen, and negative if outcome more frequent with 6-month regimen

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