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Exploring the potential of a pan tuberculosis treatment regimen to drive the emergence of novel resistance

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Abstract
New drugs and regimens are available to treat tuberculosis (TB). Taking advantage of this fact, pan-TB regimens (intended for universal use without any drug susceptibility testing prior to initiating treatment), are currently in development, where candidate regimens contain some of these same drugs. However, widespread use of the drugs in pan-TB regimens could contribute to increasing resistance prevalence in problematic ways, potentially driving resistance to both novel and current drugs. Against a background of rising resistance to these drugs, pre-existing resistance could also affect the viability of future pan-TB regimens' universal indication.

Here we developed a multi-generational cohort model to compare treatment outcomes, including the development of new resistance, between continued use of current standards of care and a hypothetical pan-TB approach. Given that current regimens in the pan-TB development pipeline contain bedaquiline and other compounds or classes that are also in currently recommended regimens for treating DR-TB, we parameterised our model using observational and trial data for bedaquiline. We used this model to explore outcomes for a single current or future treatment cohort to identify conditions under which a pan-TB regimen would fail to outperform the standard of care, and over multiple successive cohorts to identify factors leading to the rapid build-up of problematic resistance over time.

Assuming that the pan-TB regimen had similar efficacy against pan-susceptible TB as the current rifampicin-susceptible TB regimen and a shorter duration that considerably improved adherence, we found that while the probability of the pan-TB approach outperforming the standard of care was initially high, as resistance to component drugs increased that probability declined rapidly. The pan-TB approach did lead to an increase in resistance to novel drugs, however problematic resistance to both novel and current drugs was limited primarily to scenarios where either the rate of acquisition of resistance to novel drugs was high or the effect of that resistance on cure was very high.

Background

Rifampicin-resistant tuberculosis (RR-TB) is a key contributor to global antimicrobial resistance burden with over 400,000 people developing RR-TB in 2020, almost 40% of whom likely died as a result [cite]. Many who develop RR-TB disease are not enrolled on RR-TB treatment, either because they are not treated for TB at all or because they don't undergo drug susceptibility testing (DST) and are inappropriately given treatments for rifampin-susceptible (RS)-TB. For those who are enrolled on RR-TB treatment, recent advances have made it possible to cure more than 80% with 6-month oral regimens - a major improvement for a disease whose treatments were historically much longer, more toxic, and less successful [cite] - but the need to identify drug resistance and direct patients with RR-TB down a second-line treatment pathway still complicates the diagnosis and treatment of TB.

The availability of novel drugs with low/no preexisting resistance has led to suggestions of a pan-TB treatment approach, with one universal treatment regimen and no need for DST prior to initiating treatment. The World Health Organization's target regimen profile for a pan-TB regimen also calls for short duration and improved tolerability and forgiveness compared to the current standard of care [cite]. Such a regimen has the potential to be both effective and cost-effective [cite Tess paper,cite], due to improved regimen characteristics as well as removal of barriers to initiation of appropriate treatment. While such a regimen could be highly effective, its unique advantages require that resistance to its component drugs is rare.

A potential concern about such regimens is that widespread use of new drugs could drive a rapid loss in susceptibility, potentially resulting in scenarios where a new regimen's pan-TB indication is short-lived or where combined resistance to both current and novel drugs severely limits the treatment options for some patients. Once resistance to the component drugs in a pan-TB regimen began to emerge, continuing to use the regimen without routine susceptibility testing could lead to development of resistance to additional drugs in the regimen, and it is possible that this amplifying resistance could result in worse outcomes than under current regimens. Testing for both phenotypic and genotypic resistance to novel drugs remains limited, and due to the technical difficulties involved is likely to remain so for the near future[cite]. In addition, as resistance to pan-TB regimen components begins to emerge, it is possible that the use of current first-line drugs such as rifampicin to retreat those with resistance to the pan-TB regimen could cause more TB to become simultaneously resistant to both pan-TB drugs and current first-line drugs, with limited treatment options for affected individuals.

Another reason to carefully consider these resistance-related risks is that leading candidate regimens in development for the pan-TB indication share newer drugs such as bedaquiline and pretomanid with the regimens currently recommended for treating RR-TB[cite,cite,cite,cite]. Although most TB, including most RR-TB, currently remains susceptible to these new drugs, emergence of resistance has been observed – for example, as much as 8% of RR-TB was also resistant to bedaquiline in a South African cohort, where the country was an early adopter of bedaquiline for RR-TB treatment [cite]. These empirical data suggest it is possible for resistance to potential pan-TB regimen component drugs to emerge quickly in the patient populations for whom they are used, and that similar emergence might occur among RS-TB if pan-TB regimens are not designed to guard against emergent resistance. These data also suggest that, with recent guideline updates and increasingly widespread use of these novel drugs for treating RR-TB, the prevalence of resistance to some pan-TB regimen components might be substantial among the subset of patients with RR-TB by the time a pan-TB regimen becomes available.

There is currently limited evidence on the likelihood of emerging resistance and its effect on treatment outcomes, but an urgent need to anticipate pathways by which resistance could emerge. Here we use a modelling approach to explore the circumstances under which use of a pan-TB regimen could contribute in a problematic way to increasing resistance prevalence, posing resistance-related risks that could compromise the net health benefit of the pan-TB strategy.

Methods

We developed a stylized cohort model to evaluate clinical and drug-resistance outcomes over multiple cohorts of patients, each followed from the time of initial TB diagnosis,, comparing the use of a pan-TB strategy with current standards of care. All model parameters can be found in Table 1.

Modelling of drugs, regimens, and drug resistance

We explicitly modelled three drug classes as components both of treatment regimens and of drug-susceptibility phenotypes: rifamycins including rifampicin (denoted R), diarylquinolines including bedaquiline (denoted B), and an additional, unspecified novel drug (denoted X) that is a component of RR-TB and/or pan-TB regimens. Additional drugs were modelled implicitly: the standard-of-care regimen for treatment of RS-TB is denoted R but implicitly includes additional drugs such as isoniazid, and the B- and X- containing regimen (denoted BX) implicitly includes one or more additional novel drugs.

Phenotypes resistant to R, B and X were denoted as RR-TB, BR-TB and XR-TB respectively. Similar to regimens, these phenotypes implicitly included the possibility of resistance to additional drugs whose resistance was not explicitly modelled; for example, RR-TB is usually isoniazid resistant and may be fluoroquinolone resistant, and XR-TB may be resistant to one or to multiple components of the pan-TB regimen. Resistance to each drug was modelled in simplified binary fashion, corresponding to accepted breakpoints for phenotypic resistance to rifampin and bedaquiline (and modelled on bedaquiline for the unspecified drug X). DST coverage and sensitivity to detect RR, BR and XR phenotypes were combined into a single probability-of-detection parameter.

Initial treatment pathways

In the standard of care scenario, R was used to treat RS-TB, and BX was used for treatment of RR-TB. This reflects WHO guidelines recommending BPaL(M)[cite], along with our assumption that future improvements to the efficacy or safety of this regimen's component classes will be incorporated into future RR-TB as well as pan-TB regimens. We assumed current levels of DST coverage for rifampicin, with DST coverage for B and X limited to only a fraction of patients in whom RR-TB was detected (estimated based on current fluoroquinolone DST coverage). If DST was performed and detected resistance to rifamycins as well as one or more novel drugs (B or X), we assumed that an individualised regimen would be constructed consisting of any novel drugs that retained activity along with one or more second-line drugs. When resistance to both B and X was present (i.e. for RR/BR/XR-TB), the potential for cure by these individualised regimen was parameterised based on longer regimens used for RR-TB prior to use of bedaquiline, pretomanid or linezolid ("conventional second-line regimen"). When susceptibility to either B or X was retained (i.e. for RR/BR-TB or RR/XR-TB), individualised regimens were denoted "X-based" or "B-based", and the inclusion of one such drug was assumed to restore half of the incremental potential for cure that BX would offer in fully-susceptible TB.

In the pan-TB scenario, the BX regimen was used for all new TB patients, with no DST for any drugs prior to initial treatment.

Retreatment pathways

We also explored multiple scenarios for retreating those who failed or relapsed after a first round of treatment, taking into account the previous treatment regimen and, potentially, the results of additional or repeat DST. Within the standard of care scenario, the relationship between known resistance and selected regimen remained the same as for initial treatment. However, DST coverage for R increased for those with no known history of RR-TB, while for those with prior BX exposure (due to known RR-TB) RR-TB was again assumed to be known. DST coverage for B and X remained limited to patients with known RR-TB, but coverage increased among those with RR-TB and prior BX exposure. All values here were an assumption due to a lack of data.

For retreatment in the pan-TB scenario, we assumed that the regimen selected was the same as under the standard of care scenario, but that DST coverage was lower and the default regimen in the absence of DST changed from R to BX. The coverage of both R and B/X DST prior to retreatment in the pan-TB scenario was the same as prior to initial treatment in the standard of care scenario. For those with known RR-TB, we modelled an additional alternative scenario for B/X DST coverage prior to retreatment of 0%. Treatment pathways are shown in Supplementary figure 1.

Treatment outcomes

Treatment outcomes were modelled as resulting in one of four possible outcomes: durable cure, treatment failure or relapse without acquisition of resistance, treatment failure or relapse with acquisition of resistance to a component of the treatment regimen, and death. The probabilities of these outcomes depended on the regimen used (R, BX, B-based, X-based or conventional second-line) and the resistance phenotype at the start of the treatment course (drug susceptible TB, or any combination of RR-TB, BR-TB, and/or XR-TB). Initial resistance to one or more components of the regimen reduced the probability of cure and (if relevant) increased the probability of acquiring additional resistance, by amounts estimated from clinical data where available. For a B-based

individualised regimen (and similarly for an X-based regimen), the probability of acquiring resistance to X was estimated as the mean of the risk of acquisition of resistance during treatment of (i) drug susceptible TB with BX and (ii) BR-TB with BX. Acquisition of resistance to multiple regimen components simultaneously during one treatment course was not modelled due to a low likelihood. Treatment outcomes by resistance status and regimen are shown in Supplementary table 1.

Time approximation

We extended the cohort model over multiple generations to simulate the accumulation of resistance and its effect on outcomes over time. Our multiple-cohort representation captured the number of generations of transmission but ignored the (large variation in) calendar time per generation. In estimating how transmission from earlier cohorts contributed to a future cohort of new TB patients, we assumed that cohort sizes remained the same over time (i.e., an effective reproduction number of 1 in all scenarios) and that those who were unsuccessfully treated generated on average as much transmission after their initial diagnosis as before. The composition of a given treatment cohort, in terms of drug resistance, was therefore a weighted average of the prior cohort at three different time points (at the start of treatment, after initial treatment, and after retreatment), weighted by the proportion of the cohort still with TB at each of those time points. We modelled 10 generations of new treatment cohorts, running 1000 model actualisations.

We assumed that 4% of the first cohort was RR-TB [cite], of which 2% was also resistant to B, based on bedaquiline [cite, cite, cite, cite]. Simultaneously, 0.2% of RS-TB had resistance to B, also based on bedaquiline [cite,cite]. Initial prevalence of resistance to X was assumed to be zero. In a sensitivity analysis, we increased the baseline prevalence of BR as a proportion of all TB to account for the possible accumulation of resistance between the present day and when pan-TB may become available in the future.

Parameter uncertainty

Many of our parameter values had little data to inform them. As such, we selected wide uncertainty ranges based on the range of estimates available in the literature. We assumed beta distributions for all parameter values except the risk ratio for resistance acquisition given existing resistance to a regimen component (see Table 1), for which we assumed a uniform distribution due to the extremely high uncertainty and a desire to explore extreme values. We explored parameter extremes through one- and two-way sensitivity analyses.

Table 1: Parameter values (uncertainty intervals in square brackets) and sources. All parameters were assumed to follow a beta distribution except for the risk ratio for B or X resistance acquisition given pre-existing X or B resistance, respectively, which followed a uniform distribution. DS-TB=drug susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to additional novel drug X.

Parameter	Description	Value	Source
	Regimen effectiveness		
E_R	Proportion of DS-TB durably cured by rifamycin-based regimen	70.9% [58.5- 79.3%]	Cite Tess's paper
E_{BX}	Proportion of DS-TB durably cured by pan-TB regimen	76.3% [68.8- 83.1%]	Cite Tess's paper
E_{ind}	Proportion of TB durably cured by individualised regimen	43.9% [33.7- 53.6%]	Cite Tess's paper
CFR	Proportion of poor outcomes (i.e. no durable cure) that result in death	48.3% [40.3- 52.5%]	Cite excluding those not evaluated and future mortality in those who still have TB, uncertainty taken from regional variation
	Impact of resistance on cure		
P_R	Risk ratio of cure for rifamycin-based regimen given initial RR-TB	0.35 [0.22- 0.5]	Cite Tess's paper, cite, cite
P_B	Risk ratio of cure for pan-TB regimen given initial BR-TB	0.75 [0.54- 0.91]	Cite Tess's paper, cite
P_X	Risk ratio of cure for pan-TB regimen given initial XR-TB	0.75 [0.54- 0.91]	Assumed to be the same as the risk ratio given initial BR-TB
P_{BX}	Risk ratio of cure for pan-TB regimen given BR- and XR-TB	0.35 [0.22- 0.5]	Assumed to be the same as the risk ratio for a rifamycin-based regimen given initial RR-TB
	Resistance acquisition		
S_R	Probability of acquired RR-TB after rifamycin-based treatment (if initially RS-TB)	0.6% [0.3- 1.2%]	Cite, cite
S_B	Probability of acquired BR-TB after pan-TB treatment (if initially BS, XS)	1% [0.3-2.3%]	Cite, cite, cite, cite, based on observational studies and trial results, where the point

			estimate reflects where these two intersect
S_X	Probability of acquired XR-TB after pan-TB treatment (if initially BS, XS)	1% [0.3-2.3%]	Assumpted to be similar to the probability of acquired BR-TB, based on cite with an increased upper bound to represent a low barrier to resistance
Q	Risk ratio for B or X resistance acquisition given pre-existing X or B resistance, respectively	7.5 [4.0- 16.0]	Assumption based on cite, cite for other drugs
	Drug susceptibility testing		
R_soc_{new}	R DST for new patients, standard of care scenario	44.1% [33.1-55.1%]	Cite weighted by the proportion with bacteriological confirmation with an assumed 25% uncertainty interval
BX_soc_{new}	B and X DST coverage for new patients with known RR-TB, standard of care scenario	49.0% [36.8-61.3%]	Cite using fluoroquinolone testing coverage with an assumed 25% uncertainty interval
R_soc_{retR}	R DST coverage for retreatment patients previously treated with R, standard of care scenario	80.0% [60.0-100%]	Assumption
R_soc_{retBX}	R DST coverage for retreatment patients previously treated with BX, standard of care scenario	100%	Assumption
BX_soc_{retR}	B and X DST coverage for retreatment patients previously treated with R with known RR-TB, standard of care scenario	49.0% [36.8-61.3%]	Assumed to be the same as for new patients in the standard of care scenario
BX_soc_{retBX}	B and X DST coverage for retreatment patients previously treated with BX with known RR-TB, standard of care scenario	60.0% [45.0-75.0%]	Assumption, higher than retreatment patients in the standard of care scenario
R_pan	R DST coverage for retreatment patients, pan-TB scenario	44.1% [33.1-55.1%]	Assumed to be the same as for new patients in the standard of care scenario
BX_pan	B and X DST coverage for retreatment patients with known RR-TB, pan-TB scenario	0% or 49.0% [36.8-61.3%]	Assumed to be the same as for new patients in the standard of care scenario

	Baseline prevalence of resistance		
$prev_{DS}$	Initial prevalence of DS-TB	95.7%	Cite
$prev_{RR}$	Initial prevalence of RR-TB	4.2%	Cite, weighting new and previously treated patients
$prev_{BR}$	Initial prevalence of BR-TB	0.2%	Cite, cite
$prev_{XR}$	Initial prevalence of XR-TB	0.000	Assumption
$prev_{RRBR}$	Initial prevalence of RR/BR-TB	0.09%	Cite, cite, cite, cite
$prev_{RRXR}$	Initial prevalence of RR/XR-TB	0.000	Assumption
$prev_{BRXR}$	Initial prevalence of BR/XR-TB	0.000	Assumption
$prev_{RRBRXR}$	Initial prevalence of RR/BR/XR-TB	0.000	Assumption

Results

Model approach

Figure 1 illustrates the standard-of-care and pan-TB treatment pathways for one cohort of patients, demonstrating the routes by which patients with different resistance phenotypes arrive at their final treatment outcomes based on mean parameter values from Table 1. For this set of parameter values, the pan-TB scenario results in fewer deaths, less treatment failure and less drug resistance, although in both scenarios most TB that persisted after retreatment was drug-susceptible TB (DS-TB). Supplementary figure 2 demonstrates how model pathways change with changing prevalence of resistance for the same parameter set.

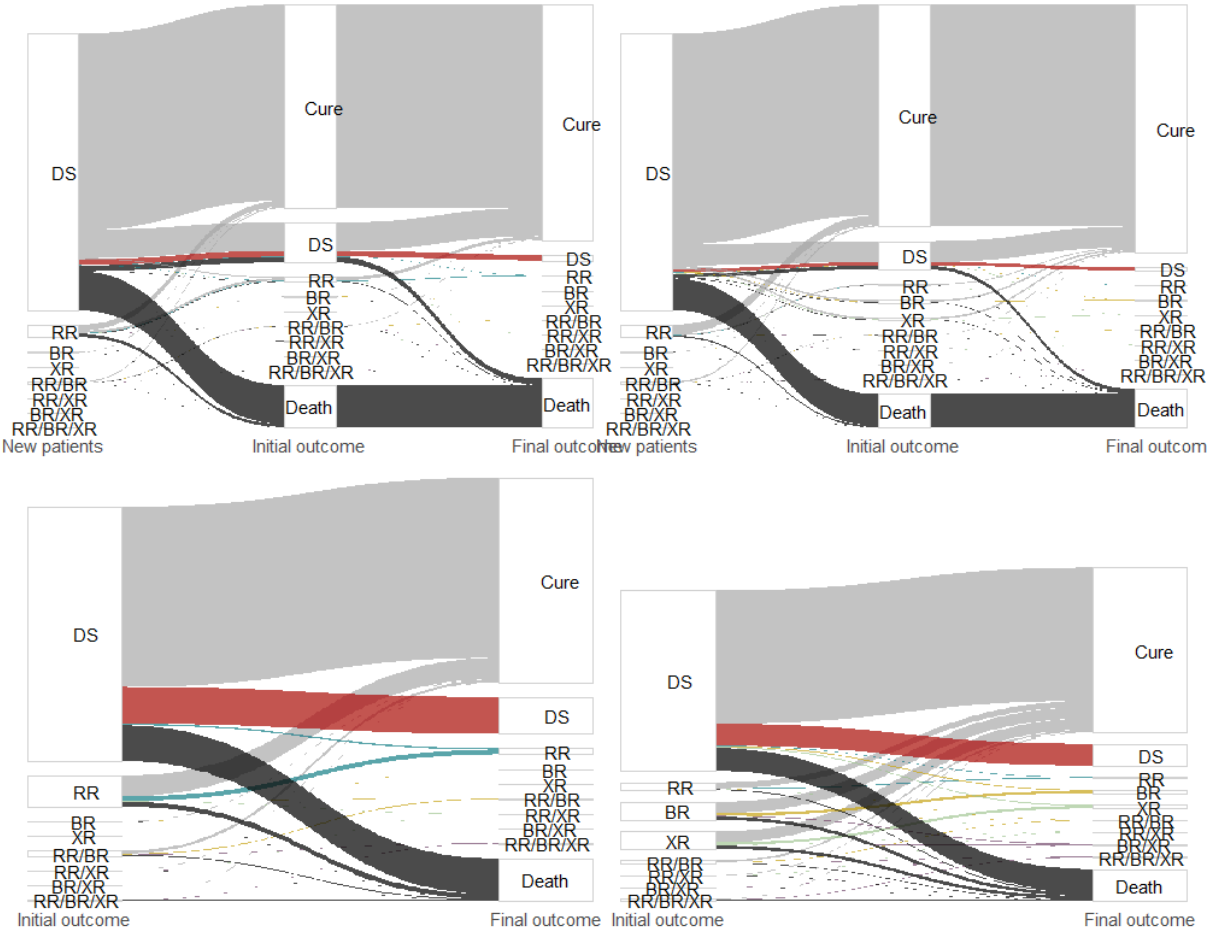

Figure 1: Sankey diagram using mean parameter values for the (a, c) standard of care and (b, d) pan-TB scenario, demonstrating (a,b) the entire treatment outcome pathway and (c,d) the final outcome after retreatment for those whose initial treatment was not curative, where y-axes are scaled based on the relative numbers of retreatments in the two scenarios. Colours indicate the final treatment outcome. DS-TB=drug susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to novel drug X.

Over multiple cohorts of patients in both scenarios, the proportion of TB that is resistant to at least one modelled drug is projected to increase (i.e. the proportion that is DS is projected to decrease, figure 2). The change was estimated to be faster in the pan-TB scenario, reaching only 61.0% [95% uncertainty interval 42.3-79.7] without any drug resistance in the 10th generation under the pan-TB scenario compared to 76.7% [95% uncertainty interval 67.3-86.0] under the standard of care. We

note, however, that these are proportion-based results and do not show changes in the absolute number of incident TB cases that may result from improved regimens and cause reductions in the absolute incidence of drug-resistant TB independent of changes in the proportion of TB that is resistant. As illustrated in figure 2, the drug resistance that initially emerges under the pan-TB scenario is primarily B or X mono-resistance (mirroring the continued selection of R resistance in the standard-of-care scenario), but over time, with DST-free use of the pan-TB regimen, simultaneous resistance to both B and X becomes more common (X% [X-Y] after 10 cohorts).

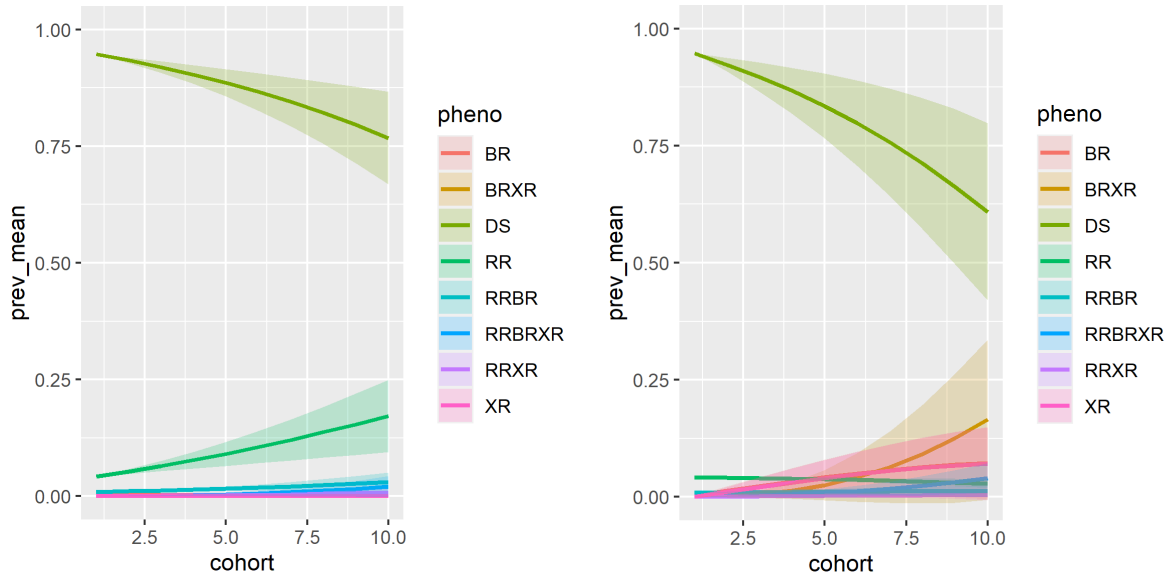

Figure 2: Prevalence of resistance phenotypes over multiple cohorts, for (a) standard of care and (b) pan-TB scenarios. Shaded areas indicate 95% uncertainty intervals. DS-TB=drug susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to novel drug X.

Performance of pan-TB vs standard of care

When sampling our best-estimate uncertainty distributions for all parameters simultaneously, pan-TB was highly (85.9%) likely to result in more cure than the standard of care for the initial cohort (figure 3 panel a). In univariate analysis (fixing one parameter at an extreme of its uncertainty range while varying the others), the probability of standard of care outperforming pan-TB was observed to depend most heavily on the relative effectiveness of the pan-TB compared to the standard of care among patients with DS-TB. Estimates of durable cure depend, in turn, on assumptions of similar regimen efficacies under optimal conditions as well as higher treatment adherence, completion, and forgiveness of missed doses for the pan-TB regimen. The performance of the pan-TB regimen was robust to variation in any single resistance-related parameter, and to simultaneous variation in the prevalence of both R and B resistance (see supplementary figure 3), although higher prevalence of B resistance increased the sensitivity to other uncertain parameters including the differences in treatment efficacy between regimens and the probability of resistance acquisition (figure 3 panel b and supplementary figure 4). However, if resistance emerged in line with the pan-TB scenario, pan-TB was unlikely (16.0%) to remain superior to the standard of care (figure 3 panel b, prevalence of resistance taken from figure 2b after 10 cohorts of treatment in the pan-TB scenario), where again

relative estimates of durable cure were most important in determining the relative performance of the two scenarios.

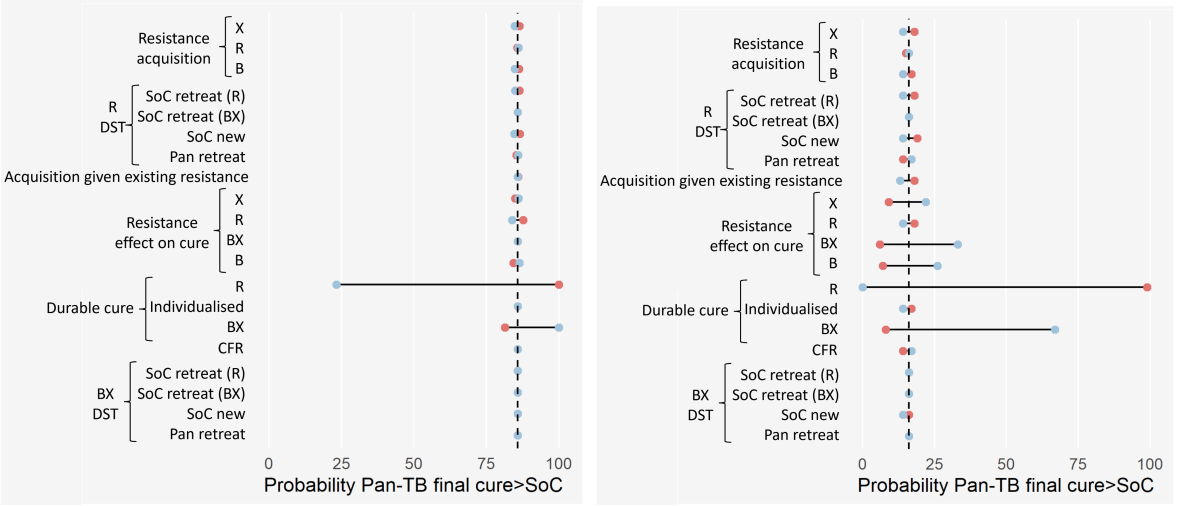

Figure 3: Univariate sensitivity analysis, sampling a parameter set and fixing each parameter in turn at the extremes of its 95% confidence interval, comparing likelihood that durable cure in the pan-TB scenario is greater than the standard of care scenario after one cohort of treatment at (a) current prevalence of resistance, and (b) higher prevalences of resistance among new TB patients, as might occur after widespread use of a pan-TB regimen (informed by the prevalences of resistance in figure 2b after 10 cohorts of treatment). Blue circles represent the parameter maximum, red circles the parameter minimum.

Pan-TB viability over time

Whereas Figure 3 showed the treatment outcomes of a single cohort with current or higher levels of initial drug resistance, Figure 4 shows how the effects of uncertain model parameters could compound over multiple generations of transmission and treatment in both the standard of care and pan-TB scenarios. As the resistance prevalence changes over time, due to use of different treatment options in each scenario, the probability that pan-TB outperforms the standard of care decreases (figure 4 panel a where the probability using mean parameter values is 38.3% compared to figure 3 panel a where the probability is 85.9%). When uncertainty is propagated through multiple TB patient cohorts, the relative effectiveness of the two regimen remains important, but resistance-related parameters are also important determinants of whether the pan-TB regimen continues to outperform the standard of care. For example, variation in either the risk of acquiring new resistance to B during BX treatment or the effects of that resistance on subsequent BX regimen efficacy could cause a >50% or 25% shift respectively in the probability that the pan-TB regimen remained superior to the standard of care after 10 generations. Varying these two parameters simultaneously (figure 4 panel b), it was apparent that continued use of the pan-TB scenario (i.e., of the pan-TB regimen without initial DST) would be likely to produce outcomes worse than the standard of care within fewer than 10 generations unless either acquisition of bedaquiline resistance was extremely rare or both parameters were near the optimistic end of their data-consistent value ranges. If the interaction of B and X is synergistic, i.e. if both B and novel drug X have a higher tendency to acquire resistance, which has a greater effect on cure, then the likelihood of one scenario consistently outperforming the other increases (see supplementary figure 5). Increasing the rate of acquisition of resistance to novel drugs beyond the range used here (see, for example, cite, cite, and the potential effect of

programmatic conditions cite) can quickly lead to the standard of care outperforming the pan-TB scenario (see supplementary figure 6).

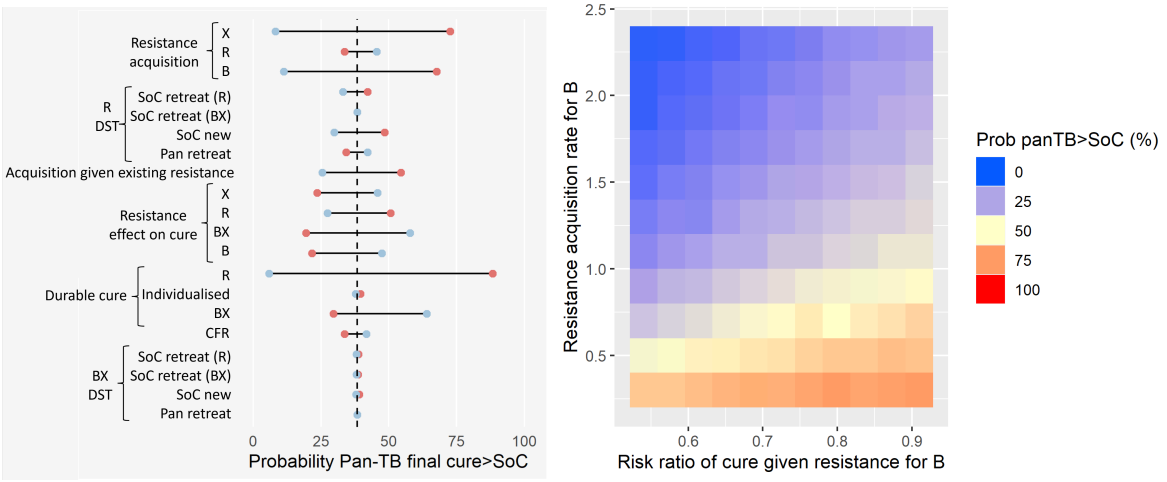

Figure 4: changing probability of pan-TB outperforming the standard of care as prevalence changes after 10 cohorts for each scenario, illustrating the effect of parameter values on durable cure in (a) a univariate sensitivity analysis, sampling a parameter set and fixing each parameter in turn at the extremes of its 95% confidence interval, where blue circles represent the parameter maximum and red circles the parameter minimum, and (b) a multivariate sensitivity analysis comparing resistance-related parameters, where red indicates when pan-TB TB performs better (greater than 50% probability of improved durable cure) and blue when SoC performs better.

Emergence of problematic resistance

Resistance both to R and to either B and/or X (termed "problematic" resistance in our model because it requires the use of less effective individualised regimens) emerges slowly for both scenarios. When using our mean model parameters, the prevalence of problematic resistance after 10 treatment cohorts reached 6.0% [2.3-9.8%] of all TB in the pan-TB scenario and 5.9% [2.9-9.0%] under the standard of care (figure 5 panel a). These trends in problematic resistance are largely unaffected by the availability of B/X DST for retreatment patients in the pan-TB scenario (see supplementary figure 7). Problematic resistance to both R and either B and/or X is higher in the pan-TB scenario than the standard of care when the acquisition rate of resistance to novel drugs is low while the effect of that resistance on cure is high (figure 5 panels b). This is a result of higher problematic resistance for the standard of care scenario when both the resistance acquisition rate and its effect on cure is high, while for the pan-TB scenario the effect on cure alone is more important in driving problematic resistance.

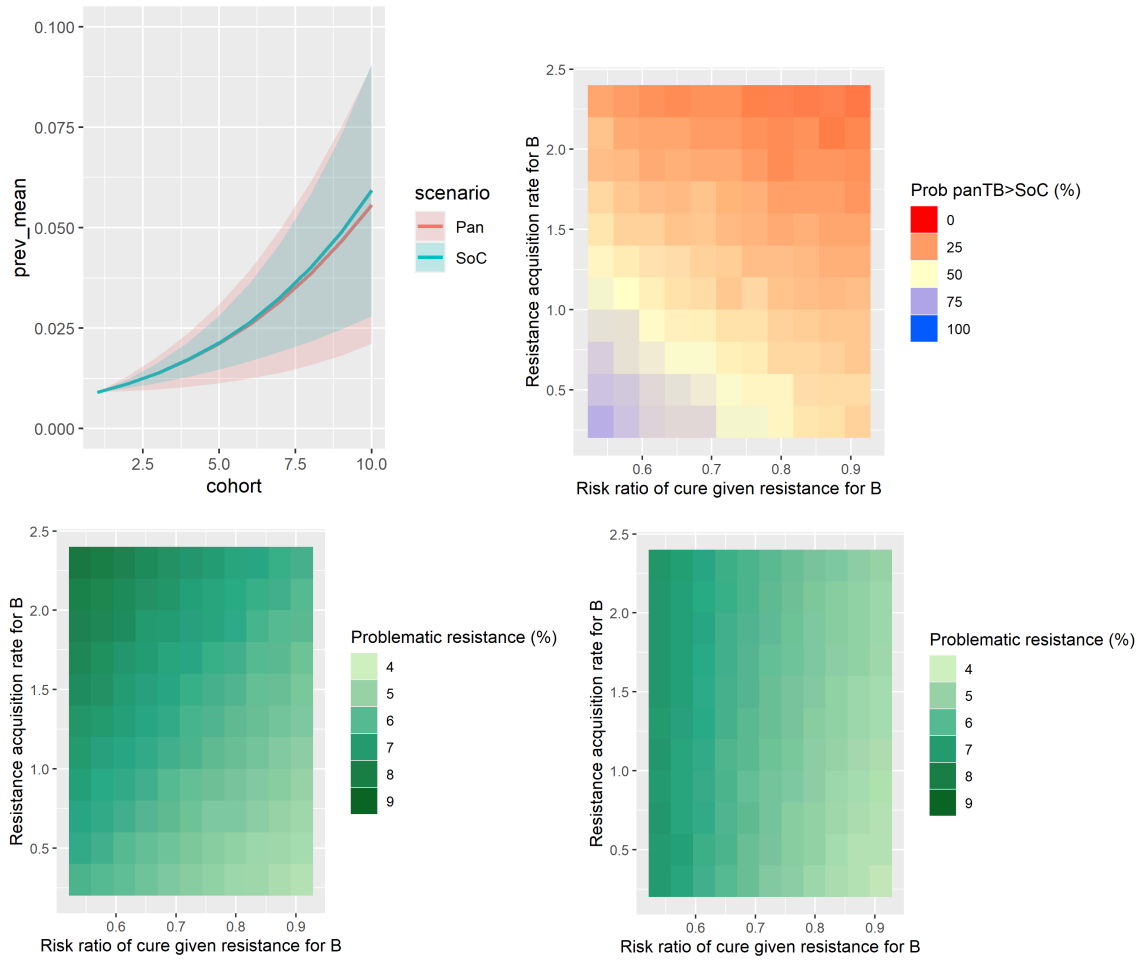

Figure 4: Prevalence of "problematic" resistance to both R and either B and/or X for the pan-TB compared to standard of care scenarios, showing (a) prevalence over time, (b) probability that the pan-TB scenario leads to higher prevalence of problematic resistance as a proportion of all TB after 10 cohorts, compared to the standard of care, and mean prevalence of problematic resistance after 10 cohorts for (c) standard of care and (d) pan-TB.

Discussion

In our model, the pan-TB scenario led to improved treatment outcomes over the standard of care and a similar proportion of "problematic" resistance, primarily as a result of improved treatment outcomes for those with drug-susceptible TB. However, in the longer term while problematic resistance remained similar, the probability of pan-TB outperforming the standard of care declined due to emerging resistance. In our model, RR-TB is treated similarly in both scenarios (with some dependence on DST coverage), with high enough rates of durable cure to cause preexisting RR-TB to decrease over time. In contrast, rifamycin-susceptible TB is not treated with a rifamycin-based regimen in the pan-TB scenario, so there is very little new emergence of RR-TB over time but a large potential to generate resistance to B and/or X. This suggests that the use of pan-TB regimens adhering to the proposed target regimen profiles would not necessarily lead to the emergence of TB with fewer and less effective treatment options (i.e. requiring individualised treatment), due to the presence of existing rifamycin-based regimens as back-ups. This similarity in outcome reflects where this resistance arises; in both scenarios primarily through the use of BX for treatment of RR-TB. Any differences reflect the second-order effects of higher selection for RR-TB in the standard of care,

counterbalanced by reduced use of BX, as well as a more effective reduction of DS-TB in the pan-TB scenario (which may result in drug resistant TB increasing as a proportion of all TB). However, use of pan-TB regimens does lead to the generation of widespread resistance to BX regimen components (particularly given current high rates of resistance acquisition for existing novel drugs). Hence, a projected gradual increase in resistance to rifamycins as a proportion of all TB in the standard of care scenario is replaced by a similar increasing trend in prevalence of resistance to diarylquinolines and other novel components in the pan-TB scenario.

In reality, many of the parameter values for future pan-TB regimens are unknown. Although the pan-TB target regimen profile seeks to improve on current outcomes for rifamycin-based regimens through shorter duration and improved tolerability and forgiveness, the effects of these improvements on adherence and ultimately effectiveness may be unpredictable and setting-dependent. Our model suggests that if the difference in effectiveness is small between a pan-TB regimen and the rifamycin-based alternative for treating RS-TB, the more limited health advantages of the pan-TB will be contingent on a low prevalence of pan-TB drug resistance. Moreover, even for pan-TB regimens that achieve the large sought-after improvements in effectiveness over standard-of-care regimens, unfavourable resistance-related regimen characteristics could eventually threaten that effectiveness. For a pan-TB regimen to continue to achieve high rates of cure in the long term, it needs to be constructed to guard against acquisition of resistance to all of its components or to ensure that regimen efficacy remains high in the presence of any forms of resistance that are likely to emerge. However, in contrast to this emergence and amplification of pan-TB drug resistance that we identified as a key threat, we projected that even when resistance-related characteristics are unfavourable, there is a low likelihood that the pan-TB approach will drive emergence of problematic concurrent resistance to both rifampicin and novel drugs.

Our results are limited by a lack of data on elements of the pan-TB regimen, in particular around the acquisition and impact of resistance. These are limited at best for current novel drugs, and based entirely on assumptions about potential new drugs and regimens. Further, our approach to model temporal trends could be improved by the use of a transmission model; higher cure rates in our model do not lead to a reduction in transmission and incidence, negating some of the benefits of improved regimens and indeed overemphasising the role of existing resistance in the population. Hence, it is possible that an increase in prevalence of resistance in our model is a result of the removal of drug-susceptible TB, and therefore an increase in resistance as a proportion of all disease, rather than the creation of additional resistance. Although our results can be loosely translated into calendar time (assuming, for example, that one cohort generation of transmission corresponds to a serial interval of between 1 and 2 years on average[cite], with some delay to diagnosis) this does not take into account either the distribution of secondary cases over time or time to diagnosis, both of which can be highly varied and setting-dependent for TB[cite,cite,cite], so overinterpretation of the generation time is inadvisable. Lastly, our results are based on target regimen profiles, which assume that pan-TB regimens will be more efficacious than existing drug-susceptible TB regimens. We assume that if these regimens were available they would be used at a minimum for patients with RR-TB, which given a lack of any resistance to regimen components for these individuals leads to the counter-intuitive scenario where treatment outcomes for those with RR-TB are better than for those with drug-susceptible TB.

Overall, we found that a pan-TB regimen adhering to the current target regimen profile was unlikely to drive an increase in problematic resistance to both novel and older TB drugs. However, high rates of acquisition of resistance combined with a large impact of that resistance on durable cure, or a low relative rate of durable cure more generally, could represent problematic scenarios, and over time, either pan-TB regimen will be need to be updated or DST will need to be re-introduced to maintain the improved health outcomes that a pan-TB regimen would initially offer.

References

Supplementary material

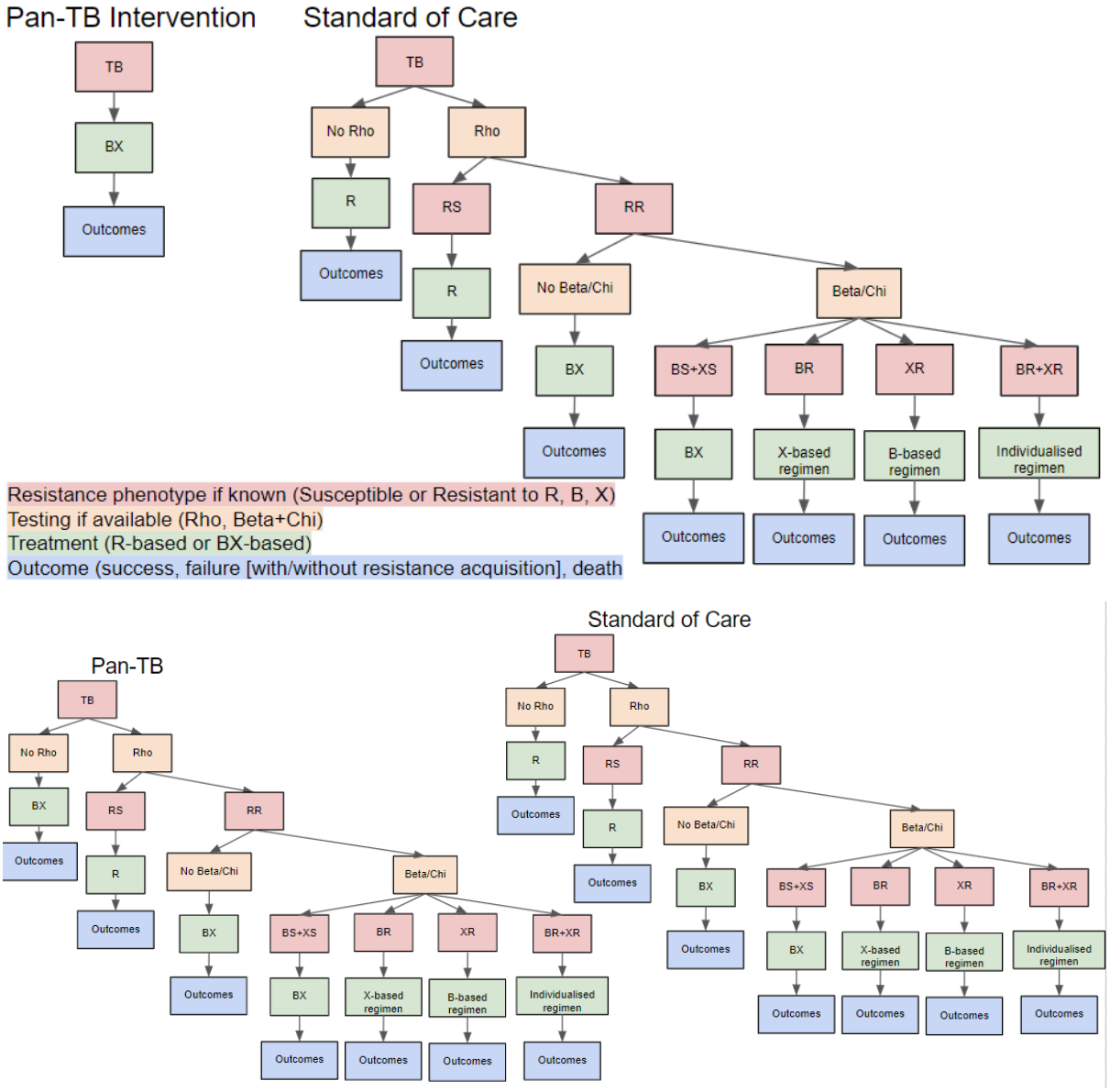

Figure S1: treatment pathways for (a) new and (b) previously treated patients, comparing the Pan-TB scenario (left) with standard of care (right). TB=tuberculosis, RS-TB=rifampicin-susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis,

XR-TB=tuberculosis resistant to additional novel drug X, Rho=rifampicin drug susceptibility testing, Beta/Chi= diarylquinoline and other novel drug(s) susceptibility testing.

Table S1: treatment success and acquisition of resistance for different resistance phenotypes given different regimens (assuming mean parameter values from table 1). TB=tuberculosis, DS-TB=drug-susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to additional novel drug X, E_R=proportion of DS-TB durably cured by rifamycin-based regimen, E_{BX}=proportion of DS-TB durably cured by pan-TB regimen, E_{ind}=proportion of TB durably cured by individualised regimen, P_R=Risk ratio of cure for rifamycin-based regimen given initial RR-TB, P_B=Risk ratio of cure for pan-TB regimen given initial BR-TB, P_X=Risk ratio of cure for pan-TB regimen given initial XR-TB, P_{BX}=Risk ratio of cure for pan-TB regimen given BR- and XR-TB, S_R=Probability of acquired RR-TB after rifamycin-based treatment (if initially RS-TB), S_B=Probability of acquired BR-TB after pan-TB treatment (if initially BS, XS), S_X=Probability of acquired XR-TB after pan-TB treatment (if initially BS, XS), Q=Risk ratio for B or X resistance acquisition given pre-existing X or B resistance, respectively.

Outcome	Regimen	Resistance type							
		DS-TB	RR-TB	BR-TB	XR-TB	RR+ BR-TB	RR+ XR-TB	BR+ XR-TB	RR+BR + XR-TB
Durable cure	R	E_R= 70.9%	$E_R \cdot P_R$ = 24.8%	E_R= 70.9%	E_R= 70.9%	$E_R \cdot P_R$ = 24.8%	$E_R \cdot P_R$ = 24.8%	E_R= 70.9%	$E_R \cdot P_R$ = 24.8%
	BX	E_{BX}= 79.7%	E_{BX}= 79.7%	$E_{BX} \cdot P_B$= 59.8%	$E_{BX} \cdot P_X$= 59.8%	$E_{BX} \cdot P_B$= 59.8%	$E_{BX} \cdot P_X$= 59.8%	$E_{BX} \cdot P_{BX}$ = 27.9%	$E_{BX} \cdot P_{BX}$ = 27.9%
	B-based	-	-	-	-	-	69.7%	-	-
	X-based	-	-	-	-	69.7%	-	-	-
	conv 2nd-line	-	-	-	-	-	-	-	E_{ind}= 43.9%
RR Acquisition	R	S_R = 0.6%	-	S_R= 0.6%	S_R= 0.6%	-	-	S_R= 0.6%	-
BR Acquisition	BX	S_B= 1.0%	S_B= 1.0%	-	$S_B \cdot Q$= 7.5%	-	$S_B \cdot Q$= 7.5%	-	-
	B-based	-	-	-	-	-	4.3%	-	-
XR Acquisition	BX	S_X= 1.0%	S_X= 1.0%	$S_X \cdot Q$= 7.5%	-	$S_X \cdot Q$= 7.5%	-	-	-
	X-	-	-	-	-	4.3%	-	-	-

	based								

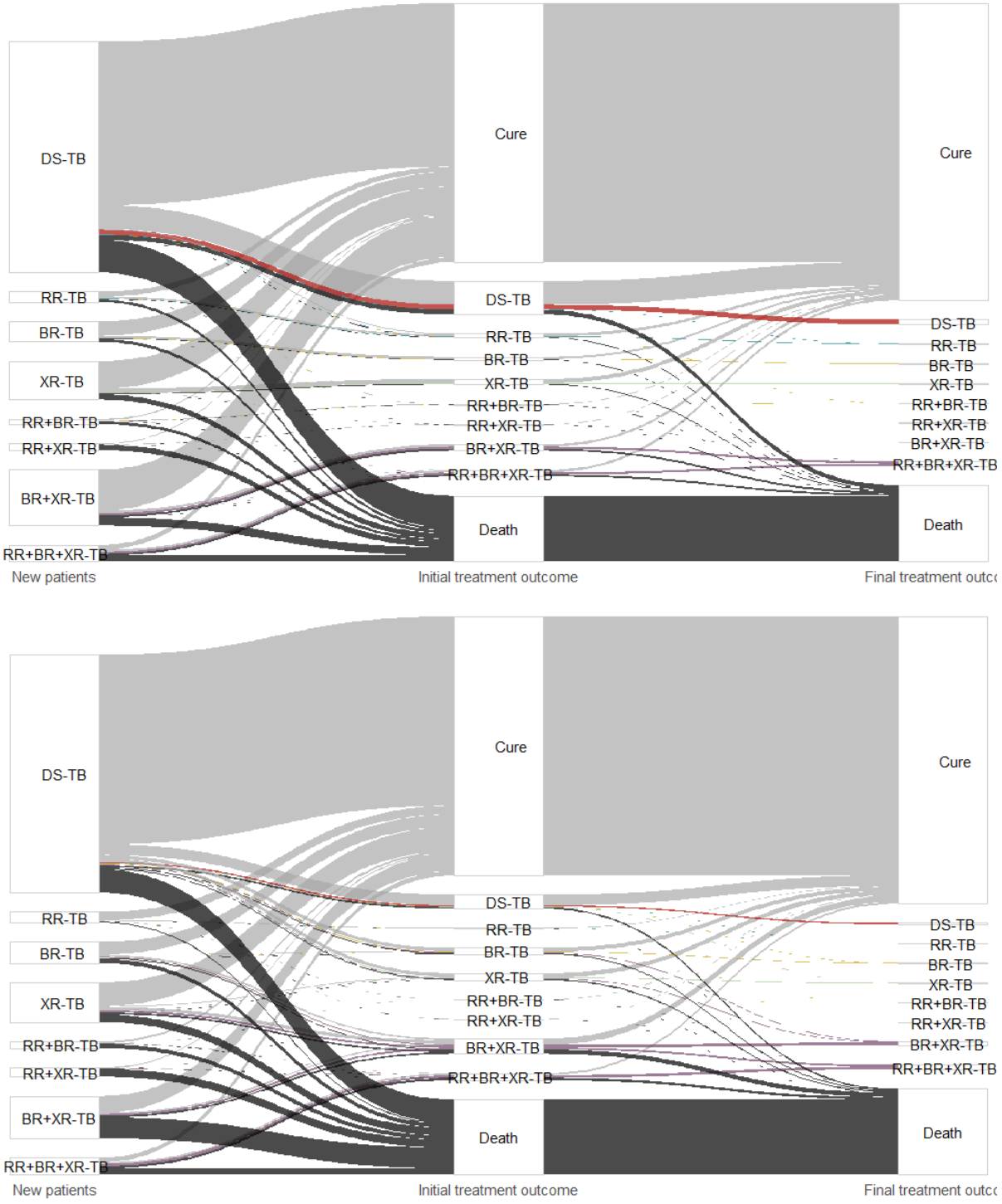

Figure S2: sankey diagram for the (a) standard of care and (b) pan-TB scenario, demonstrating the treatment outcome pathway after an initial round of treatment and the final outcome after retreatment for those whose treatment initially fails, using mean parameter values and higher initial prevalence of resistance X. Colours indicate the final treatment outcome. DS-TB=drug susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to novel drug X.

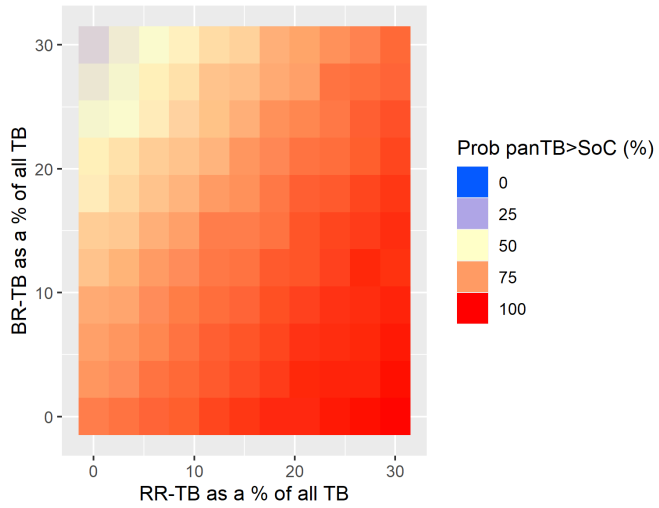

Figure S3: Probability that pan-TB leads to a higher durable cure rate than the standard of care after 1 cohort of patients for varying initial prevalence of resistance. Red indicates where pan-TB TB performs better, blue where SoC performs better. Both RR-TB and BR-TB are varied as a proportion of all TB, where RR+BR-TB is the product of both. No other forms of resistance are initially present.

The likelihood of durable cure is higher under the pan-TB scenario irrespective of underlying prevalence of resistance in the population. This is a result of assumptions about the high rate of durable cure for the BX regimen, and the relatively minimal effect of existing resistance to regimen components on this. The likelihood of both increases as the prevalence of RR-TB increases (when RR-TB is likely to be undertreated in the standard of care scenario) and decreases as the prevalence of B resistance increases (when BR-TB is likely to be undertreated in the Pan-TB scenario).

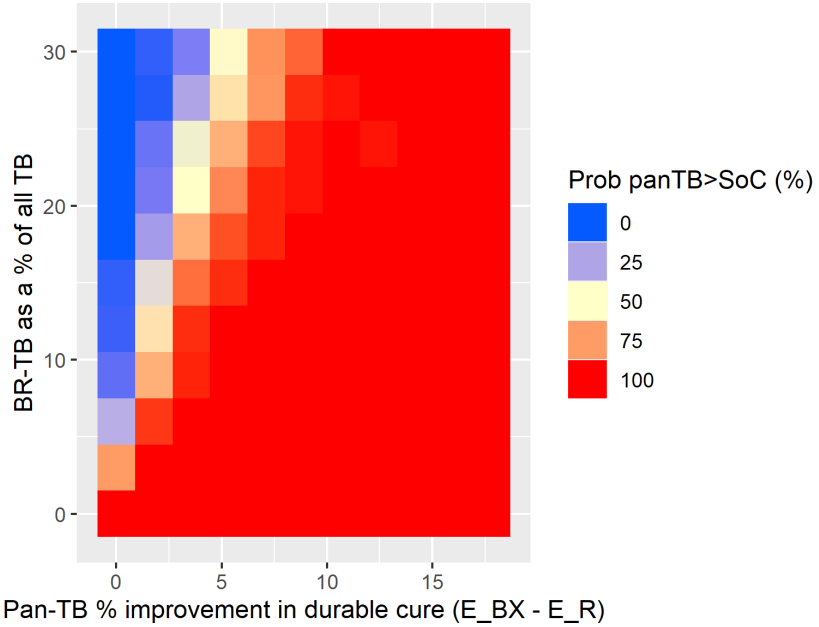

Figure S4: Effect of difference in cure rates on relative performance of regimens for varying prevalence of B resistance.

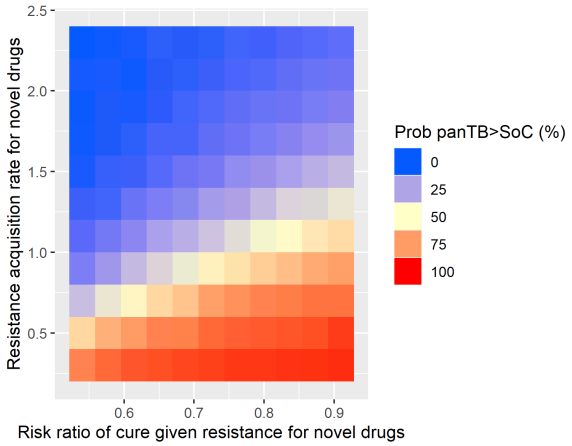

Figure S5: Probability that the pan-TB scenario leads to higher durable cure compared to the standard of care after 10 cohorts. Red indicates where pan-TB TB performs better, blue where SoC performs better. Note parameters values (resistance acquisition rate and risk ratio of cure) are varied for both novel drug types simultaneously.

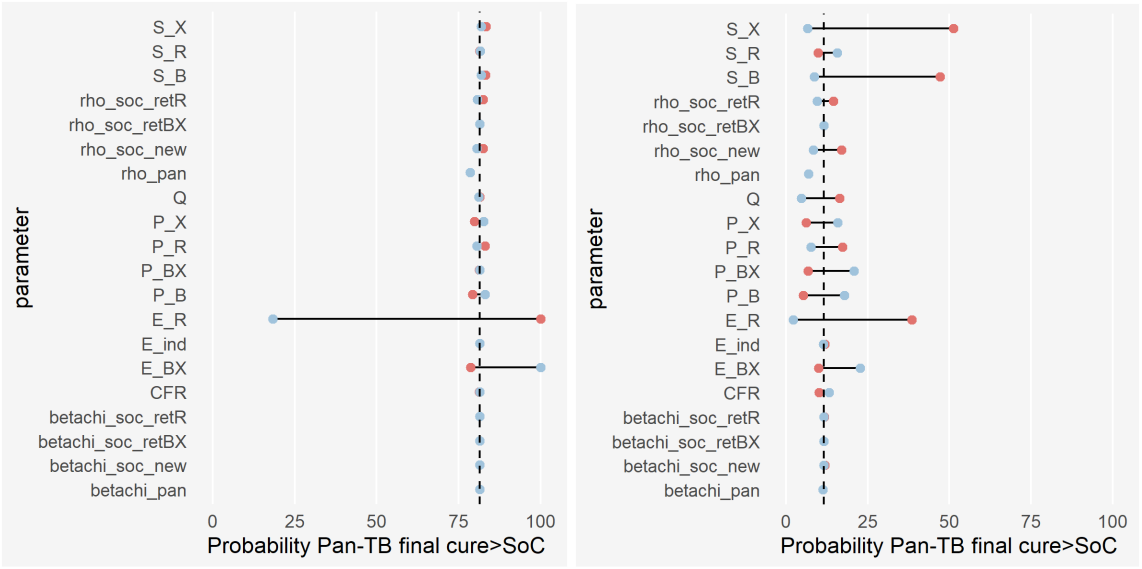

Figure S6: Univariate sensitivity analysis, sampling a parameter set and fixing each parameter in turn at the extremes of its 95% confidence interval, where the confidence interval for acquisition of resistance to novel drugs has been extended. We based this on high rates of resistance acquisition seen under programmatic conditions (e.g. in centres that were not green-light approved [cite]), such that S_B = 2.3% [0.3-8%], S_X = 1% [0.3-8%]. Comparing likelihood over that durable cure in the pan-TB scenario is greater than the standard of care scenario after (a) one cohort of treatment (b) ten cohorts. Blue circles represent the parameter maximum, red circles the parameter minimum.

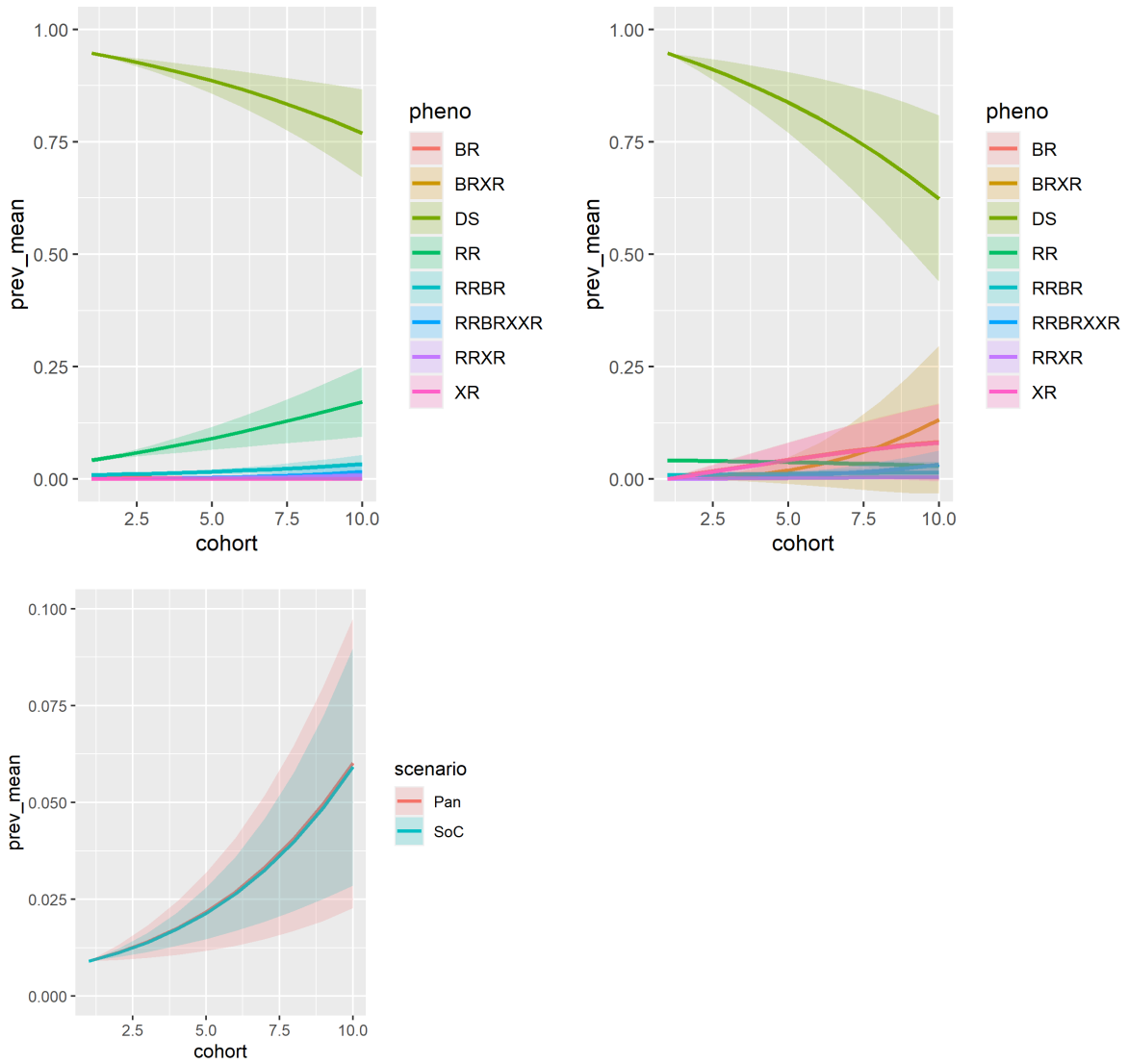

Figure S7: Prevalence of resistance phenotypes over multiple cohorts where B/X DST availability for retreatment patients with known RR-TB is the same as the current standard of care for new patients, for (a) standard of care and (b) pan-TB scenarios, and for (c) "problematic" resistance to both R and either B and/or X. Shaded areas indicate 95% uncertainty intervals. DS-TB=drug susceptible tuberculosis, RR-TB=rifampicin-resistant tuberculosis, BR-TB=diarylquinoline resistant tuberculosis, XR-TB=tuberculosis resistant to novel drug X.