Using molecular testing and whole-genome sequencing for tuberculosis diagnosis in a low-burden setting: a cost-effectiveness analysis using transmission-dynamic modelling

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ABSTRACT

Background

Despite progress in tuberculosis (TB) control in low-burden countries like England and Wales, there are still diagnostic delays. Molecular testing and/or whole-genome sequencing (WGS) provide more rapid diagnosis but their cost-effectiveness is relatively unexplored in low-burden settings.

Methods

An integrated transmission-dynamic health-economic model is used to assess the cost-effectiveness of using WGS to replace culture-based drug-sensitivity testing, vs using molecular testing vs combined use of WGS and molecular testing, for routine TB diagnosis. The model accounts for the effects of faster appropriate treatment in reducing transmission, benefiting health and reducing future treatment costs. Cost-effectiveness is assessed using Incremental Net benefit (INB) over a 10-year horizon with a Quality-Adjusted Life-Year valued at £20,000, and discounting at 3.5%p.a.

Results

WGS shortens the time to drug-sensitivity testing, and treatment modification where necessary, reducing treatment and hospitalization costs, with an INB of £7.1M. Molecular testing shortens the time to TB diagnosis and treatment. Initially this causes an increase in annual costs of treatment, but averting transmissions and future active-TB disease subsequently resulting in cost savings and health benefits to achieve an INB of £8.6M (GeneXpert MTB/RIF) or £11.1M (Xpert-Ultra) respectively. Combined use of Xpert-Ultra and WGS is the optimal strategy we consider, with an INB of £16.5M.

Conclusions

Routine use of WGS or molecular testing is cost-effective in a low-burden setting, and combined use is the most cost-effective option. Adoption of these technologies can help low-burden countries meet the WHO End TB Strategy milestones, particularly the UK, which still has relatively high TB rates.

KEY MESSAGES

What is the key question?

Can the universal use of molecular testing and/or whole-genome sequencing (WGS) from culture cost-effectively improve TB diagnosis and drug sensitivity testing in a low-incidence setting?

What is the bottom line?

Molecular testing shortens the time to initial TB diagnosis and treatment, while WGS is cheaper than culture-based DST and shortens the time of drug sensitivity testing, resulting in cost savings from reduced transmission, avoided or shorter morbidity and avoided unnecessary treatment and hospitalizations making the strategies individually and combined cost-effective.

Why read on?

This study highlights the potential strengths of the universal combined use of molecular testing and WGS in a low-incidence setting.

INTRODUCTION

The number of diagnosed tuberculosis (TB) cases in the United Kingdom (UK) remains high compared to similar European countries[1]. A total of 5,758 TB cases (3,065 pulmonary) were notified in England and Wales in 2015, of which 73% were in foreign-born individuals[2]. In 2015, England launched its strategy to meet the World Health Organisation (WHO) End TB Strategy milestone of reducing TB incidence by 50% by 2025 and eventually eliminate TB as a public health problem[3]. The strategy highlighted the importance of early detection and treatment of TB.

Current UK guidelines for pulmonary TB diagnosis involve chest X-ray, sputum-smear microscopy, culture, and culture-based drug sensitivity testing (DST)[4]. It can take up to 42 days from initiation of TB investigation to starting appropriate treatment[5], with identification of TB by culture taking 8-17 days[6], with a further delay of 20-33 days[7] for DST results obtained by further culture. Faster and accurate diagnostics and drug-resistance detection techniques have the potential to reduce this delay, reducing the duration of illness, risk of onward transmission, and loss-to-follow-up prior to treatment.

In 2017, Public Health England announced that whole-genome sequencing (WGS) from culture would for the first time used for TB diagnosis, drug-resistance detection and strain identification. WGS is faster than culture-based DST because the phenotypic drug susceptibility testing step is omitted: the time from start of sequencing to obtaining a drug resistance report is around 8 days[7], and identifies all known resistance mutations, so it can reduce the time to appropriate treatment. However, current WGS requires an initial culture step, taking around 13 days[6].

Molecular testing can reduce time to TB diagnosis from 13 days to the same day where available locally (and 1-3 days[8] in most cases). There is a particular benefit for smear-negative cases, which are detected culture in the standard diagnostic pathway but most of which are detected by GeneXpert MTB/RIF (Xpert)[9]. Additionally, it simultaneously identifies rifampicin (Rif) resistance, which is an indicator of multidrug-resistant (MDR)-TB but does not inform on the full resistance profile. A recent study showed greater sensitivity of a next-generation molecular test, Xpert-Ultra[9]. Despite Xpert's potential to provide rapid TB diagnosis, its cost has resulted in its being only recommended for patients with certain risk factors such as human immunodeficiency virus (HIV) infection[4].

As neither WGS from culture nor molecular testing is ideal for rapid diagnosis of TB with a full drug-resistance profile, but each has strengths that are potentially complementary, we examine the impact on transmission and the cost-effectiveness of using WGS and/or molecular testing in a low-incidence setting (England and Wales)[2]. We consider the universal use of the following options: (i)

replacing culture-based DST with WGS; or performing for initial TB diagnosis and Rifampicin (Rif) resistance identification with (ii) Xpert or (iii) Xpert-Ultra; or (iv) simultaneously doing (i) and (ii); or (v) simultaneously doing (i) and (iii). We use an integrated transmission-dynamic health-economic model to capture the important benefit of averting infections, which increases health and reduces future costs to the health service[10-14]. The model includes contact tracing and treatment of contacts, which is a key element of the strategy[3].

METHODS

We develop an integrated transmission-dynamic health-economic model (Figure 1) that describes the natural history of TB infection, patterns of transmission, and clinical pathways in England and Wales, based on guidelines from the National Institute for Health and Care Excellence (NICE)[4].

Model structure

We consider a population in England and Wales of people in South-Asian (SA) and Black-African (BA) ethnic/social groups, which represent the majority of the TB cases in England and Wales[2]. In the model, within each ethnic/social group there are UK-born and foreign-born individuals who mix homogeneously; there is negligible mixing relevant to TB transmission between groups, reflecting patterns of cohabitation and socialisation. The model structure representing pulmonary TB infection and transmission (Figure 1) is based on established models[10 15-17]. Interaction between uninfected individuals and those with active TB can result in TB transmission. Newly-infected individuals have latent TB infection (LTBI) which is asymptomatic and non-infectious. LTBI can progress to active TB which is symptomatic and infectious, and causes an increased mortality rate. We capture the heterogeneity in progression rates by dividing individuals with LTBI into fast- and slow-progressors. There is further heterogeneity among those with active TB, with some being sputum smear-positive TB and others smear-negative; the latter are less infectious.

The baseline clinical pathway (Figure 2a) for active-TB diagnosis uses chest X-ray as an initial rule-out test for pulmonary TB[4]. An abnormal chest X-ray prompts collection of sputum samples for smear microscopy and culture, with positive cultures followed by culture-based DST. Close contacts of people with pulmonary TB are investigated for infection using interferon-gamma release assay (IGRA); those testing positive are investigated for active TB. Prophylactic treatment is offered to LTBI cases. Active-TB cases are initially treated for either drug sensitive (DS) TB or MDR TB, depending on their risk factors. The treatment regimen can be modified when DST results become available. Patients successfully completing treatment recover (and are susceptible to new infection) while

those that are unsuccessfully-treated remain infected, and infectious if they have active TB. We assume that active-TB patients do not transmit infection if they are in isolation or adherent on appropriate treatment. Additional details of the identification and treatment of TB is given in the supplementary appendix.

Modified clinical pathway

In this study we investigate the impact of modifying the clinical pathway in England and Wales by (i) replacing the culture-based DST with WGS; or performing for initial TB diagnosis and Rif resistance identification with (ii) Xpert or (iii) Xpert-Ultra; or (iv) simultaneously doing (i) and (ii); or (v) simultaneously doing (i) and (iii). The modifications to clinical pathways and their impact on time to diagnosis, time to treatment initiation and duration of isolation are summarised in Figure 2.

Model parameter selection and model calibration

We obtain the baseline TB incidence and proportion of MDR TB cases in England and Wales from Enhanced TB Surveillance (ETS) data and population demographic data for England and Wales from the Office for National Statistics (ONS) (Supplementary Table 1). The prevalence of LTBI in migrants was estimated by Pareek et al.[18]. TB natural history parameters and data sources are summarised in Table 3; where specific data for England and Wales are not available, parameter estimates from the literature are used with sources selected for their relevance to our setting. For ethical reasons there are limited sources of data on mortality of untreated TB and therefore we have used the same source[19] as in our previous work[5 15 20].

We the fit the model to numbers of annual TB diagnoses in England and Wales by varying the ratio of slow- to fast-progressors in new arrivals, the proportion of MDR TB among new arrivals, the TB transmission parameters, and the relative transmissibility of MDR TB compared to DS TB. Additional details of the fitting methods and results is given in the supplementary appendix).

Health impact and costs

The analysis follows the NICE public health reference case, including the adoption of a public sector perspective and the use of a 3.5% annual discount rate for both costs and quality-adjusted life-years (QALYs)[21]. To compare strategies, we calculate the incremental net cost and QALYs i.e. the difference between the sum of all costs and all QALYs associated with the baseline clinical pathway vs the alternative strategy. The incremental net benefit (INB) of introducing molecular testing and/or WGS into the current pathway is calculated by determining the monetary value of the incremental QALY gains, with a QALY valued at £20,000 or £30,000 (as is standard in the UK we use both values and

compare results) and subtracting the incremental costs[21]. We consider a 10-year horizon beginning in 2016. A positive INB indicates that a strategy is cost-effective relative to the comparator.

Cost parameters are summarised in Table 4. We consider running costs for established laboratories; testing costs per sample include staff costs as well as consumables. Hospital costs are split into inpatient and outpatient costs and included the cost of staff time. Depending on an inpatient's MDR-TB risk, their sputum-smear status and their drug sensitivity (presumed or confirmed, as applicable), they can be admitted to non-isolation room, standard isolation room or negative-pressure isolation room. Additional costs included diagnostics, drug sensitivity testing, treatment drugs and adverse effects related costs. For treatment costs we used the cost of a standard 6-month regimen for drug-sensitive TB[4] and a 20-month regimen for MDR TB[5]. We assume that MDR-TB treatment is effective for DS infection (some patients with DS TB are presumptively prescribing MDR-TB treatment initially). Patients who do not complete treatment are lost to follow-up after 2 months on average[15]. They cycle back into their pre-treatment state. All prices are adjusted to 2014-15 values using the Hospital & Community Health Services (HCHS) index[22].

Health utility losses occur due to mortality and morbidity caused by active-TB disease. Additional losses are incurred from adverse effects of TB drug treatment and hospitalisation. Utility values are obtained from literature [5 23] and summarized in Table 5.

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses are conducted. In the former, parameters are individually varied across their plausible ranges (Supplementary Table 2) with the other parameters fixed at their baseline values. In the probabilistic sensitivity analysis (PSA), 1,000 parameter combinations are drawn using Latin Hypercube Sampling, using gamma distributions for costs and beta distributions for all other parameters. For each of the 1,000 model simulations we calculate the incremental costs and incremental QALYs and report the mean and 95% range.

RESULTS

Figure 3 shows changes in TB notifications (DS and MDR), discounted costs, and discounted QALYs in England and Wales associated with (i) replacing culture-based DST with WGS, (ii) & (iii) using molecular testing, or (iv) & (v) using molecular testing and WGS, compared to the baseline clinical pathway. (Supplementary Figure 3 shows incremental changes in annual transmission events, and annual undiscounted QALYs and costs.) Replacing culture-based DST with WGS has little impact on

the annual numbers of TB cases (DS and MDR) diagnosed or non-TB cases entering the treatment pathway (Figure 3a, Supplementary Figure 1: red bars). However, WGS shortens the time required for drug sensitivity testing, allowing for earlier treatment modification where necessary. This shortens slightly the overall average duration of treatment and reducing slightly the average number of patients on treatment (Supplementary Figure 1a: red bars). Importantly, WGS therefore reduces the average costs of treatment (costs of drugs, isolation, and adverse events) (Figure 3c, Supplementary Figure 2, Supplementary Table 3: red bars). WGS is also cheaper to perform than culture-based DST, reducing diagnostic costs. Overall, there is a net annual cost saving from using WGS of £780,089 (95% range: £456,600–£1,087,400) in year 1 and £602,092 (£350,475–£833,625) in year 10 (Figure 3c: red bars). With patients spending on average less time on inappropriate treatment, WGS leads to QALY gains of 0.06 (0.02–0.09) in year 1, increasing to 0.27 (0.19–0.35) in year 10 (Figure 3b: red bars). Overall, over a 10-year horizon WGS has an incremental net benefit of £7.2M (£3.3M–£11.1M) with a QALY valued at £20,000 (Table 6). The INB of WGS is mostly due to cost savings, with a small QALY gain.

Molecular testing speeds-up initial diagnosis, resulting in the mean number of patients on treatment for active TB (DS and MDR) increasing by 17 (11–22) or 22 (15–29) with Xpert or Xpert-Ultra respectively in year 1 (Supplementary Figure 1a: blue and green bars, respectively). In the long term, due to earlier initiation of appropriate treatment and consequently-reduced transmission (Supplementary Figure 3a: blue and green bars), there is a gradual decrease in the number new infections, fewer individuals on LTBI treatment, and fewer active TB cases, both treated and untreated (DS and MDR) (Figure 3a, Supplementary Figure 1: blue and green bars). Diagnostic costs are increased (despite the reduction in diagnoses in most years due to averted transmission), but this is exceeded by reduced treatment costs, resulting in a net annual cost saving in year 10 of £47,397 (but with the 95% uncertainty range spanning from a saving of £335,175 to an additional cost of £419,975) for Xpert and £48,209 (95% range: saving of £452,650 to additional cost of £370,350) for Xpert-Ultra with culture-based DST (Figure 3c, Supplementary Figure 2: blue and green bars). Note that molecular testing slightly increases the costs of MDR TB treatment, due to false-positive MDR results leading to incorrect treatment of DS TB as MDR TB until this is corrected by the DST report.

Earlier treatment brings forwards health benefits for active-TB disease cases, resulting in an increase in QALYs in year 1 of 9 (6–11) for Xpert and 12 (9–15) for Xpert-Ultra with culture-based DST (Figure 3b: blue and green bars). In subsequent years a sustained reduction in LTBI and active-TB disease

translates into further health gains from averted active-TB disease, gradually increasing annual QALY gains, reaching 62 (44–80) for Xpert and 81 (59–103) for Xpert-Ultra with culture-based DST in year 10 (Figure 3b: blue and green bars). Over a 10-year horizon, molecular testing with culture-based DST have an incremental net benefit of £8.7M (£1.8M–£15.6M) or £11.2M (£3.4M–£19M) using Xpert or Xpert-Ultra respectively, with a QALY valued at £20,000 (Table 6). The INB of molecular testing is mostly due to QALY gains, although there are also cost savings.

Introducing a combination of WGS and molecular testing into the clinical pathway combines the benefits of the individual strategies. The first year has a net cost saving of £356,128 (95% range: saving of £865,600 to additional cost of £182,000) or £251,780 (95% range: saving of £785,550 to additional cost of £301,350), mostly due to reductions in inappropriate treatment (Figure 3c: purple and orange bars). Subsequent additional savings from active-TB disease averted and shorter inappropriate treatment duration increase cost savings to £527,882 (95% range: saving of £119,475 to additional costs of £909,625) or £507,507 (95% range: saving of £82,275 to additional cost of £903,625) in year 10 respectively (Figure 3c, Supplementary Figure 1: purple and orange bars). Fewer TB disease cases, inappropriately-treated TB cases, and unnecessarily-treated non-TB cases, result in a gradual increase in QALYs throughout the 10-year period with an annual incremental QALY gain of 9 (7–11) or 12 (9–15) in year 1 increasing to 62 (44–80) or 81 (59–103) by year 10 for Xpert with WGS or Xpert-Ultra with WGS respectively (Figure 3b: purple and orange bars). Overall the combined strategy results in an incremental net benefit of £14.4M (£7.2M–£21.5M) for Xpert with WGS or £16.6M (£8.9M–£24.3M) for Xpert-Ultra with WGS over a 10-year horizon with a QALY valued at £20,000 (Table 6).

Results of the sensitivity analyses are presented in Figures 4 and 5. The probabilistic sensitivity analysis (Figure 4) shows that all strategies remain cost-effective when uncertainty in parameter values is taken into account (probability of INB>0 is 100%). The rank-order of cost-effectiveness of the strategies is robust to parameter uncertainty: combined use of Xpert-Ultra and WGS has the highest INB, and combined use of Xpert and WGS the second-highest, in 100% of samples; Xpert-Ultra alone ranks third in 91.7% of samples; Xpert alone ranks fourth in 71.6% of samples; and WGS alone ranks fifth in 71.6% of samples (Supplementary Table 4). The deterministic sensitivity analysis (Figure 5) shows that the time to culture-positivity and time to molecular test report have the largest impact on the INB of most strategies, with the proportion of TB patients assessed as being at risk of MDR TB, duration of standard isolation for DS TB, relative infectivity of smear negatives compared to smear positives, and time from culture-positivity to DST report, also having some influence. Large hypothetical changes in the proportion of TB infection in migrants that is MDR (0.35%-2%) and in the

immigration rate (halving and doubling) do not change our conclusions (Supplementary Figure 4). In summary, there is uncertainty in the magnitude of the impact of each strategy on the incremental QALYs gained (Figure 3b), and the incremental costs (Figure 3c); however, there is no uncertainty that all strategies are more cost-effective than the conventional pathway (Figure 4), or that U+WGS is the most cost-effective of the strategies considered (Supplementary Table 4) or that X+WGS is the second-most cost-effective strategy (Supplementary Table 4).

DISCUSSION

In this study we evaluated the costs and health benefits of introducing new diagnostic technologies into the TB clinical pathway in England and Wales. Our analysis finds that individually the universal use of molecular testing and/or WGS in the TB diagnostic and care pathway is cost-effective, and that combined use of molecular testing and WGS is even more cost-effective, with the most cost-effective option that we consider being Xpert-Ultra and WGS.

A strength of this economic evaluation is the incorporation of transmission-dynamic effects into the analysis, which allows us to account for population-level effects, in terms of infections averted, as well as an individual-level effects. This allows us to identify and quantify key benefits of the alternative diagnostic pathways. The molecular tests provide rapid and highly sensitive and specific detection of active TB, leading to cost savings and health gains by: (a) reducing unnecessary treatment (and associated side-effects) and hospitalization or isolation of non-TB cases; (b) reducing time to TB diagnosis and the initiation of drug treatment; (c) allowing for earlier drug sensitivity reporting allowing for earlier correction of inappropriate treatment; and (d) averting transmission which in turn reduces TB incidence and subsequently future TB disease. These improvements to the diagnostic pathway, translate into several individual-level benefits. Firstly, early diagnosis reduces time to treatment initiation by 13 days for smear-negative DS-TB cases and 27 days for MDR-TB cases. This shortens the duration of poor health associated with active TB for patients. Secondly, for LTBI patients who get treatment as a consequence of contact tracing, active TB is averted. Thirdly, the rapid detection or exclusion of RIF resistance (MDR TB) reduces initial misdiagnosis compared to the current clinical pathway which relies on risk assessment prior to having results from a slow culture-based DST. Unnecessary isolation in negative-pressure rooms and treatment with MDR-TB drugs is not only costly but can also have negative health consequences on patients, with the former being socially isolating and the latter often causing side effects[24]. (However, introduction of molecular testing alone into the diagnostic pathway increases MDR treatment costs, due to some false-positive MDR results, which are subsequently corrected by the DST report.) Lastly, due to the

high specificity of the molecular tests, individuals whose symptoms are not due to TB benefit from earlier exclusion of TB avoiding unnecessary isolation and TB treatment.

WGS is not only cheaper than culture-based DST in terms of laboratory costs[7], but it also expedites assessment of full drug resistance profiles, reducing the time to appropriate treatment (and time in isolation) for those with MDR TB and for those with DS TB who are presumptively treated for MDR TB following a risk assessment. Our analysis suggests that for these individuals WGS would shorten time spent on inappropriate drug treatment and in expensive negative-pressure isolation rooms, reducing costs as well as benefiting health. For individuals with MDR TB but who are considered to be low risk for MDR TB (initially treated as DS TB), their drug treatment regimens can be corrected earlier avoiding potential MDR-TB transmission events that could be costly.

Overall, we found that the greatest cost saving would be achieved by replacing DST with WGS. However, the greatest health utility gains and overall net benefit would be achieved by combined universal use of Xpert-Ultra and WGS. This approach combines the individual advantages of the two technologies, including faster confirmation of MDR status by WGS allowing for earlier correction than culture-based DST of inappropriate MDR treatment of DS TB due to false-positive MDR results from Xpert-Ultra, which are rare but costly. Universal combined use of WGS and molecular testing would provide universal access to high-quality diagnostics, early TB diagnosis, early contact tracing and a reduction in drug-resistant TB as outlined in the collaborative TB strategy for England[3]. Ideally, in the future, a single assay will have both characteristics, either through direct sequencing from clinical isolates, or the extension of molecular-testing platforms to test for second line drugs. There are potential limitations to using molecular approaches to detect drug resistance. Nucleic acid amplification approaches like the molecular tests we consider can only detect specific mutations and therefore may fail to detect some instances of resistance, although there is no evidence that this is a significant problem in England and Wales. WGS approaches can detect any known resistance mutation from the moment it is identified and indeed sequences can be reanalysed when newly-identified mutations are identified. Although novel or as-yet-unidentified resistance mutations would not detected by WGS, with the relatively low burden of MDR TB in England and Wales it is unlikely that they would arise in our setting prior to being detected elsewhere in the world.

To our knowledge, this is the first economic analysis to compare Xpert-Ultra, WGS, and combined use of these technologies, in a low-burden setting TB diagnosis and tailoring of TB drug treatment. There are a few studies that have evaluated the cost-effectiveness of using molecular testing or WGS separately in high-resource low-TB-burden countries such as the UK [5 7 25 26], including use of Xpert by the Find & Treat service that screen high-risk groups[15]. We extended a previous analysis of molecular

testing by incorporating WGS and contact tracing of close contacts of confirmed active-TB cases as recommended by NICE[4]. Studies in the USA and Germany[25 26] evaluated the impact of implementing molecular testing at a smaller local level setting, such as a single hospital, and showed that cost-savings could be realized in those settings. A cost evaluation of the workflow of WGS in 8 laboratories across Europe and North America calculated the costs to be around 7% cheaper than the alternative standard diagnostic workflow[7]. In addition, the study showed that WGS could significantly shorten the time-to drug susceptibility reporting, which would potentially shorten overall treatment duration through early initiation of patient-tailored treatment[7].

There is uncertainty in the natural-history parameters of TB (e.g. literature estimates of the relative infectivity of smear-negatives compared to smear-positives vary from 13%-41%) and in potential migration patterns. Extensive sensitivity analysis shows that our conclusions regarding the relative cost-effectiveness of the different diagnostic technologies considered are unaffected by the uncertainty in the natural history parameter estimates and by large changes in the proportion of TB infection in immigrants that is MDR, and large changes in immigration rates (halving and doubling).

A limitation of this analysis is that in the interests of tractability the model does not explicitly account for single-drug resistance distinct from fully drug-sensitive or MDR TB. Considering that NICE recommendations suggest that single non-rifampicin drug resistance should be treated as drug sensitive with slight modifications (extended duration of treatment)[4] we perform sensitivity analysis on the duration and cost of DS-TB treatment. Results of the analysis show that the conclusions are unchanged when we assume that all DS-TB cases are treated as single non-rifampicin drug resistant cases, including in the PSA, which considers all uncertain parameters.

Our analysis focused on pulmonary tuberculosis. The WHO recommends the use of Xpert in central nervous, spinal and lymph node TB based on low-quality evidence[27]. Given the absence of transmission from these forms of TB, it is unlikely that transmission-dynamic modelling will increase our understanding of the diagnosis and epidemiology of such disease. Further empirical clinical studies on the value of molecular tests for extra-pulmonary TB are needed. Averting transmission will avert extrapulmonary TB cases as well as pulmonary cases, which will increase the benefits of reducing transmission both in terms of QALYs gained and costs averted. This will make the benefits of faster diagnosis occurring due to molecular testing greater and will make Xpert-Ultra even more beneficial than Xpert because the higher sensitivity of the former means faster diagnosis on average (even though the tests have the same turnaround time). Therefore the rank-order of cost-effectiveness of the strategies we considered is robust.

Although most developed countries like England and Wales already have good TB control measures, there is often room for additional improvements to the accuracy and speed of TB diagnosis. Rapid molecular testing and whole-genome sequencing have a role to play in accelerating appropriate treatment initialization, shortening hospital stays and reducing unnecessary TB treatment for individuals unlikely to have tuberculosis in low TB burden settings. Our results show that combined use of molecular testing and WGS provides both individual-level benefits (faster appropriate treatment) and population-level benefits (reduced onward transmission), which produce cost-savings for the healthcare system. We provide an economic argument for the role of new clinical strategies if England and Wales are to meet the WHO End TB Strategy milestone of reducing TB incidence by 50% by 2025 and eventually eliminate TB as a public health problem[3].

Table 1: Model parameters relating to active-TB diagnosis and treatment

Parameter	Value	Unit	Source
Average duration from onset of symptoms of active TB to seeking care	73	Days	[5]
Time to culture-positivity	13	Days	[6]
Time from culture-positivity to DST report	24	Days	[7]
Time from culture-positivity to WGS report	8	Days	[7]
Time to molecular test report	1.5	Days	[5]
Duration of completed DS treatment	180	Days	[4]
Duration of completed MDR treatment	600	Days	[15]
Mean duration of treatment that is not completed	60	Days	[15]
Proportion of DS TB treated successfully	83	%	[2]
Proportion of MDR TB treated successfully	49	%	[2]
Duration of non-isolation inpatient (smear-negative MDR TB)	23	Days	[5]
Duration of standard isolation (DS TB)	14	Days	[5]
Duration of negative-pressure isolation (smear-positive MDR TB)	89	Days	[5]
TB: tuberculosis; MDR: multidrug-resistant; DS: drug sensitive; DST: drug sensitivity testing; WGS: whole-genome sequencing.			

Table 2: Model parameters relating to contact tracing and drug treatment of latent TB infection (LTBI)

Parameter	Value	Unit	Source
Contacts traced per index case	4.5	Number	[28]
Proportion of contacts with active TB	2.8	%	[28]
Proportion of contacts with latent TB infection	28	%	[29]
Proportion of contacts successfully screened with IGRA	73	%	[30]
Proportion of IGRA+ contacts successfully screened for active TB	76	%	[31]
Proportion of IGRA+ contacts accepting LTBI treatment	78	%	[32]
Proportion of IGRA+ contacts starting LTBI treatment who complete it	79	%	[32]
Duration of (completed) treatment for LTBI	90	Days	[33]
Mean duration of treatment for LTBI that it is not completed	30	Days	[33]

TB: tuberculosis; LTBI: latent tuberculosis infection; IGRA: interferon-gamma release assay

Table 3: Model parameters relating to TB natural history and transmission

Parameter description	Value	Unit	Source
TB natural history			
Proportion of incident infections that are slow-progressing	90	%	[16]
Per-capita rate of slow progression to active disease	0.001	Per year	[16]
Per-capita rate of fast progression to active disease	3.65	Per year	[16]
Proportion of incident disease that is smear-positive	52	%	[2]
Per-capita mortality rate of untreated active disease	0.23	Per year	[19]
Per-capita mortality rate of unsuccessfully treated active disease	0.077	Per year	[34]
Per-capita rate of conversion from smear-negative to positive	0.015	Per year	[35]
Per-capita rate of self-cure: natural reversion from active disease to latent infection	0.21	Per year	[19]
Prevalence of LTBI among new South Asian migrants	20	%	[18]
Prevalence of LTBI among new Black African migrants	28	%	[18]
Transmission			
Relative infectivity of smear-negatives (vs. smear-positives)	0.25	Ratio	[36]
Relative infectivity of unsuccessfully treated (vs. untreated)	0.25	Ratio	[37]
Relative susceptibility of Recovered individuals (vs. Naive)	0.35	Ratio	[35]
Test performance			
Sensitivity of chest X-ray	0.73	Proportion	[5]
Specificity of chest X-ray	0.63	Proportion	[5]
Sensitivity of sputum smear microscopy	1	Proportion	[5]
Specificity of sputum smear microscopy	0.95	Proportion	[5]
Sensitivity of X and U for smear-positive TB	1	Proportion	[9]
Sensitivity of X for smear-negative TB	0.67	Proportion	[9]
Sensitivity of U for smear-negative TB	0.92	Proportion	[9]
Specificity of X	0.973	Proportion	[9]
Specificity of U	0.966	Proportion	[9]
Sensitivity of X and U for MDR detection	0.97	Proportion	[9]
Specificity of X and U for MDR detection	0.98	Proportion	[9]
Treatment			
Proportion assessed as being at risk of MDR TB	1.3	%	[2]
Proportion lost to follow up among South Asians	6	%	[2]
Proportion lost to follow up among Black Africans	4.4	%	[2]

TB: tuberculosis; MDR: multidrug-resistant; DS: drug sensitive; DST: drug sensitivity testing; X: Xpert; U: Xpert-Ultra.

Table 4: Cost parameters

Parameter	Value	Unit	Source
Pre-referral costs	195	£ per patient referred	[5]
Cost of managing treatment adverse effects	983	average £ per MDR patient	[5]
DS TB outpatient visit costs	241	£ per patient per visit	[5]
MDR TB outpatient visit costs	375	£ per patient per visit	[5]
Negative-pressure isolation cost	1,126	£ per patient per day	[5]
Standard isolation cost	390	£ per patient per day	[5]
Non-isolation inpatient cost	282	£ per patient per day	[5]
DS TB treatment costs	0.87	£ per patient per day	[5]
MDR TB treatment costs	21.20	£ per patient per day	[7]
Molecular test cost	99.66	£ per sample	[7]
Culture cost	52.39	£ per sample	[7]
WGS cost	118.55	£ per sample	[7]
First line culture-based DST	135.47	£ per sample	[7]
Second line culture-based DST	101.27	£ per sample	[7]
Species identification	55.05	£ per sample	[33]
Cost per IGRA+ person contact-traced	234	£ per contact	[33]
Cost per IGRA- person contact-traced	180.22	£ per contact	[5]
Cost of LTBI treatment including drugs and staff time	5.36	£ per patient per day	[5]

TB: tuberculosis; MDR: multidrug-resistant; DS: drug sensitive; DST: drug sensitivity testing; WGS: whole-genome sequencing

Table 5: Health-related quality of life parameters

Parameter	Value	Source
Utility without TB (i.e. normal health)	0.88	[23]
Utility loss due to untreated active TB	0.19	[23]
Utility associated with inpatient treatment	0.210	[5]
Utility associated with outpatient treatment	0.067	[5]
Utility loss due to active TB treatment adverse effects	0.17	[5]
Utility loss due to LTBI treatment	0.2	[38]

Table 6: Cost-effectiveness analysis results of comparing the baseline clinical pathway with and without molecular testing and/or whole-genome sequencing (WGS) over a 10-year horizon. The table shows the mean and 95% range of the costs and Quality-adjusted life-years (QALYs) accrued for each strategy, and the incremental costs and QALYs, and incremental net benefit (INB) with a QALY valued at £20,000, of each intervention strategy compared with baseline. X: Xpert; U: Xpert-Ultra.

Strategy	**Cost (£M)**	**Total QALYs accrued**	**Compared with baseline**		
			Incremental costs (£M)	**Incremental QALYs**	**Incremental net benefit (£M)**
Baseline	113.9 (89.2, 138.6)	27,149,285 (27,149,005, 27,149,565)	-	-	-
WGS alone	106.8 (82.7, 130.9)	27,149,387 (27,149,007, 27,149,567)	-7.1 (-11.0, -3.3)	2 (1, 3)	7.2 (3.3, 11.1)
X + DST	113.9 (90.5, 137.3)	27,149,716 (27,149,415, 27,150,016)	-0.1 (-6.0, 5.8)	431 (268, 593)	8.7 (1.8, 15.6)
U + DST	114.0 (90.7, 137.3)	27,149,847 (27,149,527, 27,150,167)	-0.05 (-6.3, 6.4)	562 (358, 767)	11.2 (3.4, 19.0)
X + WGS	108.2 (84.7, 131.7)	27,149,717 (27,149,416, 27,150,017)	-5.7 (-12.1, 0.6)	432 (269, 595)	14.4 (7.2, 21.5)
U + WGS	108.6 (85.2, 132.0)	27,149,848 (27,149,528, 27,150,168)	-5.4 (-11.9, 1.2)	553 (359, 768)	16.6 (8.9, 24.3)

CONTRIBUTORS The study was conceived by PJW and TM, who designed the model and obtained and analysed the data. The model was implemented and analysed by TM under the guidance of PJW with input from IA. All authors contributed to the interpretation of the analysis. PJW and TM wrote the first draft of the paper and all authors contributed to subsequent drafts. All authors approve the work for publication.

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COMPETING INTERESTS None

PATIENT CONSENT Not required.

ETHICS APPROVAL Ethical approval was not required. The surveillance data analysed were routinely collected by PHE under Section 251 of the NHS Act 2006. All records were anonymised before analysis.

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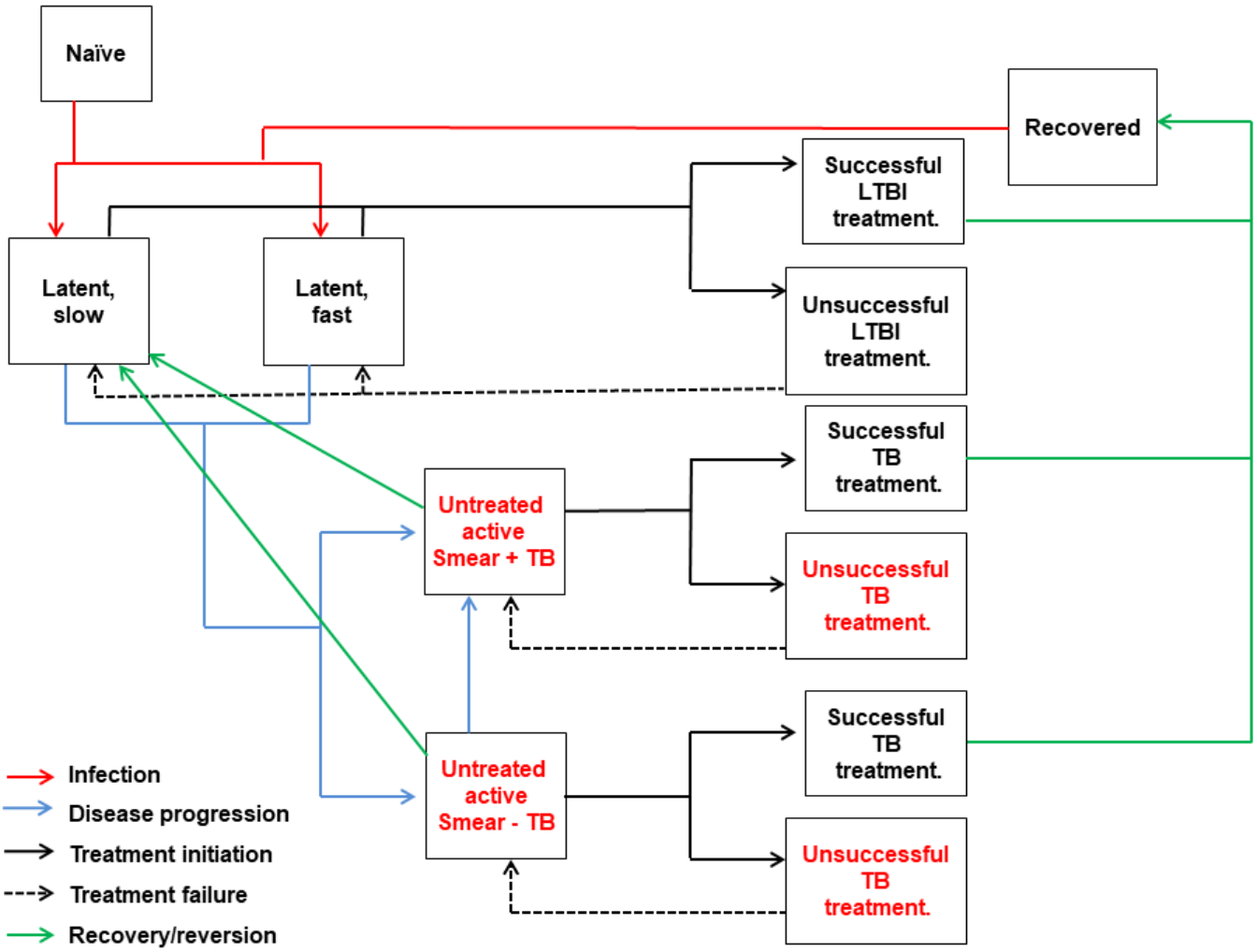


Figure 1: Flow diagram showing the health states representing the natural history and treatment of tuberculosis. Red labels denote the infectious health states. Note that for all infected states (i.e. all except Naive and Recovered) there are separate compartments for drug-sensitive and multidrug-resistant infection. Entry (birth and emigration) and exit (death and emigration) are not shown for clarity. TB: tuberculosis; LTBI: latent TB infection.

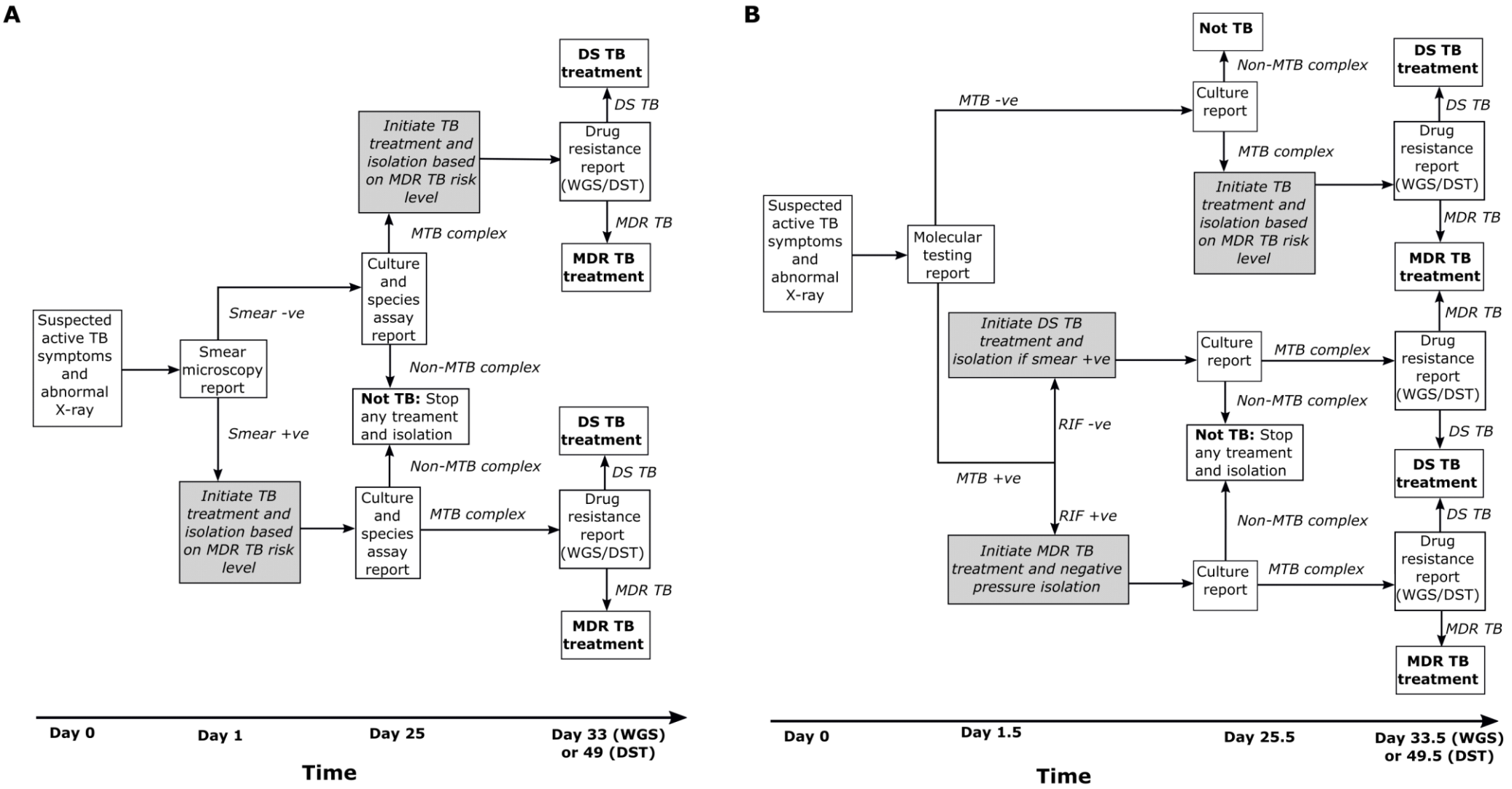


Figure 2: Summary of active-TB diagnosis clinical pathways. Panel (a) presents the conventional pathway (Baseline strategy) that uses standard culture-based drug sensitivity testing (DST). This pathway takes on average 49 days to get the final drug resistance report. Panel (a) also presents strategy (i), where whole-genome sequencing (WGS) replaces standard culture-based DST. This pathway takes on average 33 days to get the final drug resistance report. Panel (b) presents a modified clinical pathway that includes molecular testing (strategies (ii)-(v)). Similarly, to panel (a), the clinical pathway in panel (b) uses either standard culture-based DST, which makes the total pathway length 49.5 days (strategy (ii) and strategy (iii)); or (i) WGS, which reduces the total pathway length to 33.5 days (strategy (iv) and strategy (v)). In both panels drug sensitivity reports are obtained from either culture-based DST or from WGS, depending on the strategy. The average event times in the pathway are also shown with day 0 representing the day an active TB patient seeks care; note that culture is inoculated at the time of sputum smear microscopy. TB: tuberculosis; DS: drug sensitive; MDR: multidrug-resistant.

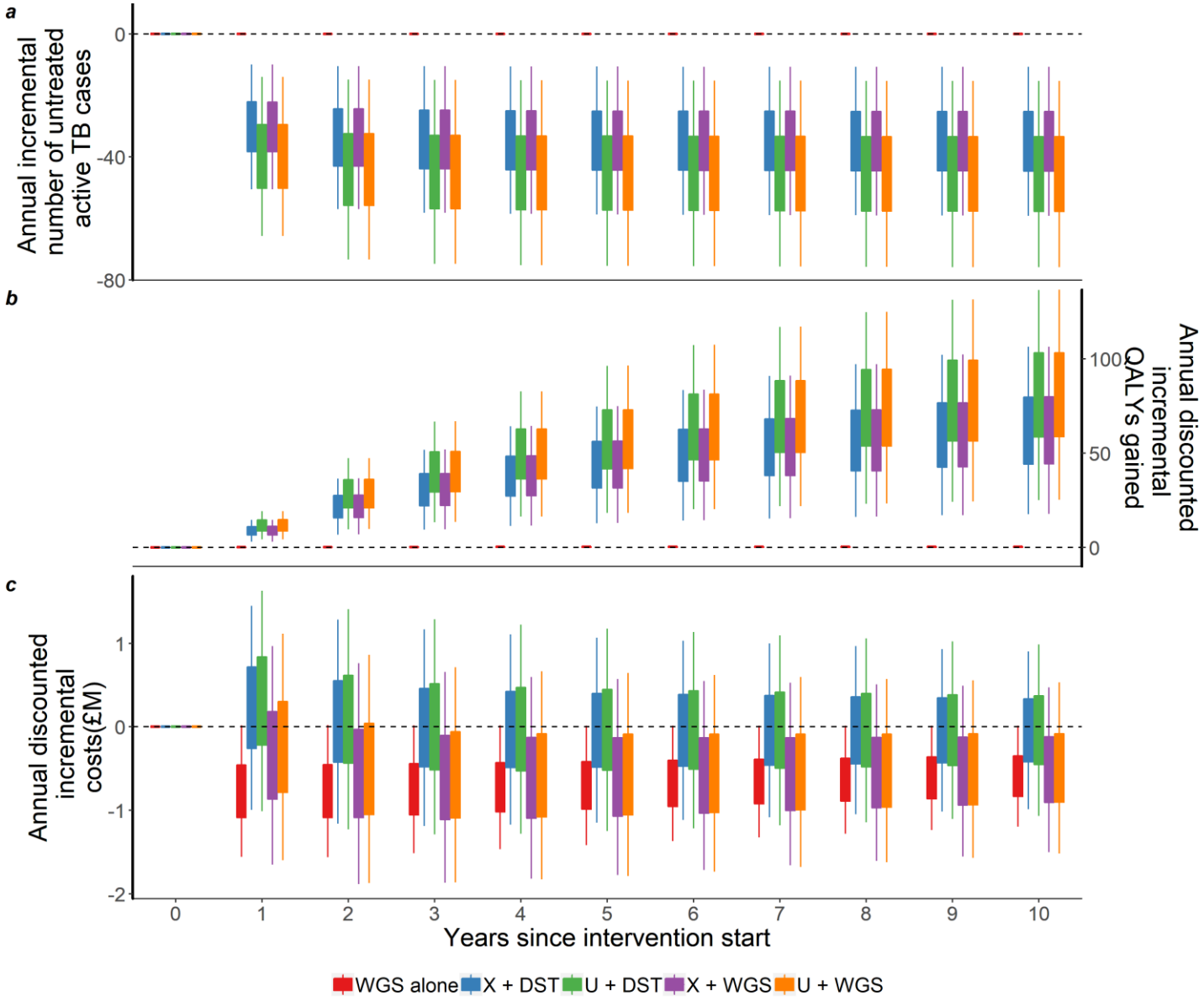


Figure 3: Incremental comparison with the baseline scenario of (a) the annual number of untreated active-TB cases (drug-sensitive and multidrug-resistant), (b) discounted annual incremental quality of life adjusted years (QALYs) gained and (c) discounted annual incremental costs incurred, where standard drug sensitivity testing (DST) is replaced by whole-genome sequencing (WGS: red bars), or molecular testing (X or U) is introduced into the conventional TB-diagnosis pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing is introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars). The boxes show the interquartile ranges, and the whiskers the 95% ranges, of the calculated values. TB: tuberculosis.

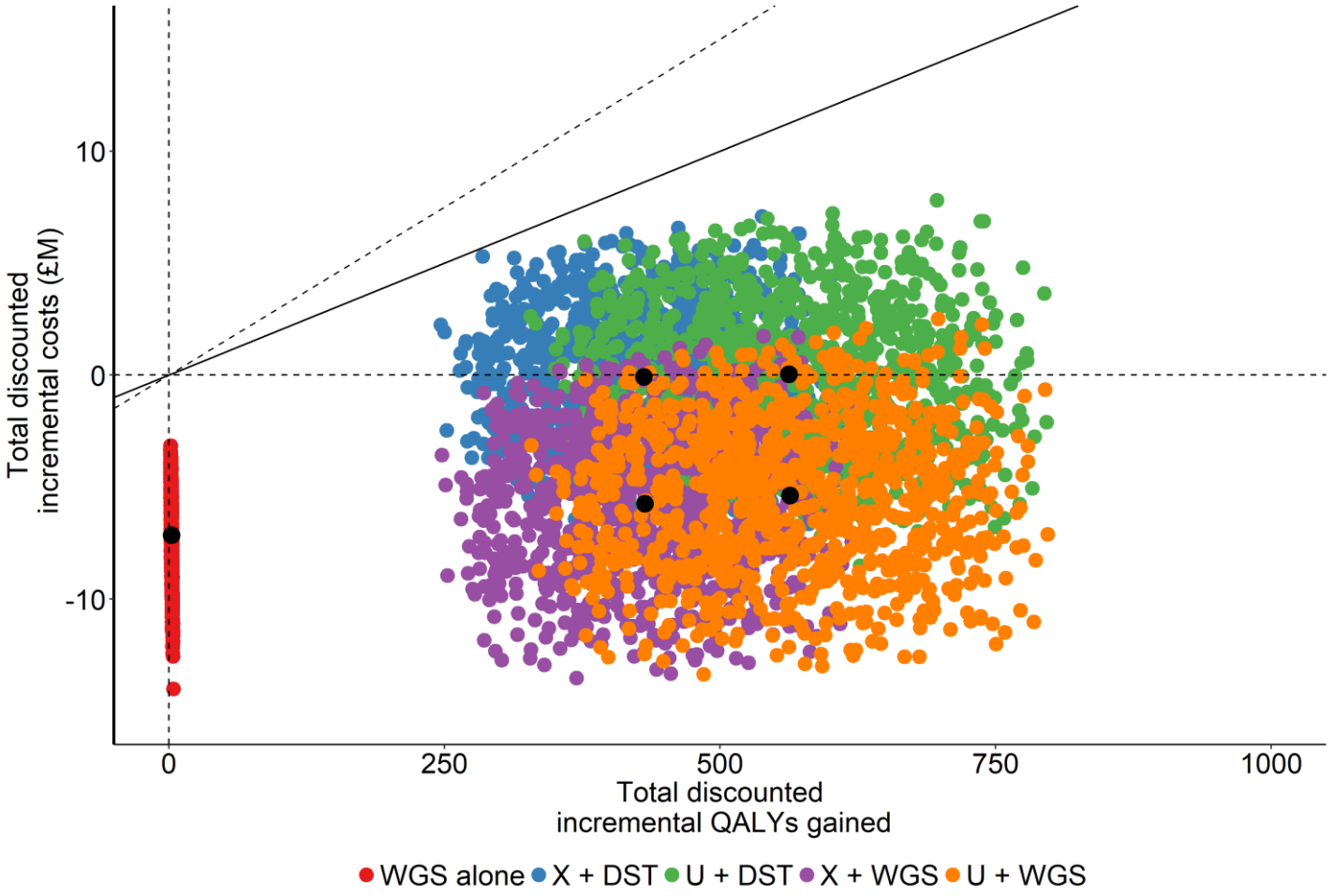


Figure 4: Cost-effectiveness plane showing incremental effects of introducing whole-genome sequencing and/or molecular testing into the diagnostic pathway. Results of probabilistic sensitivity analysis using 1,000 simulations are shown along with the median value for each strategy (black dots). The bold diagonal line indicates the threshold of £30,000 per quality of life adjusted year (QALY) and the dotted diagonal line indicates the threshold of £20,000 per QALY**.** Strategies we consider are standard drug sensitivity testing (DST) being replaced by whole-genome sequencing (WGS: red dots), or molecular testing (X or U) being introduced into the conventional pathway with DST (X + DST: blue dots, U + DST: green dots), or molecular testing being introduced into the conventional pathway with WGS in place of DST (X + WGS: purple dots, U + WGS: orange dots).

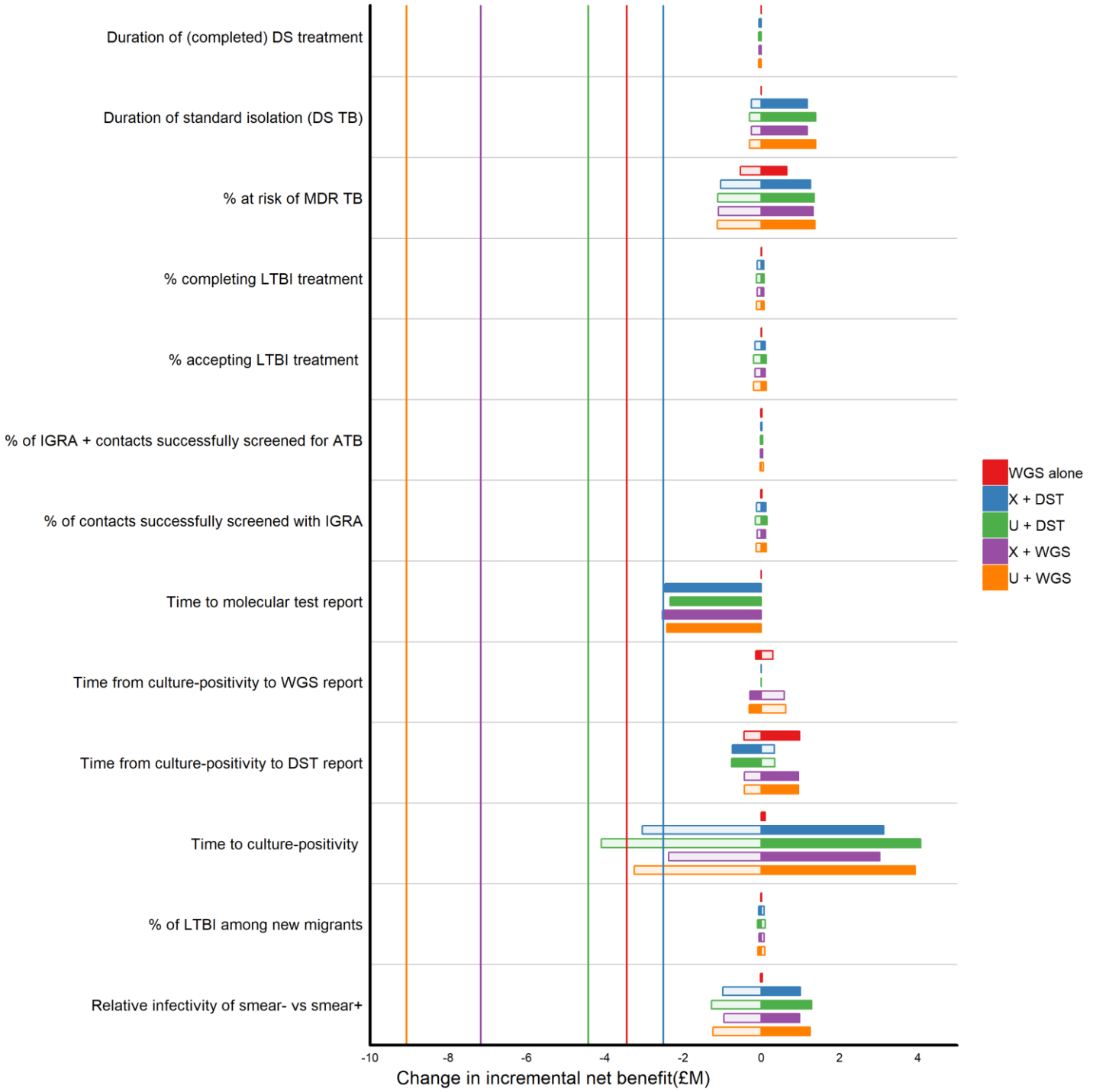
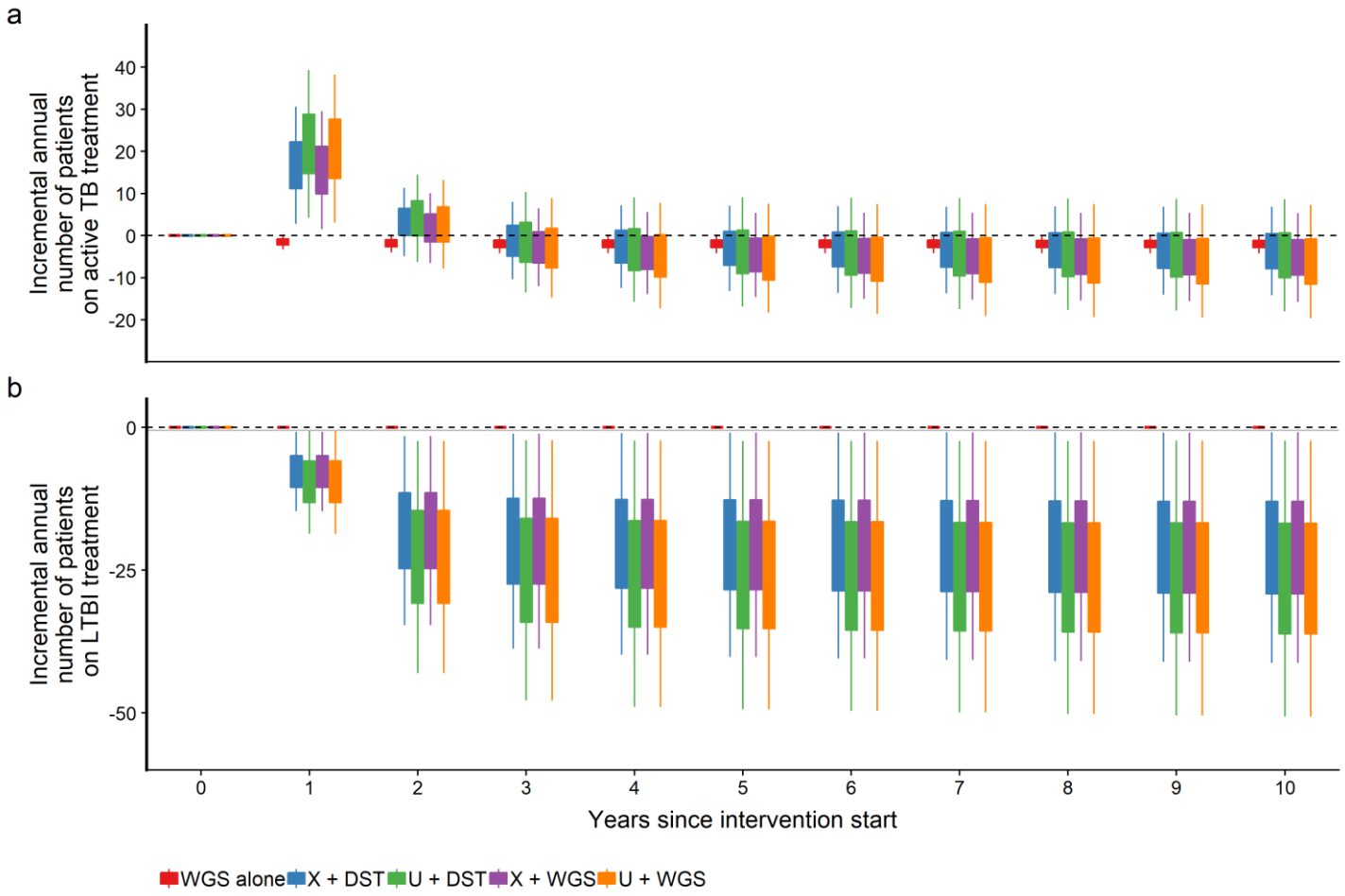
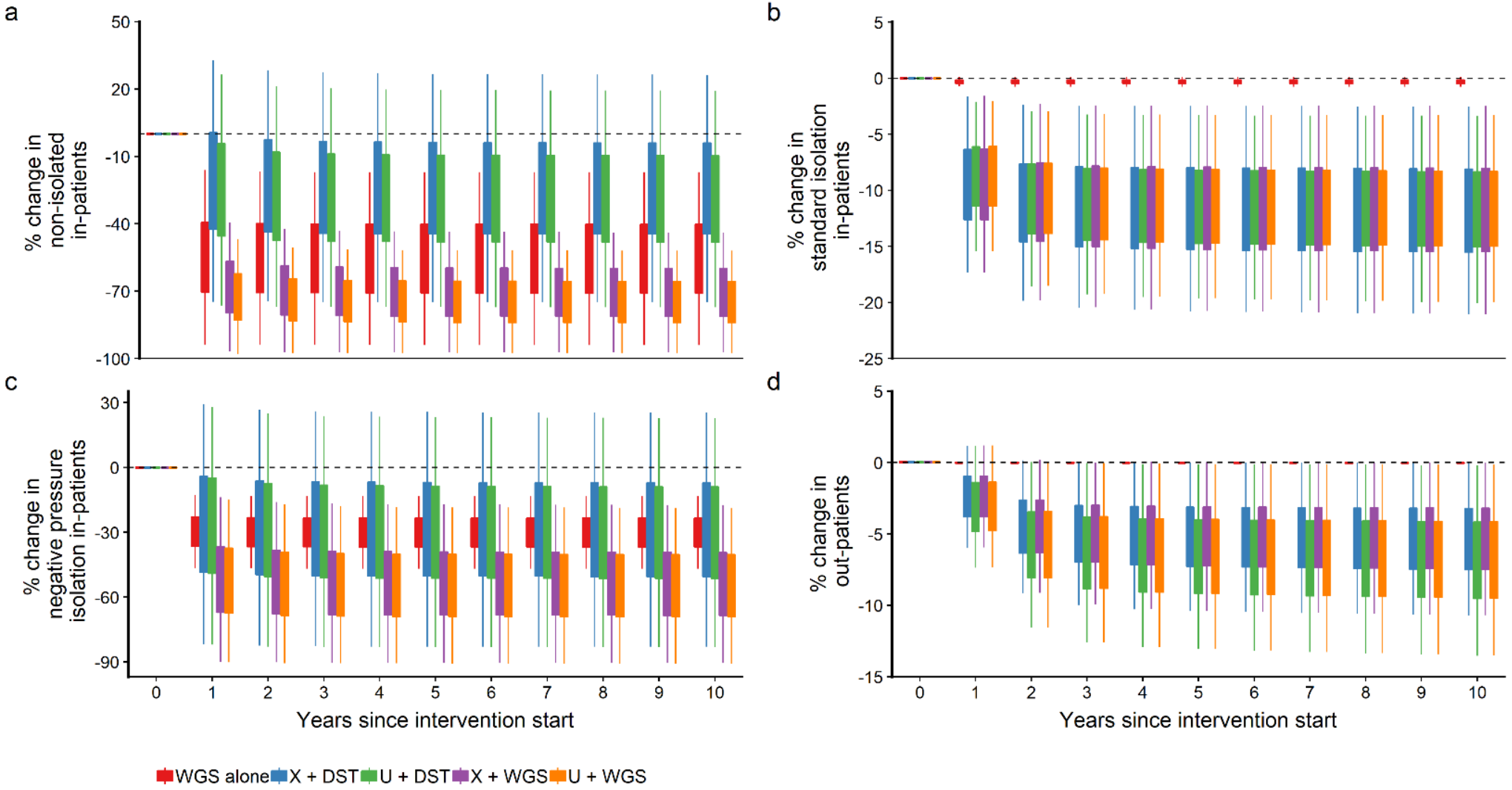


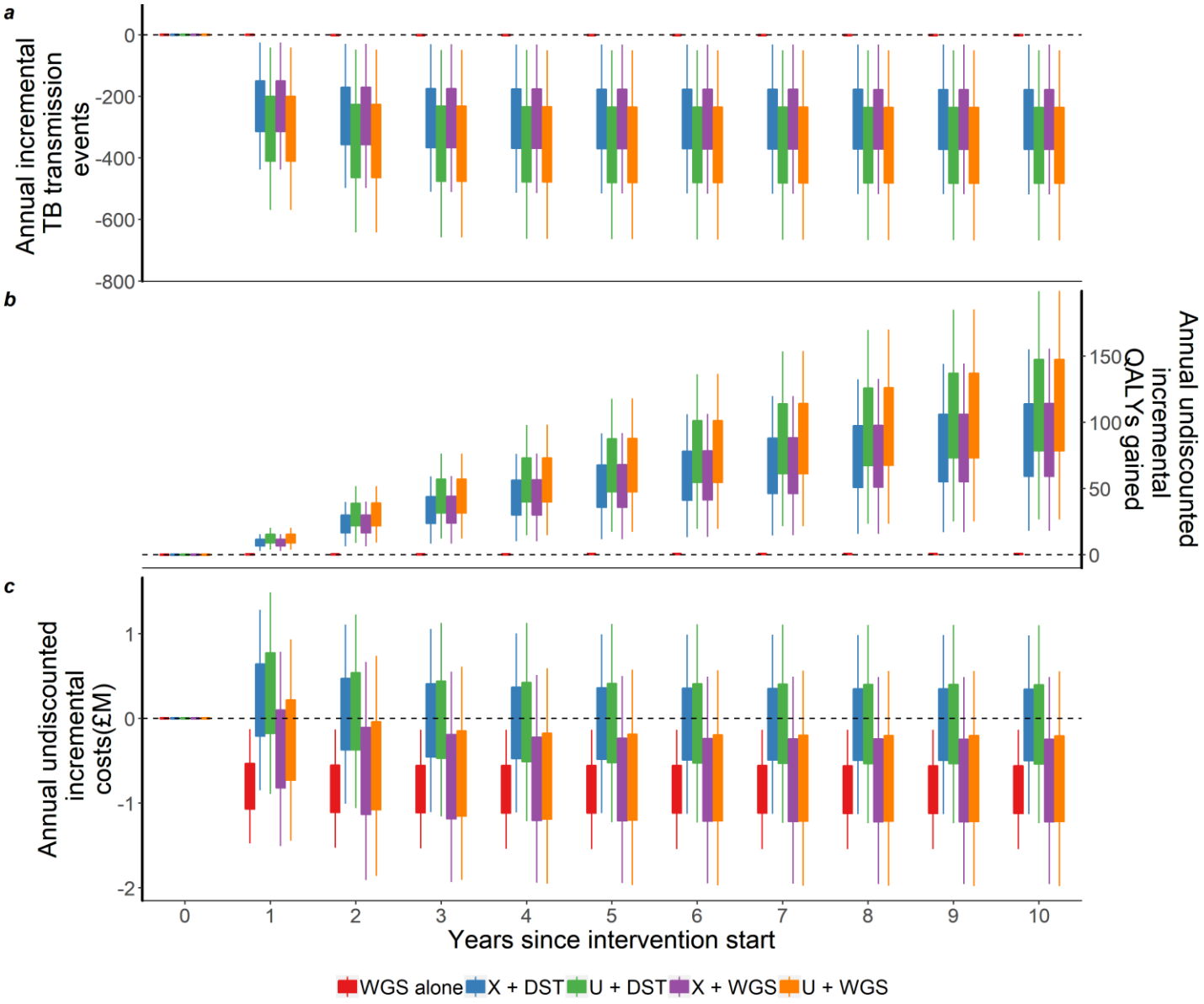
Figure 5: Tornado plot showing effects of the individual parameter changes on model results. Baseline parameters are individually varied from their minimum (open bars) to their maximum (solid bars) for strategies where standard drug sensitivity testing (DST) is replaced by whole-genome sequencing (WGS: red bars), or molecular testing (X or U) is introduced into the conventional pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing is introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars), compared to the conventional pathway. For each case the difference between incremental net benefit (INB) of the model result using the baseline parameter value and the upper- or lower-bound parameter value with a QALY valued at £20,000. The vertical lines represent the change in INB required reduce the INB to zero. DS: drug sensitive; TB: tuberculosis; MDR: multidrug-resistant; LTBI: latent TB infection; ATB: active TB; IGRA: interferon-gamma release assay.



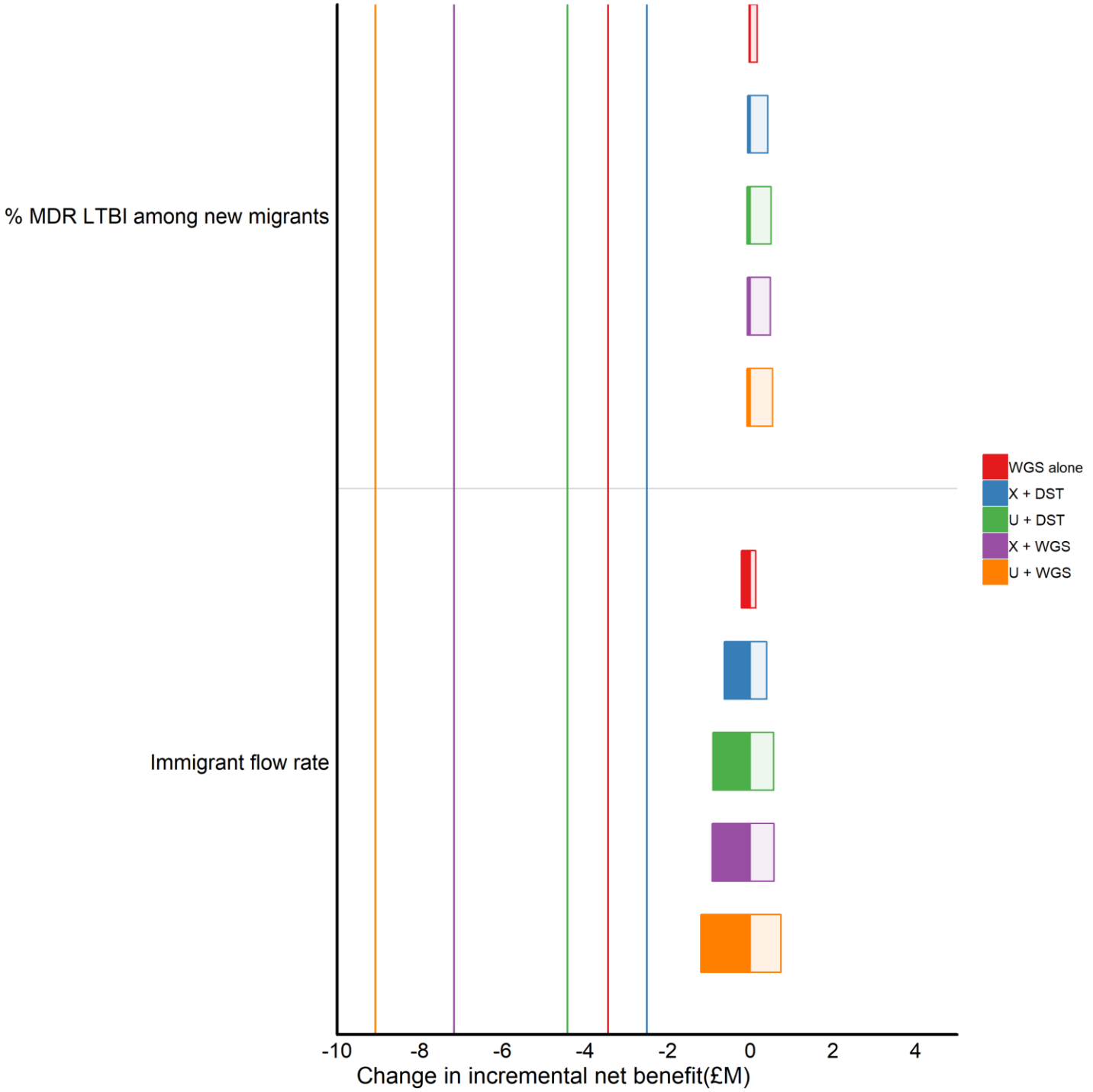
Supplementary Figure 1: Impact of introducing whole-genome sequencing and/or molecular testing on numbers of patients starting treatment each year for (a) active-TB patients (drug-sensitive and multidrug-resistant), and (b) latent TB infection (LTBI). Strategies we consider are standard drug sensitivity testing (DST) being replaced by whole-genome sequencing (WGS: red bars), or molecular testing (X or U) being introduced into the conventional TB-diagnosis pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing being introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars). The boxes show the interquartile ranges, and the whiskers the 95% ranges, of the calculated values. TB: tuberculosis.



Supplementary Figure 2: Impact of introducing whole-genome sequencing and/or molecular testing on hospital activity. Graphs show percentage incremental changes compared with the baseline scenario in numbers of patients (drug-sensitive and multidrug-resistant TB) who are (a) non-isolation inpatients, (b) standard isolation patients, (c) negative-pressure room isolation patients and (d) outpatients during drug treatment after the introduction of changes to the TB-diagnosis pathway. Strategies we consider are standard drug sensitivity testing (DST) being replaced by whole-genome sequencing (WGS: red bars), or molecular testing (X or U) being introduced into the conventional pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing being introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars). The boxes show the interquartile ranges, and the whiskers the 95% ranges, of the calculated values.



Supplementary Figure 3: Incremental comparison with the baseline scenario of (a) the incremental annual number of TB transmission events (drug-sensitive and multidrug-resistant), (b) undiscounted annual incremental quality of life adjusted years (QALYs) gained and (c) undiscounted annual incremental costs, where whole-genome sequencing and/or molecular testing (X or U) are introduced into the conventional TB-diagnosis pathway. Strategies we consider are standard drug sensitivity testing (DST) being replaced by whole-genome sequencing (WGS: red bars), or molecular testing being introduced into the conventional TB-diagnosis pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing being introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars). The boxes show the interquartile ranges, and the whiskers the 95% ranges, of the calculated values. TB: tuberculosis.



Supplementary Figure 4: Tornado plot showing effects of hypothetical changes in the proportion of TB infection in migrants that is multidrug-resistant and in the immigration rate (halving and doubling). The percentage of TB infection in new arrivals that is multidrug-resistant (MDR) is varied from its baseline value of 0.7% to 0.35% and 2%. The immigration rate is doubled and halved from the baseline values (Black Africans: 27,977 per year; South Asians: 49,142). For each case the difference between incremental net benefit (INB) of the model result using the baseline parameter value and the upper- or lower-bound parameter value with a QALY valued at £20,000. The vertical lines represent the change in INB required to reduce the INB to zero. Strategies we consider are standard drug sensitivity testing (DST) being replaced by whole-genome sequencing (WGS: red bars), or molecular testing (X or U) being introduced into the conventional TB-diagnosis pathway with DST (X + DST: blue bars, U + DST: green bars), or molecular testing being introduced into the conventional pathway with WGS in place of DST (X + WGS: purple bars, U + WGS: orange bars). TB: tuberculosis; LTBI: latent TB infection.

Supplementary Appendix

Contents

Supplementary Table 1: Population demographics and pulmonary TB rates for South Asian and Black African ethnic/social groups. The ethnic/social group population sizes, rates of birth and immigration are estimated from the latest Office for National Statistics (ONS) census data (2011). Birth rate is calculated from the number of 0- to 4-year-olds per ethnic/social group. The number of new arrivals in England and Wales is used to estimate the immigration rate. Baseline TB incidence and proportion of MDR-TB cases are from Enhanced TB Surveillance (ETS) data (2015).[1]

Ethnic/social group	Region of birth	Population size	Births per year	Immigrants per year	Annual active TB cases	Proportion of active TB cases that are MDR (%)
South Asian	England and Wales	1,461,439	70,163	-	185	1.0
	Foreign	1,258,561	-	49,142	808	0.3
Black African	England and Wales	320,615	27,259	-	64	1.1
	Foreign	607,566	-	27,977	411	1.1

Supplementary Table 2: Summary of uncertain parameters. The table shows the baseline values and plausible value ranges of the parameters considered in the sensitivity analysis.

Parameter	Baseline value (uncertainty range)	Unit	Source
Prevalence of LTBI among new South Asian migrants	20 (17-23)	%	[2]
Prevalence of LTBI among new Black African migrants	28 (22-34)	%	[2]
Relative infectivity of smear-negatives (vs. smear-positives)	0.25 (0.13-0.41)	Ratio	[3-5]
Proportion of contacts successfully screened with IGRA	73 (50-95)	%	[6]
Proportion of IGRA+ contacts successfully screened for active TB	76 (50-95)	%	[7]
Time to molecular test report	1.5 (1-3)	Days	[8]
Time to culture-positivity	13 (8-17)	Days	[9]
Time from culture-positivity to WGS report	8 (6-9)	Days	[10]
Time from culture-positivity to DST report	24 (20-33)	Days	[9,10]
Proportion assessed as being at risk of MDR TB	1.3 (1-1.7)	%	[1]
Duration of standard isolation (for DS TB)	14 (14-90)	Days	[8]
Duration of completed DS TB treatment	180 (180-270)	Days	[11]
Proportion accepting LTBI treatment	78 (50-95)	%	[12]
Proportion completing LTBI treatment	79 (50-95)	%	[12]
TB: Tuberculosis; MDR: Multi-drug resistant; DS: Drug sensitive; DST: Drug sensitivity testing; WGS: Whole-genome sequencing.			

Supplementary Table 3: Summary of breakdown of treatment and diagnosis costs for each strategy. The table shows a breakdown of discounted costs calculated over a 10-year horizon for each strategy. Values are £M and show the mean and 95% range. X, U: molecular testing options.

Strategy	DS TB treatment	MDR TB treatment	LTBI treatment	False-positive TB treatment	Diagnostics
Baseline	62.5 (38.8, 86.1)	18.3 (10.7, 25.8)	6.2 (3.5, 8.9)	1.5 (1.4, 1.5)	25.5 (25.3, 25.7)
WGS alone	62.2 (38.5, 85.8)	13.0 (9.0, 17.0)	6.2 (3.5, 8.9)	1.5 (1.4, 1.5)	23.9 (23.8, 24.0)
X + DST	61.2 (37.8, 84.5)	18.7 (16.9, 20.4)	6.1 (3.5, 8.7)	0.8 (0.8, 0.8)	27.1 (27.1, 27.2)
U + DST	60.9 (37.7, 84.1)	18.9 (17.3, 20.6)	6.0 (3.4, 8.6)	1.01 (1.01, 1.01)	27.0 (27.0, 27.1)
X + WGS	61.2 (37.8, 84.5)	14.5 (12.7, 16.2)	6.1 (3.5, 8.7)	0.8 (0.8, 0.8)	25.7 (25.6, 25.8)
U + WGS	60.9 (37.7, 84.1)	15.0 (13.1, 16.8)	6.0 (3.4, 8.6)	1.01 (1.01, 1.01)	25.7 (25.6, 25.7)

Supplementary Table 4: consistency of cost-effectiveness rank-order. The table shows the percentage of simulations that result in a given ranking by incremental net benefit over a 10-year horizon for each of the strategies. Rank 1 is the highest incremental net benefit (most cost-effective) and Rank 5 is the lowest Incremental net benefit (least cost-effective). X, U: molecular testing options.

Rank	Strategy				
	WGS alone	X + DST	U + DST	X + WGS	U + WGS
1	0	0	0	0	100
2	0	0	0	100	0
3	0	8.3	91.7	0	0
4	28.4	71.6	0	0	0
5	71.6	20.1	8.3	0	0

Description of the process of identification and treatment of TB

The baseline clinical pathway for active-TB diagnosis uses chest X-ray as an initial rule-out test for pulmonary TB.[13] An abnormal chest X-ray prompts collection of sputum samples for smear microscopy and culture, with positive cultures followed by culture-based DST.

Patients diagnosed with active TB (usually based on sputum-smear microscopy or culture) are given drug treatment. Typically, treatment is initiated prior to DST results becoming available, so the choice of regimen is based on a risk assessment for drug resistant infection, based previous TB treatment history, contact with a known MDR-TB case, or birth or residence in a country where ≥5% of new TB cases are MDR-TB.[13] Treatment can be modified if necessary when DST results become available.

We divide TB in into drug-sensitive (DS) and MDR-TB because NICE recommends that mono-resistant infection that is not rifampicin resistant be treated the same as fully drug-sensitive with only slight modifications (extended duration of treatment),[13] whilst rifampicin-resistant infection be treated as MDR-TB. This simplifying assumption may result in an underestimation of DS-TB treatment costs, which we address in sensitivity analysis by varying the treatment duration between 6 and 9 months (the recommended duration for DS-TB and isoniazid or pyrazinamide single drug resistance respectively).[13]

Close contacts of people with pulmonary TB are investigated for infection using Interferon-gamma release assay (IGRA).[13] Contacts with positive IGRA results have a chest X-ray to detect active TB. Those with an abnormal X-ray are managed as suspected active-TB patients. Individuals with a positive IGRA result and a normal chest X-ray are

offered LTBI treatment of 3 months of isoniazid, pyridoxine and rifampicin, if the index case has DS TB. (Where the index case has MDR TB, LTBI treatment is not offered to contacts in case their infection is MDR, which would make LTBI treatment ineffective; however, contacts with active TB are treated, as their MDR status is determined in the diagnostic process.)

Studies in London and Birmingham estimated that about 86% and 60%, respectively, of pulmonary TB contacts are investigated.[6, 14] We consider a midpoint baseline value of 73% and perform sensitivity analysis varying the value between 50-95%. It is also uncertain what proportion of patients accept and complete LTBI treatment. A recent study in London estimated that 78% of contacts with LTBI start treatment and 79% go on to successfully complete it.[12] We use these estimates as baseline values and perform sensitivity analysis, varying both values between 50% and 95%.

Isolation of infectious patients is recommended:[13]

(i) At least 2 weeks standard isolation of smear-positive presumed DS-TB cases, to be extended if there is delayed smear conversion.

(ii) For cases with suspected or confirmed MDR-TB, admission to a negative-pressure room until 3 consecutive weeks of negative sputum-smear results or a negative culture result.

In the model patients are not able to transmit TB while in isolation. The duration of isolation recommended by NICE is a minimum of 2 weeks.[13] However, a recent study in Germany estimated the time from treatment initiation to smear conversion, for DS-TB, to be 19 (10–32) days.[15] We perform sensitivity analysis varying this parameter over a range of 10–32 days with a baseline value of 14 days. Smear-positive MDR-TB cases are admitted to negative-pressure isolation rooms for 89 days[8, 16] whilst smear-negative MDR-TB cases are admitted to negative isolation rooms for 23 days followed by a further 23 days as a non-isolation inpatient.[8]

Detailed model description

The model considers TB transmission within each Black African and South Asian ethnic/social groups, with homogeneous mixing of UK-born and foreign-born individuals within those groups. The model makes the simplifying assumption that there is negligible transmission between Black African and South Asian groups, which is supported by both epidemiological evidence and sociological evidence. A UK study using molecular typing and cluster investigation found that 85% of transmissions were between individuals with the same country of birth, and there were no instances of transmission detected between South Asian and Black African groups[17] and the 2011 census found that <0.56% of South Asians are in relationships with Black Africans and <1.62% of Black Africans are in relationships South Asians.[18]

The population is divided into compartments representing infection and treatment status (i.e. naive, latent infection, active disease, on treatment, recovered, etc). Individuals flow between the compartments depending on per-capita rates and the number of individuals in the relevant compartment. The model structure is the same structure for DS and MDR TB, and there are separate sets of compartments for Black African (UK-born), Black African (foreign-born), South Asian (UK-born), and South Asian (foreign-born) groups.

Flows between compartments are described by a set of ordinary differential equations (see below), in which each compartment has a state variable indicating the number of individuals in that compartment at a point in time; these are listed in Supplementary Table 5. The differential equations specify the rate of change in the number in each compartment with respect to time, e.g. dS/dt is the rate of change in the number Susceptible (S) with respect to time (t).

Individuals enter the model population through birth or immigration and exit through death or emigration. The rate of entry is τ, which corresponds to births for UK-born individuals and the immigration rate for foreign-born individuals. The proportion of new entrants who have latent TB infection is p_e: in the case of UK-born entrants, who

are newborns, this has the value 0: for new entrants who are migrants its value corresponds to the LTBI prevalence estimated by Pareek et al.[2] Thus the rate of entry into the TB naïve compartment (S) is $(1-p_e)\tau$. Exit from all compartments occurs at rate μ due to emigration and death due to non-TB related causes.

Heterogeneity in rates of progression from LTBI to active TB is represented by dividing individuals with LTBI into slow-progressors (Ls) or fast-progressors (Lf). The ratio of new immigrants who are slow-progressors to fast-progressors, p_m, is estimated by model fitting (explained below). (For UK-born individuals this parameter is irrelevant.) The flow rates of new entrants into to Lf and Ls compartments are $p_e\tau/(p_m+1)$ and $p_e\tau p_m/(p_m+1)$, respectively. The proportion of TB infection in new arrivals that is drug sensitive is p_{d1} and the proportion that is MDR is p_{d2}, where $p_{d1} = (1-p_{d2})$.

Interaction between uninfected individuals and those with active TB can result in TB transmission. TB-naïve individuals are infected at rate λ, whilst those who have recovered have partial protection and are infected at rate $b_R\lambda$. Newly-infected individuals have latent TB infection (LTBI) which is asymptomatic and non-infectious. A proportion p_s have slow-progressing LTBI with a progression rate ϕ_S. The remaining individuals $(1 - p_s)$ have fast-progressing LTBI with a progression rate ϕ_F. Individuals with LTBI can have their infection diagnosed via contact tracing and be treated at rate θ_L. Details of how θ_L is calculated are provided below.

Individuals who progress to develop active TB, which is symptomatic and infectious, are either sputum smear-positive TB (USp) or sputum smear-negative TB (USn), with the former being more infectious. The proportion of nascent disease that is smear-positive is p_{Sp}. Smear-negative individuals can convert to smear-positive, at rate σ. The infectiousness of smear-negative relative to smear-positive individuals is b_N. Depending on the clinical pathway considered (Figure 2), individuals seeking care due to symptoms are diagnosed and end-up in either DS-TB or MDR-TB treatment compartments at rate θ_P. Additional active TB cases are identified by contact tracing (θ_C) as explained below. Untreated active-TB cases can naturally revert to the slow-progressing latent state at rate π. Untreated active TB causes mortality at rate μ_U.

Individuals can be treated for LTBI, DS TB or MDR TB. Treatment may be completed successfully or patients may be lost to follow-up; to account for the different corresponding durations there are separate compartments for those who will complete treatment successfully and those who will not. The proportion of successfully-treated LTBI is p_{TsL} and the proportion of successfully-treated active TB is p_{TsAi}. The durations of successful and unsuccessful LTBI treatment are $1/d_{TsL}$ and $1/d_{TuL}$, respectively. The durations of successful and unsuccessful active TB treatment are $1/d_{TsAi}$ and $1/d_{TuA}$, respectively. Successfully-treated individuals enter the Recovered state, whilst unsuccessfully-treated individuals return to their prior infection state. Those being unsuccessfully treated for active disease are subject to the additional TB-associated mortality rate, μ_{Tu}.

Individuals in the Recovered state have a reduced susceptibility (b_R) to acquisition of TB infection compared to TB naïve individuals.

For each active TB case that is diagnosed, an average number (c) of contacts are successfully traced and IGRA-tested for TB infection, with IGRA-positives being investigated by chest X-ray to detect active TB: a normal X-ray indicates LTBI. The proportion of traced individuals that have LTBI, q_L, depends on the population prevalence of LTBI thus: $q_L = (Ls+Lf)/N + p_L$, where $(Ls+Lf)/N$ is the population prevalence of LTBI and p_L is the differential between the population prevalence of LTBI and the proportion of contacts that have LTBI. The value of p_L is the difference between the proportion of contacts with latent TB infection as estimated by Fox et al.[19] and the initial population prevalence of LTBI in the model. The proportion of contact-traced LTBI cases accepting LTBI treatment is a_L, so the rate of LTBI treatment is $\theta_L = c\, q_L\, a_L\, \theta_P$. Although they are traced, contacts of MDR TB index cases who are diagnosed with LTBI are not treated. However, another proportion (q_A) of successfully traced contacts are IGRA-positive and have an abnormal chest X-ray. These individuals enter the same treatment pathway (described above) as other active cases

in the clinical pathways. The proportion of contact traced active TB cases going onto TB treatment is therefore given by $\theta_C = c\, q_A\, \theta_P$.

Supplementary Table 5: symbols for model variables and parameters. The variables correspond to model compartments (Figure 1) except N, λ, q_L, q_A, θ_L, and θ_C. Parameters specify rates of entry into and exit from compartments as described in the text and specified in the differential equations.

Symbol	Description
Variables	
S	Susceptible (naive) individuals
Ls	Individuals with slow-progressing latent infection
Lf	Individuals with fast-progressing latent infection
USn	Individuals with untreated smear-negative active TB disease
USp	Individuals with untreated smear-positive active TB disease
TsLs	Individuals with slow-progressing latent TB infection on treatment which will be successful
TuLs	Individuals with slow-progressing latent TB infection on treatment which will not be completed successfully
TsLf	Individuals with fast-progressing latent TB infection on treatment which will be successful
TuLf	Individuals with fast-progressing latent TB infection on treatment which will not be completed successfully
TsSn	Individuals with smear-negative TB disease on treatment which will be successful
TuSn	Individuals with smear-negative TB disease on treatment which will not be completed successfully
TsSp	Individuals with smear-positive TB disease on treatment which will be successful
TuSp	Individuals with smear-positive TB disease on treatment which will not be completed successfully
R	Individuals who have recovered from TB infection
N	Total sub-population size
λ	Force of infection: per-Susceptible rate of infection per unit time
c	Average number of contacts of active-TB cases who are successfully traced
q_L	Proportion of traced contacts of active-TB cases that have LTBI
q_A	Proportion of traced contacts of active-TB cases that have active TB
a_L	Proportion of contact-traced LTBI cases accepting LTBI treatment
θ_L	Rate at which individuals with LTBI are diagnosed and treated due to contact tracing
θ_C	Rate at which individuals with active TB are diagnosed and treated through contact tracing
Parameters	
β_P	Transmission coefficient of smear-positive TB
b_N	Relative infectiousness of smear-negative individuals compared with smear-positive
b_{Tu}	Relative infectiousness of individuals being unsuccessfully treated for active TB compared with untreated active TB
b_M	Relative infectivity of MDR TB compared to non-MDR TB
b_R	Relative susceptibility of Recovered individuals
τ	Rate of entrance into population sub-group: births for UK-born, immigration for foreign-born
p_e	LTBI prevalence among population entrants: prevalence in immigrants was estimated by Pareek et al.; prevalence in newborns is zero
p_m	Ratio of latent slow progressors to latent fast progressors in new arrivals
p_{d1}	Proportion of TB infection in new arrivals that is drug-sensitive
p_{d2}	Proportion of TB infection in new arrivals that is drug-sensitive
μ	Rate of exit from population due to emigration + background mortality (i.e. death due to non-TB causes)
p_s	Proportion of incident infections that are slow-progressing
p_{TsL}	Proportion of LTBI treatment that is successful
$1/d_{TsL}$	Duration of successful LTBI treatment
$1/d_{TuL}$	Duration of unsuccessful LTBI treatment
ϕ_S	Rate of slow-progression from latent infection
ϕ_F	Rate of fast-progression from latent infection
p_{Sp}	Proportion of nascent active TB that is smear-positive

σ	Rate of conversion from smear-negative to smear-positive
π	Rate of reversion from active TB to LTBI
μ_U	Additional mortality rate due to Untreated active TB
p_{TsA}	Proportion of active-TB treatment that is successful
$1/d_{TsA}$	Duration of successful active-TB treatment
$1/d_{TuA}$	Duration of unsuccessful active-TB treatment
μ_{Tu}	Additional mortality rate in patients being treated unsuccessfully for active TB
p_L	Differential between the population prevalence of LTBI and the proportion of contacts that have LTBI
θ_P	Rate at which individuals with active TB are diagnosed and treated passively (i.e. through individuals seeking care)

Model equations

With the exception of S and R (which are uninfected), the model compartments denote infection with DS TB or MDR TB, which is distinguished in the equations below using the subscript i, where i=1: DS TB; i=2: MDR TB.

$dS/dt = (1 - p_e)\,\tau - (\Sigma_i\lambda_i + \mu)\,S$

$dLs_i/dt = \lambda_i\, p_s\, (S + b_R\, R) + p_e\, p_{di}\, \tau\, p_m/(p_m+1) + \pi\, (USn_i + USp_i) + d_{TuL}\, TuLs_i - (\theta_L + \phi_S + \mu)\, Ls_i$

$dLf_i/dt = \lambda_i\, (1 - p_s)\, (S + b_R\, R) + p_e\, p_{di}\, \tau/(p_m+1) + d_{TuL} TuLf_i - (\theta_L + \phi_F + \mu)\, Lf_i$

$dUSn_i/dt = (1 - p_{Sp})\, (\phi_S\, Ls_i + \phi_F\, Lf_i) + d_{TuA}\, TuSn_i - [\sigma + \pi + (\theta_P + \theta_C) + (\mu + \mu_U)]\, USn_i$

$dUSp_i/dt = p_{Sp}\, (\phi_S\, Ls_i + \phi_F\, Lf_i) + \sigma\, USn_i + d_{TuA}\, TuSp_i - [\pi + (\theta_P + \theta_C) + (\mu + \mu_U)]\, USp_i$

$dTsLs_i/dt = \theta_L\, p_{TsL}\, Ls_i - d_{TsL}\, TsLs_i - \mu\, TsLs_i$

$dTuLs_i/dt = \theta_L\, (1 - p_{TsL})\, Ls_i - (d_{TuL} + \mu)\, TuLs_i$

$dTsLf_i/dt = \theta_L\, p_{TsL}\, Lf_i - (d_{TsL} + \mu)\, TsLf_i$

$dTuLf_i/dt = \theta_L\, (1 - p_{TsL})\, Lf_i - (d_{TuL} + \mu)\, TuLf_i$

$dTsSn_i/dt = (\theta_P + \theta_C)\, p_{TsAi}\, USn_i - (d_{TsAi} + \mu)\, TsSn_i$

$dTuSn_i/dt = (\theta_P + \theta_C)\, (1 - p_{TsAi})\, USn_i - (d_{TuA} + \mu + \mu_{Tu})\, TuSn_i$

$dTsSp_i/dt = (\theta_P + \theta_C)\, p_{TsAi}\, USp_i - (d_{TsAi} + \mu)\, TsSp_i$

$dTuSp_i/dt = (\theta_P + \theta_C)\, (1 - p_{TsAi})\, USp_i - (d_{TuA} + \mu + \mu_{Tu})\, TuSp_i$

$dR/dt = d_{TsL}\, (TsLs_1 + TsLf_1) + \Sigma_i d_{TsAi}\, (TsSn_i + TsSp_i) - [b_R\, (\Sigma_i\lambda_i) + \mu]\, R$

The total population of each of the 4 sub-groups, N, is

$N = S + \Sigma_i(Ls_i + Lf_i + USn_i + USp_i + TsLf_i + TuLf_i + TsLs_i + TuLs_i + TsSn_i + TuSn_i + TsSp_i + TuSp_i) + R$

where Σ_i denotes summation over the compartments representing infection with DS TB and MDR TB.

The force of infection (per-Susceptible rate of infection per unit time) terms, for DS TB (λ_1) and MDR TB (λ_2), are

$\lambda_1 = \Sigma\beta_P\, [b_N\, USn_1 + USp_1 + b_{Tu}\, (b_N\, TuSn_1 + TuSp_1)] / \Sigma N$

$\lambda_2 = \Sigma b_M\, \beta_P\, [b_N\, USn_2 + USp_2 + b_{Tu}\, (b_N\, TuSn_2 + TuSp_2)] / \Sigma N$

where Σ denotes summation over the UK-born and foreign-born members of the relevant ethnic/social group.

Model calibration and fitting

The model is implemented in Python 3 and solved using a forward Euler method. Fitting uses the Levenberg-Marquardt algorithm, which minimizes the sum squared residuals (difference between the data and the fitted model output).

Initial conditions are determined by fitting the model to the observed diagnoses in Black Africans and South Asians by varying the UK transmission rate, the ratio of latent slow-progressors to latent fast-progressors in new arrivals, the percentage of MDR TB cases among new arrivals and the relative transmissibility of MDR TB compared to non-MDR TB. Fitted parameter values are in Supplementary Table 6.

In the main analysis the population rates of birth, death due to non-TB causes, immigration and emigration are assumed to be constant over the 10-year time-horizon, and in sensitivity analysis the immigration rate is halved and doubled.

Supplementary Table 6: Summary of estimated parameter means and 95% ranges from 1,000 simulations.

Parameter	Black Africans	South Asians
Transmission rate of smear-positive DS TB (per person per year), β_P	11.86 (11.34, 12.35)	8.14 (7.78, 8.47)
Ratio of latent slow-progressors to latent fast-progressors in new arrivals, p_m	0.979 (0.978, 0.981)	0.974 (0.972, 0.978)
Percentage of TB infection in new arrivals that is MDR	0.715 (0.714, 0.718)	0.738 (0.735, 0.740)
Relative infectivity of MDR TB compared to DS TB	0.627 (0.624, 0.631)	0.209 (0.208, 0.210)

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