

The prospective evaluation of the TB strain typing service in England: a mixed methods study

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ABSTRACT

Background In response to rising TB notification rates in England, universal strain typing was introduced in 2010. We evaluated the acceptability, effectiveness and cost-effectiveness of the TB strain typing service (TB-STs). **Methods** We conducted a mixed-methods evaluation using routine laboratory, clinic and public health data. We estimated the effect of the TB-STs on detection of false positive *Mycobacterium tuberculosis* diagnoses (2010–2012); contact tracing yield (number of infections or active disease per pulmonary TB case); and diagnostic delay. We developed a deterministic age-structured compartmental model to explore the effectiveness of the TB-STs, which informed a cost-effectiveness analysis. **Results** Semi-structured interviews explored user experience. Strain typing identified 17 additional false positive diagnoses. The TB-STs had no significant effect on contact tracing yield or diagnostic delay. Mathematical modelling suggested increasing the proportion of infections detected would have little value in reducing TB incidence in the white UK-born population. However, in the non-white UK-born and non-UK-born populations, over 20 years, if detection of latent infection increases from 3% to 13% per year, then TB incidence would decrease by 11%; reducing diagnostic delay by one week could lead to 25% reduction in incidence. The current TB-STs was not predicted to be cost-effective over 20 years (£95 628/quality-adjusted life-years). Interviews found people had mixed experiences, but identified broader benefits, of the TB-STs. **Conclusions** To reduce costs, improve efficiency and increase effectiveness, we recommend changes to the TB-STs, including discontinuing routine cluster investigations and focusing on reducing diagnostic delay across the TB programme. This evaluation of a complex intervention informs the future of strain typing in the era of rapidly advancing technologies.

INTRODUCTION Molecular typing of *Mycobacterium tuberculosis* is a tool for TB surveillance and control. Following increases in TB notification rates in the UK, the Chief Medical Officer recommended the introduction of a national TB strain typing service (TB-STs),³ which was implemented across England in 2010. The TB-STs is a complex public health intervention involving multiple interacting components (laboratory, public health and clinical services). The first *M. tuberculosis* isolate from every

culture-confirmed TB patient is typed using 24 loci mycobacterial interspersed repetitive units-variable number tandem repeats (MIRU-VNTR), a standardised molecular typing method.⁴ Two or more patients are grouped into strain typing ‘clusters’ if they are diagnosed within two years and have indistinguishable MIRU-VNTR strain types (with at least 22 loci). Where specified criteria are met,⁵ cluster investigations are launched to try to establish epidemiological links between clustered patients, thereby identifying the transmission setting and/or an outbreak. A full description of the TB-STs, laboratory guidelines for MIRU-VNTR strain typing and reporting⁶ and a handbook for public health actions, including criteria for cluster investigations,⁵ are available.

Key messages

What is the key question?

- Is the TB strain-typing service (TB-STs) in England an effective or cost-effective public health intervention?

What is the bottom line?

- The TB-STs, which includes universal mycobacterial interspersed repetitive units-variable number tandem repeats (MIRU-VNTR) typing from each TB case and cluster investigations, was not found to be effective or cost-effective in its current form; however, broader benefits for TB control and research support the continuation of the service, though with some significant changes.

Why read on?

- In the context of the rapid development of typing methodologies (eg, whole genome sequencing), political commitment to genomic analysis¹ and the development of Public Health England’s 2014–2019 National TB Strategy,² this evaluation provides important evidence for policymakers and those working in TB control.

It was hypothesised that prospective strain typing could be used in real time to inform public health action. Strain typing could help to identify individuals that are misdiagnosed as having TB due to processing error or contamination from clinic to



laboratory. Cluster investigations could result in better-targeted contact tracing, increasing the detection of recently infected individuals who may benefit from preventive therapy, and accelerating the diagnosis of active cases.

An evaluation of the TB-STs was commissioned alongside the roll-out of the service, providing an opportunity to conduct the first prospective evaluation of a national TB-STs. We present an evaluation of the acceptability, effectiveness and cost-effectiveness of the TB-STs in England.

METHODS

We conducted a mixed-methods evaluation⁷ using routine laboratory, clinic and public health data and primary data collection through semi-structured interviews (table 1). We investigated the occurrence of false positive isolates, the contact tracing yield and diagnostic delay. These parameters, together with data obtained from initial and follow-up cross-sectional surveys evaluating user perception and implementation of the TB-STs,⁸ were used to develop a mathematical model of effectiveness of the TB-STs, which informed a model of cost-effectiveness (figure 1).

False positive detection

We hypothesised that the TB-STs would identify previously unknown incidents of false positive TB isolation, thereby reducing the cost of unnecessary treatment and public health action. Isolates from the three TB reference laboratories were queried if they had consecutive source or reference laboratory identification numbers, or were typed within seven days of each other and had matching 24 MIRU-VNTR profiles. Data on the number of incidents queried and their outcomes were collected. An email survey to source laboratories established whether the incidents were already known to them and whether any patients had been treated unnecessarily.

Contact tracing yield

We hypothesised that the number of infections and TB cases identified through contact tracing for each index case (termed contact tracing yield) would be greater in cases that were part of investigated clusters compared with cases in clusters that were

not investigated. Median contact tracing yield for pulmonary index cases, by clustering and whether the cluster was investigated, were calculated using data from the North Central London (NCL) sector and the Leicester TB service, and included index cases diagnosed in 2011. We did a sensitivity analysis that assumed that index cases with missing contact tracing information yielded no cases of active disease or latent TB infection (LTBI) (as those with positive results would be more likely to be recorded).

Diagnostic delay

We hypothesised that the diagnostic delay (the time between symptom onset and case notification) would be reduced following the introduction of the TB-STs because cluster investigations would lead to undiagnosed TB cases being actively identified earlier. Using all pulmonary TB cases diagnosed in England during 2011 that were part of clusters that were investigated, we compared the median diagnostic delay in cases that were diagnosed after a cluster investigation had started to cases that were diagnosed before the cluster was investigated. The first two cases in each cluster were excluded to remove clusters of two and to take into account possible household transmission.

Data were analysed using Stata V.12. We present medians and IQRs. The Wilcoxon–Mann–Whitney test was used to compare differences in contact tracing yield and diagnostic delay.

Effectiveness of the TB-STs

We used a deterministic age-structured model to explore the possible reductions in TB incidence as a result of the TB-STs over a 20-year period (figure 2). This extends previous models considering the transmission dynamics of *M. tuberculosis* in England and Wales⁹ and recent work on preventive therapy.¹⁰ Details of the model are provided in online supplementary file 1A. The model incorporates contact between individuals and rates of immigration and emigration based on Office for National Statistics data.¹¹ For simplicity, the model considers only pulmonary TB and considers three different epidemiological scenarios—low, medium and high incidence—comparable to that in the white UK-born population (with decreasing annual risk of

Table 1 Median contact tracing yield for pulmonary index cases by clustering and whether the cluster was investigated

	Unique cases	Total clustered cases	p Value	Cases in a cluster that was investigated	Cases that were in a cluster that was not investigated	p Value
Contacts screened						
Index cases (n)	220	97		29	68	
Contacts screened (n)	959	561		191	370	
Median (IQR)	3 (1–5)	4 (2–7)	0.007	4 (2–9)	4 (2–6)	0.474
Contacts with active disease						
Index cases with information available (n)	131	47		14	33	
Contacts screened (n)	593	341		125	216	
Contacts with active disease (n)	14	14		3	11	
Median (IQR)	0 (0–0)	0 (0–0)	0.011	0 (0–0)	0 (0–0)	0.896
Contacts with latent infection						
Index cases with information available (n)	159	59		19	40	
Contacts screened (n)	761	410		145	265	
Contacts with LTBI (n)	148	108		32	76	
Median (IQR)	0 (0–1)	1 (0–2)	0.016	1 (0–2)	1 (0–2)	0.330

LTBI, latent TB infection.

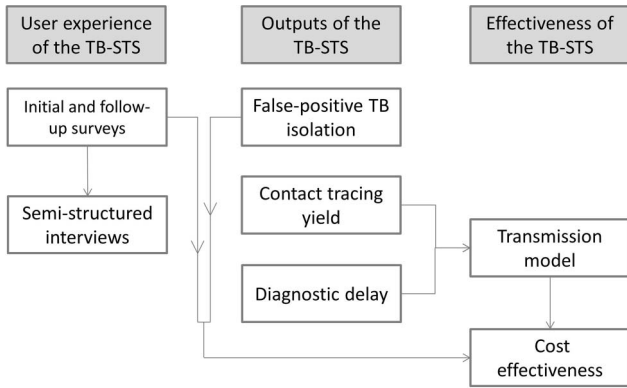


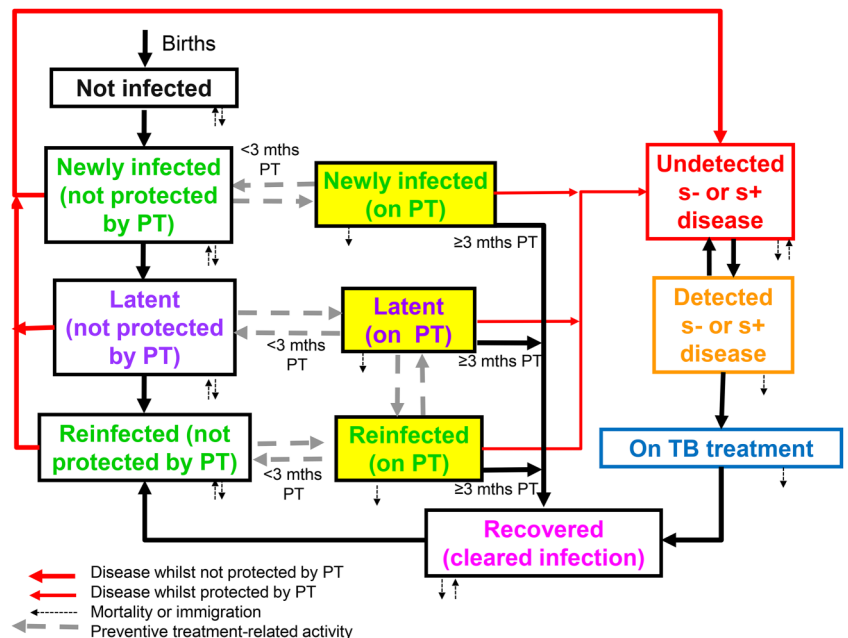
Figure 1 Components of the mixed-methods evaluation. The arrows show how the different components of the evaluation were used to inform the semi-structured interviews and parameters for the transmission and cost-effectiveness models. Detailed results from the initial and follow-up surveys are presented elsewhere.⁸ TB-STS, TB strain typing service.

infection (ARI), non-white UK born (0.1% ARI) and the non-UK born (1% ARI).

In the absence of the TB-STS, the average diagnostic delay is assumed to be that estimated for cases that were not in clusters. We explore the effect of a one week reduction in diagnostic delay due to the TB-STS and assume that patients start TB treatment (on average) two weeks after diagnosis.

In the absence of the TB-STS, 3% of all (recently or latently) infected individuals are assumed to have been detected each year. This proportion is unknown, but was probably low, given the low number of latently infected contacts per index case (see online supplementary file 1). We explore the effect of assuming that it increased to 13% after the introduction of the TB-STS. We assume that uptake of preventive treatment (PT) among those eligible is 95% and 85% complete the course of treatment. In sensitivity analyses, we explore the effect of pessimistic and optimistic assumptions about uptake (30% and 100%, respectively) and completion (50% and 100%, respectively) of PT.

Figure 2 General structure of the transmission model. PT, preventive treatment. Coloured text and shading is used to reflect similar categories of people: yellow shading is used for people on PT, purple text is used for compartments for people with latent infection, green text is used for newly infected or reinfected people, red is used for diseased people and orange, blue and pink text is used for detected cases, people on treatment and the recovered respectively.



Cost-effectiveness of the TB-STS

We aimed to estimate the cost-effectiveness of the TB-STS as an addition to the current system for TB control in England. The cost-effectiveness analysis is illustrated in figure 3, and a full description of the methods and results is given in online supplementary file 1B. The analysis adopted a public sector perspective. Estimates of the cost of setting up and operating the national TB-STS were made based on information from Public Health England (PHE) and the TB Reference Laboratories. Capital costs were annuitised over an assumed 10-year lifetime for equipment. Costs and health effects (in quality-adjusted life-years (QALYs)) were estimated over a 20-year time horizon, and applying a 3.5% annual discount rate to both costs and QALYs (as recommended by the National Institute of Health and Care Excellence (NICE)).¹² The results of the transmission model provided estimates over this 20-year period for each modelled scenario of the number of contacts with latent infection identified, the number of contacts starting preventative treatment, the number of people with active TB diagnosed and starting treatment, as well as the impact on the number of incident TB cases. The costs associated with diagnosis and the treatment of latent and active TB were estimated based on recommended practice and expert opinion. The unit costs of tests, medications, outpatient contacts and inpatient stays were obtained from national sources.^{13 14} The QALY effects of TB were estimated based on case-fatality rates¹⁵ and life expectancy by age of TB incidence, and estimates of the duration and utility loss associated with active disease.¹⁶ We applied the NICE threshold of £20 000–30 000.¹²

User experience

We conducted semi-structured telephone interviews with the TB-STS leads at 24 (of 26) local health protection units (HPUs) in December 2012, following piloting in the other two HPUs. These explored how strain typing information was used by different HPUs and the variation in user experience. Using a thematic analysis, JM extracted the data, coded and categorised it into the themes and subthemes identified across the interviews.

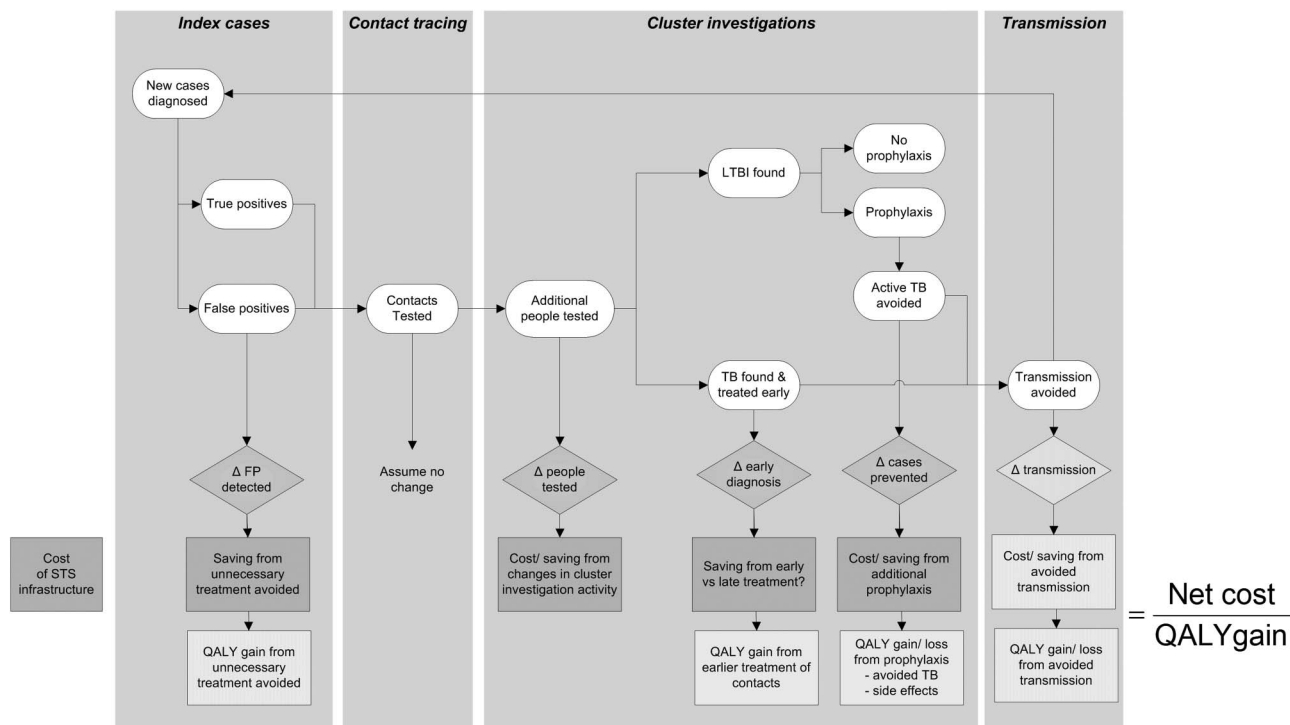


Figure 3 Structure of the cost-effectiveness analysis. QALY, quality-adjusted life-year; TB-STs, TB strain typing service.

RESULTS

False positive detection

Between June 2010 and June 2012, 11 059 TB isolates were typed at the reference laboratories. There were 70 suspected incidents of false positive TB isolation (0.6%), of which 30 (42.9%) were confirmed as false positive, giving a rate of false positive TB isolation in England of 0.3%. Seventeen (56.7%) of the suspected incidents were not known to the source laboratories, and 8 patients were started on unnecessary treatment.

Contact tracing yield

In 2011, for NCL sector and Leicester (table 1), the median number of contacts screened, with active TB and LTBI, was significantly greater in clustered compared with unique cases. No difference was observed between cases that were part of a cluster that was investigated compared with not investigated ($p=0.474$, 0.896 and 0.330, respectively, for contacts screened, with active disease or LTBI). Sensitivity analysis that assumed that index cases with missing contact tracing information yielded no cases of active disease or LTBI found that the comparison of median yields in unique and clustered cases remained the same, but were no longer significant ($p=0.06$ and 0.418 for contacts with active TB and LTBI, respectively). Median yields were broadly similar for cases in clusters investigated or not ($p=0.872$, 0.819 and 0.436, respectively, for contacts screened, with active disease or LTBI).

Diagnostic delay

We identified 318 pulmonary TB cases that were in a cluster that was investigated, of which 238 had information on diagnostic delay (table 2). The median diagnostic delay was not significantly different in cases that were in a cluster that was not investigated ($n=139$; 62 days) or diagnosed before a cluster investigation was launched ($n=117$; 85 days) compared with those diagnosed after the start of the cluster investigation ($n=121$; 77 days).

Effectiveness of the TB-STs

Figure 4 summarises the predictions of the impact of the TB-STs on TB incidence for the three epidemiological scenarios considered. For the white UK-born population, the predicted incidence decreased from 4 to <1 per 100 000 per year between 2005 and 2030 in the absence of additional interventions. Reducing diagnostic delay and/or increasing the proportion of infections that were detected in this population because of the TB-STs is predicted to have little impact on TB incidence (figure 4A).

For populations with a similar incidence to that of the non-white UK-born population, increasing the proportion of

Table 2 The diagnostic delay* for clustered pulmonary cases from 2011, based on whether they were in a cluster that was investigated, and whether they were diagnosed before or after the investigation was launched

	Cases that were in a cluster that was not investigated	Cases in a cluster that was investigated	
		Diagnosed before the investigation was launched	Diagnosed after the investigation was launched
Number of clusters	120	58	38
Number of cases	139	117	121
Mean (SD) (days)	113.2 (117.9)	140.8 (271.9)	113.5 (128.7)
Median (IQR) (days)	62 (32–127)	86 (47–155)	77 (41–157)
p Value†	0.157	0.426	ref

*Time between symptom onset and case notification in days.
†p Value for the Wilcoxon rank-sum test.

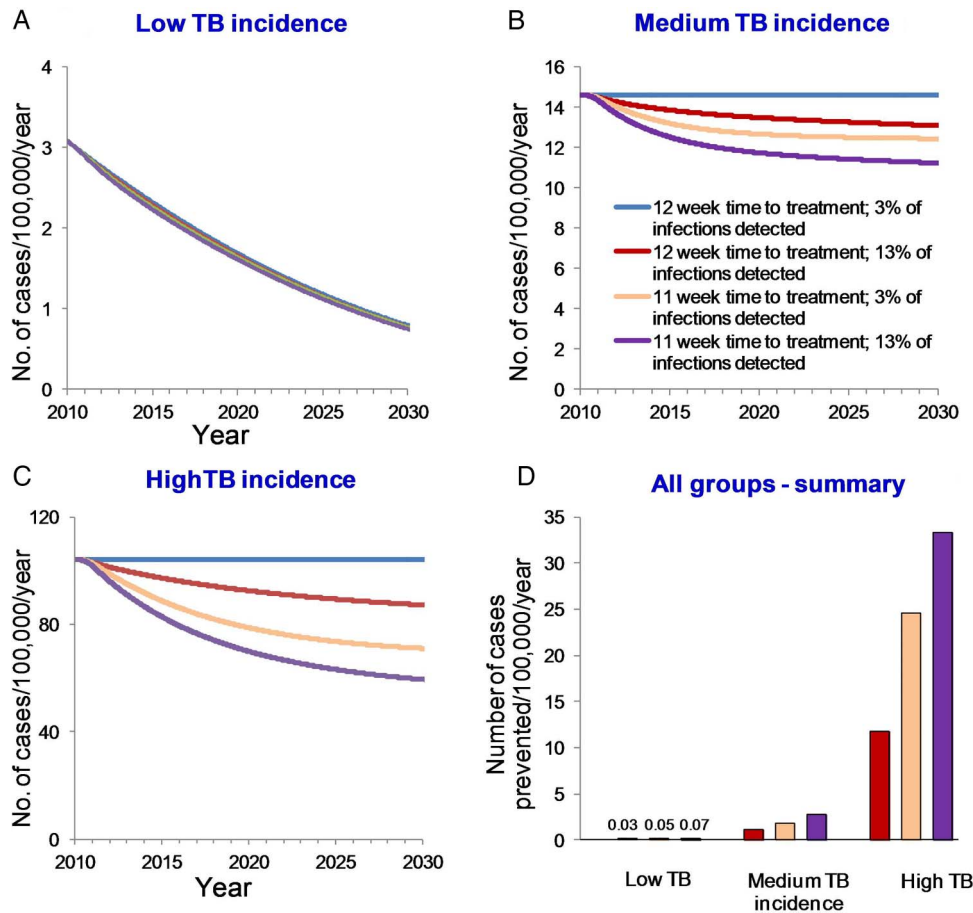


Figure 4 Predicted impact of the TB strain typing service (TB-STs). Predicted impact of reducing diagnostic delay from 12 to 11 weeks and increasing the percentage of infections that are detected through the TB-STs from 3% to 13%. The number of cases occurring per 100 000 per year in a setting in which the TB incidence is (A) similar to that in the white UK-born population (declining annual risk of infection (ARI)); (B) similar to that in the non-white UK-born population group (ARI=0.1% per year); (C) similar to that in a high transmission, non-UK-born population group (ARI=1% per year); and (D) the average annual number of cases prevented per 100 000 population for these scenarios over 20 years after the introduction of the TB-STs.

infections detected from 3% per year to 13% is predicted to lead to a small reduction in TB incidence compared with that in the absence of the TB-STs. For example, for this scenario, 20 years after the introduction of the TB-STs, the predicted incidence is 11% less than that in the absence of TB-STs (figure 4B) (ranging between 4% and 12% for pessimistic and optimistic assumptions, respectively, relating to uptake and completion of PT), with about one case prevented per 100 000 per year over this period (figure 4B). Combining an increase in the proportion of infections detected to 13% per year with a one week reduction in diagnostic delay is predicted to approximately double the reduction in TB incidence, with just over two cases prevented per 100 000 per year over the period 2010–2030 (figure 4D).

Of the scenarios considered, the TB-STs is predicted to lead to the greatest reductions in TB incidence in high transmission settings, similar to the non-UK-born population. For this scenario, 20 years after the introduction of the TB-STs, the predicted incidence is about 15% less than that in the absence of the TB-STs (figure 4C), with about 10 cases prevented per 100 000 per year over this period (figure 4C). When an increase in the proportion of infections detected to 13% per year is combined with a one week reduction in diagnostic delay, the reduction in TB incidence increases to 40% (figure 4C), with >30 cases prevented per 100 000 per year over the period 2010–2030 (figure 4D).

Cost-effectiveness of the TB-STs

The cost of implementing and running the TB-STs was estimated at approximately £1 m per year. Assuming the TB-STs leads to a small improvement in the contact tracing yield in a medium-incidence population (similar incidence to that of the non-white UK-born population), the service was not estimated to be cost-effective over a 20-year period: £95 628 per QALY if the proportion of LTBI detected were to increase from 3% to 4%. Assuming an increase from 3% to 13%, the estimated incremental cost per QALY gained (£54 539) still did not reach a level considered to be cost-effective in the UK. These results were much more sensitive to reductions in the diagnostic delay: for example, if the TB-STs reduced diagnostic delay by one week, the system would save £85 million and gain over 16 000 QALYs over 20 years.

User experience

The main themes that emerged from the semi-structured interviews are shown in box 1. The interviews demonstrated a wide variation in user engagement with the TB-STs, use of the strain typing information and experience of the service. Many strain typing leads felt that the potential added value of strain typing had not been realised with the current service; however, strain typing should not be stopped.

Box 1 User experience of the TB-STs. Main themes that emerged from the semi-structured interviews with health protection staff

- ▶ *Variation in processes.* The way the strain typing information was used and acted on at the local level was dependent on context, for example, the availability of resources and local priorities. Importantly, no additional funds were allocated for local health protection teams to act on the information provided by the TB-STs. Some areas never used the information, in other areas it had been integrated into normal practice.
 - “We have the luxury to spend more time to have a quick look if they are potentially linked.”
 - “We have done quite a bit of work getting a standardised form for TB nurses to use...they’ve adapted the questionnaire but I cannot give you assurance that it is being implemented properly. In my area the service doesn’t see it as a priority.”
 - “I have some concern on ... the full cluster investigation—in the good will of our NHS partners and how much they contribute to that. There are mutterings about not being commissioned to do them [the investigations]”.
- ▶ *Uses of the TB-STs.* The TB-STs was reported to be useful for confirming/refuting suspected transmission, informing case definitions in ongoing outbreaks, helping guide contact tracing, and monitoring and evaluating local TB services. However, many people reported that the information arrived too late, it generated more work and created confusion.
 - “By the time we get the report we already know about it and have carried out actions. It’s always too late... [the service] is not generating new information.”
- ▶ *Impact of the TB-STs.* Many respondents felt that the TB-STs had not yet delivered a public health benefit and that it generated more work that led to little benefit. The TB-STs added value in other more general ways that strengthen the TB service as a whole, such as engaging TB nurses with the public health aspects of TB. Despite the lack of outcomes and the drain on resources, people felt that it would be ‘regressive’ to stop the STs.
 - “Hasn’t added benefits so far, but hasn’t highlighted anything we weren’t already dealing with...Very happy to receive the strain typing—wouldn’t want to not receive it.”
 - “It’s a good thing. It’s been helpful for us. It’s a good way of getting people more interested in more work around TB. Doing cluster investigations has been a good way also of building up relations with the nurses.”

DISCUSSION

This is the first mixed-methods prospective evaluation of a national TB-STs, a complex intervention, and informs the future of such services in the era of rapidly advancing typing technologies. The evaluation approach can be applied to any future typing method. The TB-STs, which includes universal MIRU-VNTR typing from each TB case and cluster investigations, was not found to be effective or cost-effective in its current form. Mathematical modelling to explore the potential impact of increasing the proportion of infections detected and decreasing diagnostic delay suggests that the TB-STs would have

little value in reducing TB incidence in low-incidence settings (similar to that in the white UK-born population). Of the scenarios explored, the greatest potential impact is estimated in high-incidence settings, if the proportion of LTBI detected increases to 13% and diagnostic delay reduces by one week. According to the NICE threshold of £30 000 and assuming that (at most) the TB-STs would achieve only a modest increase in latent infections identified, the service was not predicted to be cost-effective over a 20-year period (£95 628 per QALY). However, even a small reduction in time to diagnosis of active cases has the potential to lead to a large decline in TB incidence over 20 years in some populations, leading to large cost savings. This information must be weighed up with the broader benefits of the service described in box 2 and insights captured through semi-structured interviews (such as the increased engagement with TB control at the local level and standardisation of contact tracing practices (box 1)). To reduce costs, improve efficiency and increase effectiveness, we have recommended continuation of the TB-STs but with significant changes to the service (see online supplementary file 2). These include discontinuation of routine cluster investigations and a focus on reducing diagnostic delay in the TB programme as a whole, of which the TB-STs is one part.

Complex public health interventions, especially when these are at a large-scale level, are often implemented in a way that makes rigorous evaluation a challenge.¹⁷ There were no adequate control data from before the intervention, and the national roll-out of the TB-STs made a cluster-randomised controlled study design impossible. Parallels can be drawn between the TB-STs and the National Chlamydia Screening Programme where assessing the success of the programme has been difficult.¹⁸

The lack of observed impact of the TB-STs may be due to (1) a true lack of impact, (2) the inability to observe the impact within the observation period or (3) the (limited)

Box 2 Examples of the wider benefits of a national TB strain typing service (TB-STs)

- ▶ To understand the national and local epidemiology of TB: TB strain typing in New York has enabled molecular epidemiological analyses to contribute to understanding of the TB epidemic and they have been able to tailor their public health response, especially among those with HIV or multidrug-resistant TB (MDR-TB).²⁸ National strain typing in the Netherlands has contributed greatly to their understanding of TB epidemiology.²⁹
- ▶ To understand the molecular epidemiology of TB, thereby contributing to the global knowledge of TB.²⁶
- ▶ To monitor and evaluate TB programmes: an outreach screening service in the homeless and drug-using population in Rotterdam was evaluated using strain typing;²² long-term trends are used to evaluate TB control strategies, for example, in San Francisco and the Netherlands.²⁹
- ▶ To meet international obligations for molecular surveillance: European Centre for Disease Prevention and Control Molecular surveillance of MDR-TB in Europe project.³⁰
- ▶ To create a national repository of strain types: this can be used for national and local analyses, larger research projects, and provides the opportunity for national and international collaboration.

implementation of the service. Firstly, there may have been no impact, even if the TB-STS had been implemented perfectly because the 2-year evaluation period was relatively short to observe an impact. Strain typing information may not reach TB service staff early enough to inform contact screening decisions in a meaningful way (box 1). Possible reasons for this include the time needed to produce a typing result and/or the lack of sufficiently sophisticated reporting software. Furthermore, inadequate resources to act may be contributing—the generation of the strain typing information was well-resourced but no funds were allocated to local TB teams to embed the information in their decision processes (box 1). Secondly, we are evaluating the marginal impact of the TB-STS in a setting where a TB control programme already exists (which includes traditional TB control strategies, such as stone in the pond contact tracing).¹⁹ Measuring the impact of the TB-STS in isolation may therefore not be feasible. Thirdly, there was limited implementation of the service due to delayed development of clustering software as part of an integrated TB management system to capture linked cases, contacts and strains; and limited resources for local public health action. This also influenced the ability to evaluate the TB-STS, where suboptimal data collection systems meant that although some primary data collection was conducted, the evaluation was reliant on routine data sources to estimate model parameters.

The findings of this study are important given the current trend to introduce and upgrade national typing services.^{20 21} The literature shows the value of TB typing in specific populations²² and for outbreaks,^{23 24} but there are few studies that look at the public health value of nationwide TB strain typing and the subsequent cluster investigations (box 3). Consistent with our findings, evidence from the Netherlands suggests that one may not expect to see an effect of a national TB-STS on contact tracing yield.²⁵ The added strength of our study is the use of these outputs to predictively model the effect of the TB-STS on transmission over a 20-year period and to explore cost-effectiveness. While the broader benefits of the TB-STS cannot be quantified, the importance of the service for research and surveillance is acknowledged in box 2. Put simply, the benefits are twofold. Firstly, there is the value of a national dataset combining clinical, epidemiological and molecular information for each TB patient. This will lead to the possibility of multiple future analyses, TB programme evaluations and research projects. Secondly, the outcomes of such projects will lead to the even broader benefits of increased understanding about TB epidemiology, lineage, transmission and control. These benefits, however, may not require prospective strain typing, but could be gained through retrospective strain typing.

In the context of the rapid development of typing methodologies (eg, whole genome sequencing), political commitment to genomic analysis¹ and the development of PHE's 2014–2019 National TB Strategy,² this evaluation provides important evidence for policymakers. Unless current or new typing and diagnostic techniques accelerate diagnosis (including through analysis of primary specimens), reduce diagnostic delay, dramatically reduce the time it takes to type and/or are embedded in a user-friendly standardised TB management system, the adoption of such a method alone is unlikely to impact on TB control. Comprehensive TB control strategies that aim to reduce TB incidence over the next decades need ongoing evaluation of proposed interventions. This includes evaluation of effective public health responses and appropriate use of strain typing, clinical and epidemiological information.

Box 3 'Research in context'

Systematic review

Universal national TB strain typing services (TB-STS) have been implemented in various countries including the USA, the Netherlands, Denmark, Slovenia and England, and more countries are planning such services. We searched PubMed for articles describing national TB-STS using the terms "tuberculosis" and "strain typing" or "genotyping" or "fingerprinting" or "miru vntr" or "rflp" and "routine" or "service" or "universal" or "nationwide". We conducted an additional search in PubMed using the search terms "tuberculosis" and "strain typing" or "genotyping" or "fingerprinting" or "miru vntr" or "rflp" and "cost-effectiveness". Although universal typing services have contributed greatly to the local and international understanding of TB epidemiology,²⁶ no service-wide evaluations of their effectiveness and cost-effectiveness have been conducted. This is often the case with complex public health interventions. Despite the lack of evidence for the effectiveness of such a service, there is a political and scientific momentum to upgrade the current services based on mycobacterial interspersed repetitive units-variable number tandem repeats typing to whole genome sequencing.^{1 27}

Interpretation

Based on the available quantitative data, there was no evidence to suggest that the current TB-STS in England is an effective or cost-effective public health intervention (this finding can be applied to the TB-STS, whatever the typing methodology applied); however, the broader benefits for TB control and research at a modest cost support the continuation of the service following recommended changes. Public health interventions are rarely evaluated despite mixed-method evaluations being very informative. Decision-makers planning and implementing complex public health interventions should ensure the collection of good quality data for the prospective evaluation of such interventions and be responsive to the findings in order that public funds are allocated effectively.

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The Prospective Evaluation of the National Tuberculosis Strain-typing Service in England: A Mixed Methods Study

Supplementary File 1: The Effectiveness and Cost effectiveness of the TB-STS

Supplementary File 1A: Effectiveness of the TB-STS

Overview

Figure 2 in the main text shows the general structure of the model. The model is age structured, with the population stratified into single year age groups and deterministic, describing what happens on average over time, using weekly time steps (see below for further details, the difference equations and input parameters). The model includes immigration and emigration and considers the following three epidemiological scenarios:

Scenario 1. Low incidence, comparable to that in the white UK population. For this scenario, the predicted TB incidence increases with increasing age, reaching about 7 per 100,000 for those aged ≥ 55 years (Supplementary Figure 1A), which is consistent with observed data (2-5 and 4-9 per 100,000 per year in 2011).¹ Here the infection risk is assumed to have declined since 1950² and has remained roughly constant since 1980, a small proportion ($<10\%$) of those aged <55 years are assumed to have been infected, as compared with 50% on average of those aged ≥ 55 years (Supplementary Figure 1B). The proportion of disease that is attributable to recent transmission decreases steadily with increasing age, reaching $<10\%$ for those aged ≥ 55 years (Supplementary Figure 1C).

2. Medium incidence, comparable to that in the non-white UK-born in which the disease incidence is about 20 per 100,000 per year, as compared with 9-55 per 100,000 in the observed 2009 data.³ The annual risk of infection (ARI) is assumed to have been constant over time at 0.1% per year, with a low proportion of individuals who have been infected (average of $<20\%$ for those aged ≥ 55 years).

3. High incidence, comparable to that in the non-UK born in which the disease incidence is about 120 per 100,000 year, which is comparable to observed data (notification rates of 59-273 per 100,000 in 2009, depending on the ethnic group). The ARI is assumed to have been constant over time at 1% per year, similar to

that in some developing countries, with proportion of individuals who have been infected increasing with increasing age to reach an average of 20% for those aged ≥ 55 years.

For scenarios 2 and 3, the assumed in- and out- migration rates are 8 and 6 per 1000 per year respectively, based on data from the period 2000-2010.⁴ In-migrants are assumed to be aged 15-54 years; the assumed out-migration rate is identical for all ages. The TB prevalence among in-migrants is assumed to be 0.02%, which is consistent with the predicted prevalence in the model for an ARI of 1%/year. The TB incidence in these individuals in their native populations is similar to that shown in (Supplementary Figure 1A) for an ARI of 1% year, which is similar to that in the non-UK born population in the UK,¹ but slightly lower than that estimated among immigrants, shortly after entering the UK (320-400 per 100,000 in 1998).⁵ Based on recent data, we assume that no cases are detected when entering the UK.⁶ The model parameters are shown in Supplementary Table 1.

Model assumptions

Individuals are assumed to be born uninfected and are infected at a rate $\lambda(t)$ (the force or risk of infection). The force of infection depends on the prevalence of infectious individuals and is calculated as the product of the prevalence of infectious individuals and the effective contact rate, c_e , defined as the average number of individuals effectively contacted by each infectious person per unit time. An effective contact is defined as one that is sufficient to lead to transmission if it occurs between an uninfected (“susceptible”) person and an infectious person.⁷ The effective contact rate is calculated so it leads to given values for the annual risk of infection (see below).

Following infection, individuals are assumed to face an increased rate of developing disease during the first 5 years after infection (“primary” disease), which decreases with time since infection, after which they can either experience disease through reactivation or following reinfection. The rates at which they develop disease through the various mechanisms are age-dependent and are identical to those estimated in previous work.⁸ The rate of disease onset following reinfection is less than that following new “primary” infection, due to some immunity resulting from previous infection.^{8,9}

As in previous versions of the model, the proportion of disease that is sputum smear or culture-positive (infectious) is assumed to increase with age, based on observed data.⁸ For simplicity, females are not modelled

explicitly in the model. For simplicity, the effects of HIV are also not modelled, given the low prevalence of HIV (2.4 per 1000) in England and Wales by 2008.¹⁰

Following disease onset, cases are assumed to be detected at a constant rate, with an average time to detection of 10 weeks. Given this relatively short time to detection, progression from smear negative to smear positive TB is not modelled explicitly.

Following detection, cases are assumed to start TB treatment after an average period of 2 weeks, so that the average time from disease onset to detection is 12 weeks, as observed in the strain typing data. 82% of those who start treatment are assumed to complete it, with the remainder dying (7%), defaulting from treatment (5.5%) or being lost to follow-up (5.5%).¹¹ Those who default from treatment are assumed to return to the undetected category and remain infectious. TB treatment is assumed to last a fixed period of 6 months. TB treatment is assumed to clear infection and individuals can develop disease subsequently only following reinfection. The rate at which they develop disease following reinfection is assumed to be identical to the rate at which those who have been infected for at least five years (described as those in the “latent” category in Figure 2 in the main text) develop disease following reinfection.

Based on observed data, 95% of those aged <35 years who are identified as having been infected, according to TST/IGRA, are assumed to start preventive treatment (PT) for 3 or 6 months, with 85% of these completing the full course.⁶ National policy dictates that PT is not given to those under 35 years.¹² PT is assumed to provide 65% protection against disease whilst individuals are taking it.^{13,14} Given complete compliance, the full course of PT is assumed to fully cure the infection, so that individuals can only develop disease subsequently following reinfection. It is also assumed that individuals who have either previously had TB treatment or PT would not be provided PT again.

In the absence of the TB-STIS, a small percentage (3%) of all infected individuals is assumed to have been detected and treated each year. This proportion is unknown, but was probably very low, as implied by the number of tuberculin-positive contacts of tuberculosis cases that were identified for each tuberculosis case that was investigated. For example, data on contact tracing activity suggested that after the introduction of the TB-STIS, on average, about four contacts of each identified tuberculosis case who was not in a cluster, was traced, with one of the contacts being tuberculin positive. Since approximately 9000 cases were reported in England in

2009,³ this suggests that about 9000 tuberculin-positive people were identified. If the average prevalence of tuberculous infection in England is less than 10% and given a population of 55 million in England and Wales,¹⁵ then the proportion of prevalent infections that is detected each year is likely to be less than 1%. An analogous calculation suggests that if the average prevalence of tuberculous infection in England was less than 1%, then the proportion of prevalent infections that is detected each year is likely to be less than 2%.

The amount by which the proportion of infections that were detected after the introduction of the TB-STS increased is also poorly understood. However, it is unlikely to have increased substantially, given that the number of contacts that were screened per TB case for cases who were in a cluster was similar to that for cases who were not in a cluster. We here assume that it increases by a factor of three, i.e. to 13% per year, which is likely to be close to or exceed the upper limit on the likely value.

The proportion of those eligible who take up preventive treatment, once detected, is also unknown, as is the proportion of those who start taking preventive treatment who complete it. We have assumed values of 95% (minimum and maximum values of 30% and 95% respectively) for the former and values of 85% (minimum and maximum values of 50% and 100% respectively) for the proportion of those starting preventive treatment who complete it. These values are plausible, and are consistent with those used in previous decision analyses,¹⁶ although their accuracy is unclear. Studies of contact tracing activities in the USA from the period 1996-7 found that about 74% of tuberculin-positive contacts of tuberculosis cases started preventive treatment, with 56% completing it.¹⁷ Similar data from the UK are limited. For example, studies have sometimes reported the numbers or proportions of contacts who started preventive treatment, without providing the numbers who were eligible or who completed preventive treatment.¹⁸

Model equations

The model was set up using weekly time steps using the difference equations below. The model was written using the C programming language. Supplementary Table 1 provides the main parameters and variables; Supplementary Table 2 summarizes the definitions of the compartments and variables in the model; any additional parameters are defined below.

People were allowed to experience the benefits of PT (i.e. reduced rates of disease onset) or lack of benefit in the same week as they started or stopped PT respectively. To simplify the equations whilst allowing this to

occur, the population in the PT-related compartments was transferred into subsequent strata at the end of each time step, once other transitions had been accounted for.

Uninfected compartment

$$U_a(t + \delta t) = U_a(t)(1 - \lambda(t) - \mu_a - m_{tb-,a}) \quad \text{Equation 0.1}$$

Recently (primary) infected compartment

Recently (primary) infected people who are not on PT

$$E_{z-,a}(t + \delta t, 0) = (1 - i_{z+}(t))\lambda(t)U_a(t)(1 - d_{p,z-,a}(0)) \quad \text{Equation 0.2a}$$

$$E_{z-,a}(t + \delta t, s_i + \delta s_i) = (1 - i_{z+}(t))E_{z-,a}(t, s_i)(1 - d_{p,z-,a}(s_i) - \mu_a - m_{tb-,a}) + M_{in,E,a}(t, s_i) \quad \text{Equation 0.2b}$$

Recently (primary) infected people who are on PT

$$E_{z+,a}(t + \delta t, s_i + \delta s_i, 0) = E_{z-,a}(t, s_i)i_{z+,a}(t)(1 - d_{p,z+,a}(s_i) - \mu_a - m_{tb-,a}) \quad \text{Equation 0.3a}$$

$$E_{z+,a}(t + \delta t, 0, s_z) = i_{z+,a}(t)\lambda(t)U_a(t) \quad \text{Equation 0.3b}$$

$$E_{z+,a}(t + \delta t, s_i + \delta s_i, s_z + \delta s_z) = E_{z+,a}(t, s_i, s_z) - E_{z+,a}(t, s_i, s_z)(d_{p,z+,a}(s_i) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.3c}$$

Recently (primary) infected people who have previously been on PT

$$E_{z_p,a}(t + \delta t, s_i + \delta s_i) = E_{z_p,a}(t, s_i) - E_{z_p,a}(t, s_i)(d_{p,z-,a}(s_i) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.4}$$

Latent and Reinfected compartments

To ensure that no one in the population could start PT multiple times, the latent and reinfected compartments are subdivided according to whether or not they have been on PT previously. For simplicity, this detail is omitted

from the model diagram (Figure 2 in the main text). However, the disease-related compartments have not been stratified according to previous PT – this simplification is unlikely to affect conclusions since a negligible proportion of the model population is likely to experience PT twice and treatment for tuberculosis disease.

People with Latent infection

$$L_{z-,a}(t + \delta t) = L_{z-,a}(t)(1 - i_{z+,a}(t))(1 - d_{n,z-,a} - \lambda(t) - m_{tb-,a} - \mu_a) + M_{in,L,a}(t) + R_{z-,a}(t, T_R) + E_{z-,a}(t, T_E) \quad \text{Equation 0.5a}$$

$$L_{z+,a}(t + \delta t, 0) = L_{z+,a}(t)i_{z+,a}(t)(1 - d_{n,z+,a} - \lambda(t) - m_{tb-,a} - \mu_a) \quad \text{Equation 0.5b}$$

$$L_{z+,a}(t + \delta t, s_z + \delta s_z) = L_{z+,a}(t, s_z) - L_{z+,a}(t, s_z)(d_{n,z+,a} + \lambda(t) + m_{tb-,a} + \mu_a) + E_{z+,a}(t, T_E, s_z) + R_{z+,a}(t, T_R, s_z) \quad \text{Equation 0.5c}$$

People who have completed PT but have not been reinfected in the previous 5 years

$$P_{e+,a}(t + \delta t) = P_{e+,a}(t) - (\lambda(t) + m_{tb-,a} + \mu_a)P_{e+,a}(t) + V_{z+,a}(t, T_{z_{\max}}) + L_{z+,a}(t, T_{z_{\max}}) \quad \text{Equation 0.6a}$$

$$P_{e-,a}(t + \delta t) = P_{e-,a}(t) - P_{e-,a}(t)(d_{n,z-,a} + \lambda(t) + m_{tb-,a} + \mu_a) + R_{z-,a}(t, T_R) + E_{z-,a}(t, T_E) \quad \text{Equation 0.6b}$$

Reinfected people who are not on PT

$$R_{z-,a}(t + \delta t, 0) = (1 - i_{z+}(t))\lambda(t)(L_{z-,a}(t) + V_{z-,a}(t))(1 - d_{x,z-,a}(0)) \quad \text{Equation 0.7a}$$

$$R_{z-,a}(t + \delta t, s_r + \delta s_r) = (1 - i_{z+}(t))R_{z-,a}(t, s_r)(1 - d_{x,z-,a}(s_r) - m_{tb-,a} - \mu_a) + M_{in,R,a}(t, s_r) \quad \text{Equation 0.7b}$$

Reinfected people who are on PT

$$R_{z+,a}(t + \delta t, s_r + \delta s_r, 0) = R_{z+,a}(t, s_r)i_{z+,a}(t)(1 - d_{x,z+,a}(s_r) - m_{tb-,a} - \mu_a) \quad \text{Equation 0.8a}$$

$$R_{z+,a}(t + \delta t, 0, s_z) = \lambda(t)(L_{z+,a}(t, s_z) + V_{z+,a}(t, s_z))(1 - d_{x,z+,a}(0)) \quad \text{Equation 0.8b}$$

$$R_{z+,a}(t + \delta t, s_r + \delta s_r, s_z + \delta s_z) = R_{z+,a}(t, s_r, s_z) - R_{z+,a}(t, s_r, s_z)(d_{x,z+,a}(s_r) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.8c}$$

Reinfected people who have previously been on PT

$$R_{z_p,a}(t + \delta t, 0) = \lambda(t)(P_{e+,a}(t) + P_{e-,a}(t))(1 - d_{x,z-,a}(0)) \quad \text{Equation 0.9a}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) - R_{z_p,a}(t, s_r)(d_{x,z-,a}(s_r) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.9b}$$

Cases who have not yet been detected

To allow calculation of the proportion of tuberculosis cases that have been reinfected recently, cases which have not yet been detected are further stratified according to the mechanism by which they are experiencing disease (i.e. (exogenous) reinfection or (endogenous) reactivation). Once detected (“found”), cases remain in the detected compartments for a maximum period of 6 months (denoted by $T_{f_{\max}}$), unless they start treatment in the meantime, after which they are redistributed into the undetected compartments, according to their relative size. Considering cases experiencing disease through endogenous reactivation, this redistribution is calculated using

$$p_{Dn,s,a} = \frac{D_{n,s,a}(t, T_{o_{\max}})}{D_{p,s,a}(t, T_{o_{\max}}) + D_{n,s,a}(t, T_{o_{\max}}) + D_{x,s,a}(t, T_{o_{\max}})}$$

the equation

The equation considering cases of primary or exogenous disease is analogous.

Cases experiencing disease because of primary infection, who have not yet been detected

$$D_{p,s+,a}(t + \delta t, 0) = o_{s+,a} \sum_{s_i=0}^{T_E} d_{p,z-,a}(s_i)(E_{z-,a}(t, s_i) + E_{z_p,a}(t, s_i)) \\ + o_{s+,a} \sum_{s_i=0}^{T_E} \sum_{s_z=0}^{T_{Z_{\max}}} E_{z+,a}(t, s_i, s_z) d_{p,z+,a}(s_i)$$

Equation 0.10a

$$D_{p,s-,a}(t + \delta t, 0) = (1 - o_{s+,a}) \sum_{s_i=0}^{T_E} d_{p,z-,a}(s_i)(E_{z-,a}(t, s_i) + E_{z_p,a}(t, s_i)) \\ + (1 - o_{s+,a}) \sum_{s_i=0}^{T_E} \sum_{s_z=0}^{T_{Z_{\max}}} E_{z+,a}(t, s_i, s_z) d_{p,z+,a}(s_i)$$

Equation 0.10b

$$D_{p,s,a}(t + \delta t, s_o + \delta s_o) = D_{p,s,a}(t, s_o) + (1 - p_{in,f,s}) M_{in,D_p,s,a}(t, s_o) \\ - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) D_{p,s,a}(t, s_o)$$

Equation 0.10c

$$s_o < T_{o_{\max}}$$

$$D_{p,s,a}(t + \delta t, s_o + \delta s_o) = D_{p,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) D_{p,s,a}(t, s_o) \\ + (1 - p_{in,f,s}) M_{in,D_p,s,a}(t, s_o) + p_{D_p,s,a} F_{s,a}(t, T_{f_{\max}})$$

Equation 0.10d

$$s_o = T_{o_{\max}}$$

Cases experiencing disease because of reactivation, who have not yet been detected

$$D_{n,s-,a}(t + \delta t, 0) = (1 - o_{s+,a})(L_{z-,a}(t) d_{n,z-,a} + L_{z+,a}(t) d_{n,z+,a})$$

Equation 0.11a

$$D_{n,s+,a}(t + \delta t, 0) = o_{s+,a}(L_{z-,a}(t) d_{n,z-,a} + L_{z+,a}(t) d_{n,z+,a})$$

Equation 0.11b

$$D_{n,s,a}(t + \delta t, s_o + \delta s_o) = D_{n,s,a}(t, s_o) - D_{n,s,a}(t, s_o)(r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) \\ + (1 - p_{in,f,s}) M_{in,D_n,s,a}(s_o)$$

Equation 0.11c

$$s_o < T_{o_{\max}}$$

$$\begin{aligned}
D_{n,s,a}(t + \delta t, s_o + \delta s_o) &= D_{n,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{n,s,a}(t, s_o) \\
&\quad + (1 - p_{in,f,s})M_{in,D_n,s,a}(t, s_o) + p_{D_n,s,a}F_{s,a}(t, T_{f_{\max}})
\end{aligned}$$

Equation 0.11d

$$s_o = T_{o_{\max}}$$

Cases experiencing disease because of reinfection, who have not yet been detected

$$\begin{aligned}
D_{x,s-,a}(t + \delta t, 0) &= (1 - o_{s+,a}) \sum_{s_r=0}^{T_R} d_{x,z-,a}(s_r)(R_{z-,a}(t, s_r) + R_{z\rho,a}(t, s_r)) \\
&\quad + (1 - o_{s+,a}) \sum_{s_r=0}^{T_R} \sum_{s_z=0}^{T_{z_{\max}}} R_{z+,a}(t, s_r, s_z) d_{x,z+,a}(s_r)
\end{aligned}$$

Equation 0.12a

$$\begin{aligned}
D_{x,s+,a}(t + \delta t, 0) &= o_{s+,a} \sum_{s_r=0}^{T_R} d_{x,z-,a}(s_r)(R_{z-,a}(t, s_r) + R_{z\rho,a}(t, s_r)) \\
&\quad + o_{s+,a} \sum_{s_r=0}^{T_R} \sum_{s_z=0}^{T_{z_{\max}}} R_{z+,a}(t, s_r, s_z) d_{x,z+,a}(s_r)
\end{aligned}$$

Equation 0.12b

$$\begin{aligned}
D_{x,s,a}(t + \delta t, s_o + \delta s_o) &= D_{x,s,a}(t, s_o) + (1 - p_{in,f,s})M_{in,D_x,s,a}(t, s_o) \\
&\quad - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{x,s,a}(t, s_o)
\end{aligned}$$

Equation 0.12c

$$s_o < T_{o_{\max}}$$

$$\begin{aligned}
D_{x,s,a}(t + \delta t, s_o + \delta s_o) &= D_{x,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{x,s,a}(t, s_o) \\
&\quad + (1 - p_{in,f,s})M_{in,D_x,s,a}(t, s_o) + p_{D_x,s,a}F_{s,a}(t, T_{f_{\max}})
\end{aligned}$$

Equation 0.12d

$$s_o = T_{o_{\max}}$$

Detected cases

$$F_{s-,a}(t + \delta t, 0) = \sum_{s_o=0}^{T_{0max}} (r_f(t)(D_{p,s-a}(t, s_o) + D_{n,s-a}(t, s_o) + D_{x,s-a}(t, s_o)))$$

$$+ p_{in,f,s-} \sum_{s_o=0}^{T_{0max}} (M_{in,D_p,s-,a}(t, s_o) + M_{in,D_x,s-,a}(t, s_o) + M_{in,D_n,s-,a}(t, s_o))$$

Equation 0.13a

$$F_{s-,a}(t + \delta t, s_f + \delta s_f) = F_{s-,a}(t, s_f) - (m_{tb+} + m_{tb-,a} + \mu_a + \tau(s_f))F_{s-,a}(t, s_f)$$

Equation 0.13b

$$F_{s+,a}(t + \delta t, 0) = \sum_{s_o=0}^{T_{0max}} r_f(t)(D_{p,s+,a}(t, s_o) + D_{n,s+,a}(t, s_o) + D_{x,s+,a}(t, s_o))$$

$$+ p_{in,f,s+} \sum_{s_o=0}^{T_{0max}} (M_{in,D_p,s+,a}(t, s_o) + M_{in,D_n,s+,a}(t, s_o) + M_{in,D_x,s+,a}(t, s_o))$$

Equation 0.13c

$$F_{s+,a}(t + \delta t, s_f + \delta s_f) = F_{s+,a}(t, s_f) - F_{s+,a}(t, s_f)(m_{tb+} + m_{tb-,a} + \mu_a + \tau(s_f))$$

$$0 < s_f < T_{fmax}$$

Equation 0.13d

Cases undergoing TB treatment

$$C_a(t + \delta t, 0) = \sum_{s_f=0}^{T_{fmax}} \tau(s_f)(F_{s-,a}(t, s_f) + F_{s+,a}(t, s_f))$$

Equation 0.14a

$$C_a(t + \delta t, s_r + \delta s_r) = C_a(t, s_r) - C_a(t, s_r)(m_{tb+} + m_{tb-,a} + \mu_a)$$

Equation 0.14b

$$0 < s_r < T_{rmax}$$

People who have recovered from TB disease

$$V_{z-,a}(t + \delta t) = V_{z-,a}(t) - V_{z-,a}(t)(i_{z+,a}(t) + \lambda(t) + m_{tb-,a} + \mu_a)$$

$$+ M_{in,V,a}(t) + C(T_{rmax})$$

Equation 0.15a

$$V_{z+,a}(t + \delta t, 0) = V_{z-,a}(t) i_{z+,a}(t) \quad \text{Equation 0.15b}$$

$$V_{z+,a}(t + \delta t, s_z + \delta s_z) = V_{z+,a}(t, s_z) - V_{z+,a}(t, s_z) (i_{z-,a}(t) + \lambda(t) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.15c}$$

$$0 < s_z < T_{z_{\max}}$$

Transitions at the end of each time step

$$P_{e+,a}(t + \delta t) = P_{e+,a}(t) + L_{z+,a}(t, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) + \sum_{s_z=0}^{T_{z_{\max}}} V_{z+,a}(t, s_z) i_{z-}(s_z) + \sum_{s_r \geq T_{z_{\max}}} R_{z+,a}(t, s_r, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) + \sum_{s_j \geq T_{z_{\max}}} E_{z+,a}(t, s_j, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) \quad \text{Equation 0.16}$$

$$P_{e-,a}(t + \delta t) = P_{e-,a}(t) + \sum_{s_z < T_{z_{\max}}} L_{z+,a}(t, s_z) i_{z-}(s_z) \quad \text{Equation 0.17}$$

$$L_{z+,a}(t + \delta t, s_z + \delta s_z) = L_{z+,a}(t, s_z) (1 - i_{z-}(s_z)) \quad \text{Equation 0.18}$$

$$s_z < T_{z_{\max}}$$

$$E_{z_p,a}(t + \delta t, s_j + \delta s_j) = E_{z_p,a}(t, s_j) + E_{z+,a}(t, s_j, T_{z_{\max}}) + \sum_{s_z < T_{z_{\max}}} E_{z+,a}(t, s_j, s_z) i_{z-}(s_z) \quad \text{Equation 0.19a}$$

$$s_j \neq T_{z_{\max}}$$

$$E_{z_p,a}(t + \delta t, s_i + \delta s_i) = E_{z_p,a}(t, s_i) + \sum_{s_z < T_{z_{\max}}} E_{z^+,a}(t, s_i, s_z) i_{z^-}(s_z) \quad \text{Equation 0.19b}$$

$$s_i = T_{z_{\max}}$$

$$E_{z^+,a}(t, s_i + \delta s_i, s_z + \delta s_z) = E_{z^+,a}(t, s_i, s_z)(1 - i_{z^-}(s_z)) \quad \text{Equation 0.20}$$

$$s_z < T_{z_{\max}}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) + R_{z^+,a}(t, s_r, T_{z_{\max}}) + \sum_{s_z < T_{z_{\max}}} R_{z^+,a}(t, s_r, s_z) i_{z^-}(s_z) \quad \text{Equation 0.21a}$$

$$s_r \neq T_{z_{\max}}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) + \sum_{s_z < T_{z_{\max}}} R_{z^+,a}(t, s_r, s_z) i_{z^-}(s_z) \quad \text{Equation 0.21b}$$

Equation 0.17

$$s_r = T_{z_{\max}}$$

$$R_{z^+,a}(t, s_r + \delta s_r, s_z + \delta s_z) = R_{z^+,a}(t, s_r, s_z)(1 - i_{z^-}(s_z)) \quad \text{Equation 0.22}$$

$$s_z < T_{z_{\max}}$$

$$V_{z^+,a}(t + \delta t, s_z + \delta s_z) = V_{z^+,a}(t, s_z)(1 - i_{z^-}(s_z)) \quad s_z < T_{z_{\max}} \quad \text{Equation 0.23a}$$

$$V_{z+,a}(t + \delta t, s_z + \delta s_z) = V_{z+,a}(t, s_z)(1 - i_{z-}(s_z)) + L_{z+,a}(t, s_z)(1 - i_{z-}(s_z)) + \sum_{s_r \geq T_{z\max}} R_{z+,a}(t, s_r, T_{z\max})(1 - i_{z-}(T_{z\max}))$$

Equation 0.23b

$$s_z = T_{z\max}$$

The force or risk of infection

The force of infection at time t is given in Equation 0.24 in terms of the effective contact rate (c_e) (defined as the average number of individuals effectively contacted by each infectious case), the total number of smear-negative and smear-positive cases ($I_{s-}(t)$ and $I_{s+}(t)$ respectively), the population size ($N(t)$) and the relative infectiousness of smear-negative, compared to smear-positive cases (f). The latter equals 22%, consistent with molecular epidemiological data(2).

$$\lambda(t) = \frac{c_e(f I_{s-}(t) + I_{s+}(t))}{N(t)}$$

Equation 0.24

Extending the definition used for acute infections, an effective contact is defined as one that is sufficient to lead to transmission if it occurs between an infectious individual and someone with either a “latent” infection or who has never been infected.⁷

The total number of smear-positive individuals is given by the following equation

$$I_{s+}(t) = \sum_a \sum_{s_o=0}^{T_{o\max}} (D_{p,s+,a}(t, s_o) + D_{n,s+,a}(t, s_o) + D_{x,s+,a}(t, s_o)) + \sum_{s_f=0}^{T_{f\max}} F_{s+,a}(t, s_f)$$

The equation for smear-negative cases is analogous.

The rate at which detected cases start TB treatment

The rate at which cases start treatment in the model was calculated so that the average time until cases had started treatment equalled 2 weeks and 82% of cases did not eventually start treatment. Cases who had not

started treatment within 6 months were returned to the undetected categories (see above). These rates were calculated as the values for $\tau(s_f)$ satisfying the following equations:

$$u(s_f + 1) = u(s_f) - \tau(s_f)u(s_f)$$

$$u(4) = 0.18$$

where: $\tau(s_f)$ is the rate at which cases start TB treatment in week s_f after detection (assumed to be constant in each month); $u(s_f)$ is the estimated proportion of those detected who are still untreated s_f weeks after detection.

Supplementary File 1B: Cost-Effectiveness of the TB-STs

Objective

To estimate the cost-effectiveness of the TB Strain Typing Service (TB-STs) as an addition to the current system for tuberculosis (TB) control in England.

Methods

The analysis followed the methods recommended by the National Institute for Health and Clinical Excellence (NICE) for evaluation of public health interventions.¹⁹

- Perspective – A public sector perspective was used for costing, and included costs and savings attributable to the TB-STs for the NHS, Local Authorities, Department of Health and other public bodies. The majority of costs and savings from the TB-STs fall on the Public Health England (PHE) centre, regions, Health Protection Units (HPU), laboratories and NHS TB services.
- Measure of health effects - Health benefits attributable to the TB-STs were estimated in the form of Quality Adjusted Life Years (QALYs) gained for index cases, their contacts, and for people benefiting from prevention of onward transmission of TB (as estimated from the transmission model). QALY estimates included TB-related mortality and morbidity.
- Time horizon - Costs and health effects resulting from operating the TB-STs were estimated over a period of 20 years.
- Incremental analysis – The results are presented in the form of an Incremental Cost Effectiveness Ratio (ICER), which is the additional cost per additional QALY gained with the TB-STs. Thus we estimated the expected difference in costs and in health effects with/without the TB-STs. Any costs or health effects incurred under both systems were ignored. The resulting ICER was compared with the NICE-recommended upper threshold of £30,000 per QALY gained.²⁰
- Uncertainty - Deterministic sensitivity analysis was used to test the impact of uncertainty over input parameters on the cost-effectiveness results.
- Discounting - Costs and QALYs were both discounted at the NICE recommended rate of 3.5% per year. The impact of using the Department of Health recommended discount rates of 3.5% for costs and 1.5% discount rates for QALYs were tested in sensitivity analysis.

The conceptual model underlying the economic analysis is illustrated in Figure 3 in the main text. It was hypothesised that the introduction of the TB-STS might influence outcomes or health care expenditure through the following mechanisms:

- **TB-STS infrastructure.** The TB-STS has imposed capital and revenue costs for the reference laboratories and national, regional and local Health Protection Services (HPS). These include direct costs of the tests, but also costs of establishing the infrastructure to request tests, report results and perform quality assurance.
- **Detection of false positives.** One potential benefit of strain typing is earlier identification of the false positive TB cases that can be caused by laboratory contamination. In addition to the avoidance of anxiety for patients and their families, earlier identification of such cases has health and financial implications if treatment is avoided or reduced. There might also be benefits in earlier detection of alternative diagnoses (e.g. lung cancer), but these are difficult to quantify, and have not been included in our analysis.
- **Case finding activity.** Introduction of the TB-STS might in theory have increased or decreased case finding activity and related costs. As contact tracing is usually completed before the strain type result is available (survey results described in Box 2 of the main text), one would not expect it to impact on the initial number of contacts traced by TB clinics. However, it is possible that it could have affected decisions by health protection staff to initiate or extend investigations of potential outbreaks. If strain typing identifies otherwise unsuspected clusters of cases, the number of contacts followed up could increase, increasing costs. But strain typing might also have the effect of disproving links between epidemiologically linked cases, thus reducing case finding activity and costs.
- **Case finding yield.** Regardless of the impact on the volume of case finding activity, we hypothesised that strain typing would improve the yield of case finding; increasing the number of cases of active disease and latent infection identified per case of TB. If true, this would have a number of benefits:
 - **Earlier detection of active disease.** It seems plausible that cases detected through the TB-STS-enhanced cluster investigations might benefit from earlier diagnosis and initiation of treatment, and that earlier treatment might be associated with a reduction in QALY loss from TB.
 - **Increased detection of latent infection.** One might also expect an increase in the detection of latent infection resulting from strain typing. Individuals diagnosed with Latent TB Infection (LTBI) who are suitable for and accept prophylactic treatment should then have a reduced risk of developing active

disease themselves, avoiding QALY loss and NHS costs. However, there are costs and side effects of prophylaxis, which will offset its benefits to some extent.

- Prevention of onward transmission. Both earlier detection of active disease and increased prophylactic treatment should help to prevent transmission. If so, this would lead to further QALY gains and cost savings.

In addition to the above direct effects, the TB-STS may well provide more indirect benefits. For example, the availability of a national information resource on the distribution and growth of clusters might benefit future tuberculosis research and service development (see Box 3 in the main text). Such effects are hard to quantify or value, and so were not been included in the economic analysis, but they were discussed and taken into consider by the evaluation expert group.

Estimated impact on false positive identification

The survey of reference laboratories identified 70 possible false positive TB tests, of which 59 (84%) had a known outcome. 30 of the incidents with a known outcome (51%) were confirmed as false positive results attributed to cross contamination. Of these, 17 (57%) were not known about by the source laboratory before they were contacted by the reference lab. For eight of the 30 confirmed cross-contamination incidents (27%), the patient commenced treatment. For the economic analysis, it was assumed that five cases of unnecessary treatment would be avoided per year due to the TB-STS (ten cases per year was tested in sensitivity analysis).

Estimated impact on case finding activity and yield

Evidence on the impact of the TB-STS on the volume and yield of case finding activity was sparse. There was some evidence of an increase in time spent on cluster investigations reported in the survey of health protection staff: from a mean of 2.7% before to 7.1% after implementation.²¹ However, TB specialist nurses did not report any significant increase in time spent on contact tracing. In the economic analysis, an opportunity cost for additional time spent by HPU staff on cluster investigations was assumed: 4.4% Whole Time Equivalent (WTE) for each of 26 Consultants in Communicable Disease Control (CCDC) at £99,000pa, costing a total of £113,256 per year (total annual cost of £50,000 per year and £500,000 per year tested in sensitivity analysis).

There was no clear evidence of whether introduction of the TB-STS resulted in an increase in the number of contacts screened, or in the yield of contacts with active disease or latent infection found. Analysis of the

contact tracing database, national dataset and cluster monitoring dataset showed that a greater number of contacts were screened and more contacts with latent infection were identified in cases that were clustered and investigated compared with unique cases. However, there were no significant differences in the numbers of contacts screened or cases of latent infection identified for clustered cases that were investigated compared with clustered cases that were not investigated. Similarly, evidence for a change in the rate of cluster growth after the initiation of an investigation or for a change in the duration of diagnostic delay was equivocal.

It is unclear whether these negative results reflect the absence of an effect of the TB-STS, or the difficulties in obtaining evidence. We therefore conducted a scenario analysis, in which we estimated the cost-effectiveness of the TB-STS under a series of assumptions about its possible effects.

Population assumptions

Results were estimated across the population of England (53m) and took account of the age distribution of the population (age groups <15, 15-34, 35-54, 55+).²² The results were based on an epidemiological scenario with a medium TB incidence (similar to that in the non-white UK-born population in which the average infection risk was constant over time at 0.1%). This was chosen to reflect an average risk level across the community.

Scenarios investigated

The transmission model was used to estimate the number of cases prevented under a range of assumptions about the effect of the TB-STS on: a) the proportion of previously infected individuals detected; and b) the mean length of time between onset of symptoms and treatment initiation.

The base case scenario (S0) was intended to reflect the expected costs and outcomes of the TB control system in the absence of the strain typing programme. This was modelled assuming that 3% of previously infected individuals are detected per year and that the mean time from onset of symptoms to the start of treatment is 12 weeks. The transmission model results for this base case scenario are summarised in Supplementary Table 3 for the population of England over 20 years, and assuming a constant risk of infection of 0.1% per annum. The estimated number of cases diagnosed exceeds the number of new cases in each year, as there is a pool of cases who have previously not been diagnosed or who have defaulted from treatment.

The cost-effectiveness of the TB-STS was then estimated under a range of assumptions about its effect on identification of cases of LTBI found and the Diagnostic Delay (DD) for active cases. The results of the

transmission model under these scenarios are summarised in Supplementary Table 3 for the population of England over 20 years, and assuming a constant risk of infection of 0.1% per annum. The estimated number of cases diagnosed exceeds the number of new cases in each year, as there is a pool of cases who have previously not been diagnosed or who have defaulted from treatment.

The cost-effectiveness of the TB-STS was then estimated under a range of assumptions about its effect on identification of cases of LTBI found and the Diagnostic Delay (DD) for active cases. The results of the transmission model under these scenarios are summarised in Supplementary Table 4. They suggest that increases in the proportion of people with latent infection identified and treated have a relatively modest impact on TB incidence: if an additional 10% of prevalent infections were detected each year, the number of new TB cases would fall by an estimated 736 cases per year (11%). In contrast, reductions in diagnostic delay for active cases were estimated to have a much bigger impact on TB incidence: a one week reduction in the time from onset of symptoms to treatment was associated with an estimated reduction of 1,650 TB cases (25%). Furthermore, if such a reduction in diagnostic delay could be achieved, it would also be accompanied by a reduction in the number of people requiring prophylactic treatment.

Cost estimates

The estimated costs of establishing and running the national strain typing programme were estimated from financial information obtained from Public Health England and TB Reference Laboratories. Capital expenditure was converted to an equivalent annual cost assuming a 10 year lifetime of the investment and 3.5% annual discount rate. Total costs were estimated at just under £1m per year.

The estimated costs of screening, diagnosis and treatment are shown in Supplementary Table 5. The average quantities of resource items per patient were based on standard treatment protocols, informed by expert judgement. Unit costs per resource item were taken from standard national sources: Department of Health Reference Costs 2010-11 for Tuberculosis Specialist Nurse visits, outpatient consultations (respiratory clinic), and inpatient admissions; British National Formulary, Sept 2012 for medications; and published sources for tests.^{16,23}

The cost per contact screened was estimated at £234: including contact tracing, TST and IGRA testing, and initial rule-out of active disease. The total cost of contact screening was estimated as a function of the number

of people diagnosed with latent infection, as estimated by the transmission model. The study of the yield of cluster investigations found that on average (across unique and clustered cases) 2.6 contacts were screened and 0.7 cases of LTBI were identified per TB case. Therefore, it was assumed that to diagnose one case of LTBI, 3.97 contacts would need to be screened, at a cost of £963. The cost of further follow-up and investigations for each contact suspected of having active disease was estimated at £434. We assumed that 20% of individuals investigated for active TB would receive a positive diagnosis, so the estimated cost to diagnose one case of TB was £2,170 (5 x £434). The costs of treatment for latent and active disease were estimated at £743 and £1,114 respectively for a full course, or £669 and £1,002 respectively allowing for drop out from treatment: assuming that 15% of patients drop out, after a mean of one month for latent infection and 2 months for active disease. Patients with TB who drop out are likely to be identified and offered treatment again at a later time. Such repeat cases are included in the transmission model estimates of the number of people diagnosed per year, and incur additional costs for diagnosis and treatment in the cost effectiveness analysis. For simplicity, it is assumed that the cost of diagnosis and treatment is the same for new and repeat cases.

QALY estimates

Estimates of the QALY loss per case of TB are shown in Supplementary Table 6. At ages of 15 and older, TB-related mortality contributed more to estimated QALY loss than TB-related morbidity. On average across all ages, a loss of 0.5 QALYs was attributable to case fatality out of a total estimated 0.62 QALYs lost.

QALYs lost due to TB-related mortality were estimated based on: TB incidence by age;²⁴ case-fatality rates by age group;²⁵ life expectancy (ONS); and mean quality of life by age (EQ5D scores) in the general population (Health Survey for England). The case fatality rates were taken from an analysis of national surveillance data linked to mortality data, with capture-recapture methods used to estimate the number of unascertained deaths.²⁵ In this analysis, case fatality was defined as a death within 12 months of the start (or notification) of TB treatment, and where TB was mentioned on the death certificate or if treatment outcome monitoring had stated that the death was caused by or contributed by TB. This includes deaths in which TB was reported as a contributory factor, as well as deaths directly caused by TB.

Estimates of QALY loss due to morbidity were based on some simple assumptions about the duration and quality of life reduction in three periods of time:

- a. **Pre-treatment period:** from onset of symptoms to initiation of treatment, which was assumed to last for 3 months in scenarios S0 to S10, and reduced according to the DD in scenarios S11 to S14. During this time, patients were assumed to have a utility equal to 90% of that of the general population of the same age.
- b. **Acute period:** assumed to last for 2 months from diagnosis, during which patients have a utility value of 0.675.²⁶
- c. **Post acute period:** from after the acute period to the end of treatment (4 months), during which patients have a utility value of 0.813.²⁶

Overall QALY losses per case of TB were estimated to be 0.19, 0.40, 0.59 and 1.18, respectively, for patients in age group 0-14, 15-34, 35-54, and 55 plus. It was assumed that after treatment completion there is no lasting effect of TB on quality of life or mortality risk, although within the transmission model, individuals can be re-infected, potentially incurring another QALY loss associated with a new TB incidence.

The QALY impact of adverse effects of treatment were assumed to be incorporated in the above utility multipliers for active disease. Patients with a false positive TB diagnosis who start treatment, were assumed to be treated for 4 months on average,²³ and during this time they were assumed to experience a utility loss of 0.1 due to the inconvenience and harmful health effects of TB treatment. Thus, the avoidance of treatment for a false positive case is associated with a mean QALY gain of 0.03. The QALY loss associated with the adverse effects of prophylactic treatment was estimated based on the assumption that 10% of patients experience some side effects, and that these last for one month on average, incurring a mean utility loss of 0.1. Thus the mean QALY loss per person treated with prophylaxis is 0.0008. It was assumed that there were no lasting consequences from adverse reactions to treatment for active disease or latent infection.

Results

Increased proportion of LTBI detected

Under our base case assumptions, if the TB-STIS had increased the proportion of LTBI detected from 3% to 4% with no impact on the mean time to diagnosis for active cases, it would not appear cost-effective (see Supplementary Table 7). Although the improvement would have prevented an estimated 1,726 cases of TB (over 20 years for the population of 53m), saving approximately £3.8m in diagnosis and treatment costs, this

cost was more than offset by the direct cost of the TB-STS (£14.3m), the additional costs of screening contacts (£32.5m) and of prophylactic treatment (£22.2m). The net impact on health expenditure was an estimated increase of £65.2m. This cost increase is associated with a QALY gain of around 682 years of healthy life, giving an estimated Incremental Cost Effectiveness Ratio (ICER) of £95,628 per QALY gained, which is well above the range usually considered to be cost-effective in the NHS (a maximum of £30,000 per QALY gained).

Estimated cost-effectiveness did improve if we assumed that the TB-STS achieved a greater increase in the proportion of latent infections detected. However, over the range tested this improvement was still not sufficient to bring the ICER below the £30,000 threshold. If the introduction of the TB-STS has increased the identification of an additional 10% of prevalent latent infections - an additional 281,461 people diagnosed with LTBI over 20 years - the estimated cost per QALY gained was £55,748 (Supplementary Table 8).

Reductions in diagnostic delay

In contrast, the results were very sensitive to small reductions in the average time from onset of symptoms to the start of treatment for active disease. A reduction from 12 weeks to 11 weeks was estimated to yield a large reduction in the number of incident TB cases, and hence in the numbers of contacts to be screened and in people requiring prophylactic treatment (Supplementary Table 9). There was therefore a net saving in healthcare expenditure (over £85m saved), as well as a large health improvement (16,000 QALYs gained). Bigger reductions in the diagnostic delay, would achieve even larger cost savings and health improvements.

Sensitivity to other assumptions

Results under a range of other changes to the model parameters are shown in Supplementary Table 10. Unless stated otherwise, these analyses all relate to the comparison between scenarios S1 and S0 (1% increase in the proportion of prevalent LTBI cases diagnosed with TB-STS; no difference in diagnostic delay), and with all other parameters held constant at the base case values.

Other than reductions in diagnostic delay, the only changes tested that gave an estimated ICER below the usual NICE threshold of £30,000 per QALY related to an increase in the QALY loss from TB. However, in order to achieve this result, quite strong assumptions were required about the TB-related mortality and/or morbidity: equivalent to an overall mean loss of two full years of healthy life per case.

Discussion

This analysis failed to demonstrate that the TB-STIS is a cost-effective use of NHS resources. It suggests that it is unlikely that earlier identification of false positive cases related to laboratory contamination, or increases in the identification and prophylactic treatment of contacts with a latent infection could, on their own, justify the cost of the system. We were not been able to conduct a probabilistic sensitivity analysis to characterise the overall impact of uncertainty over the parameters and assumptions over the transmission model and cost-effectiveness analysis. However, simple deterministic sensitivity analysis suggested that the results are, with one major exception, quite robust to plausible changes in most parameters. The key uncertainty relates to the lack of evidence over whether the system is associated with earlier diagnosis and treatment for active cases.

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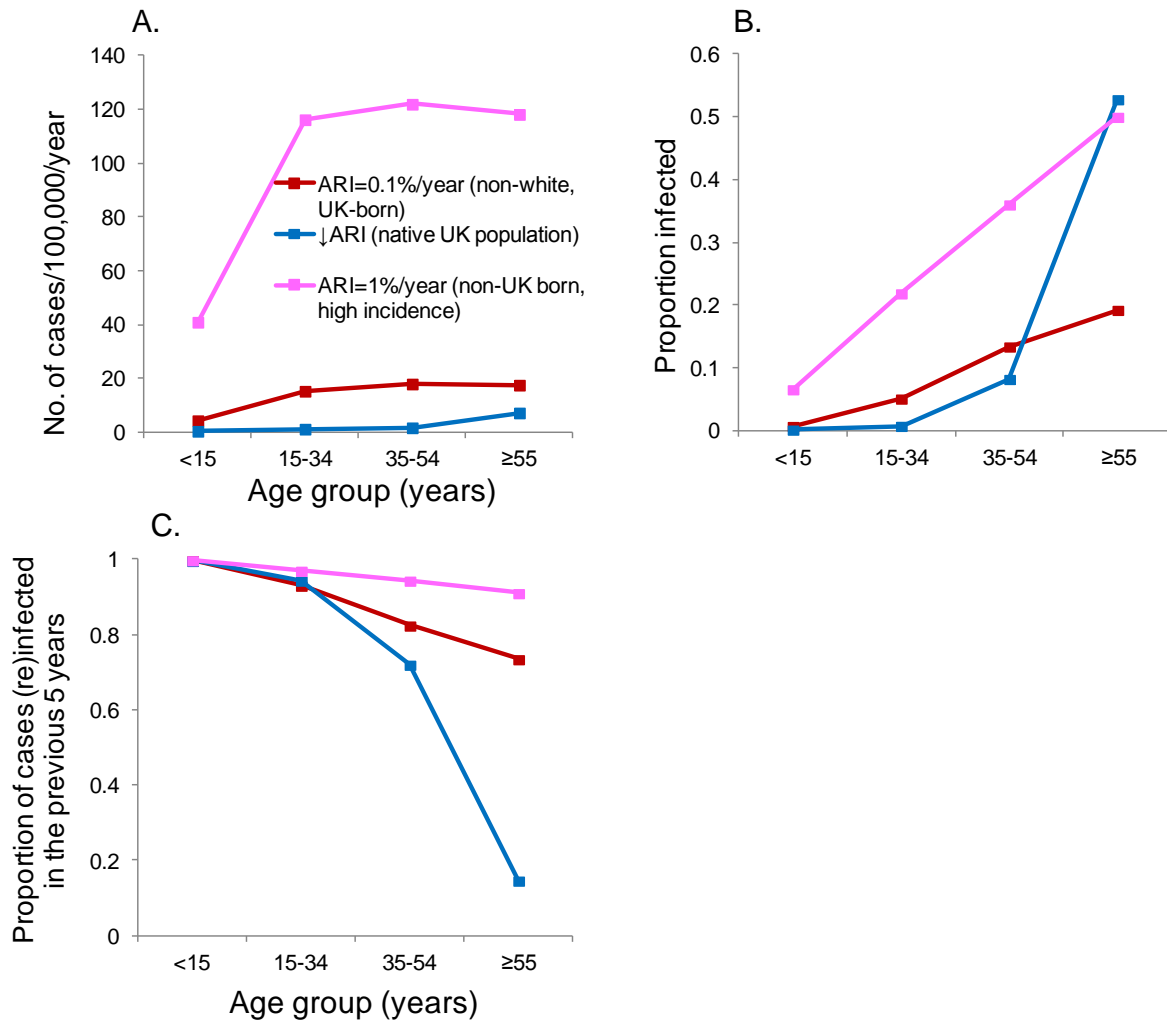
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Supplementary Figures

Supplementary Figure 1: Characteristics of the epidemiological scenarios considered in the model. A. the annual age-specific tuberculosis incidence per 100,000 population. B. The age-specific proportion of individuals who have ever been infected. C. The age-specific proportion of new cases that have been newly infected or reinfected in the previous 5 years for the epidemiological scenarios considered.



Supplementary Tables

Supplementary Table 1: Summary of assumed parameter values and their ranges. The subscript z- and z+ refer to those not on PT and on PT respectively, a refers to the age group. The abbreviations sm- and sm+ refer to those who are smear-negative and smear-positive respectively.

Definition	Symbol	Base case value	Source/comment
Transmission			
Number of people effectively contacted by each smear-positive case in a) Low incidence (similar to white UK population) b) Medium incidence (Non-white, UK-born population) c) High incidence (Non-white, non-UK-born)	c_e		Calculated to reproduce incidence consistent with observed notification rates
Infectiousness of smear-negative TB cases, compared to that of smear-positives	f	22%	²⁷
Force of infection at time t	$\lambda(t)$		See text
Disease onset			
Rate of disease onset following recent infection at time s_i since first infection among those not on PT among of age a	$d_{p,z-,a}(s_i)$	Cumulative risk over 5 years: 4% (children) 14% (adults), increases linearly between ages 10 and 20 years	^{8,9}
Rate of disease onset following recent infection at time s_i since first infection among those on PT among of age a	$d_{p,z+,a}(s_i)$	Calculated as $d_{p,z-,a}(s_i)\pi_{d,z+}$	
Rate of disease onset at time s_r following reinfection among those not on PT of age a	$d_{x,z-,a}(s_r)$	Cumulative risk over 5 years: 8%	^{8,9}
Rate of disease onset at time s_r following reinfection among those on PT of age a	$d_{x,z+,a}(s_r)$	Calculated as $d_{x,z-,a}(s_r)\pi_{d,z+}$	
Annual rate of developing disease through reactivation (%/year) among those not on PT of age a	$d_{n,z-,a}$	0.03%/year	^{8,9}
Annual rate of developing disease through reactivation (%/year) among those on PT of age a	$d_{n,z+,a}$	Calculated as $d_{n,z-,a}\pi_{d,z+}$	
Percentage of respiratory TB disease that is smear-positive among those of age a	$o_{s+,a}$	10% (children) 65% (adults)	Public Health England (PHE) Enhanced Surveillance database and data in ⁸ . Follows the age-specific pattern in ⁸ .
Duration that people spend in the reinfected compartment (experiencing the risk of disease given reinfection before being transferred to the latent	T_R	5 years	--

compartment			
Duration that people spend in the infected compartment (experiencing the high risk of disease given infection before being transferred to the latent compartment)	T_E	5 years	--
Demography			
Annual birth rate per 1000 per year		13.1	Office for National Statistics ⁴
Annual general population mortality rates	$m_{fb,a}$	Age-dependent	Office for National Statistics ⁴
Immigration rate		0.8%/year	Office for National Statistics ⁴
Outmigration rate for those of age a	μ_a	0.6%/year	Office for National Statistics ⁴
TB prevalence among immigrants		0.02%	Consistent with model predictions based on an ARI of 1%/year
Case detection			
% of immigrant TB cases with smear status s that are detected on entry to the UK	$p_{in,f,s}$	0%	⁶
Average time from disease onset to detection (among non-immigrants) at time t	$T_{detect}(t)$	10 weeks (before the start of the TB-STs); varied thereafter	PHE Enhanced Surveillance database
Average rate at which cases are found	$r_f(t)$	Calculated as $1/T_{detect}$	
Maximum duration of that people spend in the detected (found) compartment before being distributed to the undetected compartment, if they have not started TB treatment in the meantime.	$T_{f,max}$	6 months	--
Preventive treatment			
Proportion of infections that are detected at time t	$p_{i,det}(t)$	Varied between 3% and 13% per year	No data available. Assumed to differ before and after the start of the strain-typing service
Percentage of eligible contacts (TST/IGRA+ and aged <35 years) that start PT	$p_{z+,start}$	95%	Plausible value, based on national policy ¹²
Proportion of infected people that start PT at time t	$i_{z+}(t)$	Calculated as: $p_{i,det} p_{z+,start}$	--
Protection provided by PT against disease whilst taking PT	$\pi_{d,z+}$	65%	^{13,14}
Proportion of those taking PT who complete PT	$p_{z+,stop}$	85%	¹²
Rate at which those taking PT stop taking PT	i_{z-}	1.3%/week	Based on $p_{z+,stop} = 0.85$
Maximum duration of PT	$T_{z,max}$	3 months	--
Treatment			

Average time from detection to start of TB treatment	$T_{\text{treat, start}}$	2 weeks	--
Rate at which cases start TB treatment at time s_f following detection	$\tau(s_f)$	$s_f < 4$ weeks: 35%/week $s_f \geq 4$ weeks: 0%/week	Calculated so that 82% of detected cases complete treatment (see text)
Percentage of detected cases that complete TB treatment		82%	PHE Enhanced Surveillance database
Percentage of detected cases who default from treatment		5.5%	PHE Enhanced Surveillance database
Mortality rate among TB cases (before and during TB treatment)	$m_{b+,a}$	7%	PHE Enhanced Surveillance database
Percentage of detected cases that are lost to follow-up		5.5%	PHE Enhanced Surveillance database
Duration of TB treatment	T_{max}	26 weeks	--

Supplementary Table 2: Definitions of the compartments and variables in the model.

Symbol	Definition
$U_a(t)$	Number of people of age a at time t who have never been infected.
$E_{z-,a}(t,s_i)$	Number of people of age a who have been infected for duration s_i at time t , who have never had PT.
$E_{z+,a}(t,s_i,s_z)$	Number of people of age a who have been infected for duration s_i and have been on PT for duration s_z at time t .
$E_{z_p,a}(t,s_i)$	Number of people of age a who have been infected for duration s_i at time t , who have previously had PT.
$L_{z-,a}(t)$	Number of people of age a in the latent category at time t , who have never had PT.
$L_{z+,a}(t,s_z)$	Number of people of age a in the latent category at time t , who have been on PT for duration s_z .
$P_{e+,a}(t)$	Number of people of age a who have previously had PT, cleared their infection and have not been reinfected since clearing their infection.
$P_{e-,a}(t)$	Number of people of age a who have had PT, have not cleared their infection and have not been reinfected during the previous five years
$R_{z-,a}(t,s_r)$	Number of people of age a who have been reinfected for duration s_r at time t , who have never had PT.
$R_{z+,a}(t,s_r,s_z)$	Number of people of age a who have been reinfected for duration s_r and have been on PT for duration s_z at time t .
$R_{z_p,a}(t,s_r)$	Number of people of age a who have been reinfected for duration s_r at time t , who have previously had PT.
$D_{p,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease because of recent (primary) infection for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{p,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease because of recent (primary) infection for at least time $T_{o_{max}}$ at time t
$D_{n,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease through (endogenous) reactivation for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{n,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease through (endogenous) reactivation for at least time $T_{o_{max}}$.
$D_{x,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease because of (exogenous) reinfection for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{x,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease because of (exogenous) reinfection for at least time $T_{o_{max}}$ at time t
$F_{s,a}(t,s_f)$	Number of cases of smear status s , age a , who have been detected ("found") for duration s_f at time t and have not yet started TB treatment.
$C_a(t,s_t)$	Number of cases of age a , who have been on TB treatment for duration s_t at time t .
$V_{z-,a}(t)$	Number of people of age a who are in the recovered category at time t who are not on PT.
$V_{z+,a}(t,s_z)$	Number of people of age a , who are in the recovered category at time t who have been taking PT for duration s_z .
$M_{in,U,a}(t)$	Number of new immigrants at time t , who are of age a , and not infected

$M_{in,L,a}(t)$	Number of new immigrants at time t , who are of age a , and in the latent category.
$M_{in,E,a}(t, s_i)$	Number of new immigrants at time t who are of age a , and who have been newly infected for duration s_i .
$M_{in,R,a}(t, s_r)$	Number of new immigrants at time t who are of age a , and who have been reinfected for duration s_r .
$M_{in,D_p,s,a}(t, s_o)$	Number of new immigrants at time t who are of age a , who have been experiencing disease because of endogenous reactivation for duration s_o , and have smear status s .
$M_{in,D_n,s,a}(t, s_o)$	Number of new immigrants at time t who are of age a , who have been experiencing disease because of recent (primary) infection for duration s_o , and have smear status s .
$M_{in,D_x,s,a}(t, s_o)$	Number of new immigrants at time t of age a , who have been experiencing disease through exogenous reinfection for duration s_o , and have smear status s .
$M_{in,V,a}(t)$	Number of new immigrants at time t of age a , who have previously had TB, been treated and have not been reinfected since then.

Supplementary Table 3: Summary of transmission model results for base case scenario. Estimated number of cases by year for population of England (53m) over 20 years, assuming constant ARI of 0.1%.

Scenario	Year	LTBI diagnosed	LTBI starting treatment	New TB cases	TB cases diagnosed	TB cases starting treatment
S0	Year 1	9,069	8,616	6,730	7,568	6,698
	Year 2	9,060	8,607	6,723	7,561	6,691
	Year 3	9,051	8,599	6,717	7,554	6,685
	Year 4	9,043	8,590	6,711	7,547	6,679
	Year 5	9,034	8,582	6,705	7,540	6,673
	Year 6	9,025	8,574	6,698	7,532	6,666
	Year 7	9,016	8,566	6,692	7,526	6,660
	Year 8	9,008	8,557	6,686	7,519	6,654
	Year 9	8,999	8,549	6,680	7,512	6,648
	Year 10	8,991	8,541	6,674	7,505	6,642
	Year 11	8,982	8,533	6,668	7,498	6,636
	Year 12	8,974	8,525	6,662	7,491	6,630
	Year 13	8,966	8,517	6,656	7,485	6,624
	Year 14	8,957	8,509	6,650	7,478	6,618
	Year 15	8,949	8,502	6,644	7,472	6,612
	Year 16	8,941	8,494	6,638	7,465	6,607
	Year 17	8,933	8,486	6,633	7,458	6,601
	Year 18	8,925	8,478	6,627	7,452	6,595
	Year 19	8,916	8,471	6,621	7,446	6,589
	Year 20	8,908	8,463	6,615	7,439	6,584
	Total	179,747	170,760	133,431	150,046	132,794
	Mean pa	8,987	8,538	6,672	7,502	6,640

Supplementary Table 4: Summary of transmission model results for 14 scenarios. Mean number of cases per year for population of England (53m) over 20 years, assuming constant ARI of 0.1%.

*DD Diagnostic delay; LTBI latent tuberculosis infection

Scenario	% LTBI found	DD* (weeks)	LTBI diagnosed	LTBI starting treatment	New TB cases	TB cases diagnosed	TB cases starting treatment
S0	3%	12	8,987	8,538	6,672	7,502	6,640
S1	4%	12	11,298	10,733	6,585	7,408	6,556
S2	5%	12	13,334	12,668	6,502	7,316	6,475
S3	6%	12	15,131	14,375	6,420	7,227	6,397
S4	7%	12	16,718	15,882	6,342	7,140	6,321
S5	8%	12	18,120	17,214	6,265	7,056	6,246
S6	9%	12	19,361	18,393	6,191	6,974	6,174
S7	10%	12	20,459	19,436	6,118	6,895	6,104
S8	11%	12	21,432	20,360	6,048	6,817	6,036
S9	12%	12	22,295	21,180	5,979	6,742	5,969
S10	13%	12	23,060	21,907	5,912	6,668	5,904
S11	3%	11	7,835	7,443	4,964	5,631	4,990
S12	3%	10	7,011	6,661	3,828	4,379	3,884
S13	3%	9	6,412	6,091	3,051	3,520	3,125
S14	3%	8	5,964	5,666	2,504	2,912	2,588

Supplementary Table 5: Estimated costs of screening, diagnosis and treatment

¹ Assumes 4.11 contacts screened per person diagnosed with LTBI.

² Assumes 5 people investigated per person diagnosed with TB.

³ Assumes that 15% do not complete chemoprophylaxis, after an average 1 month of treatment.

⁴ Assumes that 15% do not complete treatment, after an average 2 months of treatment.

BNF British National Formulary

	Quantity	Unit cost	Cost	Source
Contact screening and follow up				
TB specialist nurse - non face to face	1	£27	£27	Ref cost 2011 ²⁸
TB specialist nurse - face to face	2	£62	£124	Ref cost 2011 ²⁸
Mantoux test	1	£1.22	£1.22	NICE 2011 ¹²
IGRA test	0.5	£56	£28	Pareek 2011 ⁶
Outpatient appointment for IGRA +	0.25	£187	£47	Ref cost 2011 ²⁸
Chest X-ray (to rule out active disease)	0.25	£28	£7	NICE 2010 ²⁹
Per contact screened			£234	
Per person diagnosed with LTBI ¹			£963	
Diagnosis of active disease				
TB specialist nurse - face to face	3	£62	£186	Ref cost 2011 ²⁸
Outpatient appointment for diagnosis	1	£187	£187	Ref cost 2011 ²⁸
Chest X-ray	1	£28	£28	NICE 2010 ²⁹
Sputum smear microscopy	1	£1.56	£1.56	Dowdy 2008 ³⁰
Culture & MDR identification	1	£30	£30	Dinnes 2007 ³¹
Liver function test	1	£1	£1	Ref cost 2011 ²⁸
Per contact with suspected TB			£434	
Per person diagnosed with TB ²			£2,170	
Management of latent infection				
Follow-up appointments nurse only	3	£62	£186	Ref cost 2011 ²⁸
Follow-up appointments nurse & consultant	2	£185	£370	Ref cost 2011 ²⁸
Isoniazid 300 mg daily (per month)	3	£41	£124	BNF 2012
Rifampicin 600 mg daily (per month)	3	£21	£63	BNF 2012
B6 pyridoxine 10mg tablets (per month)	3	£0.5	£1	BNF 2012

Per person completing treatment			£743	
Per person starting treatment ³			£669	
Management of active disease				
Admission	5%	£2,949	£147	Ref cost 2011 ²⁸
Follow-up appointments nurse only	5	£62	£310	Ref cost 2011 ²⁸
Follow-up appointments nurse & consultant	2	£185	£370	Ref cost 2011 ²⁸
Rifater (R,I ,P) 6 tablets daily for 2 months	2	£37	£74	BNF 2012
Ethambutol 15 mg/kg for 2 months	2	£63	£126	BNF 2012
Rifanah (R,I) 300/150 2 tab daily for 4 months	4	£21	£84	BNF 2012
B6 pyridoxine (per month)	6	£0.5	£3	BNF 2012
Per person completing treatment			£1,114	
Per person starting treatment ⁴			£1,002	

Supplementary Table 6: Calculation of QALY loss per case of TB

Age	Incidence		Case fatality	Life expectancy		Utility				Discounted to age of incidence											
	Male	Female		Male	Female	No TB	Pre- treat	Acute	Post acute	LYL per fatality		QALYs lost per fatality *		QALYs lost per case		TB morbidity			Total QALYs lost		
											Male	Female	Male	Female	Male	Female	Pre-treat	Acute	Post acute	Mortality	Morbidity
0-4	62	78	0.3%	78.0	82.1	0.94	0.84	0.63	0.76	26.62	26.88	24.98	25.22	0.07	0.08	0.023	0.051	0.058	11	19	29
5-9	47	46	0.2%	73.5	77.5	0.94	0.84	0.63	0.76	26.29	26.59	24.67	24.94	0.05	0.05	0.023	0.051	0.058	5	12	17
10-14	77	103	0.2%	68.5	72.5	0.94	0.84	0.63	0.76	25.86	26.21	24.27	24.60	0.05	0.05	0.023	0.051	0.058	9	24	33
15-19	192	173	1.2%	63.5	67.6	0.94	0.84	0.63	0.76	25.36	25.78	23.80	24.19	0.29	0.29	0.023	0.051	0.058	105	48	153
20-24	582	406	1.2%	58.7	62.6	0.94	0.84	0.63	0.76	24.77	25.26	23.25	23.70	0.28	0.28	0.023	0.051	0.058	278	130	408
25-29	717	547	1.2%	53.9	57.7	0.94	0.84	0.63	0.76	24.09	24.65	22.60	23.13	0.27	0.28	0.023	0.051	0.058	346	167	513
30-34	686	500	1.2%	49.0	52.8	0.91	0.82	0.62	0.74	23.28	23.93	21.29	21.88	0.26	0.26	0.023	0.050	0.057	307	153	459
35-39	531	365	1.2%	44.3	47.9	0.91	0.82	0.61	0.74	22.34	23.08	20.26	20.93	0.24	0.25	0.023	0.049	0.057	221	114	335
40-44	416	294	1.2%	39.6	43.1	0.88	0.79	0.60	0.72	21.24	22.08	18.74	19.48	0.22	0.23	0.022	0.048	0.055	162	88	250
45-49	343	227	4.8%	34.9	38.3	0.86	0.78	0.58	0.70	19.97	20.92	17.25	18.07	0.83	0.87	0.022	0.047	0.054	481	68	549
50-54	290	223	4.8%	30.3	33.6	0.83	0.75	0.56	0.68	18.50	19.58	15.44	16.34	0.74	0.78	0.021	0.045	0.052	390	59	449
55-59	245	180	4.8%	25.9	29.1	0.82	0.74	0.55	0.67	16.85	18.05	13.86	14.84	0.67	0.71	0.021	0.045	0.051	291	48	340
60-64	200	163	4.8%	21.7	24.6	0.81	0.73	0.54	0.66	15.03	16.33	12.13	13.18	0.58	0.63	0.020	0.044	0.050	220	41	260
65-69	164	126	17.6%	17.7	20.4	0.80	0.72	0.54	0.65	13.05	14.40	10.49	11.58	1.85	2.04	0.020	0.044	0.050	560	30	590
70-74	168	133	17.6%	14.1	16.4	0.78	0.70	0.53	0.63	10.98	12.29	8.55	9.57	1.50	1.69	0.019	0.042	0.049	477	31	508
75-79	167	109	17.6%	10.8	12.6	0.75	0.68	0.51	0.61	8.86	10.08	6.67	7.59	1.17	1.34	0.019	0.041	0.047	342	27	369
80-84	127	82	17.6%	8.0	9.4	0.70	0.63	0.47	0.57	6.86	7.87	4.79	5.49	0.84	0.97	0.017	0.038	0.044	186	19	205
85-89	77	35	17.6%	5.8	6.7	0.65	0.58	0.44	0.53	5.16	5.87	3.35	3.81	0.59	0.67	0.016	0.035	0.040	69	9	78
90+	21	21	17.6%	4.2	4.6	0.65	0.58	0.44	0.53	3.80	4.17	2.47	2.71	0.43	0.48	0.016	0.035	0.040	19	4	23
5,112	3,811																		4,477	1,092	5,569

Utility multipliers	0.9	0.675	0.813
Duration of health states (months)	3	2	4

0-14	0.06	0.13	0.19
15-34	0.27	0.13	0.40
35-54	0.47	0.12	0.59
55+	1.07	0.10	1.18
All ages	0.50	0.12	0.62

* Approximation - assumes current QoL persists for life
 Utility values from Kruijshaar et al 2010, reported in NICE PH guidance 2011

Supplementary Table 7: Cost-effectiveness if TB-STS increased the proportion of LTBI detected from 3% to 4%

Comparison S1 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	£32,539,484	-
Prophylactic treatment	£22,240,304	-27.70
TB diagnosis & treatment	-£3,809,472	707.27
Total	£65,219,944	682
Incremental cost effectiveness ratio (ICER)	£95,628	per QALY gained

Supplementary Table 8: Cost-effectiveness if TB-STS increased the proportion of LTBI detected from 3% to 13%

Comparison S10 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	£209,685,394	-
Prophylactic treatment	£143,317,116	-178.53
TB diagnosis & treatment	-£33,848,402	6,289.25
Total	£333,403,736	6,113
Incremental cost effectiveness ratio (ICER)	£54,539	per QALY gained

Supplementary Table 9: Cost-effectiveness if TB-STS reduced time to diagnosis from 12 to 11 weeks

Comparison S11 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	-£13,640,543	-

Prophylactic treatment	-£9,323,117	11.61
TB diagnosis & treatment	-£76,153,948	16,032.60
Total	-£84,867,979	16,047
Incremental cost effectiveness ratio (ICER)	S11 dominant	

Supplementary Table 10: Deterministic sensitivity analysis results

Parameter changed (base case value)	Parameter values tested	Incremental cost (£)	Incremental effect (QALYs)	ICER (£ per QALY)
% LTBI detected	+1% with TB-STC (base case)	£65,219,944	682	£95,628
	+10% with TB-STC	£333,403,736	6,113	£54,539
Diagnostic delay	-1 week with TB-STC	-£64,867,979	16,047	Dominant
(no reduction)	-4 weeks with TB-STC	-£239,774,497	40,078	Dominant
Discount rates	1.5% for QALYs	£65,219,944	1,093	£59,682
(3.5% QALYs, 3.5% costs)	0% for QALYs	£65,219,944	1,643	£39,707
Time horizon	15 years	£55,453,941	431	£128,807
(20 years)	10 years	£42,475,021	212	£200,212
Cost of software	£500,000	£65,622,236	682	£96,218
(£264,593)	£1,000,000	£66,476,695	682	£97,471
Cost to HPUs	£50,000 pa	£64,289,459	682	£94,234
(£113,256 pa)	£500,000 pa	£70,908,886	682	£103,970
False positives	10 cases avoided pa	£65,170,792	684	£95,214
(5 avoiding treatment pa)	100 cases avoided pa	£64,286,046	729	£88,233
Utility loss from FP	0.5 for 4 months	£65,219,944	692	£94,273
(basecase 0.1 for 4 months)	0.5 for 12 months	£65,121,639	716	£90,909
Contacts screened	2 contacts per LTBI diagnosed	£49,073,148	682	£71,953
(basecase 4.11)	6 contacts per LTBI diagnosed	£81,858,521	682	£120,025
Adverse effects of CPx	0%	£65,219,944	710	£91,896
(basecase 10%)	100%	£65,219,944	433	£150,737
Yield of TB diagnosis	2 per case	£66,844,254	682	£98,010
(5 investigated per case)	10 per case	£62,512,761	682	£91,659
TB case fatality	1% all ages	£65,219,944	330	£197,537

(0.3% 0-4 to 17.6% 55+)	10% all ages	£65,219,944	2,249	£28,995
TB morbidity	0.05 QALYs lost per case	£65,219,944	599	£108,832
(0.12 QALYs lost per case)	1 QALY lost per case	£65,219,944	1,684	£38,732
Cost of prophylaxis	£300 per case	£51,955,851	682	£77,180
(£743 per case)	£1,000 per case	£72,900,343	682	£106,890
Cost of treatment	£500 per case	£65,854,499	682	£96,559
(£1,114 per case)	£5,000 per case	£61,202,523	682	£89,738

Supplementary File 2: Recommendations for the TB-STs

1. **The timely universal typing of all culture-confirmed TB cases should be continued.** This includes the first isolate of all new TB cases as well as an isolate from each TB episode in those with treatment failure or recurrent TB. The resulting database of strain types linked to national surveillance data should be analysed nationally and locally, and be fully accessible across Public Health England (PHE), the NHS, UK universities and for international collaborations. The database could be used for the following:
 - a. To access typing results in **response** to local or national incidents of suspected transmission, enabling the prospective, proactive, local-led application of strain typing for TB control and public health protection;
 - b. To understand the national and local **epidemiology** of TB, including the identification of risk groups for TB attributable to recent transmission;
 - c. To understand the **molecular epidemiology** of TB, including circulating strains, lineages and virulence ;
 - d. To monitor TB programmes by analysing the trends in **estimates of recent transmission**;
 - e. To meet international obligations for **molecular surveillance**, Europe-wide and globally;
 - f. To create a national **repository of strain types**.
2. The **epidemiological analysis** of the data should be prioritised. Findings should be reported back to local Health Protection Teams (HPTs) and NHS partners. The first three years of data from the service linked to the epidemiological surveillance data should be available for analysis imminently. Looking forward, it is recommended that a small group be responsible for supporting the analysis and the clear and timely communication of the data downstream. CIs and Field Epidemiologists could very usefully assist with the important routine analysis of data.
3. **Cluster investigations** should be reconsidered. The evaluation found no evidence to suggest that cluster investigations were effective or cost effective. However, as acknowledged in the limitations, this may be due to insufficient evidence.

Local cluster investigations We recommend that cluster investigations are no longer led by CIs but are **initiated from the local level** in response to local demand. Under this scenario, the CIs and Field Epidemiologists should be available to assist Local HPTs when they choose to launch a cluster investigation.

Regional cluster investigations We recommend that regional cluster investigations are **discontinued** as they appear to add little value. However, the assistance of CIs in the coordination of cluster investigations was highly appreciated.

National cluster investigations We recommend that the routine investigations of national cluster investigations are discontinued and that national cluster investigations be limited to clusters that have been

identified to be of **public health importance**, e.g. rapidly growing clusters and clusters of drug resistant TB.

Under this scenario, CIs and Field Epidemiologists should be available to support these investigations.

4. The **STM** should be released as a priority. If this is not possible using the current in-house support, then the option of outsourcing this work should be explored. The release of the *STM* will lead to the standardisation of laboratory reporting and enable local access to strain typing data to inform the local initiation of cluster investigations.
5. Public health and laboratory **quality assurance** should continue.
 - a. The **actions and outcomes of all cluster investigations** that *are* conducted should be routinely recorded and be accessible for future evaluations.
 - b. A **false positive TB isolation identification and reporting protocol** should be agreed between the reference laboratories.
 - c. The **completeness of typing data** (i.e. the proportion of all isolates typed and the availability of full 24-loci typing profiles) for meaningful analysis and interpretation should be improved.
6. A review of the **human resources and capacity** across the TB-STS is recommended. This should include any potential impact the TB-STS has on the TB service more broadly. Moving forward, there is a need to recognise the potential capacity available to implement a complex intervention such as the TB-STS.
7. The key driver for the effectiveness and cost-effectiveness of TB control identified in this evaluation was **diagnostic delay**. The TB service should focus on and invest in interventions and TB control strategies that will lead to the earlier diagnosis of TB.

The Prospective Evaluation of the National Tuberculosis Strain-typing Service in England: A Mixed Methods Study

Supplementary File 1: The Effectiveness and Cost effectiveness of the TB-STS

Supplementary File 1A: Effectiveness of the TB-STS

Overview

Figure 2 in the main text shows the general structure of the model. The model is age structured, with the population stratified into single year age groups and deterministic, describing what happens on average over time, using weekly time steps (see below for further details, the difference equations and input parameters). The model includes immigration and emigration and considers the following three epidemiological scenarios:

Scenario 1. Low incidence, comparable to that in the white UK population. For this scenario, the predicted TB incidence increases with increasing age, reaching about 7 per 100,000 for those aged ≥ 55 years (Supplementary Figure 1A), which is consistent with observed data (2-5 and 4-9 per 100,000 per year in 2011).¹ Here the infection risk is assumed to have declined since 1950² and has remained roughly constant since 1980, a small proportion ($<10\%$) of those aged <55 years are assumed to have been infected, as compared with 50% on average of those aged ≥ 55 years (Supplementary Figure 1B). The proportion of disease that is attributable to recent transmission decreases steadily with increasing age, reaching $<10\%$ for those aged ≥ 55 years (Supplementary Figure 1C).

2. Medium incidence, comparable to that in the non-white UK-born in which the disease incidence is about 20 per 100,000 per year, as compared with 9-55 per 100,000 in the observed 2009 data.³ The annual risk of infection (ARI) is assumed to have been constant over time at 0.1% per year, with a low proportion of individuals who have been infected (average of $<20\%$ for those aged ≥ 55 years).

3. High incidence, comparable to that in the non-UK born in which the disease incidence is about 120 per 100,000 year, which is comparable to observed data (notification rates of 59-273 per 100,000 in 2009, depending on the ethnic group). The ARI is assumed to have been constant over time at 1% per year, similar to

that in some developing countries, with proportion of individuals who have been infected increasing with increasing age to reach an average of 20% for those aged ≥ 55 years.

For scenarios 2 and 3, the assumed in- and out- migration rates are 8 and 6 per 1000 per year respectively, based on data from the period 2000-2010.⁴ In-migrants are assumed to be aged 15-54 years; the assumed out-migration rate is identical for all ages. The TB prevalence among in-migrants is assumed to be 0.02%, which is consistent with the predicted prevalence in the model for an ARI of 1%/year. The TB incidence in these individuals in their native populations is similar to that shown in (Supplementary Figure 1A) for an ARI of 1% year, which is similar to that in the non-UK born population in the UK,¹ but slightly lower than that estimated among immigrants, shortly after entering the UK (320-400 per 100,000 in 1998).⁵ Based on recent data, we assume that no cases are detected when entering the UK.⁶ The model parameters are shown in Supplementary Table 1.

Model assumptions

Individuals are assumed to be born uninfected and are infected at a rate $\lambda(t)$ (the force or risk of infection). The force of infection depends on the prevalence of infectious individuals and is calculated as the product of the prevalence of infectious individuals and the effective contact rate, c_e , defined as the average number of individuals effectively contacted by each infectious person per unit time. An effective contact is defined as one that is sufficient to lead to transmission if it occurs between an uninfected (“susceptible”) person and an infectious person.⁷ The effective contact rate is calculated so it leads to given values for the annual risk of infection (see below).

Following infection, individuals are assumed to face an increased rate of developing disease during the first 5 years after infection (“primary” disease), which decreases with time since infection, after which they can either experience disease through reactivation or following reinfection. The rates at which they develop disease through the various mechanisms are age-dependent and are identical to those estimated in previous work.⁸ The rate of disease onset following reinfection is less than that following new “primary” infection, due to some immunity resulting from previous infection.^{8,9}

As in previous versions of the model, the proportion of disease that is sputum smear or culture-positive (infectious) is assumed to increase with age, based on observed data.⁸ For simplicity, females are not modelled

explicitly in the model. For simplicity, the effects of HIV are also not modelled, given the low prevalence of HIV (2.4 per 1000) in England and Wales by 2008.¹⁰

Following disease onset, cases are assumed to be detected at a constant rate, with an average time to detection of 10 weeks. Given this relatively short time to detection, progression from smear negative to smear positive TB is not modelled explicitly.

Following detection, cases are assumed to start TB treatment after an average period of 2 weeks, so that the average time from disease onset to detection is 12 weeks, as observed in the strain typing data. 82% of those who start treatment are assumed to complete it, with the remainder dying (7%), defaulting from treatment (5.5%) or being lost to follow-up (5.5%).¹¹ Those who default from treatment are assumed to return to the undetected category and remain infectious. TB treatment is assumed to last a fixed period of 6 months. TB treatment is assumed to clear infection and individuals can develop disease subsequently only following reinfection. The rate at which they develop disease following reinfection is assumed to be identical to the rate at which those who have been infected for at least five years (described as those in the “latent” category in Figure 2 in the main text) develop disease following reinfection.

Based on observed data, 95% of those aged <35 years who are identified as having been infected, according to TST/IGRA, are assumed to start preventive treatment (PT) for 3 or 6 months, with 85% of these completing the full course.⁶ National policy dictates that PT is not given to those under 35 years.¹² PT is assumed to provide 65% protection against disease whilst individuals are taking it.^{13,14} Given complete compliance, the full course of PT is assumed to fully cure the infection, so that individuals can only develop disease subsequently following reinfection. It is also assumed that individuals who have either previously had TB treatment or PT would not be provided PT again.

In the absence of the TB-STIS, a small percentage (3%) of all infected individuals is assumed to have been detected and treated each year. This proportion is unknown, but was probably very low, as implied by the number of tuberculin-positive contacts of tuberculosis cases that were identified for each tuberculosis case that was investigated. For example, data on contact tracing activity suggested that after the introduction of the TB-STIS, on average, about four contacts of each identified tuberculosis case who was not in a cluster, was traced, with one of the contacts being tuberculin positive. Since approximately 9000 cases were reported in England in

2009,³ this suggests that about 9000 tuberculin-positive people were identified. If the average prevalence of tuberculous infection in England is less than 10% and given a population of 55 million in England and Wales,¹⁵ then the proportion of prevalent infections that is detected each year is likely to be less than 1%. An analogous calculation suggests that if the average prevalence of tuberculous infection in England was less than 1%, then the proportion of prevalent infections that is detected each year is likely to be less than 2%.

The amount by which the proportion of infections that were detected after the introduction of the TB-STS increased is also poorly understood. However, it is unlikely to have increased substantially, given that the number of contacts that were screened per TB case for cases who were in a cluster was similar to that for cases who were not in a cluster. We here assume that it increases by a factor of three, i.e. to 13% per year, which is likely to be close to or exceed the upper limit on the likely value.

The proportion of those eligible who take up preventive treatment, once detected, is also unknown, as is the proportion of those who start taking preventive treatment who complete it. We have assumed values of 95% (minimum and maximum values of 30% and 95% respectively) for the former and values of 85% (minimum and maximum values of 50% and 100% respectively) for the proportion of those starting preventive treatment who complete it. These values are plausible, and are consistent with those used in previous decision analyses,¹⁶ although their accuracy is unclear. Studies of contact tracing activities in the USA from the period 1996-7 found that about 74% of tuberculin-positive contacts of tuberculosis cases started preventive treatment, with 56% completing it.¹⁷ Similar data from the UK are limited. For example, studies have sometimes reported the numbers or proportions of contacts who started preventive treatment, without providing the numbers who were eligible or who completed preventive treatment.¹⁸

Model equations

The model was set up using weekly time steps using the difference equations below. The model was written using the C programming language. Supplementary Table 1 provides the main parameters and variables; Supplementary Table 2 summarizes the definitions of the compartments and variables in the model; any additional parameters are defined below.

People were allowed to experience the benefits of PT (i.e. reduced rates of disease onset) or lack of benefit in the same week as they started or stopped PT respectively. To simplify the equations whilst allowing this to

occur, the population in the PT-related compartments was transferred into subsequent strata at the end of each time step, once other transitions had been accounted for.

Uninfected compartment

$$U_a(t + \delta t) = U_a(t)(1 - \lambda(t) - \mu_a - m_{tb-,a}) \quad \text{Equation 0.1}$$

Recently (primary) infected compartment

Recently (primary) infected people who are not on PT

$$E_{z-,a}(t + \delta t, 0) = (1 - i_{z+}(t))\lambda(t)U_a(t)(1 - d_{p,z-,a}(0)) \quad \text{Equation 0.2a}$$

$$E_{z-,a}(t + \delta t, s_i + \delta s_i) = (1 - i_{z+}(t))E_{z-,a}(t, s_i)(1 - d_{p,z-,a}(s_i) - \mu_a - m_{tb-,a}) + M_{in,E,a}(t, s_i) \quad \text{Equation 0.2b}$$

Recently (primary) infected people who are on PT

$$E_{z+,a}(t + \delta t, s_i + \delta s_i, 0) = E_{z-,a}(t, s_i)i_{z+,a}(t)(1 - d_{p,z+,a}(s_i) - \mu_a - m_{tb-,a}) \quad \text{Equation 0.3a}$$

$$E_{z+,a}(t + \delta t, 0, s_z) = i_{z+,a}(t)\lambda(t)U_a(t) \quad \text{Equation 0.3b}$$

$$E_{z+,a}(t + \delta t, s_i + \delta s_i, s_z + \delta s_z) = E_{z+,a}(t, s_i, s_z) - E_{z+,a}(t, s_i, s_z)(d_{p,z+,a}(s_i) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.3c}$$

Recently (primary) infected people who have previously been on PT

$$E_{z_p,a}(t + \delta t, s_i + \delta s_i) = E_{z_p,a}(t, s_i) - E_{z_p,a}(t, s_i)(d_{p,z-,a}(s_i) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.4}$$

Latent and Reinfected compartments

To ensure that no one in the population could start PT multiple times, the latent and reinfected compartments are subdivided according to whether or not they have been on PT previously. For simplicity, this detail is omitted

from the model diagram (Figure 2 in the main text). However, the disease-related compartments have not been stratified according to previous PT – this simplification is unlikely to affect conclusions since a negligible proportion of the model population is likely to experience PT twice and treatment for tuberculosis disease.

People with Latent infection

$$L_{z-,a}(t + \delta t) = L_{z-,a}(t)(1 - i_{z+,a}(t))(1 - d_{n,z-,a} - \lambda(t) - m_{tb-,a} - \mu_a) + M_{in,L,a}(t) + R_{z-,a}(t, T_R) + E_{z-,a}(t, T_E) \quad \text{Equation 0.5a}$$

$$L_{z+,a}(t + \delta t, 0) = L_{z-,a}(t)i_{z+,a}(t)(1 - d_{n,z+,a} - \lambda(t) - m_{tb-,a} - \mu_a) \quad \text{Equation 0.5b}$$

$$L_{z+,a}(t + \delta t, s_z + \delta s_z) = L_{z+,a}(t, s_z) - L_{z+,a}(t, s_z)(d_{n,z+,a} + \lambda(t) + m_{tb-,a} + \mu_a) + E_{z+,a}(t, T_E, s_z) + R_{z+,a}(t, T_R, s_z) \quad \text{Equation 0.5c}$$

People who have completed PT but have not been reinfected in the previous 5 years

$$P_{e+,a}(t + \delta t) = P_{e+,a}(t) - (\lambda(t) + m_{tb-,a} + \mu_a)P_{e+,a}(t) + V_{z+,a}(t, T_{z_{\max}}) + L_{z+,a}(t, T_{z_{\max}}) \quad \text{Equation 0.6a}$$

$$P_{e-,a}(t + \delta t) = P_{e-,a}(t) - P_{e-,a}(t)(d_{n,z-,a} + \lambda(t) + m_{tb-,a} + \mu_a) + R_{z-,a}(t, T_R) + E_{z-,a}(t, T_E) \quad \text{Equation 0.6b}$$

Reinfected people who are not on PT

$$R_{z-,a}(t + \delta t, 0) = (1 - i_{z+}(t))\lambda(t)(L_{z-,a}(t) + V_{z-,a}(t))(1 - d_{x,z-,a}(0)) \quad \text{Equation 0.7a}$$

$$R_{z-,a}(t + \delta t, s_r + \delta s_r) = (1 - i_{z+}(t))R_{z-,a}(t, s_r)(1 - d_{x,z-,a}(s_r) - m_{tb-,a} - \mu_a) + M_{in,R,a}(t, s_r) \quad \text{Equation 0.7b}$$

Reinfected people who are on PT

$$R_{z+,a}(t + \delta t, s_r + \delta s_r, 0) = R_{z-,a}(t, s_r)i_{z+,a}(t)(1 - d_{x,z+,a}(s_r) - m_{tb-,a} - \mu_a) \quad \text{Equation 0.8a}$$

$$R_{z+,a}(t + \delta t, 0, s_z) = \lambda(t)(L_{z+,a}(t, s_z) + V_{z+,a}(t, s_z))(1 - d_{x,z+,a}(0)) \quad \text{Equation 0.8b}$$

$$R_{z+,a}(t + \delta t, s_r + \delta s_r, s_z + \delta s_z) = R_{z+,a}(t, s_r, s_z) - R_{z+,a}(t, s_r, s_z)(d_{x,z+,a}(s_r) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.8c}$$

Reinfected people who have previously been on PT

$$R_{z_p,a}(t + \delta t, 0) = \lambda(t)(P_{e+,a}(t) + P_{e-,a}(t))(1 - d_{x,z-,a}(0)) \quad \text{Equation 0.9a}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) - R_{z_p,a}(t, s_r)(d_{x,z-,a}(s_r) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.9b}$$

Cases who have not yet been detected

To allow calculation of the proportion of tuberculosis cases that have been reinfected recently, cases which have not yet been detected are further stratified according to the mechanism by which they are experiencing disease (i.e. (exogenous) reinfection or (endogenous) reactivation). Once detected (“found”), cases remain in the detected compartments for a maximum period of 6 months (denoted by $T_{f_{\max}}$), unless they start treatment in the meantime, after which they are redistributed into the undetected compartments, according to their relative size. Considering cases experiencing disease through endogenous reactivation, this redistribution is calculated using

$$p_{Dn,s,a} = \frac{D_{n,s,a}(t, T_{o_{\max}})}{D_{p,s,a}(t, T_{o_{\max}}) + D_{n,s,a}(t, T_{o_{\max}}) + D_{x,s,a}(t, T_{o_{\max}})}$$

the equation

The equation considering cases of primary or exogenous disease is analogous.

Cases experiencing disease because of primary infection, who have not yet been detected

$$D_{p,s+,a}(t + \delta t, 0) = o_{s+,a} \sum_{s_i=0}^{T_E} d_{p,z-,a}(s_i)(E_{z-,a}(t, s_i) + E_{z_p,a}(t, s_i)) \\ + o_{s+,a} \sum_{s_i=0}^{T_E} \sum_{s_z=0}^{T_{z\max}} E_{z+,a}(t, s_i, s_z) d_{p,z+,a}(s_i)$$

Equation 0.10a

$$D_{p,s-,a}(t + \delta t, 0) = (1 - o_{s+,a}) \sum_{s_i=0}^{T_E} d_{p,z-,a}(s_i)(E_{z-,a}(t, s_i) + E_{z_p,a}(t, s_i)) \\ + (1 - o_{s+,a}) \sum_{s_i=0}^{T_E} \sum_{s_z=0}^{T_{z\max}} E_{z+,a}(t, s_i, s_z) d_{p,z+,a}(s_i)$$

Equation 0.10b

$$D_{p,s,a}(t + \delta t, s_o + \delta s_o) = D_{p,s,a}(t, s_o) + (1 - p_{in,f,s}) M_{in,D_p,s,a}(t, s_o) \\ - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) D_{p,s,a}(t, s_o)$$

Equation 0.10c

$$s_o < T_{o\max}$$

$$D_{p,s,a}(t + \delta t, s_o + \delta s_o) = D_{p,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) D_{p,s,a}(t, s_o) \\ + (1 - p_{in,f,s}) M_{in,D_p,s,a}(t, s_o) + p_{D_p,s,a} F_{s,a}(t, T_{f\max})$$

Equation 0.10d

$$s_o = T_{o\max}$$

Cases experiencing disease because of reactivation, who have not yet been detected

$$D_{n,s-,a}(t + \delta t, 0) = (1 - o_{s+,a})(L_{z-,a}(t) d_{n,z-,a} + L_{z+,a}(t) d_{n,z+,a})$$

Equation 0.11a

$$D_{n,s+,a}(t + \delta t, 0) = o_{s+,a}(L_{z-,a}(t) d_{n,z-,a} + L_{z+,a}(t) d_{n,z+,a})$$

Equation 0.11b

$$D_{n,s,a}(t + \delta t, s_o + \delta s_o) = D_{n,s,a}(t, s_o) - D_{n,s,a}(t, s_o)(r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a) \\ + (1 - p_{in,f,s}) M_{in,D_n,s,a}(s_o)$$

Equation 0.11c

$$s_o < T_{o\max}$$

$$\begin{aligned}
D_{n,s,a}(t + \delta t, s_o + \delta s_o) &= D_{n,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{n,s,a}(t, s_o) \\
&\quad + (1 - p_{in,f,s})M_{in,D_n,s,a}(t, s_o) + p_{D_n,s,a}F_{s,a}(t, T_{f_{\max}}) \\
s_o &= T_{o_{\max}}
\end{aligned}
\tag{Equation 0.11d}$$

Cases experiencing disease because of reinfection, who have not yet been detected

$$\begin{aligned}
D_{x,s-,a}(t + \delta t, 0) &= (1 - o_{s+,a}) \sum_{s_r=0}^{T_R} d_{x,z-,a}(s_r)(R_{z-,a}(t, s_r) + R_{z\rho,a}(t, s_r)) \\
&\quad + (1 - o_{s+,a}) \sum_{s_r=0}^{T_R} \sum_{s_z=0}^{T_{z_{\max}}} R_{z+,a}(t, s_r, s_z) d_{x,z+,a}(s_r)
\end{aligned}
\tag{Equation 0.12a}$$

$$\begin{aligned}
D_{x,s+,a}(t + \delta t, 0) &= o_{s+,a} \sum_{s_r=0}^{T_R} d_{x,z-,a}(s_r)(R_{z-,a}(t, s_r) + R_{z\rho,a}(t, s_r)) \\
&\quad + o_{s+,a} \sum_{s_r=0}^{T_R} \sum_{s_z=0}^{T_{z_{\max}}} R_{z+,a}(t, s_r, s_z) d_{x,z+,a}(s_r)
\end{aligned}
\tag{Equation 0.12b}$$

$$\begin{aligned}
D_{x,s,a}(t + \delta t, s_o + \delta s_o) &= D_{x,s,a}(t, s_o) + (1 - p_{in,f,s})M_{in,D_x,s,a}(t, s_o) \\
&\quad - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{x,s,a}(t, s_o)
\end{aligned}
\tag{Equation 0.12c}$$

$$s_o < T_{o_{\max}}$$

$$\begin{aligned}
D_{x,s,a}(t + \delta t, s_o + \delta s_o) &= D_{x,s,a}(t, s_o) - (r_f(t) + m_{tb+} + m_{tb-,a} + \mu_a)D_{x,s,a}(t, s_o) \\
&\quad + (1 - p_{in,f,s})M_{in,D_x,s,a}(t, s_o) + p_{D_x,s,a}F_{s,a}(t, T_{f_{\max}})
\end{aligned}
\tag{Equation 0.12d}$$

$$s_o = T_{o_{\max}}$$

Detected cases

$$F_{s-,a}(t + \delta t, 0) = \sum_{s_o=0}^{T_{0max}} (r_f(t)(D_{p,s-a}(t, s_o) + D_{n,s-a}(t, s_o) + D_{x,s-a}(t, s_o)))$$

$$+ p_{in,f,s-} \sum_{s_o=0}^{T_{0max}} (M_{in,D_p,s-,a}(t, s_o) + M_{in,D_x,s-,a}(t, s_o) + M_{in,D_n,s-,a}(t, s_o))$$

Equation 0.13a

$$F_{s-,a}(t + \delta t, s_f + \delta s_f) = F_{s-,a}(t, s_f) - (m_{tb+} + m_{tb-,a} + \mu_a + \tau(s_f))F_{s-,a}(t, s_f)$$

Equation 0.13b

$$F_{s+,a}(t + \delta t, 0) = \sum_{s_o=0}^{T_{0max}} r_f(t)(D_{p,s+,a}(t, s_o) + D_{n,s+,a}(t, s_o) + D_{x,s+,a}(t, s_o))$$

$$+ p_{in,f,s+} \sum_{s_o=0}^{T_{0max}} (M_{in,D_p,s+,a}(t, s_o) + M_{in,D_n,s+,a}(t, s_o) + M_{in,D_x,s+,a}(t, s_o))$$

Equation 0.13c

$$F_{s+,a}(t + \delta t, s_f + \delta s_f) = F_{s+,a}(t, s_f) - F_{s+,a}(t, s_f)(m_{tb+} + m_{tb-,a} + \mu_a + \tau(s_f))$$

$$0 < s_f < T_{fmax}$$

Equation 0.13d

Cases undergoing TB treatment

$$C_a(t + \delta t, 0) = \sum_{s_f=0}^{T_{fmax}} \tau(s_f)(F_{s-,a}(t, s_f) + F_{s+,a}(t, s_f))$$

Equation 0.14a

$$C_a(t + \delta t, s_r + \delta s_r) = C_a(t, s_r) - C_a(t, s_r)(m_{tb+} + m_{tb-,a} + \mu_a)$$

Equation 0.14b

$$0 < s_r < T_{rmax}$$

People who have recovered from TB disease

$$V_{z-,a}(t + \delta t) = V_{z-,a}(t) - V_{z-,a}(t)(i_{z+,a}(t) + \lambda(t) + m_{tb-,a} + \mu_a)$$

$$+ M_{in,V,a}(t) + C(T_{rmax})$$

Equation 0.15a

$$V_{z+,a}(t + \delta t, 0) = V_{z-,a}(t) i_{z+,a}(t) \quad \text{Equation 0.15b}$$

$$V_{z+,a}(t + \delta t, s_z + \delta s_z) = V_{z+,a}(t, s_z) - V_{z+,a}(t, s_z) (i_{z-,a}(t) + \lambda(t) + m_{tb-,a} + \mu_a) \quad \text{Equation 0.15c}$$

$$0 < s_z < T_{z_{\max}}$$

Transitions at the end of each time step

$$P_{e+,a}(t + \delta t) = P_{e+,a}(t) + L_{z+,a}(t, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) + \sum_{s_z=0}^{T_{z_{\max}}} V_{z+,a}(t, s_z) i_{z-}(s_z) + \sum_{s_r \geq T_{z_{\max}}} R_{z+,a}(t, s_r, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) + \sum_{s_j \geq T_{z_{\max}}} E_{z+,a}(t, s_j, T_{z_{\max}}) i_{z-}(T_{z_{\max}}) \quad \text{Equation 0.16}$$

$$P_{e-,a}(t + \delta t) = P_{e-,a}(t) + \sum_{s_z < T_{z_{\max}}} L_{z+,a}(t, s_z) i_{z-}(s_z) \quad \text{Equation 0.17}$$

$$L_{z+,a}(t + \delta t, s_z + \delta s_z) = L_{z+,a}(t, s_z) (1 - i_{z-}(s_z)) \quad \text{Equation 0.18}$$

$$s_z < T_{z_{\max}}$$

$$E_{z_p,a}(t + \delta t, s_j + \delta s_j) = E_{z_p,a}(t, s_j) + E_{z+,a}(t, s_j, T_{z_{\max}}) + \sum_{s_z < T_{z_{\max}}} E_{z+,a}(t, s_j, s_z) i_{z-}(s_z) \quad \text{Equation 0.19a}$$

$$s_j \neq T_{z_{\max}}$$

$$E_{z_p,a}(t + \delta t, s_i + \delta s_i) = E_{z_p,a}(t, s_i) + \sum_{s_z < T_{z_{\max}}} E_{z^+,a}(t, s_i, s_z) i_{z^-}(s_z) \quad \text{Equation 0.19b}$$

$$s_i = T_{z_{\max}}$$

$$E_{z^+,a}(t, s_i + \delta s_i, s_z + \delta s_z) = E_{z^+,a}(t, s_i, s_z)(1 - i_{z^-}(s_z)) \quad \text{Equation 0.20}$$

$$s_z < T_{z_{\max}}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) + R_{z^+,a}(t, s_r, T_{z_{\max}}) + \sum_{s_z < T_{z_{\max}}} R_{z^+,a}(t, s_r, s_z) i_{z^-}(s_z) \quad \text{Equation 0.21a}$$

$$s_r \neq T_{z_{\max}}$$

$$R_{z_p,a}(t + \delta t, s_r + \delta s_r) = R_{z_p,a}(t, s_r) + \sum_{s_z < T_{z_{\max}}} R_{z^+,a}(t, s_r, s_z) i_{z^-}(s_z) \quad \text{Equation 0.21b}$$

Equation 0.17

$$s_r = T_{z_{\max}}$$

$$R_{z^+,a}(t, s_r + \delta s_r, s_z + \delta s_z) = R_{z^+,a}(t, s_r, s_z)(1 - i_{z^-}(s_z)) \quad \text{Equation 0.22}$$

$$s_z < T_{z_{\max}}$$

$$V_{z^+,a}(t + \delta t, s_z + \delta s_z) = V_{z^+,a}(t, s_z)(1 - i_{z^-}(s_z)) \quad s_z < T_{z_{\max}} \quad \text{Equation 0.23a}$$

$$V_{z+,a}(t + \delta t, s_z + \delta s_z) = V_{z+,a}(t, s_z)(1 - i_{z-}(s_z)) + L_{z+,a}(t, s_z)(1 - i_{z-}(s_z)) + \sum_{s_r \geq T_{z\max}} R_{z+,a}(t, s_r, T_{z\max})(1 - i_{z-}(T_{z\max}))$$

Equation 0.23b

$$s_z = T_{z\max}$$

The force or risk of infection

The force of infection at time t is given in Equation 0.24 in terms of the effective contact rate (c_e) (defined as the average number of individuals effectively contacted by each infectious case), the total number of smear-negative and smear-positive cases ($I_{s-}(t)$ and $I_{s+}(t)$ respectively), the population size ($N(t)$) and the relative infectiousness of smear-negative, compared to smear-positive cases (f). The latter equals 22%, consistent with molecular epidemiological data(2).

$$\lambda(t) = \frac{c_e(f I_{s-}(t) + I_{s+}(t))}{N(t)}$$

Equation 0.24

Extending the definition used for acute infections, an effective contact is defined as one that is sufficient to lead to transmission if it occurs between an infectious individual and someone with either a “latent” infection or who has never been infected.⁷

The total number of smear-positive individuals is given by the following equation

$$I_{s+}(t) = \sum_a \sum_{s_o=0}^{T_{o\max}} (D_{p,s+,a}(t, s_o) + D_{n,s+,a}(t, s_o) + D_{x,s+,a}(t, s_o)) + \sum_{s_f=0}^{T_{f\max}} F_{s+,a}(t, s_f)$$

The equation for smear-negative cases is analogous.

The rate at which detected cases start TB treatment

The rate at which cases start treatment in the model was calculated so that the average time until cases had started treatment equalled 2 weeks and 82% of cases did not eventually start treatment. Cases who had not

started treatment within 6 months were returned to the undetected categories (see above). These rates were calculated as the values for $\tau(s_f)$ satisfying the following equations:

$$u(s_f + 1) = u(s_f) - \tau(s_f)u(s_f)$$

$$u(4) = 0.18$$

where: $\tau(s_f)$ is the rate at which cases start TB treatment in week s_f after detection (assumed to be constant in each month); $u(s_f)$ is the estimated proportion of those detected who are still untreated s_f weeks after detection.

Supplementary File 1B: Cost-Effectiveness of the TB-STs

Objective

To estimate the cost-effectiveness of the TB Strain Typing Service (TB-STs) as an addition to the current system for tuberculosis (TB) control in England.

Methods

The analysis followed the methods recommended by the National Institute for Health and Clinical Excellence (NICE) for evaluation of public health interventions.¹⁹

- Perspective – A public sector perspective was used for costing, and included costs and savings attributable to the TB-STs for the NHS, Local Authorities, Department of Health and other public bodies. The majority of costs and savings from the TB-STs fall on the Public Health England (PHE) centre, regions, Health Protection Units (HPU), laboratories and NHS TB services.
- Measure of health effects - Health benefits attributable to the TB-STs were estimated in the form of Quality Adjusted Life Years (QALYs) gained for index cases, their contacts, and for people benefiting from prevention of onward transmission of TB (as estimated from the transmission model). QALY estimates included TB-related mortality and morbidity.
- Time horizon - Costs and health effects resulting from operating the TB-STs were estimated over a period of 20 years.
- Incremental analysis – The results are presented in the form of an Incremental Cost Effectiveness Ratio (ICER), which is the additional cost per additional QALY gained with the TB-STs. Thus we estimated the expected difference in costs and in health effects with/without the TB-STs. Any costs or health effects incurred under both systems were ignored. The resulting ICER was compared with the NICE-recommended upper threshold of £30,000 per QALY gained.²⁰
- Uncertainty - Deterministic sensitivity analysis was used to test the impact of uncertainty over input parameters on the cost-effectiveness results.
- Discounting - Costs and QALYs were both discounted at the NICE recommended rate of 3.5% per year. The impact of using the Department of Health recommended discount rates of 3.5% for costs and 1.5% discount rates for QALYs were tested in sensitivity analysis.

The conceptual model underlying the economic analysis is illustrated in Figure 3 in the main text. It was hypothesised that the introduction of the TB-STS might influence outcomes or health care expenditure through the following mechanisms:

- **TB-STS infrastructure.** The TB-STS has imposed capital and revenue costs for the reference laboratories and national, regional and local Health Protection Services (HPS). These include direct costs of the tests, but also costs of establishing the infrastructure to request tests, report results and perform quality assurance.
- **Detection of false positives.** One potential benefit of strain typing is earlier identification of the false positive TB cases that can be caused by laboratory contamination. In addition to the avoidance of anxiety for patients and their families, earlier identification of such cases has health and financial implications if treatment is avoided or reduced. There might also be benefits in earlier detection of alternative diagnoses (e.g. lung cancer), but these are difficult to quantify, and have not been included in our analysis.
- **Case finding activity.** Introduction of the TB-STS might in theory have increased or decreased case finding activity and related costs. As contact tracing is usually completed before the strain type result is available (survey results described in Box 2 of the main text), one would not expect it to impact on the initial number of contacts traced by TB clinics. However, it is possible that it could have affected decisions by health protection staff to initiate or extend investigations of potential outbreaks. If strain typing identifies otherwise unsuspected clusters of cases, the number of contacts followed up could increase, increasing costs. But strain typing might also have the effect of disproving links between epidemiologically linked cases, thus reducing case finding activity and costs.
- **Case finding yield.** Regardless of the impact on the volume of case finding activity, we hypothesised that strain typing would improve the yield of case finding; increasing the number of cases of active disease and latent infection identified per case of TB. If true, this would have a number of benefits:
 - **Earlier detection of active disease.** It seems plausible that cases detected through the TB-STS-enhanced cluster investigations might benefit from earlier diagnosis and initiation of treatment, and that earlier treatment might be associated with a reduction in QALY loss from TB.
 - **Increased detection of latent infection.** One might also expect an increase in the detection of latent infection resulting from strain typing. Individuals diagnosed with Latent TB Infection (LTBI) who are suitable for and accept prophylactic treatment should then have a reduced risk of developing active

disease themselves, avoiding QALY loss and NHS costs. However, there are costs and side effects of prophylaxis, which will offset its benefits to some extent.

- Prevention of onward transmission. Both earlier detection of active disease and increased prophylactic treatment should help to prevent transmission. If so, this would lead to further QALY gains and cost savings.

In addition to the above direct effects, the TB-STS may well provide more indirect benefits. For example, the availability of a national information resource on the distribution and growth of clusters might benefit future tuberculosis research and service development (see Box 3 in the main text). Such effects are hard to quantify or value, and so were not been included in the economic analysis, but they were discussed and taken into consider by the evaluation expert group.

Estimated impact on false positive identification

The survey of reference laboratories identified 70 possible false positive TB tests, of which 59 (84%) had a known outcome. 30 of the incidents with a known outcome (51%) were confirmed as false positive results attributed to cross contamination. Of these, 17 (57%) were not known about by the source laboratory before they were contacted by the reference lab. For eight of the 30 confirmed cross-contamination incidents (27%), the patient commenced treatment. For the economic analysis, it was assumed that five cases of unnecessary treatment would be avoided per year due to the TB-STS (ten cases per year was tested in sensitivity analysis).

Estimated impact on case finding activity and yield

Evidence on the impact of the TB-STS on the volume and yield of case finding activity was sparse. There was some evidence of an increase in time spent on cluster investigations reported in the survey of health protection staff: from a mean of 2.7% before to 7.1% after implementation.²¹ However, TB specialist nurses did not report any significant increase in time spent on contact tracing. In the economic analysis, an opportunity cost for additional time spent by HPU staff on cluster investigations was assumed: 4.4% Whole Time Equivalent (WTE) for each of 26 Consultants in Communicable Disease Control (CCDC) at £99,000pa, costing a total of £113,256 per year (total annual cost of £50,000 per year and £500,000 per year tested in sensitivity analysis).

There was no clear evidence of whether introduction of the TB-STS resulted in an increase in the number of contacts screened, or in the yield of contacts with active disease or latent infection found. Analysis of the

contact tracing database, national dataset and cluster monitoring dataset showed that a greater number of contacts were screened and more contacts with latent infection were identified in cases that were clustered and investigated compared with unique cases. However, there were no significant differences in the numbers of contacts screened or cases of latent infection identified for clustered cases that were investigated compared with clustered cases that were not investigated. Similarly, evidence for a change in the rate of cluster growth after the initiation of an investigation or for a change in the duration of diagnostic delay was equivocal.

It is unclear whether these negative results reflect the absence of an effect of the TB-STIS, or the difficulties in obtaining evidence. We therefore conducted a scenario analysis, in which we estimated the cost-effectiveness of the TB-STIS under a series of assumptions about its possible effects.

Population assumptions

Results were estimated across the population of England (53m) and took account of the age distribution of the population (age groups <15, 15-34, 35-54, 55+).²² The results were based on an epidemiological scenario with a medium TB incidence (similar to that in the non-white UK-born population in which the average infection risk was constant over time at 0.1%). This was chosen to reflect an average risk level across the community.

Scenarios investigated

The transmission model was used to estimate the number of cases prevented under a range of assumptions about the effect of the TB-STIS on: a) the proportion of previously infected individuals detected; and b) the mean length of time between onset of symptoms and treatment initiation.

The base case scenario (S0) was intended to reflect the expected costs and outcomes of the TB control system in the absence of the strain typing programme. This was modelled assuming that 3% of previously infected individuals are detected per year and that the mean time from onset of symptoms to the start of treatment is 12 weeks. The transmission model results for this base case scenario are summarised in Supplementary Table 3 for the population of England over 20 years, and assuming a constant risk of infection of 0.1% per annum. The estimated number of cases diagnosed exceeds the number of new cases in each year, as there is a pool of cases who have previously not been diagnosed or who have defaulted from treatment.

The cost-effectiveness of the TB-STIS was then estimated under a range of assumptions about its effect on identification of cases of LTBI found and the Diagnostic Delay (DD) for active cases. The results of the

transmission model under these scenarios are summarised in Supplementary Table 3 for the population of England over 20 years, and assuming a constant risk of infection of 0.1% per annum. The estimated number of cases diagnosed exceeds the number of new cases in each year, as there is a pool of cases who have previously not been diagnosed or who have defaulted from treatment.

The cost-effectiveness of the TB-STS was then estimated under a range of assumptions about its effect on identification of cases of LTBI found and the Diagnostic Delay (DD) for active cases. The results of the transmission model under these scenarios are summarised in Supplementary Table 4. They suggest that increases in the proportion of people with latent infection identified and treated have a relatively modest impact on TB incidence: if an additional 10% of prevalent infections were detected each year, the number of new TB cases would fall by an estimated 736 cases per year (11%). In contrast, reductions in diagnostic delay for active cases were estimated to have a much bigger impact on TB incidence: a one week reduction in the time from onset of symptoms to treatment was associated with an estimated reduction of 1,650 TB cases (25%). Furthermore, if such a reduction in diagnostic delay could be achieved, it would also be accompanied by a reduction in the number of people requiring prophylactic treatment.

Cost estimates

The estimated costs of establishing and running the national strain typing programme were estimated from financial information obtained from Public Health England and TB Reference Laboratories. Capital expenditure was converted to an equivalent annual cost assuming a 10 year lifetime of the investment and 3.5% annual discount rate. Total costs were estimated at just under £1m per year.

The estimated costs of screening, diagnosis and treatment are shown in Supplementary Table 5. The average quantities of resource items per patient were based on standard treatment protocols, informed by expert judgement. Unit costs per resource item were taken from standard national sources: Department of Health Reference Costs 2010-11 for Tuberculosis Specialist Nurse visits, outpatient consultations (respiratory clinic), and inpatient admissions; British National Formulary, Sept 2012 for medications; and published sources for tests.^{16,23}

The cost per contact screened was estimated at £234: including contact tracing, TST and IGRA testing, and initial rule-out of active disease. The total cost of contact screening was estimated as a function of the number

of people diagnosed with latent infection, as estimated by the transmission model. The study of the yield of cluster investigations found that on average (across unique and clustered cases) 2.6 contacts were screened and 0.7 cases of LTBI were identified per TB case. Therefore, it was assumed that to diagnose one case of LTBI, 3.97 contacts would need to be screened, at a cost of £963. The cost of further follow-up and investigations for each contact suspected of having active disease was estimated at £434. We assumed that 20% of individuals investigated for active TB would receive a positive diagnosis, so the estimated cost to diagnose one case of TB was £2,170 (5 x £434). The costs of treatment for latent and active disease were estimated at £743 and £1,114 respectively for a full course, or £669 and £1,002 respectively allowing for drop out from treatment: assuming that 15% of patients drop out, after a mean of one month for latent infection and 2 months for active disease. Patients with TB who drop out are likely to be identified and offered treatment again at a later time. Such repeat cases are included in the transmission model estimates of the number of people diagnosed per year, and incur additional costs for diagnosis and treatment in the cost effectiveness analysis. For simplicity, it is assumed that the cost of diagnosis and treatment is the same for new and repeat cases.

QALY estimates

Estimates of the QALY loss per case of TB are shown in Supplementary Table 6. At ages of 15 and older, TB-related mortality contributed more to estimated QALY loss than TB-related morbidity. On average across all ages, a loss of 0.5 QALYs was attributable to case fatality out of a total estimated 0.62 QALYs lost.

QALYs lost due to TB-related mortality were estimated based on: TB incidence by age;²⁴ case-fatality rates by age group;²⁵ life expectancy (ONS); and mean quality of life by age (EQ5D scores) in the general population (Health Survey for England). The case fatality rates were taken from an analysis of national surveillance data linked to mortality data, with capture-recapture methods used to estimate the number of unascertained deaths.²⁵ In this analysis, case fatality was defined as a death within 12 months of the start (or notification) of TB treatment, and where TB was mentioned on the death certificate or if treatment outcome monitoring had stated that the death was caused by or contributed by TB. This includes deaths in which TB was reported as a contributory factor, as well as deaths directly caused by TB.

Estimates of QALY loss due to morbidity were based on some simple assumptions about the duration and quality of life reduction in three periods of time:

- a. **Pre-treatment period:** from onset of symptoms to initiation of treatment, which was assumed to last for 3 months in scenarios S0 to S10, and reduced according to the DD in scenarios S11 to S14. During this time, patients were assumed to have a utility equal to 90% of that of the general population of the same age.
- b. **Acute period:** assumed to last for 2 months from diagnosis, during which patients have a utility value of 0.675.²⁶
- c. **Post acute period:** from after the acute period to the end of treatment (4 months), during which patients have a utility value of 0.813.²⁶

Overall QALY losses per case of TB were estimated to be 0.19, 0.40, 0.59 and 1.18, respectively, for patients in age group 0-14, 15-34, 35-54, and 55 plus. It was assumed that after treatment completion there is no lasting effect of TB on quality of life or mortality risk, although within the transmission model, individuals can be re-infected, potentially incurring another QALY loss associated with a new TB incidence.

The QALY impact of adverse effects of treatment were assumed to be incorporated in the above utility multipliers for active disease. Patients with a false positive TB diagnosis who start treatment, were assumed to be treated for 4 months on average,²³ and during this time they were assumed to experience a utility loss of 0.1 due to the inconvenience and harmful health effects of TB treatment. Thus, the avoidance of treatment for a false positive case is associated with a mean QALY gain of 0.03. The QALY loss associated with the adverse effects of prophylactic treatment was estimated based on the assumption that 10% of patients experience some side effects, and that these last for one month on average, incurring a mean utility loss of 0.1. Thus the mean QALY loss per person treated with prophylaxis is 0.0008. It was assumed that there were no lasting consequences from adverse reactions to treatment for active disease or latent infection.

Results

Increased proportion of LTBI detected

Under our base case assumptions, if the TB-STIS had increased the proportion of LTBI detected from 3% to 4% with no impact on the mean time to diagnosis for active cases, it would not appear cost-effective (see Supplementary Table 7). Although the improvement would have prevented an estimated 1,726 cases of TB (over 20 years for the population of 53m), saving approximately £3.8m in diagnosis and treatment costs, this

cost was more than offset by the direct cost of the TB-STS (£14.3m), the additional costs of screening contacts (£32.5m) and of prophylactic treatment (£22.2m). The net impact on health expenditure was an estimated increase of £65.2m. This cost increase is associated with a QALY gain of around 682 years of healthy life, giving an estimated Incremental Cost Effectiveness Ratio (ICER) of £95,628 per QALY gained, which is well above the range usually considered to be cost-effective in the NHS (a maximum of £30,000 per QALY gained).

Estimated cost-effectiveness did improve if we assumed that the TB-STS achieved a greater increase in the proportion of latent infections detected. However, over the range tested this improvement was still not sufficient to bring the ICER below the £30,000 threshold. If the introduction of the TB-STS has increased the identification of an additional 10% of prevalent latent infections - an additional 281,461 people diagnosed with LTBI over 20 years - the estimated cost per QALY gained was £55,748 (Supplementary Table 8).

Reductions in diagnostic delay

In contrast, the results were very sensitive to small reductions in the average time from onset of symptoms to the start of treatment for active disease. A reduction from 12 weeks to 11 weeks was estimated to yield a large reduction in the number of incident TB cases, and hence in the numbers of contacts to be screened and in people requiring prophylactic treatment (Supplementary Table 9). There was therefore a net saving in healthcare expenditure (over £85m saved), as well as a large health improvement (16,000 QALYs gained). Bigger reductions in the diagnostic delay, would achieve even larger cost savings and health improvements.

Sensitivity to other assumptions

Results under a range of other changes to the model parameters are shown in Supplementary Table 10. Unless stated otherwise, these analyses all relate to the comparison between scenarios S1 and S0 (1% increase in the proportion of prevalent LTBI cases diagnosed with TB-STS; no difference in diagnostic delay), and with all other parameters held constant at the base case values.

Other than reductions in diagnostic delay, the only changes tested that gave an estimated ICER below the usual NICE threshold of £30,000 per QALY related to an increase in the QALY loss from TB. However, in order to achieve this result, quite strong assumptions were required about the TB-related mortality and/or morbidity: equivalent to an overall mean loss of two full years of healthy life per case.

Discussion

This analysis failed to demonstrate that the TB-STIS is a cost-effective use of NHS resources. It suggests that it is unlikely that earlier identification of false positive cases related to laboratory contamination, or increases in the identification and prophylactic treatment of contacts with a latent infection could, on their own, justify the cost of the system. We were not been able to conduct a probabilistic sensitivity analysis to characterise the overall impact of uncertainty over the parameters and assumptions over the transmission model and cost-effectiveness analysis. However, simple deterministic sensitivity analysis suggested that the results are, with one major exception, quite robust to plausible changes in most parameters. The key uncertainty relates to the lack of evidence over whether the system is associated with earlier diagnosis and treatment for active cases.

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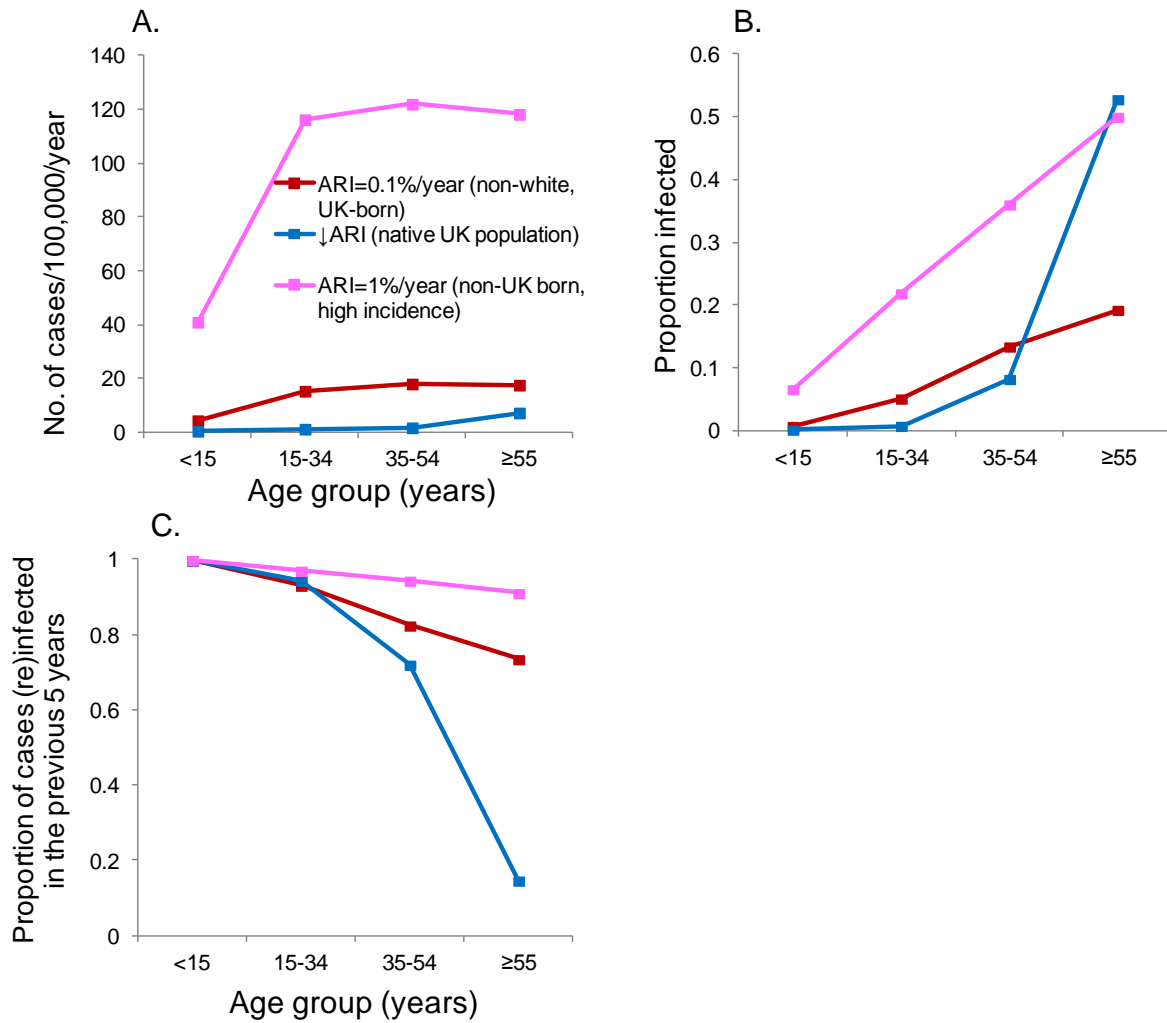
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Supplementary Figures

Supplementary Figure 1: Characteristics of the epidemiological scenarios considered in the model. A. the annual age-specific tuberculosis incidence per 100,000 population. B. The age-specific proportion of individuals who have ever been infected. C. The age-specific proportion of new cases that have been newly infected or reinfected in the previous 5 years for the epidemiological scenarios considered.



Supplementary Tables

Supplementary Table 1: Summary of assumed parameter values and their ranges. The subscript z- and z+ refer to those not on PT and on PT respectively, a refers to the age group. The abbreviations sm- and sm+ refer to those who are smear-negative and smear-positive respectively.

Definition	Symbol	Base case value	Source/comment
Transmission			
Number of people effectively contacted by each smear-positive case in a) Low incidence (similar to white UK population) b) Medium incidence (Non-white, UK-born population) c) High incidence (Non-white, non-UK-born)	c_e		Calculated to reproduce incidence consistent with observed notification rates
Infectiousness of smear-negative TB cases, compared to that of smear-positives	f	22%	²⁷
Force of infection at time t	$\lambda(t)$		See text
Disease onset			
Rate of disease onset following recent infection at time s_i since first infection among those not on PT among of age a	$d_{p,z-,a}(s_i)$	Cumulative risk over 5 years: 4% (children) 14% (adults), increases linearly between ages 10 and 20 years	^{8,9}
Rate of disease onset following recent infection at time s_i since first infection among those on PT among of age a	$d_{p,z+,a}(s_i)$	Calculated as $d_{p,z-,a}(s_i)\pi_{d,z+}$	
Rate of disease onset at time s_r following reinfection among those not on PT of age a	$d_{x,z-,a}(s_r)$	Cumulative risk over 5 years: 8%	^{8,9}
Rate of disease onset at time s_r following reinfection among those on PT of age a	$d_{x,z+,a}(s_r)$	Calculated as $d_{x,z-,a}(s_r)\pi_{d,z+}$	
Annual rate of developing disease through reactivation (%/year) among those not on PT of age a	$d_{n,z-,a}$	0.03%/year	^{8,9}
Annual rate of developing disease through reactivation (%/year) among those on PT of age a	$d_{n,z+,a}$	Calculated as $d_{n,z-,a}\pi_{d,z+}$	
Percentage of respiratory TB disease that is smear-positive among those of age a	$o_{s+,a}$	10% (children) 65% (adults)	Public Health England (PHE) Enhanced Surveillance database and data in ⁸ . Follows the age-specific pattern in ⁸ .
Duration that people spend in the reinfected compartment (experiencing the risk of disease given reinfection before being transferred to the latent	T_R	5 years	--

compartment			
Duration that people spend in the infected compartment (experiencing the high risk of disease given infection before being transferred to the latent compartment)	T_E	5 years	--
Demography			
Annual birth rate per 1000 per year		13.1	Office for National Statistics ⁴
Annual general population mortality rates	$m_{fb,a}$	Age-dependent	Office for National Statistics ⁴
Immigration rate		0.8%/year	Office for National Statistics ⁴
Outmigration rate for those of age a	μ_a	0.6%/year	Office for National Statistics ⁴
TB prevalence among immigrants		0.02%	Consistent with model predictions based on an ARI of 1%/year
Case detection			
% of immigrant TB cases with smear status s that are detected on entry to the UK	$p_{in,f,s}$	0%	⁶
Average time from disease onset to detection (among non-immigrants) at time t	$T_{detect}(t)$	10 weeks (before the start of the TB-STs); varied thereafter	PHE Enhanced Surveillance database
Average rate at which cases are found	$r_f(t)$	Calculated as $1/T_{detect}$	
Maximum duration of that people spend in the detected (found) compartment before being distributed to the undetected compartment, if they have not started TB treatment in the meantime.	$T_{f,max}$	6 months	--
Preventive treatment			
Proportion of infections that are detected at time t	$p_{i,det}(t)$	Varied between 3% and 13% per year	No data available. Assumed to differ before and after the start of the strain-typing service
Percentage of eligible contacts (TST/IGRA+ and aged <35 years) that start PT	$p_{z+,start}$	95%	Plausible value, based on national policy ¹²
Proportion of infected people that start PT at time t	$i_{z+}(t)$	Calculated as: $p_{i,det} p_{z+,start}$	--
Protection provided by PT against disease whilst taking PT	$\pi_{d,z+}$	65%	^{13,14}
Proportion of those taking PT who complete PT	$p_{z+,stop}$	85%	¹²
Rate at which those taking PT stop taking PT	i_{z-}	1.3%/week	Based on $p_{z+,stop} = 0.85$
Maximum duration of PT	$T_{z,max}$	3 months	--
Treatment			

Average time from detection to start of TB treatment	$T_{\text{treat, start}}$	2 weeks	--
Rate at which cases start TB treatment at time s_f following detection	$\tau(s_f)$	$s_f < 4$ weeks: 35%/week $s_f \geq 4$ weeks: 0%/week	Calculated so that 82% of detected cases complete treatment (see text)
Percentage of detected cases that complete TB treatment		82%	PHE Enhanced Surveillance database
Percentage of detected cases who default from treatment		5.5%	PHE Enhanced Surveillance database
Mortality rate among TB cases (before and during TB treatment)	$m_{b+,a}$	7%	PHE Enhanced Surveillance database
Percentage of detected cases that are lost to follow-up		5.5%	PHE Enhanced Surveillance database
Duration of TB treatment	T_{max}	26 weeks	--

Supplementary Table 2: Definitions of the compartments and variables in the model.

Symbol	Definition
$U_a(t)$	Number of people of age a at time t who have never been infected.
$E_{z-,a}(t,s_i)$	Number of people of age a who have been infected for duration s_i at time t , who have never had PT.
$E_{z+,a}(t,s_i,s_z)$	Number of people of age a who have been infected for duration s_i and have been on PT for duration s_z at time t .
$E_{z_p,a}(t,s_i)$	Number of people of age a who have been infected for duration s_i at time t , who have previously had PT.
$L_{z-,a}(t)$	Number of people of age a in the latent category at time t , who have never had PT.
$L_{z+,a}(t,s_z)$	Number of people of age a in the latent category at time t , who have been on PT for duration s_z .
$P_{e+,a}(t)$	Number of people of age a who have previously had PT, cleared their infection and have not been reinfected since clearing their infection.
$P_{e-,a}(t)$	Number of people of age a who have had PT, have not cleared their infection and have not been reinfected during the previous five years
$R_{z-,a}(t,s_r)$	Number of people of age a who have been reinfected for duration s_r at time t , who have never had PT.
$R_{z+,a}(t,s_r,s_z)$	Number of people of age a who have been reinfected for duration s_r and have been on PT for duration s_z at time t .
$R_{z_p,a}(t,s_r)$	Number of people of age a who have been reinfected for duration s_r at time t , who have previously had PT.
$D_{p,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease because of recent (primary) infection for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{p,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease because of recent (primary) infection for at least time $T_{o_{max}}$ at time t
$D_{n,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease through (endogenous) reactivation for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{n,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease through (endogenous) reactivation for at least time $T_{o_{max}}$.
$D_{x,s,a}(t,s_o)$	Number of undetected cases of age a and smear status s who have had disease because of (exogenous) reinfection for duration s_o at time t , if $S_o < T_{o_{max}}$. If $S_o = T_{o_{max}}$, $D_{x,s,a}(t,s_o)$ represents the number of cases of age a , smear status s who have had disease because of (exogenous) reinfection for at least time $T_{o_{max}}$ at time t
$F_{s,a}(t,s_f)$	Number of cases of smear status s , age a , who have been detected ("found") for duration s_f at time t and have not yet started TB treatment.
$C_a(t,s_t)$	Number of cases of age a , who have been on TB treatment for duration s_t at time t .
$V_{z-,a}(t)$	Number of people of age a who are in the recovered category at time t who are not on PT.
$V_{z+,a}(t,s_z)$	Number of people of age a , who are in the recovered category at time t who have been taking PT for duration s_z .
$M_{in,U,a}(t)$	Number of new immigrants at time t , who are of age a , and not infected

$M_{in,L,a}(t)$	Number of new immigrants at time t , who are of age a , and in the latent category.
$M_{in,E,a}(t, s_i)$	Number of new immigrants at time t who are of age a , and who have been newly infected for duration s_i .
$M_{in,R,a}(t, s_r)$	Number of new immigrants at time t who are of age a , and who have been reinfected for duration s_r .
$M_{in,D_p,s,a}(t, s_o)$	Number of new immigrants at time t who are of age a , who have been experiencing disease because of endogenous reactivation for duration s_o , and have smear status s .
$M_{in,D_n,s,a}(t, s_o)$	Number of new immigrants at time t who are of age a , who have been experiencing disease because of recent (primary) infection for duration s_o , and have smear status s .
$M_{in,D_x,s,a}(t, s_o)$	Number of new immigrants at time t of age a , who have been experiencing disease through exogenous reinfection for duration s_o , and have smear status s .
$M_{in,V,a}(t)$	Number of new immigrants at time t of age a , who have previously had TB, been treated and have not been reinfected since then.

Supplementary Table 3: Summary of transmission model results for base case scenario. Estimated number of cases by year for population of England (53m) over 20 years, assuming constant ARI of 0.1%.

Scenario	Year	LTBI diagnosed	LTBI starting treatment	New TB cases	TB cases diagnosed	TB cases starting treatment
S0	Year 1	9,069	8,616	6,730	7,568	6,698
	Year 2	9,060	8,607	6,723	7,561	6,691
	Year 3	9,051	8,599	6,717	7,554	6,685
	Year 4	9,043	8,590	6,711	7,547	6,679
	Year 5	9,034	8,582	6,705	7,540	6,673
	Year 6	9,025	8,574	6,698	7,532	6,666
	Year 7	9,016	8,566	6,692	7,526	6,660
	Year 8	9,008	8,557	6,686	7,519	6,654
	Year 9	8,999	8,549	6,680	7,512	6,648
	Year 10	8,991	8,541	6,674	7,505	6,642
	Year 11	8,982	8,533	6,668	7,498	6,636
	Year 12	8,974	8,525	6,662	7,491	6,630
	Year 13	8,966	8,517	6,656	7,485	6,624
	Year 14	8,957	8,509	6,650	7,478	6,618
	Year 15	8,949	8,502	6,644	7,472	6,612
	Year 16	8,941	8,494	6,638	7,465	6,607
	Year 17	8,933	8,486	6,633	7,458	6,601
	Year 18	8,925	8,478	6,627	7,452	6,595
	Year 19	8,916	8,471	6,621	7,446	6,589
	Year 20	8,908	8,463	6,615	7,439	6,584
	Total	179,747	170,760	133,431	150,046	132,794
	Mean pa	8,987	8,538	6,672	7,502	6,640

Supplementary Table 4: Summary of transmission model results for 14 scenarios. Mean number of cases per year for population of England (53m) over 20 years, assuming constant ARI of 0.1%.

*DD Diagnostic delay; LTBI latent tuberculosis infection

Scenario	% LTBI found	DD* (weeks)	LTBI diagnosed	LTBI starting treatment	New TB cases	TB cases diagnosed	TB cases starting treatment
S0	3%	12	8,987	8,538	6,672	7,502	6,640
S1	4%	12	11,298	10,733	6,585	7,408	6,556
S2	5%	12	13,334	12,668	6,502	7,316	6,475
S3	6%	12	15,131	14,375	6,420	7,227	6,397
S4	7%	12	16,718	15,882	6,342	7,140	6,321
S5	8%	12	18,120	17,214	6,265	7,056	6,246
S6	9%	12	19,361	18,393	6,191	6,974	6,174
S7	10%	12	20,459	19,436	6,118	6,895	6,104
S8	11%	12	21,432	20,360	6,048	6,817	6,036
S9	12%	12	22,295	21,180	5,979	6,742	5,969
S10	13%	12	23,060	21,907	5,912	6,668	5,904
S11	3%	11	7,835	7,443	4,964	5,631	4,990
S12	3%	10	7,011	6,661	3,828	4,379	3,884
S13	3%	9	6,412	6,091	3,051	3,520	3,125
S14	3%	8	5,964	5,666	2,504	2,912	2,588

Supplementary Table 5: Estimated costs of screening, diagnosis and treatment

¹ Assumes 4.11 contacts screened per person diagnosed with LTBI.

² Assumes 5 people investigated per person diagnosed with TB.

³ Assumes that 15% do not complete chemoprophylaxis, after an average 1 month of treatment.

⁴ Assumes that 15% do not complete treatment, after an average 2 months of treatment.

BNF British National Formulary

	Quantity	Unit cost	Cost	Source
Contact screening and follow up				
TB specialist nurse - non face to face	1	£27	£27	Ref cost 2011 ²⁸
TB specialist nurse - face to face	2	£62	£124	Ref cost 2011 ²⁸
Mantoux test	1	£1.22	£1.22	NICE 2011 ¹²
IGRA test	0.5	£56	£28	Pareek 2011 ⁶
Outpatient appointment for IGRA +	0.25	£187	£47	Ref cost 2011 ²⁸
Chest X-ray (to rule out active disease)	0.25	£28	£7	NICE 2010 ²⁹
Per contact screened			£234	
Per person diagnosed with LTBI ¹			£963	
Diagnosis of active disease				
TB specialist nurse - face to face	3	£62	£186	Ref cost 2011 ²⁸
Outpatient appointment for diagnosis	1	£187	£187	Ref cost 2011 ²⁸
Chest X-ray	1	£28	£28	NICE 2010 ²⁹
Sputum smear microscopy	1	£1.56	£1.56	Dowdy 2008 ³⁰
Culture & MDR identification	1	£30	£30	Dinnes 2007 ³¹
Liver function test	1	£1	£1	Ref cost 2011 ²⁸
Per contact with suspected TB			£434	
Per person diagnosed with TB ²			£2,170	
Management of latent infection				
Follow-up appointments nurse only	3	£62	£186	Ref cost 2011 ²⁸
Follow-up appointments nurse & consultant	2	£185	£370	Ref cost 2011 ²⁸
Isoniazid 300 mg daily (per month)	3	£41	£124	BNF 2012
Rifampicin 600 mg daily (per month)	3	£21	£63	BNF 2012
B6 pyridoxine 10mg tablets (per month)	3	£0.5	£1	BNF 2012

Per person completing treatment			£743	
Per person starting treatment ³			£669	
Management of active disease				
Admission	5%	£2,949	£147	Ref cost 2011 ²⁸
Follow-up appointments nurse only	5	£62	£310	Ref cost 2011 ²⁸
Follow-up appointments nurse & consultant	2	£185	£370	Ref cost 2011 ²⁸
Rifater (R,I ,P) 6 tablets daily for 2 months	2	£37	£74	BNF 2012
Ethambutol 15 mg/kg for 2 months	2	£63	£126	BNF 2012
Rifanah (R,I) 300/150 2 tab daily for 4 months	4	£21	£84	BNF 2012
B6 pyridoxine (per month)	6	£0.5	£3	BNF 2012
Per person completing treatment			£1,114	
Per person starting treatment ⁴			£1,002	

Supplementary Table 7: Cost-effectiveness if TB-STS increased the proportion of LTBI detected from 3% to 4%

Comparison S1 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	£32,539,484	-
Prophylactic treatment	£22,240,304	-27.70
TB diagnosis & treatment	-£3,809,472	707.27
Total	£65,219,944	682
Incremental cost effectiveness ratio (ICER)	£95,628	per QALY gained

Supplementary Table 8: Cost-effectiveness if TB-STS increased the proportion of LTBI detected from 3% to 13%

Comparison S10 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	£209,685,394	-
Prophylactic treatment	£143,317,116	-178.53
TB diagnosis & treatment	-£33,848,402	6,289.25
Total	£333,403,736	6,113
Incremental cost effectiveness ratio (ICER)	£54,539	per QALY gained

Supplementary Table 9: Cost-effectiveness if TB-STS reduced time to diagnosis from 12 to 11 weeks

Comparison S11 vs S0	Incremental Cost (£)	Incremental Effect (QALYs)
Programme	£14,298,781	-
False positives	-£49,153	2.45
Contact screening	-£13,640,543	-

Prophylactic treatment	-£9,323,117	11.61
TB diagnosis & treatment	-£76,153,948	16,032.60
Total	-£84,867,979	16,047
Incremental cost effectiveness ratio (ICER)	S11 dominant	

Supplementary Table 10: Deterministic sensitivity analysis results

Parameter changed (base case value)	Parameter values tested	Incremental cost (£)	Incremental effect (QALYs)	ICER (£ per QALY)
% LTBI detected	+1% with TB-STC (base case)	£65,219,944	682	£95,628
	+10% with TB-STC	£333,403,736	6,113	£54,539
Diagnostic delay	-1 week with TB-STC	-£64,867,979	16,047	Dominant
(no reduction)	-4 weeks with TB-STC	-£239,774,497	40,078	Dominant
Discount rates	1.5% for QALYs	£65,219,944	1,093	£59,682
(3.5% QALYs, 3.5% costs)	0% for QALYs	£65,219,944	1,643	£39,707
Time horizon	15 years	£55,453,941	431	£128,807
(20 years)	10 years	£42,475,021	212	£200,212
Cost of software	£500,000	£65,622,236	682	£96,218
(£264,593)	£1,000,000	£66,476,695	682	£97,471
Cost to HPU	£50,000 pa	£64,289,459	682	£94,234
(£113,256 pa)	£500,000 pa	£70,908,886	682	£103,970
False positives	10 cases avoided pa	£65,170,792	684	£95,214
(5 avoiding treatment pa)	100 cases avoided pa	£64,286,046	729	£88,233
Utility loss from FP	0.5 for 4 months	£65,219,944	692	£94,273
(basecase 0.1 for 4 months)	0.5 for 12 months	£65,121,639	716	£90,909
Contacts screened	2 contacts per LTBI diagnosed	£49,073,148	682	£71,953
(basecase 4.11)	6 contacts per LTBI diagnosed	£81,858,521	682	£120,025
Adverse effects of CPx	0%	£65,219,944	710	£91,896
(basecase 10%)	100%	£65,219,944	433	£150,737
Yield of TB diagnosis	2 per case	£66,844,254	682	£98,010
(5 investigated per case)	10 per case	£62,512,761	682	£91,659
TB case fatality	1% all ages	£65,219,944	330	£197,537

(0.3% 0-4 to 17.6% 55+)	10% all ages	£65,219,944	2,249	£28,995
TB morbidity	0.05 QALYs lost per case	£65,219,944	599	£108,832
(0.12 QALYs lost per case)	1 QALY lost per case	£65,219,944	1,684	£38,732
Cost of prophylaxis	£300 per case	£51,955,851	682	£77,180
(£743 per case)	£1,000 per case	£72,900,343	682	£106,890
Cost of treatment	£500 per case	£65,854,499	682	£96,559
(£1,114 per case)	£5,000 per case	£61,202,523	682	£89,738

Supplementary File 2: Recommendations for the TB-STs

1. **The timely universal typing of all culture-confirmed TB cases should be continued.** This includes the first isolate of all new TB cases as well as an isolate from each TB episode in those with treatment failure or recurrent TB. The resulting database of strain types linked to national surveillance data should be analysed nationally and locally, and be fully accessible across Public Health England (PHE), the NHS, UK universities and for international collaborations. The database could be used for the following:
 - a. To access typing results in **response** to local or national incidents of suspected transmission, enabling the prospective, proactive, local-led application of strain typing for TB control and public health protection;
 - b. To understand the national and local **epidemiology** of TB, including the identification of risk groups for TB attributable to recent transmission;
 - c. To understand the **molecular epidemiology** of TB, including circulating strains, lineages and virulence ;
 - d. To monitor TB programmes by analysing the trends in **estimates of recent transmission**;
 - e. To meet international obligations for **molecular surveillance**, Europe-wide and globally;
 - f. To create a national **repository of strain types**.
2. The **epidemiological analysis** of the data should be prioritised. Findings should be reported back to local Health Protection Teams (HPTs) and NHS partners. The first three years of data from the service linked to the epidemiological surveillance data should be available for analysis imminently. Looking forward, it is recommended that a small group be responsible for supporting the analysis and the clear and timely communication of the data downstream. CIs and Field Epidemiologists could very usefully assist with the important routine analysis of data.
3. **Cluster investigations** should be reconsidered. The evaluation found no evidence to suggest that cluster investigations were effective or cost effective. However, as acknowledged in the limitations, this may be due to insufficient evidence.

Local cluster investigations We recommend that cluster investigations are no longer led by CIs but are **initiated from the local level** in response to local demand. Under this scenario, the CIs and Field Epidemiologists should be available to assist Local HPTs when they choose to launch a cluster investigation.

Regional cluster investigations We recommend that regional cluster investigations are **discontinued** as they appear to add little value. However, the assistance of CIs in the coordination of cluster investigations was highly appreciated.

National cluster investigations We recommend that the routine investigations of national cluster investigations are discontinued and that national cluster investigations be limited to clusters that have been

identified to be of **public health importance**, e.g. rapidly growing clusters and clusters of drug resistant TB.

Under this scenario, CIs and Field Epidemiologists should be available to support these investigations.

4. The **STM** should be released as a priority. If this is not possible using the current in-house support, then the option of outsourcing this work should be explored. The release of the *STM* will lead to the standardisation of laboratory reporting and enable local access to strain typing data to inform the local initiation of cluster investigations.
5. Public health and laboratory **quality assurance** should continue.
 - a. The **actions and outcomes of all cluster investigations** that *are* conducted should be routinely recorded and be accessible for future evaluations.
 - b. A **false positive TB isolation identification and reporting protocol** should be agreed between the reference laboratories.
 - c. The **completeness of typing data** (i.e. the proportion of all isolates typed and the availability of full 24-loci typing profiles) for meaningful analysis and interpretation should be improved.
6. A review of the **human resources and capacity** across the TB-STS is recommended. This should include any potential impact the TB-STS has on the TB service more broadly. Moving forward, there is a need to recognise the potential capacity available to implement a complex intervention such as the TB-STS.
7. The key driver for the effectiveness and cost-effectiveness of TB control identified in this evaluation was **diagnostic delay**. The TB service should focus on and invest in interventions and TB control strategies that will lead to the earlier diagnosis of TB.