

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

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4    **Authors:** Sean M. Cavany<sup>1,2</sup>, Emilia Vynnycky<sup>1,2</sup>, Charlotte Anderson<sup>4</sup>, Helen Maguire<sup>4,5</sup>, Frank  
5    Sandmann<sup>2,6</sup>, H. Lucy Thomas<sup>3</sup>, Richard G. White<sup>1</sup>, Tom Sumner<sup>1</sup>

6    **Affiliations and positions:**

- 7           1. TB Modelling Group, TB Centre and CMMID, Faculty of Epidemiology and Population Health,  
8           London School of Hygiene and Tropical Medicine, London.
- 9           2. Statistics, Modelling and Economics Department, Public Health England, London
- 10          3. Respiratory Diseases Department, Public Health England, London
- 11          4. Field Epidemiology Service, Public Health England, London
- 12          5. Institute for Global Health, University College London
- 13          6. CMMID, Faculty of Epidemiology and Population Health, London School of Hygiene and  
14          Tropical Medicine, London.

15    **\*Corresponding author:** SM Cavany, email: [sean.cavany@lshtm.ac.uk](mailto:sean.cavany@lshtm.ac.uk), phone: +447861234239

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## 17 **Abstract (245)**

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

23 **Methods** – We carried out a cross-sectional analysis of data collected on tuberculosis index cases  
24 and contacts in the London tuberculosis register, and an economic evaluation using a static model  
25 describing contact tracing outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated  
26 using no screening as the baseline comparator. All adult TB cases ( $\geq 15$  years old) in London from  
27 2012-15, and their contacts, were eligible (2465/5084 PTB and 2559/6090 ETB index cases were  
28 included).

29 **Results** – Assuming each contact with PTB infects 1 person/month, the ICER of screening contacts of  
30 ETB cases was £78000/QALY (95% CI: 39000 to 140000) and screening contacts of PTB cases was  
31 £30000/QALY (95% CI: 18000 to 50000). The ICER of screening contacts of ETB cases was  
32 £30000/QALY if each contact with PTB infects 3.4 people/month. Limitations of this study include  
33 the use of self-reported symptomatic periods, and lack of knowledge about onward transmission  
34 from PTB contacts.

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

38 **Key Messages**

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

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

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

49

## 50 Introduction (542)

51 Following four years of decline, the incidence of tuberculosis (TB) in England had fallen to  
52 10.2/100000 in 2016<sup>1</sup>, but is still higher than most other countries in western and northern Europe<sup>2</sup>.  
53 Contact tracing, the systematic screening of contacts of cases, is a fundamental part of TB control in  
54 high-income countries, and is highlighted as a key element of the Public Health England  
55 (PHE)/National Health Service (NHS) England collaborative tuberculosis strategy 2015-2020<sup>3</sup>. It is  
56 also used around the world for other infectious diseases, including Ebola<sup>4</sup>, meningococcal disease<sup>5</sup>  
57 and sexually transmitted infections<sup>6</sup>. The aim of contact tracing for TB is threefold: to reduce  
58 morbidity and mortality in contacts with TB by finding them sooner; to reduce transmission from  
59 those contacts with active TB; and to find contacts with latent *M. tuberculosis* infection (LTBI) who  
60 are eligible for preventive therapy (PT)<sup>7</sup>.

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

68 England has a high proportion of cases with non-pulmonary TB (51% in the most recent year),  
69 associated particularly with immigrants from the Indian subcontinent<sup>1,13</sup>.

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

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

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

## 90 **Methods (1177)**

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

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

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

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

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

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

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

124 The reduction in morbidity was calculated using the number of contacts with TB per index case ( $Y_\sigma$ ),  
125 the proportion of contacts with TB that have ETB ( $\epsilon_\sigma$ ) and the difference in symptomatic period of  
126 cases found through contact tracing and those found through other routes:

$$127 \quad t_{\text{morbidity}, \sigma} = N_\sigma \left( Y_\sigma (1 - \epsilon_\sigma) \left( \frac{S_{P,\text{passive}} - S_{P,\text{traced}}}{365.25} \right) + Y_\sigma \epsilon_\sigma \left( \frac{S_{E,\text{passive}} - S_{E,\text{traced}}}{365.25} \right) \right)$$

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

$$129 \quad N_{\text{prevention}, \sigma} = N_\sigma \left( \sum_{j=a,c} y_\sigma \phi_{\sigma,j} \theta_{j,\sigma,B} \theta_{j,\sigma,C} \tau_j \right) P$$

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

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

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

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  $\mu$  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.*<sup>27,28</sup>; 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)<sup>8</sup>, and assumed this has the same  
 153 efficacy as 6 months of isoniazid<sup>29</sup>.

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



157 an ICER greater than £20000-30000/QALY was cost-effective<sup>30</sup> – this is the threshold often used in  
158 NICE guidance to determine whether an intervention is cost-effective, and is also known as the  
159 “willingness-to-pay” threshold. We included secondary cases which occurred at any time after  
160 infection, but assumed most occur in the first year<sup>24</sup>. Consequently, most costs and QALY gains  
161 occurred in the first year, and so no discounting was included in the main analysis (see Appendix part  
162 5 for a discussion of discounting).

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

166 We explored the sensitivity to the symptomatic period by doubling each of these periods, and to  
167 assumptions about risk of disease following infection and preventive therapy by using estimates of  
168 these from Erkens *et al.*<sup>31</sup> instead of the estimates from Sloot *et al.*<sup>24</sup>.

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

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

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

## 180 **Results (951)**

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

186 During the same period there were 6090 ETB cases, of whom 2559 were included and had data on  
187 symptomatic period. Of these, 26 were found through contact tracing and had a mean symptomatic  
188 period of 152 days (95% CI: 15.0, 289 days). Those who accessed care through other routes had a  
189 mean symptomatic period of 180 days (95% CI: 165, 195 days) ( $p=0.36$ ). See Table E in Appendix part  
190 2 for further details.

191 **Preventive therapy.** Of 1497 contacts with LTBI identified in the study period, 1165 (77.8% (95% CI:  
192 74.9%, 80.7%) started PT and 918 of those that started (78.6% (95% CI: 75.4%, 81.8%) completed PT  
193 (Table 2). See Table G in Appendix part 2 for further details; of note is that children are much more  
194 likely than adults to start PT and, for contacts of PTB cases, to complete PT.

### 195 **Effectiveness**

196 *Reduction in morbidity of contacts:* On average, in a single year, not screening contacts of adult ETB  
197 cases would have led to those contacts with TB being undiagnosed for a combined additional 2.58  
198 years (95% CI: 0.660 to 8.59) (Table 3). For contacts of PTB cases this would be 10.5 years (95% CI:  
199 4.02 to 26.4).

200 *Cases prevented by preventive therapy:* By giving PT to contacts of ETB cases we would expect to  
201 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  
202 prevented by giving PT to contacts of PTB index cases.

203 *Cases prevented by reduced transmission from contacts:* Finding contacts of ETB index cases with TB  
204 sooner via contact tracing, thereby reducing onward transmission, could prevent 1.71 cases (95% CI:  
205 0.584 to 3.33) when  $r = 1$  new infections per PTB case per month infectious. The corresponding  
206 value for PTB index cases is 8.76 (95% CI: 3.56 to 14.9). This reduction in cases is directly  
207 proportional to the assumed value of  $r$ .

208 *Prevention of subsequent generations of cases:* Preventing cases from occurring amongst contacts of  
209 contacts of ETB cases could avert 1.62 cases (95% CI: 0.772 to 3.11) when  $r = 1$ , and 5.19 cases (95%  
210 CI: 2.08 to 12.2) when  $r = 2$ . The corresponding figures for PTB index cases are 8.63 (95% CI: 4.77 to  
211 14.7) and 33.1 (95% CI: 16.1 to 66.7).

212 *Reduction in mortality:* When  $r = 1$ , screening contacts of ETB cases could prevent 0.551 deaths  
213 (95% CI: 0.303 to 1.14) and screening contacts of PTB cases 2.27 deaths (95% CI: 1.36 to 3.94).

214 **Cost-effectiveness:** The cost per QALY of screening the contacts of ETB cases is £101000/QALY (95%  
215 CI: 46200 to 178000) when transmission is not included ( $r = 0$ ), £77700/QALY (95% CI: 38800 to  
216 139000) for  $r = 1$  new infection per PTB case per month infectious and £56400/QALY (95% CI:  
217 29300 to 102000) for  $r = 2$  (Table 3, Figure 1a). The equivalent values for PTB cases are  
218 £43700/QALY (95% CI: 23700 to 70100), £30300/QALY (95% CI: 17700 to 50100) and £18700/QALY  
219 (95% CI: 10500 to 32700) respectively (Figure 1b). Screening contacts of ETB cases becomes cost-  
220 effective at a £30000/QALY threshold when  $r = 3.40$ . If  $r = 1$ , the yield of ETB index cases would  
221 need to be 0.0959 (an almost 5-fold increase above the observed yield, and greater than current  
222 PTB yield) in order for screening contacts of ETB cases to become cost-effective at £30000/QALY.

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

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

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

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

## 245 **Discussion (1627)**

### 246 **Principal findings:**

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

### 256 **Strengths and limitations:**

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

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

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

#### 286 **Relation to other studies:**

287 In recent years, studies in the UK have evaluated the cost-effectiveness of screening new migrants<sup>36</sup>  
288 and hard to reach populations using a mobile X-ray unit (MXU, known as Find & Treat)<sup>33</sup>. In 2011  
289 Pareek et al.<sup>36</sup> found that screening migrants from countries with an incidence exceeding  
290 150/100000 cost £21000 per case averted. This is cheaper than screening ETB contacts, and similar  
291 to screening PTB contacts for  $r = 1$  new infections per PTB case per month infectious (Table 3). Jit  
292 et al. found that screening hard-to-reach groups in London cost £6400-£10000/QALY gained, so was  
293 more cost-effective than screening PTB cases even if  $r = 2$ . In their study, Jit et al.<sup>33</sup> found that  
294 about 80% of QALYs gained were due to improved case-management of these complex cases, and

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

#### 307 **Interpretation of results:**

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

319 than those seen in London<sup>16</sup>, implying that it would also not be cost-effective to screen contacts of  
320 ETB cases nationally.

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

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

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



343 tracing<sup>23</sup>, it is plausible that faster turnaround times and improved targeting available with WGS may  
344 affect contact tracing yields.

345 **Further research:**

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

358 **Tables**

359 **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  
 360 for Health & Care Excellence, PT = preventive therapy, TB = tuberculosis, BNF = British National Formulary, QALY = quality-adjusted life years, UK = United Kingdom. †=this was calculated  
 361 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  
 362 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,  
 363 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  
 364 details of cost and utility calculations.

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

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

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366  
367

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 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	$\epsilon_E$	0.486	[0.329, 0.643]
	PTB	$\epsilon_P$	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	$S_{P,passive}$	110	[103, 117]
Mean symptomatic period of PTB cases found through contact tracing (days)	N/a	$S_{P,traced}$	76.6	[58.5, 94.7]
Mean symptomatic period of PTB cases (days)	N/a	$S_{P,overall}$	109	[102, 116]
Mean symptomatic period of ETB cases not found through contact tracing (days)	N/a	$S_{E,passive}$	181	[166, 196]
Mean symptomatic period of ETB cases found through contact tracing (days)	N/a	$S_{E,traced}$	152	[15.0, 289]
Mean symptomatic period of all cases (days)	N/a	$S_{overall}$	147	[139, 155]



369 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  
370 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-  
371 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  
372 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  
373 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  
374 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

375 **Figure caption**

376 **Figure 1: Summary of incremental cost-effectiveness ratios and 95% confidence intervals (shaded region) for different**  
377 **levels of transmission from contacts. The comparator is no screening. The dashed horizontal line indicates the**  
378 **£30000/QALY cost-effectiveness threshold and the dotted horizontal line the £20000/QALY threshold. The solid**  
379 **horizontal line indicates when contact tracing becomes cost-saving. (a) and (b) represent the main results for ETB and**  
380 **PTB index cases respectively. (c) and (d) represent results for a symptomatic period which is double the self-reported**  
381 **period. GBP = pounds sterling, ETB = non-pulmonary, non-laryngeal tuberculosis, PTB = pulmonary or laryngeal**  
382 **tuberculosis, QALY = quality-adjusted life years, ICER = incremental cost-effectiveness ratio.**

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504

## 505 **Statements**

506 **Declaration of interests:** The authors have declared that no competing interests exist.

507 **Details of contributors:** SMC, EV and TS conceived and designed the work, with input from all other  
508 authors. CA and HM are responsible for the acquisition and maintenance of the data. SMC  
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522 **Software:** All data were analysed using Microsoft Excel 14.0, Stata 13.1 and Python 2.7.9 (including  
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524 **Ethics.** Ethical approval was not required. The data analysed were routinely collected surveillance  
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