Supplementary Web Appendices for Tuberculosis in hard-to-reach populations 2 Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review

Supplementary Material I: PICOS (Population – Intervention – Comparator – Outcome – Study design)

1. Review questions

The primary review question was:
What interventions are effective and cost-effective at identifying and managing TB and/or raising awareness about TB among hard-to-reach populations?

Secondary review questions were:

(i) What factors affect the effectiveness of those interventions?
(ii) How transferable are the findings on effectiveness across hard-to-reach populations or settings?
(iii) What, if any, are the adverse or unintended effects (for example, increased stigma) of the interventions to identify and manage individuals with TB in hard-to-reach populations?

2. PICOS

Population

Hard-to-reach populations, like:

- homeless people including rough sleepers and shelter users
- people who abuse drugs or alcohol
- sex workers
- prisoners or people with a history of imprisonment
- migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
- children within vulnerable and hard-to-reach populations
- people living with HIV

Studies focusing on hard-to-reach populations from Organisation for Economic Co-operation and Development (OECD) countries, European Union, European Economic Area (EU/EEA) countries and the EU candidate countries were included.

EU/EEA and candidate countries

1. Albania
2. Austria
3. Belgium
4. Bulgaria
5. Croatia
6. Cyprus
7. Czech Republic
8. Denmark
9. Estonia
10. Finland
11. France
12. Germany
13. Greece
14. Hungary
15. Iceland
16. Ireland
17. Italy
18. Latvia
19. Liechtenstein
20. Lithuania
21. Luxembourg
22. Malta

OECD countries

1. Australia
2. Austria
3. Belgium
4. Canada
5. Chile
6. Czech Republic
7. Denmark
8. Estonia
9. Finland
10. France
11. Germany
12. Greece
13. Hungary
14. Iceland
15. Ireland
16. Israel
17. Italy
18. Japan
19. Korea
20 Luxembourg
21. Mexico
22. Netherlands

23. Montenegro
24. Netherlands
25. Norway
26. Poland
27. Portugal
28. Romania
29. Serbia
30. Slovakia
31. Slovenia
32. Spain
33. Sweden
34. The former Yugoslav Republic of Macedonia
35. Turkey
36. United Kingdom

23. New Zealand
24. Norway
25. Poland
26. Portugal
27. Slovak Republic
28. Slovenia
29. Spain
30. Sweden
31. Switzerland
32. Turkey
33. United Kingdom
34. United States

Studies that do not specifically look at any of these target populations or were conducted in a different geographical area were excluded.

Intervention

This review aimed to collect evidence on all areas of interventions related to the identification and management of tuberculosis (TB) in hard-to-reach populations, predefined interventions included in the protocol were:

- Active screening and case finding by:
    - tracing household contacts
    - using (mobile) chest X-rays
    - using tuberculin skin tests, interferon gamma release assays, only if used as an initial step in the diagnostic pathway to identify active TB cases
    - symptom-based questionnaires
- Improve coverage and uptake of screening, active case finding, case holding and treatment by:
    - using small monetary incentives or food vouchers
    - identifying more members of hard-to-reach populations
    - (family based) DOT(S) programme
    - legal detention to manage active TB
    - continuity of care in the public sector for prisoners released from prison
- Educational interventions:
    - information and education among vulnerable groups as well as health care providers and staff of social welfare and Non Governmental Organisations (NGO) that interact with the vulnerable populations
    - group discussion (over more traditional education methods)
- Social care support e.g.:
    - provision of housing
    - nutritional programmes
    - addressing challenges related to immigration from high-TB burden countries
    - addressing inequalities and socioeconomic deprivation
- Test and treat
- Treatment of comorbidities, including HIV and substance use disorders
- Enhanced case management
- Stigma-related interventions
- Programmes aimed at detection of patients from vulnerable or hard-to-reach populations who were lost to follow-up
- The existence of programs aimed at collaborations with, or interventions aimed at, alternative, traditional, and / or spiritual medicine in TB treatment

<u>The following interventions were identified in the review process:</u>

- Pre- and post-migration screening
- Sputum smear and sputum culture as part of pre-migration screening

Comparator

Not relevant.

The comparator was re-defined during the review process into:
Every intervention group was compared to a relevant comparison group. These included for example, no intervention or usual care, another intervention, or historical comparison.

Outcome
Primary outcome measures were quantitative outcomes focusing on the effectiveness and cost-effectiveness of interventions to improve TB identification and management as well as raising awareness about TB targeting hard-to-reach populations, including a qualitative description of these interventions. The secondary outcome measures were the factors that impact the effectiveness of the intervention, the transferability of the findings regarding effectiveness to other hard-to-reach populations or other settings, the adverse and unintended effects of the interventions to identify and manage those individuals with TB from hard-to-reach populations.

Study design
Randomised controlled trials (RCTs) focusing on interventions on the selected hard-to-reach populations were included. Since it is very likely that few RCTs will be identified, we also included non-randomised quantitative and qualitative studies, like, but not exclusively, case-control studies, cohort studies, cross-sectional studies, observational studies etc. Systematic reviews were included for reference checking only.

3. Further notes on PICOS
For this systematic review of interventions with a scoping component, a very broad and sensitive search was conducted to cover a wide range of interventions. Predefined interventions were included in our registered protocol but the list of interventions was not exclusive and interventions were added to the list during the review process. Supplementary Material I reflects the registered protocol. Changes made during the implementation of the systematic review protocol are stated at the end of each section.

Supplementary Material II: Search strategies

The previous NICE review[1] on the same topic was used as a framework for the search strategy and extended to the non- Organisation for Economic Co-operation and Development (OECD), countries of the European Union and European Economic Area and to the two newly included hard-to-reach groups (people living with HIV co-infected with TB and children within vulnerable and hard-to-reach populations). The search for the NICE review[1] was subtracted from our search to prevent double screening of records. The search was conducted by René Spijker, clinical librarian at the Academic Medical Center in Amsterdam, the Netherlands. All studies identified by the search were imported to an Endnote database. The original search was done on the 10th of December 2014 and updated on the 10th of April 2015.

The following two databases were used for the search:

- MEDLINE(R) In-Process & Other Non-Indexed Citations (OvidSP)
- Embase Classic + Embase 1947 to 2015 April 10

Database	**Hits**
Medline + Medline In-Process	9,078
Embase	10,255
Total	19,333
Total de-duplicated	**13,783**

References:

1. Rizzo M, Martin A, Jamal F, et al. Evidence review on the effectiveness and cost-effectiveness of service models or structures to manage tuberculosis in hard-to-reach groups. London: Matrix evidence/National Institute for Health and Clinical Excellence 2011. https://www.nice.org.uk/guidance /PH37/ documents/review-4-evidence-review-on-the-effectiveness-and-cost-effectiveness-of-service-models-or-structures-to-manage-tuberculosis-in-hardtoreach-groups-2 (last assessed March 2016).

1. Search in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1990 January 1 to 2015 April 10

Hits: 9,078

1	exp Tuberculosis/ or (tuberculosis or tb).ti,ab.
2	((hard$ adj2 reach) or (hard$ adj2 locate) or (hard$ adj2 find) or (hard$ adj2 treat) or (difficult adj2 locate) or (difficult adj2 engage) or social$ exclu$ or social inequalit$ or (difficult$ adj2 reach) or (difficult$ adj2 find) or (difficult$ adj2 treat) or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*) or (muslim* or islam* or mosque* or imam*)).ti,ab. or jews/ or (jew* or judaism* or synagogue*).ti,ab. or exp religion/ or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab. or jews/ or (jew* or judaism* or synagogue*).ti,ab. or (sikh* or hindu* or buddhis* or temple*).ti,ab. or ((religion* or religious* or faith*) and (people* or person* or group* or population or neighbour* or neighbor* or patient* or communit*)).ti,ab.
3	((geograph$ or transport$ or physical) and barrier$).ti,ab.
4	((low$ or poor$ or negative) and (quality adj2 life)).ti,ab.
5	((vulnerable or disadvantaged or at risk or high risk or low socioeconomic status or neglect$ or affected or marginal$ or forgotten or non-associative or unengaged or hidden or excluded or transient or inaccessible or underserved or stigma$ or inequitable) and (people or population$ or communit$ or neighbourhood$1 or neighborhood$1 or group$ or area$1 or demograph$ or patient$ or social$)).ti,ab. or Vulnerable populations/
6	poverty area/
7	(refuser$1 or nonuser$1 or non-user$1 or non user$1 or discriminat$ or shame or prejud$ or racism or racial discriminat$).ti,ab.
8	social support/ or *social conditions/ or stigma/ or Social Isolation/ or *quality of life/ or Prejudice/ or Socioeconomic Factors/
9	prisoner$1.ti,ab.
10	(recent$ adj2 release$ adj2 (inmate$ or prison$ or detainee$ or felon$ or offender$ or convict$ or custod$ or detention or incarcerat$ or correctional or jail$ or penitentiar$)).ti,ab.
11	((prison$ or penal or penitentiar$ or correctional facilit$ or jail$ or detention centre$ or detention center$) and (guard$1 or population or inmate$ or system$ or remand or detainee$ or felon$ or offender$1 or convict$ or abscond$)).ti,ab.
12	(parole or probation).ti,ab.
13	*prisoners/
14	((custodial adj (care or sentence)) or (incarceration or incarcerated or imprisonment)).ti,ab.
15	(immobile or (disabled and (house bound or home bound)) or ((house or home) adj3 bound)).ti,ab. or Homebound Persons/
16	((hous$ and (quality or damp$ or standard$ or afford$ or condition$ or dilapidat$)) or ((emergency or temporary or inadequate or poor$ or overcrowd$ or over-crowd$ or over-subscribed) and (hous$ or accommodation or shelter$ or hostel$ or dwelling$))).ti,ab. or housing/st
17	(rough sleep$ or runaway$1 or ((homeless$ or street or destitut$) and (population or person$1 or people or group$ or individual$1 or shelter$ or hostel$ or accommodation$1))).ti,ab. or exp homeless persons/

18	((drug$ or substance) and (illegal or misus$ or abuse or intravenous or IV or problem use$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)).ti,ab. or *Substance-Related Disorders/ or Drug users/ or Substance Abuse, Intravenous/
19	((alcohol$ and (misus$ or abuse or problem$ use$ or problem drink$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)) or alcoholic$1).ti,ab. or *Alcohol-Related Disorders/ or Alcoholics/
20	(prostitution or sex work$ or transactional sex$ or prostitute$1).ti,ab. or Prostitution/
21	(poverty or deprivation or financial hardship$ or (illitera$ or welfare benefit$ or social benefit$)).ti,ab.
22	((low-income or low income or low pay or low paid or poor or deprived or debt$ or arrear$) and (people or person$1 or population$1 or communit$ or group$ or social group$ or neighbourhood$1 or neighborhood$1 or famil$)).ti,ab.
23	poverty/
24	(low$ and social class$).ti,ab.
25	(traveller$1 or Gypsies or Gypsy or Gipsy or Romany or Roma).ti,ab. or gypsies/
26	(mental$ and (health or ill or illness)).ti,ab. or *mental health/ or Mentally Ill Persons/
27	(health care worker$1 or (health care adj2 service provi$) or (health-care adj2 provi$) or (((community adj1 leader$) or (community adj1 (Manag$ or advocat$ or champion$))) and (engag$ or involv$))).ti,ab.
28	(complex adj2 (patient$ or Need$)).ti,ab.
29	(outreach adj2 worker$1).ti,ab. or Community health aides/
30	(support adj2 worker$1).ti,ab.
31	(case adj2 worker$1).ti,ab.
32	(social adj2 worker$1).ti,ab.
33	social care professional$1.ti,ab.
34	((social care adj2 service provi$) or (social-care adj2 provi$)).ti,ab.
35	(((language$ or communicat$) and (barrier$ or understand$ or strateg$ or proficien$)) or translat$ or interpret$ or (cultur$ and competen$)).ti,ab. or Communication Barriers/ or *Language/
36	(immigrant$ or migrant$ or asylum or refugee$ or undocumented or foreign born or UK born or non-UK born or non UK born or (born adj overseas) or (displaced and (people or person$1))).ti,ab. or "Emigration and Immigration"/ or refugees/
37	"Transients and Migrants"/
38	"Emigrants and Immigrants"/
39	or/2-38
40	Intervention$.ti,ab. or Crisis Intervention/
41	((early or primary) adj2 Intervention$).ti,ab.
42	((person$ or individual or local$ or community or cultural or structural or supported or indicated or target$ or multi?component or comprehensive or pilot or media) and Intervention$).ti,ab.
43	((midstream or mid-stream) and intervention$).ti,ab.
44	(Identify$ or find or finding or locat$ or trac$ or contact$ or discover$ or detect or recruit$ or attract$).ti,ab.
45	(case finding or ((active or passive) adj3 case finding)).ti,ab.
46	((program$ or scheme$1 or service$1 or campaign$ or mobili?ation or strateg$ or measure or policy or policies) and (tuberculosis or tb)).ti,ab.

47	((case adj3 management) or case-managed).ti,ab. or Case Management/ or Patient Care Planning/ or Managed Care Programs/ or Patient care management/
48	(case adj3 manag$ adj3 strategy).ti,ab. or continuity of patient care/
49	((treat$ or diagnosis) and management).ti,ab.
50	((active or passive) and (Case adj3 Management)).ti,ab.
51	(risk assess$ or risk profile or risk Indicator or care plan$).ti,ab.
52	(service and (model$ or deliver$)).ti,ab. or delivery of health care/ or *health services/ or Urban health services/
53	((primary adj3 healthcare) or ((primary adj3 health$) or care)).ti,ab. or exp Primary Health Care/
54	(nurse or ((general or family) adj3 (practice$ or practitioner$ or physicians$ or doctor$))).ti,ab. or Nurses/ or (exp Tuberculosis/ or (tuberculosis/ or tb/)) or Family practice/ or Physicians, Family/
55	((health or extension or multi-disciplinary or multidisciplinary) and (professional$ or personal$ or practitioner or worker$ or partner$ or promot$ or provider or care team or care provider or unit or casework$ or (case adj2 work$))).ti,ab. or *Health Personnel/ or Nurses' Aides/
56	(social adj2 (work$ or Support$ or Outreach)).ti,ab. or social work/ or Social Support/
57	((lay or allied or link) and (professional$ or practitioner$1 or worker$1 or advocate$1 or personnel)).ti,ab. or Allied Health Personnel/
58	(volunteer$ or voluntary or charit$ or third sector).ti,ab. or Voluntary Workers/ or exp Voluntary health agencies/
59	(health adj1 (center$1 or centre$1 or facilit$ or service$ or clinic$1 or hospital$1 or program$1)).ti,ab. or Community Health/ or "Catchment Area (Health)"/
60	((day adj2 (care or hospital$ or patient$)) or workshop$).ti,ab. or day care/
61	rehab$.ti,ab. or rehabilitation centers/
62	((dedicated or permanent or rapid access or fixed or TB or tuberculosis) and (clinic$1 or centre$1 or center$1 or program$)).ti,ab.
63	(((drug adj2 dependency) or substance abuse or HIV) and (unit$ or clinic$1 or centre$1 or center$1 or program$) and (tuberculosis or tb)).ti,ab. or Substance Abuse Treatment Centers/
64	(pharmac$ or dispensary).ti,ab. or Pharmacies/ or Community Pharmacy Services/
65	(communit$ or (support$ adj2 communit$)).ti,ab. or *Community Health Services/ or *Community Networks/ or Community Health Aides/ or *Community-Institutional Relations/ or community hospital/ or Community Health Nursing/
66	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
67	(ambulatory adj2 care).ti,ab. or ambulatory care/ or Ambulatory Care Facilities/
68	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (health adj3 (care or work$ or practitioner$ or professional$ or service$ or center$1 or centre$1 or unit$1 or program$))).ti,ab. or Mobile Health Units/
69	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (nurs$ or doctor$)).ti,ab.
70	((out adj3 hours) or (after adj3 hours) or telephone or telemedicine).ti,ab. or after-hours care/ or Telemedicine/
71	((walk-in or walkin or walk in) adj2 (center$1 or centre$1 or service or program$ or Clinic$1 or Session or Assesment$1)).ti,ab.

72	(drop$ adj1 in adj2 (center$1 or centre$1 or service or program$ or clinic$1 or session or meeting or assesment$1)).ti,ab.
73	(((health or home$ or house$) and (call$ or visit$)) or (home-care or home-based or (support$ adj1 hous$))).ti,ab. or Home Health Aides/ or home care services/ or *House Calls/
74	((early adj2 discharge) or (recent$ adj2 discharged) or (out adj2 patient)).ti,ab. or patient care/ or outpatient clinics, hospital/ or patient care team/
75	(counselling or counseling or counsellor or counselor or (integrated counselling adj1 testing centre$1) or (integrated counselling adj1 testing center$1) or ICTC).ti,ab. or Counseling/ or Directive Counseling/
76	((help adj2 group$) or (self adj2 help) or support$ or (peer adj2 peer)).ti,ab. or Self-Help Groups/
77	(collaborat$ or shared or (integrated adj1 care$) or ICP or network$ or co-locat$ or (one adj1 stop)).ti,ab. or "delivery of health care, integrated"/
78	((health adj2 education) or (skill adj2 mix) or (role adj2 develop$) or leadership or ((interdisciplinary or inter-team or Professional or team) adj2 communicate$)).ti,ab. or exp Health Education/ or Interdisciplinary Communication/ or Leadership/ or professional-family relations/ or professional-patient relations/ or nurse-patient relations/ or physician-patient relations/ or patient relationship*.ti,ab.
79	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
80	or/40-79
81	test$.ti,ab.
82	(examination$1 or assessment$1 or identification or assay$ or detection).ti,ab.
83	diagnosi$.ti,ab. or *diagnostic tests, routine/
84	((chest adj2 x?ray) or chest radiograph or MXU).ti,ab. or Mass Chest X-Ray/
85	(screen$ or (new$ adj1 screen$)).ti,ab.
86	(monitor$ or sampling).ti,ab.
87	((target$ or focus$ or community or population or individual$ or person$ or opportunistic or coerc$ or voluntary or initiated) and (test$ or diagnosis or screen$ or assay$ or detection)).ti,ab.
88	PIT.ti,ab.
89	provider initiated test$.ti,ab.
90	((rapid or prompt or quick$ or earl$ or (point adj2 care)) and (test$ or screen$ or diagnosi$ or assay$ or detection)).ti,ab.
91	((provider or anonymous or accurate or support$ or incentiv$ or counsel$) and (test$ or diagnosis or screen$ or assay$)).ti,ab. or Anonymous Testing/
92	(test$ adj2 (center$1 or centre$1 or unit$1 or setting)).ti,ab.
93	or/81-92
94	(acceptability or acceptable or attend$ or access$ or availab$ or non-attend$ or increas$ or promot$ or opt$ or particip$ or adhere$ or involvement or uptake or take-up or utiliz$ or utilis$ or refus$ or referr$ or self-referr$ or self-report$ or barrier$ or decreas$ or isolation or interven$ or aware$ or opportunit$ or advice or information or incentiv$ or recruit$ or find or finding or compliance or comply or retain or retention or provision or encour$ or usage).ti,ab.
95	(socio sanitary support or reimburs$ or (social adj2 support) or ((cash or financial or money or monetary or economic or voucher or credit or drug$1 or methadone or telephone) adj2 (benefit$ or support or incentive or assist$ or credit))).ti,ab. or Reimbursement, Incentive/
96	(((lifestyle or behavio?r) adj2 (therapy or modif$ or chang$ or adapt$ or adopt$)) and (tuberculosis or tb)).ti,ab. or social marketing/
97	"Marketing of Health Services"/

98	Attitude to health/
99	Health Services Accessibility/
100	Access to information/
101	Confidentiality/
102	Health education/
103	Health promotion/
104	Patient acceptance of health care/
105	Patient compliance/
106	Motivation/
107	Stigma.ti,ab.
108	prevalence/
109	*Consumer Participation/
110	or/94-109
111	treat$.ti,ab. or Treatment Outcome/
112	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
113	(disease management or (treat$ and (management or control))).ti,ab.
114	((adherence or compli$ or non-compli$ or default$ or finish$ or Retention or attrition or (drop adj1 out) or disappear$ or abscond$) and treat$).ti,ab. or exp Patient Compliance/
115	((referr$ or self-referr$ or (self adj diagnos$)) and treat$).ti,ab.
116	((suitab$ or eligib$) and treat$).ti,ab.
117	((follow adj1 up) or discharge).ti,ab. or Follow-Up Studies/
118	((positive or negative) and test).ti,ab.
119	((interrupt$ or relapse$ or stop$ or cessation or with?ld$ or avoidance or (lost adj2 follow)) and treat$).ti,ab. or *Withholding Treatment/
120	((medicine$1 or drug or treat$) and (regimen or adherence)).ti,ab. or exp self care/
121	(treat$ and (appointment$ or Schedule$)).ti,ab. or "Appointments and Schedules"/
122	((care adj2 seeking) and pathway$).ti,ab.
123	((case adj3 management) or case-managed).ti,ab. or Case Management/ or Patient Care Planning/ or Managed Care Programs/ or Patient care management/
124	(case adj3 manag$ adj3 strategy).ti,ab. or continuity of patient care/
125	((case or treat$ or diagnosis) and management).ti,ab.
126	((active or passive) and (case adj3 management)).ti,ab.
127	((risk assessment or care plan$) and (case adj3 management)).ti,ab.
128	or/111-127
129	1 and 39 and (80 or (93 and (110 or 128)))
130	limit 129 to yr="1990 -Current"
131	limit 130 to "english language"
132	(animal$ or badger$ or Cow$ or Cattle or bovine).ti,ab. or (animals/ not humans/)
133	131 not 132
134	limit 133 to yr="1990 - 2010"
135	130 not 132
136	135 not 134

137	(albania or bulgaria or cyprus or croatia or latvia or lithuania or luxembourg or malta or montenegro or romania or serbia or yugoslav or turkey).ti,ab,hw,in.
138	1 and 137 and (80 or (93 and (110 or 128)))
139	limit 138 to yr="1990 -Current"
140	139 not 132
141	140 not 135
142	**136 or 141**

2. Search in Ovid: Embase Classic+Embase 1990 January 1 to 2015 April 10
Hits: 10,255

1	exp *tuberculosis/ or (tuberculosis or tb).ti,ab.
2	((hard$ adj2 reach) or (hard$ adj2 locate) or (hard$ adj2 find) or (hard$ adj2 treat) or (difficult adj2 locate) or (difficult adj2 engage) or social$ exclu$ or social inequalit$ or (difficult$ adj2 reach) or (difficult$ adj2 find) or (difficult$ adj2 treat) or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*) or (muslim* or islam* or mosque* or imam*)).ti,ab. or exp *Jew/ or (jew* or judaism* or synagogue*).ti,ab. or exp *religion/ or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab. or (jew* or judaism* or synagogue*).ti,ab. or (sikh* or hindu* or buddhis* or temple*).ti,ab. or ((religion* or religious* or faith*) and (people* or person* or group* or population or neighbour* or neighbor* or patient* or communit*)).ti,ab.
3	((geograph$ or transport$ or physical) and barrier$).ti,ab.
4	((low$ or poor$ or negative) and (quality adj2 life)).ti,ab.
5	((vulnerable or disadvantaged or at risk or high risk or low socioeconomic status or neglect$ or affected or marginal$ or forgotten or non-associative or unengaged or hidden or excluded or transient or inaccessible or underserved or stigma$ or inequitable) and (people or population$ or communit$ or neighbourhood$1 or neighborhood$1 or group$ or area$1 or demograph$ or patient$ or social$)).ti,ab. or exp *vulnerable population/
6	*poverty/
7	(refuser$1 or nonuser$1 or non-user$1 or non user$1 or discriminat$ or shame or prejud$ or racism or racial discriminat$).ti,ab.
8	*social support/ or exp *social status/ or *social stigma/ or exp *social isolation/ or exp *"quality of life"/ or exp *prejudice/ or exp *socioeconomics/
9	prisoner$1.ti,ab.
10	(recent$ adj2 release$ adj2 (inmate$ or prison$ or detainee$ or felon$ or offender$ or convict$ or custod$ or detention or incarcerat$ or correctional or jail$ or penitentiar$)).ti,ab.
11	((prison$ or penal or penitentiar$ or correctional facilit$ or jail$ or detention centre$ or detention center$) and (guard$1 or population or inmate$ or system$ or remand or detainee$ or felon$ or offender$1 or convict$ or abscond$)).ti,ab.
12	(parole or probation).ti,ab.
13	exp *prisoner/
14	((custodial adj (care or sentence)) or (incarceration or incarcerated or imprisonment)).ti,ab.

15	(immobile or (disabled and (house bound or home bound)) or ((house or home) adj3 bound)).ti,ab. or exp *homebound patient/
16	((hous$ and (quality or damp$ or standard$ or afford$ or condition$ or dilapidat$)) or ((emergency or temporary or inadequate or poor$ or overcrowd$ or over-crowd$ or over-subscribed) and (hous$ or accommodation or shelter$ or hostel$ or dwelling$))).ti,ab. or exp *housing/
17	(rough sleep$ or runaway$1 or ((homeless$ or street or destitut$) and (population or person$1 or people or group$ or individual$1 or shelter$ or hostel$ or accommodation$1))).ti,ab. or exp *homelessness/
18	((drug$ or substance) and (illegal or misus$ or abuse or intravenous or IV or problem use$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)).ti,ab. or exp *addiction/
19	((alcohol$ and (misus$ or abuse or problem$ use$ or problem drink$ or illicit use$ or addict$ or dependen$ or delinquency)) or alcoholic$1).ti,ab.
20	(prostitution or sex work$ or transactional sex$ or prostitute$1).ti,ab. or Prostitution/
21	(poverty or deprivation or financial hardship$).ti,ab.
22	((low-income or low income or low pay or low paid or poor or deprived or debt$ or arrear$) and (people or person$1 or population$1 or communit$ or group$ or social group$ or neighbourhood$1 or neighborhood$1 or famil$)).ti,ab. or exp *lowest income group/
23	*poverty/
24	(low$ and social class$).ti,ab.
25	(traveller$1 or gypsies or gypsy or Romany or roma).ti,ab. or exp *"Romani (people)"/
26	(mental$ and (health or ill or illness)).ti,ab. or *mental patient/ or exp *mental health/
27	(health care worker$1 or (health care adj2 service provi$) or (health-care adj2 provi$) or (((community adj1 leader$) or (community adj1 (Manag$ or advocat$ or champion$))) and (engag$ or involv$))).ti,ab.
28	(complex adj2 (patient$ or Need$)).ti,ab.
29	(outreach adj2 worker$1).ti,ab. or exp *health auxiliary/
30	(support adj2 worker$1).ti,ab.
31	(case adj2 worker$1).ti,ab.
32	(social adj2 worker$1).ti,ab.
33	social care professional$1.ti,ab.
34	((social care adj2 service provi$) or (social-care adj2 provi$)).ti,ab.
35	(((language$ or communicat$) and (barrier$ or understand$ or strateg$ or proficien$)) or translat$ or interpret$ or (cultur$ and competen$)).ti,ab. or *language ability/
36	(immigrant$ or migrant$ or asylum or refugee$ or undocumented or foreign born or (born adj overseas) or (displaced and (people or person$1))).ti,ab. or exp *refugee/
37	exp *migrant/
38	*immigration/
39	or/2-38
40	Intervention$.ti,ab. or exp *crisis intervention/
41	((early or primary) adj2 Intervention$).ti,ab.
42	((person$ or individual or local$ or community or cultural or structural or supported or indicated or target$ or multi?component or comprehensive or pilot or media) and Intervention$).ti,ab.
43	((midstream or mid-stream) and intervention$).ti,ab.

44	(Identify$ or find or finding or locat$ or trac$ or contact$ or discover$ or detect or recruit$ or attract$).ti,ab.
45	(case finding or ((active or passive) adj3 case finding)).ti,ab.
46	((program$ or scheme$1 or service$1 or campaign$ or mobili?ation or strateg$ or measure or policy or policies) and (tuberculosis or tb)).ti,ab.
47	((case adj3 management) or case-managed).ti,ab. or *case management/ or *patient care planning/ or *case management/ or exp *health care management/
48	(case adj3 manag$ adj3 strategy).ti,ab. or continuity of * patient care/
49	((treat$ or diagnosis) and management).ti,ab.
50	((active or passive) and (Case adj3 Management)).ti,ab.
51	(risk assess$ or risk profile or risk Indicator or care plan$).ti,ab.
52	(service and (model$ or deliver$)).ti,ab. or delivery of * health care/ or *health service/
53	((primary adj3 healthcare) or ((primary adj3 health$) or care)).ti,ab. or exp *primary health care/
54	(nurse or ((general or family) adj3 (practice$ or practitioner$ or physicians$ or doctor$))).ti,ab. or exp *nurse/ or (exp *tuberculosis/ or (tuberculosis or tb).ti,ab.) or exp *general practice/
55	((health or extension or multi-disciplinary or multidisciplinary) and (professional$ or personal$ or practitioner or worker$ or partner$ or promot$ or provider or care team or care provider or unit or casework$ or (case adj2 work$))).ti,ab. or *health care personnel/ or exp *nursing assistant/
56	(social adj2 (work$ or Support$ or Outreach)).ti,ab. or *social work/ or *social support/
57	(volunteer$ or voluntary or charit$ or third sector).ti,ab. or *voluntary worker/ or exp *health care organization/
58	(health adj1 (center$1 or centre$1 or facilit$ or service$ or clinic$1 or hospital$1 or program$1)).ti,ab. or *public health/ or *residential care/
59	((day adj2 (care or hospital$ or patient$)) or workshop$).ti,ab. or *day care/
60	rehab$.ti,ab. or *rehabilitation center/
61	((dedicated or permanent or rapid access or fixed or TB or tuberculosis) and (clinic$1 or centre$1 or center$1 or program$)).ti,ab.
62	(((drug adj2 dependency) or substance abuse or HIV) and (unit$ or clinic$1 or centre$1 or center$1 or program$) and (tuberculosis or tb)).ti,ab.
63	(pharmac$ or dispensary).ti,ab. or *pharmacy/
64	(communit$ or (support$ adj2 communit$)).ti,ab. or *community care/ or *health auxiliary/ or *public relations/ or *community hospital/ or *community health nursing/
65	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
66	(ambulatory adj2 care).ti,ab. or exp *ambulatory care/
67	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (health adj3 (care or work$ or practitioner$ or professional$ or service$ or center$1 or centre$1 or unit$1 or program$))).ti,ab. or *preventive health service/
68	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (nurs$ or doctor$)).ti,ab.
69	((out adj3 hours) or (after adj3 hours) or telephone or telemedicine).ti,ab. or after-hours care/ or exp *telehealth/ or *emergency care/ or *health care delivery/

70	((walk-in or walkin or walk in) adj2 (center$1 or centre$1 or service or program$ or Clinic$1 or Session or Assesment$1)).ti,ab.
71	(drop$ adj1 in adj2 (center$1 or centre$1 or service or program$ or clinic$1 or session or meeting or assesment$1)).ti,ab.
72	(((health or home$ or house$) and (call$ or visit$)) or (home-care or home-based or (support$ adj1 hous$))).ti,ab. or Home Health Aides/ or *health auxiliary/ or exp *home care/
73	((early adj2 discharge) or (recent$ adj2 discharged) or (out adj2 patient)).ti,ab. or *patient care/ or *outpatient department/
74	(counselling or counseling or counsellor or counselor or (integrated counselling adj1 testing centre$1) or (integrated counselling adj1 testing center$1) or ICTC).ti,ab. or *counseling/ or *directive counseling/
75	((help adj2 group$) or (self adj2 help) or support$ or (peer adj2 peer)).ti,ab. or *self help/
76	(collaborat$ or shared or (integrated adj1 care$) or ICP or network$ or co-locat$ or (one adj1 stop)).ti,ab. or *integrated health care system/
77	((health adj2 education) or (skill adj2 mix) or (role adj2 develop$) or leadership or ((interdisciplinary or inter-team or Professional or team) adj2 communicate$)).ti,ab. or exp *health education/ or exp *interdisciplinary communication/ or *leadership/ or *doctor patient relation/ or *nurse patient relationship/ or patient relationship*.ti,ab.
78	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
79	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
80	or/40-79
81	test$.ti,ab.
82	(examination$1 or assessment$1 or identification or assay$ or detection).ti,ab.
83	diagnosi$.ti,ab. or *diagnostic test/
84	((chest adj2 x?ray) or chest radiograph or MXU).ti,ab. or *thorax radiography/
85	(screen$ or (new$ adj1 screen$)).ti,ab.
86	(monitor$ or sampling).ti,ab.
87	((target$ or focus$ or community or population or individual$ or person$ or opportunistic or coerc$ or voluntary or initiated) and (test$ or diagnosis or screen$ or assay$ or detection)).ti,ab.
88	PIT.ti,ab.
89	provider initiated test$.ti,ab.
90	((rapid or prompt or quick$ or earl$ or (point adj2 care)) and (test$ or screen$ or diagnosi$ or assay$ or detection)).ti,ab.
91	((provider or anonymous or accurate or support$ or incentiv$ or counsel$) and (test$ or diagnosis or screen$ or assay$)).ti,ab. or *anonymous testing/
92	(test$ adj2 (center$1 or centre$1 or unit$1 or setting)).ti,ab.
93	or/81-92
94	(acceptability or acceptable or attend$ or access$ or availab$ or non-attend$ or increas$ or promot$ or opt$ or particip$ or adhere$ or involvement or uptake or take-up or utiliz$ or utilis$ or refus$ or referr$ or self-referr$ or self-report$ or barrier$ or decreas$ or isolation or interven$ or aware$ or opportunit$ or advice or information or incentiv$ or recruit$ or find or finding or compliance or comply or retain or retention or provision or encour$ or usage).ti,ab.

95	(socio sanitary support or reimburs$ or (social adj2 support) or ((cash or financial or money or monetary or economic or voucher or credit or drug$1 or methadone or telephone) adj2 (benefit$ or support or incentive or assist$ or credit))).ti,ab.
96	(((lifestyle or behavio?r) adj2 (therapy or modif$ or chang$ or adapt$ or adopt$)) and (tuberculosis or tb)).ti,ab. or *social marketing/
97	*marketing/
98	*attitude to health/
99	*health care delivery/
100	*access to information/
101	*confidentiality/
102	*Health education/
103	*health promotion/
104	*patient compliance/
105	*motivation/
106	Stigma.ti,ab.
107	*prevalence/
108	*patient participation/
109	*patient attitude/ or *refusal to participate/ or *treatment refusal/
110	or/94-109
111	treat$.ti,ab. or Treatment Outcome/
112	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or *directly observed therapy/
113	(disease management or (treat$ and (management or control))).ti,ab.
114	((adherence or compli$ or non-compli$ or default$ or finish$ or Retention or attrition or (drop adj1 out) or disappear$ or abscond$) and treat$).ti,ab. or exp *patient compliance/
115	((referr$ or self-referr$ or (self adj diagnos$)) and treat$).ti,ab.
116	((suitab$ or eligib$) and treat$).ti,ab.
117	((follow adj1 up) or discharge).ti,ab. or *follow up/
118	((positive or negative) and test).ti,ab.
119	((interrupt$ or relapse$ or stop$ or cessation or with?ld$ or avoidance or (lost adj2 follow)) and treat$).ti,ab. or *treatment withdrawal/
120	((medicine$1 or drug or treat$) and (regimen or adherence)).ti,ab. or exp *self care/
121	(treat$ and (appointment$ or Schedule$)).ti,ab. or *patient scheduling/
122	((care adj2 seeking) and pathway$).ti,ab.
123	((case adj3 management) or case-managed).ti,ab. or Case Management/ or *patient care planning/ or *health insurance/
124	(case adj3 manag$ adj3 strategy).ti,ab. or continuity.mp. or *patient care/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
125	((case or treat$ or diagnosis) and management).ti,ab.
126	((risk assessment or care plan$) and (case adj3 management)).ti,ab.
127	((active or passive) and (case adj3 management)).ti,ab.
128	or/111-127
129	1 and 39 and (80 or (93 and (110 or 128)))
130	limit 129 to yr="1990 -Current"
131	limit 130 to "english language"

132	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
133	131 not 132
134	limit 133 to yr="1990 - 2010"
135	(albania or bulgaria or cyprus or croatia or latvia or lithuania or luxembourg or malta or montenegro or romania or serbia or yugoslav or turkey).ti,ab,hw,in.
136	1 and 135 and (80 or (93 and (110 or 128)))
137	limit 136 to yr="1990 -Current"
138	137 not 132
139	138 not 130
140	133 not 134
141	**139 or 140**

Supplementary Material III. Evidence tables

Study details	Population and setting	Method of allocation to intervention/ control	Outcomes and methods of analysis	Results	Note by review team
Country: *US/Mexico* **Authors:** *Assael R., Cervantes J., Barrera G.* **Year:** *2013* **Citation:** *Assael R., Cervantes J., Barrera G.* *Smears and cultures for diagnosis of pulmonary tuberculosis in an asymptomatic immigrant population.* *International Journal of General Medicine 2013:6 777–779* **Aim of study:** *To demonstrate the proportion of smear-positive/culture-positive cases compared with smear-negative/culture-positive TB cases in Mexican immigrants bound for the USA* **Study design:** *Retrospective record study* **Quality score:** -	**Source population(s):** *Immigrants* **Eligible population:** *Mexican immigrants to the US* **Selected population:** *Culture confirmed active TB in Mexican immigrants to the US* **Excluded population:** *NR* **Setting:** *TB screening for Mexican migrants to the US* **Sample characteristics:** *- 122 active TB* *- 42% female, 58% male* *- mean age 61.4 years (19-93 y.o)* - Active TB disease was most prevalent in the Mexican state of Jalisco, followed by in Chihuahua, Guerrero, and Baja, California	**Method of allocation:** *All US bound immigrants with a positive CXR* **Intervention(s) description:** *Sputum culture for immigrant screening* **Comparator/ control(s) description:** *Sputum smear* **Baseline comparisons:** *TB confirmation by smear vs culture* **Study sufficiently powered?:** *NR*	**Primary outcomes:** *Proportion smear vs culture* **Secondary outcomes:** *Characteristics (age, sex, city etc.)* **Method of analysis:** *Proportion* **Modelling method and assumptions:** *NR* **Time horizon:** *2009-2012*	**Primary results:** - 80% (n = 97) negative smears - 20% (n = 25) positive smears *- 8/10 actual cases are being missed when sputum smear is the only diagnostic tool in asymptomatic patients with abnormal chest X-rays* **Secondary results:** *See characteristics*	**Limitations identified by author:** *NR* **Limitations identified by review team:** *Very limited study, not compared with symptoms, no notice about drug sensitivity* *Not an RCT* **Evidence gaps and/or recommendations for future research:** *RCT, wider analysis, , adjust for confoudners etc.* **Source of funding:** *NR* **Conflict of interests:** *None*

Applicability: +					

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *US* **Authors:** *Bell T.R. Molinari N.A.M., Blumensaadt S. et al.* **Year:** *2013* **Citation:** *Bell T.R. Molinari N.A.M., Blumensaadt S. et al. Impact of port of entry referrals on initiation of follow-ip evaluations for immigrants with suspected tuberculosis: Illinois. J Immigrant Minority Health (2013) 15:673-679* **Aim of study:** *the efficacy of referral processes at US POE* **Study design:** *non-research program evaluation:* *Comparing different types of referral for follow up versus a control group* **Quality score:** *+*	**Source population(s):** *Immigrants* **Eligible population:** *Immigrants with suspected TB* **Selected population:** *Immigrants with suspected TB arriving through all POE between 1.10.08-30.9.10 with final destination Illinois* **Excluded population:** *- Immigrants entered through Detroit, Honolulu or Minneapolis* *- reports with inconsistent or missing data* **Setting:** *US immigrants with suspected TB arriving at all Port-of-Entry's* **Sample characteristics:** *1512 immigrants with suspected TB arriving through all Port-of-Entry's* *- 1218 (81%) included in evaluation* *- Male : Female = 50.1%:49.8%* *- Mean age 42 years*	**Method of allocation:** *Place of destination* **Intervention(s) description:** *These four categories included 3 referral types and* *a group that received no referral serving as the referent or control group* **Comparator/ control(s) description:** *No referral* **Baseline comparisons:** *Number of days until follow up* **Study sufficiently - powered?:** *Yes*	**Primary outcomes:** *Difference between different referral types on domestic follow-up within 30 days of arrival* **Secondary outcomes:** *Difference between referral types in number of days elapsed before follow-up; from date of arrival into the United States until the date of initiating a TB follow-up evaluation, first clinic visit* **Method of analysis:** *- Pearson's and Cochran-Mantel–Haenszel Chi squared tests* *- Kaplan–Meier survival curves were generated to examine the time to evaluation initiation by the 3 referral types and no referral* *- To compare: Cox proportional hazard models was used* *- The effect of covariates was assessed using Wald Chi squared tests*	**Primary results:** *- 733/1218 (60%) initiated F/U* *- 489/1218 (40%) in 30 days* *- 441/489 (90 %) received any type of referral* **31 % receiving an appointment* **29 % provided a direct phone number* ** 30 % provided an indirect phone number.* *Initiation of follow-up evaluation within 30 days was significantly related to receiving any referral ($p<0.0001$) and referral category ($p>0.0001$).* *The proportion of immigrants who initiated follow-up within the first 30 days of arrival was greatest for those receiving a direct phone number (67 %), followed by those receiving appointments (53 %) then those receiving an indirect phone number (43 %). Only 11 % of immigrants receiving no referral initiated follow-up within 30 days.* **Secondary results:** *- median time to initiate follow-up was 20 days (range 1–602 days; Table 2).* ** Immigrants with any referral*	**Limitations identified by author:** *- constraints of the appointment-scheduling process, in that CQS staff had a limited number of available appointment times with the City of Chicago TB clinics* *- outcome data were available for only 81 % of immigrants resettling in Illinois, possibly limiting the representativeness of our findings.* *- it was not possible to distinguish between CQS referrals made in person during business hours versus by mail after business hours.* *- Those who received the referral in the mail may not have been so apt to initiate follow-up because they did not receive face-to-face counselling - the hazard ratios could be underestimated* *- not possible to control for other influences, such as pre-migration instructions received overseas and the quality of*

Applicability: ++	*- Majority of South-Eastern Asia (47.5%), Americas (25.0%) and Eastern Europe (8.2%), Eastern Asia (8.1%)* *- The majority (97.4%) departed from another country than their birth country*		**Modelling method and assumptions:** *- Multivariate analysis adjusting for covariates and potential confounders (jurisdiction of residence (City of Chicago, suburban Cook County or other Illinois county), region of birth, year of US arrival, age at US arrival, sex, overseas suspected TB status, and whether immigrants resided in a country other than their birth country before arriving in the United States)* *- Assumption that immigrants that enter via other POEs have had no referral* **Time horizon:** *1st of October 2008- 30th of September 2010*	*type showed a significantly lower median time to initiate follow-up compared with those who received no referral (16 vs. 69 days, respectively; Wilcoxon test = 12.9, p<0.0001).* *- Immigrants resettling in suburban Cook County and receiving a direct phone number had the shortest median time (14 days) and lowest maximum time (71 days) to initiation.* **<u>Conclusion:</u>** *immigrants receiving any referral initiated follow-up at 4 times the rate of those receiving no referral* *Those receiving a direct phone number had the highest rate of evaluation initiation and initiated follow-up evaluation at 7 times the rate of those receiving no referral* *No significant difference in rate of evaluation initiation was observed between those receiving a direct phone number and those receiving an appointment*	*information provided by different CQS staff.* *- referral type was determined by jurisdiction of destination, and it was therefore impossible to identify the independent effects of referral type and jurisdiction.* **Limitations identified by review team:** *- non-research program evaluation* *- small group of direct phone number* *- ?outcome of follow-up – did patients with symptoms come for follow-up sooner than patients without any symptoms* **Evidence gaps and/or recommendations for future research:** *- Different referral types in the same location of resettlement. As the place of resettlement might be a source of bias.* *- And randomisation per country of birth/departure (or TB incidence) as the information given in these countries might be of influence as well.* *- Evaluate the difference between face-to-face interview and referral via mail* *- What % of early follow-up appointments had active TB versus late follow-ups*

					- Or adjust for level of education **Source of funding:** *CDC* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *France* **Authors:** *Bernard C., Sougakoff W. Fournier A. et al.* **Year:** *2012* **Citation:** *Bernard C., Sougakoff W. Fournier A. et al. Impact of a 14-year screening programme on tuberculosis transmission among the homeless in Paris, Int J Tuberc Lung Dis 16(5):649-655* **Aim of study:** *To measures the impact of an active TB case finding programme on the transmission of TB among the homeless in Paris* **Study design:** *Observational study*	**Source population(s):** *Homeless* **Eligible population:** *All people that present to the shelter on the day of screening were invited to participate irrespective if the were regular or occasional users of the facility* **Selected population:** *28 shelter facilities with the highest number of beds or in which TB cases had already been identified were included in the study* **Excluded population:** *Shelters not having implemented the TB programme* **Setting:** *Homeless shelters Paris, France* **Sample characteristics:** *Not reported*	**Method of allocation:** - **Intervention(s) description:** *Active TB case-finding programme implemented in 28 shelters between end 1994 and 1997* *1 day active CXR screening, several sessions per year in each shelter with mobile X-ray equipment – if CXR abnormal – referred to hospital for further investigations* **Comparator/ control(s) description:** *Change over time, during implementation and after implementation* **Baseline comparisons:** *- TB screening* *- TB cases detected*	**Primary outcomes:** *Time trend of screening done, number of TB cases* **Secondary outcomes:** *Related cases - used RFLP genotyping to detect related cases* **Method of analysis:** *- Poisson regression analysis* *- Time trends in these 3-year moving average proportions were analysed using $\chi 2$ for trend analysis* **Modelling method and assumptions:** *NR* *The newly implemented TB programme has impact on the screening coverage and on the TB transmission* **Time horizon:** *1994 and 2007*	**Primary results:** *- 514 1-day active screening sessions were organised in the 28 shelters with around 22 000 CXRs performed* ** number of CXR/per year increased over the implementation period (1994-1997) and remained stable at around 2000 CXR's/year from 1998 to 2007 (the overall trend is an increase in no. CXR's/year) – no change in no. of beds at shelters* *- 313 TB cases were diagnosed in the homeless population: 179 shelter users, 134 non-shelter users* ** in shelter users the number of cases detected increased during the implementation of the programme between 1994-1997 and decreased progressively after 1997 (due to Rx and rules in some shelters – need a negative sputum sample or 2 weeks of Rx before returning to shelter)* ** non-shelter users fluctuated until 2000 and then decreased*	**Limitations identified by author:** *- observational study* *- some cases not notified as homeless* *- not sure if they received a sample of each person (lab)* *- identical strains may be the same for other reasons than recent transmission* *- should be cautious with the association between the decline in related cases and the intervention* *- no data on Rx completion* **Limitations identified by review team:** *- Unclear which percentage of people present at shelters agreed to participate*

Quality score: + **Applicability:** ++		**Study sufficiently powered?** *Yes*		**Secondary results:** *- 160/313 (51%) were related cases* *- related cases decreased steadily between 1997-2007* ** 1997-1999: crude average 14.3/year & proportion of related cases among all TB cases 75%* ** 2005-2007: 2.7/year (p<0.01); 30% (p<0.01)* *- related cases of all cases decreased significantly (p<0.01) but less in the homeless group not using shelters* ** 1997 4.3/year* ** 2007 2.7/years* *- non-related cases remained stable* *- no MDR-TB* *<u>1994:</u>* *- 58% of the homeless TB cases were related cases* *- related cases in homeless people using shelters: 88%* *- related cases in homeless people not using shelters: 41%* *<u>Conclusion:</u>* *TB screening programme has had a very positive impact on TB transmission in shelters* *- Slight indirect impact on non-shelter users*	*- Characteristics of the study population over time and possible confounders not assessed* *- Not RCT but comparison over time = important confounder* **Evidence gaps and/or recommendations for future research:** *RCT based research* **Source of funding:** *? Direction de l'Action sociale, de L'Enfance et de la Sante (DASES), a health institution supervised by the Paris city council* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**

Country: *Vietnam for immigration to US* **Authors:** *Chuke S.O., Yen N.T.N., Laserson K.F. et al.* **Year:** *2014* **Citation:** *Chuke S.O., Yen N.T.N., Laserson K.F. et al. Tuberculin Skin Tests versus Interferon-Gamma Release Assays in Tuberculosis screening among immigrant visa applicants. Tuberculosis Research and Treatment, 2014. ID 217969* **Aim of study:** *Prevalence of MTBI among immigrants* **Study design:** *Comparison of different tests* **Quality score:** - **Applicability:** +	**Source population(s):** *Migrants* **Eligible population:** *Vietnamese migrants to the US* **Selected population:** *Subjects were recruited on Wednesday among adults presenting for immigrant medical examinations at Cho Ray Hospital in Ho Chi Min City, Vietnam* **Excluded population:** *QTF-G not completed* **Setting:** *Clinic for immigrant medical examinations at Cho Ray Hospital in Ho Chi Min City, Vietnam* **Sample characteristics:** *Vietnamese adults who want to migrate to the US.* *- Mean age 38.8 y.o.* *- M:F = 67.6%:32.4%* *- 99.1% from Vietnam* *- TB symp 0.2%* *- BCG 41%* *- HIV +ve 0.6%* *- 12 positive sputum* *Sample size: 1246*	**Method of allocation:** *None* **Intervention(s) description:** *Subjects were recruited on Wednesday among adults presenting for immigrant medical examinations at Cho Ray Hospital in Ho Chi Min City, Vietnam* *Blood samples for QTF and QTF-G taken before Mantoux (read 2-3 days later)* *Mantoux readers were blinded for QTF(-G) results* *Mantoux +ve >10 mm* *QTF(-G) interpreters blinded for other test results* *CXR suggestive of TB = 3x sputum for AFB and culture* *CXR were interpreted by physicians blinded for TST, QTF(-G) results but were aware of clinical findings* **Comparator/ control(s) description:** *CXR, Culture, smear* **Baseline comparisons:** *Nativity, gender, medical Hx, examination findings, HIV results, CXR findings, prior TB Hx (Rx, exposure, symptoms, BCG vaccination)*	**Primary outcomes:** *Prevalence of MTBI* **Secondary outcomes:** *test agreement, PPV, NPV* **Method of analysis:** *PPV, NPV (predictive value statistic that utilized the Wald procedure).* *McNemar test to compare estimates of prevalence* *Agreement beyond chance was assessed using Cohen's Kappa coefficient (κ) with a $\kappa > 0.75$ representing excellent agreement,* 0.40-0.75 representing fair to good agreement, and <0.40 representing poor agreement *Hosmer-Lemeshow test* **Modelling method and assumptions:** *- Multivariate models were created using factors with values < 0.2* *- univariate analysis <0.05 in stepwise logistic regression* *until the best fitting, parsimonious model was identified* *- No interactions between subject characteristics were considered to be of interest a priori.* **Time horizon:** *12 June 2002 – 12 March 2003*	**Primary results:** *This study demonstrated that substantially fewer adult immigrant applicants had evidence of TB on CXR (22%) than had a positive TST (57.9%) or a positive QFT-G (28.3%).* **Secondary results:** *Agreement between TST and QFT-G, CXR and TST, and CXR and QFT-G was poor* *Test agreement:* *- TST & QFT-G: 59.4%* *- CXR & TST: 50.1%* *- CXR & QFT-G: 63.5%* *Agreement beyond chance was poor.* *PPV:* *- TST + CXR: 25.9% (95% CI: 22.6%-29.2%)* *- QFT-G + CXR: 25.6% (95% CI: 21.0%-30.1%)* *NPV:* *- TST + CXR: 83.8% (95% CI: 80.5%-87.1%)* *- QFT-G + CXR: 79.8% (95% CI: 77.0%-85.6%)* *PPV for TST and QFT-G for a positive CXR were similar (p = 0.87) but NPV for TST was greater than the NPV for QFT-G (p < 0.01).* *Neither TST nor QFT-G performed well as predictors of an abnormal CXR consistent with TB in this population (low PPV, high NPV). Too few cultures results were available to assess*	**Limitations identified by author:** *- selection bias could have occurred due to restriction of enrollment to applicants presenting on Wednesday* *- recall bias (questionnaire) BCG vaccination (41% versus 93.7% in population)* **Limitations identified by review team:** *- What was used as the gold standard* *- small number of culture positives* *- low % of sputum tests* *- statistical methods weak; not mentioned what confounders were inserted in the multivariate model* **Evidence gaps and/or recommendations for future research:** *All patients with a CXR suggestive of TB should have a sputum smear/ culture as well to use as gold standard* **Source of funding:** *CDC* **Conflict of interests:** *None*

		Study sufficiently powered?: *Low number of sputum confirmed TB cases*		*the sensitivity of TST or QTF-G for culture confirmed TB*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *Portugal* **Authors:** *Duarte R., Santos A., Mota M. et al.* **Year:** *2011* **Citation:** *Duarte R., Santos A., Mota M. et al. Involving community partners in the management of tuberculosis among drug users.Public Health. 2011;125: 60-62* **Aim of study:** *To evaluate the effect of the intervention on diagnosis of TB and Rx compliance* **Study design:** *Retrospective review of records* *Compare before and after intervention (2004)* **Quality score:** -	**Source population(s):** *IVDU in Vila Nova de Gaia, Portugal* **Eligible population:** *IVDU in Vila Nova de Gaia, Portugal* *<u>Population:</u> 290,000* **Selected population:** *Screening and treatment records for all IVDU visiting Chest Disease Centre (CDP) between 2001-2007* **Excluded population:** *NR* **Setting:** *All IVDU screened and treated at the outpatient TB clinic (Chest Disease Centre) 2001-2007 were reviewed* **Sample characteristics:**	**Method of allocation:** *Before and after 2004 – intervention was implemented in 2004* **Intervention(s) description:**	**Primary outcomes:** *Diagnosis of active TB, treatment compliance & abandonment before and after intervention* **Secondary outcomes:** *OR and 95% CI's to measure association* **Method of analysis:** *OR and 95% CI's* **Modelling method and assumptions:** *Improve early identification and treatment of drug users with TB* **Time horizon:** *2001-2003 intervention* *2005-2007*	*Primary results:*	**Limitations identified by author:** *- Not a controlled trial – risk for bias* *- What part of the intervention contributed more* **Limitations identified by review team:** *- Retrospective design = risk of bias* *- Methods not well described* *- What percentage did not come for screening (how many people recruited for screening)* *- Difference in time zone = risk for confounders, might have been on the political agenda, been on the news etc. = bias* *- low precise estimates of effects (indicated by wide 95% CI's) probably due to small sample size* **Evidence gaps and/or recommendations for future research:**

Applicability: ++	*2001-2003:* *- 125 IVU @CDP* *- 52 screened (100% male, mean age 32 years)* *- 73 for sympt or following discharge with diagnosis TB* *2005-2007:* *- 465 screened (86% male, mean age 36 years)* *- 30 for sympt. or following discharge with diagnosis TB* **Study definitions:** *Active TB: culture M. tuberculosis or clinical & radiology criteria* *Latent TB: asymptomatic individuals with normal chest radiography and positive TST (TST > 5 mm in immunocompromised persons, TST > 10 mm in immunocompetent persons).*	*After 2003:* *Intervention to improve early identification and Rx of drug users with TB.* *The key partners (outpatient TB clinic, drug users support centres, shelters and street teams, local public health department and the local hospital) identified IVDU in their population* *- promotion of health-seeking behaviour* *- notification card for screening in CDP* *- elimination of potential barriers:* ** street teams offered free transport* **all care at CDP free of charge* *- encouraged referral but tried to manage TB screening locally* *- seriously ill: immediate referral to CDP/local hospital (with transport and attendance.* *At CDP:* *- Screening: symptom questionnaire, TST & CXR: annual screening/after contact/symptoms* *- DOTS at CDP, combined with other medical Rx/ drug abuse Rx* *- CDP offered HIV testing in case of active TB* **Comparator/ control(s) description:**		*2001-2003:* *- 125 IVU @CDP* *- 52 screened (100% male, mean age 32 years)* *- 73 for symptoms or following discharge with diagnosis TB* **41.6% no symptoms* **65.6% (82)active TB –13.4% (11) identified by screening* **47.6% (39/82) poor compliance* **35.4% (29/82) stopped Rx* ** 76.4% did not finish Rx correctly* *- Total TB cases in VNdG 2001-2003: 515 – 15.9% (82) IVDU* *- Deaths: 32 – 15 IVDU (18.3% TB deaths among IVDU)* *- TB/HIV co-infection: 63 (71%)* *2005-2007: (after implementation of the programme)* *- 465 screened (86% male, mean age 36 years)* *- 30 for sympt or following discharge with diagnosis TB* ** 94% no symptoms* **11.9% (59) active TB – 61% (36) identified by screening* ** 23.7% (14) poor compliance* ** 10.2% (6) stopped Rx* **34.5% did not finish Rx correctly* **13.6% died* *- Total TB cases in VNdG 2005-2007: 386 – 15.3% (59) IVDU* *- Deaths: 19 – 8 IVDU (13.6% TB deaths among IVDU)* *- TB/HIV co-infection: 37 (64%)* *Conclusion:* *the number of screened drug users had increase, therapy was available to a higher proportion*	*- Case-control trial to compare 2 different cities (one with intervention other without intervention* *- Check cost-effectiveness* **Source of funding:** *None* **Conflict of interests:** *None* **Ethical approval**: *Yes, approved by the CDP de Vila Nova de Gaia body*

		Before 2003: *- IVDU referred to CDP with a diagnosis of TB after Dx from hospital* *– Rx was not compulsory* *– to improve compliance: info was provided, Rx of family, psychosocial support, full Rx, transport & free breakfast.* *- No active screening policy* **Baseline comparisons:** *Number of TB cases screened* **Study sufficiently powered:** NR but wide 95% CI's		*of TB cases and active TB treatment compliance had improved significantly* **Secondary results:** *- IVDU screened for TB without symptoms: OR 21.76; 95%CI 13.03-36.33* *- IVDU with active TB: OR 10.1; 95%CI 4.44-23.0* *- poor compliance: OR 0.34; 95%CI 0.16-0.72* *- Rx stopped OR 0.21; 95%CI 0.08-0.54* *- %IVDU under TB cases OR 0.95; 95%CI 0.66-1.37* *- TB deaths among IVDU OR 0.7; 95%CI 0.28-1.78* *-TB/HIV co-infection OR 1.37; 95%CI 0.68-2.78*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *USA* **Authors:** *George S.A., Ko C.A., Kirchner H.L. et al.* **Year:** *2011* **Citation:** *George S.A., Ko C.A., Kirchner H.L. et al. The rol of chest radiographs and tuberculin skin test in tuberculosis screening of internationally adopted children.*	**Source population(s):** *Migrant children* **Eligible population:** *Internationally adopted children (IAC) entering the US* **Selected population:** *Asymptomatic IAC at the Adoption Health Services (AHS) of Rainbow Babies and Children Hospital in Cleveland, Ohio.* *TST done within 6 months of arrival in the US* **Excluded population:**	**Method of allocation:** *NA* **Intervention(s) description:** *- Chest X-rays to rule out pulmonary TB when TST indurations are >5 mm but treat for LTBI when TST indurations are >10 mm.* *- TST <5 mm within 3/12 of arrival need repeat TST at 6/12 if false negatives due to malnutrition* *- CXR was marked: normal, abnormal but not TB or TB*	**Primary outcomes:** *To evaluate the clinical usefulness of using a 5-mm TST cut point as the threshold beyond which further chest radiographic screening for TB disease is done in asymptomatic IAC* **Secondary outcomes:** *the relationship between documented chest radiograph readings and TST indurations in IAC* **Method of analysis:** *- frequency and percentages for*	**Primary results:** *No indication to complete chest radiographs in IAC with 5mm<TST<10mm as this TST induration range does not identify a group of children with increased risk for LTBI or progression to TB.* *- 35% (193 of 544) had TST induration>5 mm* *- 103 children (53.4%) had 5mm<TST<10mm and 90 children (46.6%) had TST>10 mm* *- Normal CXR in 71.8% and 78.9%* *- 1% (1 of 103) of the group with*	**Limitations identified by author:** *- Subjectivity of CXR reading for TB* **Limitations identified by review team:** *Potential important confounders are not considered; BCG vaccination status, socio-economic status* *HAZ could as well be caused by the outcome (active TB); I think it may lie in the causal pathway*

Pediatr Infect Dis J 2011;30:387-391 **Aim of study:** *To examine the clinical utility of tuberculin skin testing (TST) and subsequent chest radiograph screening for TB disease in recently immigrated, asymptomatic internationally adopted children* **Study design:** *Prospective cross-sectional study* **Quality score:** *+* **Applicability:** *-*	*Incomplete documentation (3.9%)* **Setting:** *Adoption Health Services (AHS) of Rainbow Babies and Children Hospital in Cleveland, Ohio* **Sample characteristics:** *Children from Russia, China, Guatemala and other countries* *Size: 566*	**Comparator/ control(s) description:** *Other TST induration groups* **Baseline comparisons:** *TB diagnosis* **Study sufficiently powered?:** *No, small group of CXR's*	*categorical variables* *- mean, standard deviation, and range for continuous variables* *- comparison between TST induration groups Pearson _2 statistic and analysis of variance (ANOVA)* *- Multiple logistic regression was used to investigate the relationship between TST induration and demographic and birth characteristics. - odds ratios (ORs) & 95% confidence intervals (CIs).* **Modelling method and assumptions:** *Multivariate regression using predefined co-variates sex, age, country of origin and HAZ. No other confounders considered.* **Time horizon:** *between August 2000 and June 2009*	*5mm<TST<10 mm had CXR's that were "Abnormal, Consistent with TB" compared with 3.3% (3 of 90) of those with TST>10 mm. → none had final diagnosis TB* *- Both groups had 6 children with abnormal CXR not TB* *- 29 children had CXR done somewhere else = no result (21 vs 8)* *- 3 children had no CXR done (1 vs 2)* **Secondary results:** *- There were insufficient counts to assess the association between radiographic results and TST induration groups, gender, or birth country* *- Children with a TST induration >10 mm were older* *- Children with TST induration >10 mm were more stunted (chronically malnourished) – no association with stunting (severely malnourished, demised immune responds)* *- birth country was associated with TST>10 mm (p= 0.0228) → Guatemala and Russia were kore than 2x more likely to have TST >10 mm (?bias due to large group or BCG variant used in these countries)*	*No information on potential bias due to missing data* **Evidence gaps and/or recommendations for future research:** *Larger study needed, with more information on important confounders* **Source of funding:** *NR* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**

Country: *Italy* **Authors:** *Girardi, E., Palmieri F, Angeletti C. et al.* **Year:** *2012* **Citation:** *Girardi, E., Palmieri F, Angeletti C. et al., Impact of previous ART and of ART initiation on outcome of HIV-associated tuberculosis. Clinical & Developmental Immunology, 2012.* ***2012****: p. 931325* **Aim of study:** *To estimate the impact of cART on TB outcome* **Study design:** *Multicenter, prospective, observational study* **Quality score:** *+* **Applicability:** *+*	**Source population(s):** *HIV infected individuals* **Eligible population:** *HIV infected individuals in Italy* **Selected population:** *HIV infected individuals presenting to one of the 96 Italian hospitals* *- >18 years of age* *- confirmed HIV infection* *- diagnosed with tuberculosis* **Excluded population:** *NR* **Setting:** *HIV +ve patients diagnosed with TB presenting to Infectious disease hospitals in Italy* **Sample characteristics:** *- 271 HIV-infected patients* *- M:F = 199:47* *- 48% intravenous drug users* *- 34% foreign born* *- 25 (9.22%) did not start tuberculosis treatment (5 transferred-out and 20 lost to follow up immediately after diagnosis)* *- 246 patients included* *- 80.2% male* *- median age: 36.9 years (21.27–76.03)* *- 160 culture confirmed TB (22 DR-TB, 4 MDR-TB)* *- Median time from first*	**Method of allocation:** *NA* **Intervention(s) description:** *The effect of cART on TB outcome* **Comparator/ control(s) description:** *cART naïve* **Baseline comparisons:** *TB outcome, (success, failure, death)* **Study sufficiently powered?:** *NR*	**Primary outcomes:** *The impact of cART on TB outcome* **Secondary outcomes:** *The impact of use of cART during TB treatment on death rate of HIV-infected patients with TB* **Method of analysis:** *- Descriptive statistical methods* *- $\chi 2$ or Fisher's Exact Test, as appropriate, were used to compare proportions.* *- Odds ratios (ORs) with the associated 95% confidence intervals (CI) were calculated to measure the association between variables and treatment outcome* **Modelling method and assumptions:** *- Polytomous logistic regression, we analyzed association of baseline characteristics associated with outcome* *- Poisson regression to investigate the impact of cART on mortality rate - presented as mortality rate ratios + 95% CI's* **Time horizon:** *NR – 15 month period*	**Primary results:** *<u>TB treatment outcome:</u>* *- 130/246 (52.8%) successful – 75 (30.5%) cured & 55 (22.4%) completed treatment* *- 80/246 (32.5%) unsuccessful outcome – 44 (17.9%) LoF in a median time of 1 month, 25 (10.2%) defaulters, 9 (3.7%) transferred out, 2 (0.8%) faulures* *- 36/246 (14.6%) died a median time of 2 months after starting TB treatment* *<u>Multivarianle polytomous logistic regression:</u>* *- not being ART-naïve was associated with an increased probability of unsuccessful outcomes* *- foreign born was associated with a 3x increase of the risk of unsuccessful outcomes (OR: 3.38, 95% CI: 1.38–8.29, p = 0.008)* *- also for IVDU* *<u>Risk of death associated with:</u>* *- IVDU* *- lower CD4 count at time of TB diagnosis* *- MDR-TB* *<u>cART during TB treatment:</u>* *- 151 (61.4%) received cART and TB treatment concurrently* ** 62 were already on cART at TB diagnosis (median of 24 months on ART)* ** 89 started cART during TB treatment: 56 (62.9%) in the initial phase and 33 (37.1%) in the continuation phase* *- 21 patients were not ART-naive but not on ART at TB diagnosis*	**Limitations identified by author:** *- No clinical details to evaluate severity of TB in patients* *- Couldn't determine if ART-naive had virological treatment failures and/or antiretroviral resistance at the time of tuberculosis diagnosis* *- high % of patients abandoned treatment may have affected the analysis of factors associated with death* *- study was conducted on patients treated relatively early in the cART era, and thus the conclusions on the effect on new cART regimens may not necessarily be applicable* **Limitations identified by review team:** *Harms, like IRIS, side effects of cART etc not assessed* **Evidence gaps and/or recommendations for future research:** *- Include history of failing to adhere to cART* *- TB history to be included* *- A study to examine the TB prevention due to cART* **Source of funding:** *Italian Ministry of Health-Progetto AIDS* **Conflict of interests:** *NR*

	date of HIV seropositivity was 36.9 months (0–201.3) *- 96 (39%) were not ART-naive at the time of TB diagnosis* ** 34 received ART for a median of 13.5 months (1–86), not in the 3 months preceding TB diagnosis* ** last ART regimen included a PI in 20 patients and a NNRTI in 11 patients* *- Baseline median CD4 count: 120.5/mmc (0–1111)* *- median VL (calculated in 241 patients): 4.94 log copies/mL.* *- At least 1 AIDS defining illness disease was recorded in 60 (24.4%) patients*			**Secondary results:** *-36 deaths of the 161.2 person-years (PY) observed = an overall mortality rate of 22.3 per 100 PY (95% CI: 16.1–31.0).* *- 17/36 were not ART-naive* *- 7/36 were ART-naive and started cART during TB treatment* *- 12/36 never started cART.* *<u>Multivariable analysis</u>* *- cART during TB treatment significantly reduced the risk of death (IRR 0.14, 95% CI 0.06–0.30, p < 0. 001)* *- not being ART-naive at TB diagnosis > 4x increase in the same risk (IRR 4.04, 95% CI 1.09–14.96, p = 0.037)* *<u>Risk of death was associated with:</u>* *- lower CD4 cell count* *- age ≥ 40 at diagnosis* *- MDR-TB*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *Germany (Frankfurt/Main)* **Authors:** *Goetsch U., Bellinger O.K., Buettel K.L., Gottschalk R.* **Year:** *2012*	**Source population(s):** *Homeless & IVDU* **Eligible population:** *Homeless & IVDU recruited from homeless and drug services in Frankfurt/Main* **Selected population:**	**Method of allocation:** *NA* **Intervention(s) description:** *Community health worker educated staff and users at services for homeless and IVDU about TB transmission and promoted*	**Primary outcomes:** *Feasibility and sustainability of a TB programme focussing on TB education and voluntary X-ray investigation in homeless and IVDU* **Secondary outcomes:**	**Primary results:** *It is feasible when included in already existing public health services* **Secondary results:**	**Limitations identified by author:** *- selection bias, illegal immigrants might avoid authorities* *- small number of TB patients makes it difficult to say anything about age and gender differences*

Citation: *Goetsch U., Bellinger O.K., Buettel K.L., Gottschalk R. Tuberculosis among drug users and homeless persons: impact of voluntary X-ray investigation on active case finding Infection;2012:40:389-395* **Aim of study:** *To evaluate the feasibility and sustainability of the program, its coverage and both the case-finding rates and characteristics of cases. Also to assess the treatment outcomes* **Study design:** *Before and after comparison* **Quality score:** - **Applicability:** +	*All subjects seen at the Public Health Department for CXR and fulfilled the criteria for homeless (stayed at shelter for >2 nights) /IVDU (attend day-care facilities, night shelter for IVDU or needle exchange programme)* **Excluded population:** *Patients with TB symptoms detected in clinics and were notified throught the Protection against Infection Act* **Setting:** *CHW went to services to promote CXR – CXR performed at Public Health Department* **Sample characteristics:** *4529 CXR's in 3477 people* *- 66% homeless* *- 34% IVDU* <u>Homeless:</u> *- 40.9 years ± 12.5 years* *- 90.1% male* *- 29.65 foreign born* <u>IVDU:</u> *- 35.8 years ±8.3 years* *- 76.2% male* *- 28% foreign born (increased over study period → 2002: 15%, 2007:37%)*	*voluntary CXR at Public Health Department 1x/year or at least 1x/2years* *Community Health Worker obtained the medical history through standardised questionnaire* *CXR read by TB physician – referral and F/U test in a clinic could be initiated immediately* *Suspicion for active TB – CHW took care of further diagnostics and F/U Active TB needed hospitalisation for Rx* *CHW kept contact with doctors/social workers 2x/month later monthly Contact tracing in shelter* *HIV was only notified in active TB patients* **Comparator/ control(s) description:** *Before intervention – no CHW who gave TB education and promoted CXR* **Baseline comparisons:** *Coverage of CXR screening before and after intervention* **Study sufficiently powered?:** *Low number of active TB cases*	*Estimate the coverage of the programme, assess other risk factors and determine TB rates & Rx outcome in these 2 groups* **Method of analysis:** *- t-test or analysis of variance for continuous variables* *- chi-square test or Fisher's exact test for categorical data* **Modelling method and assumptions:** *- Multivariate logistic regression effect of risk groups, birth place, age & gender* **Time horizon:** *1 May 2002- 30 April 2007*	*- No. CXR: 10/month in homeless & 9/month in IVDU* *After intervention 46/month in homeless & 25/month in IVDU* *-Coverage: screening 1x/2 years: 18% of IVDU& 26% of homeless and 10% and 15% every year (based on IVDU & homeless group between 6416 and 9,000 in Frankfurt/Main)* *- Chao's heterogeneity model: 18-26.3%* *1CXR/2 years (2002-2004: 18.0%, 2003-2005: 19.3%, 2004-2006: 26.4%, 2005-2007: 23.4%) and 10-15% CXR/year (2002-2004: 10.0%, 2003-2005: 10.7%, 2004-2006: 15.0%, 2005-2007: 23.4%)* *- Case finding:* *39 TB cases in 5 years: 14 IVDU & 25 homeless* *= 8.7% of total TB cases in Frankfurt* *19 cases smear +, 7 smear –ve but culture +ve, 13 cases clinical/radiological diagnosis* *- case finding rate 861/100 000 CXR's* *- IVDU 10/14 HIV+ve, homeless 1/25 HIV+ve* *- 76.3% (29/38) completed Rx* **5 needed admission because of non-compliance (3IVDU, 2 homeless)* *- 5 died of other causes than TB (3 homeless and 2 IVDU)* *- 4 stopped Rx (lack of compliance) – 10.5%* *- No difference in Rx outcome between IVDU & homeless*	*- no data on length of IVDU and homelessness* *- the impact of HIV can't be estimated* *- unknown fluctuations of the study population make the denominator unstable* **Limitations identified by review team:** *- Patients had to travel to the public health department* *- selection bias as it is voluntary and therefor not everyone comes to the screening, maybe only the sick ones* *- comparison over time, important confounder* *- not adjusted for distance from service to public health department* **Evidence gaps and/or recommendations for future research:** *Use a control group and use mobile CXR unit to increase screening* **Source of funding:** *NR* **Conflict of interests:** *None*

				- No difference in foreign borne or nationals (selection bias – avoid authorities)	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *Norway* **Authors:** *Harstad I., Henriksen A.H., Sagvik E.* **Year:** *2014* **Citation:** *Harstad I., Henriksen A.H., Sagvik E. Collaboration between municipal and specialist public health care in tuberculosis screening in Norway. BMC Health Services Research.2014; 14:238* **Aim of study:** *Improve follow-up of patients with positive TB screening results through intervention that included increasing the collaboration between municipal and specialist public health care and new routines for summoning patients* **Study design:** *Non-randomized study comparing before-and-after intervention*	**Source population(s):** *People living in the Sor-Trondelag county who underwent TB screening at the 2 public health services* **Eligible population:** *Patients with positive TB screening referred to local TB clinic* **Selected population:** *All patients referred from the 2 public health centres to the TB clinic between Sep 2009 and June 2012* **Excluded population:** *Patients with alarming symptoms or grossly abnormal X-rays* **Setting:** *Patients suspected of TB referred to the Pulmonary Out-patient Department (POPD) of the St. Olavs University Hospital, Trondheim, Norway* **Sample characteristics:** *VICO (1st public health centre)* *<u>134 control group</u>* *- 30 contact tracing*	**Method of allocation:** *Time based: Inclusion controls: September 2009 – August 2010 for VICO; October 2010 – April 2011 for RHC* *Inclusion intervention: July 2011 – June 2012 for VICO; September 2011 – June 2012 for RHC* **Intervention(s) description:** *Migrants in Norway are screened by Mantoux, followed by CXR ± IGRA. In the old system they received a letter for follow-up appointment* *<u>2 problems identified:</u>* *- high rate of no show* *- long time between screening and appointment* *<u>Main intervention:</u>* *1. change practice of summoning patients for follow-up* *- letters* *- patient contacted by phone, directly, through a contact person, or through a translator.*	**Primary outcomes:** *- Frequency of patients who attended their first consultation at the TB clinic* *- The time from screening in the municipality to examination at the TB clinic* **Secondary outcomes:** *- Final attendance* **Method of analysis:** *Frequencies with proportions and 95% confidence intervals* **Modelling method and assumptions:** *Medians compared across independent groups by non-parametric test (Mann-Whitney test) using Median Test for k samples $p < 0.05$ statistically significant*	**Primary results:** *Attendance increased from:* *- 97/134 (72%) to 109/123 (89%) in VICO* *- 28/46 (61%) to 55/59 (93%) in RHC* *Time from screening to examination at the hospital reduced from:* *- median 30 to 10 weeks in VICO ($p < 0.001$)* *- median 15 to 8 weeks in RHC ($p = 0.04$).* **Secondary results:** *Final attendance increased from:* *- VICO 115/134 (86% [95% CI 80–92%]) to 115/123 (93% [95% CI 89–98%])* *- RHC 44/46 (96% [95% CI 90–100)%] to 58 (98% [95% CI 95–100%])* *Attendence at first consultation increased from:* - VICO 97/134 (72% [95% CI 65-80%]) to 109/123 (89% [95% CI 83-94]) RHC 28/46 (61% [95% CI 47-75%]) to 55/56 (93% [95% CI 87-100%])	**Limitations identified by author:** *- For the control group: information was not available at the municipality it was retrieved from the hospital: data could be missing or registered in a different way at different levels = risk of bias* *- Yearly differences in patients' country of origin* **Limitations identified by review team:** *- Sparse reporting of results* *- No description or adjusting for possible confounders (country of origin)* *- Small sample size* **Evidence gaps and/or recommendations for future research:** *Adjust for country of origin, large sample size* **Source of funding:** *The Central Norway regional Health Authority funded the project.*

Quality score: - **Applicability:** +	*- 47 family reunion* *- 19 labour migrants* *- median 30 y.o. (16-74)* *- 82 females (61% - 95% CI 53-69%)* *Countries of origin* *- 49 different countries* *- 30 Norway* *- 11 Philippines* *- 10 China* *<u>123 intervention group</u>* *- 38 family reunion* *- 16 contact tracing* *- 28 labour migrants* *- 13 students* *- median age 29 y.o. (19-77)* *- 86 females (70% - 95% CI 62-78%)* *Country of origin* *- 42 different countries* *- 20 Philippines* *- 15 Norway* *- 8 Vietnam* *Higher % of LTBI in intervention group* *RHC (2nd public health centre)* *- asylum seekers* *- refugees* *<u>46 in control group:</u>* *15 different countries* *- 12 Eritrea* *- 10 Somalia* *- 4 Liberia* *- 3 Ethiopia* *- median age 28,5 y.o. (17-59)* *- 19 female (41%- 95% CI 27-56%)*	*2. - Change timing of the tests to reduce number of tests done at POPD appointment* *- Reduce number of blood samples drawn* **Comparator/ control(s) description:** *Same population, pre-intervention (retrospective record check)* **Baseline comparisons:** *Effect of intervention by comparing pre- and post-intervention* **Study sufficiently powered?:** *Not described*	**Time horizon:** *September 2009 – June 2012* *VICO (1st public health centre)* *Controls: Sep. 2009- Aug. 2010* *Intervention group: July 2011-June 2012* *RHC (2nd public health centre)* *Controls: Oct. 2010-April 2011* *Intervention group: Sep. 2011-June 2012*		**Conflict of interests:** *None declared*

	59 in intervention group: *12 different countries* *- 20 Somalia* *- 8 Ethiopia* *- 6 Afghanistan* *- 6 Eritrea* *- 6 Myanmar* *- median age 27 y.o. (16-71)* *- 29 females (49%- 95% CI 36-62%)*				

Study details	**Population and setting**	**Intervention/comparator**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *UK* **Authors:** *Jit M. Stagg H.R., Aldridge R. et al.* **Year:** *2011* **Citation:** *Jit M. Stagg H.R., Aldridge R. et al. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ 2011;343:d5376* **Aim of study:** *To assess the cost effectiveness of the Find and Treat service for diagnosing and managing hard to reach individuals with active tuberculosis in London*	**Source population(s):** *Hard to reach individuals* **Eligible population:** *Hard to reach individuals with active pulmonary tuberculosis* **Selected population:** *Hard to reach individuals with active pulmonary tuberculosis screened or managed by the Find and Treat service* **Excluded population:** *- cases of extrapulmonary tuberculosis* *- latent tuberculosis* *- suspected tuberculosis* *- cases merely receiving prophylaxis (and hence unlikely to have active tuberculosis)* *- cases for which the diagnostic delay could not be calculated*	**Method of allocation:** *NA* **Intervention(s) description:** *All individuals are screened on voluntary basis.* *1. Mobile screening clinic X-ray visited locations where high risk groups could be found (homeless shelters, drug treatment centres, criminal services, street outreach etc.)* *2. raise awareness* *3. under take case holding* *4. provide support for treatment completion (supported by peer workers)* **Comparator/ control(s) description:** *Controls: passively detected control cases with active pulmonary*	**Primary outcomes:** *Incremental costs, quality adjusted life years (QALYs), for the Find and Treat service.* **Secondary outcomes:** *cost effectiveness ratios for the Find and Treat service* **Method of analysis:** *NR* **Modelling method and assumptions:** *- discrete, multiple age cohort, compartmental model to model a population of individuals with active tuberculosis* *4 groups:* *- active untreated tuberculosis* *- active treated tuberculosis with up to 125 days of*	**Primary results:** *The model estimated that, on average, the Find and Treat service identifies 16 and manages 123 active cases of tuberculosis each year in hard to reach groups in London. The service has a net cost of £1.4 million/year and, under conservative assumptions, gains 220 QALYs. The incremental cost effectiveness ratio was £6400-£10,000/QALY gained (about €7300-€11,000 or $10,000-$16,000 in September 2011).* *- 22.9% of patients detected by the mobile screening unit with the longest delays between symptom onset and treatment presentation were unlikely to present for treatment without the activities of the Find and Treat service* *- 35.4% of mobile screening unit patients were asymptomatic on detection, and hence would not*	**Limitations identified by author:** *- absence of a trial randomising tuberculosis cases to be either managed or not managed by the Find and Treat service* *- the service also manages extremely hard to reach individuals, who are often already lost to follow-up at the time of referral or who would never present for care without the mobile screening unit. Hence the comparison of cases with retrospective controls probably underestimates the incremental benefit of the service, although we cannot be certain without a randomised study* *- did not incorporate secondary transmission into the economic*

Study design: *Economic evaluation using a discrete, multiple age cohort, compartmental model of treated and untreated cases of active tuberculosis.* **Type of economic analysis:** *Cost-effectiveness* **Economic perspective:** *healthcare taxpayer perspective* **Internal validity:** *Yes* **Quality score:** *+* **Applicability:** *+*	*- cases younger than 16 years* **Setting:** *London, United Kingdom.* **Sample characteristics:** *- 48 mobile screening unit cases* *- 188 cases referred for case management support* *- 180 cases referred for loss to follow-up* *- 252 passively presenting control cases* **Economic analysis data source:** *Find and Treat database for information (including risk factors and clinical information) of individuals, diagnosed with PTB (between Sep 2007- Sep 2010)* *Passive cases from the Health Protection Agency between Jan 2009 and Aug 2010.* *Risk factors and clinical information for the controls were obtained from the enhanced tuberculosis surveillance system.*	*tuberculosis (individuals who presented to London tuberculosis services of their own accord without screening and referral to the Find and Treat service* *- notified to the Health Protection Agency's enhanced tuberculosis surveillance system between 1 January 2009 (when the system began recording risk factor information) and 9 August 2010.* *Controls were age matched with actively detected cases (within five year age categories) and that displayed one or more risk factors (a history of homelessness or imprisonment, drug or alcohol abuse, or mental health problems).* **Baseline comparisons:** *Compared:* *- having no Find and Treat service,* *- having only one part of the service (the mobile screening unit or the case management component)* *- having both parts of the service* **Study sufficiently powered:** *NR but a small number of PTB cases in the Find and Treat group*	*continuous treatment* *- active treated tuberculosis with more than 125 days of continuous treatment* *- lost to follow-up* *4 final outcomes (from which they do not leave):* *- completion of treatment* *- death due to tuberculosis related causes* *- death due to other causes* *- other final outcomes that the Find and Treat service is not expected to change (such as patients being transferred out of London or stopping treatment for clinical reasons).* *<u>Assumptions:</u>* *- the cost of a new mobile unit £600 000 were added to the costs of the first year of the service, with discounted costs and outcomes totalled over five years* *- costs of £8300 and £75000 for treatment of DS-TB and MDR-TB* *- only 50% of asymptomatic cases with a positive result from the mobile screening unit would progress to symptomatic disease* *- Find and Treat cases would be lost to follow-up at the same rate as enhanced tuberculosis surveillance controls (17.2% per year) in the*	*have presented for treatment without the unit.* *- Once on treatment, mobile screening unit cases managed by the Find and Treat service had a much lower risk of loss to follow-up than passively presenting controls (loss to follow-up probability after one year: 2.1% for cases, 17.2% for controls)* *- cases referred to Find and Treat because of complex case management issues had higher rates of completing treatment (61.2% after one year) and lower rates of loss to follow-up (3.3% after one year) than controls* **Secondary results:** *- every year the service has a net cost of £1.4 million and gains 220 QALYs* *- Incremental cost effectiveness of the Find and Treat service was £6,400/QALY gained* *- both components of the service are cost-effective at the same threshold. The mobile screening unit had an incremental ratio of £18,000/QALY gained, whereas the case management component had an incremental ratio of £4,100/QALY gained (In the most unfavourable (and highly unlikely) scenario, which combined all the unfavourable assumptions, the mobile screening unit and case management components had incremental ratios of £26,000/QALY gained and £6,800/QALY gained, respectively)* *0.5% of mobile screening unit*	*evaluation, even though the mobile screening unit in particular probably averts several secondary cases by finding highly infectious individuals.* *- did not measure the effect of the Find and Treat service on reducing the likelihood of patients developing and transmitting acquired drug resistance (as a result of poor treatment adherence). Drug resistance increases the duration and costs of treatment, as well as the risk of severe disease, thus prevention could be an important benefit of the service.* **Limitations identified by review team:** *Small group of PTB in intervention group* **Evidence gaps and/or recommendations for future research:** *Include a larger intervention group, longer follow up study* **Source of funding:** *grant from the English Department of Health grant reference number 0150305* *PJW was partly funded by centre funding from the Medical Research Council. IA and HS are*

			absence of the service, rather than at the higher rate we estimated for this extremely hard to reach group (34.7% per year). *- even without Find and Treat involvement, these cases could still passively re-engage with treatment at the same rate as enhanced tuberculosis surveillance controls (51% per year).* **Time horizon:** *Sep 2007 – July 2010*	*patients and 5.3% of other Find and Treat patients had multidrug or extensively drug resistant infection*	*partly funded by the National Institute for Health Research.* **Conflict of interests:** *None*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *US* **Authors:** *Lowenthal P., Westenhouse J., Moore M. et al.* **Year:** *2011* **Citation:** *Lowenthal P., Westenhouse J., Moore M. et al. Reduced importation of tuberculosis after the implementation of an enhanced pre-migration screening protocol. Int J Tuberc Lung Dis 15(6);761-766* **Aim of study:**	**Source population(s):** *Migrants* **Eligible population:** *California-bound immigrants* **Selected population:** *California-bound immigrants from Mexico, Phillipines and Viet Nam with suspected TB classification* *TB diagnosis within 6 months of arrival* **Excluded population:** *Immigrants were excluded if they moved out of California prior to evaluation.*	**Method of allocation:** *Everyone who wants to immigrate to the US from Mexico, Phillipines and Viet Nam* **Intervention(s) description:** *Culture for all suspected CXR's, symptoms for TB and HIV+ & DOTS* **Comparator/ control(s) description:** *Pre-intervention, Mexico & Philippines: October 2006-September 2007* *Viet Nam February - September 2007* **Baseline comparisons:**	**Primary outcomes:** *TB case detection among immigrants in the US within their first 6 months of arrival* **Secondary outcomes:** *Comparison between countries* **Method of analysis:** *Chi-square test and Fisher's exact test to compare proportions* *The Wilcoxon rank sum test was used to compare differences between medians* **Modelling method and assumptions:**	**Primary results:** *The proportion of immigrants identified in California with TB disease within 6 months of arrival decreased from 4.2% (86 cases) in the pre-intervention cohort to 1.5% (22 cases) in the post-intervention cohort.* *The only statistically significant decrease in cases was among immigrants originating from the Philippines (P<0.001)* *- case frequency did not decline among immigrants originating from countries where prei-mmigration screening was not modified* **Secondary results:** *Philippines contributing the*	**Limitations identified by author:** *- Observational design* *- small number* *- limited to 3 countries* *- first year after implementation* **Limitations identified by review team:** *- short follow up time (only 6 months)* *- we do not know how many extra cases were picked up by this intervention (but it was said it was not significant)* *- big size difference in the 2 comparison groups* *- No estimation of the effect nor adjustment for*

to determine whether TB disease importation has decreased following the intervention of adding sputum cultures for people with abnormal CXR, symp of TB or HIV+ to the screening protocol and if the intervention reduced the frequency of infectiousness (e.g., smear-positive and culture-positive) among persons with imported TB **Study design:** *Retrospective, observational, comparison, before after intervention* **Quality score:** *+* **Applicability:** *+*	**Setting:** *Importation of infectious tuberculosis (TB) threatens TB control in California and the United States* **Sample characteristics:** *California-bound immigrants from Mexico, Phillipines and Viet Nam* *2/3 >45 y.o.* *Size: 3479*	*% development of active TB in first 6 months in US* **Study sufficiently powered?** *Seems large enough but small number of TB cases in immigrants from Mexico and Viet Nam - ?lower TB incidence in these countries than in the Philippines*	*No multivariate model used* **Time horizon:** *October 2006 – March 2009*	*largest fraction of cases, followed by Viet Nam, then Mexico* *The median time from pre-migration evaluation to US arrival increased significantly, from 81 days (interquartile range [IQR] 53–117) in the pre-intervention cohort to 112 days (IQR 98–133, P=0.005) in the post-intervention cohort.* *A smaller proportion of cases in the post-intervention cohort had either a positive AFB sputum smear or a positive M. tuberculosis sputum culture, but the differences were not statistically significant*	*confounders in a multivariate model* **Evidence gaps and/or recommendations for future research:** *- Comparable group sizes* *- add numbers picked up in these countries* *- add logistic regression analysis to estimate the effect measure* **Source of funding:** *NR* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *US* **Authors:** *Liu Y., Posey D.L., Cetron M. S. et al.* **Year:** *2015* **Citation:** *Liu Y., Posey D.L., Cetron*	**Source population(s):** *Migrants* **Eligible population:** *Migrants to the US* **Selected population:** *Immigrants and refugees who were initially screened for TB overseas between 2007 and 2012 and arrived in the United States before 1 May 2014*	**Method of allocation:** *All immigrants after the implementation of the new strategy received the intervention* **Intervention(s) description:** *1. standard posteroanterior radiography of the chest for*	**Primary outcomes:** *Annual number of TB cases* **Secondary outcomes:** *Follow-up numbers* **Method of analysis:** *Proportions* *Mean*	**Primary results:** *- Annual number of CXR suspicion but sputum negative identified by the culture based algorithm:* **1532 in 2007* **14,292 in 2012* *- Annual number of cases diagnosed overseas by the culture-based algorithm:* ** 14 in 2007* ** 1058 in 2012*	**Limitations identified by author:** *- This analysis did not control for the decline in new arrivals of non-immigrant visitors (students etc) to the United States and the decrease of incidence of TB in their countries of origin.* *- Assumptions used for estimating the number of*

M. S. et al., Effect of a Culture-Based Screening Algorithm on Tuberculosis Incidence in Immigrants and Refugees Bound for the United States: A Population-Based Cross-sectional Study. Annals of Internal Medicine, 2015. ***162****(6): p. 420-8.* **Aim of study:** *To evaluate the effect of the culture-based algorithm on preventing the importation of TB to the United States by immigrants and refugees from foreign countries.* **Study design:** *Population-based, cross-sectional study* **Quality score:** *+* **Applicability:** *+*	**Excluded population:** *NR* **Setting:** *Pre-migration screening at US migration stations* **Sample characteristics:** *Previous programme:* *- F:M = 54.5% - 45.5%* *- 50.7% 15-44 years old* *- Larges group= Mexicans* *- TB incindence rate home country: 20-99/100,00 = 45%* *>100/110,000 = 44.3%* *New programme:* *- F:M = 54.8% - 45.2%* *- 51.2% 15-44 years old* *- Larges group= Mexicans* *- TB incindence rate home country: 20-99/100,00 = 50.2%* *>100/110,000 = 47.1%* *- The highest TB prevalence: Vietnamese (890 cases/100,000) and Philippines (854 cases/100,000).* *- Between 2007 and 2012, refugees made up only 14.9% of persons screened by the culture-based algorithm but accounted for 27.4% of TB cases diagnosed overseas among immigrants and refugees bound for the United States.*	*persons aged 15 years or older* *2. chest radiographs suggestive of active TB or with symptoms of TB, sputum specimens were collected 2007 M. tuberculosis culture* *3. persons aged 2 to 14 years in countries with a WHO-estimated incidence of 20 cases or greater per 100 000 persons per year to have screening for latent M. tuberculosis infection* *4. complete overseas TB treatment (DOT)* *5. Persons with a class A TB waiver were mandated to report to health departments for follow-up evaluation after arrival.* *We analyzed a national data set from the CDC's Electronic Disease Notification (EDN) database to evaluate the effect of implementing the culture-based algorithm in immigrants and refugees from 2007 to 2012* **Comparator/ control(s) description:** *annual number of reported TB cases among foreign-born persons within 1 year after arrival from the U.S. National Tuberculosis Surveillance System between 2002 and 2012* We compared the	**Modelling method and assumptions:** *The authors assumed that the number of immigrants screened overseas was equal to the number of immigrant arrivals during a specific year, and the number of immigrant arrivals was uniformly distributed by month within a specific year.* **Time horizon:** *2007 and 2012 arriving in the US before 01.05.2014*	*- Number of people screened by culture increased from 6.2% in 2007 to 76.2% in 2012* *- The number of smear positive cases were not reported by the CDC before 2007* *- 1,561,460 persons screened by sputum culture strategy (2007-2012):* *- 4032 active TB* **751 smear-positive/ culture-positive TB* **606 smear-positive/culture-negative TB* **2195 smear-negative/culture-positive TB* **480 clinically diagnosed TB* *-Smear-negative/ culture-positive TB* *= 54.4% of cases diagnosed (2007-2012)* **Secondary results:** *- Of the 21,638 suspicious CXR but negative sputum smear identified (2002-2006) 11,686 (54.0%) completed follow-up evaluation in the United States* *- Of the 60,423 suspicious CXR but with a negative sputum smear/ culture identified by the culture-based algorithm, 40,896 (67.7%) completed follow-up evaluation* *Follow-up evaluation active TB cases in: *410 (3.5%) screened by the smear-based algorithm* **731 (1.8%) screened by the culture-based algorithm (p < 0.001)* *Before implementation (2002 to 2006), the annual number of*	*immigrants screened by the culture-based algorithm may be invalid.* *- Misclassification may have happened* *- In 2007, the CDC started requiring state and local health departments to enter follow-up evaluation data via its newly developed EDN database.- before that limited data collected* **Limitations identified by review team:** *- Not corrected for possible confounders* *- active TB cases diagnosed in home country not recorded before 2007.* **Evidence gaps and/or recommendations for future research:** *Cost-effectiveness study of the culture-based algorithm* **Source of funding:** *None* **Conflict of interests:** *No conflicts of interest*

		cumulative sum of the differences with the total number of smear-negative/culture-positive TB cases diagnosed overseas among immigrants and refugees bound for the United States by the culture-based algorithm during implementation. **Baseline comparisons:** *Annual number of reported TB cases among foreign-born persons within 1 year after arrival before implementation (2002 to 2006) as the baseline, we calculated the difference between the baseline and the annual number of reported TB cases among foreign-born persons within 1 year after arrival during implementation (2007 to 2012).* **Study sufficiently powered:** *Yes, large number*		*reported cases among foreign-born persons within 1 year after arrival in the United States was relatively constant (range, 1424 to 1626 cases; mean, 1504 cases). During the implementation (2007 to 2012), the annual number of reported TB cases among foreign-born persons within 1 year after arrival decreased from 1511 to 940.* *During the same period, the annual number of smear-negative/culture-positive TB cases diagnosed overseas among immigrants and refugees bound for the United States by the culture-based algorithm increased from 4 to 629*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *Israel* **Authors:** Mor Z., Leventhal A., Weiler-Ravell D. et al. **Year:**	**Source population(s):** *Migrants* **Eligible population:** *Ethiopian migrants to Israel* **Selected population:**	**Method of allocation:** All non-pregnant immigrants older than 1 year coming from Ethiopia get a CXR 2-3 weeks prior to air-travel	**Primary outcomes:** *The efficacy and is a statistically pure characteristic of CXR* **Secondary outcomes:** *The effectiveness of this instrument and may better*	**Primary results:** *<u>CXR as a screening tool for clinical detection of PTB:</u>* *- Sensitivity: 80.1% (95% CI 68.1– 89.9%)* *- Specificity: 99.2% (95% CI 99.1–99.4%)* *- PPV: 31% (95% CI 23.4 –*	**Limitations identified by author:** *- Incomplete access to TST results and the missing clinical symptoms of the immigrants screened weaken the study* *- CXRs were read by*

2012 **Citation:** Mor Z., Leventhal A., Weiler-Ravell D. et al. *Chest Radiography Validity in Screening Pulmonary Tuberculosis in Immigrants From a High-Burden Country. Respir Care.2012;57(7): 1137–1144* **Aim of study:** *To determine the validity of CXR screening in detecting radiological findings compatible with active PTB or with old healed tuberculosis (OHTB)* **Study design:** *Retrospective record review* *Cross-sectional study* **Quality score:** *+* **Applicability:** *+*	*Jewish Ethiopian migrants to Israel* **Excluded population:** *Pregnant women* *Infants <1 y.o.* *Low quality CXR or missing CXR* **Setting:** *Pre-migration screening for Jewish Ethiopian migrants to Israel* **Sample characteristics:** *- 14,768 Jewish Ethiopian immigrants arrived in Israel* *- 13,379 (90.6%) underwent CXR in Ethiopia.* *- 1,131 were pregnant women or infants <1 year.* *- PTB was suggested in 150 (1.1%) of films* *- OHTB was suggested in 257 (1.9%)* *- 12,972 (97%) films were unremarkable or demonstrated other abnormalities unrelated to tuberculosis* *- Of all immigrants screened in Ethiopia, 57 (0.4%) were diagnosed with active PTB, including the undocumented cases. Of those, 46 (81%) had a CXR suggestive of PTB, and 11 (19%) patients had an unremarkable CXR (clinical diagnosis/ questionnaire suggestive – smear/culture +ve).*	**Intervention(s) description:** <u>*Ethiopia:*</u> *- CXR prior to immigration (*all films are read by radiography department Carmel Hospital, Haifa, Israel) *- Symptom questionnaire* *- Physical examination* *- one-step TST* *If previous Rx for TB / CXR abnormalities / questionnaire positive → 3 sputum samples (smear and culture)* *If sputum +ve treated in Ethiopia by DOTs, later resumed in Israel* <u>*In Israel:*</u> *- housed in absorption centre for >1 year* *- within 1 week: nurse comes to check HIV status and do 2nd TST (if 1st one <10 mm)* *If TB suspected – referral to TB clinic (for testing ± DOTS)* *All other pt's with unremarkable CXR are followed by nurse for 1 year* **Comparator/ control(s) description:** *Accuracy of CXR was determined by the diagnosis of active PTB using 2 end points as a*	*reflect the "real life" clinical use of CXR, as some areas in developing countries may lack the capacity to perform culture.* **Method of analysis:** *Comparisons between groups were made using the chi-square or Fisher exact test for categorical variables and the Student t test for continuous attributes* *The accuracy attributes of CXR were expressed by sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and positive and negative diagnostic likelihood ratios.* **Modelling method and assumptions:** *Accuracy of CXR in detecting PTB in mass screening of individuals from high-burden countries justifies the process* **Time horizon:** *July 2001- Dec 2005*	*38.7%)* *- NPV: 99.9% (95% CI 99.8–99.95%) (Table 2).* <u>*CXR as a screening tool for microbial detection of PTB:*</u> *- Sensitivity: 86.1% (95% CI 72.1–94.7%)* *- Specificity: 99.1% (95% CI 99.0 -99.3%)* *- PPV: 24.7% (95% CI 18.0–32.4%)* *- NPV: 99.9% (95% CI 99.92–99.99%)* *The positive diagnostic likelihood ratio for a CXR suggestive of PTB was 100.1 (the probability of an immigrant whose CXR is suggestive of PTB to be diagnosed with active PTB is 100 times greater than those who CXR is unremarkable).* *The negative diagnostic likelihood ratio was 0.2 (unremarkable CXR is 5 times more common in healthy immigrants than in those who developed active PTB).* *The diagnostic yield of OHTB-CXR using active PTB diagnosis during the first year following immigration as the end point was calculated:* *Sensitivity was 17.2% (95% CI 10.0–26.9%), specificity was 98.2% (95% CI 97.9–98.4%), and PPV was 5.8% (95% CI 3.31–9.4%).* *The positive diagnostic like-lihood ratio for a CXR suggestive of OHTB was 9.4.*	*several radiologists, so the results are subject to interobserver differences. In order to minimize over- and under-reporting, all the readings were performed in the same radiology ward, supervised by a single senior physician* *- PPV is dependent on the prevalence of the disease in the population studied.* **Limitations identified by review team:** - Patients with a normal CXR had no sputum culture comparison *- Costs-analysis / argument is not completely convincing: what are the costs of treatment in Ethiopia? And, authors say "Treatment is later continued in Israel" – after how long are TB+ migrants allowed to enter the country – and what will then be the in-country cost for treatments?* **Evidence gaps and/or recommendations for future research:** *Cost-effectiveness analysis* **Source of funding:** *This study was partially sponsored by the League Against Tuberculosis and Lung Diseases, Rehovot, Israel, and by the National Institute for Health Policy and Health*

	- Five PTB patients had negative cultures and unremarkable CXR *- 3 PTB pt's were HIV +ve*	*gold standard for PTB: microbial and clinical.* **Baseline comparisons:** - CXR PTB vs PTB clinical suspicion- CXR PTB vs PTB Microbial Confirmation - CXR OHTB vs PTB Microbial confirmation within first year **Study sufficiently powered:** Yes.		**Secondary results:** *PTB pre-test probability of this cohort was 0.43% (57/13,379), pre-test odds were 0.75 and the post-test odds for CXR suggestive of PTB were 75.5. These calculations represent a more accurate estimation of the yield of CXR in a "real life" setting, meaning that an Ethiopian immigrant whose CXR demonstrates changes suggestive of PTB is >75 times more likely to be diagnosed with PTB than an immigrant whose CXR is unremarkable.* *- 291 films are required to detect a single case of active PTB upon immigration.* *- The cost of performing a single CXR in Ethiopia, including its reading in Israel, is $20 (including direct cost of CXR in Addis Ababa, reading of CXR in Israel, and indirect costs in Ethiopia, such as maintenance of the health station and salaries). Thus, the total amount required to detect one PTB case among immigrants is $5,820. Treating an active PTB patient in Israel, which is $7,619 (based on the Israeli Ministry of Health tariffs in Israel, January 2005).*	*Services Research, Tel-Hashomer, Israel.* **Conflict of interests:** *None*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**

Country: *Israel* **Authors:** *Mor Z., Weinstein O., Tischler-Aurkin D. et al.* **Year:** *2015* **Citation:** *Mor Z., Weinstein O., Tischler-Aurkin D. et al. The Yield of Tuberculosis Screening of Undocumented Migrants from the Horn of Africa based on Chest Radiography. IMAJ, 2015(17):11-13* **Aim of study:** *To evaluate the validity of CXR and assess its related costs in detecting TB among undocumented migrants in Israel from the Horn of Africa.* **Study design:** *cross-sectional study* **Quality score:** - **Applicability:** -	**Source population(s):** *Migrants* **Eligible population:** *Illegal immigrants* **Selected population:** *Detained illegal immigrants in Israel from the Horn of Africa (Sudan, Ethiopia & Eritrea)* **Excluded population:** *Everyone who had a CXR done at another institution* **Setting:** *TB screening for illegal immigrants from the Horn of Africa in an detention centre in Israel.* **Sample characteristics:** *- 5335 migrants who crossed the southern Israeli border illegally and were detained during 2009* *- 1087 (20.4%) underwent CXR at a single institution.* *- 641 (59.0%) were Eritreans* *- 280 (25.7%) Sudanese* *- 166 (15.3%) Ethiopians.* *- male:female= 8.1:1* *- average age = 34.8 ± 17.2 years.*	**Method of allocation:** *Random selection by the Israeli Prison Services* **Intervention(s) description:** *1. Detention centre* *2. Screened for TB by interview and CXR* *3. If positive referred to TB clinic for checkup & sputum* *4. If positive DOTS* **Comparator/ control(s) description:** *CXR compared with final TB diagnosis* **Baseline comparisons:** CXR vs TB diagnosis (culture +ve or full course anti-TB therapy) **Study sufficiently powered:** *Large sample size but small group of TB diagnosis*	**Primary outcomes:** *Point prevalence* **Secondary outcomes:** *Commutative incidence: 3-year follow up, who developed TB* **Method of analysis:** *- Comparisons between categorical and continuous variables were performed by the chi-square and Student's t-test, respectively* *- Validity of the CXRs was expressed by sensitivity, specificity and positive predictive values (PPV), while active TB detection was considered the end-point.* *- If positive in 3-year follow-up period: reevaluation CXR + medical records* **Modelling method and assumptions** NR **Time horizon:** *2009*	**Primary results:** *- 62/1087 (5.7%) of the CXRs demonstrated suggestive of TB* *- 11/62 were finally diagnosed as having TB at TB clinic (17.7% of all suspicious CXRs)* *- sensitivity 100%* *- specificity 96.1%* *- PPV 17.7%* *- 10/11 (90.9%) pulmonary TB* *- 1/11 (9.1%) extra-pulmonary TB* *- Smear +ve results in 3/11 (27.3%)* *- Culture positive in 8/11 (72.7%)* *- All 8 cultures were sensitive for first-line drugs, while 3/8 (37.5%) were streptomycin resistant.* *TB point-prevalence on arrival was 1000 cases per 100,000 migrants (1.0%)* *The interview, which failed to identify most of the migrants who were diagnosed with TB (mainly negative answers), is considered a low sensitivity instrument due to linguistic barriers and possible reporting bias, since incarcerated migrants may respond in a way that they believe would hasten their discharge.* *The detection of 11 TB patients required 1078 CXRs and 62 TB clinic evaluations, at direct costs of 98 and 1434 shekels (NIS) (US$ 25 and 367) each, respectively, accumulating in NIS 17,970 ($ 4585) to detect one TB patient. Conversely, the cost for treating a single TB patient in*	**Limitations identified by author:** *- only the questionnaires of confirmed TB cases were traced; the questionnaires from the entire cohort could not be found.* *- only ± 70% of the CXRs of the migrants diagnosed in the community could be located because of technical factors* *- the small number of TB patients who were diagnosed with TB limits comparisons.* *- CXR is not indicated for detecting cases of extra-pulmonary TB, although it is less prioritized in terms of public health concerns* **Limitations identified by review team:** *- Only CXR's done at 1 institution analysed – risk of selection bias* *- No information on lost-to-follow up (3 years!)* *- No procedures described for random selection – potential selection bias* *- No information on the follow-up on X-rayed participants (although this was not a study objective, could have provided interesting information)* *- none of the included migrants developed active TB during the detention period – but detention time is too short – sensitivity calculated too high*

				Israel is ~ NIS 28,700 ($ 7335). **Secondary results:** *88 pt's developed TB but not in scope of this review*	*- No real cost-analysis given, the costs of the screening was presented but no comparison was made if this is cost effective.* **Evidence gaps and/or recommendations for future research:** *Real cost-effectiveness study* **Source of funding:** *This study was partially funded by the Israeli Lung and Tuberculosis Association* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *US/Vietnam* **Authors:** *Painter J.A. Graviss E.A. Hoa Hai H. et al.* **Year:** *2013* **Citation:** *Painter JA, Graviss EA, Hai HH. et al. (2013) Tuberculosis Screening by Tuberculosis Skin Test or QuantiFERON®-TB Gold In-Tube Assay among an*	**Source population(s):** *Migrants* **Eligible population:** *Migrants to the US from Vietnam* **Selected population:** *Vietnamese visa applicants during the standard immigrant medical examination at the Cho Ray Hospital Medical Visa Unit, age >14 years* **Excluded population:** *NR*	**Method of allocation:** *Every applicant with a chest radiograph consistent with tuberculosis was approached for enrollment. Each week, the first available participants with a normal chest radiograph were enrolled to maintain the 2:1 ratio* **Intervention(s) description:** *QFT was performed on the day of enrollment, followed by TST, TST reading in 48*	**Primary outcomes:** *To measure the sensitivity of TST and QFT in detecting culture-confirmed pulmonary tuberculosis* **Secondary outcomes:** *To estimate the overall and age-specific prevalence of LTBI for using TST and QFT in the same adult immigrant population (not for our study)* **Method of analysis:** *To measure the sensitivity*	**Primary results:** *- 1,475 participants >14 y.o. enrolled* *- 479 had Normal-CXR* *- 996 had CXR consistent with TB* *- 100 applicants declined* *- 5 did not complete examination* *- 132 (13.3%) were culture-confirmed for tuberculosis (TB)* *- 864 were not culture confirmed (TBCXR)* *- Culture-confirmed cases were identified on the first sputum sample for 95 (72.0%)* *- 27 (20.4%) additional cases*	**Limitations identified by author:** *1. no acid-fast bacilli sputum smears or cultures were obtained for applicants with chest radiographs not suggestive of tuberculosis – unlikely but may be TB +ve* *2. the tuberculosis infection status cannot be determined with certainty because there is no gold standard for LTBI detection → unable to calculate specificity* *3. BCG immunization Hx*

Immigrant Population with a High Prevalence of Tuberculosis and BCG Vaccination. PLoS ONE 2013. 8(12): e82727 **Aim of study:** *To measure the sensitivity of TST and QFT in detecting culture-confirmed pulmonary tuberculosis* **Study design:** *Comparison study* **Quality score:** *+* **Applicability:** *+*	**Setting:** *Cho Ray Hospital Medical Visa Unit* **Sample characteristics:** *- 20,100 visa applicants 15 years of age and older* *- mean age was 37.3 years* *- 17,802 (88.6%) normal-CXR* *- 2,087 (10.4%) TB-CXR* *- 211 (1,040 per 100,000 population) culture-confirmed pulmonary TB*	*to 72 hours. Followed by sputum cultures* **Comparator/ control(s) description:** *1) having a chest radiograph not consistent with TB (Normal-CXR)* *2) having a chest radiograph consistent with TB but not culture confirmed (TB-CXR)* *3) having culture-confirmed pulmonary tuberculosis (TB) when M.tuberculosis was isolated from any of the three sputum samples.* **Baseline comparisons:** *Sensitivity of TST versus QFT-G for culture confirmed pulmonary TB* **Study sufficiently powered:** *Did not meet the 150 culture confirmed cases that was determined before the start of the study (included 132 culture confirmed cases)*	*for culture-confirmed pulmonary tuberculosis, we calculated the percent positive results only among those having culture-confirmed pulmonary tuberculosis (TB).* *Estimated the annual percent change for having a chest radiograph consistent with tuberculosis, culture confirmed tuberculosis, and a positive TST or QFT.* **Modelling method and assumptions:** *NR* **Time horizon:** *From December 2008 through January 2010*	*were identified on the second sputum sample* *- 10 (7.6%) on the third sputum sample* *The sensitivity for detecting culture-confirmed tuberculosis was:* *- 86.4% (95% CI = 79.3%-91.7%) for QFT* *- 89.4% (82.8%-94.1%) for TST-5* *- 81.1% (73.3%-87.5%) for TST-10* *- 52.3% (43.4%-61.0%) for TST-15* *These results were significantly different for QFT versus TST-15 (Pearson's chi-squared probability [p]=<0.001) but not for QFT versus TST-5 (p=1) or TST-10 (p=0.12)* *Neither the TST at the most sensitive (5-mm) cutoff or QFT detected all the culture-positive pulmonary tuberculosis cases detected by the rigorous radiologic and microbiologic screening,* **Secondary results:** *The annual percentage increase per year of age was 5.5% [95% confidence interval = 5.2%—5.8%] for a CXR consistent with TB and 2.9% [2.0%—3.8%] for culture-confirmed TB* *<u>Conclusion</u>:* *In addition to similar sensitivity in detection of tuberculosis, two principal findings support the use of QFT over TST for two-stage TB screening in this BCG-*	*not obtained – assumed everyone was immunized* *4. Only 1 HIV positive patient* **Limitations identified by review team:** *- Only sensitivity measured, not specificity* *- No cost-effectiveness analysis* *- Harms/side effects of different tests not assessed* **Evidence gaps and/or recommendations for future research:** *- Study the specificity as well* *- Cost-effectiveness analysis* *- Assess harms* **Source of funding:** *CDC* *- QFT-G kits were provided by the Foundation for Innovative New Diagnostics* **Conflict of interests:** *NR*

				vaccinated population. *- positive test result for LTBI would lead to radiography of only 37% of the entire population with a positive QFT compared with 72% of those with a positive TST-5 with no difference in case detection*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *US* **Authors:** *Posey D.L., Naughton M.P., Willacy E.A. et al.* **Year:** *2014* **Citation:** *Posey D.L., Naughton M.P., Willacy E.A. et al. Implementation of New TB Screening Requirements for U.S.-Bound Immigrants and Refugees – 2007-2014. Morbidity and Mortality Weekly Report 2014(63):11;234-236* **Aim of study:** *Summarizes the worldwide implementation of the new screening requirements (2007) – CDOT TB TI* **Study design:** *Quantitative report*	**Source population(s):** *Migrants* **Eligible population:** *US bound migrants* **Selected population:** *US bound migrants applying for a visa and attend TB screening in their home country* **Excluded population:** *Not reported* **Setting:** *Not reported* **Sample characteristics:** *Not reported*	**Method of allocation:** *pre- and post-intervention* **Intervention(s) description:** *Overseas identification and treatment of TB in US bound immigrants by:* *- medical examination* *- CXR* *- sputum smears* *<u>CDOT TB TI:</u>* *CDC added sputum cultures, drug susceptibility testing and DOTS in 2007* *In 2009 TST & IGRA for children 2-14 y.o.* **Comparator/ control(s) description:** *no comparison done* **Baseline comparisons:** *Not done*	**Primary outcomes:** *Increased yield by new screening method* **Secondary outcomes:** *- Prevalence TB cases* *- Cost effectiveness* **Method of analysis:** *prevalence of smear-negative culture positive TB cases* **Modelling method and assumptions:** *authors assumed that smear-negative, culture positive cases without the intervention would have been missed* **Time horizon:** *2007-2014*	**Primary results:** *In 2012:* *1,100 cases of TB were diagnosed* *- Approximately 60% of all cases were smear negative, but culture-positive Because the previous system did not require cultures, the smear-negative but culture-positive cases represent a gain in TB diagnoses with the new CDOT TB TI requirements.* *- 14 cases were MDR-TB* **Secondary results:** *In addition to increasing the yield of diagnoses overseas, implementation of CDOT TB TI was temporally associated with a decline in TB cases among foreign-born persons in the United States since 2007* *During the period in which the 1991 TB TI was in use, 7% of immigrants and refugees who had abnormal CXR suggestive of TB, but negative sputum smears, were diagnosed with TB disease after their arrival in the United States.*	**Limitations identified by author:** *None* **Limitations identified by review team:** *Is a report, not true comparison study* **Evidence gaps and/or recommendations for future research:** *- Cost-effectiveness study* *- True comparison study* **Source of funding:** *NR* **Conflict of interests:** *NR*

Quality score: - **Applicability:** -		**Study sufficiently powered?:** *NA*		*Under CDOT TB TI, early data suggest that percentage has declined to 1%–2%* *Although formal economic analyses have not been completed,* *the gains in overseas diagnosis and the decrease in cases suggest that successful implementation of this screening program* *could result in crude savings in excess of $15 million yearly.*	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Country: *Estonia* **Authors:** *Ruutel K. Loit H-M. Sepp T. et al.* **Year:** *2011* **Citation:** *Ruutel K. Loit H-M. Sepp T. et al. Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. BMC Research Notes 2011,**4**:192* **Aim of study:** *To evaluate case management interventions aimed at increasing tuberculosis screening &*	**Source population(s):** *IVDU* **Eligible population:** *IVDU at community-based methadone substitution treatment center* **Selected population:** *IVDU at community-based methadone substitution treatment center in Johvi.* *- participate in substitution treatment program* *- >18 y.o.* *- read/write in Estonian/Russian* *- provide informed consent* **Excluded population:** *No return for TST reading* **Setting:**	**Method of allocation:** *Random allocation by nurse to passive (self) or active (nurse led) referral* **Intervention(s) description:** *Active referral (referral made and chased by study staff) to TB centre for TB screening* *At substitution center: - Mantoux (read 2-3/7 later; >5 mm = +)* *- Self administrated questionnaire* *- HIV + IGRA test (counselling)* *Random allocation to passive (self)/active (nurse)referral* *- F/U 2/12 after enrolment*	**Primary outcomes:** *The influence of active referral on TB clinic attendance* *Association between participant characteristics and attendance to TB services* **Secondary outcomes:** *Cost assessment* **Method of analysis:** *Wilcoxon ranksum test/ Fisher exact test followed by univariate and multivariable log regression* **Modelling method and assumptions:** *The intervention will increase TB screening and*	**Primary results:** *43.8% (49/112) attended TB clinic* ** 17 control group (30.4%)* ** 32 intervention group (57.1%)* ** no TB diagnosed* *Appointment organised and chased by nurse had 3.9x higher rate of attendance to TB service than making an appointment themselves (95% CI 1.4-10.4, p=0.007)* *TB clinic was not associated with any of the variables (age, education, work, prison, years of IVDU, Mantoux/HIV result, sex). Only with type of referral!* **Secondary results:** *Active case management costs an additional 18 euros per patient (food voucher, extra time nursing staff, transport)*	**Limitations identified by author:** *- small sample size* *- one centre* *- methadone using group = not active IVDU, so results can't be generalised to whole IVDU population* *- modest responds rate at methadone centre* **Limitations identified by review team:** *- IVDU had to travel 16 km to other hospital, in the active referral group transport was organised not for the passive referral = risk for bias* *- All TB negative cases ?good representation of the population and unable to calculate cost made to detect 1 active TB case*

treatment entry among IVDU **Study design:** *Pilot - RCT* **Quality score:** *+* **Applicability:** *+*	*community-based methadone substitution treatment center in Johvi.* **Sample characteristics:** *189 invited – 112 responded (59%)* *56 (50%) intervention, 56 (50%) control group*	*- Food voucher given for TST reading* *TB centre:* *- screened for active TB* *- doctors filled out questionnaire + final diagnosis* **Comparator/ control(s) description:** *Passive referral – IVDU has to make the referral appointment himself* **Baseline comparisons:** *TB screening attendance* **Study sufficiently powered?:** *P=0.007*	*treatment entry among IVDU* **Time horizon:** *16-18 October 2007*	**Conclusion:** *TB screening services can be increased with more active referral, help in transportation and incentives*	**Evidence gaps and/or recommendations for future research:** *- TB screening centre closer by or screening closer to 'home'* *- - Longer enrolment period /larger sample size too be able to calculate costs made to detect 1 active TB case* *- broader spectrum of IVDU not just at methadone clinic* **Source of funding:** *National institute for health development Estonia, National HIV/AIDS strategy 2006-2015, National Tuberculosis Control Program 2003-2007, Estonian Ministry of Education and research, New York State International Training and Research Program, National Institute of Health/Fogarty International Center and the National Institute of Drug Abuse* **Conflict of interest:** *None*

Study details	Population and setting	Method of allocation to intervention/ control	Outcomes and methods of analysis	Results	Note by review team
Country: *Switzerland* **Authors:** *Schneeberger Geisler S., Helbling P., Zellweger J.P., Altpeter E.S.* **Year:** *2010* **Citation:** *Schneeberger Geisler S., Helbling P., Zellweger J.P., Altpeter E.S. Screening for tuberculosis in asylum seekers: comparison of chest radiography with an interview-based system. Int J Tuberc Lung Dis 14(11):1388-1394* **Aim of study:** *To compare the detection of pulmonary TB by TB screening by a symptom-based questionnaire (2007-2008) versus TB screening by chest radiography (2004-2005)* **Study design:** *Cross-sectional retrospective comparison of two 2-year periods* **Quality score:** *+*	**Source population(s):** *Migrants* **Eligible population:** *Asylum seekers* **Selected population:** *Asylum seekers in Switzerland form high endemic countries* **Excluded population:** *- Double entries* *- Repeated screening examinations* **Setting:** *Mandatory initial screening of asylum seekers* *for tuberculosis (TB) in Switzerland, 2004–2005 and* *2007–2008.* **Sample characteristics:** *- A total of 25,856 persons applied for asylum in Switzerland during the period from 2004 to 2005, and* *27,450 in the period from 2007 to 2008* *- Men were more frequently affected than women.* *- Asylum seekers between the ages of 15 and 54 years had a higher prevalence of*	**Method of allocation:** *All cases 2004-2005 had screening with CXR all cases 2007-2008 were screened with questionnaire.* *The national register of all TB cases notified in Switzerland was merged with the central database of TB screening procedures of asylum seekers to identify cases appearing in both databases.* **Intervention(s) description:** *An expert system for a symptom-based interview was developed to replace routine radiography.* *The score is based on:* *- the estimated prevalence of TB in the country of origin (0 to 10 points)* *- symptoms elicited in the interview (up to 11 points)* *- the personal and family TB history (up to 2 points)* *- the overall impression gained by the interviewing nurse (0 or 3 points).* *Above a defined threshold of the score (10 points) or at the discretion of the*	**Primary outcomes:** *The overall yield was the number of culture confirmed pulmonary TB cases that had been started on anti-tuberculosis combination treatment within* *90 days after screening in the two periods* **Secondary outcomes:** *Coverage and the initial results of the screening tool* *measured as sensitivity, specificity and, as a summary measure for both sensitivity and specificity, the likelihood ratios with 95% confidence intervals (CIs):* *Sensitivity/(1 − specificity) for the positive and specifi city/(1 −sensitivity)/ for the negative ratio* **Method of analysis:** *- Sens/spec/ 95% CI's/ pos. & neg. likelihood ratio* *- Treatment delay* **Modelling method and assumptions:** *The delay* *from screening to start of treatment was estimated using Kaplan-Meier survival analysis.*	**Primary results:** *- 2004-2005:* *21,987 (coverage 84%)* *- 2007-2008:* *23,722 (coverage 85%)* *- Radiography led to more diagnoses of pulmonary TB that remained unconfirmed by culture* *- 2004–2005: all 31 cases of PTB had an abnormal CXR @ screening* *- 2007–2008: only 16/29 cases (55%) were identified as TB suspects at screening. The 13 cases not detected by screening had scores below the threshold for which further investigations for TB were required. These cases also needed medical attention in the weeks following the screening procedure when they developed symptoms.* *- CXR screening resulted in a faster identification of PTB. The median delay from screening to treatment was 6 days in 2004–2005 (range 0–79) and 25 days (range 0–85) in 2007–2008* *The median delay in the subgroup not identified by screening in 2007–2008 was 40 days (range 16–85).* **Secondary results:** *<u>2004-2005:</u>* *- sensitivity 100%*	**Limitations identified by author:** *- The effect of the new system cannot be determined accurately, as the two systems were not run in parallel. (geographic origins changed, but both groups could stay in the country for 90 days – 90 days was chosen as the effect of screening diminishes rapidly over time, after 90 days it might be reactivation of LTBI instead of earlier active TB)* *- Communication problems, including differential conceptual representation* *of illness, and the belief that being ill might negatively affect the chances of being granted asylum, may play a role. Interestingly, most such cases originated from the Horn of Africa* **Limitations identified by review team:** *- Small number of people starting Rx in 90 days* *- Did not evaluated culture negative cases started on TB treatment*

Applicability: ++	*pulmonary TB than other age groups.*	*nurse, the screened asylum seeker is referred to a clinician for further evaluation, which always includes a chest radiograph. Abnormal radiographs require microbiological examinations.* **Comparator/ control(s) description:** *Compare with systematic radiographic screening (system in 2004-2005).* **Baseline comparisons:** *Compare the detection of pulmonary TB within 90 days (microbiological confirmation + start of TB treatment)* **Study sufficiently powered:** *Yes, but small number of TB patients identified*	*- two-by-two tables were evaluated* **Time horizon:** *2004–2005 and 2007–2008*	*- specificity 89.6%* *- positive likelihood ratio was 9.99 (95%CI 9.99–10.0)* *- negative likelihood ratio was 0.00 (95%CI 0–∞)* *<u>2007–2008:</u>* *- sensitivity 55.2%,* *- specificity 96.0%* *- positive likelihood ratios 13.7 (95%CI 12.37–15.15)* *- negative likelihood ratios 0.5 (95%CI 0.40–0.54)* *The three highest positive likelihood ratios were for subjects presenting with:* *- illness as judged by the nursing staff (21.3, 95%CI 3.22–141)* *- mentioning previous anti-tuberculosis treatment (17.9, 95%CI 7.38–43.50)* *- stating cough (3.4, 95%CI 2.83–4.09)* *- 12% of all screened asylum seekers in 2004–2005 vs. 4% in 2007–2008, with corresponding yields of respectively 1.4% and 1.7% needed further investigations*	**Evidence gaps and/or recommendations for future research:** *- Compare the 2 systems over the same time period and the same populations* *- Cost-effectiveness study* **Source of funding:** *NR* *(Study was performed by the Federal Office of Public Health)* **Conflict of interests:** *NR*

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**

Country: *UK* **Authors:** *Story A., Aldridge R.W., Abubakar I. et al.* **Year:** *2012* **Citation:** *Story A., Aldridge R.W., Abubakar I. et al. Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. Int J Tuberc Lung Dis. 2012. 16(11):1461–1467* **Aim of study:** *1. To calculate the sensitivity and specificity of mobile digital CXR for identifying pulmonary TB among high risk groups in an urban setting (London)* *2. to determine whether cases of active pulmonary TB identified by MXU were less likely to be sputum smear positive on diagnosis than passively identified cases from the same populations* **Study design:** *Observational study* **Quality score:** *+* **Applicability:** *++*	**Source population(s):** *Homeless, drug users, prisoners and asylum seekers* **Eligible population:** *Homeless, drug users, prisoners and asylum seekers in London, the UK* **Selected population:** *Homeless, drug users, prisoners and asylum seekers in London, the UK using services for their population group* **Excluded population:** *- Aged under 16 years at the time of screening* *- If not classified in the homeless, asylum, drug user or prison risk groups* *- Non-pulmonary cases notified within 90 days, including those with extra-pulmonary but intrathoracic disease* **Setting:** *TB screening in hard-to-reach groups in London* **Sample characteristics:** *47 510 CXRs were performed among individuals:* *- 19,801 homeless (41.7%)* *- 15,580 prisoners (32.8%)* *- 4,220 asylum seekers (8.9%)* *- 4,173 drug users (8.8%)* *- 3736 others (7.9%)*	**Method of allocation:** *All homeless, drug users, prisoners and asylum seekers present at the venue at the time of screening* **Intervention(s) description:** *Mobile CXR unit screening 2x a year at different venues* *- CXR evaluated on the spot by 2 radiographers* **CXR positive = suspected TB* **CXR negative = normal, old TB, abnormal CXR referred or not referred for further investigations* *- Everyone with a positive CXR was referred for further investigation* **Comparator/ control(s) description:** *culture-confirmed cases of PTB notified to the ETS (Enhanced Tuberculosis Surveillance) within 90 days of screening* **Baseline comparisons:** *TB diagnosis*	**Primary outcomes:** *sensitivity and specificity of mobile digital CXR screening* **Secondary outcomes:** *Smear positive disease as specified by the Health Protection Agency (HPA)* *Actively identified cases (screening) were compared with passively identified cases (self presentation)* *odds ratios of sputum smear positivity* **Method of analysis:** *Sensitivity, specificity, NPV, PPV* *Logistic regression* *Univariate and multivariate analysis* **Modelling method and assumptions:** *Logistic regression adjusting for confounders (age, sex a priori), potential confounding variables identified at univariate analysis were added* **Time horizon:** *1 April 2005 to 31 March 2010*	**Primary results:** *- 38 717 deduplicated CXRs at MXU* *- 414 suspected TB cases at CXR* *- 33 culture confirmed within 90 days → 27 CXR +ve (so 6 CXR -ve)* *- Sensitivity: 81.8% (95%CI 64.5–93.0)* *- Specificity: 99.2% (95%CI 99.1–99.3)* *- PPV: 6.5% (27/414)* *NPV: 100% (47,090/47,096)* **Secondary results:** *- The odds of smear-positive disease was reduced in individuals seen by the MXU in the past 90 days (OR 0.37, 95%CI 0.15–0.90, p = 0.03).* *- After adjusting for age and sex, there was evidence that the odds of smear positive disease were lower in MXU-identified cases of pulmonary disease than in passively identified cases from the same population (OR 0.34, 95%CI 0.14–0.85, likelihood ratio test p = 0.022)* *<u>Conclusion:</u>* *Digital CXR achieves a high level of sensitivity and specificity in an operational setting; targeted Mobile radiographic screening can reduce the risk of onward transmission by identifying cases before they become infectious*	**Limitations identified by author:** *- risk factors such as homelessness, drug use and incarceration were assigned depending on where screening occurred, therefore cannot account for the heterogeneity of these populations. For example, a high proportion of persons classified as homeless may also have concurrent drug use or a history of incarceration, and vice versa.* *- The linkage of individuals screened by the MXU to TB cases within the national surveillance system should not be differentially biased, but is likely to underestimate the total number of cases.* *- Analysis was based on existing data, collection of additional confounding variables was not impossible.* *- HIV status was not known* **Limitations identified by review team:** *- What % was sputum culture negative but had a suspected CXR?* *- And what % did not show up for sputum test? The gold standard is now PTB notification to ETS* *- Selection bias* **Evidence gaps and/or recommendations for future research:**

		Study sufficiently powered?: *Power calculation: estimated that 150 culture confirmed cases would show difference in % of smear positive disease of 25%, with a power of 84% and a difference of 30% with 99% power and 0.05 level of significance between active and passive case finding* *Study only found 33 culture confirmed cases*			*Compare CXR with sputum culture, so at the day of screening, everyone with a positive CXR should have a sputum sample done as well* **Source of funding:** *National Institute for Health Research* **Conflict of interests:** *None*

Supplementary Material IV: Evidence statements

Grading of evidence

No evidence – no evidence or clear conclusions from any studies;
Weak evidence – no clear or strong evidence/conclusions from high quality studies and only tentative evidence/conclusions from moderate quality studies or clear evidence/conclusions from low quality studies;
Moderate evidence – tentative evidence/conclusions from multiple high quality studies, or clear evidence/conclusions from one high quality study or multiple medium quality studies, with minimal inconsistencies across all studies;
Strong evidence – clear conclusions from multiple high quality studies.

Tuberculosis identification

Evidence statement 1: Effectiveness of interventions aiming to improve TB identification among migrants

Pre-migration screening

1·1 **Moderate evidence** from four studies reporting on the effectiveness of including sputum culture as part of pre-migration screening in migrants to the United States (US) suggested that more active tuberculosis (TB) cases are identified during pre-migration screening and less active TB cases are diagnosed in the country of destination (Lowenthal et al.,2011 [+]; Assael et al., 2013 [-]; Posey et al., 2014 [-] and Lui et al., 2015 [+]).[1-4]

Lowenthal et al., 2011 [+] showed a decrease (4·2% to 1·5%) in newly diagnosed TB cases in migrants from countries that implemented the new US TB screening strategy.[1] Assael et al., 2013 [-] concluded that 8 out of 10 culture confirmed TB cases in Mexican migrants to the US, were missed if sputum culture was not used for TB screening.[2] Posey et al., 2014 [-] concluded that the new screening programme improved identification of active TB cases.[3] The most recent study by Lui et al., 2015 [+] found that more than 50% of the diagnosed TB cases were smear-negative and culture-positive; the number of active TB cases among migrants diagnosed within one year of arrival in the US decreased from 1,500 per year to 940 per year; and the follow-up in the US improved by 13·7%.[4]

1·2 **Weak evidence** from Mor et al., 2012 [+] showed that pre-migration screening by chest X-ray (CXR) had a high sensitivity and specificity for identification of TB among migrants from high endemic countries.[5]

1·3 **Weak evidence** reported by the NICE review[6] from one before-and-after study (Mor et al., 2008 [-]) suggested that pre-migration screening in Ethiopian migrants moving to Israel may reduce the risk of developing TB in Israel compared to post-migration screening, with a reduction in time between entry into Israel and TB diagnosis (Odds Ratio (OR) = 0·72, 95% Confidence Interval (95% CI) 0·59-0·89; p-value (p) = 0·002).[7] The study did not adjust for potential differences in TB incidence between the cohorts screened over different time periods.

1·4 The NICE review[6] reported **inconclusive evidence** from one retrospective cohort study (Sciortino et al., 1999 [+])[8] on the effectiveness of pre-migration screening of latent TB infection to identify active TB among US migrants within the first year of arrival in the US.

Post-migration screening

1·5 The NICE review[6] reported **moderate evidence** from three retrospective cohort studies (Verver et al., 2001 [+]; Monney and Zellweger, 2005 [+] and Laifer et al., 2007 [+]), suggesting that active screening by CXR and/or tuberculin skin test (TST) reduced the number of identified symptomatic TB cases and reduced the number of sputum smear or culture positive cases.[9-11] However, these studies did not adjust for differences in baseline characteristics between the intervention (active screening) and control groups (passive presentation).

1·6 **Weak evidence** from Mor et al. 2015 [+] showed that CXR had a sensitivity of 100% and specificity of 96·1% to screen for TB in migrants from high endemic countries.[12]

1·7 **Weak evidence** from Schneeberger Geisler et al., 2010 [+] suggested that TB screening by symptom-based questionnaire had a low sensitivity (55·2%), a high specificity (96·0%) and that the time from diagnosis to start of treatment was prolonged (40 days).[13]

1·8 **Weak evidence** from two studies on the effectiveness of TB screening by Interferon Gamma Release Assay (IGRA) or TST. Painter et al., 2013 [+] showed that TST screening using a 10 mm induration as cut off and QuantiFERON-TB Gold Test (QFT-G) had a similar sensitivity (86·4% (95% CI: 79·3% - 91·7%) and 81·1% (95% CI: 73·3% - 87·5%), respectively) when screening for culture confirmed TB cases in migrants from a high endemic country with a high coverage of BCG vaccination.[15]
Chuke et al. 2014 [-] showed that QFT-G had a better agreement with CXR than TST but the PPV was similar for both tests in migrants from a high endemic country with a high coverage of BCG vaccination.[16]

1·9 **Weak evidence** from George et al., 2011 [-] suggesting that a TST cut of point of 10 mm would be more sensitive and specific for latent TB and active TB in adopted children than a 5 mm TST cut of point.[17] This study had major limitations, the sample size was too small and only a small number of children had a comparative test done (CXR).

Other measurements
1·10 **Moderate evidence** from two studies identified by this review (Bell et al., 2013 [+] and Harstad et al., 2014 [-]) showed that active referral increased the screening uptake among migrants.[18,19]

Evidence statement 2: Cost-effectiveness of interventions aiming to improve TB identification among migrants

The NICE review[6] found five studies focussing on an economic evaluation of interventions aiming to improve identification of active TB among migrants (Dasgupta et al., 2000 [+];Schwartzman and Menzies, 2000 [++];Schwartzman et al., 2005 [++]; and Mor et al., 2008 [-])[7,20-22] This review found two studies that reported on the cost-effectiveness of TB screening interventions (Mor et al., 2012 [+] and Mor et al., 2015 [+])[5,12]

2·1 **Moderate evidence** from five economic studies suggesting that screening by CXR among migrants is cost-effective and less costly than screening by TST per case identified[5,12,21,22] and cost-saving when secondary transmission of TB disease is taken into account.[21] Adding TST to a screening algorithm with a CXR did not result in cost-savings for new entrants.[22] Although the studies are of varying quality, they all supported the same conclusions.

2·2 **Weak evidence** from Dasgupta et al., 2000 [+] suggesting that active case finding had an incremental cost of $20,328 for treating active TB compared with passive case detection and would have only been cost-saving if the future risk of TB was higher than the baseline estimate of 0·05%.[20]

2·3 **Weak evidence** from Mor et al., 2008 [-] suggesting that pre-migration screening has a direct net saving of $449,817 over five years compared to post-migration screening.[7]

Evidence statement 3: Effectiveness of interventions aiming to improve TB identification among homeless people

3·1 **Weak evidence** from Bernard et al., 2012 [+] showed that screening homeless people by Mobile X-ray Unit (MXU) improved screening coverage and reduced TB transmission among homeless people using shelters but also among non-shelter users.[23]

Seven studies identified by the NICE review[6] reported on the use of incentives, two studies focussed on homeless people (Citron et al., 1995 [+] and Pilote et al., 1996 [++]).[24,25]

3·2 **Moderate evidence** from two studies (Citron et al., 1995 [+] and Pilote et al., 1996 [++]) showed that the screening uptake improved among homeless people when a monetary incentive was given.[24,25]

Evidence statement 4: Effectiveness of interventions aiming to improve TB identification among drug users

4·1 **Weak evidence** from two studies (Ruutel et al., 2011 [+], Duarte et al., 2011 [-]) showed that active referral of intravenous drug users to a TB clinic increased TB screening among drug users for minimal extra costs.[26,27]

Monetary incentives
Two studies identified by the NICE review[6] reported on the use of incentives, one study reported on the effectiveness of the use of incentives among drug users (Perlman et al., 2003 [++])[28] and one study reported on the cost-effectiveness (Perlman et al., 2001 [++])[31].

4·2 **Moderate evidence** from one study showing that the use of small monetary incentives improved the attendance for TB screening by CXR among drug users with a positive TST.[28]

4·3 **Weak evidence** from one study showed that the provision of monetary incentives to drug users improved TB screening and was cost-effective.[29]

Evidence statement 5: Effectiveness of interventions aiming to improve TB identification among prisoners

Two studies identified by the NICE review[6] (Puisis et al., 1996 [-] and Yates et al., 2009 [-])[30,31] reported on the effectiveness of interventions aiming to improve TB identification among prisoners.

5·1 **Weak evidence** from one before-and-after study identified by the NICE review[6] (Puisis et al., 1996 [-]), suggesting that the yield of identifying active TB among prisoners was comparable when screening was done by TST (0·069%) or by CXR (0·056%).[30] The findings are of limited quality as there was no statistical analysis done and no adjustment for baseline differences between the two groups was done.

5·2 **Weak evidence** from one retrospective cohort study identified by the NICE review[6] suggesting that all prisoners should be offered TB screening by MXU regardless if the prisoners present with TB symptoms, as a substantial number of TB cases will be missed if only symptomatic prisoners will be screened.[31] Due to the retrospective character of this study the conclusions that could be drawn from this study were limited.

Evidence statement 6: Cost-effectiveness of interventions aiming to improve TB identification among prisoners

Weak evidence from one cost-comparison study identified by the NICE review[6] (Jones and Schaffner, 2001 [+])[32] suggesting that screening for active TB among prisoners was most cost-effective if it was done by CXR ($9,600 per positive case) compared to TST ($32,100) or symptom-based questionnaire ($54,100). The findings of this study are of limited quality as the incremental

cost-effectiveness ratio was not calculated and the start-up costs for CXR were not included in the cost calculation.

Evidence statement 7: Effectiveness of interventions aiming to improve TB identification among mixed hard-to-reach groups

Moderate evidence from three studies, one study identified by the NICE review[6] (Watson et al., 2007 [++])[33] and two studies identified by this review (Story et al., 2012 [+] and Jit et al., 2011 [+])[34,35] about the effectiveness of TB screening by MXU.
Watson et al., 2007 [++] showed that TB screening by MXU reduced diagnostic delay (adjusted hazard ratio = 0·35, 95%CI 0·21 - 0·59, $p < 0·0001$) and cases identified by MXU were less likely to be symptomatic than passively presented cases (adjusted OR 0·35, 95%CI 0·15 to 0·81, $p < 0·001$).[33]
Jit et al., 2001 [+] showed that MXU screening is effective, as 35% of the TB cases identified by MXU screening were asymptomatic and would not have presented for TB diagnostics.[34]
Story et al., 2012 [+] showed that MXU screening had a high sensitivity (81·8%) and specificity (99·2%), and people detected by MXU screening were less infective and therefore TB transmission could be reduced.[35]

Evidence statement 8: Cost-effectiveness of interventions aiming to improve TB identification among mixed hard-to-reach groups

Moderate evidence from two studies, one study identified by the NICE review[6] (Watson et al., 2007 [++])[33] and one study identified in this update of the review (Jit et al., 2011 [+]).[34]
Watson et al., 2007 [++] showed that screening by MXU was cost-effective compared to passive case detection if the costs of TB treatment was assumed to be £10,000, incremental cost-effectiveness ratio £1,912·33.[33]
Jit et al., 2011 [+] suggested that MXU screening is cost-effective, the incremental cost was £18,000 per Quality of Life Year (QALY) gained.[34]

Evidence statement 9: Effectiveness and cost-effectiveness of interventions aiming to improve TB identification among sex workers

No studies were identified that focussed on the effectiveness and/or cost-effectiveness of interventions aiming to improve TB identification among sex workers.

Evidence statement 10: Effectiveness of interventions aiming to improve TB identification among children within vulnerable and hard-to-reach populations

Weak evidence from George et al., 2011 [-] suggesting that a TST cut of point of 10 mm would be more sensitive and specific for latent TB and active TB in adopted children than a 5 mm TST cut of point.[17] This study had major limitations, the sample size was too small and only a small number of children had a comparative test done (CXR).

Tuberculosis management

Evidence statement 11: Effectiveness of directly observed therapy (DOT) to manage active TB in migrants

Inconsistent evidence from two studies identified by the NICE review[36] about the effectiveness of DOT in migrants: one study[37] (MacIntyre et al. 2003 [+]) found no significant difference in treatment completion rates between DOT administered by a family member (96·5%) and receiving regular treatment consisting of monthly check-ups (90·6%; RR for non-completion 2·7, 85% CI 0·66-14·2; p=0·11), although this study was underpowered. The second study[38] (Chemtob et al., 2003 [-]) reported an increase in successful treatment outcome for those who received DOT (78·5% in 1999 and 76·9% in 2000) vs. standard treatment (26·7%). However, no statistical comparison between these differences was made and potential sources of bias remained.

Evidence statement 12: Effectiveness of enhanced case management for management of active TB in homeless people

Weak evidence from one study (Goetsch et al. 2012 [-]) that enhanced case management leads to high treatment success rates in homeless people.[39] The authors found that the involvement of an experienced community worker providing education, communication management (between patient and health care (HC) professionals) and treatment monitoring, combined with a streamlined screening service, led to 76% treatment completion. A limitation is that they compared their post-intervention results retrospectively without correction for possible confounders.

Evidence statement 13: Effectiveness of a service model approach/social support to manage active TB in homeless people

The NICE review[36] reported **weak evidence** from one Spanish study (Diez et al. 1996 [-]) that a social care programme increased treatment completion.[40] They found that their intervention decreased annual TB incidence in the homeless population in the district (p=0·03), while it did not in other districts (p=0·34). It was not clear whether this change was caused by the intervention.

Evidence statement 14: Effective management of drug users with active TB

14·1 **Moderate evidence** from two studies, one identified in this update[39] and one[41] from the NICE review[36] showing that enhanced case management leads to improved treatment outcome in drug users. The results presented by Goetsch et al. show that community workers providing education and facilitating communication with health care professionals combined with streamlined screening procedures leads to 72% treatment completion.[39] However, a possible source of confounding remained by not correcting for time differences in this retrospective effectiveness study. Ricks 2008 [++] reports **moderate evidence** that enhanced case management by a former drug user peer led to higher treatment completion rates than limited case management by a health worker (Relative Risk (RR) =2·68, 95% CI 1·24 to 5·82; p=0·01), although this was a small study with high dropout rates.[41]

14·2·1 **Weak evidence** from one study identified in this update that a combination of enhanced case management in combination with improved service models could improve treatment outcome of drug users.[27] Duarte et al. 2011 [-] reported that treatment compliance increased, defaulting rates decreased and the mortality rate decreased (OR 0·7, 95% CI 0·28-1·78). Because the results were obtained in two different time periods and the authors did not correct for this, the evidence is of limited quality.

14·2·2 One study[42] identified by the NICE review[36] (Bock et al., 2001 [+]) provided **weak evidence** that in a population in which more than 50% were drug users, adding incentives to Direct Observed Treatment (DOT) improved treatment completion rates compared to DOT alone (OR = 5·73, 95% CI 2·25-14·84).[42]

14·3 One study from the NICE review[36] (Alwood, 1994 [-]) provided **weak evidence** that DOT led to a significantly higher treatment adherence when people living with HIV (64% being intravenous drug users) received DOT (96%, 44/48) compared with standard treatment (76%, 22/30, p=0·02).[43] However, only data for patients who adhered to treatment for more than eight weeks was reported.

14·4 One study from the NICE review[36] (Oscherwitz et al. 1997 [-]) provided **weak evidence** that in a population mainly consisting of drug or alcohol users (81%), treatment completion increased when patients were not detained: 82% of participants who were not detained completed treatment versus 20% who were (p<0·001).[44] However, significant differences were found between the two groups that may have confounded the results.

Evidence statement 15: Effective management of prisoners with active TB

One study from the NICE review[36] (Rodrigo et al., 2002 [-]) provided **weak evidence** that prisoners with active TB showed improved treatment adherence with DOT (from 95 per 100 in 1993 to 100 per 100 in 2000; controls 60 per 100 in 1987 to 76 per 100 in 1992).[45] No details were given about the sample characteristics.

Evidence statement 16: Effectiveness of concurrent antiretroviral therapy (ART) and TB therapy in people living with HIV (Human Immunodeficiency Virus) co-infected with active TB

Weak evidence from one study identified in this update that concurrent ART and TB therapy in people living with HIV co-infected with active TB leads to decreased mortality. Girardi et al. [+] report a successful TB outcome in 52·8% of the included patients co-infected with TB and HIV, 32·5% had an unsuccessful outcome and 14·6% died.[46] Concurrent ART and TB treatment reduces the mortality rate by six fold. Those who were not ART-naïve and not receiving ART during TB treatment had a fourfold higher chance of dying.

Evidence statement 17: Effectiveness of early initiation of ART in people living with HIV co-infected with active TB

Conflicting evidence from one study that early initiation of ART in people living with HIV co-infected with active TB is effective. Girardi et al. [+] conclude that with a six fold reduction in mortality, ART should be started as early as possible.[46]

Evidence statement 18: Effectiveness of DOT in the management of people living with HIV co-infected with active TB

One study identified by the NICE review[36] (Alwood, 1994) provided **weak evidence** that DOT can improve treatment adherence.[43] In the DOT group, 96% (44/48) completed six months of therapy versus 76% (22/30) in the standard treatment group. However, since patients who failed to adhere to more than eight weeks of treatment were excluded from the analysis these results are of limited quality.

Evidence statement 19: Effectiveness of combined interventions in the management of mixed hard-to-reach populations with active TB

19·1 **Weak evidence** from Goetsch et al. 2012 [-] that enhanced case management combined with improved service models leads to improved TB treatment outcome.[39] With an experienced community worker involved in and responsible for caring for these patients, as well as a streamlined low-threshold screening process, several active TB cases could be identified and treated, with a treatment completion rate of 76·3%.

19·2 One study identified by the NICE review[36] (Déruaz & Zellweger, 2004 [-]) provided **weak evidence** that the treatment outcome of patients undergoing full DOT (89·5%) does not significantly differ from that of patients undergoing partial DOT (89·5%), where only the first two months of treatment were observed (p=1·0).[47] Treatment outcome did not differ significantly between providing DOT on site (92·6%) or via social outreach (85·2%; p=0·67). Evidence is of limited quality because of differences and biases in data collection, and patients at risk for non-adherence were assigned to full DOT.

19·3 One study identified by the NICE review[36] (Juan et al., 2006 [+]) provided **weak evidence** that DOT combined with incentives improved treatment completion rates among mixed hard-to-reach populations compared to self-administration (RR = 3·07, 95% CI 2·13-4·41).[48] However, evidence is of limited quality because the intervention group was compared with a retrospective cohort without being corrected for differences.

Evidence statement 20: Cost-effectiveness of enhanced case finding and improved service models for mixed hard-to-reach populations with active TB

Weak evidence from Jit et al. 2011 [+] that a mobile "Find and Treat" service that predominantly screens homeless individuals and drug users is cost-effective.[34] It is estimated that the service would cost £6,400 per QALY gained with an incremental cost ratio of the mobile screening unit of £18,000/QALY gained.

Evidence statement 21: Effectiveness and cost-effectiveness of interventions for sex-workers with active TB

No evidence for effective or cost-effective TB interventions for sex-workers with active TB was identified in the NICE review[36] or this review.

Evidence statement 22: Effectiveness and cost-effectiveness of interventions on children within vulnerable and hard-to-reach populations
No evidence for effective or cost-effective interventions on children within vulnerable and hard-to-reach populations with active TB was identified in the NICE review[36] or this review.

List of Abbreviations

ART = Antiretroviral Therapy; CXR = Chest X-ray; DOT = Direct Observed Treatment; HC = Health Care; HIV = Human Immunodeficiency Virus; IGRA = Interferon Gamma Release Assay; IRIS = Immune Reconstitution Inflammatory Syndrome; LTBI = Latent TB Infection; MXU = Mobile X-ray Unit; OR = Odds Ratio; p = p-value; QALY = Quality Adjusted Life Year; QFT-G = QuantiFERON-TB Gold Test; RR = Relative Risk; TB = Tuberculosis; TST = Tuberculin Skin Test; US = United States; 95% CI = 95% Confidence Interval

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Supplementary Material V - Quality Assessment

Table S1. Quality assessment of included effectiveness studies

	Questions about:	Population		Method of selection						Outcomes					Analysis				Summary		
Year	First author (year)	1·1	1·2	1·3	2·1	2·2	2·3	2·4	2·5	3·1	3·2	3·3	3·4	3·5	4·1	4·2	4·3	4·4	5·1	5·2	Score
2010	Schneeberger et al.[45]	++	++	++	+	++	++	-	++	++	+	-	++	++	+	++	-	++	+	+	+
2011	Duarte et al.[40]	++	+	-	NA	+	++	-	++	+	+	-	+	++	NA	+	-	+	-	-	-
2011	George et al.[41]	++	+	+	++	++	+	-	++	-	-	-	NA	-	-	-	+	+	-	-	-
2011	Lowenthal et al.[43]	++	+	++	+	++	++	-	+	++	++	-	+	+	+	++	-	+	+	+	+
2011	Ruutel et al.[44]	++	-	+	+	++	++	+	++	++	-	-	++	NR	-	++	++	+	+	+	+
2012	Bernard et al.[37]	++	++	+	-	++	NA	NA	++	++	+	+	NA	NA	+	+	-	++	-	+	+
2012	Chuke et al.[31]	++	+	+	-	-	NA	-	+	-	-	-	NR	NA	-	-	-	-	-	-	-
2012	Girardi et al.[47]	++	++	+	NA	++	NA	++	++	+	+	-	NA	++	NR	++	++	++	+	+	+
2012	Goetsch et al.[46]	++	+	-	NA	+	++	-	++	++	-	-	NA	NA	NR	++	-	-	-	-	-
2012	Mor et al.[38]	+	++	++	NA	+	NA	NR	+	+	++	+	NA	++	++	+	-	+	+	++	+
2012	Story et al.[39]	++	+	+	-	-	NA	+	++	+	-	-	NA	++	-	+	+	+	+	+	+
2013	Assael et al.[34]	+	++	+	NR	+	NA	-	+	++	-	-	NA	NA	NR	-	-	-	-	-	-
2013	Bell et al.[35]	++	+	++	-	++	++	+	++	++	+	-	+	+	+	+	+	++	+	+	+
2013	Painter et al.[36]	++	++	++	++	++	NA	NA	+	++	++	-	++	++	-	++	-	+	+	+	+
2014	Posey et al.[33]	+	-	-	++	-	+	-	++	-	+	-	NR	NR	-	-	-	-	-	-	-
2015	Liu et al.[29]	++	++	++	++	++	+	-	+	++	++	-	++	++	++	++	+	-	-	++	+
2015	Mor et al.[30]	+	-	-	-	+	NA	-	+	+	-	-	NA	-	-	-	-	-	-	-	-
	Studies identified for the NICE reviews[24,25]																				
1994	Alwood et al.[67]	+	+	++	-	+	++	-	+	+	++	+	++	++	NR	-	+	+	-	-	-
1995	Citron et al.[50]	++	++	+	+	++	+	+	++	++	++	++	+	++	NR	+	-	+	+	+	+
1996	Diez et al.[71]	+	+	-	-	-	NR	NA	+	-	NA	-	++	++	NR	NR	+	++	-	-	-
1996	Pilote et al.[56]	+	++	+	++	++	NR	++	++	+	++	++	++	NR	NA	NA	++	++	++	+	++
1996	Puisis et al.[59]	++	+	++	-	+	++	-	+	+	+	+	NR	NR	NR	-	-	-	-	-	-
1997	Oscherwitz et al.[74]	+	+	+	NA	+	++	++	+	+	++	++	NR	NR	NR	-	++	+	-	+	-
1999	Sciortino et al.[63]	+	+	++	+	-	NR	+	+	++	++	++	++	++	NR	++	++	++	++	+	+
2001	Bock et al.[68]	+	+	++	++	+	++	++	+	++	++	+	++	++	NR	+	++	++	++	+	+
2001	Verver et al.[64]	++	++	+	-	+	NR	-	+	++	+	++	++	++	NR	-	+	++	+	+	+
2002	Rodrigo et al.[75]	+	++	NR	NA	+	++	++	+	+	++	++	NR	NR	NR	NR	++	+	-	+	-
2003	Chemtob et al.[69]	++	+	-	NA	+	++	++	+	+	++	+	NR	NR	NR	NR	-	-	-	+	-
2003	MacIntyre et al.[73]	+	+	+	++	++	++	+	+	+	++	+	++	++	-	NR	+	+	+	+	+
2003	Perlman et al.[57]	++	+	++	+	++	+	+	+	++	++	++	++	++	NR	++	++	++	++	+	++
2004	Deruaz & Zellweger[70]	++	+	+	-	+	-	-	+	-	++	++	++	++	NR	-	++	+	-	+	-
2005	Monney and Zellweger[54]	++	+	NR	-	++	++	-	+	+	+	+	++	++	NR	-	-	+	-	+	+
2006	Juan et al.[72]	++	+	+	-	++	++	++	+	++	++	+	++	++	NR	+	++	++	+	+	+
2007	Laifer et al.[53]	++	++	++	-	++	++	-	+	++	++	+	NR	NR	NR	-	++	+	-	+	+
2008	Ricks[60]	++	+	++	++	++	++	++	+	+	++	++	++	+	NR	++	++	++	++	+	++
2009	Yates et al.[66]	++	+	+	+	+	++	+	++	-	+	++	NA	+	NR	-	+	-	+	-	-

NICE National Institute for Health and Clinical Excellence

++	well designed study, minimal risk of bias
+	study may not have addressed all potential sources of bias
-	significant risk of bias
NA	Not Applicable
NR	Not Reported

Quality assessment questions for effectiveness studies:

1·1	Is the source population or source area well described?
1·2	Is the eligible population or area representative of the source population or area?
1·3	Do the selected participants or areas represent the eligible population or area?
2·1	Selection of exposure (and comparison) group. How was selection bias minimised?
2·2	Was the selection of explanatory variables based on a sound theoretical basis?
2·3	Was the contamination acceptably low?
2·4	How well were likely confounding factors identified and controlled?
2·5	Is the setting applicable to Europe?
3·1	Were the outcome measures and procedures reliable?
3·2	Were the outcome measurements complete?
3·3	Were all the important outcomes assessed?
3·4	Was there a similar follow-up time in exposure and comparison groups?
3·5	Was follow-up time meaningful?
4·1	Was the study sufficiently powered to detect an intervention effect (if one exists)?
4·2	Were multiple explanatory variables considered in the analyses?
4·3	Were the analytical methods appropriate?
4·4	Was the precision of association given or calculable? Is association meaningful?
5·1	Are the study results internally valid (i.e. unbiased)?
5·2	Are the findings generalisable to the source population (i.e. externally valid)?

Table S2. Quality assessment of included cost-effectiveness studies

	Questions about:	Applicability								Study limitations											
Year	**First author**	**1·1**	**1·2**	**1·3**	**1·4**	**1·5**	**1·6**	**1·7**	**1·8**	**2·1**	**2·2**	**2·3**	**2·4**	**2·5**	**2·6**	**2·7**	**2·8**	**2·9**	**2·10**	**2·11**	**Overall**
	Studies identified for this review																				
2011	Jit et al.[42]	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	**Minor limitations**
	Studies identified for the NICE reviews[24,25]																				
2000	Dasgupta et al.[51]	Y	Y	PA	N	PA	PA	N	PA	Y	Y	Y	PA	N	PA	PA	PA	Y	Y	U/C	**Potential serious limitations**
2000	Schwartzman and Menzies[62]	Y	Y	PA	Y	PA	Y	N	PA	Y	Y	Y	PA	PA	Y	PA	PA	Y	Y	N	**Minor limitations**
2001	Jones and Schaffner[52]	PA	Y	PA	Y	A	Y	N	PA	Y	Y	Y	PA	Y	Y	PA	PA	Y	Y	U/C	**Potential serious limitations**
2001	Perlman et al.[58]	Y	Y	PA	Y	Y	Y	N	PA	Y	Y	Y	Y	Y	Y	PA	PA	Y	Y	U/C	**Minor limitations**
2005	Schwartzman et al.[61]	Y	Y	PA	Y	Y	PA	N	Y	PA	Y	Y	PA	PA	Y	PA	PA	N	Y	N	**Minor limitations**
2007	Watson et al.[65]	Y	Y	Y	Y	PA	Y	Y	PA	PA	PA	PA	PA	PA	Y	PA	PA	Y	Y	N	**Minor limitations**
2008	Mor et al.[55]	PA	Y	PA	N	PA	N	N	PA	PA	PA	PA	N	PA	PA	U/C	U/C	Y	N	N	**Very serious limitations**

NICE National Institute for Health and Clinical Excellence
Y Yes to question
N No to question
PA Partially applicable
NA Not Applicable
U/C Unclear

Quality assessment questions for cost-effectiveness studies:

1·1 Is the study population appropriate for the topic being evaluated?
1·2 Are the interventions appropriate for the topic being evaluated?
1·3 Is the system in which the study was conducted sufficiently similar to the current European context?
1·4 Was/were the perspective(s) clearly stated and what were they?
1·5 Are all direct health effects on individuals included, and are all other effects included where they are material?
1·6 Are all future costs and outcomes discounted appropriately?

1·7	Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?
1·8	Are costs and outcomes from other sectors fully and appropriately measured and valued?
2·1	Does the model structure adequately reflect the nature of the topic under evaluation?
2·2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?
2·3	Are all important and relevant outcomes included?
2·4	Are the estimates of baseline outcomes from the best available source?
2·5	Are the estimates of relative 'treatment' effects from the best available source?
2·6	Are all important and relevant costs included?
2·7	Are the estimates of resource use from the best available source?
2·8	Are the unit costs of resources from the best available source?
2·9	Is an appropriate incremental analysis presented or can it be calculated from the data?
2·10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?
2·11	Is there any potential conflict of interest?

Table S3. Quantitative Intervention Studies

	Questions about:	Population			Method of selection										Outcomes						Analysis						Summary		
Year	**First Author**	**1·1**	**1·2**	**1·3**	**2·1**	**2·2**	**2·3**	**2·4**	**2·5**	**2·6**	**2·7**	**2·8**	**2·9**	**2·10**	**3·1**	**3·2**	**3·3**	**3·4**	**3·5**	**3·6**	**4·1**	**4·2**	**4·3**	**4·4**	**4·5**	**4·6**	**5·1**	**5·2**	**Over-all**
	Study identified for this review																												
2014	Harstad et al.[32]	+	++	++	+	-	NA	NA	++	++	-	+	++	++	++	++	+	+	NA	NA	++	NR	NR	NR	+	++	+	++	-

++ Well designed study, minimal risk of bias
+ Study may not have addressed all potential sources of bias
- Significant risk of bias
NA Not Applicable
NR Not Reported

Quality Assessment Questions:
1·1 Is the source population or source area well described?
1·2 Is the eligible population or area representative of the source population or area?
1·3 Do the selected participants or areas represent the eligible population or area?
2·1 Allocation to intervention (or comparison). How was selection bias minimised?
2·2 Were interventions (and comparisons) well described and appropriate?
2·3 Was the allocation concealed?
2·4 Were participants or investigators blind to exposure and comparison?
2·5 Was the exposure to the intervention and comparison adequate?
2·6 Was contamination acceptably low?
2·7 Were other interventions similar in both groups?
2·8 Were all participants accounted for at study conclusion?
2·9 Did the setting reflect European practice?
2·10 Did the intervention or control comparison reflect European practice?
3·1 Were outcome measures reliable?
3·2 Were the outcome measurements complete?
3·3 Were all the important outcomes assessed?
3·4 Were outcomes relevant?
3·5 Were there similar follow-up times in exposure and comparison groups?
3·6 Was follow-up time meaningful?
4·1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?
4·2 Was intention to treat (ITT) analysis conducted?
4·3 Was the study sufficiently powered to detect an intervention effect (if one exists)?
4·4 Were the estimates of effect size given or calculable?
4·5 Were the analytical methods appropriate?

4·6 Was the precision of intervention effects given or calculable? Were they meaningful?
5·1 Are the study results internally valid (i.e. unbiased)?
5·2 Are the findings generalisable to the source population (i.e. externally valid)