Should NICE reconsider the 2016 UK guidelines on tuberculosis contact tracing? A cost-effectiveness analysis of contact investigations in London

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Abstract (245)

Background – In January 2016, clinical TB guidance in the UK changed to no longer recommend screening contacts of non-pulmonary, non-laryngeal (ETB) index cases. However, no new evidence was cited for this change, and there is evidence that screening these contacts may be worthwhile. The objective of this study was to estimate the cost-effectiveness of screening contacts of adult ETB cases and adult pulmonary or laryngeal tuberculosis (PTB) cases in London, UK.

Methods – We carried out a cross-sectional analysis of data collected on tuberculosis index cases and contacts in the London tuberculosis register, and an economic evaluation using a static model describing contact tracing outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated using no screening as the baseline comparator. All adult TB cases (≥15 years old) in London from 2012-15, and their contacts, were eligible (2465/5084 PTB and 2559/6090 ETB index cases were included).

Results – Assuming each contact with PTB infects 1 person/month, the ICER of screening contacts of ETB cases was £78000/QALY (95% CI: 39000 to 140000) and screening contacts of PTB cases was £30000/QALY (95% CI: 18000 to 50000). The ICER of screening contacts of ETB cases was £30000/QALY if each contact with PTB infects 3.4 people/month. Limitations of this study include the use of self-reported symptomatic periods, and lack of knowledge about onward transmission from PTB contacts.

Conclusions –Screening contacts of ETB cases in London was almost certainly not cost-effective at any conventional willingness-to-pay threshold in England, supporting recent changes to NICE national guidelines.

Key Messages

What is the key question? Was NICE correct to change its tuberculosis clinical guidelines to no longer recommend screening contacts of non-pulmonary TB cases?

What is the bottom line? It is almost certainly not cost-effective to screen contacts of non-pulmonary TB cases in London at a willingness-to-pay-threshold of £30000/QALY, providing strong evidence that the decision to cease recommending screening contacts of non-pulmonary cases was the correct one.

Why read on? In addition to helping an answer an important policy question that has been questioned by several recent papers, this article provides the first cost-effectiveness analysis of contact tracing in the UK and the first to incorporate non-pulmonary cases, and proposes a novel way to evaluate contact tracing effectiveness.

Introduction (542)

Following four years of decline, the incidence of tuberculosis (TB) in England had fallen to 10.2/100000 in 2016[1], but is still higher than most other countries in western and northern Europe[2]. Contact tracing, the systematic screening of contacts of cases , is a fundamental part of TB control in high-income countries, and is highlighted as a key element of the Public Health England (PHE)/National Health Service (NHS) England collaborative tuberculosis strategy 2015-2020[3]. It is also used around the world for other infectious diseases, including Ebola[4], meningococcal disease[5] and sexually transmitted infections[6]. The aim of contact tracing for TB is threefold: to reduce morbidity and mortality in contacts with TB by finding them sooner; to reduce transmission from those contacts with active TB; and to find contacts with latent *M. tuberculosis* infection (LTBI) who are eligible for preventive therapy (PT)[7].

In January 2016, the UK National Institute for Health & Care Excellence (NICE) TB guidelines changed from recommending screening contacts of all cases, to only screening contacts of pulmonary or laryngeal TB (PTB) cases. No new evidence was cited to justify this change[8]. Although the guidance on whether contacts of non-pulmonary, non-laryngeal cases (ETB) are screened differs between countries[9,10], most advocate not screening contacts of these cases. Neither the CDC nor the WHO advocate screening contacts of these cases, although the WHO guidance is mainly aimed at low- and middle-income countries[11,12].

England has a high proportion of cases with non-pulmonary TB (51% in the most recent year), associated particularly with immigrants from the Indian subcontinent[1,13].

Whilst ETB cases are typically not infectious, there is evidence that their contacts are more likely to have TB than the general population. Between 2012-15, the prevalence of active TB amongst contacts of ETB index cases in London was 0.7%[14], compared to 0.027% in the general population[15]. Similar patterns are observed in Birmingham[16,17], and in both cities the prevalence of disease amongst contacts of ETB cases was higher than the prevalence of disease amongst migrants eligible

for pre-entry screening[18] ,and more than 10 times higher than the NICE threshold for new entrant screening[17]. Additionally, studies have shown only 25% of pairs of cases sharing an address in the UK[19], and 20% of case-contact pairs in London[20] had different *M. tuberculosis* isolates, implying the risk of disease in household contacts is high irrespective of whether transmission has occurred. This suggests that the fact that ETB cases are not infectious may not be a valid justification for not screening their contacts.

In light of this evidence, key stakeholders have questioned the change in guidance and a cost-effectiveness analysis has been called for[17]. To our knowledge, only one previous study has attempted to evaluate the cost-effectiveness of contact tracing[21], and no studies have done so in the UK or London, nor have any studies attempted to evaluate the cost-effectiveness of contact tracing delineated by site of disease of the index case. In this study we aim to evaluate the effectiveness and cost-effectiveness of contact tracing, for ETB and PTB index cases, in London. We first estimate symptomatic periods and the number of contacts found with active disease or LTBI per index case. We then use these values alongside previously published data to develop a simple static model to calculate the cost-effectiveness.

Methods (1177)

Data analysis: We used data on adult and adolescent (≥ 15 years old) TB cases notified to the London TB register (LTBR) during 2012-2015. The LTBR is a web-based register containing demographic and clinical data on all TB cases notified in London since 2002[14]. We excluded index cases that were notified in a region and year where the completeness was less than 80%, or were children (≤ 14 years old) (because contacts of children with ETB will still be screened under new guidelines)[8]. When estimating yield we excluded index cases who first accessed health-care through contact investigation, as the number of contacts is not recorded consistently[14] . Further details of exclusions and the representativeness of data are discussed in Cavany et al(see table 1 in that paper in particular), but demographic characteristics were similar between included and excluded data[14]. Costs were calculated based on national accounting expenditures and current treatment guidance for England[8,22] (see Appendix part 1 for details). Note that, in this manuscript, ETB refers exclusively to non-pulmonary, non-laryngeal TB, and so patients with pulmonary and/or laryngeal TB are classified in PTB, irrespective of whether they have involvement in other organs.

Other data sources: Estimates of utility scores were taken from Jit et al[23]. The life-time risk of developing disease following infection was taken from Sloot et al.[24] and the efficacy of PT from Smieja et al.[25] and Ayieko et al.[26] See Table 1 for details of data sources.

Effectiveness: We quantified the effectiveness of contact tracing with four outcomes:

1. Morbidity: the reduction in time contacts with TB are symptomatic if they are found earlier due to contact tracing.
2. Prevention: the number of contacts with LTBI prevented from developing active TB following PT.
3. Transmission: the number of cases prevented by reducing transmission from: a) contacts with prevalent TB found earlier through contact tracing; b) cases prevented from occurring due to PT.

4. Mortality: the number of TB deaths prevented by contact tracing.

Model description: We developed a simple static model to estimate the cost-effectiveness of screening contacts of ETB and PTB cases in London during the period 2012-2015. The model was used to calculate the four measures of effectiveness and estimate the quality-adjusted life-years (QALYs) gained by contact tracing using the following equations (see Table 1 and Table 2 for definitions of symbols).

In all equations σ is either P or E, and represents the site of disease of the index cases under analysis. The number of PTB index cases is given by $N_P = (1 - f_E)N$ and the number of ETB index cases is given by $N_E = f_E N$, where f_E is the fraction of all adult cases that have ETB.

The reduction in morbidity was calculated using the number of contacts with TB per index case (Y_σ), the proportion of contacts with TB that have ETB (ϵ_σ) and the difference in symptomatic period of cases found through contact tracing and those found through other routes:

$$t_{\text{morbidity},\,\sigma} = N_\sigma \left(Y_\sigma (1 - \epsilon_\sigma) \left(\frac{S_{P,\text{passive}} - S_{P,\text{traced}}}{365.25} \right) + Y_\sigma \epsilon_\sigma \left(\frac{S_{E,\text{passive}} - S_{E,\text{traced}}}{365.25} \right) \right)$$

The number of cases of TB prevented by PT, assuming contacts with LTBI are recently infected is:

$$N_{\text{prevention},\,\sigma} = N_\sigma \left(\sum_{j=a,c} y_\sigma \phi_{\sigma,j}\, \theta_{j,\sigma,B} \theta_{j,\sigma,C} \tau_j \right) P$$

where $\phi_{\sigma,c} = 1 - \phi_{\sigma,a}$. As the efficacy of PT is different in children (c) and adults (a), and children are more likely to begin preventive therapy than are adults (Appendix part2, Table G), we calculated the effectiveness of PT separately for these two groups.

The number of cases of TB prevented by reducing transmission from contacts with PTB by finding them sooner is:

135 $$N_{\text{transmission},\,\sigma} = N_\sigma Y_\sigma (1-\epsilon_\sigma)\left(\frac{S_{P,\text{passive}} - S_{P,\text{traced}}}{365.25}\right) rP$$

136 The prevention of subsequent generations of TB cases which would have occurred in the absence of
137 contact tracing is given by $N_{\text{later generations},\,\sigma}$ (see Appendix part 3).

138 The number of TB-related deaths prevented by screening contacts is calculated as follows:

139 $$N_{\text{mortality},\,\sigma} = \left(\frac{365.25 t_{\text{morbidity},\,\sigma}}{S_{\text{overall}}} + N_{\text{transmission},\,\sigma} + N_{\text{prevention},\,\sigma} + N_{\text{later generations},\,\sigma}\right)\mu$$

140 where μ is the case fatality ratio. The first term in this equation describes the reduction in mortality
141 among prevalent cases in contacts identified sooner via contact tracing.

142 To calculate the amount of onward transmission from prevented cases, we assumed a range of
143 values for the number of new infections per PTB case per month infectious, r, and explored the
144 dependence of results on this parameter. This parameter, r, can be related to the updated Styblo
145 rules developed by Trunz *et al.* and van Leth *et al.*[27,28]; these studies calculated that each case of
146 smear positive TB would lead to approximately 3 to 6 new infections, equating to a value of r
147 between 0.5 and 1 (see Appendix part 4).

148 **Cost-effectiveness:** Costs were calculated from a health system perspective. We excluded diagnostic
149 and treatment costs of contacts with TB, as we assumed these contacts would be treated later
150 regardless of whether the contact investigation took place. However, we subtracted the costs of
151 diagnosis and treatment of cases that are prevented. We assumed latently infected contacts are
152 given a 3 month course of rifampicin and isoniazid (with pyridoxine)[8], and assumed this has the same
153 efficacy as 6 months of isoniazid[29].

154 We calculated the resulting incremental cost-effectiveness ratio (ICER) for contact tracing of both
155 PTB and ETB index cases, using no screening as the baseline comparator for both. Equations for
156 these calculations are given in the Appendix part 3. Following NICE recommendations, we assumed a

an ICER greater than £20000-30000/QALY was cost-effective[30] – this is the threshold often used in NICE guidance to determine whether an intervention is cost-effective, and is also known as the "willingness-to-pay" threshold. We included secondary cases which occurred at any time after infection, but assumed most occur in the first year[24]. Consequently, most costs and QALY gains occurred in the first year, and so no discounting was included in the main analysis (see Appendix part 5 for a discussion of discounting).

Uncertainty and sensitivity: 95% confidence intervals were calculated by randomly selecting 10000 parameter sets from the distributions shown in Table 1 and Table 2. Correlation coefficients were calculated between the distribution of each parameter and distribution of the ICER.

We explored the sensitivity to the symptomatic period by doubling each of these periods, and to assumptions about risk of disease following infection and preventive therapy by using estimates of these from Erkens *et al.*[31] instead of the estimates from Sloot *et al*.[24].

We explored sensitivity to utility scores by using values from Mears et al.[23]. These were derived from the same source [32] as those of Jit et al.[33] used in our primary analysis, but differ as the Jit et al values were based on London specific data.

Additional analyses: We undertook an additional analysis to estimate the cost-effectiveness of screening of ETB cases that have pleural TB, because it has been reported that 55% of patients with pleural involvement according to X-ray are culture positive on induced sputum[34]. We also examined whether there were differences in the cost-effectiveness of screening contacts of UK-born and non-UK born ETB cases, due to the large differences in the proportion of cases that are ETB between these two groups (51.4% vs 31.9% respectively[1].

Role of finding source: The funding sources played no part in the study design, data analysis, writing of the manuscript or decision to submit for publication.

Results (951)

Mean symptomatic periods. During the period 2012-2015 in London, there were 5084 PTB cases, of whom 2465 met the inclusion criteria and had data on symptomatic period. Of these, 82 were found through contact tracing, and were symptomatic for a mean period of 76.6 days (95% CI: 58.5, 94.7). Those who accessed care through other routes were symptomatic for a longer mean period of 110 days (95% CI: 103, 117 days) (p=0.0016) (Table 2)

During the same period there were 6090 ETB cases, of whom 2559 were included and had data on symptomatic period. Of these, 26 were found through contact tracing and had a mean symptomatic period of 152 days (95% CI: 15.0, 289 days). Those who accessed care through other routes had a mean symptomatic period of 180 days (95% CI: 165, 195 days) (p=0.36). See Table E in Appendix part 2 for further details.

Preventive therapy. Of 1497 contacts with LTBI identified in the study period, 1165 (77.8% (95% CI: 74.9%, 80.7%) started PT and 918 of those that started (78.6% (95% CI: 75.4%, 81.8%) completed PT (Table 2). See Table G in Appendix part 2 for further details; of note is that children are much more likely than adults to start PT and, for contacts of PTB cases, to complete PT.

Effectiveness

Reduction in morbidity of contacts: On average, in a single year, not screening contacts of adult ETB cases would have led to those contacts with TB being undiagnosed for a combined additional 2.58 years (95% CI: 0.660 to 8.59) (Table 3). For contacts of PTB cases this would be 10.5 years (95% CI: 4.02 to 26.4).

Cases prevented by preventive therapy: By giving PT to contacts of ETB cases we would expect to prevent 5.45 (95% CI: 3.71 to 7.59) cases. This value would be 18.9 (95% CI: 13.1 to 25.8) cases prevented by giving PT to contacts of PTB index cases.

Cases prevented by reduced transmission from contacts: Finding contacts of ETB index cases with TB sooner via contact tracing, thereby reducing onward transmission, could prevent 1.71 cases (95% CI: 0.584 to 3.33) when $r = 1$ new infections per PTB case per month infectious. The corresponding value for PTB index cases is 8.76 (95% CI: 3.56 to 14.9). This reduction in cases is directly proportional to the assumed value of r.

Prevention of subsequent generations of cases: Preventing cases from occurring amongst contacts of contacts of ETB cases could avert 1.62 cases (95% CI: 0.772 to 3.11) when $r = 1$, and 5.19 cases (95% CI: 2.08 to 12.2) when $r = 2$. The corresponding figures for PTB index cases are 8.63 (95% CI: 4.77 to 14.7) and 33.1 (95% CI: 16.1 to 66.7).

Reduction in mortality: When $r = 1$, screening contacts of ETB cases could prevent 0.551 deaths (95% CI: 0.303 to 1.14) and screening contacts of PTB cases 2.27 deaths (95% CI: 1.36 to 3.94).

Cost-effectiveness: The cost per QALY of screening the contacts of ETB cases is £101000/QALY (95% CI: 46200 to 178000) when transmission is not included ($r = 0$), £77700/QALY (95% CI: 38800 to 139000) for $r = 1$ new infection per PTB case per month infectious and £56400/QALY (95% CI: 29300 to 102000) for $r = 2$ (Table 3, Figure 1a). The equivalent values for PTB cases are £43700/QALY (95% CI: 23700 to 70100), £30300/QALY (95% CI: 17700 to 50100) and £18700/QALY (95% CI: 10500 to 32700) respectively (Figure 1b). Screening contacts of ETB cases becomes cost-effective at a £30000/QALY threshold when $r = 3.40$. If $r = 1$, the yield of ETB index cases would need to be 0.0959 (an almost 5-fold increase above the observed yield, and greater than current PTB yield) in order for screening contacts of ETB cases to become cost-effective at £30000/QALY.

Sensitivity: Cost-effectiveness results are most sensitive to the symptomatic period of those found through contact tracing (Appendix table H) (especially of contacts of ETB index cases), the probability of developing disease, and the yield of ETB index cases. At low levels of transmission from PTB contacts, the symptomatic period of contacts with ETB explains most of the variation in the ICER. As

the number of infections generated by contacts is increased, the results become more sensitive to the probability of developing disease and the symptomatic period of PTB index cases, and less sensitive to the symptomatic period of ETB index cases. Increasing each symptomatic period by a factor of 2 (Figure 1c and d), then for $r \geq 1.60$ the mean cost-effectiveness of screening contacts of ETB cases is below the £30000/QALY threshold. Calculating the probability of developing disease from Erkens et al. rather than Sloot et al. does not qualitatively change the cost-effectiveness results (not shown). Using utility scores used by Mears et al.[23] instead of those used by Jit et al.[33] leads to a slight decrease in cost-effectiveness (Appendix part 6).

Additional analyses: While screening contacts of pleural TB cases is more cost-effective than screening contacts of other ETB cases, it still appears to be probably not cost-effective at a threshold of £30000/QALY for values of r less than 3 (Appendix figure B).

Similarly, If we restrict our analysis to UK-born cases only, then screening contacts of ETB cases is probably not cost-effective at a threshold of £30000/QALY for values of r below 3 (Appendix figure C). It is also unlikely to be cost-effective to screen contacts of non-UK born ETB cases for values of r below 4. For PTB cases, it is probably cost-effective to screen contacts of non-UK born PTB cases at a threshold of £30000/QALY when r is greater than 1.65 (Appendix figure C). Screening contacts of UK born PTB cases is probably cost-effective at £30000/QALY even if no transmission takes place, and becomes probably cost-effective at £20000/QALY when r is greater than 0.834.

Discussion (1627)

Principal findings:

On average, we estimate that in a single year, screening contacts of ETB would save a total of 2.58 years of morbidity in contacts with prevalent TB, and prevent at least 5.45 cases through reduced transmission and PT. However, screening ETB contacts was very unlikely to be cost-effective at a threshold of £30000/QALY, even with the assumption of high levels of transmission from contacts. Hence, the results presented here support recent changes to the NICE guidelines to remove screening of contacts of ETB cases from their guidance. In contrast, screening contacts of PTB cases was probably cost effective at a £30000/QALY threshold, especially when assuming high levels of transmission from contacts. Neither was likely to be cost-effective at a £20000/QALY threshold at plausible levels of transmission.

Strengths and limitations:

This study used high quality data on contact tracing yield in London to answer an important question for TB care and prevention, which has implications for TB policy in the UK. The approach used proposes a novel way of quantifying the effectiveness of contact tracing across four potential impacts (reduced morbidity, preventive therapy, reduced transmission and reduced mortality). The main limitation of the study is the large uncertainty in several parameters. However, we explored this first by varying the number of infections generated by each case (r), and by carrying out a probabilistic sensitivity analysis of all other parameters. A related limitation is the treatment of transmission. It is difficult to know the rate at which infectious contacts would infect further contacts, so we explored a range of assumptions. We did not characterise the indirect effect of contact tracing on transmission at a population level, though as only five percent of all cases in London are found through contact tracing, this is probably negligible over short time-scales. The quantitative nature of this approach is unable to assess broader outcomes of contact tracing, such as community engagement and tackling stigma. Finally, we used the self-reported symptomatic period

to estimate the time during which cases are infectious. Due to issues with patient recall and the fact that the ratio of estimated prevalence to incidence in London[15,35] is much greater than the mean self-reported symptomatic period found in this study, it is likely that this value systematically underestimates the true time people are symptomatic. Our sensitivity analysis showed that cost-effectiveness of contact tracing would increase and screening contacts of ETB cases would be possibly cost-effective at a £30000/QALY threshold if the symptomatic period was double that estimated by self-reported symptom onset (Figure 1c and d).

Our approach should not suffer from selection bias as, although we only included those cases and contacts detected by healthcare, in this case we are interested in the actual effect that would be experienced by the healthcare system, and so we are only interested in those cases and contacts that are actually found. Whilst we did exclude some regions and time-periods from the underlying dataset due to large amounts of missing data (see Cavany et al for details[14]), meaning some ascertainment bias may have been present, the excluded cases had similar demographic characteristics to those included. It is also possible some differential bias may have been present if cases were incorrectly classified as ETB or PTB, which is possible as a 24% of PTB cases and 51.9% of extrapulmonary cases were not culture confirmed in 2017 in England[1].

Relation to other studies:

In recent years, studies in the UK have evaluated the cost-effectiveness of screening new migrants[36] and hard to reach populations using a mobile X-ray unit (MXU, known as Find & Treat)[33]. In 2011 Pareek et al.[36] found that screening migrants from countries with an incidence exceeding 150/100000 cost £21000 per case averted. This is cheaper than screening ETB contacts, and similar to screening PTB contacts for $r = 1$ new infections per PTB case per month infectious (Table 3). Jit et al. found that screening hard-to-reach groups in London cost £6400-£10000/QALY gained, so was more cost-effective than screening PTB cases even if $r = 2$. In their study, Jit et al.[33] found that about 80% of QALYs gained were due to improved case-management of these complex cases, and

the cost-effectiveness of screening alone was similar to screening contacts of PTB cases. The case management impact would likely be smaller for contact tracing than for the MXU, because the population of contacts is less complex, and case management is not an explicit aim of contact tracing. When Dasgupta et al.[21] compared the cost-effectiveness of screening close contacts to migrant screening in Montreal, they found that close contact investigation was cost saving. This was due to much lower treatment costs of contacts as opposed to cases found through other routes, due largely to much higher rates of hospitalization amongst passively detected cases. However, this assumption was based on only six cases found through contact tracing. We did not explore the impact of decreased hospitalization rates here due to a lack of data. Finally, a 2008 study in British Columbia, Canada[37] found that giving PT to contacts was cost-effective, though this study focused on infectious index cases. Our results are not directly comparable with this study due to its focus on PT, but both support the continued screening of contacts of PTB cases.

Interpretation of results:

These results support the recent decision to remove screening contacts of adult ETB cases from NICE guidance. In order for screening these contacts to be cost-effective at a £30000/QALY threshold, r would need to be 3.40 new infections per PTB case per month infectious, which would mean each smear positive case would need to generate 21 new infections. This is likely to be high for some settings[27], but may be plausible in crowded environments, such as homeless shelters[38]. Additionally, we found that if the yield per ETB index case was above 0.0959, then the ICER for screening contacts of these cases was below £30000/QALY. In London, ETB cases with a history of homelessness or drug use have a yield greater than this (unpublished data), supporting recommendations for active case-finding amongst this group. Additionally, subgroups for whom the yield is higher, are also those for whom r is likely to be higher, further increasing the impact of screening contacts of those subgroups. It is unlikely that the average yield of ETB cases in other parts of the UK are much higher

than those seen in London[16], implying that it would also not be cost-effective to screen contacts of ETB cases nationally.

If we stratify our data into UK born and non-UK born groups, we see that it is more cost-effective to screen contacts of UK born PTB cases than it is non-UK born PTB cases (Appendix figure C). This is in part due to the much greater difference in symptomatic period between those found through contact tracing and those found through other routes for UK born cases compared to non-UK born cases (Appendix table M and N). This implies the gap in cost-effectiveness of contact tracing for UK born cases compared to non-UK born cases could be closed if contact tracing found non-UK born cases more quickly. The caveat to this result is that there is an assumption that contacts of UK born cases are also UK born, and non-UK born cases are non-UK born, which is not true, and which means we underestimate the impact of contact screening for non-UK born cases.

The impact on the ICER caused by changing the amount of transmission (r) indicates the importance of reducing transmission from contacts as one of the impacts of contact tracing. It is plausible, though, that the number of infections generated by a contact with PTB (i.e. the value of r) will be lower than that suggested by the re-estimated Styblo rule[27,28], as the household contacts of someone themselves found through contact tracing are more likely to have already been infected.

The main reason for the low ICER for ETB index cases was the small difference in symptomatic period of contacts with ETB and cases with ETB found through other routes (Appendix table H), suggesting that the impact may be improved by hastening contact tracing for these contacts. The NICE guidelines now recommend PT for anyone aged under 65 years. This may cause a small improvement in cost-effectiveness, as we would now expect a higher yield of LTBI per case, as more contacts will be tested for LTBI, provided it is not accompanied by lower rates of PT enrolment and completion. The introduction in 2017 of whole genome sequencing (WGS) in the UK[39] may also affect our conclusions. Whilst a study of the current strain typing service found no impact on contact

tracing[23], it is plausible that faster turnaround times and improved targeting available with WGS may affect contact tracing yields.

Further research:

This work would benefit from an improved understanding of the rate of onward transmission from contacts. Mathematical modelling work incorporating transmission on a network structure may help to understand this. It would also help to have a greater understanding of the proportion of contacts that have pulmonary TB and how this differs across groups. If there are subgroups for whom a greater than average proportion of contacts with TB have PTB, then this would increase the cost-effectiveness in these groups. Whilst we were able to estimate this proportion for the whole population, our small sample meant we could not stratify this estimate. Work to understand how the different screening approaches (migrant, hard-to-reach populations and contacts) interact would help our understanding of the impact of each. Our results were very sensitive to estimates of the symptomatic period of contacts, both due to the uncertainty of these estimates and the fact that they are based on self-reported periods. A more thorough understanding of diagnostic delay amongst both contacts and non-contacts is needed.

Tables

Table 1: Variables and constants from other sources. CI = confidence interval, ETB = non-pulmonary and non-laryngeal tuberculosis, LTBR = London TB register, NICE = National Institute for Health & Care Excellence, PT = preventive therapy, TB = tuberculosis, BNF = British National Formulary, QALY = quality-adjusted life years, UK = United Kingdom. †=this was calculated using the age-specific case-fatality ratios given in Mears et al. and the age-structure of cases calculated from the LTBR. Note that some confidence intervals differ slightly from those in the literature due to the use of beta distributions. Following current treatment guidance (NICE 2016), we used the following references to calculate cost values: NICE 2011, Pareek et al. 2011, Reference costs 2016, Dowdy et al. 2008, Dinnes et al. 2007, BNF 2017; where necessary, we inflated costs according to inflation to the base year 2016. See Appendix parts 1 and 6 for details of cost and utility calculations.

Name of variable (units, if applicable)	Symbol	Value	95% CI, (or *range)	Distribution	Source
Life-time probability of developing disease following infection	P	0.1	(0.08, 0.12)	Beta	Sloot et al.[24]
Efficacy PT in adults	τ_a	0.6	(0.49, 0.70)	Beta	Smieja et al.[25]
Efficacy PT in children	τ_c	0.4	(0.16, 0.57)	Beta	Ayieko et al.[26]
Average number of cases per year	N	2790	N/a	N/a	LTBR
Fraction of all adult cases that have ETB	f_E	0.545	N/a	N/a	LTBR
Fraction of those tested for active TB that have active TB	f_c	0.2	N/a	N/a	Mears et al.[23]
Case fatality ratio	μ	0.0363	N/a	N/a	Mears et al.[23†]and LTBR
Relative average treatment length of non-completed PT	f_i	0.33	N/a	N/a	Assumption
Contact tracing, per contact traced, £	C_0	244	N/a	N/a	See Appendix part 1
Further tests if case is suspected to have active disease, £	C_1	497	N/a	N/a	See Appendix part 1

Cost per full course PT (3 month rifampicin and isoniazid, with pyridoxine), £	C_{PT}	852	N/a	N/a	See Appendix part 1
Cost per full course (6 months) of treatment of tuberculosis disease, £	C_{FT}	1694	N/a	N/a	See Appendix part 1
Average utility of a healthy person, given age structure of TB cases in London	U_H	0.876	N/a	N/a	Calculated from Kruijshaar et al *via* Mears et al
Symptom onset to diagnosis	U_0	$0.68U_H$	N/a	N/a	Kruijshaar et al *via* Jit et al
On treatment	U_1	$0.79U_H$	N/a	N/a	Kruijshaar et al *via* Jit et al
Utility preventive therapy	U_{PT}	$0.9992U_H$	N/a	N/a	Kruijshaar et al *via* Mears et al
Average # of QALYs at death for someone living in UK	A_H	72.6	N/a	N/a	Calculated from Mears et al. and LTBR
Average # of QALYs at death for someone living in UK with TB as cause of death	A_{TB}	52.2	N/a	N/a	Calculated from Mears et al. and LTBR

365

366 Table 2: Estimates of parameters calculated from the LTBR. All parameters are chosen from a normal distribution. ETB = non-pulmonary and non-laryngeal tuberculosis, PTB=Pulmonary
367 or laryngeal tuberculosis. LTBI = latent M.Tb infection, LTBR = London TB report, PT = preventive therapy, TB = tuberculosis

Name of variable (units, if applicable)	Index case disease type	Symbol	Value	95% Confidence intervals
Number of contacts screened per index case	ETB	n_E	2.50	[2.41, 2.59]
	PTB	n_P	3.86	[3.72, 4.00]
Number of contacts found with TB per index case	ETB	Y_E	0.0196	[0.0119, 0.0273]
	PTB	Y_P	0.0938	[0.0774, 0.110]
Proportion of contacts with TB that have ETB	ETB	ϵ_E	0.486	[0.329, 0.643]
	PTB	ϵ_P	0.337	[0.278, 0.396]
Number of contacts found with LTBI per index case	ETB	y_E	0.119	[0.104, 0.134]
	PTB	y_P	0.471	[0.428, 0.514]
Proportion of index contact's with LTBI that are children	ETB	$\phi_{E,c}$	0.206	Not varied
	PTB	$\phi_{P,c}$	0.360	Not varied
Proportion of contacts with LTBI that begin PT, adult contact	ETB	$\theta_{a,E,B}$	0.611	[0.510, 0.712]
	PTB	$\theta_{a,P,B}$	0.666	[0.604, 0.728]
Proportion of contacts with LTBI that begin PT, child contact	ETB	$\theta_{c,E,B}$	0.931	[0.838, 1.02]
	PTB	$\theta_{c,P,B}$	0.969	[0.922, 1.02]
Proportion of contacts starting PT that complete PT, adult contact	ETB	$\theta_{a,E,C}$	0.875	[0.793, 0.957]
	PTB	$\theta_{a,P,C}$	0.803	[0.742, 0.864]
Proportion of contacts starting PT that complete PT, child contact	ETB	$\theta_{c,E,C}$	0.81	[0.638, 0.982]
	PTB	$\theta_{c,P,C}$	0.906	[0.845, 0.967]
Mean symptomatic period of PTB cases not found through contact tracing (days)	N/a	$S_{P,\text{passive}}$	110	[103, 117]
Mean symptomatic period of PTB cases found through contact tracing (days)	N/a	$S_{P,\text{traced}}$	76.6	[58.5, 94.7]
Mean symptomatic period of PTB cases (days)	N/a	$S_{P,\text{overall}}$	109	[102, 116]
Mean symptomatic period of ETB cases not found through contact tracing (days)	N/a	$S_{E,\text{passive}}$	181	[166, 196]
Mean symptomatic period of ETB cases found through contact tracing (days)	N/a	$S_{E,\text{traced}}$	152	[15.0, 289]
Mean symptomatic period of all cases (days)	N/a	S_{overall}	147	[139, 155]

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Table 3: Summary of the effectiveness measures included, costs incurred, quality adjusted life years(QALYs) gained and resulting incremental cost effectiveness ratio (ICER) for screening contacts of the indicated index cases compared to a baseline of not screening those contacts. Numbers are given for a year with a case-load that is the average caseload of the years 2012-15 (i.e. 2790 cases); note that the case-load does not affect the ICER. No discounting was applied; see Appendix part 5 for a discussion of discounting. Case-equivalents averted refers to both cases averted, and the reduction in the time contacts are symptomatic divided by the mean symptomatic period of TB cases. ETB = non-pulmonary, non-laryngeal; PTB = pulmonary or laryngeal; r = the number of infections generated by a pulmonary contact per month infectious; ICER = incremental cost-effectiveness ratio; PT = preventive therapy (3 months of isoniazid and rifampicin). Numbers in brackets indicate the 95% confidence intervals.

Quantity (units, if applicable)	ETB indexes			PTB indexes		
	$r = 0$	$r = 1$	$r = 2$	$r = 0$	$r = 1$	$r = 2$
Reduction in time contacts are symptomatic (years)	2.58 [0.66, 8.59]	2.58 [0.66, 8.59]	2.58 [0.66, 8.59]	10.5 [4.02, 26.4]	10.5 [4.02, 26.4]	10.5 [4.02, 26.4]
Cases prevented by administering PT (cases)	5.45 [3.71, 7.59]	5.45 [3.71, 7.59]	5.45 [3.71, 7.59]	18.9 [13.1, 25.8]	18.9 [13.1, 25.8]	18.9 [13.1, 25.8]
Transmission reduced by finding contacts sooner (cases)	0.0 [0.0, 0.0]	1.71 [0.584, 3.33]	3.41 [1.17, 6.62]	0.0 [0.0, 0.0]	8.76 [3.56, 14.9]	17.5 [7.02, 29.8]
Transmission reduced from prevented cases (cases)	0.0 [0.0, 0.0]	1.62 [0.772, 3.11]	5.19 [2.08, 12.2]	0.0 [0.0, 0.0]	8.63 [4.77, 14.7]	33.1 [16.1, 66.7]
Reduction in mortality (deaths)	0.431 [0.238, 0.977]	0.551 [0.303, 1.14]	0.743 [0.408, 1.45]	1.64 [0.997, 3.08]	2.27 [1.36, 3.94]	3.47 [2.04, 5.89]
Total case-equivalents averted	11.9 [6.56, 26.9]	15.2 [8.34, 31.4]	20.5 [11.2, 39.9]	45.0 [27.5, 85.0]	62.4 [37.5, 109.0]	95.6 [56.2, 162.0]
Total QALYs gained	10.6 [5.98, 23.4]	13.7 [7.66, 27.6]	18.7 [10.4, 35.6]	39.9 [24.8, 73.9]	56.3 [34.2, 95.9]	87.5 [51.7, 148.0]
Total costs incurred (£ 000 000s)	1.07 [1.03, 1.12]	1.06 [1.02, 1.11]	1.05 [1.01, 1.1]	1.74 [1.67, 1.82]	1.71 [1.63, 1.78]	1.63 [1.52, 1.72]
Incremental cost-effectiveness ratio (£ 000s/QALY)	101.0 [46.2, 178.0]	77.7 [38.8, 139.0]	56.4 [29.3, 102.0]	43.7 [23.7, 70.1]	30.3 [17.7, 50.1]	18.7 [10.5, 32.7]
Probability the ICER is less than £30000/QALY	0.09%	0.260%	3.08%	14.8%	54.0%	95.6%
Probability the ICER is less than £20000/QALY	0.00%	0.01%	0.02%	0.42%	7.26%	64.7%
Threshold which the ICER is 80% probable to be below (£ 000s/QALY)	135	99.6	71.9	54.0	36.6	22.9

Figure caption

Figure 1: Summary of incremental cost-effectiveness ratios and 95% confidence intervals (shaded region) for different levels of transmission from contacts. The comparator is no screening. The dashed horizontal line indicates the £30000/QALY cost-effectiveness threshold and the dotted horizontal line the £20000/QALY threshold. The solid horizontal line indicates when contact tracing becomes cost-saving. (a) and (b) represent the main results for ETB and PTB index cases respectively. (c) and (d) represent results for a symptomatic period which is double the self-reported period. GBP = pounds sterling, ETB = non-pulmonary, non-laryngeal tuberculosis, PTB = pulmonary or laryngeal tuberculosis, QALY = quality-adjusted life years, ICER = incremental cost-effectiveness ratio.

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References

1. Tuberculosis in England: annual report - GOV.UK [Internet]. [cited 2017 Jun 22]. Available from: https://www.gov.uk/government/publications/tuberculosis-in-england-annual-report

2. Data and statistics [Internet]. 2018 [cited 2018 May 26]. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/data-and-statistics

3. Tuberculosis (TB): collaborative strategy for England - GOV.UK [Internet]. [cited 2017 Jun 14]. Available from: https://www.gov.uk/government/publications/collaborative-tuberculosis-strategy-for-england

4. Dixon MG, Taylor MM, Dee J, Hakim A, Cantey P, Lim T, et al. Contact Tracing Activities during the Ebola Virus Disease Epidemic in Kindia and Faranah, Guinea, 2014. Emerg Infect Dis. 2015 Nov;21(11):2022–8.

5. Kamiya H, MacNeil J, Blain A, Patel M, Martin S, Weiss D, et al. Meningococcal disease among men who have sex with men - United States, January 2012-June 2015. MMWR Morb Mortal Wkly Rep. 2015 Nov 13;64(44):1256–7.

6. van Aar F, van Weert Y, Spijker R, Götz H, Op de Coul E, Partner Notification Group. Partner notification among men who have sex with men and heterosexuals with STI/HIV: different outcomes and challenges. Int J STD AIDS. 2015 Jul;26(8):565–73.

7. Erkens CGM, Kamphorst M, Abubakar I, Bothamley GH, Chemtob D, Haas W, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. Eur Respir J. 2010 Oct 1;36(4):925–49.

8. Tuberculosis | Guidance and guidelines | NICE [Internet]. [cited 2017 Jun 13]. Available from: https://www.nice.org.uk/guidance/ng33/chapter/Recommendations

9. Bothamley GH, Ditiu L, Migliori GB, Lange C, Contributors T. Active case finding of tuberculosis in Europe: a Tuberculosis Network European Trials Group (TBNET) survey. Eur Respir J. 2008 Oct 1;32(4):1023–30.

10. Rodriguez CA, Sasse S, Yuengling KA, Azzawi S, Becerra MC, Yuen CM. A systematic review of national policies for the management of persons exposed to tuberculosis. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2017 Aug 1;21(8):935–40.

11. Public health guidance on management of contacts of MDR TB and XDR TB patients [Internet]. European Centre for Disease Prevention and Control. 2012 [cited 2018 Jul 8]. Available from: http://ecdc.europa.eu/en/publications-data/public-health-guidance-management-contacts-mdr-tb-and-xdr-tb-patients

12. WHO | Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries [Internet]. WHO. [cited 2018 Jul 8]. Available from: http://www.who.int/tb/publications/2012/contact_investigation2012/en/

13. Kruijshaar ME, Abubakar I. Increase in extrapulmonary tuberculosis in England and Wales 1999-2006. Thorax. 2009 Dec;64(12):1090–5.

14. Cavany SM, Sumner T, Vynnycky E, Flach C, White RG, Thomas HL, et al. An evaluation of tuberculosis contact investigations against national standards. Thorax. 2017 Apr 7;thoraxjnl-2016-209677.

15. Story A, Murad S, Roberts W, Verheyen M, Hayward AC, London Tuberculosis Nurses Network. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax. 2007 Aug;62(8):667–71.

16. Saunders MJ, Koh GCKW, Small AD, Dedicoat M. Predictors of contact tracing completion and outcomes in tuberculosis: a 21-year retrospective cohort study. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2014 Jun;18(6):640–6.

17. Wingfield T, MacPherson P, Cleary P, Ormerod LP. High prevalence of TB disease in contacts of adults with extrapulmonary TB. Thorax. 2017 Nov 16;

18. Aldridge RW, Zenner D, White PJ, Muzyamba MC, Loutet M, Dhavan P, et al. Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study. Lancet Infect Dis. 2016 Aug;16(8):962–70.

19. Lalor MK, Anderson LF, Hamblion EL, Burkitt A, Davidson JA, Maguire H, et al. Recent household transmission of tuberculosis in England, 2010-2012: retrospective national cohort study combining epidemiological and molecular strain typing data. BMC Med. 2017 Jun 13;15(1):105.

20. Cavany SM, Vynnycky E, Sumner T, Macdonald N, Thomas HL, White J, et al. Transmission events revealed in tuberculosis contact investigations in London. Sci Rep. 2018 Apr 27;8(1):6676.

21. Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, Menzies D. Comparison of Cost-Effectiveness of Tuberculosis Screening of Close Contacts and Foreign-Born Populations. Am J Respir Crit Care Med. 2000 Dec 1;162(6):2079–86.

22. Committee JF, editor. BNF 73 (British National Formulary) March 2017. 73rd Revised edition edition. London: Pharmaceutical Press; 2017. 1480 p.

23. Mears J, Vynnycky E, Lord J, Borgdorff MW, Cohen T, Crisp D, et al. The prospective evaluation of the TB strain typing service in England: a mixed methods study. Thorax. 2016 Aug 1;71(8):734–41.

24. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Risk of Tuberculosis after Recent Exposure. A 10-Year Follow-up Study of Contacts in Amsterdam. Am J Respir Crit Care Med. 2014 Sep 29;190(9):1044–52.

25. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 1999 [cited 2017 May 2]. Available from: http://doi.wiley.com/10.1002/14651858.CD001363

26. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta–analysis. BMC Infect Dis. 2014;14(1):1.

27. van Leth F, van der Werf MJ, Borgdorff MW. Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. Bull World Health Organ. 2008 Jan;86(1):20–6.

28. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet Lond Engl. 2006 Apr 8;367(9517):1173–80.

29. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015 Dec;46(6):1563–76.

30. Guide to the methods of technology appraisal 2013 | Guidance and guidelines | NICE [Internet]. [cited 2017 May 31]. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making

31. Erkens CGM, Slump E, Verhagen M, Schimmel H, Cobelens F, Hof S van den. Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands. Eur Respir J. 2016 Oct 6;ERJ-01157-2016.

32. Kruijshaar ME, Lipman M, Essink-Bot M-L, Lozewicz S, Creer D, Dart S, et al. Health status of UK patients with active tuberculosis. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2010 Mar;14(3):296–302.

33. Jit M, Stagg HR, Aldridge RW, White PJ, Abubakar I. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ. 2011 Sep 13;343:d5376.

34. Conde MB, Loivos AC, Rezende VM, Soares SLM, Mello FCQ, Reingold AL, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med. 2003 Mar 1;167(5):723–5.

35. Tuberculosis (TB): regional and devolved administration reports - GOV.UK [Internet]. [cited 2017 Jun 22]. Available from: https://www.gov.uk/government/publications/tuberculosis-tb-regional-reports

36. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis. 2011 Jun 1;11(6):435–44.

37. Tan MC, Marra CA, Sadatsafavi M, Marra F, Morán-Mendoza O, Moadebi S, et al. Cost-effectiveness of LTBI treatment for TB contacts in British Columbia. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2008 Oct;11(5):842–52.

38. Crisan A, Wong HY, Johnston JC, Tang P, Colijn C, Otterstatter M, et al. Spatio-temporal analysis of tuberculous infection risk among clients of a homeless shelter during an outbreak. Int J Tuberc Lung Dis. 2015 Sep 1;19(9):1033–8.

39. Walker TM, Cruz ALG, Peto TE, Smith EG, Esmail H, Crook DW. Tuberculosis is changing. Lancet Infect Dis. 2017 Apr;17(4):359–61.

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