Original research

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 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, versus using molecular testing versus 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% per year.

Results WGS shortens the time to drug sensitivity testing and treatment modification where necessary, reducing treatment and hospitalisation costs, with an INB of £7.1 million. 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 £8.6 million (GeneXpert MTB/RIF) or £11.1 million (Xpert-Ultra). Combined use of Xpert-Ultra and WGS is the optimal strategy we consider, with an INB of £16.5 million.

Conclusion 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 (DST) 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 DST, resulting in cost savings from reduced transmission, avoided or shorter morbidity, and avoided unnecessary treatment and hospitalisations, 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 TB cases in the UK remains high compared with similar European countries.[1] A total of 5758 TB cases (3065 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 WHO End TB Strategy milestone of reducing TB incidence by 50% by 2025 and eventually eliminating 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 to 17 days[6], with a further delay of 20 to 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 to 3 days[8] in most cases). There is a particular benefit for smear-negative cases, which are eventually detected by culture in the standard diagnostic pathway but most of which are detected rapidly 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 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 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 and Black African 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

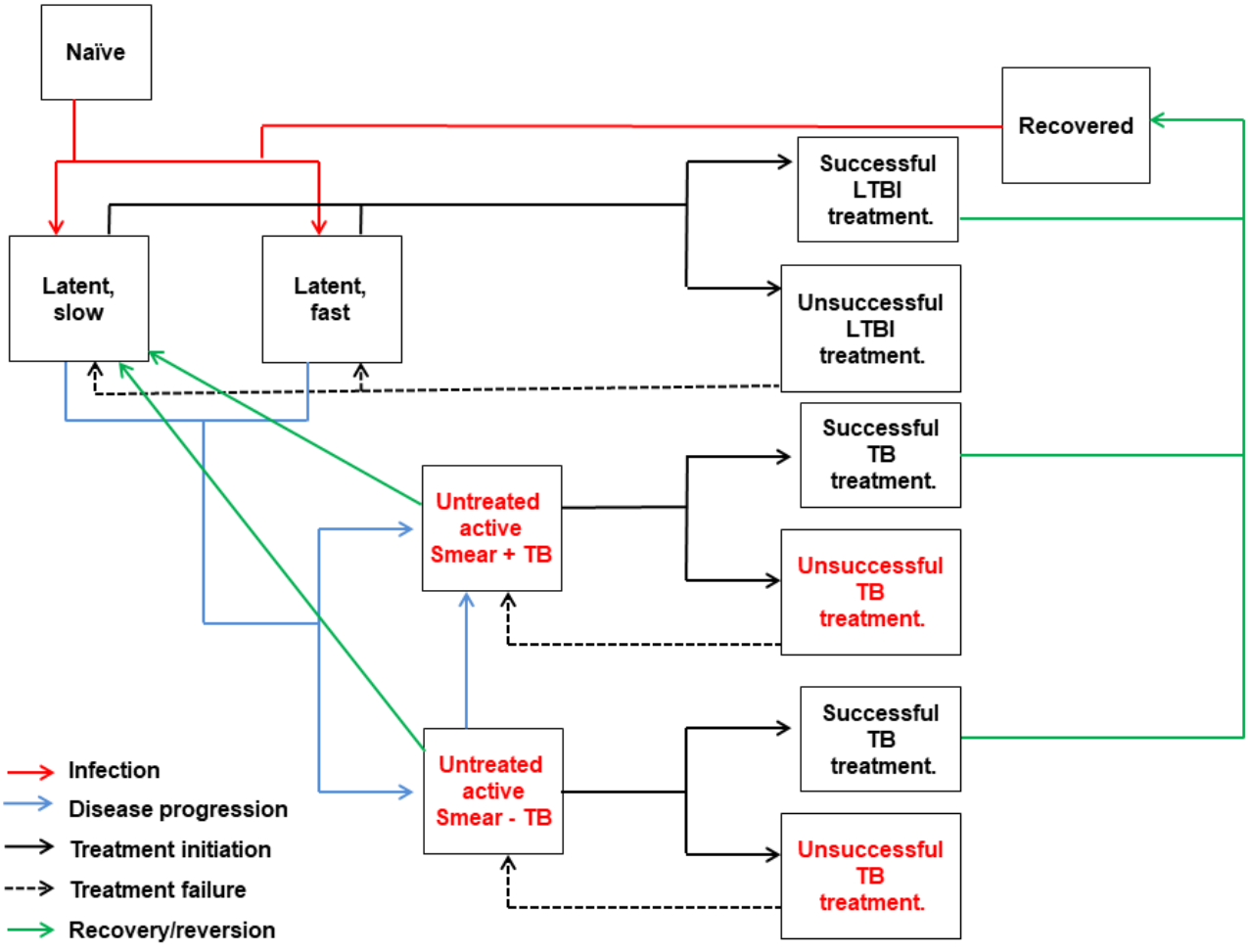

Figure 1 Flow diagram showing the health states representing the natural history and treatment of tuberculosis. Red labels denote the infectious health states. Note that for all infected states (ie, all except Naive and Recovered), there are separate compartments for drug-sensitive and multidrug-resistant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

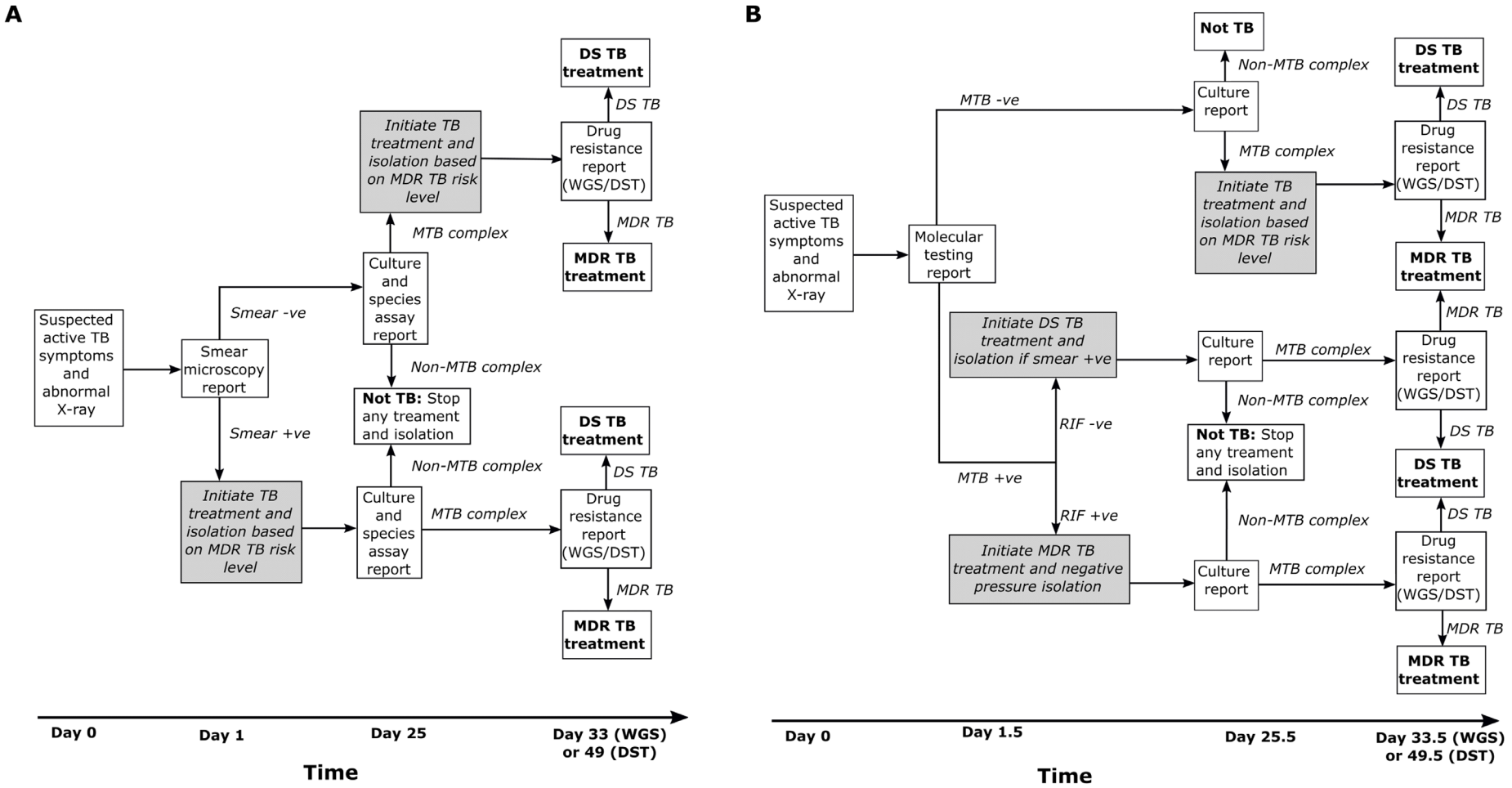

Figure 2 Summary of active TB diagnosis clinical pathways. Panel (a) presents the conventional pathway (baseline strategy) that uses standard culture-based drug sensitivity testing (DST). This pathway takes, on average, 49 days to get the final drug resistance report. Panel (a) also presents strategy (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 to 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. DS, drug sensitive; MDR, multidrug resistant.

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

DS, drug sensitive; DST, drug sensitivity testing; MDR, multidrug resistant; WGS, whole-genome sequencing.

Table 2 Model parameters relating to contact tracing and drug treatment of 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 LTBI	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

IGRA, interferon-gamma release assay; LTBI, latent TB infection.;

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-progressors 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 to appropriate treatment. Additional details of the identification and treatment of TB is given in the supplementary appendix. The parameters related to active TB diagnosis and treatment are given in table 1 and those related to contact tracing, diagnosis and treatment of LTBI are given in table 2.

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 data and population demographic data for England and Wales from the Office for National Statistics (online supplemental table 1). The prevalence of LTBI in migrants was estimated by Pareek *et al*.[18] Parameters relating to natural history of TB 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 fit the model to numbers of annual TB diagnoses in England and Wales by varying the ratio of slow-progressors 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 with 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, that is, the difference between the sum of all costs and all QALYs associated with the baseline clinical pathway versus 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.

Table 3 Model parameters relating to natural history of TB, transmission, test performance, and treatment of active TB

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	73	%	5
Specificity of chest X-ray	63	%	5
Sensitivity of sputum smear microscopy	100	%	5
Specificity of sputum smear microscopy	95	%	5
Sensitivity of X and U for smear-positive TB	100	%	9
Sensitivity of X for smear-negative TB	67	%	9
Sensitivity of U for smear-negative TB	92	%	9
Specificity of X	97.3	%	9
Specificity of U	96.6	%	9
Sensitivity of X and U for MDR detection	97	%	9
Specificity of X and U for MDR detection	98	%	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

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

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, DST, treatment drugs and adverse effects related costs. For treatment costs, we used the cost of a standard 6-month regimen for DS 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 prescribed 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 to 2015 values using the Hospital & Community Health Services 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 summarised in table 5.

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses are conducted. In the former, parameters individually vary across their plausible ranges (online supplemental table 2) with the other parameters fixed at their baseline values. In the probabilistic sensitivity analysis, 1000 parameter combinations are drawn using Latin Hypercube Sampling, using gamma distributions for costs and beta distributions for all other parameters. For each of the 1000 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) and (iii) using molecular testing, or (iv) and (v) using molecular

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	1126	£ 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

DS, drug sensitive; DST, drug sensitivity testing; IGRA, interferon-gamma release assay; LTBI, latent TB infection; MDR, multidrug-resistant; TB, tuberculosis; WGS, whole-genome sequencing.

testing and WGS, compared with the baseline clinical pathway (online supplemental 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, online supplemental figure 1: red bars). However, WGS shortens the time required for DST, allowing for earlier treatment modification where necessary. This shortens slightly the overall average duration of treatment and reduces slightly the average number of patients on treatment (online supplemental figure 1: red bars). Importantly, WGS therefore reduces the average costs of treatment (costs of drugs, isolation and adverse events) (figure 3C, online supplemental figure 2), (online supplemental 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 to £1 087 400) in year 1 and £602 092 (£350 475 to £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 to 0.09) in year 1, increasing to 0.27 (0.19 to 0.35) in year 10 (figure 3B: red bars). Overall, over a 10-year horizon, WGS has an INB of £7.2 million (£3.3 to £11.1 million) with a QALY valued at £20 000 (table 6). The INB of WGS is mostly due to cost savings, with a small QALY gain.

Table 5 Health-related quality of life parameters

Parameter	Value	Source
Utility without TB (ie, normal health)	0.88	23
Utility loss due to untreated active TB	0.19	23
Utility loss associated with inpatient treatment	0.210	5
Utility loss 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

LTBI, latent TB infection.

Molecular testing speeds up the initial diagnosis, resulting in the mean number of patients on treatment for active TB (DS and MDR) increasing by 17 (11 to 22) or 22 (15 to 29) with Xpert or Xpert-Ultra, respectively, in year 1 (online supplemental figure 1: blue and green bars, respectively). In the long term, due to earlier initiation of appropriate treatment and consequently-reduced transmission (online supplemental figure 3: 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, online supplemental 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, online supplemental 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 to 11) for Xpert and 12 (9 to 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 to 80) for Xpert and 81 (59 to 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 INB of £8.7 million (£1.8 to £15.6 million) or £11.2 million (£3.4 to £19 million) 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, online supplemental 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 to 11) or 12 (9 to 15) in year 1 increasing to 62 (44 to 80) or 81 (59 to 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 INB of £14.4 million (£7.2

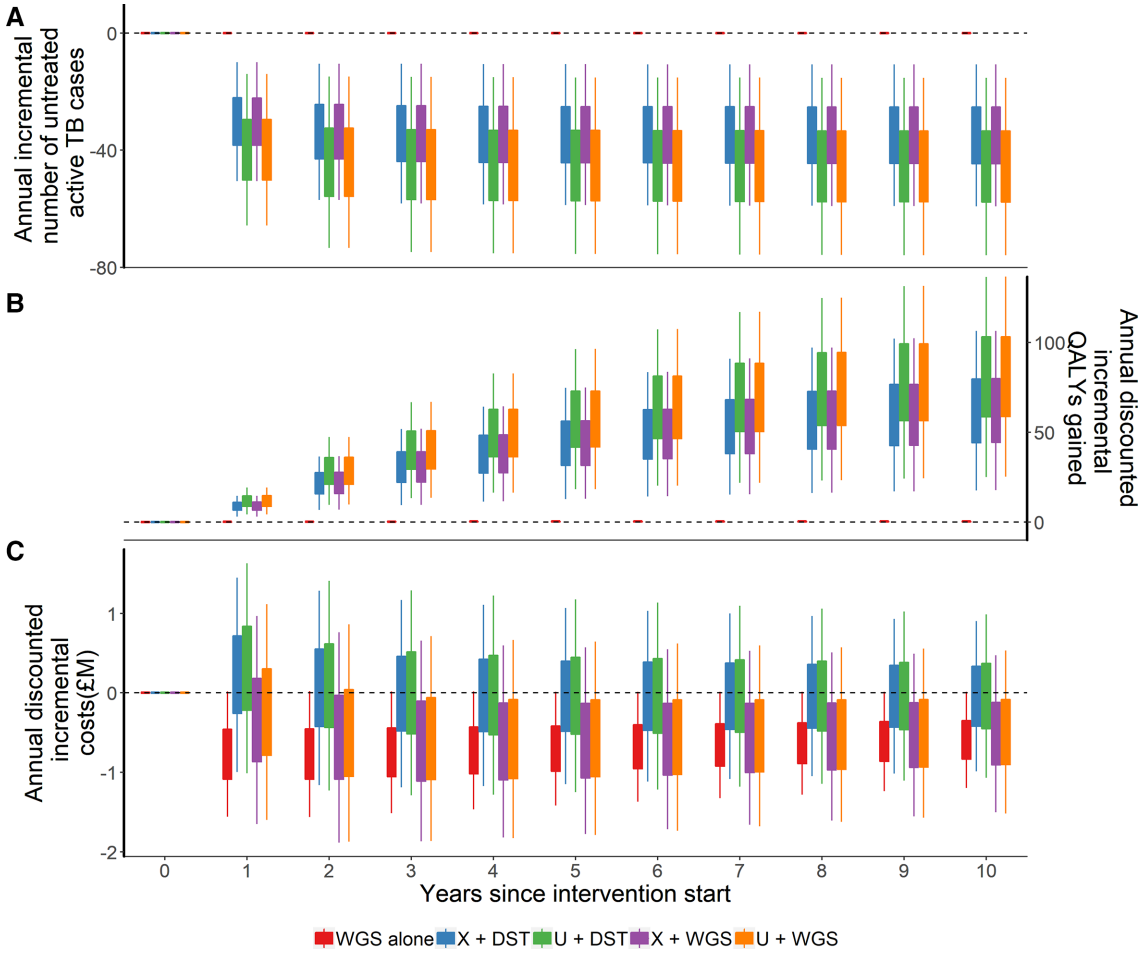

Figure 3 Incremental comparison with the baseline scenario of (a) the annual number of untreated active TB cases (drug-sensitive and multidrug-resistant), (b) discounted annual incremental quality-adjusted life-years (QALYs) gained and (c) discounted annual incremental costs incurred, where standard 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 IQR, and the whiskers the 95% ranges of the calculated values. U, Xpert-Ultra; X, Xpert.

to £21.5 million) for Xpert with WGS or £16.6 million (£8.9 to £24.3 million) 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

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

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

DST, drug sensitivity testing; U, Xpert-Ultra; X, Xpert.

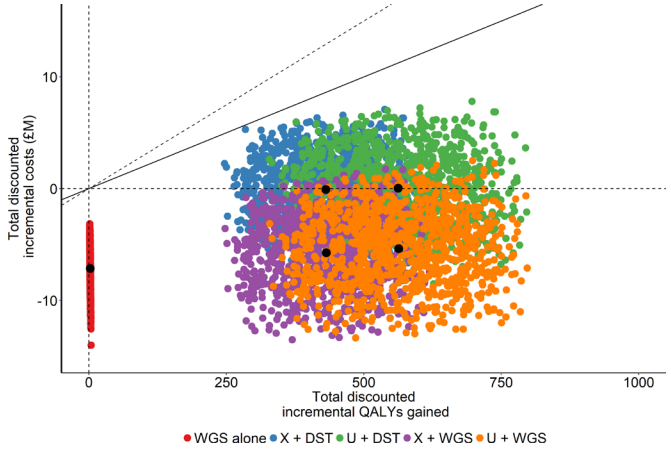

Figure 4 Cost-effectiveness plane showing incremental effects of introducing whole-genome sequencing (WGS) and/or molecular testing into the diagnostic pathway. Results of probabilistic sensitivity analysis using 1000 simulations are shown along with the median value for each strategy (black dots). The bold diagonal line indicates the threshold of £30 000 per quality-adjusted life-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 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). U, Xpert-Ultra; X, Xpert.

samples; and WGS alone ranks fifth in 71.6% of samples (online supplemental 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 with 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% to 2%) and in the immigration rate (halving and doubling) do not change our conclusions (online supplemental 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 we consider (online supplemental table 4) or that X+WGS is the second most cost-effective strategy (online supplemental 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 hospitalisation 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. First, 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. Second, 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 with 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.) Finally, 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,

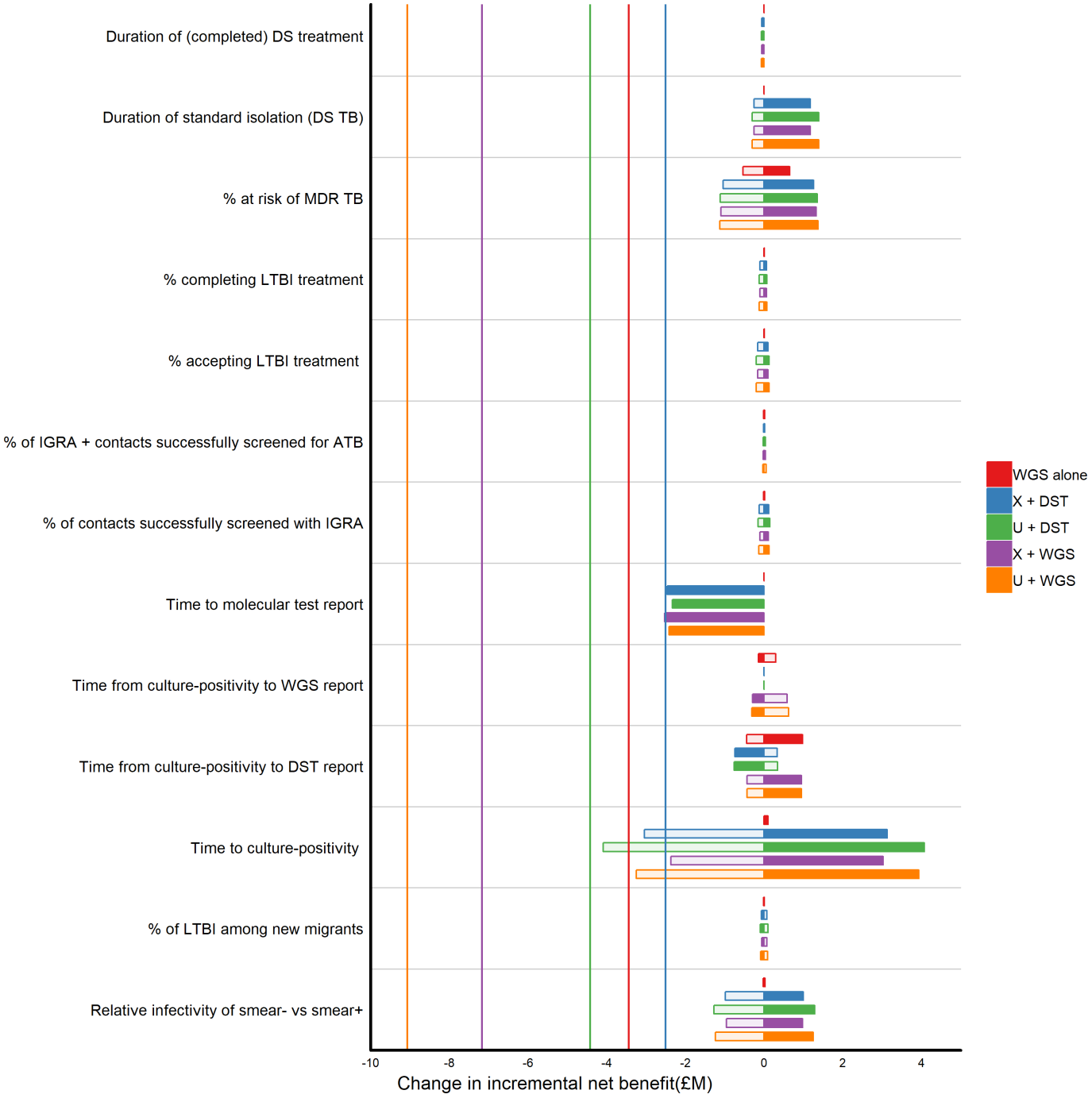

Figure 5 Tornado plot showing effects of the individual parameter changes on model results. Baseline parametersindividually vary from their minimum (open bars) to their maximum (solid bars) for strategies where standard drug sensitivity testing (DST) is replaced by whole-genome sequencing (WGS:red bars), 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-bound or lower-bound parameter value with a quality-adjusted life-year valued at £20 000. The vertical lines represent the change in INB required reduce the INB to zero. ATB, active TB; DS, drug sensitive; IGRA, interferon-gamma release assay; LTBI, latent TB infection; MDR, multidrug-resistant.

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 re-analysed 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 realised in those settings. A cost evaluation of the workflow of WGS in eight 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 (eg, literature estimates of the relative infectivity of smear-negatives compared with smear-positives vary from 13% to 41%) and in potential migration patterns. Extensive sensitivity analysis shows that our conclusions regarding the relative cost-effectiveness of the different diagnostic technologies we consider are unaffected by the uncertainty in the natural history parameter estimates and by large changes in the proportion of TB infection in immigrants that are 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 DS TB or MDR-TB. Considering that NICE recommendations suggest that single non-Rif 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-Rif drug-resistant cases, including in the probabilistic sensitivity analysis, which considers all uncertain parameters.

Our analysis focussed 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 consider 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 WGS have a role to play in accelerating appropriate treatment initialisation, 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]

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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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Patient consent for publication Not required.

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