

**AThe benefits to communities and individuals of screening
for active tuberculosis disease: a systematic review**

Journal:	<i>The International Journal of Tuberculosis and Lung Disease</i>
Manuscript ID:	IJTLD-09-12-0743.R1
Manuscript Type:	State of the Art
Date Submitted by the Author:	28-Nov-2012
Complete List of Authors:	Kranzer, Katharina; London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology Afnan-Holmes, Hoviyeh; London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology Tomlin, Keith; London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology Golub, Jonathan; Johns Hopkins School of Medicine, Center for Tuberculosis Research Shapiro, Adrienne; Johns Hopkins School of Medicine, Center for Tuberculosis Research Schaap, Ab; London School of Hygiene and Tropical Medicine, Department of Clinical Research Corbett, Elizabeth; London School of Hygiene and Tropical Medicine, Department of Clinical Research Lönnroth, Knut; World Health Organization, TB Strategy and Operations, Stop TB Department Glynn, Judith; London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology
Key Words:	Screening, Impact evaluation, Mortality, Transmission

A systematic literature review of the benefits to communities and individuals of screening for active tuberculosis disease

Katharina Kranzer^a, Hoviyeh Afnan-Holmes^a, Keith Tomlin^a, Jonathan E Golub^b, Adrienne Shapiro^b,
Ab Schaap^c, Liz Corbett^c, Knut Lönnroth^d, Judith R Glynn^a

^a Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

^b Johns Hopkins School of Medicine, Baltimore, MD, USA

^c Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom

^d Stop TB Department, WHO, Geneva, Switzerland

World Count: Abstract = 246; Text = 5430; Tables = 6; Figures = 1; References = 81

1 **Abstract**

2

3 **Background:** Screening for tuberculosis (TB) disease aims to improve early TB case detection. The
4 ultimate goal is to improve outcomes for people with TB and to reduce *Mycobacterium tuberculosis*
5 transmission in the community through improved case detection, reduction in diagnostic delays and
6 early treatment. Before screening programmes are recommended evidence is needed of individual
7 and/or community-level benefit.

8 **Methods:** We reviewed the literature for evidence that screening for TB disease (i) initially increases the
9 number of TB cases initiated on TB treatment, (ii) identifies cases earlier in the course of disease (iii)
10 reduces mortality and morbidity and (iv) impacts on TB epidemiology.

11 **Results:** A total of 846 publications were identified by the search strategy, 785 publications were
12 excluded leaving 61 publications which addressed at least one of the study questions.

13 Screening increases the number of cases found in the short term. In many settings more than half the
14 prevalent TB cases in the community are undiagnosed. Screening tends to find cases earlier and with
15 less severe disease, but this may be attributed to case-finding studies using more sensitive diagnostic
16 methods than routine programmes. Treatment outcomes among people identified through screening
17 are similar to treatment outcomes among those identified through passive case-finding. Current studies
18 provide insufficient evidence to show that active screening for TB disease impacts on TB epidemiology.

19 **Conclusion:** Individual and community-level benefits from active screening for TB disease remain
20 uncertain. So far the benefits of earlier diagnosis on patient outcomes and transmission have not been
21 established.

22

23

24 **Introduction**

25

26 Investments in TB control on a global scale have resulted in reductions in prevalence and deaths from
27 TB. However TB case detection has stagnated in recent years, while estimated TB incidence is
28 declining very slowly. This has resulted in renewed interest in the potential contribution to early case
29 detection from systematic TB screening. TB screening in HIV-infected individuals has been
30 recommended by the World Health Organization (WHO) as part of the 'Three I's' policy initiative^{1,2}.
31 Systematic screening of household contacts of infectious TB cases has been recommended^{3,5}, but
32 population-wide mass-screening has been discouraged due to uncertain impact, high cost, and poor
33 sustainability^{6,8}. Recently there has been renewed interest in systematic screening for active TB disease in
34 risk groups, as well as population-wide screening interventions. National TB prevalence surveys have
35 demonstrated that a large pool of undetected prevalent cases exist even in settings with well-functioning
36 TB programmes, and many of the prevalent cases would have been difficult to reach with passive case-
37 finding (PCF) approaches^{9,11}. Several screening initiatives have been launched recently, and some have
38 shown promising results^{6,12-13}.

39 The ultimate goals of systematic TB screening are to improve health outcomes among people
40 with TB and to reduce *M.tuberculosis* transmission in the community through improved TB detection,
41 reduction in diagnostic delays and early treatment⁷. Impact evaluation of TB control interventions,
42 however, is technically difficult and expensive and so is rarely included in programmatic or research
43 studies.

44 Before screening programmes are recommended, evidence is needed of individual or
45 community-level benefit from early diagnosis provided by screening, and that benefits outweigh any
46 harms incurred. We reviewed the evidence of individual and/or community benefit from active TB
47 screening focusing on: additional TB cases detected; reduction in diagnostic delay; improved treatment
48 outcomes; and impact on TB epidemiology.

49

50

51 **Methods**

52

53 *Definitions*

54 We define screening for active tuberculosis as the *systematic identification of people with suspected*
 55 *active TB in a predetermined target group by the application of tests, examinations, or other procedures*
 56 *which can be applied rapidly*. Among those with suspected TB, the diagnosis needs to be established
 57 through application of one or several diagnostic tests and clinical assessment. Screening can be either
 58 done as an outreach activity in the general community, among TB contacts, and in other specific high
 59 risk groups, or among people seeking care, including people who seek care for other reasons than
 60 symptoms compatible with TB. The latter category includes, for example, people coming for regular
 61 check-up of conditions that are risk factors for TB, such as HIV and diabetes. PCF is defined as
 62 detecting active TB disease among symptomatic patients who self-present to medical services for
 63 diagnosis of symptoms, with a specific focus on people with typical TB symptoms, such as chronic
 64 cough. Active case-finding (ACF) implies screening through outreach activities outside health services.
 65 Enhanced Case Finding (ECF) primarily aims to make a population aware of TB symptoms (through
 66 publicity and education), and encourages self-presentation to medical services, which may be
 67 decentralised as part of the intervention. This in effect means ECF is PCF combined with intensified
 68 health information⁷. However, ECF can also include a screening element, for example as part of a
 69 chest/health camp, in which case the intervention is a combined ACF/ECF intervention. In this paper,
 70 we will use “screening” to describe ACF interventions and ECF for interventions that mainly focus on
 71 health information.

72

73 *Specific questions*

74 The review addressed 4 specific questions:

- 75 1. Does screening for TB disease increase the number of TB cases detected compared to PCF?
- 76 2. Does screening for TB disease identify cases at an earlier stage of TB disease than PCF?
- 77 3. Is there a difference in TB treatment outcomes between TB cases found by screening and
 78 those found through PCF?
- 79 4. Does the addition of screening for TB disease to PCF affect TB incidence or prevalence in the
 80 community?

81

82 *Inclusion criteria*

83 Inclusion criteria for studies addressing the four questions are outlined below.

84 Does screening for TB disease increase case detection? Studies would ideally be longitudinal
 85 with continuous or repeated rounds of screening in addition to PCF, reporting the number of cases
 86 detected by screening and PCF over time. This would allow the effects of screening to be assessed
 87 beyond the first round, in which a large number of long-term undetected cases may be found. However,

88 due to the paucity of such studies the inclusion criteria were widened to include cross-sectional studies
89 of one-off screening, reporting the number or proportion of TB cases detected by screening and
90 passively; and prevalence surveys reporting the proportion of undiagnosed TB.

91 Does screening for TB disease identify cases earlier? All studies comparing at least one of i) the
92 length of time between reported onset of symptoms and start of treatment, ii) sputum positivity rate or iii)
93 chest X-ray abnormalities at time of diagnosis, in TB cases detected through screening and passively
94 were eligible. Contact tracing studies were eligible if the index cases were representative of all TB cases
95 detected passively (so that they could form the comparison group).

96 Does screening for TB disease affect treatment outcome? Ideally studies should allow direct
97 comparison of outcomes of patients identified actively or passively in the same area. However, as there
98 were few such studies, we included all studies reporting on outcomes of TB cases identified actively, for
99 comparison with WHO target outcomes.

100 Does screening for TB disease affect TB epidemiology? All studies comparing TB prevalence,
101 incidence or transmission in communities receiving screening and PCF and communities receiving PCF
102 only were eligible. Studies investigating impact in specific groups (such as prisons, mines or risk groups)
103 and did not investigate the impact on the general population were excluded. Study designs could be
104 before-after comparisons, cluster randomised controlled trials or quasi-experimental designs.

105

106 *Search strategy*

107 The initial search used papers selected on initial screening by an existing systematic review¹⁴ which had
108 already identified TB case-finding studies published up to October 2010. No exclusions were made on
109 the study population, geographical setting, language or year of publication. This review identified a total
110 of 827 publications and abstracts: 759 published in English, 20 in Spanish, 25 in Japanese and 23 in
111 Russian. In addition, data from prevalence surveys provided by the WHO were added, together with
112 further papers identified by experts in the field, and unpublished data from the recently completed
113 Zamstar study. Since treatment outcome data might be published separately from the initial screening
114 results, additional searches were undertaken to identify subsequent publications reporting TB treatment
115 outcomes of all studies with at least 40 TB cases identified through screening and published after 1992
116 (the time when DOTS became widely available). Searches used Ovid Medline using the first or the last
117 authors' names combined with "treatment outcomes" and "tuberculosis". In addition first and last
118 authors of studies published between 2005 and 2011 were contacted directly.

119

120 *Selection of publications for inclusion*

121 The full text of all publications identified was screened for relevance for any of the four outcomes. This
122 was done in stages: an initial screen to check for possible eligibility, then a more detailed screen of
123 retained papers, then data extraction of eligible publications. The first 120 publications reviewed in the
124 initial screen were done in duplicate to ensure consistency, and all data extraction of included papers

125 was done in duplicate using a standardised data extraction tool. Any discrepancies were resolved by
126 discussion.

127

128 *Data synthesis and analysis*

129 Settings, populations (e.g. homeless, refugees, general population) and screening approach differed
130 considerably. Due to the heterogeneity of studies a narrative approach was adopted for data synthesis. A
131 formal meta-analysis was conducted where appropriate, which was only for the treatment outcome
132 analysis. The relative risk (RR) of successful treatment by case-finding method was calculated, and
133 pooled with the DerSimonian-Laird random-effects method, which treats studies as a sample of all
134 potential studies, and incorporates an additional between-study component to the estimate of variability.
135 The I-squared statistic was calculated as a measure of the proportion of the overall variation that is
136 attributable to between study heterogeneity.

137 **Results**

138

139 Identification of studies

140

141 Of the 828 publications identified in the previous search, 737 were full articles and 91 abstracts. In
 142 addition we reviewed unpublished studies and studies identified through expert opinion, prevalence
 143 surveys from Cambodia and Myanmar and conference abstracts and unpublished reports from the
 144 Zamstar study and identified 19 relevant studies. 712 publications were excluded on the initial screen
 145 and 74 subsequently leaving 61 publications which addressed at least one of the study questions.

146 The studies covered a range of different populations and used a variety of screening algorithms.
 147 Details are summarised in table 1. Screening included symptoms, chest X-ray and sputum for smear
 148 microscopy and/or culture. A key distinction is whether the methods were used sequentially or together,
 149 and in particular, whether only symptomatic cases were screened further, or whether the initial screen
 150 included bacteriology or X-ray even on asymptomatic cases (thus increasing the sensitivity of the screen).

151

152 1) Does screening for TB disease increase the number of TB cases detected?

153

154 *a) Studies assessing the contribution of screening over time*

155 One recent study and two historical studies were identified in which the proportion of cases identified
 156 through screening could be assessed over time. In Morocco, household contacts were screened for TB¹⁵.
 157 National figures were reported from 1993-2004, involving more than one million identified contacts. In
 158 this context, with different individuals involved in screening every year, no change in the proportion
 159 found due to removal of prevalent cases is expected. The proportion of TB in the population detected
 160 through this screening averaged 5.6% and decreased slightly over time; this decrease may be attributed
 161 to a fall in the ratio of household contacts screened to index cases over time.

162 In a district in Czechoslovakia mass miniature radiography (MMR) surveys with >95% coverage
 163 were carried out every 3 years since 1960 (together with BCG vaccination of the newborn and
 164 revaccination of adolescents), while screening was also done at regular check-up of people with a
 165 previously known CXR lesion¹⁶. The prevalence of smear and/or culture-positive TB was 73/100,000
 166 population at the beginning of the study and declined to 56/100,000 population in 1972. The total
 167 number of smear- and/or culture-positive TB cases was 79 in 1966 and 52 in 1972. The proportion
 168 detected through screening declined from 0.86 (95%CI 0.76-0.93) in 1966 to 0.56 (95%CI 0.41-0.70)
 169 in 1972. Over the whole period, the contribution of MMR was 102/379 cases (27%), which was similar
 170 to the contribution of other screening approaches (108/379=28%). In the Netherlands MMR surveys
 171 were initiated in 1941¹⁷. A quarter to a third of the adult population was examined each year. In addition
 172 individuals with fibrotic lesions, recent TB contacts and skin test converters were regularly followed.
 173 The overall number of smear-positive TB cases declined between 1951-55 (n=2393) and 1962-67

174 (n=1011). The proportion of bacteriologically positive cases found through mass surveys and active
 175 surveillance was 0.35 (95%CI 0.33-0.37) at the beginning of the study and 0.47 (95%CI 0.44-0.50) in the
 176 later years

177 The studies from Czechoslovakia and the Netherlands were conducted before DOTS and
 178 standard short-course treatment regimens were available. The screening algorithm applied to individuals
 179 with positive chest X-rays were not described, but cases were disaggregated by both smear and culture
 180 status, so most likely all patients were investigated with both tests. The Czech study achieved very high
 181 coverage at 3-yearly screening intervals. The Dutch study screened continuously with lower coverage.
 182 Both studies show a decrease in smear and/or culture-positive TB cases but this may reflect underlying
 183 secular trends and/or the combined effect of screening and PCF. The contribution of ACF to the
 184 overall number of cases remained high in the Netherlands, but decreased substantially from very high
 185 initial levels in Czechoslovakia. Both studies used both MMR surveys and CXR screening in specific
 186 high risk groups, notably people with CXR lesions identified in previous screening, and the contribution
 187 by the two screening approaches was similar in both countries. Recent community-based screening
 188 programs in high prevalence countries have mainly relied on symptom screening, sputum smears and
 189 culture partly due to the logistical and operational challenges of mass X-ray screening^{6, 18}. It is difficult to
 190 assess how the results from these two historic studies compare with the current situation in high TB
 191 prevalence countries. Despite these limitations these are the only studies evaluating mass screening
 192 activities over prolonged periods of time.

193

194 *b) Cases identified in trials of screening*

195 Four randomised trials were identified that investigated the effect of screening on TB case-finding, all
 196 over a short time period (table 2). They compared TB case notification rates among communities or
 197 individuals actively screening or not screened. Different interventions were used, as summarised in the
 198 table. In Brazil, door-to-door screening increased the case yield during the intervention, but not overall
 199 during the whole period of the study so the effect seemed to be on delay rather than on the total
 200 number diagnosed¹⁹. The Ethiopian studies used community health workers in different ways to
 201 increase awareness, case-finding and diagnosis, and were thus ECF interventions with a screening
 202 element. One of the Ethiopian studies used pre-advertised outreach clinics²⁰, whereas the other
 203 implemented a combination of increased awareness, facilitation of sputum collection and treatment
 204 support²¹. Both found higher case rates in the intervention communities. The South African study
 205 followed a cohort of infants randomized to screening or PCF and found that screening increased case-
 206 finding by 2.6 times²².

207

208 *c) Prevalence surveys*

209 Prevalence surveys provide an estimate of the burden of undiagnosed TB, which could potentially be
 210 diagnosed by systematic TB screening. These surveys are summarised in table 3. They vary in scope

211 from small studies in high prevalence areas, to and national surveys. The prevalence of TB varied
212 considerably between studies, but the proportion of previously undiagnosed TB was high in all: 35-85%
213 of cases. Recent surveys have calculated the “patient diagnostic rate” (reported cases/100,000/year
214 divided by prevalence/100,000). Higher numbers imply a faster rate of diagnosis (less undiagnosed TB),
215 but exactly how this relates to the proportion of cases detected depends on duration of untreated
216 tuberculosis²³. Many of these studies were large, covered randomly selected representative populations
217 and included a high proportion of eligible individuals (although this was not always stated). Screening
218 algorithms varied (see table 1) and would have had varying sensitivity. Case definitions also varied, and
219 culture was only available in some settings. As shown by the study in Cambodia, the proportion of cases
220 undiagnosed is crucially dependent on the definition used. The case definitions used for those already
221 on treatment were not usually given. The number on treatment sometimes depended on reports by the
222 individuals, sometimes on verification of registers and sometimes on notifications, but as illustrated in
223 the Ethiopian studies^{21,24} the discrepancy between reports and registers could be large. In all studies the
224 number on treatment is an underestimate of the period prevalence of diagnosed TB, as only survivors
225 and non hospitalised patients will be included.

226

227 *d) Contribution of screening to total number of TB cases diagnosed*

228 In addition to the longitudinal studies cited above, a total of 14 studies provided data on the
229 contribution of screening to the total TB cases diagnosed (table 4). These included studies of home
230 visits to higher risk members of the community, outreach screening combined with information
231 activities in the community, contact screening, or clinic screening. Community-based studies that
232 covered a high proportion of the total community found a substantial proportion of the total cases. In
233 contrast, studies targeting specific groups contributed relatively few cases. Notably none of the studies of
234 contacts, even those from low prevalence areas contributed more than 9% of the total cases identified.
235 Screening algorithms varied widely and the TB case definitions used to estimate the total number of TB
236 cases diagnosed in the region were not clear. Thus it is difficult to draw firm conclusions.

237

238 *2. Does screening for TB disease identify cases earlier?*

239

240 Several studies compared delay to treatment or extent of disease at presentation between those
241 identified through screening and PCF (see table 5). All studies found that those who were identified
242 through screening were more likely to be at an earlier stage of disease: they were less likely to be smear-
243 positive, had a lower degree of smear positivity, and were less likely to have severe X-ray changes such
244 as cavitations. There was less direct evidence of a difference in duration of symptoms, but there was a
245 marked shortening of delay in the only large study to measure it²⁵ In addition, in the case-finding
246 intervention trial in Ethiopia²⁰ patients from communities with the intervention had shorter delay than
247 did those in comparison communities. In the Brazilian trial, at the community level there was little

248 difference in the delay with the door-to-door intervention group having a mean delay of 57 days (95%CI
249 33-82), compared to the pamphlet group with a mean delay 53 days (95%CI 38-68)¹⁹. However, the
250 short term increase in case-finding during the door-to-door screening, but not subsequently suggests a
251 reduction in delay for those cases (see table 2).

252 A difficulty in assessing these studies is to know what diagnostic procedures were applied to the
253 passively detected cases. Unfortunately these data were not available for the majority of studies (see table
254 5). The proportion smear-positive was consistently lower among cases identified through screening and
255 ECF than among passively found cases, but this would be expected if smear is the main method of
256 routine diagnosis in PCF, as was the case in South Africa, where culture was not routinely used for those
257 found passively. The degree of smear positivity (routinely graded from +++ to scanty positive) among
258 smear-positive cases may be a better indicator: in three studies presenting these data (in South Africa,
259 Cambodia and India) the degree of smear positivity was higher in passively diagnosed cases. X-ray
260 grading was restricted to those with X-ray: all three studies reporting this found less extensive disease
261 among screened cases. However, in none of the studies were all cases bacteriologically confirmed, and
262 less severe changes without independent confirmation of TB may have other diagnoses, particularly in
263 actively found patients. Delay is difficult to measure, and some studies were small, but most results were
264 consistent with a reduction in delay.

265 Overall only three studies, in India, Taiwan and Cambodia, included large numbers of cases
266 identified through screening. Therefore although the evidence was largely consistent that screening
267 reduces delay and leads to diagnosis of cases at an earlier stage of disease, inherent biases – the use of
268 more sensitive and sometimes less specific diagnostic techniques in screening compared to the routine
269 programme - would tend to give the same result. The strongest evidence comes from comparison of the
270 degree of smear positivity which was lower in actively found cases.

271

272 3. Does screening for TB disease affect TB treatment outcome?

273

274 Unpublished data from two further studies was included. As well as looking at the outcome for those
275 who started treatment, we recorded the proportion who were identified but who did not register for
276 treatment through default, death or loss to follow-up (“initial defaulters”).

277 Table 6 summarises the results from studies reporting on outcomes in TB cases identified
278 through screening (restricted to those that presented results for more than 10 patients). Initial default
279 was not always reported, but was as high as a quarter of cases identified through screening in the South
280 African and Indian studies. Given the range of time periods, settings, treatment regimens, drug
281 resistance and patients, absolute values of treatment outcome are difficult to compare between studies,
282 but many achieved more than 80% successful outcomes, and the Cambodian studies more than 90%.

283 Five studies (2 in Nepal, 1 in Cambodia, 1 in India and 1 in South Africa) presented
284 comparable data on cases found through screening and passively. In all five the outcomes for cases

285 found through screening and PCF within each study were very similar (figure 1), and this was seen in the
 286 meta-analysis: RR 1.01 (95%CI 0.98, 1.03)), with low heterogeneity (I-squared 0%). In India,
 287 subsequent studies reported the initial default rates for actively and passively found cases²⁶⁻²⁷. Initial
 288 default was higher in cases identified through screening (29% in 1999-2001 and 24% in 2001-2002) than
 289 in passively found cases 14% and 15%. There were no deaths among the 57 actively found initial
 290 defaulters and 23 (19%) deaths among passively found initial defaulters²⁶. The reasons given by the 57
 291 patients identified through screening for initial default included: unwillingness to start treatment;
 292 symptoms too mild to warrant treatment; too sick; and work related problems²⁶. For all the other
 293 settings initial default rates in passively found cases were not reported, but they can be high, and such
 294 patients have poor outcomes²⁸⁻³³.

295 There were many differences between the cases found through screening and passively (see
 296 tables 5 and 6) including a tendency for cases identified through screening to have less severe disease
 297 (which would tend to give lower mortality but possibly higher default rates) and to be older (which
 298 would tend to give worse outcomes). There were large differences between the 5 studies in the
 299 proportions with successful outcomes, but the internal comparisons were consistent: treatment success
 300 was comparable in TB cases found through PCF and screening.

301 Length time bias (through which slowly progressing and less severe cases with potentially higher
 302 chance of treatment success are more likely to be detected through screening than PCF) is likely in all
 303 studies comparing outcomes between screened vs. not screened individuals. Controlled trials with
 304 comparison of treatment outcomes between the arms are required for firm conclusions. Only two such
 305 trial was identified: , In the community randomized trial in Ethiopia²⁰, the proportion successfully
 306 treated was similar in the intervention communities (81%, 128/159) and comparison communities (75%,
 307 165/221), with 3% deaths in each. The South African trial in infants did not find any difference in
 308 mortality between infants receiving ACF and PCF despite an increase in case detection, but overall
 309 mortality was low (<3%)²². These studies are not included in the table or in the meta-analysis as they
 310 used a trial design, but findings are consistent with studies for which meta-analysis was performed.

311 Only one study showed a difference in mortality among TB cases identified through screening
 312 (yearly X-ray) compared to TB cases identified through PCF³⁴. The study was conducted among South
 313 African miners with high HIV prevalence and before the availability of antiretroviral therapy. TB
 314 specific mortality was 15.1 (95%CI 2.1-65.5) times higher in HIV-negative and 2.6 (0.7-14.9) HIV-
 315 positive TB cases identified through passive case finding compared to those identified through
 316 screening. Length time bias and residual confounding might explain part of the result.

317

318 4.Does screening for TB disease affect TB epidemiology in the community?

319

320 Five studies provide evidence for the affect of TB screening on the overall epidemiology of TB in the
321 general population over several years (Table 7). The interventions, assessment and settings all vary so
322 they are discussed individually.

323 The community randomised trial in Zimbabwe used two different case-finding interventions
324 (mobile vans or door-door)⁶. There was no control group without an intervention, so for the purposes of
325 this question the comparison of interest is the TB prevalence in the communities before and after the
326 intervention, as assessed by prevalence surveys. This showed a 41% reduction over 3 years. The
327 reduction was similar in areas covered by the different interventions, although the cumulative yield of
328 cases during the intervention was higher in the mobile van group. The population of the area increased
329 by 10% over the study period. Furthermore HIV prevalence significantly declined during the study
330 period and Zimbabwe experienced a period of severe political unrest. All of these factors may have
331 influenced the TB prevalence

332 The Zamstar study was conducted in communities in Zambia and South Africa and was a 2x2
333 factorial trial comparing ECF, a household intervention, both or neither¹⁸. The ECF sites received
334 community mobilisation and easy access to sputum collection points either at clinics or mobile outreach
335 activities, aiming to return results within 48 hours. In the household intervention sites, households of
336 TB patients were visited three times for education and screening for TB and HIV, and HIV positive
337 household members without active TB were offered isoniazid preventive therapy. The household
338 intervention only directly saw 6% of individuals in the community. Outcomes assessed were TB
339 prevalence from surveys, and *M. tuberculosis* infection incidence, assessed from tuberculin conversion
340 in children. As shown in the table, the household intervention, but not the ECF was associated with a
341 reduction in TB prevalence. From the preliminary results (table 6) it seems that only 13% of patients in
342 the ECF communities were found directly through the ECF.

343 A follow-up study was conducted in Cambodia two years after a TB prevalence survey, to
344 capture incident TB cases in community clusters screened for TB as part of the National survey³⁵. The
345 standardized TB notification ratio was 0.38 (95%CI: 0.27-0.52) in communities included in the National
346 TB prevalence survey, showing a two-thirds reduction in notification in the study areas. Cases identified
347 during the National TB prevalence survey were not included in the calculation of the standardized TB
348 notification ratio. It is thus not clear if screening really decreased the total number of TB notifications or
349 simply diagnosed these cases earlier.

350 In Brazil four matched pairs of communities were randomized: intervention communities
351 received intensive household screening of contacts including TST testing and isoniazid prophylaxis¹⁹.
352 The control communities received the standard DOTS package. Although this theoretically includes
353 referral of contacts for investigation, this was thought to be rare in practice and no data on contact
354 tracing were available. Outcomes were assessed from registration data, with the denominator from the
355 national census. Overall TB notifications decreased by 10% in the intervention communities and
356 increased by 5% in the control communities, but long term trends in TB incidence are not presented.

357 A study in the US evaluated a programme of mandatory screening and mandatory prophylaxis
358 and treatment as indicated for those wanting to use homeless shelters³⁶. Trends in tuberculosis in the
359 whole district fell by almost 90% over 10 years. Incidence of TB state-wide, or in other areas shown
360 were much lower, but showed no such fall. The study did not assess the effect of screening alone, and
361 the population of the district was noted to have changed over the period, due to gentrification, which
362 may have accounted for some of the fall.
363

For Review Only

364 **Discussion**

365

366 This review assessed four potential beneficial effects of screening for TB disease. The increase in TB
367 cases and earlier diagnosis through screening could be considered intermediate outcomes. Reduction in
368 morbidity, mortality and transmission through earlier detection and detection of cases who would
369 otherwise remain undiagnosed are the ultimate outcomes of interest to assess individual and
370 community-level benefits. Despite extensive implementation of systematic TB screening during the last
371 century, there have been very few studies primarily addressing mortality or transmission and only one
372 (Zamstar) with a cluster-randomised design that directly evaluated impact on TB epidemiology. Thus
373 the available evidence base is weak and shows little evidence of benefit of systematic TB screening for
374 individuals and communities.

375 There is moderate evidence that screening increases the number of cases found in the short term. The
376 extent depends on the setting and the methods used. In many settings more than half the prevalent TB
377 cases in the community are undiagnosed. Targeting of some high risk groups, or combination of risk
378 groups can contribute a high proportion of cases, but targeting contacts did not contribute more than 9%
379 of cases. It is possible that part of the impact on case detection is due to detection of additional false
380 positive TB diagnosis. The proportion false positive cases out of all cases detected is inversely
381 correlated with TB prevalence, and target groups for screening typically have much lower TB
382 prevalence than people tested through PCF. High proportion false positive is particularly likely when
383 the specificity of the final diagnostic test is suboptimal. Specificity of sputum smear microscopy ranges
384 between 93% and 100%³⁷⁻³⁹.

385 There is moderate evidence that screening tended to find cases earlier and with less severe
386 disease. This may partly be attributed to screening studies using more sensitive diagnostic methods than
387 routine programmes, rather than the screening *per se*. A recent study conducted in miners in South
388 Africa compared 6-monthly versus 12-monthly chest X-ray screening (not included in this review
389 because it did not have a “no screening intervention” arm). TB cases detected in the 6-monthly
390 screening arm had less extensive disease and a lower TB specific mortality compared to TB cases
391 detected in the 12-monthly screening arm⁴⁰. However, South African mines are a special setting, with
392 high prevalence of both HIV and silicosis and a high risk of rapid progression to TB disease, as well as
393 a background of active TB case-finding programs with yearly chest X-ray screening. It is therefore
394 difficult to extrapolate these findings to other settings.

395 Treatment outcomes for those identified through screening or passively were very similar in all
396 studies. This is surprising, as patient characteristics were different and length time bias is likely in all
397 studies, but the results were consistent in varied settings with different proportions of successful
398 treatment. However, only two studies reported initial default rates in actively and passively found cases³⁶
399²⁷. It is well documented that a high proportion of passively found cases die before initiating TB
400 treatment^{26, 32-33}. Thus “on treatment” mortality in passively found cases might underestimate overall

401 mortality due to survival bias. The reasons for initial default in cases identified through screening might
402 be different: they are less symptomatic and less likely to use health care^{18, 25}. Therefore the overall
403 mortality in cases diagnosed through screening might be lower than in cases diagnosed through PCF,
404 but only one study identified in this review provided data on overall mortality in adults. The South
405 African trial in infants²² and the community randomized trial in Ethiopia²⁰ both showed similar outcomes
406 in intervention and control arms

407 The evidence that screening in addition to PCF impacts on TB epidemiology remains weak,
408 but with an insufficient body of evidence to allow firm conclusions to be drawn about absence of effect.
409 The Zamstar study provides the most thorough assessment, in challenging circumstances of high HIV
410 prevalence. The study evaluated 2 different interventions (TB household and community-wide ECF,
411 respectively) using a factorial design, and reported a significant reduction in undiagnosed TB at
412 community level from the household intervention but not the ECF intervention. The household
413 intervention went beyond the usual remit of TB contact tracing, with multiple visits and a strong focus
414 on HIV as well as TB prevention, but had direct contact with only 6% of the population. Possible
415 explanations include that the household intervention might have had extended benefit beyond the
416 household, through heightened awareness. The ECF intervention detected only a small proportion of
417 cases directly, and did not provide community TB screening as such, instead promoting early diagnosis
418 through facility-based services, and so the negative trial outcomes are not necessarily generalisable to
419 interventions using more intensive TB screening approaches. The study from Cambodia provides some
420 evidence of reduced TB notifications among individuals who underwent intensive screening for TB, but
421 the follow-up time in this study was short (2 years)³⁵. The study from Zimbabwe showed a decrease in
422 TB prevalence following 3 years of implementation of community-based TB case-finding, but this was
423 based on before-after comparison with no non-intervention group to control for secular trends⁶.

424 The main limitations of this review include a search strategy starting from a previously
425 conducted review and high heterogeneity in screening algorithms, study setting and population. We
426 supplemented the search strategy by contacting experts in the field and authors and by conducting
427 additional more targeted searches. We adopted a narrative approach to account for the heterogeneity of
428 study designs and settings and only conducted a meta-analysis to calculate pooled risk ratios for
429 treatment outcome.

430 In conclusion, the evidence of individual and community-level benefit of systematic screening is
431 remarkably limited given the high public health significance, long history, and scale on which this
432 approach has been implemented in the past. Large cluster randomized trials such as the Zamstar study
433 with long term follow-up would be needed to provide more evidence for such a benefit if indeed it exists,
434 ideally including studies that evaluate a range of interventions with different screening intensities in
435 different epidemiological settings. In the meantime more rigorous and consistent reporting of TB
436 notification and mortality rates over prolonged periods of time in settings where large scale screening
437 programs have been implemented should be encouraged, together with capture of mode of detection

438 and other variables to support TB impact assessment. Furthermore a better understanding of the
439 magnitude of initial defaulting within national TB programs is needed and could be facilitated by
440 including initial defaulters in the routine TB notification registers.
441

For Review Only

Table 1 Studies included in the review

ID	Year of study	Rural or Urban	Setting	How was screening performed?	Order of screening ¹					
					Symptom screen	Clinical	Smear	Culture	CXR	Anti-biotics
<i>African Region</i>										
Ethiopia 2003a ⁴¹	2003	Rural	Community	Home visits, TB suspects identified by head of household	1 (C2w)		2 (MMS)			
Ethiopia 2003b ³⁶	2003-2004	Rural	Community	Outreach teams (once per month), advertised by local lay health care worker	1		2 (MSS)			
Ethiopia 2006 ³¹	2006-2008	Rural	Community	Lay health care workers identified TB suspects in the community and facilitated sample transport	1 (C2w)		2 (MSS)			
Ethiopia 2008 ⁴²	2008	Urban/ rural	Community	Home visits, TB suspects identified by head of household	1 (C2w)		2 (MS)			
Ethiopia 2009 ⁴³	2009	Rural	Community	Home visits	1 (C2w)		2 (MS)	2 (MS)		
Ethiopia 2010 ²⁴	2010	Rural	Community	Home visits	1 (C2w)		2,5 (MS)	4	3	
Botswana 2004 ⁴⁴	2004-2006	Urban	HIV Clinics	IPT program		2	2	2	1	
Guinea-Bissau 2006 ⁴⁵	2006-2007	Urban	Community	Home visits	1 (C)		2	2	2	3
Ivory Coast 1990 ⁴⁶	1990-1992	Urban	Prison camp			1	2	2	2	
Kenya 2006 ⁴⁷	2006-2007	Rural	Community	Home visits	1		1 (MS)	2	1	
Malawi 1999 ⁴⁸	1999-2001		Prison	At time of entry into prison	1 (C1w)		2 (UUU)			
South Africa 1993 ³⁴	1993-1997		Mines	Workplaces screening program			2	2	1	
South Africa 2002 ⁴⁹	2002	Urban	Community (township)	Home visits			1	1	1	

South Africa 2005a ²⁴	2005- 2008	Urban	Community (township), infants	Home visits, TB register checks to identify adult smear positive cases	1 (C2w)	2	2	2	2
South Africa 2005b ²⁰	2005	Urban	Community (township)	Home visits and referral to clinic		1 (MS)		1 (MS)	
South Africa 2008 ³¹	2008	Urban	Community (township)	Home visits and referral to clinic		1 (MS)		1 (MS)	
South Africa 2009 ¹³	2009- 2011	Urban	Community (township)	Mobile HIV testing unit	1 (C2w) (if HIV-)		2: HIV- (S) 1: HIV+ (S)	2: HIV- (S) 1: HIV+ (S)	
Uganda 2001 ³²	2001- 2002	Urban	Community	Home visits and referral to clinic	1 (C2w)	2	2	2	2
Uganda 2005 ³³	2005	Urban	Slum	Home visits	1 (C)		2 (MS)		
Zambia 2006 ¹⁸	2006- 2011	Urban/rural	Communities in Zambia and South Africa	Household, clinic, sputum collection points					
Zimbabwe 2005a ⁴	2005	Urban	Community	Home visits		1 (MS)		1 (MS)	
Zimbabwe 2005b ⁶	2005- 2008	Urban	Community	Home visits and mobile van	1 (C2w)		2 (MS)		
<i>Eastern Mediterranean Region</i>									
Morocco 1993 ¹⁵	1993- 2004	Urban/rural	Household contacts of index cases	Active follow-up of contacts at home/by phone and referral to clinic	1	1	2 (MS)		1
<i>Region of the Americas</i>									
Brazil 2005 ¹⁰	2005- 2006	Urban	Community	Home visits	1 (C3w)		2 (MS)		
Brazil 2000 ⁵⁵	2000- 2004	Urban	Household contacts of index cases	Home visits	1	2	2	1	1

Canada 1960 ¹⁷	1960-1969	Rural	Community, 1960-63 > 20 years of age, 1964-1969 > 30 years of age	Mass miniature radiography in communities where a case of active TB was discovered in the previous year	1				
Canada 1967 ¹⁷	1967-1968	Mixed	Hospital, workplace, community	Chest x-ray survey at admission to hospital, jail, industrial and community surveys	1				
Cuba 2003 ³⁶	2003-2005	Urban/rural	Community	Home visits by family doctors performed for other reasons than TB	2	2	2		
Mexico 1995 ³⁷	1995-1996	Rural	Households, shelters, jails, orphanages, support for alcoholics, diabetics, intravenous drug users (IVDU)	Health promoters identified TB suspects and referred them to clinics	1 (C2w)	2(MSS)			
US 1985 ³⁸	1985-1995	Urban	Homeless, shelters, jails						
US 1999 ³⁸	1999	National							
US 2001 ³⁹	2001-2003	Part of immigration process	Refugees and immigrants	TB suspects identified in the country of departure and screening repeated at entry	1	2	2	1	
<i>South-East Asia Region</i>									
India 1981 ⁴⁰	1981-1982	Rural	Community	Lay health care workers identified TB suspects in the community, prepared microscopy slides and facilitated transport	1			1	
India 1999 ^{45,47}	1999-2000	Rural/urban	Community	Home visits	1	2(UU)	2(UU)	1	
India 1999 ^{36,61}	2001-2003	Rural/urban	Community	Home visits	1	2(UU)	2(UU)	1	
India 2003 ⁶²	2003-2004	Urban	VCT centres at hospitals		1 (C3w)	2			
Myanmar 2009 ⁶³	2009-2010	National	National prevalence survey	Home visits	1 (C3w)	2(MS)	2(MS)	1	

Nepal 1979 ⁶⁴	1979-1980	Rural	Community	Home visits	1 (C3w)	2 (MMMM)	
Nepal 1990 ⁶⁵	1990-1993	Rural	Community	Temporary microscopy camps with pre-camp publicity	1 (C3w)	2	
Western Pacific Region							
Cambodia 2002a ⁶	2002	National	National prevalence survey	Home visits	1 (C3w)	2(MS) 2(MS) 1	
Cambodia 2002b ³⁵	2002-2004	National	Follow-up of National prevalence survey	Home visits	1 (C3w)	2 (MS) 2 (MS) 1	
Cambodia 2009 ⁶⁶	2009-2010	National	Household contacts and neighbours of index cases	Home visits and referral to clinic	1	2 (UUU) 2	
China 2000 ²⁶	2000	National	National prevalence survey		1 (C2w)	2 (UUU) 2 (UUU) 1	
Hong Kong 2000 ⁶⁷	2000	Urban	Contact of TB cases				
Japan 2002 ⁶⁸	2002-2004	Urban	Tertiary hospital			2 2 1	
Korea 1995 ⁶⁹	1995	National	National prevalence survey	Home visits	2	2(SSS) 2(SSS) 1	
Papua New Guinea 2010 ⁷⁰	Unk	Rural	Community	Home visits	1 (C)	2	
Philippines 1985 ⁷¹	1985	Urban	Community	Health promoters identified TB suspects in the community and took them to a temporary clinic	1	2	
Philippines 1997 ¹¹	1997	National	National prevalence survey	Home visits		2(UUU) 2(UUU) 1	
Taiwan 1993 ⁷²	1993-1996	Urban	Household contacts	Home visits and referral to clinic	1	1 2 2 1	
Vietnam 1992 ⁷³	1992-1993	Mixed	Individuals applying for departure	Hospital	1	2 (MMMM) 1	
Vietnam 2006 ¹⁰	2006-2007	National	National prevalence survey	Home visits	1	2(UUU) 2(U) 1	

<i>European Region</i>					
Netherlands 1951 ¹⁷	1951- 1967	National	Community	Mass miniature radiography screening and surveillance of risk groups (contact tracing, recent TST converters, person with fibrotic lesions)	1
Netherlands 2002 ²¹	2002- 2005	Urban	Methadone centres, night care facilities, street prostitution zones	Mobile X-ray unit	1
Czechoslovakia 1965 ¹⁶	1965- 72	Mixed	Community	Mass miniature radiography survey, surveillance of people with fibrotic lesion	2 2 1
UK 1967 ²³	1967- 1975	Urban	Hostels	Mobile X-ray unit	1
UK 1968 ²⁶	1968- 1982	Urban	Homeless and hostel dwellers	Mobile X-ray unit	2 3 3 1
UK 1977 ²⁷	1977- 1981	Urban	Contacts of TB cases		1 1
UK 1982 ²⁸	1982- 1990	Urban	Contact of TB cases		1
UK 2008 ²⁹	unk	Urban	Hard to reach groups (homeless, drug users, prisoners)	Mobile X-ray unit	1

Table 2: Community randomized trials , comparing cases registered in the intervention and control communities
See table 1 for screening algorithms used

ID	Setting	Intervention	TB in intervention communities/infants	TB in control communities	Effect of intervention (95% CI)
Ethiopia 2003b ³⁰	Rural area	Community promoters and outreach sputum collection for symptomatics over 1 year (12 intervention vs 20 control communities)	All: 125/100,000 (159 / 127,607) Adults: 207/100,000 (153 / 74,012)	All: 98/100,000 (221 / 225,284) Adults: 158/100,000 (207/130,665)	Difference 27/100,000 (-19 to 72) Difference 49/100,000 (-27 to 123)
Ethiopia 2006 ³¹	Rural area	Health extension workers advised symptomatics to attend and collected sputum samples at health posts over 20 months. 30 intervention vs 20 control communities	All: 122/100,000 (230/178,138) Adults: 194/100,000	All: 69/100,000 (88/118,673) Adults: 118/100,000	Difference 52.8/100,000(39.8-65.4) Difference 76/100,000 (56-96)
South Africa 2005a ²²	Urban (township)	4786 infants were randomised to 3 monthly household visits or passive case finding; suspected TB disease was investigated as inpatient	2.2/100 py	0.8/100 py	Rate ratio 2.6 (1.8-4.0)
Brazil 2000 ¹⁹	Favela in Rio de Janeiro	Door-to-door screening 7 vs 7 communities (paired) During intervention (ave 27 days) Intervention + 60 days Whole period (283 days)	N=11249 934/100,000 py (n=19) 516/100,000 py (n=32) 818/100,000 py (n=92)	N=12304 604/100,000 py (n=16) 493/100,000 py (n=41) 821/100,000 py (n=101)	Rate ratio 1.55 (1.10-1.99) 1.05 (0.56-1.54)

py = person years at risk

Table 3: Prevalence surveys in general populations: extent of undiagnosed tuberculosis in house-to-house surveys in the general population. See table 1 for screening algorithms used

ID	Setting	Population	Proportion included	Type of TB	Number of previously undiagnosed TB cases (diagnosed in the survey)	Number of TB cases on treatment at the time of the survey	Undiagnosed TB as a proportion of the total number of TB cases	Patient diagnostic rate (smear-positive)
<i>Africa</i>								
Ethiopia 2003a ⁴¹	Rural	16,697 adults	not stated	Smear+	13	24	0.35	
Ethiopia 2008 ⁴²	Rural and urban	47,478 adults	not stated	Smear +	38	15 ¹	0.72	
Ethiopia 2009 ⁴³	Rural area	29,257 adults	not stated	Smear +	22	4	0.85	
Ethiopia 2010 ⁴⁴	Rural and urban	23,590 adults	not stated	Smear + All pulmonary	41 58	22 ²	0.65 0.73	
Guinea-Bissau 2006 ⁴⁵	Urban	3,714 adults	80%	Pulmonary	2	2	0.50	
Kenya 2006 ⁴⁷	Rural	30,416 adults	68%	Pulmonary	117	86	0.58 ³	0.93
South Africa 2005b ⁴⁶	Urban high density	971 adults	78%	Pulmonary	12	11	0.52	
South Africa 2008 ⁴⁸	Urban high density	1,383 adults	90%	Pulmonary	8	12	0.40	
Uganda 2001 ⁴²	Urban	1,142 all ages	not stated	All	10	9	0.53	
Uganda 2005 ⁴⁸	Urban	1,000 adults	88%	Pulmonary	33	9	0.79	
Zimbabwe 2005a ⁴⁴	Urban	12,426 adults	82%	Pulmonary	82	74	0.53	
<i>Asia</i>								
Cambodia 2002a ⁹	National	23,084 age 10+	96%	Smear+ Smear or culture+ All pulmonary	74 260 552	42	0.64 ⁵ 0.86 0.93	0.63
China 2000 ⁴⁹	National							0.24
Korea 1995 ^{49, 50}	National	~73,000 age 5+	88%	Smear or culture	106			0.43

Myanmar 2009 ⁸³	National	57,607 adults	89%	Pulmonary	280	79	0.78 ³	0.47 (0.36-0.62)
Papua New Guinea 2010 ⁷⁰	Rural	7211	not stated	Smear+?	19	29[estimated]	0.40	
Philippines 1997 ^{1,25}	National	15,905 age 10+	81%	Smear or culture+	127			0.51
Vietnam 2006 ¹⁰	National	114,389 adults	82%	Pulmonary	263			0.60 (0.49-0.78)

¹ 83 reported being on treatment; 15 found in registers

² 150 reported being on treatment; 22 found in registers

³ Not adjusted for cluster sampling

Table 4: Contribution of screening to total notified cases

ID	Screening program	Total number of TB cases diagnosed by screening	Total number of diagnosed TB cases through PCF in same area	Proportion of TB cases diagnosed by screening of all TB cases
<i>Community-based</i>				
Canada 1960 ¹⁷	Mass miniature radiography and tuberculin skin surveys had been carried out since 1941. From 1960-63 individuals with negative TST and aged <20 were not surveyed, and from 1964-1969 individuals with a negative TST and aged <30 were not surveyed. 18% of the total population was examined annually, the screening procedure following an abnormal radiograph was not described	47 (smear + TB)	354 (smear+ TB)	0.12 (smear + TB)
		43 (culture+ TB)	202 (culture+ TB)	0.18 (culture+ TB)
Canada 1967 ¹⁷	Mass chest X-ray surveys on a community and industrial bases were performed from 1948-1968. From 1968 a hospital admission chest X-ray program was added. In addition contact tracing chest X-ray screening, pre-employment and in jails was conducted. The screening procedure following an abnormal radiograph was not described,	145 (smear+ TB)	420 (smear+ TB)	0.26 (smear+ TB)
		136 (culture + TB)	183 (culture+ TB)*	0.43 (culture+ TB)
Cuba 2003 ³⁶	Home visits to risk groups (elderly, heavy alcohol users, ex-prisoners, HIV positive, socio-economically vulnerable)	24	19	0.56
Mexico 1995 ³⁷	Health promoters (each promoter serving 3000 individuals) were trained to identify individuals with cough. They sought out individuals at their houses, jails, shelters, orphanages, alcohol support groups and other risk groups. TB suspects were asked to attend the clinic to submit sputum samples.	92	15	0.86
India 1981 ⁶⁰	Lay health care workers identified TB suspects in the community, prepared microscopy slides and facilitated transport to microscopy centres.	26	13	0.67
India 1999 ³⁵	Door-door in approx one third of the population	211	508	0.25
Nepal 1990 ⁶⁵	Temporary microscopy camps were put up in remote villages (at an average walking time from the nearest health post of 4.25h). Pre-camp publicity included theatre shows, house-to-house visits. The camps lasted for 2-4 days	71	1175 [estimate]	0.06
<i>Contact tracing</i>				
Hong Kong 2000 ³⁷	Contacts of TB cases were screened.	31	1635	0.02
Morocco 1993 ¹⁵	Contacts of TB cases were screened	? ~ 20,000	?	0.048 (age ≥10) 0.19 (age <10)
UK 1977 ⁷⁷	Contacts of pulmonary TB cases were	78	816	0.09

	screened.			
UK 1982 ²⁸	Contacts of TB cases were screened.	50	649	0.07
US 1999 ³⁸	Contacts of smear or culture-positive cases were screened.	561	9199	0.06
<i>High risk settings</i>				
India 2003 ⁸²	TB suspects were identified among VCT clients (both HIV+ and HIV-). A total of 5 VCT centres in the district participated: 2 at medical schools, 1 a tertiary hospital, 2 at district hospitals.	83	15835	0.01
Netherlands 2002 ⁷¹	Drug users and homeless in Rotterdam	28	562 [estimate]	0.05

See table 1 for screening algorithms used

* 136 additional cases (67 smear-positive TB cases and 69 culture-positive TB cases) were found through routine chest x-rays

Table 5: Symptom duration, smear status and cavitations in screened and passively found cases*
See table 1 for screening algorithms used

ID	Total number of cases		Average/median delay from onset of symptoms to start of treatment.		% of smear-positive cases among pulmonary cases		Smear+ grade (% scanty, 1+,2+,3+)		% of those with CXR which show severe disease		Comments
	Screening	Passive	Screening	Passive	Screening	Passive	Screening	Passive	Screening	Passive	
<i>Africa</i>											
Ethiopia 2003a [†]	13	24	54% had symptoms for more than 90 days	58% had symptoms for more than 90 days							No information on diagnostic algorithm for passively found cases
South Africa 2002 [®]	27	473			67%	94%	17,28,22,33	4,26,18,52			Passively found cases from 2-3 years later. Passive cases more symptomatic, eg weight loss in 92% vs 44% in active. Culture not routinely done for passively found cases. Smear grade P trend=0.03 No information on diagnostic algorithm for passively found cases.
<i>Americas</i>											
Brazil 2005 [®]	9	64	Median time = 56 days (range 28-336)	Median time = 53 days (range 7-336)							Diagnostic algorithm was probably the same in actively and passively found cases.
Canada 1960 ¹⁷	90	425			52%	62%					No information on diagnostic algorithm for passively found cases
Canada 1967 ¹⁷	140	403			45%	70%					No information on diagnostic algorithm for passively found cases
US 2001 [®]	39	61			26%	59%			3%	21%	Screening in arriving immigrants/refugees compared to passive cases in immigrants arrived in last year. P<0.01. Diagnostic algorithm unclear for both actively and passively found cases.
<i>Asia</i>											
Cambodia 2009 [®]	405	602			29%	60%	9,48,26,17	2,40,39,19			P<0.001. smear+ P trend=0.009 smear grade, No information on diagnostic algorithm for passively found cases.
India 1999 [§]	211	508	Cough < 3 wks: 37%	Cough < 3 wks: 18%	45%	65%	0,59,38,3	3,28,27,42			P<0.001 for all Diagnostic algorithm did not include routine

		CXR and culture in passively found cases			
		284	3903	6%	16%
Taiwan 1993 ²²		284	3903		
<i>Europe</i>					
Czechoslovakia 1965 ¹⁶		100	119	29%	44%
Netherlands 1951 ¹⁷		1682	2209	38%	58%
UK 1967 ²⁵		54	71	58%	85%
UK 1968 ²⁶		42	26	26%	58%
UK 2008 ²⁹		35	240	44%	66%
		Passively found cases had 3 times the diagnostic delay of actively found cases.			
		Adjusted odds ratio for smear positivity comparing active and passive cases was 0.36 (p<0.001)			
		No information on diagnostic algorithm for passively found cases.			
		No information on diagnostic algorithm for passively found cases.			
		No information on diagnostic algorithm for passively found cases.			
		No information on diagnostic algorithm for passively found cases.			

*Two studies of mass x-ray screening were not included in this table as all data regarding the screening algorithm following a positive chest-rays were unknown^{16,17}.

Table 6: Treatment outcomes of cases detected through screening and passively detected cases
See table 1 for screening algorithms used

ID	Type of TB	Actively found (N)	Initial Defaulter		Started Treatment		Treatment Successful		Died		Defaulted, transferred, failed, missing		Comments
			Active	Passive	Active	Passive	Active	Passive	Active	Passive	Active	Passive	
<i>Africa Region</i>													
Botswana 2004 ⁴¹	Pulmonary	43		43		35 (81%)		5 (12%)		3 (7%)			All HIV positive
Ivory Coast 1990 ⁴⁶	All	108		108		80 (74%)		28 (26%)					Prisoners, 30% HIV+
Malawi 1999 ⁴⁸	Smear+	318		296		181 (61%)		36 (12%)		79 (27%)			Prisoners
South Africa 2002 ⁴⁹	Smear or culture +	27		20		16 (80%)		380 (80%)					Initial defaulter defined as not starting treatment within 2 month of diagnosis.
South Africa 2009 ⁴³	Smear or culture +	56		42		34 (81%)		2 (5%)					Mobile HIV testing service, 54% HIV+
Zimbabwe 2005a ⁵¹	Pulmonary	91		4 ²		58 (73%)		9 (11%)		13 (16%)			Unpublished results
Zimbabwe 2005b ⁵	Smear+	249		234		175 (75%)		26 (11%)					Unpublished results
<i>South East Asia Region</i>													
India 1999 ³⁷	Pulmonary	211		58 (27%)	153	508	107 (70%)	361 (71%)	5 (3%)	36 (7%)	41 (27%)	111 (22%)	ACF older, more men, poorer backgrounds
Nepal 1979 ⁴⁴	Smear+	111		11 (10%)	100	159	62 (62%) [†]	110 (69%)	9 (9%)	17 (11%)	29 (29%)	32 (20%)	Treatment: 2 months streptomycin, 12-18 months of isoniazid and thiacetazone.
Nepal 1990 ⁴⁵	New smear+	68		68	1306	997 (76%)	50 (74%)	5 (7%)	104 (8%)	13 (19%)	203 (16%)		
<i>Western Pacific Region</i>													
Cambodia 2002b ³⁵	Smear+ or culture+	271		27 (10%)	244	232 (95%)							
Cambodia 2009 ⁴⁶	Pulmonary	405		21 (5%)	384	602	370 (96%)	573 (95%)	3 (0.8%)	11 (2%)	8 (2%)	10 (2%)	Screening cases older and higher proportion smear negative

Japan 2002 ⁶⁸	Pulmonary 17	17	12 (71%)	5 (29%)	From homeless shelters
Philippines 1985 ⁷¹	Smear+ or culture +	158	14 (9%)	144	Regimen: 1 month IRPE, 7 months IEP (twice weekly). 82% resistant to at least one drug ¹
Vietnam 1992 ⁷³	Smear+	322	322	0 (0%)	34% previously treated
<i>European Region</i>					
Netherlands 2002 ⁷⁴	Pulmonary 28	28	25 (89%)	3 (1%)	Homeless and drug users Outcome of other 3 not given

¹ Adjusted for cluster-sampling.

² Seven started treatment elsewhere, outcomes unknown

³ Outcomes were reported including those who did not start treatment. We have assumed they were not among the 62 with “sputum conversion recorded”

⁴ IRPE=Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, IEP=Isoniazid, Rifampicin, Pyrazinamide

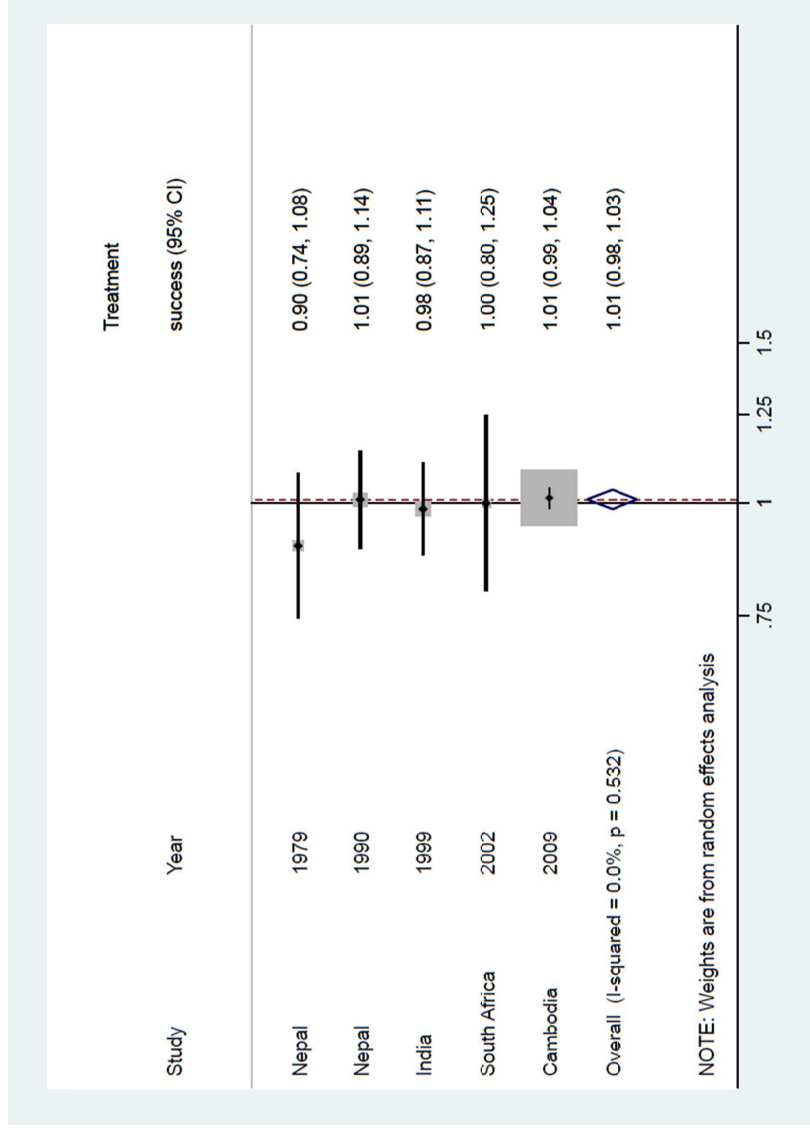
Table 7: Studies which have measured the general population impact of case-finding interventions
See table 1 for screening algorithms used

ID	Setting	Intervention	Time to assess impact	Outcome in control arm	Outcome in intervention arm	Comparison (values in brackets are 95% CI)
Cambodi a 2002) ³⁵	2 year follow-up of individuals screened in the National prevalence survey	Household screening with chest X-ray and symptom screen followed by sputum investigations in randomly selected clusters	2 years	Expected TB notification	Actual TB notification	Standardised TB notification ratio 0.38 (0.27-0.52)
Brazil 2005 ³³	8 urban communities Rio de Janeiro	CRT Intensive screening + IPT in household contacts	5 years	Incidence increased 5% to 358/100,000	Incidence decreased 10% to 305/100,000	P=0.04
Zimbabwe c 2005) ⁶	High-density suburbs, Harare	CRT Mobile van or door-door vs baseline pre-intervention	3 years	Baseline prevalence 6.5/1000 (5.1-8.3) (66 cases)	3.7/1000 (2.6-5.0) (41 cases)	Adj RR 0.59 (0.40-0.89) p=0.01
Zambia 2006 ³⁸	Communities in South Africa and Zambia	Factorial CRT (i) ECF vs no ECF (ii) household intervention vs no household intervention	3 years	TB prevalence 711/100,000 Infection incidence 1.05%	TB prevalence 927/100,000 Infection incidence 1.41%	Adj RR TB: 1.11 (0.87-1.42) Adj RR infection: 1.36 (0.59-3.14)
US 1985 ³⁶	Oregon, Burnside area	Mandatory screening, prophylaxis and treatment for those wanting to use homeless shelters vs baseline	3 years	TB prevalence 883/100,000 Infection incidence 1.71%	TB prevalence 746/100,000 Infection incidence 0.87%	Adj RR TB: 0.78 (0.61-1.00) Adj RR infection: 0.45 (0.20-1.05)
			10 years	Annual notifications in area in 1985 227/100,000 (39 cases)	Annual notifications in area in 1995 29/100,000 (5 cases)	Decline over the 10 year period in this district much greater than decline in other districts or state-wide.

CRT= community randomised trial, IPT=isoniazid preventive therapy

For Review Only

Figure 1: Meta-analysis: risk ratio comparing successful treatment in cases found through screening with passively found cases



6. References

1. WHO Three I's Meeting. Geneva: World Health Organization; 2008.
2. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: World Health Organization; 2010.
3. Williams G, Alarcon E, Jittimanee S, Walusimbi M, Sebek M, Berga E, et al. Best Practice for the Care of Patients with Tuberculosis: a Guide for Low-Income Countries. Paris, France: International Union Against Tuberculosis and Lung Disease; 2007.
4. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva, Switzerland: World Health Organization 2006.
5. Rieder H. Interventions for TB control and elimination. Paris, France: International Union Against Tuberculosis and Lung Disease; 2002.
6. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet*. 2010 Oct 9;376(9748):1244-53.
7. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis*. 2005 Nov;9(11):1183-203.
8. Scoping meeting for the development of guidelines on screening for active TB. Geneva: World Health Organization; 2011.
9. National TB prevalence survey. Cambodia: National Tuberculosis Control Programme; 2002.
10. Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FG. National survey of tuberculosis prevalence in Viet Nam. *Bull World Health Organ*. 2010 Apr;88(4):273-80.
11. Tupasi TE, Radhakrishna S, Rivera AB, Pascual ML, Quelapio MI, Co VM, et al. The 1997 Nationwide Tuberculosis Prevalence Survey in the Philippines. *Int J Tuberc Lung Dis*. 1999 Jun;3(6):471-7.
12. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. *Lancet Infect Dis*. 2012 Aug;12(8):608-16.
13. Kranzer K, Lawn SD, Meyer-Rath G, Vassall A, Radithalo E, Govindasamy D, et al. Feasibility, Yield, and Cost of Active Tuberculosis Case Finding Linked to a Mobile HIV Service in Cape Town, South Africa: A Cross-sectional Study. *PLoS Med*. 2012 Aug;9(8):e1001281.
14. Shapiro A, Golub JE. Systematic review of number needed to screen (NNS) in selected risk groups with different screening approaches. Scoping meeting for the development of guidelines on screening for active TB 31 May - 1 June 2011. WHO Stop TB Department, Geneva; 2011.
15. Ottmani S, Signol M, Bencheikh N, Laasri L, Blanc L, Mahjour J. TB contact investigations: 12 years of experience in the National TB Programme, Morocco 1993-2004. *East Mediterr Health J*. 2009 May-Jun;15(3):494-503.
16. Krivinka R, Drapela J, Kubik A, Dankova D, Krivanek J, Ruzha J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia. Second report (1965-1972). *Bull World Health Organ*. 1974;51(1):59-69.
17. Meijer J, Barnett GD, Kubik A, Styblo K. [Identification of sources of infection]. *Bulletin of the International Union against Tuberculosis*. 1971 Nov;45:5-54.
18. Ayles H. A Household-based HIV and TB Intervention Increases HIV Testing in Households and Reduces Prevalence of TB at the Community Level: The ZAMSTAR Community Randomized Trial. 19th Conference of Retroviruses and Opportunistic Infections. Seattle; 2012.
19. Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z, et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. *Int J Tuberc Lung Dis*. 2010 Jun;14(6):720-6.

20. Shargie EB, Morkve O, Lindtjorn B. Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: community randomized trial. *Bull World Health Organ.* 2006 Feb;84(2):112-9.
21. Datiko DG, Lindtjorn B. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. *PLoS One.* 2009;4(5):e5443.
22. Moyo S, Verver S, Hawkridge A, Geiter L, Hatherill M, Workman L, et al. Tuberculosis case finding for vaccine trials in young children in high-incidence settings: a randomised trial. *Int J Tuberc Lung Dis.* 2012 Feb;16(2):185-91.
23. Borgdorff MW. New measurable indicator for tuberculosis case detection. *Emerg Infect Dis.* 2004 Sep;10(9):1523-8.
24. Tadesse T, Demissie M, Berhane Y, Kebede Y, Abebe M. Two-thirds of smear-positive tuberculosis cases in the community were undiagnosed in Northwest Ethiopia: population based cross-sectional study. *PLoS One.* 2011;6(12):e28258.
25. Santha T, Renu G, Frieden TR, Subramani R, Gopi PG, Chandrasekaran V, et al. Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India. *Int J Tuberc Lung Dis.* 2003 Mar;7(3):258-65.
26. Gopi PG, Chandrasekaran V, Subramani R, Narayanan PR. Failure to initiate treatment for tuberculosis patients diagnosed in a community survey and at health facilities under a DOTS programme in a district of South India. *Indian Journal of Tuberculosis.* 2005;52:153-56.
27. Balasubramanian R, Garg R, Santha T, Gopi PG, Subramani R, Chandrasekaran V, et al. Gender disparities in tuberculosis: report from a rural DOTS programme in south India. *Int J Tuberc Lung Dis.* 2004 Mar;8(3):323-32.
28. Harries AD, Rusen ID, Chiang CY, Hinderaker SG, Enarson DA. Registering initial defaulters and reporting on their treatment outcomes. *Int J Tuberc Lung Dis.* 2009 Jul;13(7):801-3.
29. Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? *Int J Tuberc Lung Dis.* 2008 Jul;12(7):820-3.
30. Botha E, den Boon S, Lawrence KA, Reuter H, Verver S, Lombard CJ, et al. From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. *Int J Tuberc Lung Dis.* 2008 Aug;12(8):936-41.
31. Buu TN, Lonnroth K, Quy HT. Initial defaulting in the National Tuberculosis Programme in Ho Chi Minh City, Vietnam: a survey of extent, reasons and alternative actions taken following default. *Int J Tuberc Lung Dis.* 2003 Aug;7(8):735-41.
32. Sai Babu B, Satyanarayana AV, Venkateshwaralu G, Ramakrishna U, Vikram P, Sahu S, et al. Initial default among diagnosed sputum smear-positive pulmonary tuberculosis patients in Andhra Pradesh, India. *Int J Tuberc Lung Dis.* 2008 Sep;12(9):1055-8.
33. Glynn JR, Warndorff DK, Fine PE, Munthali MM, Sichone W, Ponnighaus JM. Measurement and determinants of tuberculosis outcome in Karonga District, Malawi. *Bull World Health Organ.* 1998;76(3):295-305.
34. Churchyard GJ, Kleinschmidt I, Corbett EL, Murray J, Smit J, De Cock KM. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2000 Aug;4(8):705-12.
35. Okada K, Onozaki I, Yamada N, Yoshiyama T, Miura T, Saint S, et al. Epidemiological impact of mass tuberculosis screening: a two-year follow-up after a national tuberculosis prevalence survey. Unpublished. 2012.
36. Rendleman NJ. Mandated tuberculosis screening in a community of homeless people. *Am J Prev Med.* 1999 Aug;17(2):108-13.
37. Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006 Oct;6(10):664-74.

38. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006 Sep;6(9):570-81.
39. Cattamanchi A, Davis JL, Pai M, Huang L, Hopewell PC, Steingart KR. Does bleach processing increase the accuracy of sputum smear microscopy for diagnosing pulmonary tuberculosis? *J Clin Microbiol.* 2010 Jul;48(7):2433-9.
40. Churchyard GJ, Fielding K, Roux S, Corbett EL, Chaisson RE, De Cock KM, et al. Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: a randomised controlled trial. *Thorax.* 2011 Feb;66(2):134-9.
41. Shargie EB, Yassin MA, Lindtjorn B. Prevalence of smear-positive pulmonary tuberculosis in a rural district of Ethiopia. *Int J Tuberc Lung Dis.* 2006 Jan;10(1):87-92.
42. Yimer S, Holm-Hansen C, Yimaldu T, Bjune G. Evaluating an active case-finding strategy to identify smear-positive tuberculosis in rural Ethiopia. *Int J Tuberc Lung Dis.* 2009 Nov;13(11):1399-404.
43. Amare D, Abebe G, Apers L, Alemseged A, Fetene D. Prevalence of pulmonary TB and HIV among TB suspects in rural community in Southwest Ethiopia. 41st World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease. 2010.
44. Agizew TB, Arwady MA, Yoon JC, Nyirenda S, Mosimaneotsile B, Tedla Z, et al. Tuberculosis in asymptomatic HIV-infected adults with abnormal chest radiographs screened for tuberculosis prevention. *Int J Tuberc Lung Dis.* 2010 Jan;14(1):45-51.
45. Bjerregaard-Andersen M, da Silva ZJ, Ravn P, Ruhwald M, Andersen PL, Sodemann M, et al. Tuberculosis burden in an urban population: a cross sectional tuberculosis survey from Guinea Bissau. *BMC Infect Dis.* 2010;10:96.
46. Koffi N, Ngom AK, Aka-Danguy E, Seka A, Akoto A, Fadiga D. Smear positive pulmonary tuberculosis in a prison setting: experience in the penal camp of Bouake, Ivory Coast. *Int J Tuberc Lung Dis.* 1997 Jun;1(3):250-3.
47. van't Hoog AH, Laserson KF, Githui WA, Meme HK, Agaya JA, Odeny LO, et al. High prevalence of pulmonary tuberculosis and inadequate case finding in rural western Kenya. *Am J Respir Crit Care Med.* 2011 May 1;183(9):1245-53.
48. Harries AD, Nyirenda TE, Yadidi AE, Gondwe MK, Kwanjana JH, Salaniponi FM. Tuberculosis control in Malawian prisons: from research to policy and practice. *Int J Tuberc Lung Dis.* 2004 May;8(5):614-7.
49. den Boon S, Verver S, Lombard CJ, Bateman ED, Irusen EM, Enarson DA, et al. Comparison of symptoms and treatment outcomes between actively and passively detected tuberculosis cases: the additional value of active case finding. *Epidemiol Infect.* 2008 Oct;136(10):1342-9.
50. Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med.* 2007 Jan 1;175(1):87-93.
51. Middelkoop K, Bekker LG, Myer L, Whitelaw A, Grant A, Kaplan G, et al. Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township. *Am J Respir Crit Care Med.* 2010 Oct 15;182(8):1080-5.
52. Guwatudde D, Zalwango S, Kamya MR, Debanne SM, Diaz MI, Okwera A, et al. Burden of tuberculosis in Kampala, Uganda. *Bull World Health Organ.* 2003;81(11):799-805.
53. Sekandi JN, Neuhauser D, Smyth K, Whalen CC. Active case finding of undetected tuberculosis among chronic coughers in a slum setting in Kampala, Uganda. *Int J Tuberc Lung Dis.* 2009 Apr;13(4):508-13.
54. Corbett EL, Bandason T, Cheung YB, Makamure B, Dauya E, Munyati SS, et al. Prevalent infectious tuberculosis in Harare, Zimbabwe: burden, risk factors and implications for control. *Int J Tuberc Lung Dis.* 2009 Oct;13(10):1231-7.

55. Cavalcante SC, Durovni B, Barnes GL, Souza FB, Silva RF, Barroso PF, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis.* 2010 Feb;14(2):203-9.
56. Gonzalez-Ochoa E, Brooks JL, Matthys F, Caliste P, Armas L, Van der Stuyft P. Pulmonary tuberculosis case detection through fortuitous cough screening during home visits. *Trop Med Int Health.* 2009 Feb;14(2):131-5.
57. Garcia-Garcia M, Palacios-Martinez M, Ponce-de-Leon A, Jimenez-Corona ME, Jimenez-Corona A, Balandrano-Campos S, et al. The role of core groups in transmitting Mycobacterium tuberculosis in a high prevalence community in Southern Mexico. *Int J Tuberc Lung Dis.* 2000 Jan;4(1):12-7.
58. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. *Int J Tuberc Lung Dis.* 2003 Dec;7(12 Suppl 3):S384-90.
59. LoBue PA, Moser KS. Screening of immigrants and refugees for pulmonary tuberculosis in San Diego County, California. *Chest.* 2004 Dec;126(6):1777-82.
60. Aneja KS, Seetha MA, Shunmuganandan VC, Samuel R. Active case finding in tuberculosis as a component of primary health care. *Ind J Tub.* 1984;31:65-73.
61. Gopi PG, Subramani R, Sadacharam K, Narayanan PR. Yield of pulmonary tuberculosis cases by employing two screening methods in a community survey. *Int J Tuberc Lung Dis.* 2006 Mar;10(3):343-5.
62. Shetty PV, Granich RM, Patil AB, Sawant SK, Sahu S, Wares DF, et al. Cross-referral between voluntary HIV counselling and testing centres and TB services, Maharashtra, India, 2003-2004. *Int J Tuberc Lung Dis.* 2008 Mar;12(3 Suppl 1):26-31.
63. Report on National TB prevalence survey 2009-2010. Myanmar: Ministry of Health.
64. Cassels A, Heineman E, LeClerq S, Gurung PK, Rahut CB. Tuberculosis case-finding in Eastern Nepal. *Tubercle.* 1982 Sep;63(3):175-85.
65. Harper I, Fryatt R, White A. Tuberculosis case finding in remote mountainous areas--are microscopy camps of any value? Experience from Nepal. *Tuber Lung Dis.* 1996 Aug;77(4):384-8.
66. Eang MT, Satha P, Yadav RP, Morishita F, Nishikiori N, van-Maaren P, et al. Early detection of tuberculosis through community-based active case finding in Cambodia. *BMC Public Health.* 2012 Jun 21;12(1):469.
67. Lee MS, Leung CC, Kam KM, Wong MY, Leung MC, Tam CM, et al. Early and late tuberculosis risks among close contacts in Hong Kong. *Int J Tuberc Lung Dis.* 2008 Mar;12(3):281-7.
68. Yagi T, Yamagishi F, Sasaki Y, Hashimoto T, Bekku R, Yamanaka M, et al. [Clinical review of patients with pulmonary tuberculosis who were detected by the screening of homeless persons admitted in the shelter facilities]. *Kekkaku : [Tuberculosis].* 2006 May;81(5):371-4.
69. Hong YP, Kim SJ, Kwon DW, Chang SC, Lew WJ, Han YC. The sixth Nationwide Tuberculosis Prevalence Survey in Korea, 1990. *Tuber Lung Dis.* 1993 Oct;74(5):323-31.
70. Phuanukoonnon S, Mueller I, Usurup J, Siba P. Burden of tuberculosis and health seeking behaviours of people with prolonged cough in rural PNG. 41st World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease. 2010.
71. Manalo F, Tan F, Sbarbaro JA, Iseman MD. Community-based short-course treatment of pulmonary tuberculosis in a developing nation. Initial report of an eight-month, largely intermittent regimen in a population with a high prevalence of drug resistance. *Am Rev Respir Dis.* 1990 Dec;142(6 Pt 1):1301-5.
72. Wang PD, Lin RS. Tuberculosis transmission in the family. *J Infect.* 2000 Nov;41(3):249-51.
73. Keane VP, O'Rourke TF, Bollini P, Pampallona S, Siem H. Prevalence of tuberculosis in Vietnamese migrants: the experience of the Orderly Departure Program. *Southeast Asian J Trop Med Public Health.* 1995 Dec;26(4):642-7.