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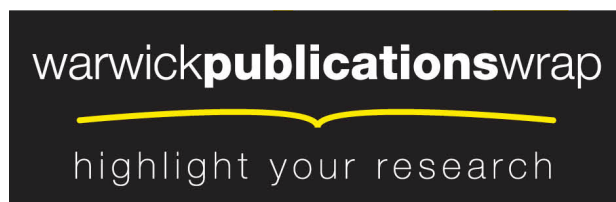
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**Detection & Identification of Infectious Agents (DIIA) Innovation
Platform: Health Econometrics**

ECONOMIC ANALYSIS REPORT

Point of Care Tests for Tuberculosis (TB)

*Prepared by Division of Health Sciences, Warwick Medical School
for
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Detection & Identification of Infectious Agents (DIIA) Innovation Platform: Health Econometrics

Area: Tuberculosis (TB)

1 Background

A number of clinical/disease areas have been prioritised by the TSB and DH for the DIIA Innovation Platform. To support commissioning of technology developments in the area of tuberculosis detection in humans, a scoping review has been undertaken to help identify the specific requirements for new diagnostic test development and likely payback in the area of point of care (POC) tuberculosis tests in the UK.

There has been a gradual rise in the number of tuberculosis (TB) cases observed in the UK over the last 20 years, with a 4.2% rise in 2009 giving an overall 9,040 TB cases diagnosed or 15 cases per 100,000 population [1].

The aims of this economic review are to identify available information on the following for tuberculosis (TB):

- economic burden of disease in the UK;
- current NHS cost of TB detection and cost of treating identified TB cases;
- evidence on cost-effectiveness of current tests for detection of active and latent TB infection; and
- estimates of the economic benefits which new POC tests might provide in the UK.

The following sections present an analysis of the four areas above. Cost figures are inflated to 2009 prices.

2 Economic burden of disease and cost of TB tests and treatment

2.1 Economic burden of disease

UK data on the economic burden associated with TB are incomplete. We have therefore collected information through a literature review and contacting experts. There were:

2.1.1 TB mortality:

Identifying the costs associated with TB mortality is complex. The Health Protection Agency (HPA) enhanced surveillance schemes (Enhanced Tuberculosis Surveillance (ETS) in England, Wales and N Ireland and Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland) provide an estimate of UK mortality. Twelve month follow up by ETS/ESMI of TB cases identified 168 deaths in 2009 where TB caused or contributed directly to death [1].

It has been suggested these figures may underestimate deaths associated with TB for a number of reasons. Firstly, outcome information was not reported in 3.1% of cases. Also, although 474 patients were reported to have died in the UK in 2009 [2], only 268 reports included information which clarified the cause of death; of these, 168/268 were directly linked to TB.

An alternative source of information is the Office for National Statistics (ONS) notifications of infectious disease deaths, classified according to the International Classification of Disease coding system (ICD10) [3]. ONS identifies all deaths where TB is reported to be the underlying cause of death, but only for England and Wales only [4].

For the UK, using HPA mortality figures, the number of life years (LYs) and Quality Adjusted Life years (QALYs) lost can be calculated as follows. Based on an estimated median age at death from TB in the UK of 64 years [3, 5] combined with a reported life expectancy in the UK for 2009 of 80.1 years [6], 474 deaths reported by the HPA in 2009 would equal **~7,630 Life Years (LYs) lost**. After discounting at 3.5%, weighting by quality of life (0.75 for people in this age group [7]), and valuing an additional life year at £30k [8], this produces a **total mortality cost of approximately £99.0 million per annum** for the UK. Some of this mortality burden might be prevented through more efficient TB diagnosis.

2.1.2 TB morbidity:

There is no published estimate of the UK morbidity burden associated with TB cases. The health related quality of life (EQ-5D) for individuals with TB has been quantified as 0.726 [9]. Other publications report Quality of Life (QoL) weights at 0.675 for patients starting on treatment and 0.813 for patients 2 months into treatment [10]. For the purpose of this analysis we assumed a QoL weight of 0.7. Based on this figure and the fact that non-fatal tuberculosis lasts for about six months [9], it is possible to estimate that approximately **1,356 QALYs** were lost due to morbidity associated with the 9,040 TB cases reported in 2009 [1]. This assumes that an individual's quality of life is affected for the six months during which treatment is provided [11, 12], and then returns to full health. This figure can be converted to a **morbidity cost of approximately £40.7 million per annum** in the UK (assuming a life year is valued at £30k, no discount rate applied). Once again, some of this morbidity burden might be preventable through earlier and more efficient diagnosis.

2.1.3 Costs to society:

An estimate of the total cost to society associated with TB is not available for the UK. However, in Germany the total cost of an adult with TB, including productivity loss/sick benefit, is estimated at €11,240 (£8,654 at 2009 prices) [13]. Based on the number of cases identified in the UK in 2009 (9,040), and assuming a similar demographic (i.e. working age), this would translate to a UK cost of **approximately £78.0 million per annum**.

2.1.4 Total economic burden of disease

Totalling the separate costs above for mortality, morbidity and societal costs produces a UK figure of **approximately £584 million per annum** or £94, 510 per 100,000 population¹.

2.2 Cost of treating TB

In this section we attempt to quantify the various healthcare costs associated with TB cases (active and latent infections) once diagnosed. All assumptions are stated. A more complete description of the calculations is given in the **Annex 1**.

2.2.1 Standard TB drug therapy:

A 2007 HTA review reported an annual drug costs for TB of £1.95 million/year in 2002 prices [11]. Updated to net present value [14] this would represent £2.3 million per annum (2009 prices). A more accurate cost figure can be calculated based on the number of cases (9,040) diagnosed in 2009 [1], mean standard drug therapy costs (excluding multi-drug resistant TB) per patient over 6 months, and the cost of drug administration.

¹ Office for National Statistics (ONS) number of people in the UK 61,792,000 in mid-2009

Standard drugs can be administered in clinics or, for more difficult cases, through intensive supervised support, termed Directly Observed Therapy (DOT). For cases requiring DOT, the cost of delivery has been estimated at £2,964 per ‘hard to reach’ (HTR) patient and £300 per ‘not hard to reach’ patient in the UK [15]. Although national figures on the number of DOT cases are not available, data from Greater Manchester indicate that 5.5% (19/345) of patients were managed in this way in 2004²; and a similar figure of approximately 5% has been provided from Liverpool³. Experts acknowledge that the percentage is likely to be higher in London. More recently, the HPA has reported that social risk factors exist for at least 10% of TB cases [2], and that data show that 42% of cases with at least one social risk factor are started on DOT [2]. In addition, HPA economic modelling assumes that 10% of the ‘not hard to reach’ population will complete DOT [15]. We have assumed that 4.2% of all TB patients (380) will fall into the expensive HTR group for DOT therapy (£2,964 per patient) and that a further 9% of cases (814) will require less expensive DOT administration (£300 per case). Excluding MDR cases (see below) this will leave 7,788 patients who receive standard treatment.

For the estimated 1,194 TB patients who had their drugs administered through DOT, and the unit costs above for DOT, intensive therapy support for UK cases in 2009 would be £1.1 million for the HTR population and £0.21 million for the remaining ‘not hard to reach’ population. This produces a grand total of **approximately £1.37 million per annum** for drug costs and their DOT administration.

The remaining 7,788 patients who received standard therapy in 2009 would incur **approximately £1.63 million per annum** for standard drug and administration costs (2009 prices) based on a mean drug therapy cost per patient over 6 months of £181.47 in 2003 prices [11] or £210 per case (2009 prices). The total (£3.0 million)

2.2.2 Multi-drug resistant (MDR) TB drug therapy:

Multi-drug resistant TB is an important issue worldwide, with increasing rates reported and new drugs being developed [16, 17]. The current cost of drugs alone for treating the average patient is estimated to be 50 to 200 times higher than for treating a drug-susceptible TB patient, with the overall costs of care 10 times higher or more [18].

For the relatively small number of UK patients whose TB is multi-drug resistant the mean cost of managing a patient with pulmonary MDR TB is reported at £60,000 in 2000 prices (£75,510 in 2009 prices) [19]. This figure is consistent with the data from the 2011 NICE clinical guideline [12]. Based on this price and 58 cases reported in the UK in 2009 [1], the total cost of managing MDR cases is estimated at **approximately £4.38 million per annum**.

2.2.3 Inpatient episodes:

Inpatient care costs are difficult to estimate for TB. Based on 2,426 finished consultant episodes recorded in 2002 at a mean cost of £2,219 each (£2,652 in 2009 prices) [11], UK costs associated with non-elective pulmonary admissions and pleural TB cases were estimated to be £6.4 million. This figure may overestimate TB costs because it does not allow for the influence of co-morbidities (e.g. 4.9% of TB cases were co-infected with HIV in 2010 [2]). On the other hand, it may underestimate true costs since this figure excludes elective pulmonary TB admissions and all extra-pulmonary TB cases. If elective mean inpatient care costs are assumed to be similar to non-elective admission costs, the total inpatient cost estimate would rise to £9.6 million. Or, using a base case cost estimate of £3,457 per non-elective episode reported elsewhere [20] and levels of emergency admissions assumed in the 2006 NICE report, a higher figure of £15.4 million (2009 prices) is obtained. Both these figures still exclude extra-pulmonary TB cases; 53% of TB cases had extra-pulmonary disease only in 2010 [1].

² Personal communication, Dr Marko Petrovic, HPA

³ Personal communication, Dr Peter Ormerod, Liverpool

The most recent HPA report for NICE [2] adopts a different approach which produces a somewhat higher figure. Based on this approach, HTR patients are said to incur hospitalisation costs of £7,320 and non-HTR patients a hospitalisation cost of £3,386. According to HES data, 56% of TB patients are hospitalised [21]. HPA estimates that HTR TB patients represent 10% of the TB patient population. Using these figures, we estimate that in 2009 the UK inpatient costs for TB patients would have amounted to **approximately £19.0 million per annum**.

2.2.4 Primary Care/ Outpatients:

In addition to inpatient care, individuals diagnosed with TB will also require outpatient visits and GP consultations. For the purpose of the present analysis, costs of £921 [15] are applied to both hospitalised and non-hospitalised populations. If it is assumed that about 90% of all active TB cases will comply with appointments, the total cost of primary and outpatient care is estimated at **approximately £7.60 million per annum**.

2.2.5 Prophylaxis:

The Health Protection Agency's systems of notification and enhanced surveillance do not collect data on cases of latent TB infection (LTBI), or on the number of people screened and given preventive treatment. This consists of isoniazid prescribed over 3 months. The total isoniazid cost for 2007 was reported as £604,181 (£631,101 per annum at 2009 prices) [11]. However, there is no estimate of the cost of administering prophylaxis. We estimate the total cost of latent TB treatment for the 17,040 Tuberculin Skin Test positive cases identified annually (see Annex 1) at a unit cost of £647 per LTBI [22] as **approximately £11.0 million per annum**.

2.2.6 Summary of cost for TB treatment:

Based on the figures presented above, the total cost of treatment for TB cases in the UK is estimated at **approximately £45.0 million per annum** (2009 prices). This represents £72,825 per 100,000 general population. Excluding LTBI and MDR costs, other TB cases are estimated to cost approximately £3,300 each.

2.3 Cost of diagnostic services for TB

In this section we attempt to quantify the resources used to diagnose patients with suspected active TB and to identify whether any of their contacts have active or latent TB. Once again, any assumptions made are stated. A more complete description of the calculations is given in the **Annex 1**.

2.3.1 Numbers tested:

Because the incidence of TB in patients referred with suspected active TB is not routinely recorded in the UK it is difficult to accurately quantify the number of people tested annually. However, a long-term study in Leicester & Rutland (over the period 2005-8) documented the proportion of active TB cases in all GP referrals for chest X-rays for suspected TB as 36%.⁴ A similar figure (between 25% and 33% of suspects referred) was independently reported, based on expert opinion, in London⁵. The ratio is likely to be smaller in other parts of the country with a lower incidence of TB, so we assumed an incidence of less than one in four referrals. Based on this figure, and the number of cases diagnosed in 2009, we estimated a crude figure of approximately 35,200 diagnostic referrals made for suspected TB. This figure *excludes* screening tests and contacts testing.

For the latter, it has been reported that there are an average of 6.5 contacts tested per primary case [23], of which 1% will have active TB [12]. Addition of contact tracing tests to diagnostic referrals produces a UK figure of approximately 90,000 patients being tested for suspected TB or screened as contacts annually. This excludes people who might be screened at port of entry or in prisons,

⁴ Personal communication, Dr Gerrit Woltmann, Leicester

⁵ Personal communication, Dr Graham Bothamley, Homerton Hospital NHS Trust, London

hostels for the homeless or new entrant clinics. The HPA economic model developed for NICE estimates that 10,000 homeless people and 10,000 prisoners could be screened annually by mobile X-ray units [15]. Inclusion of all these cases indicates that over 110,000 people are tested or screened annually in the UK (excluding port of entry screening of immigrants and refugees – see section 3.3).

2.3.2 Cost of chest X-rays:

The unit cost for outpatient chest X-rays is £28 (NHS reference cost); for mobile X-ray the cost is £16 [15]. The number of X-rays performed annually in UK hospitals for suspected TB cannot be directly identified. Radiology departments do not record these⁶. Similarly, GP practice records do not consistently distinguish X-rays requested because there is some suspicion of TB⁷. If it is assumed that symptomatic patients being referred for suspected TB (approximately 35,200) all undergo a chest X-ray as advised [12], the cost would equal £0.99 million per annum. If, in addition, 20,000 homeless/prisoners are screened annually using mobile X-ray, the added cost would be £0.32 million per annum, giving a total cost for chest X-rays of **approximately £1.31 million per annum** (this excludes port of entry screening).

2.3.3 Cost of laboratory tests:

Unit test costs for the most common laboratory tests were identified through a literature search and are shown in **Table 1**. The figures presented should be treated with some caution because full laboratory-based costs are not usually reported. Articles vary in terms of whether all key elements are included (i.e. particularly staff, capital equipment, accommodation and overheads); and certain costs associated with laboratory testing are generally excluded e.g. sample collection, transport, results reporting [24].

National laboratory TB test costs are difficult to estimate because laboratory testing protocols involve the use of sequential tests and assumptions have to be made about the numbers of referrals at each stage. For suspected TB cases (~35,200 referrals per annum), we assumed that GPs will provide three laboratory samples as advised [12], and that all three samples will have a sputum smear (microscopy) test (£1.5per sample) plus liquid culture (£27.16 each). Also, that at least one sample will undergo standard solid culture (£16.7) and that each person will have a NAAT test or gene probe MTBC (£15.67) [11]. In addition, we assumed that the 9,040 positive cases identified will undergo a further test to screen for antibiotic susceptibility (~£70 per case) [25]. This produces a total cost of laboratory testing for suspected TB of **approximately £4.44 million per annum**.

In addition, if we assume two primary care consultations are linked to this process, one as part of the test referral process and one for communicating the result (at £36 each [26]), primary care costs linked to suspected TB cases will total **approximately £2.52 million per annum**.

2.3.4 Cost of contact tracing and testing:

The cost for tracing contacts of patients diagnosed with TB has been estimated by Eralp *et al* as £23 per contact [22]. This covers the cost of tracing people and telephone contact, but excludes the subsequent cost of any tests and treatment. For the 9,040 TB cases identified in 2009, based on 6.5 contacts traced per index case, the UK cost of contact tracing is **approximately £1.35 million per annum**.

In order to calculate the cost of *testing contacts*, for the purpose of this cost analysis it was assumed that all contacts of active cases (ca 58,760 based on 6.5 contacts per case) will be tested for latent TB infection as per procedures recommended in the NICE guideline [12]. We assumed that this first involves a Tuberculin Skin Test (TST) or Mantoux test; and that 30% of these will be positive [27] and will then undergo the Interferon-Gamma Test (IGT). The total cost of testing contacts in 2009 is therefore estimated at **approximately an additional £1.85 million** (see Annex 1).

⁶ Personal communication, Dr Richard Wellings, Radiology Department, UHCW Trust, Coventry

⁷ Personal communication, Dr Tim Holt, Assoc Prof General Practice, Warwick Medical School

2.3.5 Total diagnostic service costs:

Based on the estimates above, the resources used to identify patients with TB in the UK (including contact tracing) total of **approximately £11.47 million per annum** (2009 prices). This represents £18,560 per 100,000 general population. This figure excludes the national cost of the Health Protection Agency's systems for disease notification and surveillance.

2.4 Total cost of UK TB detection and treatment

Totalling the separate costs estimated above for treatment and tests produces a UK figure of **£56.47 million per annum** or £91,390 per 100,000 population. Alternatively, a crude cost per case can be estimated based on global prices reported by the HPA (£15,000 for a hard to reach case and £4,606 for other cases) [15]. When applied to the 9,040 cases detected in 2009, this would provide a weighted average of £5,645 per case and indicate a slightly lower figure of **approximately £51.0 million per annum**.

2.5 Conclusions: Economic burden of disease & TB diagnosis and treatment costs

- In terms of mortality, the annual TB burden in the UK is estimated to be 7,630 Life Years lost. This equates to an estimated mortality cost of £99.0 million per annum.
- In terms of morbidity, the estimated annual burden of disease in the UK is 1,355 QALYs lost for cases diagnosed in 2009. This equates to an estimated morbidity cost of £40.7 million per annum.
- Although the total cost to society associated with TB is not available for the UK; a rough annual figure of £78.0 million (to include productivity loss) can be estimated based on international data.
- TB treatment, including drugs for active TB, MDR cases and prophylaxis (and their administration), hospital inpatient episodes, outpatient visits and primary care consultations are estimated to total at £45.0 million per annum in the UK. Within this figure, the annual cost of treating MDR cases is estimated to be £4.38 million.
- The cost for diagnosis of TB in the UK is in the region of £11.47 million per annum, including contact tracing and testing for latent TB infection. There is a high level of uncertainty around the unit cost of tests currently used in the NHS. The number of patients being tested annually in the UK for suspected TB is estimated to be in the order of 35,200. Inclusion of contact tracing raises this figure to ~90,000 people. A further 20,000 homeless people and prisoners screened would raise the total to 110,000; screening at port of entry would add to this figure even further.
- In terms of mortality and morbidity, the UK economic burden for TB is modest compared to countries in the developing world. UK expenditure on TB treatment and diagnosis, which is roughly estimated at £91,390 per 100,000 population, is significantly lower than the figure reported from the USA of \$US 700 million/year [28], equivalent to a net present value of ~£194,000 per 100,000 population.

3 Evidence on cost-effectiveness of current TB tests

Ideally, the value for money (cost-effectiveness) any new POC test should be compared to that of current TB tests. However, from our review of the literature, published articles assessing the various tests currently available are inconsistent in the way that results are presented and of varying quality. Reported cost-effectiveness will not only be sensitive to factors such as technical performance (sensitivity/ specificity) and test cost, but also demographics of the population tested and the testing strategy used (e.g. testing high-risk individuals versus testing a whole population) [29]. This is rarely reported. For more rapid tests, as well as speed of test result and impact on TB transmission, cost-effectiveness will also be affected by any impact on associated services (e.g. other tests, hospitalisation rates etc) and the effectiveness of available treatment interventions, plus the comparator test or 'status quo' chosen [30]. These are rarely all reported in the articles identified. Finally, an economic evaluation should ideally report cost-utility (e.g. cost per QALY). Ratios such as the cost per active case detected and treated or the cost per case detected are less useful for policy makers.

3.1 Evidence on cost-effectiveness of tests currently used for active TB infections

The review of the literature found relatively few studies which reported the cost-effectiveness of current TB tests listed in **Table 1**. In the articles identified, economic results were usually presented in the form of a 'cost per case detected' (see **Table 2**). Cost-utility analyses (i.e. cost/QALY) were lacking.

3.1.1 General evidence on cost-effectiveness of chest X-rays:

Chest X-rays are reported to have a low sensitivity (67%) and specificity (61%) [15, 31]. Therefore, although they can be used as a screen for TB, the reported cost per case detected is too high for them to be considered 'cost-effective'. For example, research in Canada has estimated a value of \$CAD 9,898 per active TB case detected [30], equivalent to £5,863 (2009). If treatment costs are included, this figure rises to £15,809 (2009) per active case detected and treated. Thus, X-rays appear not to be cost-effective as a diagnostic tool.

It has been suggested instead that X-rays may be cost-effective when used to rule out pulmonary TB in a person who has a positive reaction to the TST but no symptoms of disease [23, 32]. However, the cost-effectiveness of such case-finding, for example using a mobile X-ray unit combined with enhanced case management interventions for homeless and imprisoned populations, is reported to be highly context-specific [15]. So a general statement about cost-effectiveness is not possible.

3.1.2 Cost-effectiveness of chest X-rays vs. symptom checklists:

The cost-effectiveness of a symptom checklist versus chest X-ray for initial screening for active disease depends on the relative accuracy of the two options and their costs. Under base case assumptions, an economic modelling exercise indicates that screening by X-ray is more expensive although it may lead to an overall saving in NHS expenditure, due to a predicted lower number of false positive results [12].

3.1.3 Evidence on cost-effectiveness of current laboratory tests for TB detection:

Although several articles purporting to assess tests currently available to detect active TB report that a test is 'cost-effective', the evidence to support this statement is usually limited. Articles are generally of a poor quality and it is difficult to compare studies due to differences in the scope of the costs included and the types of outcomes measured. None of the studies identified were of a quality to fully meet accepted HTA standards for reporting test performance [33]. Cost-effectiveness, when quantified, was most commonly described in terms of the cost per case detected. The potential for comparison across studies was limited due to differences in the populations studied (particularly TB incidence) and the comparator used. Because economic findings are highly

dependent on the clinical context and the economic perspective adopted in a study, differences in these made comparison across the studies identified difficult if not impossible. As a result, even the most common measure of cost-effectiveness reported in the literature (i.e. cost per case detected) showed a very wide variation.

Furthermore, most published studies focused on individual steps (tests) in the diagnostic process. The overall cost-effectiveness of the system-wide diagnostic pathway, including sequential tests, was usually not considered. This **represents an important gap in the evidence** for current laboratory tests for TB detection

Specific examples of ‘cost-effectiveness’ results are presented below. These illustrate the variability in tests, method for reporting of cost-effectiveness, and the quality of findings. This variability made any synthesis of the economic findings impossible:

- **Culture tests:** the cost per active TB case detected is reported to be between \$CAD 6,757 (based on 1 specimen) and \$CAD 17,284 (3 specimens) [30].
- **TST:** the cost per active TB case detected in Canada is estimated at \$CAD 12,407 [30].
- **PCR test:** the cost per active TB case detected is reported to be \$CAD 10,990 [30].
- **PCR cross-blot hybridization:** this is reported to cost \$US 1.50/sample. This cost is stated to be ‘more than offset’ by potential savings linked to earlier reporting [34].
- **AMTD (Gen-Probe Inc):** the testing strategy that incorporates dilution of smear-positive but not smear-negative respiratory specimens is simply reported to be ‘cost-effective’ [35].
- **MMGIT, AMGIT CLJ and HLJ:** the cost per case detected is ~US\$ 95 when modelled for maximum throughput in Zambia. When performed among smear-negative specimens, the cost per additional case identified is predicted to rise to US\$ 487 for MMGIT, and to be even higher for other methods [36].
- **INNO-LiPA Rif.TB PCR-based hybridization assay:** this is simply reported to be ‘cost-effective’ and highly reliable when run in parallel with a conventional TB laboratory diagnostic algorithm [37].
- **RT-LAMP-ELISA-hybridization assay:** this is reported to be more cost-effective than real-time TaqMan RT-PCR and AMTD assays [38].

Table 2 indicates the very wide range in cost per case values reported for various TB tests. A range of £87 - £3,348 per case (£91- £3,497 in 2009 prices) was identified.

3.1.4 Evidence on cost-effectiveness of tests for detecting multiple drug resistant (MDR) TB:

Based on the most recent data, at least 7.1% of TB patients are resistant to at least one antibiotic [2]. Drug resistant TB is important because patients who are sputum smear positive remain infectious for much longer than those with susceptible organisms. MDR cases also have a higher mortality rate and they require more costly treatment with drugs of higher toxicity. Once again, cost-effectiveness was mainly reported in terms of the cost per case diagnosed; no cost-utility analyses were identified. A number of individual studies did report the cost-effectiveness of tests for detection of MDR cases, but the lack of a systematic review of economic studies **represents a second important gap in the evidence** for current laboratory TB tests. Examples of ‘cost-effectiveness’ studies identified include:

- **rpoB test:** this is estimated to cost ~£120/test, and £2,958 per MDR-TB case diagnosed. However, the test is 7 weeks faster than conventional culture [39].
- **Direct amplification and reverse hybridization of the rpoB gene:** this is reported to be ‘cost-effective’ compared to indirect proportion method on Lowenstein-Jensen medium. As would be expected, the method is reported to be most cost-effective in patient groups with a high prevalence of TB [25].

- **Five different tests:** the average cost per case detected has been estimated for a 2% prevalence of MDR-TB. When transmission effects are included (e.g. savings due to lower transmission as a result of case detection), the cost per case detected ranges from US\$ 3,031 to US\$ 8,672 in 2004 [25] or £2,252-£6,444 (2009 prices).

In **Table 2**, a fairly conservative figure of £2,958 per MDR case detected is presented.

3.2 Evidence on cost-effectiveness of tests used for screening

New POC test should also be compared to existing tests in the context of screening, in addition to their potential use for detecting active disease in people presenting with symptoms. The literature on cost-effectiveness of current TB tests used for screening and testing contacts mostly considers two types of test: the tuberculin skin test (TST) and the interferon-gamma test (IGT)/interferon gamma release assay (IGRA). IGRA/IGT has proved a useful addition for the diagnosis of dormant (or latent) TB infection in the absence of active disease. However, the issue of latent infection, particularly among non-UK born people, remains a largely unaddressed source of future disease; there are no statistics providing a breakdown of LTBI cases identified in new entrants versus via contact tracing for people with infectious TB.

There is currently no single, reliable test for detecting latent TB infection (LTBI). Although TST is inexpensive (see **Table 1**) and relatively easy to perform, testing requires two patient visits which increases the overall cost to the NHS of this test. Effectiveness is dependent on the patient returning within the specified time period for the second visit. As pointed out above, the NICE guidelines recommend the use of the TST with positive test results followed by the IGT [12].

The overall cost-effectiveness of any detection programme for LTBI is likely to be influenced particularly by levels of compliance with therapy once latent (or dormant) TB is detected. At the same time, a 2008 systematic review of the literature has highlighted poor adherence to LTBI therapy [40]. The degree to which compliance levels are built into cost-effectiveness analyses varies. The overall cost-effectiveness of any testing regime for LTBI will ultimately be dependent on the number of active TB cases *prevented*.

The cost-effectiveness literature identified considers IGRA both as a replacement for, and as an add-on to, TST. For England and Wales, economic modelling has indicated that a two-stage strategy (TST/IGT) will be cost-effective (£26,000 per QALY) for identifying LTBI in the context of a contact tracing programme, while TST and IGT on their own are not cost-effective methods [23]. Cost-effectiveness is reported to be higher in high incidence/ high risk populations. Two systematic reviews of IGRA note excellent specificity for the tests to distinguish latent TB from prior vaccination [11, 41]. However, for detection of *active* TB infection, IGRA has reduced specificity due to its ability to detect latent TB [42].

There is a lack of consistency in the manner in which ‘cost-effectiveness’ results are presented for TB screening/contact testing. Studies also do not always distinguish active and latent TB findings. This variability once again made synthesis of the economic findings difficult. Examples of findings reported include the following:

- **QuantIFERON-TB test:** QFT-based screening programmes (with QFT as an add-on or replacement for TST) are both reported to provide superior clinical and economic outcomes in comparison to programmes based on TST alone in Germany, and at a ‘comparatively small additional cost’ [32]. The same authors subsequently reported that the cost of screening and treatment when using QFT alone amounted to €215.79 (£166.15) per close contact [43].

- **QuantiferON-TB Gold test:** the cost per positive case detected for QFT-G is reported as \$US 171.78; compared to \$US 145.99 using TST [32]; equivalent to £89.73 vs £76.25 (2009 prices).
- **T-Spot.TB:** TST followed by confirmation of positive results by T-Spot.TB test is reported to be the most cost-effective option for screening for latent TB infection in Switzerland [44]. More recently, Swiss researchers have suggested that TST should be replaced by the TIGRA test (T-cell interferon gamma release assays) [45].
- **T-Spot.TB:** more recent company material reports that use of T-SPOT.TB, either alone or in combination with TST, greatly reduces the number of contacts treated to prevent one TB case in [46].
- **DHPLC:** Denaturing high-performance liquid chromatography has been reported to be a 'cost-effective, rapid, sensitive, and high-throughput technique' for TB screening [47].

Table 2 includes an estimated cost per 'active case detected' for screening/ contact testing (£5,442 at 2009 prices).

3.3 Evidence on screening of immigrants and refugees

The cost analysis in section 2 excluded the cost of screening immigrants and refugees e.g. at port of entry. However, surveys have consistently shown the highest rates of clinical TB disease in recent arrivals, particularly within the first few years after initial entry [23]. A recent UK epidemiological study has also identified that transmission within England accounts for only one in four cases, with the remainder arising from reactivation or acquisition outside England [48].

There is a mixed evidence base on the economics of screening immigrants and refugees. As might be expected, screening overseas born children/adults is reported to be more cost-effective than screening all [49]. In low-incidence countries, screening of all migrants at port of entry using existing technology is thought to have little overall impact and not to be very cost-effective as a TB control strategy. More efficient alternatives in this situation may include contact tracing delivered through primary care, as well as increased investment in global tuberculosis control [30]. Early UK research has indicated that contact tracing is more effective at detecting TB than new-entrant screening [50]. Findings from Canada also confirm that contact tracing is highly cost-effective, compared to immigrant TB screening at entry [51]. The 2011 NICE clinical guideline on new entrant screening suggests that as the prevalence of TB and the conversion rate of TB increase the tests (TST/IGT and IGT alone) will become cost-effective [15]. The UK Home Office and the Department of Health have piloted pre-entry TB screening in 8 countries.

Recent NICE guidelines state that new entrants should be identified for TB screening [12]. Research undertaken in the UK has estimated that screening individuals in general practice, new entrant clinics, and hostels for the homeless and would cost £1.26, £13.17 and £96.36 per person respectively, while the cost per person screened per case of tuberculosis prevented would be £6.32, £23.00, and £10.00 respectively [52]. In contrast, a more recent study of TB screening services for asylum seekers in one of the UK induction centres has reported that, although screening can achieve a high uptake, cost-effectiveness is questionable, particularly where the yield of active disease is low. TST is not an ideal screening procedure in this setting because it may be uncompleted and the benefit of detecting latent infections is uncertain. The annual cost of screening was estimated to be £350,000 [53]. Economic modelling also suggests that prophylaxis is not cost-effective in the context of new entrant screening [12].

4 Overview of economic literature and improvements required in the UK

There is very little published on the cost-effectiveness of existing tests for TB; this represents a major research gap. In economic terms, rapid case detection, provision of drug therapy and ensuring completion of treatment are all important in reducing the burden associated with TB infection. The question is – *where in the system is it best to intervene for maximum economic benefit?*

In the UK context, a rapid POC test to screening contacts of TB patients to identify other active TB cases might provide benefits. In particular, a more rapid test would be valuable since current tests can take up to 12 weeks. The UK HTA Programme has commissioned research to assess the cost-effectiveness of existing tests for rapid identification of active TB disease. The study, which started in 2011, focuses on whole blood interferon-gamma enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunospot assay (ELISPOT) tests and is due to report in mid-2015 [54]. The cost-effectiveness of other emerging tests e.g. Sequella TB Patch, also needs to be assessed before the cost-effectiveness of rapid POC technologies can be adequately considered for the UK.

In economic terms, tests which offer increased *speed of diagnosis* are likely to have a direct cost saving in terms of people currently falsely suspected of having active TB. Among these patients, a more rapid diagnosis ruling out TB will save money in terms of reducing unnecessary treatment costs and possibly improving contact tracing, although this is difficult to quantify. However, speed of diagnosis is not necessarily the same as diagnostic turn-around time. A recent systematic review of studies examining delays in diagnosis and treatment of TB has highlighted a ‘vicious cycle’ of repeated visits at the same healthcare level and failure to refer on to specialised TB services [55]. Although earlier discharge of false positives and earlier correct treatment of TB cases will both improve cost-utility.

Drug resistant TB remains a problem, particularly in London, and as our analysis indicates it incurs high treatment and mortality costs, although the latter could not be quantified. *Rapid, early indication of multiple drug resistance* would enable clinicians to tailor drug therapy more accurately. Improved cost-effectiveness should result from earlier correct treatment of atypical and drug-resistant TB.

In the context of contact tracing, latent TB infection can currently be identified using a two-stage strategy (TST/IGT) with an incremental cost-effectiveness ratio of £26,000 per QALY; one of the few areas in which cost-utility data are available for existing TB tests. Population programmes in the range £20,000-£30,000 are unlikely to be accepted by NICE on cost-effectiveness grounds alone. In this case, cost-effectiveness will depend crucially on the prevalence within the population groups tested; 70 percent of LTBI cases are in non-UK born residents. More importantly, there is currently no certain way of *predicting which 10% of latently infected people will go on to present with active disease*. This will severely limit the cost-effectiveness of extending screening beyond the contact tracing context. A test which is highly predictive of future development of disease would allow targeted chemoprophylaxis for individuals at risk of disease. The UK HTA Programme has commissioned research in this area which is due to report in early 2016 [56]. Improved predictive performance may also help to address the underlying issue of poor adherence to LTBI therapy reported in a recent review [40]. If patients at particular risk of progression to active TB can be identified then adherence to prophylaxis may be improved through DOT-like approaches. A recent Australian study has reported economic findings on the implementation of telecare technology as a cost saving device and to improve Directly Observed Therapy for TB [57]

General points which can be drawn from our overview of the literature include:

- The current size of the market for different TB tests in the UK is unknown. Consequently, it is difficult to estimate the economic impact of existing TB diagnostic and screening tests or the economic advantage of new tests.
- Our analysis suggests that investment in the development of new diagnostic tests for TB is unlikely to offer significant cost savings for the UK healthcare system. Tests currently available to diagnose active TB appear to demonstrate adequate performance, although the total cost of testing suspected TB cases could not be estimated with complete accuracy.
- In order to establish the actual economics of TB detection in the UK, additional modelling of costs and benefits of system-wide diagnostic pathways (including imaging and laboratory tests for extra-pulmonary TB) would need to be undertaken.
- The main problem in the UK appears to be late diagnosis of TB. Earlier diagnosis would lead to fewer deaths and a lower number of cases per year, as active TB cases are diagnosed sooner and infect fewer healthy people. From an economic perspective, it is important to identify whether cost or the poor performance of currently available tests influences this. There is no robust evidence that either the price of current tests or their performance significantly delays diagnosis. However, the role of primary care in the referral process, and improvements in this area, are clearly also important. Consideration of this was outside the scope of the current report.
- Our conclusion from the available evidence is that the problem with TB diagnosis in the UK is systemic. The key changes required are ones which will facilitate identification of TB cases as early as possible.
- The major market for new TB tests will clearly be in high incidence countries in the developing world. In this context, there is a need to introduce more cost-effective technologies which can test large populations at low costs.
- While developing countries would benefit from high throughput new screening tests, low-incidence countries such as the UK may be in need of more highly-specific diagnostic tests (e.g. MDR tests). In some low-incidence countries, like the US, which have a significantly higher expenditure on TB than the UK, improvements in other diagnostic tests may prove to be an important tool to contain costs.

5 Estimating the economic benefits which new POC tests could provide

5.1 Overview of economic analysis and model used

Current testing scenarios (Table 3):

Table 3 presents an overview of the UK status quo for TB screening and diagnostic tests (excluding chest X-rays). Comparative data are provided for the technical performance (sensitivity/specificity) of tests currently used; times to result; and the setting where testing is currently undertaken. The numbers of patients being tested annually is also presented (where this can be estimated). The final two columns summarise current economic impact in the UK as detailed in section 2 above. The penultimate column provides an estimate of the current laboratory cost of testing for suspected TB and screening costs associated with following contacts of active TB cases. The final column lists annual costs associated with mortality, morbidity and NHS treatment of cases detected.

New testing scenarios (Table 4):

Table 4 presents the characteristics of an 'ideal' new test to replace the *status quo* sequential testing for suspected TB. The Table includes information on test requirements (sensitivity/ specificity, time to result, and test process) for the new test.

An economic model has been constructed to estimate the predicted economic benefits at national level of moving from the current status quo to implementation of a new test.

The economic model:

A relatively simple cost model was constructed in Excel to estimate national level costs for TB diagnosis following a referral for suspected disease in the two scenarios presented in Table 3 (status quo) and Table 4 (new test). This analysis excluded tests for screening/ detection of latent TB infections, for which accurate national level test data could not be identified.

Data in the model:

The model parameters were based on the highest level of evidence available from our review of the literature, and through contacting experts.

The main economic drivers for the new diagnostic tests were assumed to be changes in the number of false negatives/false positives and increases in the number of true positives detected. These in their turn were assumed to impact on the number of infections transmitted and on mortality.

The impact on morbidity could not be quantified due to lack of robust data (e.g. QALYs), and was not included in the model.

Costs:

For each testing scenario, we estimated the number of cases of detected/ undetected and treated/ untreated infections and subsequent direct cost consequences. Indirect and intangible costs associated with TB infections, including lost time from work, pain, anxiety, and morbidity were not included in the analysis. Thus, the results presented below are likely to be an underestimate.

5.2 Overview of economic results

The current pattern and sequence of testing (status quo) for detection and antibiotic susceptibility testing was assumed to involve 3 samples per person and the following sequence: (i) all 3 samples undergo sputum smear (microscopy) test and liquid culture; (ii) 1 sample undergoes standard solid culture; (iii) 1 NAAT test or gene probe MTBC is carried out per person to confirm culture positive samples for MTB; (iv) all positive MTB samples undergo further test to screen for antibiotic

susceptibility. For the new single-step test, it is assumed that the same number of people will be tested.

For cost modelling purposes it was assumed that the ideal new test would cost (per person tested) the same as the current combination of laboratory tests. Comparison of the costs and financial benefits of the two scenarios, status quo (Table 3) versus new test (Table 4), was undertaken. For the current system, in the economic model, significant losses were associated with a high number of false negatives which lead to increased mortality (maximum potential loss estimated at ~£30 million) and additional infections (potential losses up to £0.1million). The characteristics of an ideal new test will result in (i) fewer steps; (ii) improved sensitivity i.e. more cases accurately detected (model not actual); and (iii) a more rapid test result.

In terms of improved sensitivity, the cost model indicated that additional cases detected will lead to extra treatment costs (~£11 million) in year 1, compared to the status quo scenario. However, a financial benefit will be realised from a significantly lower number of false negatives resulting in a decrease in deaths from TB (modelled losses due to death amount to £0.14million).

The reduced turn-around time for a diagnostic result (from 4-6 weeks for culture to <2 hr for new Point of Care (PoC) test) may provide an additional benefit in economic terms. However, in the current model, it was not possible to quantify this benefit in financial terms. Although, the low TB infectivity rate means that there will be relatively little impact on the overall number of infections and therefore associated costs, a saving linked to speedier diagnosis could be reduced expenditure on contact tracing. This will only occur if contact tracing is currently initiated before culture and NAAT test results are available. In this case, a more rapid test would limit contact tracing to the 36% of cases that are positive which could add a further saving of £0.5 million per annum⁸.

Comparison of the two scenarios predicts an **annual saving of ~£18 million** following replacement of the status quo with a single new test with high sensitivity and specificity (98/98). Although a break-even test cost could not be calculated, any new test should probably not be more expensive than the current cost of laboratory testing (combination of tests). This is an average £118 per referral.

It should be remembered, however, that TB transmission within the UK may account for only a quarter of total cases, with the remainder arising from reactivation or acquisition outside the country. This emphasises the importance of considering new test development in the screening context, as well as for laboratory diagnosis. Additional data would need to be acquired in order to be able to model the economic benefits of new POC technology in this broader context.

⁸ Further potential savings on screening of contacts is not included here as it is not clear whether the new test will impact the number of LTBI cases that are being screened annually.

TB: ECONOMIC TABLES & FIGURES

TABLE 1: TB – Published Unit Test Costs (*All costs are converted to 2009 GBP*)

Diagnosis of	Test name	Cost/test (£) (consumables only)	Cost/test (£) (total)	Source(s)
Active/Latent TB				
	Tuberculin Skin Test (TST)		16.44	[27]
	Interferon – gamma test (QFT-G)		50	[27]
	Standard Culture test	7.31	16.70	[11]
	Liquid Culture test		27.16	[11]
	Acid-Fast Microscopy		~0.36	[58]
	Auramin/Acridine orange commercial kit	11.19 /100 slides		
	Fluorochrome method	13.02/100 slides		
	GenoType Mycobacteria Direct assay	36.56-69.46		[59]
	GenProbe AMTD	29.25-58.50		[11]
	BACTEC 9000		6.51/analysis	[60]
	Blood agar		1.39/analysis	[60]
	RT-LAMP-ELISA	6.27		[38]
	TaqMan RT-PCR	7.52		[38]
	AMTD	31.34		[38]

Diagnosis of...	Test name	Cost/test (£) (consumables only)		Cost/test (£) (total)	Source(s)
Multiple drug resistance					
	<i>rpoB</i> sequencing			125.35	[39]
	DHPLC		0.63		[47]
	PCR-RFLP (Isoniazid only)		0.94		[61]
	NAAT commercial kit		15.67-31.34		[62]
	IDLJ		25.07 (23.19)*		[25]
	FASTPlaque-Response		25.91		[25]
	INNO-Lipa		69.99		[25]
	DLJ		19.01 (15.67)		[25]
	MTT assay		22.25 (19.08)		[25]
		Detection	4 drugs susceptibility		
	MODS	0.48	1.13		[63]
	MGIT	4.39	39.51		[63]
	BACTEC	1.60	14.41		[63]
	LJ	0.08	0.98		[63]
	Microagar 7H11	0.18	1.83		[63]
	MABA	0.77	4.30		[63]
	PCR	1.82			[63]
	Acid-fast stain smear	0.06			[63]

* In brackets rifampicin only cost

TABLE 2: Tuberculosis Economic Summary for the UK (2009)

	Number of cases (2009)	Cost/patient tested (£)	Cost per case detected	Cost per case treated (£)
Active TB	9,040	£252 ¹	£91- £3,497 ²	~£3,300 ³
Multiple drug resistant TB	58	N/A ⁴	£2,958	£75,510
Contact tracing	58,760	£23	£5,442 ⁵	N/A
Latent TB infection	17,040	£24.2		£647 [22]

N/A Not available

¹ Includes cost of X-rays & antibiotic susceptibility testing

² Published cost/ active TB case detection varies widely; international figures will depend on the type of test used & TB incidence in population tested. No cost-utility data reported.

³ Includes standard treatment including Directly Observed Therapy (DOT), hospitalisation and outpatient costs

⁴ Antibiotic susceptibility testing is provided for all active TB cases and included in the above figure.

⁵ Cost of tracing (£1.35 million) and further diagnosis (1.85 million) per active case detected (1% of 58,760 contacts)

TABLE 3: Overview and summary of current tests for screening and diagnosing active TB cases

Test Type	Current UK test context		Current tests used			Current test capability		Current economic impact	
	Number of UK patients tested annually	Settings where tests undertaken	Type of tests used	Test process	Type of specimen	Time to perform test/ result	Sensitivity/ Specificity	Annual lab testing Cost	Annual Burden of disease
Host response	NA	POC	TST	2 visits. If negative repeat in 1-3 weeks	NA	Result 48 and 72h	77/97 Non-vaccinated 77/59 BCG Vaccinated [64]	£1.85 million	Mortality: £99 million Morbidity: £40.7million NHS treatment/ care costs: £45 million
Host response	NA	Use after positive skin test	IGRA	Enzyme linked assay	Blood	~24h	95/97 [11]		
Microscopy	35,200 ¹	Laboratory	Sputum Smear	Slides stained and examined. Then requires confirmation using culture.	Sputum	~24h	31-98/95-100 [65]	£4.44 million ²	
Culture	35,200	Laboratory	Culture	Culture, which then requires confirmation as MTB.	Multiple	Solid media 4-6 wk Liquid media ≥12d	Solid media 98/NA Liquid media 91/NA		
Molecular	11,981 ³	Laboratory	NAAT	Confirmation of culture positive samples for MTB	Culture	3-6h	73/94 [11]		

¹ Patients referred with suspected TB (excludes screening)

² Excludes annual cost of screening tests (N/A), chest X-ray, primary care visits, and contact tracing

³ Based on 'cases' identified by culture stage (True positives + False positives)

TABLE 3 (contd): Overview and summary of current tests for screening and diagnosing active TB cases

Test Type	Current UK test context		Current tests used			Current test capability		Current economic impact	
	Number of UK patients tested	Settings where tests undertaken	Type of tests used	Test process	Type of specimen	Time to perform test/result	Sensitivity/ Specificity	Annual lab testing cost	Annual Burden of disease
MDR	Only culture positives will be screened for antibiotic susceptibility	Laboratory	Solid-phase hybridization*	Genetic resistance markers	Multiple	<2h - 2d	95†/98	Included in figures above	Included in figures above
MDR	As above	Laboratory	Radiometric systems**	Genetic resistance markers	Culture samples or smear +ve patient material	6-12d	97/100		
MDR	As above	Laboratory	Phage-based assay‡	Sample infected with phages	Respiratory	1d	NA		

* e.g. INNO LiPA, GenoType MTBDR; ** e.g. BACTEC † smear positive samples ‡e.g. In house assays, FastPlaque TB

¹ Excludes annual cost of screening tests (N/A), chest X-ray, primary care visits, and contact tracing

TABLE 4: Predicted likely economic benefits of new test for diagnosing active TB and MDR cases

Main driver(s) for technology development	New test UK role	Target population/ sub-population		Ideal new test requirement				Predicted economics of new test	
		Target population to be tested	Number of UK patients	Time to result (hrs)	Sensitivity/ Specificity	Setting for test	Test process	Break-even Test Cost	Annual Cost saving ³
<ul style="list-style-type: none"> • Current diagnosis of MTB and MDRTB is a multi-step process taking place over a prolonged time period. • Decreased time to diagnosis will aid in more rapid contact tracing. • Will limit transmission & enable more patients to commence appropriate treatment earlier. 	Detection and screening	Community/ Hospital (suspected TB)	35,200 ¹	<1h	98/98	POC/ Rapid lab	Single step	N/A ²	~£18 million

¹ Patients referred with suspected TB (excludes screening & contact tracing)

² Model assumes that the new test cost is comparable to the combination of current tests

³ It is assumed that the new test costs the same as current laboratory testing (combination of microscopy, culture and NAAT).

Annex 1: TB Treatment and Diagnosis Cost Estimates: Input parameters and assumptions

TREATMENT	Source	Unit cost/ number	Total annual cost (UK)	Comment
Standard drug therapy			£1.63 million	
	[11]	£210 per case x 7,788 (non MDR, non DOT TB cases)	£1.63million	HTA review unit price
DOT therapy			£1.37 million	
	[66]	DOT 814 x £300 (Assume 10% of UK not HTR cases) DOT HTR: 380*£2,964 (Assume ~42% of hard to reach cases in UK)	£0.24 million £1.13 million	HTR = hard to reach
Multi-drug resistant TB			£4.38 million	
	[23] [19]	58 cases in UK 2009 £75,510 per base case	£4.38 million	
Non-elective inpatient episodes			£19.0 million	
	[11]	~56% of patients are hospitalised Non-HTR cases 4,527*£3,386 HTR cases 503*£7,320	£19 million	
Outpatient/			£7.60 million	
	[15]	£921 x 8,254 outpatients (Assume ~90% UK cases)	£7.6million	
Latent TB*			£11.0 million	
	[12] [22]	17,040 of TST positive cases (in which no active TB is identified) *£647	11million	
TOTAL TREATMENT			£45.0 million	

* Assumed Latent TB treatment is provided only for TST positive cases.

DIAGNOSIS	Source	Unit cost/ number	Total annual cost (UK)	Comment
X-rays: diagnostic			£1.31 million	
	NHS reference cost [14]	Chest X-rays @ £28 Assumed 35,200 patients Mobile Xray @ £16 on 20,000 HTR and prison population	£0.99 million £0.32 million	
Lab tests: suspected TB⁹			£4.44 million	
	[12, 22]	Assumed all 3 samples have sputum smear (microscopy) = 3x1.5x35,200 patients	£0.16 million	
	[11]	Assumed 3 samples have liquid + 1 standard culture) @ (£27.17x3 + £16.71) = £98 per case x 35,200 patients	£3.46 million	HTA review prices
	[11]	NAAT test or gene probe MTBC @ £15.67 per case x 11,981 patients	£0.19 million	HTA review prices
	[63]	Susceptibility testing (4 drugs) @ £7. Assumed 9,040 patients tested	£0.63 million	Literature price [25] uplifted to 2009
Primary care visits			£2.52million	
		Assumed 1 GP surgery consultation prior to referral & second following test results @ £36 x 2 x 35,200 patients	£2.52 million	2009 PSSRU prices
Contact tracing			£1.35 million	
	[12]	£23 per contact x 58,760	£1.35 million	
Latent TB*			£1.85 million	
	[27]	TST test for all contacts: 58,760*£16.44 IGRA test only for positive TST: 17,628*£50	£0.97 million £0.88million	
TOTAL DIAGNOSIS (INCL. CONTACT TRACING)			£11.47 million	
TOTAL: DIAGNOSIS & TREATMENT			£56.47 million	

* Assumed only traced contacts are tested for Latent TB infection.

⁹ Tuberculosis prevention and treatment: a toolkit for planning, commissioning & delivering high-quality services in England- DH - TB Action Plan Team June 2007

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